Journal of Research in Medical and Dental Science
2022, Volume 10, Issue 11, Page No: 06-18

Available Online at: www.jrmds.in
eISSN No. 2347-2367: pISSN No. 2347-2545

Frequency and Risk Factors of Carbapenem-Resistant Gram-Negative Bacteria in Taif, Saudi Arabia

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ABSTRACT

This study aims to identify carbapenem-resistant gram-negative bacterial infection (CR-GNB) prevalence in King Faisal Medical Complex Hospital (KFMC), at Taif, Saudi Arabia, and to determine the distribution of biotypes, antibiotypes, site of infection, hospital wards, multiple associated demographics, clinical characteristics, & comorbidity risk factors. Clinical samples were obtained from patients admitted to KFMC, over a period of 6 months and were screened for carbapenem resistance by Phoenix System. Patients' demographic and comorbidity data were collected. Overall, 763 clinical infections by gram-negative isolates during 6 months in KFMC were identified, 236 (32%) of the clinical isolates were determined as CR-GNB from 8 different sites of a body, the most isolates came from blood, (71/236, 30.1%), then isolates from sputum (63/236, 26.7%), isolates from urine (54/236, 22.9%), and isolates from wound (22/236, 9.3%). The highest incidences of carbapenem resistance infections (25.48%) were recorded in ICU-CCU. The most incidences of CR-GNB were recorded in Klebsiella spp. (65.7%), Acinetobacter baumannii (16.1%), Pseudomonas spp. (12.7%), and slightly in Proteus spp., (3%), Escherichia coli (1.3%), Providencia rettgeri (0.85%) and Morganella morganii (0.4%). The highest MDR percentages were in Pseudomonas spp. (40%) and Proteus spp. (46.15%), while the highest PDR percentage was in A. baumannii. According to sensitivity to the 19 tested antibiotics, the tested CR isolates were classified into 29 antibiotypes patterns. The CR-GNB infection increased at the high age, male gender, & long hospitalization of the patient and there were significant association between CR-GNB infection and comorbidities including cardiovascular, pulmonary, neurologic, renal, bed sores, hepatic, & malignancy disease. The most prevalent clinical characteristics observed at current study were urinary catheter insertion (72.5%), invasive procedure (70.1%), artificial ventilation (65.3%), ICU administration (61.7%), and dialysis (14.4%). CR-GNB infection increased in COVID-19 patients (40.7%) and death rate among CR patients was 40.7%. In conclusion, carbapenem resistance gram-negative bacterial infection was determined and the incidence percentage, distribution, multiple associated risk factors including demographics, comorbidities, clinical characteristics, COVID-19 infection and the outcomes of these infections were recorded.

Key words: Carbapenem, Enterobacteriaceae, Saudi Arabia, Carbapenemases metallo-β-lactamase

HOW TO CITE THIS ARTICLE: Rawan Abou-assy, Reda Amashah, Manhal Mahmoud Shbat, Magda Mohammed Aly, Frequency and Risk Factors of Carbapenem-Resistant Gram-Negative Bacteria in Taif, Saudi Arabia, J Res Med Dent Sci, 2022, 10 (11):06-18.

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Received: 19-October-2022, Manuscript No. JRMDS-22-77746;

Editor assigned: 21-October-2022, PreQC No. JRMDS-22-77746(PQ);

Reviewed: 04-November-2022, QC No. JRMDS-22-77746(Q);

Revised: 08-November-2022, Manuscript No. JRMDS-22-77746(R);

Published: 15-November-2022

INTRODUCTION

Carbapenem is a class antibiotics which used for treatment for serious infections caused by Enterobacterales, carbapenem resistance (CR) bacteria is a major and an ongoing public health problem which is aggravated by inadequate infection control in developing countries due to poor hygiene, resource and structural constraints, deficient surveillance data, and lack of awareness regarding nosocomial infections [1,2]. It occurs mainly among gram-negative pathogens such as Klebsiella pneumoniae, Pseudomonas aeruginosa and *Acinetobacter baumannii* [3], and may be intrinsic or mediated by transferable carbapenemase-encoding genes, the most effective carbapenemases, in terms of carbapenem hydrolysis and geographical spread, are KPC, VIM, IMP, NDM and OXA-48 types [4-6] and there is a widespread acquisition of resistance genes. Thus, effective antimicrobial options for Carbapenem-Resistant Enterobacterales (CRE) are often lacking, and treatment typically requires reliance on drugs with a risk of toxicity or other safety concerns [7].

Carbapenem-resistant K. pneumoniae is a prominent cause of nosocomial infections associated with high rates of morbidity and mortality, particularly in immune-compromised individuals, it causes a broad spectrum of diseases including pneumonia, urinary tract infections, bloodstream infections, & skin and soft tissue infections [8]. In healthcare settings, carbapenem resistance gram-negative bacteria (CR-GNB) are transmitted from person to person, often via the hands of healthcare personnel or through contaminated medical equipment [9]. Additionally, sink drains and toilets are increasingly recognized as an environmental reservoir and CRE transmission source [10]. There are several public health concerns related to the spread and acquisition of CR-GNB in Saudi Arabia including: i) the massive importation of people during Hajj seasons and the transfer of patients for health care purposes. ii) the non-restricted use of antibiotics. iii) the presence of poor and inadequate waste disposal system in the western province of Saudi Arabia with the possibility of transmission of intestinal CR-GNB strains to the sources of drinking water [11]. The aim of this study is to isolate and identify carbapenem resistance gram-negative bacterial infection from King Faisal Medical Complex Hospital, Taif, Saudi Arabia, and to determine the incidence percentage, distribution, multiple associated risk factors including demographics, comorbidities, clinical characteristics, COVID-19 infection and the outcomes of these CR-GNB infections during a study period.

MATERIALS AND METHODS

Source of isolates and study design

Isolates of CR-GNB were collected from KFMC in Taif, Saudi Arabia. The bed capacity of the hospital is 800 beds distributed over different sections; 27 beds of ICU, 13 beds of CCU (cardiac care unit), 13 beds of HDU-BED (high dependent unit), 10 beds of burn units, 54 beds of MMW (male medical ward), 54 beds of FMW (female medical ward), 80 beds of MSW (male surgical ward), 80 beds of FSW (female surgical ward), 54 beds of ISO (isolation), 27 beds of FMM (fetal and maternal medicine), 300 beds of maternity wards, 27 beds of inpatient medical ward, 61 beds distributed between ER (emergency), LTCU (long term care unit), NICU (nursery intensive care unit), INPS (infants & pediatrics isolation), ANT5 (antenatal care).

Ethics statement

The study was approved by the ethics committee review Board of Research and Studies Department of Directorate of Health Affairs at Taif in October 2021. The approval number 615 of IRB Registration Number with King Abdulaziz City for Science and Technology (KACST) in Riyadh, KSA, (HAP-02-T-067).

Identification and susceptibility test by phoenix system

All clinical specimens from all units of KFMC to the Clinical Microbiology Laboratory were cultured on blood agar & MacConkey agar (Oxoid, UK) to get pure culture. The Phoenix panel was inoculated with the prepared ID Broth and the absorbance was adjusted to 0.50–0.60 McFarland (Standard inoculum) by using the Phoenix Spec™ Nephelometer (BD Diagnostic Systems). Then, 25 microliters of the prepared ID Broth with one drop from the indicator were added to Phoenix AST broth, placed closure securely on the panel to seal, then panels were loaded into BD Phoenix System 100 (Sparks, MD, USA). After 24 h of incubation, the identification of the bacterial isolate and sensitivity to 19 antibiotics were obtained through the computer [12].

Carbapenem resistance confirmation

Samples that were identified as carbapenem-resistant by Phoenix System were confirmed by disc diffusion method to imipenem and meropenem (10 µg, Oxoid Ltd, UK) and this test was done using Disk Diffusion Susceptibility Test Protocol [13].

Clinical carbapenem resistance isolates collection

About 236 bacterial isolates belonging to CR-GNB were collected in a period of six months, from November 2021 to April 2022. Duplicate samples from the patient's body site were excluded from the study. All the isolates were sub-cultured and maintained on Glycerol Nutrient Broth medium (20% glycerol) at -70 to 80°C for long period of storage [14].

Patient data collection

Carbapenem resistance infected patients' demographic, clinical characteristics, comorbidity, & outcome data were collected from patient files and the electronic databases in the hospital (Oasis), in addition to the Infection Control Department of KFMC.

Statistical analysis

All statistical analyses were conducted with SPSS software (IBM Corp. released 2017, IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Categorical variables were compared by Chi-square test or Fisher exact test, and P values ≤0.05 were considered significant [15].

RESULTS

Carbapenem resistance prevalence in KFMC at Taif

A total of 13,501 clinical specimens were sent from different KFMC wards from various clinical samples (4,947 blood samples & 8,554 other samples including urine, sputum, swabs, body fluids & catheter) during the study period from November 2021 to April 2022. Overall, 763 clinical infections by gram-negative isolates of the specimens collected were culture-positive (Table 1). Overall, 236 (32%) of the clinical samples were determined as CR-GNB, these isolates were referred to 167 patients. All the bacterial isolates from various samples (Ex., urine, blood, sputum, and bed sores) to the same patient and have the same sensitivity profile were considered the same biotype. The repeated bacterial

isolates for the same patients from the same body site which sent for infection monitoring purposes were ignored.

Sources & biotypes of CR-GNB isolates

All carbapenem resistance isolates (236 isolates) were obtained from 8 different sites of the patient's body, the clinical distribution of these isolates was as the following (Figure 1): the most isolates came from blood, (71/236, 30.1%), then isolates from sputum (63/236, 26.7%), isolates from urine (54/236, 22.9%), isolates from wound (22/236, 9.3%), isolates from catheter (11/236, 4.7%), isolates from body fluids (9/236, 3.8%), isolates from vaginal swabs (2/236, 0.8%) and from other locations (4/236, 1.7%). There was a significant difference between CR-GNB and the body's source or site of isolation (P-value=0.000). Forty-one isolates, nearly 17.4% of the CR-GNB isolates which refer to 13 patients had a systematic CR infection, CR-GNB same isolates were found in the blood, urine/catheter, & sputum of the same patient and in some cases isolated from the bed sores.

The highest incidence of Carbapenem resistance was recorded in *Klebsiella spp*. (155/236, 65.7%), *A. baumannii* (38/236, 16.1%), *Pseudomonas spp.* (30/236, 12.7%), *Proteus sp.,* (7/236, 3%), *E. coli* (3/236, 1.3%), *Providencia rettgeri* (2/236, 0.85%) and *Morganella morganii* (1/236, 0.4%).

Distribution of CR-GNB in KFMC service wards

As previously known, all isolates of CR-GNB (n=236) were obtained from 167 patients hospitalized in 15 different service wards at KFMC from November 2021 to April 2022. The highest incidence of carbapenem resistance gram-negative bacteria was recorded in ICU-CCU where 66 (25.48%) isolates were recovered from 44 patients. Moreover, 48 isolates (18.53%) were from 28 patients at HDU-BED. Concerning the male surgical ward, 35 isolates (13.51%) were from 26 patients at MSW. About 31 isolates (11.97%) were from 11 patients

Table 1: Counts of clinical bacterial isolates for six months from KFMC and CR-GNB prevalence.

	Blood samples	Other samples	All bacterial isolates	CRE patients	CRE isolates	CRE prevalence
Month 11	735	1,490	145	27	41	28%
Month 12	679	1,568	138	26	39	28%
Month 1	940	1,520	134	17	30	22%
Month 2	920	1,520	136	40	30	22%
Month 3	845	1,228	90	37	43	48%
Month 4	828	1,228	120	20	53	44%
Total	4,947	8,554	763	167	236	32%
	13,501					

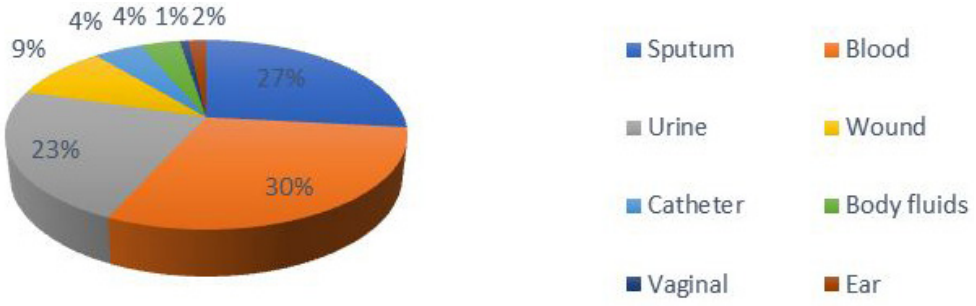

Figure 1: Diagram of percentage of CR-GNB isolated from different sites of the body.

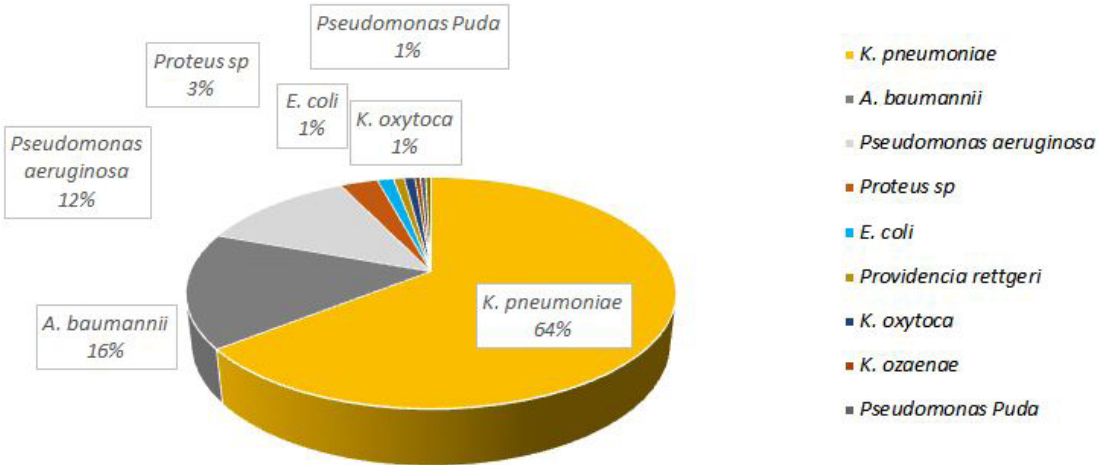

Figure 2: Diagram of percentage of CR-GNB several biotypes.

hospitalized at FMW, 18 isolates (6.95%) were from 16 patients at MMW, 16 isolates (6.18%) were from 12 patients at LTCU, 12 isolates (4.63%) were from 12 patients at FSW, respectively (Figure 2).

Eight isolates (3.09%) were obtained from Emergency, six isolates (2.32%) from each isolation and ANT5, two isolates were obtained from each Burn Unit (0.77%), INPS (0.77%), OPD (0.77%), and NICU (0.77%). One isolate (0.42 %) was obtained from Maternity & Delivery (Table 2).

From the data in Table 2, we also noted that most of the isolates were recovered from the respiratory tract

Table 2: Distribution of CR-GNB isolated from different specimens collected from different service wards at KFMC.

Service Units	Sputum	Wounds	Urine+Catheter	Blood	Body fluids	Other	Total	Pt. No.
ICU-CCU (NO.)	37 *	4	9	16	0	0	66	
Hospital Units (%)	56.06	6.06	13.64	24.24	0	0	100	44
Site of isolation (%)	54.41	18.18	10.71	22.54	0	0	25.48	
Burn Unit (NO.)	0	2	0	0	0	0	2	
Hospital Units (%)	0	100	0	0	0	0	100	18
Site of isolation (%)	0	9.09	0	0	0	0	0.77	
HDU-BED (NO.)	12	2	12	16	6	0	48	
Hospital Units (%)	25	4.17	25	33.33	12.5	0	100	28
Site of isolation (%)	17.65	9.09	14.29	22.54	100	0	18.53	
MMW (NO.)	4	2	8	4	0	0	18	
Hospital Units (%)	22.22	11.11	44.44	22.22	0	0	100	16
Site of isolation (%)	5.88	9.09	9.52	5.63	0	0	6.95	
FMW (NO.)	2	2	16	10	0	1	31	
Hospital Units (%)	6.45	6.45	51.61	32.26	0	3.23	100	20
Site of isolation (%)	2.94	9.09	19.05	14.08	0	12.5	11.97	
MSW (NO.)	3	8	14	10	0	0	35	
Hospital Units (%)	8.57	22.86	40	28.57	0	0	100	26
Site of isolation (%)	4.41	36.36	16.67	14.08	0	0	13.51	
FSW (NO.)	2	2	2	3	0	3	12	
Hospital Units (%)	16.67	16.67	16.67	25	0	25	100	10
Site of isolation (%)	2.94	9.09	2.38	4.23	0	37.5	4.63	
ISO (NO.)	2	0	2	2	0	0	6	
Hospital Units (%)	33.33	0	33.33	33.33	0	0	100	4
Site of isolation (%)	2.94	0	2.38	2.82	0	0	2.32	
Maternity & Delivery (NO.)	0	0	1	0	0	0	1	
Hospital Units (%)	0	0	100	0	0	0	100	1
Site of isolation (%)	0	0	0.01	0	0	0	0	
ER (NO.)	0	0	6	2	0	0	8	
Hospital Units (%)	0	0	75	25	0	0	100	8
Site of isolation (%)	0	0	7.14	2.82	0	0	3.09	
LTCU (NO.)	4	0	6	6	0	0	16	
Hospital Units (%)	25	0	0	37.5	0	0	100	12
Site of isolation (%)	5.88	0	7.14	8.45	0	0	6.18	
NICU (NO.)	0	0	0	2	0	0	2	
Hospital Units (%)	0	0	0	100	0	0	100	2
Site of isolation (%)	0	0	0	2.82	0	0	0.77	
OPD (NO.)	0	0	0	0	0	2	2	
Hospital Units (%)	0	0	0	0	0	100	100	2
Site of isolation (%)	0	0	0	0	0	25	0.77	
INPS (NO.)	2	0	0	0	0	0	2	
Hospital Units (%)	100	0	0	0	0	0	100	2
Site of isolation (%)	2.94	0	0	0	0	0	0.77	
ANT5A -B (NO.)	0	0	4	0	0	2	6	
Hospital Units (%)	0	0	66.67	0	0	33.33	100	6
Site of isolation (%)	0	0	4.76	0	0	25	2.32	
Total	68	22	84	71	6	8	259	199*
P-value				0				

ICU: Intensive Care Unit; CCU: Cardiac Care Unit; HDU-BED: High Dependent Unit; MMW: Male Medical Ward; FMW: Female Medical Ward; MSW: Male Surgical Ward; FSW: Female Surgical Ward; ISO: Isolation; ER: Emergency; LTCU: Long Term Care Unit; NICU: Nursery Intensive Care Unit; OPD: Outpatient Department; INPS: Infants and Pediatrics Isolation; ANT5: Antenatal Care.

* CR-GNB patients transported among various wards.

samples (n=37) in ICU-CCU, followed by blood samples (n=16) in each ICU-CCU and HDU-BED, addition to (n=16) samples of urine in FMW. Statistical analysis showed that there is a highly significant difference between service wards and sites of isolation using Fisher's Exact test (P=0.00).

Antibiotypes categories of CR-GNB in KFMC

Antimicrobial susceptibility test was determined for the panel of 19 antibiotics against 236 CR-GNB clinical isolates using microdilution method. Multiple drug resistance (MDR) is antimicrobial resistance shown by a species of microorganism to at least one antimicrobial drug in three or more antimicrobial categories, extensively drug-resistant (XDR) is the resistance of one bacteria species to all antimicrobial agents except in two or fewer antimicrobial categories but pan-drug resistant (PDR) is the non-susceptibility of bacteria to all antimicrobial agents in all antimicrobial categories. The antibiotic susceptibility profiles of CR-GNB isolates were studied to detect MDR, XDR, & PDR percentages among several organisms. 143 (60.59%) of carbapenem resistance isolates belong to XDR profile whereas XDR was the most common susceptibility profile among CR isolates, then 51 isolates (21.61%) belong to PDR which is defined as no susceptibility to all agents in all antimicrobial categories which tested. The lowest percentage was referred to MDR profile with 42 CR isolates (17.80%). The highest MDR percentages were in Pseudomonas spp. (40%) and other organisms including Proteus spp. (46.15%), while the highest PDR percentage was in *A. baumannii* (34.21%) as shown in Table 3. Statistical analysis showed that there was a highly significant difference in Antibiotypes categories (AC) and type of CR organisms using the Chi square test (P<0.000).

Antimicrobial resistance percentages of CR-GNB of KFMC

Figure 3 showed the susceptibility of CR-GNB (n=236) for each antimicrobial agent. For imipenem and meropenem, 0 and 23 CR isolates (0% & 9.75%) were susceptible, 232 CR isolates (98.31%) were resistant for ampicillin and 4 (1.69%) were sensitive. For piperacillin/tazobactam, 219 CR isolates (92.8%) were resistant, and 17 CR isolates (7.20%) were sensitive. For amikacin, 187 CR isolates (79.24%) were resistant, and 49 CR isolates (20.76%) were sensitive. For gentamicin, 203 CR isolates (86.02%) were resistant, and 33 CR isolates (13.98%) were sensitive. Moreover, 156 CR isolates (66.1%) were resistant to tigecycline, and 33.90% CR isolates (33.90%) were sensitive, 209 CR isolates (88.56%) were resistant to cefepime, and 27 CR isolates (11.44%) were sensitive. Finally, 130 (55.17%) of CR isolates were sensitive to colistin as shown in Figure 3.

Antimicrobial resistance percentages of various CR-GNB organisms

The resistance percentage of CR *A. baumannii* (CRAB) was 100% for most antibiotics including ampicillin, amoxicillin/clavulanic acid, piperacillin/tazobactam, cefalotin, cefoxitin, ceftazidime, ceftriaxone, imipenem, meropenem, gentamicin, ciprofloxacin, tigecycline, nitrofurantoin, & azetronam, while the resistance percentage of colistin was 34.21%, so the colistin the most effective antibiotics against CRAB as shown in (Table 4).

Antimicrobial susceptibility patterns of CR-GNB in KFMC at Taif

Nineteen different antibiotic susceptibility profiles were observed among the 236 CRE isolates. These antibiotypes give a designated code for pattern numerals. According to sensitivity to the 19 tested antibiotics, the tested CR *Klebsiella spp*., *Pseudomonas spp*., *A. baumannii* and other organisms were classified into twenty-nine antibiotypes

Table 3: Antibiotypes categories (MDR, XDR, & PDR) of CR-GNB isolates.

Biotype (n)	MDR	XDR	PDR	Total
Klebsiella spp. (NO.)	22	103	30	155
Recording to biotype (%)	14.19	66.45	19.35	100
Recording to AC (%)	52.4	72	58.8	65.7
Pseudomonas spp. (NO.)	12	12	6	30
Recording to biotype (%)	40	40	20	100
Recording to AC (%)	28.6	8.4	11.8	12.7
Acinetobacter baumannii (NO.)	2	23	13	38
Recording to biotype (%)	5.26	60.53	34.21	100
Recording to AC (%)	4.8	16.1	25.5	16.1
Others (NO.)	6	5	2	13
Recording to biotype (%)	46.15	38.46	15.38	100
Recording to AC (%)	14.3	3.5	3.9	5.5
Total	42	143	51	236
	17.80%	60.59%	21.61%	100%
P-value	0.0002			
MDR: Multidrug Resistant				
XDR: Extensively Drug Resistance				
PDR: Pan Drug Resistance				
AC: Antibiotypes Categories				

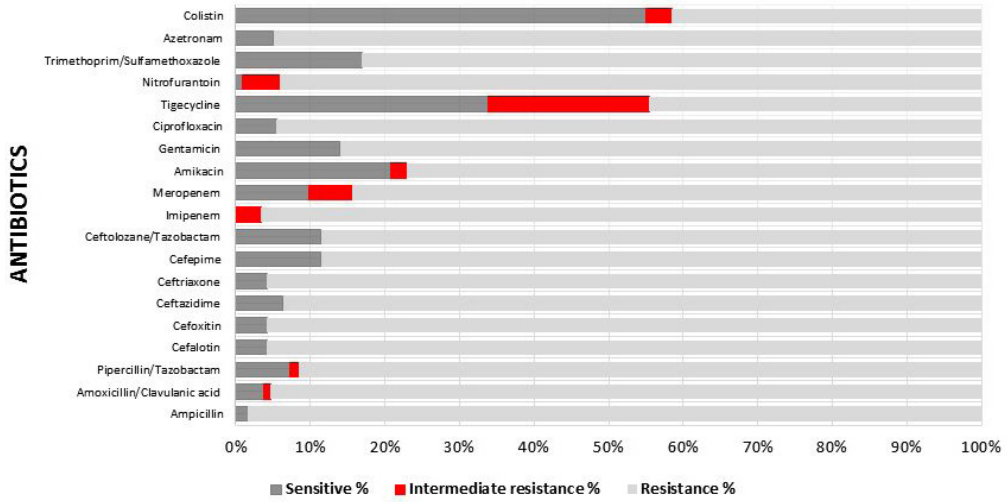

Figure 3: Diagram of antibiotics resistance percentage of CR-GNB isolates for 6 months.

Table 4: Antimicrobial resistance isolates and percentages to different antibiotics among different CR-GNB organisms.

Antimicrobial agent	Resistance species				Total
	Klebsiella spp. (%)	Pseudomonas spp. (%)	*Acinetobacter baumannii* (%)	Others (%)	
Ampicillin	155	28	38	11	232
	100	93.33	100	84.62	
Amoxicillin/Clavulanic acid	153	28	38	8	227
	98.71	93.33	100	61.54	
Pipercillin/Tazobactam	151	21	38	9	219
	97.42	70	100	69.23	
Cefalotin	153	26	38	9	226
	98.71	86.67	100	69.23	
Cefoxitin	153	26	38	9	226
	98.71	86.67	100	69.23	
Ceftazidime	153	21	38	9	221
	98.71	70	100	69.23	
Ceftriaxone	153	26	38	9	226
	98.71	86.67	100	69.23	
Cefepime	147	21	35	6	209
	94.84	70	92.11	46.15	
Ceftolozane/Tazobactam	147	21	35	6	209
	94.84	70	92.11	46.15	
Imipenem	155	30	38	13	236
	100	100	100	100	
Meropenem	147	22	38	6	213
	94.84	73.33	100	46.15	
Amikacin	129	19	35	4	187
	83.23	63.33	92.11	30.77	
Gentamicin	140	19	38	6	203
	90.32	63.33	100	46.15	
Ciprofloxacin	155	21	38	9	223
	100	70	100	69.23	
Tigecycline	88	26	38	4	156
	56.77	86.67	100	30.77	
Nitrofurantoin	153	30	38	13	234
	98.71	100	100	100	
Trimethoprim/Sulfamethoxazole	129	26	30	11	196
	83.23	86.67	78.95	84.62	
Azetronam	151	30	38	5	224
	97.42	100	100	38.46	
Colistin	80	8	13	5	106
	51.61	26.67	34.21	38.46	
P-value	0				

patterns (Table 5). Antibiotype P1 was resistant for all the broad-spectrum antimicrobials tested including colistin and tigecycline and was the largest predominate antibiotype contained a total of 51 PDR strains including 30 CR Klebsiella spp., 6 Pseudomonas spp., 13 Acinetobacter spp. and 2 other organisms. Statistical analysis showed that there is generally significant difference between antibiotic patterns and type of CR organisms (P ≤ 0.05, Fisher's exact test).

Socii-demographic data of CR patients in KFMC

A total of 167 patients admitted to the hospital developed 236 carbapenem resistance isolates. The median of CR patients' age was 61+23 years (P-value=0.00) and ranged from 2 months to 97 years. The mean duration of hospitalization (DOH) of CR patient was 18 ± 92 days (P-value=0.00). The CR-GNB infection increased when the age of the patient, the duration of hospitalization, & male gender (97/167, 58.1%, P-value= 0.037) increased.

CR-GNB infection had a high incidence rate in ICU-CCU (46/167, 27.5%), MSW (30/167, 18%), HDU-BED (28/167, 16.8%), MMW (18/167, 10.8%), FMW (14/167, 8.4%), & LTCU (12/167, 7.2%) and some cases distributed to the rest ward's services. There is a significant difference between CR-GNB in KFMC wards (P-value=0.000). In addition, most CR patients were Saudi (155/167, 92.8%).

Demographics of CR patients distributed to various antimicrobial categories of the CR isolates were calculated for three categories as MDR, XDR and PDR. Out of 97 male patients, 60 male patients were infected with XDR, 19 male patients were infected with MDR, and 18 male patients were infected with PDR. Moreover, 40 female patients were infected with XDR, 20 female patients were infected with MDR, and 10 female patients were infected with PDR (Table 6). It isn't a significant difference between males and females among antibiotype categories of CR infection shown in Table 6. Also, there is a significant difference (P>0.05, using Chi-Square test) between antibiotype categories of CR infection and hospital wards, age, day of hospitalization (DOH), & CR infection source of patient.

Comorbidity of CR-GNB infected patients in KFMC at Taif

There were significant association between CR-GNB infection & comorbidities including cardiovascular disease (107/167, 64.1%, P-value=0,00), pulmonary disease (99/167, 59.3 %, P-value= 0.016), neurologic disease (66/167, 39.5%, P-value=0.007), renal disease (61/167, 36.5%, P-value=0.00), bed sores (33/167, 19.8%, P-value=0.00), hepatic disease (24/167, 14.4%. P-value=0.00) and malignancy disease (21/167, 12.6%, P-value=0.00). In our result, the diabetes mellitus in CR patients had a high prevalence (43.1%) but the P-value showed an unsignificant value (0.49). The most prevalent clinical characteristics observed at current study were urinary catheter insertion (121/167, 72.5%, P-value=0.00), invasive procedure (117/167, 70.1%, P-value=0.00), artificial ventilation (109/167, 65.3%, P-value=0.00), ICU administration (103/167, 61.7%, P-value=0.003), and dialysis (24/167, 14.4%, P-value=0.00). There were association between CR-GNB and the use of carbapenem in prior 3 months (44/167, 26.3%, P-value=0.00), cephalosporins (52/167, 31.1%, P-value=0.00), fluoroquinoles (48/167, 28.7%, P-value=0.00), Glycopeptides (30/167, 18%, P-value=0.00), & penicillins (28/167,16.8%, P-value=0.00). CR-GNB infection increased in COVID-19 patients (68/167, 40.7%, P-value=0.016). Also, referred from other hospitals considered as CR-GNB risk factors (24/167, 14.4%, P-value=0.00).

About CR antibiotype categories infection and comorbidity disease, there is a significant association between diabetic patients, pulmonary diseases, CVC insertion, ICU administration, artificial ventilation, & previous antibiotics usage and different CR antibiotype categories infection (P>0.05, using Chi-Square test or LSD Fisher, ANOVA test) but there is no significant association between all the others comorbidity disease and CR antibiotypes infection (P < 0.05, using Chi-Square test). Ninety-five diabetic patients and 72 nondiabetic patients were infected. In addition, 29 non-diabetic patients were infected with MDR isolates compared to ten diabetic patients. 52 non-diabetic patients were infected with XDR isolates compared to 48 diabetic patients. Statistically, P-value using Chi-square test was less than 0.05, which mean diabetes disorder impact the various CR antibiotypes infection.

Ten COVID-19 patients were infected with PDR isolates, 40 COVID-19 patients were infected with XDR and 18 COVID-19 patients were infected with MDR as shown on (Table 7). But there is no significant association between COVID-19 and CR antibiotype categories infections using Chi-square test. Sixty-eight patients died during their stay at the hospital (40.7% mortality rate), 48 died patients were infected with XDR isolates, 12 died patients were infected with PDR isolates and 8 died patients were infected with MDR isolates, there is a significant association between antibiotype categories infection and the mortality rates using (P> 0.05, Chi-square test).

DISCUSSION

Carbapenemase-producing Enterobacterales have been increasingly reported in Saudi Arabia and this problem is aggravated by inadequate infection control in developing countries due to poor hygiene, resource and structural constraints, deficient surveillance data, and lack of awareness regarding nosocomial infections [16,17]. Detecting infection and colonization with metallo-β-lactamases producing bacteria. However, the rates of CR-GNB detection in our study at KFMC in Taif were higher than those previously reported in Saudi Arabia except the study from Al-Jouf rejoin which report the percentage of CR among Enterobacteriales ales was 32% in 2019 [18]. In this study, 32% of the clinical samples were determined

Table 5: Antimicrobial Susceptibility Patterns of CR-GNB collected from KFMC.

Antibiotype Patterns	Antimicrobial susceptibility																			No.	Biotype			
	Ampicillin	Amoxicillin/ Clavulanic acid	Piperacillin/ Tazobactam	Cefalotin	Cefoxitin	Ceftazidime	Ceftriaxone	Cefepime	Ceftolozane/ Tazobactam	Imipenem	Meropenem	Amikacin	Gentamicin	Ciprofloxacin	Tigecycline	Nitrofurantoin	Trimethoprim/ Sulfamethoxazole	Azetronam	Colistin		*Klebsiella spp.*	*Pseudomonas spp.*	*Acinetobacter baumannii*	Others
P1	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	51	30	6	13	2
P2	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	S	50	28	10	12	0
P3	R	R	R	R	R	R	R	R	R	R	R	R	R	R	S	R	R	R	R	30	30	0	0	0
P4	R	R	R	R	R	R	R	R	R	R	R	R	R	R	S	R	R	R	S	26	25	0	0	1
P5	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	S	R	R	10	10	0	0	0
P6	R	R	R	R	R	R	R	R	R	R	R	S	S	R	R	R	S	R	S	9	8	0	1	0
P7	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	S	R	S	7	0	0	7	0
P8	R	R	R	R	R	R	R	R	R	R	R	S	R	R	S	R	R	R	R	6	6	0	0	0
P9	R	R	R	R	R	R	R	R	R	R	R	S	S	R	S	R	R	R	R	6	4	2	0	0
P10	R	R	S	S	S	S	S	S	S	R	S	S	S	S	R	R	S	R	S	4	0	4	0	0
P11	R	R	R	R	R	R	R	S	S	R	R	R	R	R	R	R	R	R	S	3	0	0	3	0
P12	R	S	S	R	R	S	R	S	S	R	R	S	S	S	R	R	R	R	S	3	0	3	0	0
P13	R	R	R	R	R	R	R	R	R	R	S	S	S	R	S	R	R	S	S	3	0	0	0	3
P14	R	R	S	S	S	S	S	S	S	R	S	S	R	S	R	R	R	S	S	2	0	0	0	2
P15	R	R	R	R	R	R	R	R	R	R	R	S	R	R	S	R	R	R	S	2	0	0	0	2
P16	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	S	R	S	2	2	0	0	0
P17	S	S	S	S	S	S	S	S	S	R	S	S	S	S	S	R	S	S	S	2	0	0	0	2
P18	R	R	R	R	R	R	R	S	S	R	S	S	S	R	S	S	S	S	S	2	2	0	0	0
P19	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	S	R	S	2	2	0	0	0
P20	R	R	R	R	R	R	R	R	R	R	S	R	R	R	R	R	R	S	S	2	2	0	0	0
P21	R	R	R	R	R	R	R	R	R	R	S	R	R	S	S	R	R	R	S	2	0	2	0	0
P22	S	S	S	R	R	S	R	S	S	S	S	S	S	R	R	R	R	R	S	2	0	2	0	0
P23	R	S	S	S	S	S	S	S	S	R	R	S	R	R	R	R	R	R	S	2	2	0	0	0
P24	R	R	R	R	R	R	R	S	S	R	S	S	R	R	R	R	R	R	S	2	2	0	0	0
P25	R	R	R	R	R	R	R	R	R	R	S	S	R	R	R	R	S	R	S	2	2	0	0	0
P26	R	R	R	R	R	R	R	R	R	R	R	S	R	R	R	R	R	R	S	1	0	0	1	0
P27	R	R	R	R	R	R	R	S	S	R	R	R	R	R	R	R	R	R	S	1	0	1	0	0
P28	R	R	R	R	R	R	R	R	R	R	R	S	S	R	R	R	R	R	S	1	0	0	1	0
P29	R	R	R	R	R	R	R	R	R	R	R	R	R	R	S	R	R	S	S	1	0	0	0	1
P-Value= 0.000																				236	155	30	38	13

Table 6: Demographic data of 167 CR-GNB patients from KFMC by Chi- square & ANOVA test.

Prognostic factors		CR-Pt (n=167)		P-value	MDR (n=39)	XDR (n=100)	PDR (n=28)	P-value
		(No.)	(%)		(No.)	(No.)	(No.)	
Age	0 to ≤ 15	4	2.4	0.000*	2	0	2	0.002*
	>15 to ≤ 30	22	13.2		8	6	8	
	>30 to ≤ 45	17	10.2		5	12	0	
	>45 to ≤ 65	42	25.1		10	24	8	
	> 65	82	49.1		14	58	10	
Gender	Male	97	58.1	0.037	19	60	18	0.242
	Female	70	41.9		20	40	10	
Biotype	*Klebsiella spp.*	99	59.3	0.000*	21	58	20	0.000*
	Pseudomonas spp.	23	13.8		8	13	2	
	A. baumannii	32	19.2		0	26	6	
	Others	13	7.8		10	3	0	
Day of hospitalization (DOH)	<4	31	18.6	0.000*	12	17	2	0.016*
	4 <DOH> 12	33	19.8		8	21	4	
	12 <DOH> 19	10	6		0	10	0	
	>19	93	55.7		19	52	22	
Hospital Service	ICU-CCU	46	27.5	0.000*	2	30	14	0.000*
	Burn Unit	0	0		2*	0	0	
	HDU-BED	28	16.8		4	18	6	
	MMW	18	10.8		6	12	0	
	FMW	14	8.4		4	10	0	
	MSW	30	18		10	14	6	
	FSW	12	7.2		4	4	4	
	ISO	6	3.6		0	6	0	
	Maternity & Delivery	1	0.6		1	0	0	
	ER	6	3.6		2*	6	0	
	LTCU	12	7.2		4	8	0	
	NICU	2	1.2		0	2	0	
	OPD	2	1.2		2	0	0	
	INPS	2	1.2		2	0	0	
	ANT5A -B	6	3.6		2	2	2	
Source	Sputum	63	37.7	0.000*	5	43	15	0.000*
	Blood	71	42.5		11	49	11	
	Urine	65	38.9		20	35	10	
	Wound	22	13.2		4	10	8	
	Others	15	9		4	3	8	
Nationality	Saudi	155	92.8	0.000*	33	94	28	0.043*
	Non- Saudi	12	7.2		6	6	0	

*Significant association

Table 7: Comorbidity data of 167 CR-GNB patients from KFMC by Chi-square & ANOVA test.

Prognostic factors		CR-Pt (n=167)		P-value	MDR (n=39)	XDR (n=100)	PDR (n=28)	P-value
		(No.)	(%)		(No.)	(No.)	(No.)	
Diabetic patient	Yes	72	43.1	0.075	10	48	14	0.041*
	No				29	52	14	
Bed Sores	Yes	33	19.8	0.000*	6	21	6	0.735
	No				33	79	22	
Comorbidity	Pulmonary Disease	99	59.3	0.016*	18	67	14	0.044*
	Cardiovascular Disease	107	64.1	0.000*	19	70	18	0.063
	Renal Disease	61	36.5	0.000*	13	38	10	0.872
	Hepatic Disease	24	14.4	0.000*	10	12	2	0.059
	Neurologic Disease	66	39.5	0.007*	18	42	6	0.09
	Malignancy Disease	21	12.6	0.000*	3	16	2	0.264
Clinical characteristics	CVC	88	52.7	0.49	15	53	20	0.029*
	Urinary Catheter	121	72.5	0.000*	29	74	18	0.569
	ICU	103	61.7	0.003*	13	68	22	0.000*
	Surgery	87	52.1	0.59	22	53	12	0.527
	Artificial Ventilation	109	65.3	0.000*	17	72	20	0.005*
	Invasive Procedure	117	70.1	0.000*	30	70	17	0.36

	Dialysis	24	14.4	0.000*	4	16	4	0.686
COVID-19	Yes	68	40.7	0.016*	18	40	10	0.673
	No	97	58.1		21	58	18	
Previous antibiotic usage	Carbapenem	44	26.3	0.000*	4	28	12	0.016*
	Fluroquinolones	48	28.7	0.000*	6	36	6	
	Glycopeptides	30	18	0.000*	6	18	6	
	Aminoglycosides	8	4.8	0.000*	4	4	0	
	Beta-lactam	28	16.8	0.000*	6	16	6	
	Macrolides	4	2.4	0.000*	0	2	2	
	Cephalosporins	52	31.1	0.000*	14	30	8	
	Oxazolidinones	4	2.4	0.000*	0	4	0	
	Polymyxin	4	2.4	0.000*	0	2	2	
	Clindamycin	4	2.4	0.000*	0	2	2	
	Nitroimidazole	6	3.6	0.000*	4	2	0	
Referred from other Hospital	Yes	24	14.4	0.000*	4	14	6	0.48
	No	139	83.2		33	84	22	
Outcome	Expired	68	40.7	0.016*	8	48	12	0.012*
	Survived	99	59.3		31	52	16	

*Significant association

as carbapenem-resistant, while the carbapenem resistance percentages were 26.1% of rectal swabs in Gulf Cooperation Council [19], 23.2% of clinical isolates in Riyadh and Al-Qassim [20], 21.7% of clinical isolates in Makkah [21]. The CR percentage in our study among all clinical specimens was 1.8% which was lower than the percentage reported from Al-Qatif city which was 2.8% of all the patients [22]. In this study, several methods to detect and confirm the carbapenem resistance infection were used including Phoenics automated system, & Kirby Bauer. However, the culture methods capture all mechanisms of carbapenem resistance, including efflux and porin-mediated resistance, but molecular method detect carbapenemase genes which are known as transmissible mechanisms of resistance.

The most incidence of carbapenem resistance in the current study was recorded in Klebsiella spp. (65.7%) that was similar to that reported in previous studies [18,23-26]. Bshabshe, et al. [27] reported 65.2% and 61.7% resistance in K. pneumoniae towards ertapenem and meropenem, respectively, which is consistent with our results. In another study, 38.4% and 46.1% resistance rates to imipenem and meropenem, respectively, were noted in K. pneumoniae [28]. The second CR organisms' dissemination referred *to A. baumannii* and *Pseudomonas*. In contrast, Al Mutair, et al. [29] study reported the most CR prevalence was *A. baumanii* and *P. aeruginosa*, then in *K. pneumonia* and *E. coli* and there was a lot of Saudi studies focused on CR *A. baumanii* and *P. aeruginosa* [22,30,31], which have emerged as a serious nosocomial infection in wet warm environments [32]. This study is the first study describes carbapenem resistance in all gram-negative bacteria at Taif, there was one study from Taif city reported phenotypic and genotypic traits of 45 clinical carbapenem-resistant *A. baumannii* isolates which were categorized into ten genotypes [33]. The most CR-GNB isolates of KFMC at Taif came from blood and sputum. CR infections have become major pathogens, especially in ICUs, implicated in healthcare-associated sepsis, causing prolonged hospitalization, high mortality, and increased costs [34,35]. Recent data have shown an increase in the rate of carbapenem-resistant K. pneumoniae isolated in 2017 and 2018 from different infection sites including urine and blood isolates [36] while, the most common types of CR infections in a recent study of Lebanon were respiratory tract infections followed by wound and soft tissue infections, bloodstream and urinary tract infections [24,26] referred higher percentage of CR in blood cultures to the carbapenemase-producing ability of these organisms which was a virulence factor of CR infection.

In this study, sixty-six percent were resistant to tigecycline and 45% were resistant to colistin. Similarly, tigecycline exhibited 45% sensitivity against CR K. pneumoniae. In contrast, the sensitivity of colistin against CR K. pneumoniae was 82.1% [18]. In Riyadh, an increase in tigecycline sensitivity from 33% to 50% for CR K. pneumoniae was reported, whereas a decline in colistin sensitivity from 80% to 76% against CR K. pneumoniae was observed [37]. The results this study reported that the increase in age of the patient, male gender and the duration of hospitalization increased the presence of CR infection which was in consistent with prior reports [19,38]. Also, 66 years was the median age of the patients who acquired CRE infection, and 45.2% of the patients were men while the median age appeared lower in CR bacteremia patients which was similar to the results of Moghnieh et al. [24,39]. The mean duration of hospitalization of CR patients was 18 days which is consistent with reports singling long-term care facilities out as a major risk factor for CPE acquisition [33, 46]. The most prevalent comorbidities recorded were cardiovascular disease which was similar to the results of [24,26]. In our result, the diabetes mellitus in CR patients had a high prevalence 43.1% but the P-value showed an unsignificant value (0.49) which contrasts with prior studies that considered diabetic patients at risk of CR infections [39,24,26]. Other comorbid conditions were significantly associated with CR-GNB like peptic ulcer disease, and gastroesophageal reflux disease but didn't

include as CR criteria in our study [26].

Our analysis is consistent with prior studies, confirming associations between CR-GNB and receipt of mechanical ventilation, invasive or indwelling devices, length of hospital stay or recent hospitalization, and recent exposure to various antibiotics [40]. The most prevalent clinical characteristics observed at current study were urinary catheter insertion (72.5%,), invasive procedure (70.1%), artificial ventilation (65.3%,), ICU administration (61.7%,), and dialysis (14.4%). Similar results were obtained by Imai et al. [40,41]. The infection of carbapenem-resistance organisms is significantly higher in ICU patients, so they are at greater risk for CR-GNB infection and transmission and there were lots of studies described CR infection in ICU patients [42-45]. Extensive use of antimicrobial drugs led to a wide prevalence of CR-GNB infections in hospitals in Saudi Arabia [42] which is similar to our results, the patients who received carbapenem in the previous 3 months had a significant association with CR-GNB and appeared to be at greater risk for infected by CR-GNB (44/167, 26.3%, P-value=0.00), and there was association between CR-GNB and the use of cephalosporins (52/167, 31.1%, P-value=0.00), fluoroquinolones (48/167, 28.7%, P-value=0.00), Glycopeptides (30/167, 18%, P-value=0.00), and penicillin (28/167,16.8%, P-value=0.00) [24,39-41,46]. This is consistent with a prior report showing that 67% of the patients were on antibiotics 4 days before blood culture & the three most prevalent empiric antibiotics were piperacillin/tazobactam (27%), meropenem (22%), and vancomycin (6.5%) [39]. In contrast, receipt of colistin at the time of admission was more likely to have carbapenemase-producing organisms as previously reported [41].

Within 3 months before CRE acquisition, (52.1%,) of the patients underwent a surgical procedure including endoscopy which is higher than the percentages reported by Moghnieh, et al. [24] 25% of the patients underwent a surgical procedure and 17.4% underwent endoscopy. The insignificant P-value may refer to be the surgical procedure essential cause of all bacterial infection including CR-GNB. The increased risk for CR-GNB may arise owing to the inaccessibility to clean certain mechanical aspects of scope devices even when manufacturer standards are followed. Cleaning and disinfecting scope devices are a hot issue where they pose a risk owing to the challenging nature of cleaning certain areas within them. A significant association between the diagnosis of COVID-19 patients and CR-GNB infection was observed which consists of many studies published last year confirm that CR-GNB outbreaks dissemination during Corona Virus pandemic [47-49]. Another study found the same association with CR-*A. bumanni*, a total of 913 COVID-19 patients were admitted to the ICUs; 19% became positive for CR-Ab, either colonization or infection, and the ICU mortality rate in CR-Ab patients was 64.7% [48]. Super infections by CRE as secondary infections developed in COVID-19 patients were associated with a high risk of 30-day mortality in patients with COVID-19 [47]. Outcomes of CR-GNB appeared as a highly significant association between CR infection and death rate which is consistent with mortality rates reported in several studies [50], other study report higher mortality rate reached to 80% in patients requiring ICU care [39].

CONCLUSIONS

CR-GNB infections have high morbidity and mortality rates in KFMC at Taif. The age of the patient, male gender, the duration of hospitalization, pulmonary disease, neurologic disease, renal disease, bed sores, hepatic disease, malignancy disease, urinary catheter insertion, invasive procedure, artificial ventilation, ICU administration, dialysis, cephalosporins usage prior 3 months, fluoroquinoles, glycopeptides and penicillins were found to be independent risk factors for CR-GNB infections. CR-GNB infection increased in COVID-19 patients. Therefore, antimicrobial stewardship, avoidance of invasive procedures, use of strict infection control measures, and increasing hand hygiene compliance are essential strategies for the prevention of CR-GNB infections. The mortality rate among CR patients was high reach to 41%. Further research to re-evaluate the CR-GNB carriage & mortality percentage in populations is required.

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