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Original article

Prevalence of carbapenem non-susceptible multidrug resistant *Acinetobacter baumannii* in Madinah, Saudi Arabia

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ABSTRACT

Background: Saudi Arabia hosts millions of tourists yearly in Hajj pilgrimage, particularly in Makkah and Madinah, which serves as a global center for the exchange of microorganisms. An international hub for the interchange of germs is provided by the population and the yearly Hajj pilgrimage, which brings millions of tourists, particularly to Makkah and Madinah. Understanding the prevalence and therapeutic significance of multidrug-resistant organisms in this nation is rather of common interest. *Acinetobacter baumannii*, particularly carbapenem non-susceptible multidrug-resistant (CRAB) strains, represents a global health threat. **Methods:** Our study investigated the prevalence of CRAB strains in Madinah, Saudi Arabia. 305 confirmed *A. baumannii* isolates were collected from King Salman bin Abdulaziz Medical City. These pathogens were isolated from different specimen types which includes stool, urine, sputum, swabs, and others. The isolates were subjected to antimicrobial susceptibility testing using the Vitek-2 automated system for bacterial identification and antibiotic susceptibility testing, based on Clinical and Laboratory Standards Institute (CLSI) guidelines. Our study focused on 25 antibiotics representing 11 classes that include penicillins, cephalosporins, carbapenems, and others. **Results:** Out of the 305 confirmed *A. baumannii* isolates, 288 (94.4 %) exhibited resistance to multiple antibiotics, with 127 (41.6 %) classified as extensively drug-resistant (XDR) and 269 (88.2 %) as multidrug-resistant (MDR). Some of these isolates are CRAB strains. **Conclusion:** Our study showed that the importance of understanding local resistance patterns of CRAB and MDR *A. baumannii* in Madinah.

Introduction

Worldwide, multidrug-resistant (MDR) bacteria represent a critical issue that not only pose significant medical burdens to healthcare facilities, but also represent a threat to human beings. MDR bacteria are usually responsible for most bacterial healthcare-associated infections (HAIs). In 2014, MDR pathogens were recognized as a special threat to human beings by the World Health Organization (WHO) [1]. Also, in 2016, the United Nations declared them "the greatest and most urgent global

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risk" [2]. These bacteria can spread through contact with contaminated surfaces, equipment, or personnel, and they can resist multiple classes of antibiotics. As a consequence, patients may stay longer at healthcare facilities that leads to increased healthcare costs and higher patient morbidity and mortality [3]. Most of these infections are caused by a group of bacteria known as the ESKAPE bacterial pathogens which includes methicillin-resistant *Staphylococcus aureus* (MRSA), *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* [4].

A. baumannii is a Gram-negative, strictly aerobic and non-fermentative coccobacillary bacterium [5]. This bacterium is one of the most important MDR bacterial pathogens due to its ability to rapidly develop resistance to a wide range of antibiotics and cause various diseases such as pneumonia, bacteremia and wound infections [6]. *A. baumannii* infections can be treated with different classes of antibiotics, some of which are used to treat a wide range of Gram-negative and Gram-positive bacterial infections [7]. Choosing the right antibiotic class depends on the bacterial strain and its resistance profile. The most effective and reasonably safe treatment options for patients with MDR *A. baumannii* infections are still combinations of colistin and tigecycline with carbapenems or other antibiotics [8]. The mechanisms of action of antibiotics can vary from one class to another. For example, beta-lactams which include penicillins, cephalosporins, and carbapenems target bacterial cell wall synthesis, leading to cell lysis [9]. Carbapenems bind to penicillin-binding proteins (PBPs) which prevents the cross-linking of peptidoglycan [10]. Fluoroquinolones interfere with bacterial DNA replication and repair, while macrolides and tetracyclines inhibit protein synthesis. Also, aminoglycosides affect protein synthesis, but can be more potent against certain bacteria [11].

The ability of *A. baumannii* to acquire and disseminate genetic elements such as plasmids and transposons that carry resistance genes presents an additional challenge [12]. This horizontal gene transfer not only facilitates rapid dissemination of resistance traits among *Acinetobacter* spp, but also to other bacterial species, thereby broadening the impact of resistance mechanisms. As a result, bacterial pathogens have developed mechanisms of resistance against a wide range of antibiotics, such as fluoroquinolones, cephalosporins, oxazolidinones, lipopeptides, and even antibiotics considered the last line of defense, including glycopeptides and carbapenems [13]. To date, the most dangerous strains of these bacteria is CRAB, particularly MDR isolates [14]. The presence of CRAB strains represents a time-sensitive threat because it limits the effectiveness of one of the few remaining classes of antibiotics capable of treating severe infections. The WHO declared *A. baumannii* to have "priority status" in a report released in 2017 and stated that it is one of the pathogens that urgently need the development of new antibiotics [15].

Carbapenem resistance in *A. baumannii* stems from its array of intrinsic and acquired resistance mechanisms. These include the production of carbapenemases, such as NDM-type metallo-beta-lactamases and OXA-23, OXA-24, and OXA-58 class D carbapenemases [16]. These enzymes which have been identified in various outbreaks worldwide, degrade carbapenems. Another reason for resistance could be biofilm formation, along with efflux pump overexpression, alterations in penicillin-binding proteins, and changes in membrane permeability which can reduce antibiotic accumulation inside bacterial cells [17].

In this study, we investigate the prevalence of CRAB in Madinah, Saudi Arabia which is crucial for several reasons. This bacterial pathogen can cause severe healthcare-associated infections, including pneumonia and bloodstream infections, and its resistance to multiple drugs makes it challenging to treat. Understanding its prevalence helps healthcare providers and policymakers identify trends, risk factors, and transmission patterns, enabling them to implement effective infection control measures.

Materials and Methods

Study design and data sources

Reports from January 2023 to November 2023 showed that 305 confirmed *A. baumannii* isolates were collected from KSAMC in Madinah, Saudi Arabia. These reports, which were obtained from different departments at the hospital with various specimen types including stool, urine, fluid, aspirate, sputum, swabs, tissue, whole blood, peripheral blood, and other unspecified types, included information on sample types, gender, nationality, and antimicrobial susceptibility testing. To identify isolates and determine antimicrobial susceptibility patterns, specimens were cultured on Mueller-Hinton agar (MHA) agar (Oxoid, CM0337) for 24 hours at 37°C.

Determination of antimicrobial susceptibility

After preparing the bacterial suspensions of each *A. baumannii* isolate, they were directly inoculated onto cards 1A and 2A for bacterial identification and antibiotic susceptibility testing, respectively. The VITEK-2 Compact automated system (bioMérieux, USA) was utilized according to the manufacturer's instructions to detect the minimum inhibitory concentration MICs of 25 antibiotics. The interpretation of antibiotic susceptibility tests was based on the guidelines provided by CLSI 2023 (Clinical and Laboratory Standards Institute). A reference strain NCTC 13304 of *A. baumannii* served as a quality control to ensure data accuracy and compatibility. To determine antimicrobial susceptibility patterns, 25 different antibiotics representing 11 different classes were utilized. The antibiotics investigated include Tobramycin (TOB), Tetracycline (TCY), Minocycline (MNO), Ampicillin (AMP), Amoxicillin-clavulanic acid (AMC), Piperacillin (PIP), Piperacillin/tazobactam (TZP), Ticarcillin (TIC), Amikacin (AMK), Gentamicin (GEN), Streptomycin (SAM), Tigecycline (TGC), Ciprofloxacin (CIP), Levofloxacin (LVX), Trimethoprim/Sulfamethoxazole (TS), Aztreonam (ATM), Cefoxitin (FOX), Ceftriaxone (CRO), Ceftazidime (CAZ), Cefixime (CXM), Cefotaxime (CTX), Cefepime (FEP), Meropenem (MEM), Imipenem (IPM), and Nitrofurantoin (NIT).

Resistance definitions

The US Centers for Disease Control and Prevention (CDC) and the European Centre for Disease Prevention and Control (ECDC) define MDR as resistance to three or more classes of antibiotics. In contrast, XDR refers to resistance to all antibiotics except for one or two classes [18]. After comparing the number of resistant *A. baumannii* isolates, the prevalence of MDR and XDR among the isolates was determined.

Statistical analysis

The variables of the imported data were extracted from the hospital's system in the form of an Excel spreadsheet (Excel, Microsoft Corp), including the total number of confirmed *A. baumannii* patients, gender, specimen types, and antimicrobial susceptibility testing. Descriptive analysis was conducted to determine the frequency and distributions of all data variables.

Results

A total of 305 *A. baumannii* strains isolated from clinical samples were collected during routine microbiological diagnostic procedures performed in the diagnostic laboratory of KSAMC Hospital. The specimens were obtained from 110 females (36%) and 195 males (64%) **(Fig. 3)**. Among these samples, sputum was the most common isolate with 148 (48.5%) samples, followed by 57 (18.7%) isolates from swabs, 34 (11.1%) from whole blood, 31 (10.2%) from urine, 16 (5.2%) from other sources, 10 (3.3%) from unspecified tissue, 1 (0.3%) from peripheral blood, 1 (0.3%) from fluid, 1 (0.3%) from stool/fecal samples, and 6 (2%) from aspirate **(Fig. 1)**.

Assessment of Antimicrobial Susceptibility Profile

In this study, a total of 305 *A. baumannii* isolates were investigated to determine the antimicrobial resistance profiles. Minimum inhibitory concentrations (MICs) of all 25 antimicrobial agents were determined using the VITEK-2 system. Seventeen (5.6%) isolates were susceptible to all antimicrobial agents. In contrast, a total of 288 (94.4%) *A. baumannii* isolates exhibited resistance to 25 antimicrobial agents belonging to 11 classes, with resistance rates as follows: Tobramycin (TOB) 139 (45.6%), Tetracycline (TCY) 16 (5.2%), Minocycline (MNO) 17 (5.6%), Ampicillin (AMP) 28 (9.2%), Amoxicillin-clavulanic acid (AMC) 15 (5%), Piperacillin (PIP) 24 (7.9%), Piperacillin/tazobactam (TZP) 209 (68.5%), Ticarcillin (TIC) 32 (10.5%), Amikacin (AMK) 44 (14.4%), Gentamicin (GEN) 234 (76.7%), Streptomycin (SAM) 125 (41%), Tigecycline (TGC) 15 (4.9%), Ciprofloxacin (CIP) 261 (85.6%), Levofloxacin (LVX) 151 (49.5%), Trimethoprim/Sulfamethoxazole (TS) 124 (40.7%), Aztreonam (ATM) 14 (4.6%), Cefoxitin (FOX) 2 (0.7%), Ceftriaxone (CRO) 118 (38.7%), Ceftazidime (CAZ) 254 (83.3%), Cefixime (CXM) 2 (0.7%), Cefotaxime (CTX) 16 (5.6%), Cefepime (FEP) 249 (81.6%), Meropenem (MEM) 242 (79.3%), Imipenem (IPM) 246 (80.7%), and Nitrofurantoin (NIT) 1 (0.3%). In addition, some of the isolates exhibited intermediate resistance. Intermediate resistance was observed against: Tobramycin (TOB) 1 (0.3%), Tetracycline (TCY) 4 (1.3%), Minocycline (MNO) 16 (5.2%), Piperacillin (PIP) 1 (0.3%), Piperacillin/tazobactam (TZP) 1

(0.3%), Gentamicin (GEN) 4 (1.3%), Streptomycin (SAM) 3 (1%), Tigecycline (TGC) 138 (45.2%), Ciprofloxacin (CIP) 1 (0.3%), Ceftazidime (CAZ) 6 (2%), Cefotaxime (CTX) 4 (1.3%), Cefepime (FEP) 1 (0.3%), Meropenem (MEM) 1 (0.3%), Imipenem (IPM) 1 (0.3%). The susceptibility profile of *A. baumannii* isolates is summarized in **(Fig. 2)**.

Multiple Antimicrobial Resistance Patterns of *A. baumannii*

A. baumannii resistance isolates were classified as XDR and MDR. A total of 127 (41.6%) resistant isolates exhibited extensive drug resistance (XDR) **(Fig. 4)**. In terms of MDR, out of 288 resistant *A. baumannii* isolates, 269 (88.2%) displayed MDR: 4 (1.5%), 6 (2.2%), 33 (12.3%), 125 (46.5%), 81 (30.1%), and 20 (7.4%) isolates exhibited MDR to 3, 4, 5, 6, 7, and 8 antimicrobial classes, respectively. The estimated MDR incidence is shown in **(Fig. 5)**.

Figure 1. Distribution of *A. baumannii* isolates from different clinical samples. The bar graph provides a visual representation of the number of isolates of each sample source. The sources of the isolates are as follows: Sputum (148 isolates), Swab (57 isolates), Whole blood (34 isolates), Urine (31 isolates), Other sources (16 isolates), Tissue, unspecified (10 isolates), Blood – peripheral (1 isolate), Fluid (1 isolate), Stool (1 isolate), and Aspirate (6 isolates).

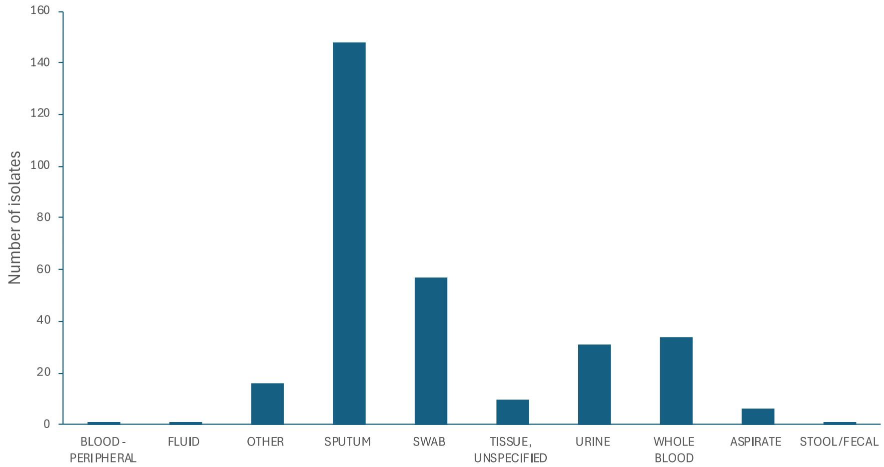


Figure 2. Number of resistant (R) and intermediate (I) *A. baumannii* isolates across antibiotics and their associated classes. The bar graph presents the number of *A. baumannii* isolates exhibiting resistance (R) and intermediate resistance (I) to 25 antimicrobial agents across 11 classes.

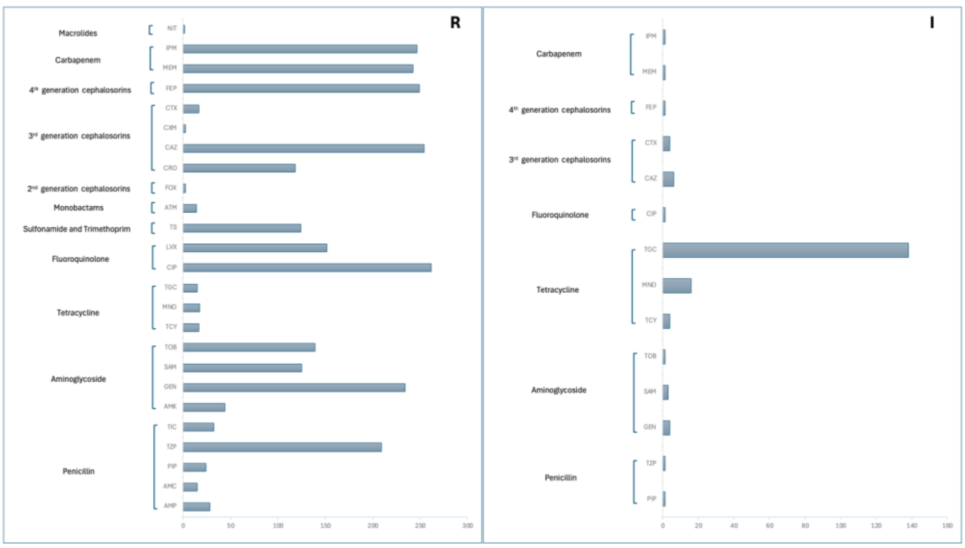
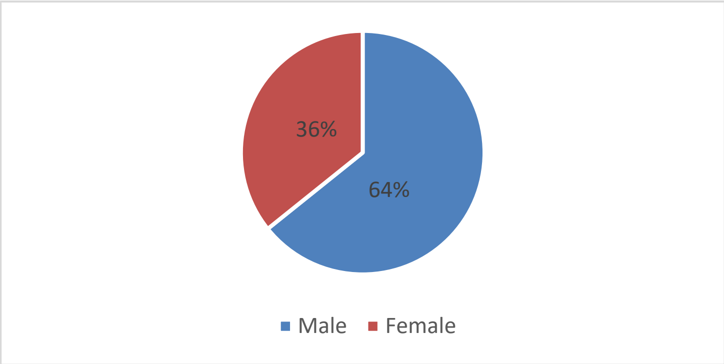


Figure 3. A) Distribution of *A. baumannii* isolates between female and male patients. The pie chart illustrates the distribution of 305 *A. baumannii* strains isolated from clinical samples. The specimens were obtained from 110 female patients (36%) and 195 male patients (64%). The chart visually represents the proportion of isolates from female and male patients, highlighting the higher incidence of isolates from male patients. **B)** Resistant profiles of *A. baumannii* to antibiotic classes stratified by patients' sex. The bar graph illustrates the resistant profiles of 305 *A. baumannii* isolates to various antibiotic classes stratified by patients' sex. The data represents the number of isolates from male and female patients that exhibit resistance to each antibiotic class. The bars representing male patients are colored in blue, while those representing female patients are colored in orange. The graph provides a comparative visual representation of the resistance levels of *A. baumannii* to different antibiotic classes between male and female patients.

A)



B)

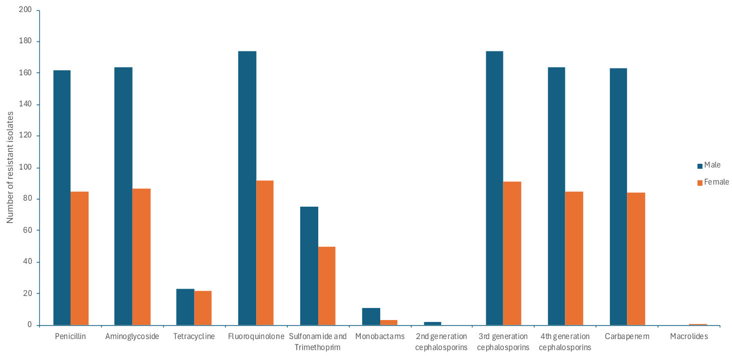


Figure 4. Number of XDR and MDR *A. baumannii* isolates based on specimen types. The bar graph displays the number of XDR and MDR *A. baumannii* isolates based on different specimen types. MDR isolates are represented by blue bars and XDR isolates are represented by red bars. The graph provides a comparative visual representation of the incidence of XDR and MDR among the isolates obtained from various specimen types collected from patients.

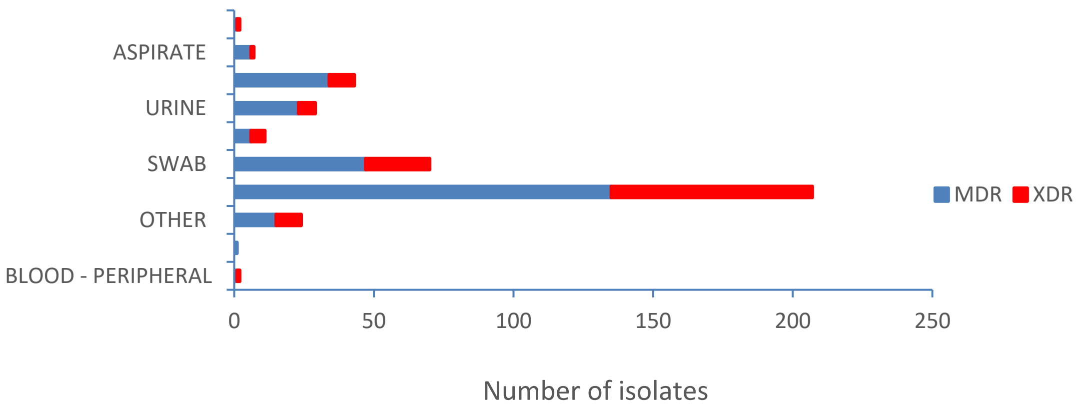
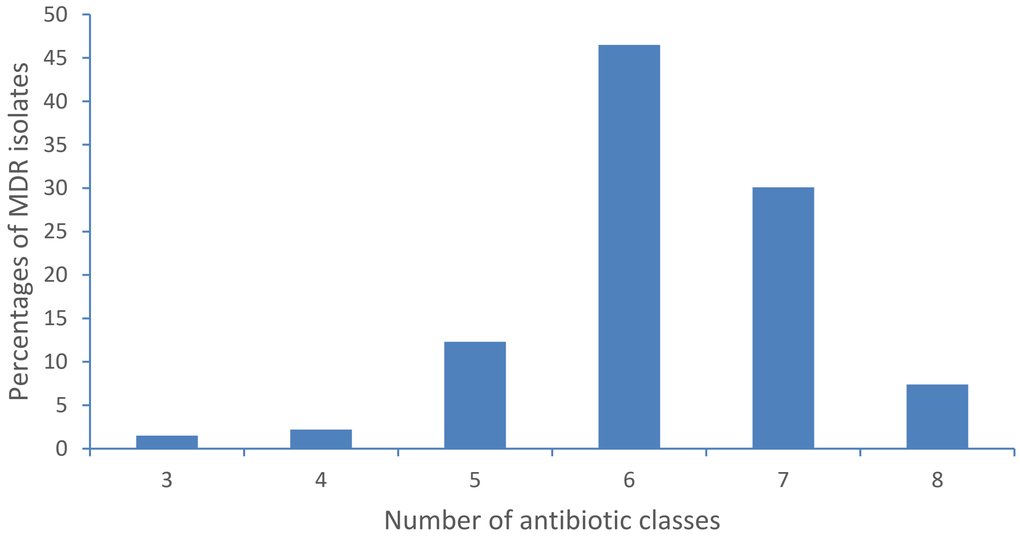


Figure 5. Prevalence of MDR patterns within resistant *A. baumannii* isolates. The bar graph illustrates the prevalence of MDR patterns within 269 resistant *A. baumannii* isolates. The bars represent the number of isolates exhibiting resistance to different numbers of antimicrobial classes: Class 3 (1.5%), Class 4 (2.2%), Class 5 (12.3%), Class 6 (46.5%), Class 7 (30.1%), Class 8 (7.4%).



Discussion

Prior to the emergence of the *A. baumannii* infection, carbapenems were a crucial component of the available therapeutic choices. CRAB first appeared in the early 1990s, spread to the Middle East in 2006, and started to pose a significant threat to the European Union in 2015. Ibrahim revealed the *A. baumannii* infection outbreak in Saudi Arabia, which is a topic of interest in this research. Ibrahim asserts that the high prevalence of MDR *A. baumannii* in Saudi hospitals suggests that extensive research in this field is necessary in addition to studies on the existing therapeutic effects resulting from the elevated risk of MDR *A. baumannii* in Saudi Arabia [19].

The present study was conducted in one of the main hospitals in Madinah, Saudi Arabia. To study the resistance pattern of *A. baumannii*, 25 different antibiotics from 11 classes were used. Our study analyzed 305 isolates of *A. baumannii* obtained from 305 patients (110 female, 195 male) across various clinical specimens. The distribution of isolates from different specimens' sources, underscores the pathogen's adaptability and its ability to colonize diverse anatomical sites. This broad distribution is consistent with *A. baumannii*'s known capacity to thrive in a range of environments, including respiratory and wound sites [20].

The detection of isolates from various sources, including aspirates, blood, and urine, further highlights the pathogen's versatility and its ability to colonize mechanical equipment, including respiratory support equipment, suction devices, and feeding tubes [21]. It can easily spread through the vicinity of infected patients. That's why the World Health Organization (WHO) issued updated guidance for cleaning and disinfecting respiratory equipment.

However, the predominance of isolates from sputum suggests that the respiratory tract is a significant reservoir for *A. baumannii* in our study population. Due to *A. baumannii*'s strong ability to adhere to epithelial cells in the respiratory tract and form biofilms, it can cause a variety of infections, mostly involving the respiratory tract, especially ventilator-associated pneumonia (VAP) [22]. This ability makes it resistant to antimicrobials, and it is considered one of the most common pathogens detected in sputum cultures and endotracheal aspirates among long-term hospitalized patients [23]. Samah *et al*. indicated that the greatest source of *Acinetobacter* isolates was sputum samples, which were followed by wound swabs in a Saudi hospital in Madinah [24]. In a tertiary care hospital in Riyadh, Saudi Arabia, it was reported that *A. baumannii* was the most prevalent and significant pathogen linked to ventilator-associated pneumonia, especially the late-onset and recurrent types [25]. According to Mah *et al*. endemic strains of *A. baumannii* were common among ICU patients receiving mechanical ventilation and discovered that the colonization site in these individuals was tracheal secretions [26]. Furthermore, a study in a community hospital in Madinah suggested that previous antibiotic medication and mechanical ventilation were the primary risk factors for CRAB infections [27].

The resistance rates to all antibiotic classes in men were higher than in women in this study. The reasons behind this sex bias are unclear. It is possible that the nosocomial *A. baumannii* infection was more frequent in men than in women in our study. Another reason could be that men have a higher prevalence of underlying health conditions that increase their risk of infection. Conditions like chronic obstructive pulmonary disease (COPD), diabetes, or immunosuppression could contribute to a higher incidence of *A. baumannii* infections [28]. Samah *et al*. concluded that compared to female patients, samples taken from male patients were a larger source of *A. baumannii*, maybe because men make up the majority of Saudi Arabia's workforce, they are more susceptible to illness.

Our results indicated a high level of resistance, with 94.4% of isolates exhibiting resistance to at least one antibiotic. Moreover, the prevalence of MDR and XDR strains among the isolates is alarming. Specifically, 88.2% isolates were classified as MDR, 41.6% isolates were classified as XDR. The high incidence of MDR and XDR strains emphasizes the critical need for effective antimicrobial stewardship and infection control measures to mitigate the spread of these resistant strains.

The resistance patterns observed in our study reflect the broader global trend of increasing antimicrobial resistance among *A. baumannii* isolates [29]. The use of 25 antibiotics from 11 different classes in our resistance pattern study revealed a concerning level of resistance across multiple antibiotic classes. This extensive resistance spectrum underscores the pathogen’s ability to acquire and disseminate resistance determinants, complicating treatment options [30]. Notably, the high resistance rates to carbapenems, a last-resort class of antibiotics, highlight the urgent need for alternative therapeutic strategies and novel antimicrobial agents [31]. The bacterium's ability to resist eleven major classes of antibiotics through various mechanisms, including enzymatic degradation, target modification, efflux pumps, and reduced permeability, underscores the need for novel therapeutic strategies and stringent infection control measures [32]. Combating *A. baumannii* requires a multifaceted approach, including the development of new antibiotics, the implementation of antibiotic stewardship programs, and the enhancement of diagnostic capabilities to rapidly identify and respond to resistant infections.

These results are in accordance with previous studies conducted in Saudi Arabia. The incidence of *Acinetobacter* in eight intensive care units in five Saudi Arabian cities (Jeddah, Makkah, Medinah, Riyadh, Tabuk) with varying geographic and climatic conditions was studied by Kharaba *et al*. [33]. The results revealed that incidence ranged from 1.0 to 7.9% across the eight ICUs. According to the Al-Sultan study, there are two different kinds of epidemic clones and genetic fingerprints of carbapenem-resistant *A. baumannii* in the Makkah and Madinah regions of Saudi Arabia [34]. Aloraifi *et al*. also reported that the prevalence of Gram-negative bacteria that are not sensitive to carbapenem is relatively high in Saudi Arabia's tertiary care hospitals [35]. In another study, MDR *A. baumannii* clinical isolates were identified from over 80% of the ICU patient specimens at Aseer Central Hospital, Saudi Arabia. Mass gatherings in Holy Makkah during the Hajj season may increase the risk of contracting and spreading MDR *A. baumannii*, according to Leangapichart *et al*. [36]. MDR *A. baumannii* strains were isolated from 16 pharyngeal swab samples and 26 post-Hajj rectal swab samples of pilgrims in Makkah.

Acinetobacter spp. that are resistant to carbapenem are also becoming more prevalent in many countries. The frequency of *A. baumannii* infection is 14.8% in Africa, 5.6% in Western Europe, 3.7% in North America, 13.8% in Central and South America, 17.1% in Eastern Europe, 4.4% in Oceania, and 19.2% in Asia, according to a global survey of ICUs [37]. This highlights the importance of international AMR surveillance efforts.

Conclusion

The high prevalence of carbapenem non-susceptible MDR *A. baumannii* in Madinah, Saudi Arabia, represents a significant public health challenge. The extensive resistance observed across multiple antibiotic classes underscores the need for robust infection control measures, effective antimicrobial stewardship programs, and ongoing surveillance to combat the spread of this pathogen. The national antimicrobial resistance surveillance program plays a substantial role in minimizing antimicrobial resistance (AMR) by evaluating AMR rates at the national level. Saudi Arabia's Vision 2030, emphasized by the Kingdom, is considered the cornerstone of healthcare quality improvement. Therefore, future research should focus on identifying the genetic mechanisms underlying resistance in *A. baumannii* and exploring novel therapeutic approaches to address this critical issue. This study has several limitations. First, all *A. baumannii* isolates were obtained from a single hospital in Madinah. Second, our study does not explore the mechanisms of antibiotic resistance. These factors may have influenced the findings of the study. Future studies involving multiple hospitals in Madinah are needed to evaluate the prevalence of *A. baumannii* resistance and to investigate the genetic mechanisms underlying resistance in this bacterium.

Ethical statement

Ethical approval was obtained from the scientific research ethical committee of King Salman Bin Abdulaziz Medical City (KSAMC). As this was a retrospective study and patients names and IDs were removed from data, patient written consents were not required.

Conflict of interest

The authors declare no conflict of interest.

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