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Original Article

Prevalence of Vancomycin-Resistant *Van A* and *Van B* Genes in ESKAPE Gram-Positive Bacteria Isolated from Hospitalized Patients in Mashhad, Iran

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ABSTRACT

Introduction: The ESKAPE group, comprising *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterococcus faecium*, is known for its role in hospital-acquired infections and its growing resistance to antimicrobial agents. This resistance complicates treatment options, particularly with last-resort antibiotics, such as vancomycin. This study aims to determine the prevalence of vancomycin-resistant genes *(Van A* and *Van B*) in *Staphylococcus aureus* and *Enterococcus* species isolated by polymerase chain reaction (PCR) method from hospitalized patients in Mashhad, Iran.

Materials and Methods: A total of 1000 clinical samples were collected over six months from hospitalized patients in four hospitals in Mashhad, Iran. The samples included blood, urine, wound swabs, and respiratory secretions. *Staphylococcus aureus* and *Enterococcus* isolates were identified through standard microbiological tests. Vancomycin susceptibility was assessed using the E-test method. The presence of vancomycin-resistant genes (*Van A* and *Van B*) was determined by PCR method.

Results: Out of a total of 98 bacterial isolates, 77 were identified as *Staphylococcus aureus* and 21 as *Enterococcus* species. Among the *Enterococcus* isolates, 15 were identified as *Enterococcus faecium* and 6 as *Enterococcus faecalis*. Vancomycin resistance genes were detected in 7 isolates in total, with 6 of these isolates harboring the *Van A* gene and 1 carrying the *Van B* gene.

Conclusion: The study reveals 40% and 1.3% prevalences of vancomycin resistance in *Enterococcus faecium* and *Staphylococcus aureus* isolates, respectively. These findings underscore the critical need for vigilant antibiotic stewardship and the implementation of appropriate treatment strategies to effectively manage infections caused by these resistant pathogens.

1. Introduction

The emergence of antibiotic resistance among hospital-acquired pathogens represents a significant global health challenge, particularly with the rise of the ESKAPE group of bacteria[1]. This group, comprising *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species, is notorious for its ability to "escape" the effects of antimicrobial agents, leading to persistent and difficult-to-treat infections in hospitalized patients[1]. These pathogens are responsible for a substantial proportion of healthcare-associated infections, and their resistance to a wide array of antibiotics has severely limited treatment options, thereby increasing morbidity and mortality rates in affected patients. Among the ESKAPE pathogens, *Staphylococcus aureus* and *Enterococcus faecium* are

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particularly concerning due to their developing resistance to vancomycin- a glycopeptide antibiotic that is often considered the last line of defense against severe infections caused by Gram-positive bacteria[2]. *Staphylococcus aureus* is implicated in a variety of clinical conditions, ranging from minor skin infections to life-threatening diseases, such as septicemia, endocarditis, and pneumonia[3]. Similarly, *Enterococcus* species, particularly *Enterococcus faecium* and *Enterococcus faecalis*, are commonly associated with urinary tract infections, bacteremia, and endocarditis, especially in immunocompromised individuals[4]. The increasing resistance of these pathogens to vancomycin poses a serious threat to public health, as it severely restricts the available therapeutic options for treating these infections. The mechanism underlying vancomycin resistance in these pathogens is primarily mediated by the acquisition of *Van A* and *Van B* genes. These genes, located on mobile genetic elements, such as transposons *Tn1546* and *Tn1547*, respectively, alter the bacterial cell wall structure by modifying the terminal dipeptide of the peptidoglycan precursor from D-Ala-D-Ala to D-Ala-D-Lac[5]. This modification reduces the binding affinity of vancomycin, thereby rendering the antibiotic ineffective[6]. The presence of these genes not only complicates treatment but also facilitates the horizontal transfer of resistance to other bacterial species, exacerbating the spread of resistance within hospital environments. The prevalence of vancomycin-resistant *Staphylococcus aureus* (VRSA) and vancomycin-resistant *Enterococcus* (VRE) has been documented in various regions globally, with alarming trends observed in both developed and developing countries.

Accordingly, cases of VRSA were reported among burn patients as early as 2012, and by 2022, vancomycin resistance was identified in 98.4% of *Staphylococcus aureus* isolates obtained from blood, urine, and other bodily fluids in pediatric patients[7-10]. The situation is similarly concerning for *Enterococcus* species, with studies indicating a higher prevalence of vancomycin resistance in *Enterococcus faecium*, compared to *Enterococcus faecalis*, particularly in clinical isolates from hospital settings[8]. In Iran, the rise in antibiotic resistance, including resistance to vancomycin, among hospital pathogens has become increasingly problematic. Previous studies conducted in various hospitals across the country have reported varying levels of resistance among *Enterococcus* isolates, with a notable presence of *Van A* and *Van B* genes in both environmental and clinical samples[9,10]. These findings highlight the urgent need for continuous monitoring and a comprehensive understanding of the local epidemiology of antibiotic resistance, which is essential for developing effective infection control strategies and optimizing treatment protocols. Given this context, the present study aims to investigate the prevalence of vancomycin resistance genes (*Van A* and *Van B*) in *Staphylococcus aureus* and *Enterococcus* species isolated from hospitalized patients in Mashhad, Iran. By identifying the presence and distribution of these resistance genes, this research seeks to provide valuable insights that could inform the development of more effective treatment protocols and enhance infection control measures within local healthcare settings.

2. Materials and Methods

This study utilized an evidence-based study technique to compare the role of miR-146a and mir-222 in Wistar albino rats with polycystic ovarian syndrome.

2.1. Ethical approval

The study was carried out after approval by the ethics committee of the Islamic Azad University of Mashhad (IR.MUMS.PHARMACY.REC.1400.042).

2.2. Sample Collection and Identification

This cross-sectional study was conducted over four months from November 2021 to February 2022 in Mashhad, Iran, focusing on the collection and analysis of *Staphylococcus aureus* and *Enterococcus* isolates from clinical samples obtained at three major hospitals, namely Imam Reza, Qaem, and Razavi. Clinical samples, including urine, blood, and wound swabs, were collected from patients suspected of having infections caused by these bacteria. The samples were purposefully selected based on clinical indications of infection rather than randomly, ensuring that the isolates were relevant to the study's objectives. A total of 98 isolates were obtained and carefully transferred to the microbiology laboratory at the Kavian Institute of Higher Education for further analysis. The isolates underwent a series of biochemical tests to definitively identify *Staphylococcus aureus* and *Enterococcus* species. For *Staphylococcus aureus*, catalase and coagulase tests were performed, while *Enterococcus* species were identified using mannitol salt agar, bile esculin agar, and arabinose fermentation tests[11]

2.3. Determination of Minimum Inhibitory Concentration by E-test Method

The Minimum Inhibitory Concentration (MIC) for vancomycin was determined using the E-test method[11]. Initially, a 0.5 McFarland standard was prepared following standard protocols, representing a bacterial concentration of approximately 1.5 × 10^8 CFU/mL. The bacterial suspension was prepared in Mueller-Hinton broth and uniformly spread onto Mueller-Hinton agar plates using the lawn culture method. This was done by dipping a sterile cotton swab into the bacterial suspension, removing excess liquid by pressing the swab against the tube's inner wall, and then swabbing the surface of the agar plate. After allowing the plates to dry for 15 min, E-test strips impregnated with vancomycin were applied to the agar surface using sterile tweezers. Care was taken to ensure

Table 1. Primer sequences and annealing temperatures for *Van A* and *Van B* genes in *Staphylococcus aureus* and *Enterococcus* species

Gene	Primer Sequence (5´-3´)	Annealing temperature(°C)	Size (bp)	References
Van A	F- AATACTGTTTGGGGGTTGCTC R- CTTTTTCCGGCTCGACTTCCT	57	734	12
Van B	F- GCG GGG AGG ATG GTG CGA R- GGA AGATACCGTGGCTCAAAC	75	420	12

that each strip was placed 15 mm away from the plate edge and at appropriate distances from each other. The plates were then incubated at 37°C for 18 to 24 h. Post-incubation, the inhibition zones around each strip were measured and interpreted according to the Clinical and Laboratory Standards Institute guidelines. For quality control, *Staphylococcus aureus* ATCC 25923 was used as the reference strain[12].

2.4. DNA Extraction and Evaluation of Isolates

DNA was extracted from vancomycin-resistant isolates using a commercial kit (Roche, Germany). The purity and concentration of the extracted DNA were assessed by measuring the optical density at 260 and 280 nm using a UV bio spectrophotometer (Eppendorf, Germany).

2.5. Preparation of Primers

The detection of *Van A* and *Van B* genes in the bacterial isolates was performed using Polymerase Chain Reaction (PCR) method. The primers and their sequences, along with the corresponding annealing temperatures, are detailed in Table 1. PCR reactions were conducted in a final volume of 25 µL, with the concentrations and volumes of reagents listed in Table 2. Each reaction included the appropriate positive and negative controls; therefore, *Enterococcus faecalis* ATCC 51299 and *Enterococcus faecium* ATCC V583 were used as positive controls, while distilled water served as the negative control. The PCR was performed on a thermal cycler (Eppendorf, Germany) using the temperature profile outlined in Table 3.

Table 2. PCR reaction components

Material name	Stock concentration	Total concentration	Volume
PCR buffer	10×	1×	2.5
MgCl2	50 mM	2 mM	0.8 µl
Taq Polymerase	5 U/µl	1 U/µl	0.2 µl
DNTPs	10 mM	0/2 mM	0.4 µl
Forward Primer	10 µM	0/4 µM	1 µl
Reverse Primer	10 µM	0/4 µM	1 µl
DNA Template	200 ng/µl	50 ng/µl	5 µl
Distilled Water			14.1 µl
Total			25 µl

* dNTPs (deoxynucleotide triphosphates)

2.6. Electrophoresis of Products

Following PCR amplification, 5 µL of each PCR product was subjected to electrophoresis on a 1.5% agarose gel. Electrophoresis was performed at 90 volts for 50 min using an electrophoresis apparatus (Paya Research Company, Iran). The gel was then visualized using a Geldocument imaging system (Protein Simple, USA) to confirm the presence or absence of bands corresponding to the *Van A* and *Van B* genes. The results were recorded based on the expected fragment sizes as determined by the gel electrophoresis.

Table 3. PCR cycling conditions

Phase	Temperature (°C)	Time (seconds)	Number of cycles
Initial Denaturation	94	300	**1**
Denaturation	94	30	
Annealing	57	30	**30**
Extension	72	40	
Final Extension	72	420	**1**

3. Results

A total of 98 bacterial isolates were collected and confirmed through biochemical and microbiological testing. Among these, 21 (21.4%) isolates were identified as *Enterococcus* species, with 15 (71.4%) isolates classified as *Enterococcus faecium* and 6 (28.6%) isolates as *Enterococcus faecalis*. The remaining 77 (78.6%) isolates were identified as *Staphylococcus aureus*. The gender distribution of the isolates indicated that 52 (53.1%) were obtained from male patients, while 46 (46.9%) were from female patients.

3.1. Distribution of Staphylococcus aureus

Staphylococcus aureus isolates (n=77) were further analyzed according to the type of clinical sample from which they were obtained to understand the distribution of infections across different body sites. The highest number of isolates was derived from blood samples (n=14, 18.1%), followed by wound swabs (n=13, 16.9%) and catheter samples (n=11, 14.3%). The distribution of *Staphylococcus aureus* isolates across various clinical samples is illustrated in Figure 1.

3.2. Distribution of Enterococcus faecium and Enterococcus faecalis Isolates

Out of 21 *Enterococcus* isolates, the majority were obtained from urine samples, with 12 (57.1%) isolates identified. The relative frequency distribution of *Enterococcus faecium* and *Enterococcus faecalis* isolates across various clinical samples is depicted in Figure 2.

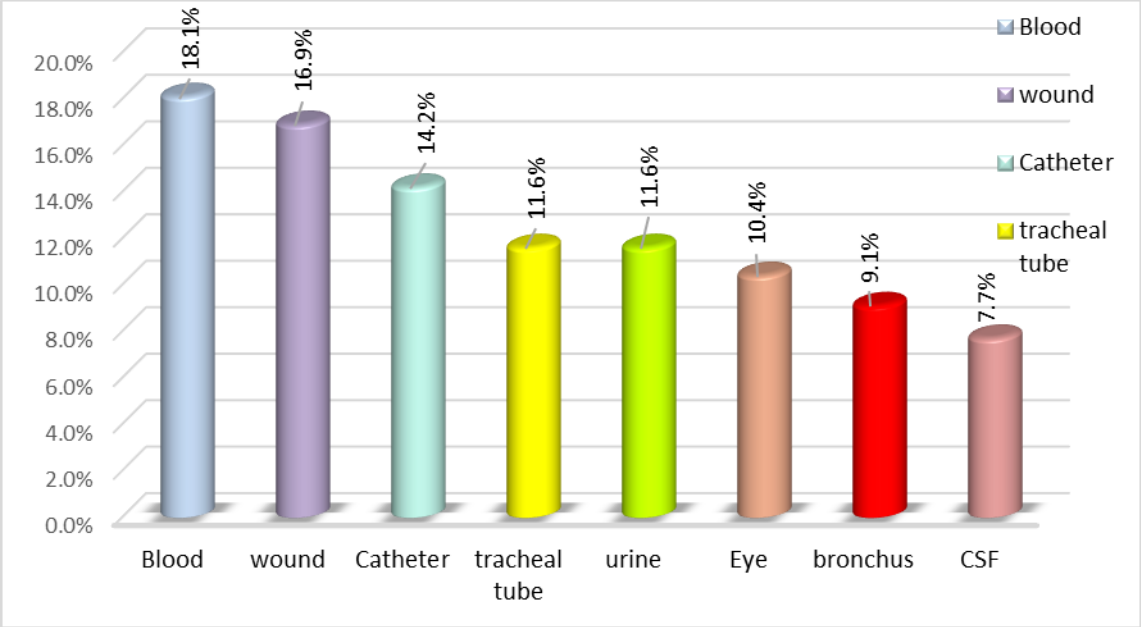

Figure 1. Relative frequency distribution of *Staphylococcus aureus* isolates in different clinical samples

3.3. Distribution of Staphylococcus aureus Isolates by Hospital Department

The distribution of *Staphylococcus aureus* isolates was also examined across different hospital departments. The General Department accounted for the highest number of isolates, with 26 (33.8%) of the total. This was followed by the Intensive Care Unit (n=17, 22.1%), the Emergency Department (n=13, 16.8%), the Surgical Department (n=10, 12.9%), and the Neonatal Intensive Care Unit (n=6, 7.8%). The Department of Pediatrics had the lowest number of isolates (n=5, 6.5%).

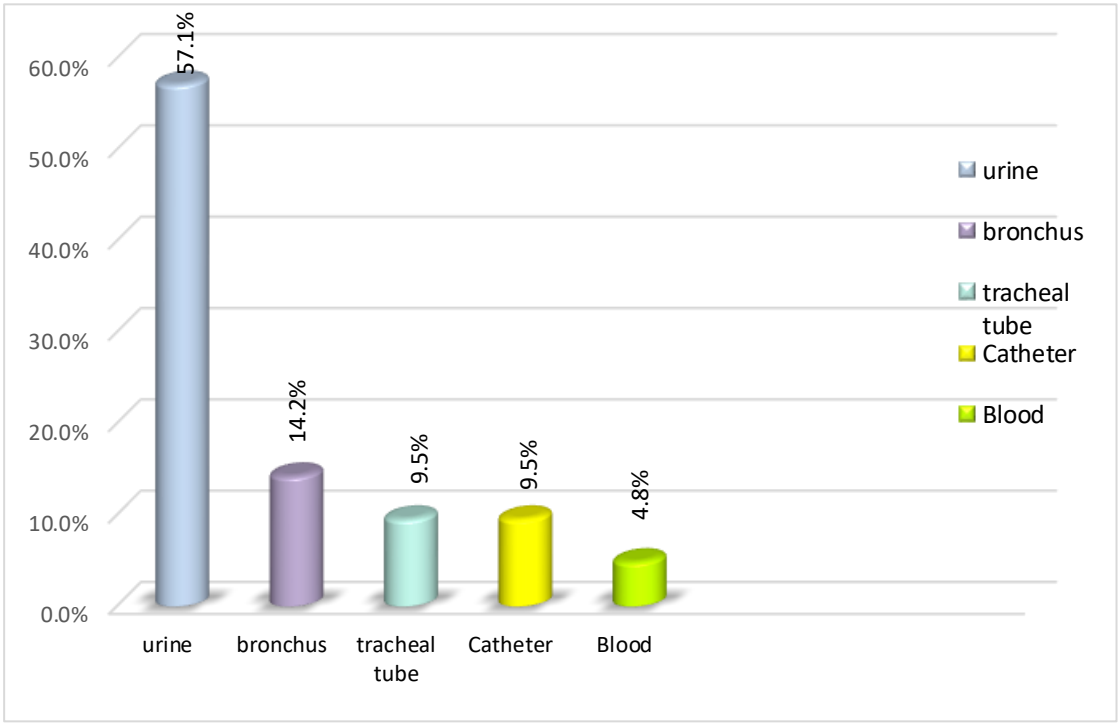

Figure 2. Relative frequency distribution of *Enterococcus* isolates in different clinical samples
X-Axis: Types of clinical samples, including urine, bronchus, tracheal tube, catheter, and blood.
Y-Axis: Relative frequency (%) of *Enterococcus* isolates found in each type of clinical sample.
Urine: Percentage of *Enterococcus* isolates from urine samples.
Bronchus (B): Percentage of *Enterococcus* isolates from bronchial samples.
Tracheal Tube (T): Percentage of *Enterococcus* isolates from tracheal tube samples.
Catheter (C): Percentage of *Enterococcus* isolates from catheter samples.
Blood (Bl): Percentage of *Enterococcus* isolates from blood samples.

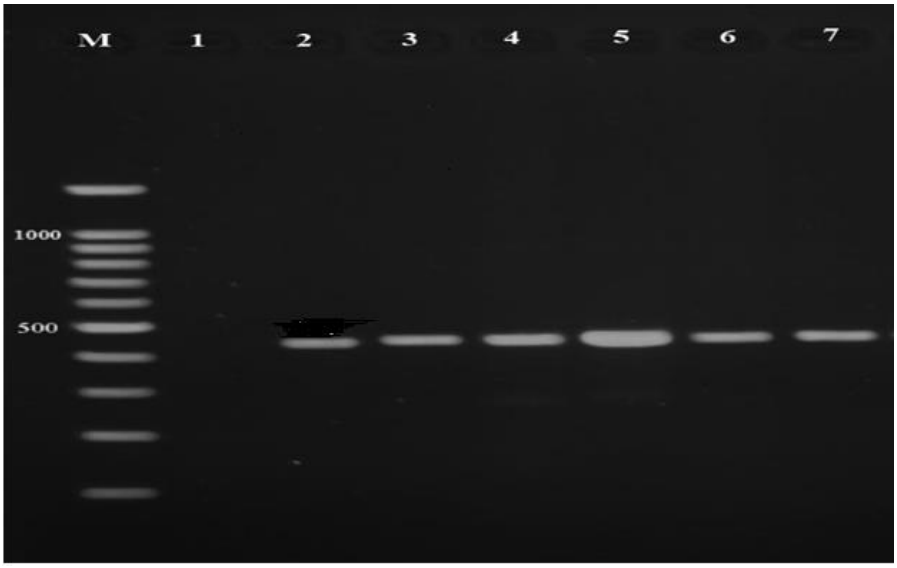

Figure 3. Electrophoresis of dictation *Van A* and *Van B* gene product: 100bp size DNA marker, well M: marker, well 2: negative control, separate wells 3, 4, 5, 6, and 7

3.4. Distribution of Enterococcus faecium and Enterococcus faecalis Isolates by Hospital Departments

For the *Enterococcus* isolates, the highest number was obtained from the Emergency Department, which accounted for 10 (47.6%) of the total isolates. The Intensive Care Unit and Neonatal Intensive Care Unit contributed 5 (23.8%) and 4 (19.1%) isolates, respectively. It is worth mentioning that the Surgical Department had the fewest *Enterococcus* isolates (n=2, 9.5%).

3.5. PCR Results for Van A and Van B Genes

The evaluation of vancomycin resistance genes using PCR revealed that out of 11 vancomycin-resistant isolates, 7 (63.6%) isolates were positive for either the *Van A* or *Van B* genes. Specifically, 5 (71.4%) isolates were positive for *Van A* gene, and 2 (28.6%) isolates were positive for *Van B* gene. The PCR results illustrating the presence of *Van A* and *van B* genes are shown in Figures 3 and 4.

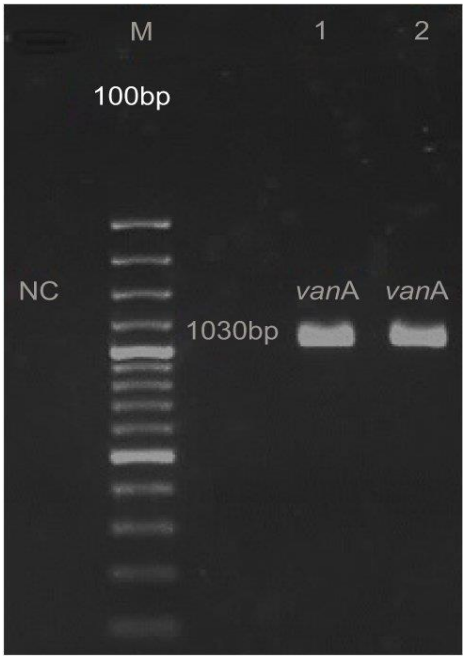

Figure 4. Electrophoresis of the detection *Van A* and *Van B* gene product: 100bp size DNA marker, well 1: positive control, well 2: negative control

4. Discussion

The emergence of antibiotic resistance among hospital-acquired pathogens, particularly within the ESKAPE group, continues to present a significant global health challenge[1,2]. This study focused on the prevalence of VRSA and VRE in hospitalized patients in Mashhad, Iran. The findings provide important insights into regional antibiotic resistance patterns and align with broader global trends, emphasizing the urgent need for effective intervention strategies. The detection of *Van A* and *Van B* genes in 63.6% of vancomycin-resistant isolates in this study is consistent with findings from other regions. A high prevalence of *Van A* gene in *Staphylococcus aureus* isolates has been documented as a significant contributor to vancomycin resistance[3]. Similarly, previous studies have highlighted the critical role of *Van A* and *Van B* genes in mediating resistance in *Enterococcus* species[4,5]. These results are corroborated by recent studies from 2023, which continue to report high levels of *Van A*-mediated resistance across different global regions, including Southeast Asia and Europe, where the prevalence of these genes remains a significant concern[6,7]. Moreover, the prevalence of vancomycin resistance observed in this study mirrors the trends reported in previous research conducted in Iran. Notably, studies conducted over the past decade, such as those by Moghim Biki et al.[6] and Samadi et al.[7], have shown significant resistance in clinical and environmental samples[8,9]. These findings are further

supported by a 2024 study, which reported an alarming increase in vancomycin resistance in hospital settings across the Middle East, particularly in Iran, where VRE and VRSA strains are becoming increasingly prevalent in intensive care units[10]. The identification of *Van A* as the predominant resistance gene has significant implications for treatment strategies. *Van A*-mediated resistance confers high-level resistance to vancomycin, severely limiting the effectiveness of this critical antibiotic[3]. The presence of these genes in a substantial proportion of isolates suggests that vancomycin may no longer be a reliable option for treating infections caused by these pathogens in this region. This is consistent with recent reports from 2024, which indicate that alternative treatment options, such as linezolid and daptomycin, are increasingly being used in response to rising vancomycin resistance[11]. Furthermore, the distribution of resistant isolates across different hospital departments, particularly in general and special care units, highlights the need for targeted infection control measures in these high-risk areas. The findings suggest that intensive use of antibiotics in these departments may contribute to the selection pressure driving the emergence of resistant strains[12]. This is supported by recent studies that have identified intensive care units and surgical wards as primary hotspots for the spread of resistant bacteria due to high antibiotic usage and cross-transmission among patients[13,14]. The methodological approaches employed in this study, including PCR for gene detection and the E-test for determining MICs, were crucial in ensuring the accuracy of the results. These techniques are well-established in clinical microbiology and have been shown to provide reliable data on antibiotic resistance patterns[15,16].

However, it is important to acknowledge the limitations inherent in these methods, such as the potential for false positives or negatives in PCR assays. Recent advancements in molecular diagnostics, including whole-genome sequencing, have been suggested as complementary tools that could provide a more comprehensive analysis of resistance mechanisms[17,18]. An unexpected finding in this study was the relatively low prevalence of *Van B* gene, compared to *Van A*. While *Van B* is typically associated with intermediate levels of resistance and variable expression, its lower prevalence in this study could suggest regional differences in the distribution of resistance genes or differences in the selective pressures acting on these bacterial populations. This observation warrants further investigation, particularly in light of recent studies that have reported fluctuating prevalence rates of *Van B* in different geographic regions, suggesting that local environmental factors and healthcare practices may significantly influence these patterns[19]. For policymakers and healthcare practitioners, these findings underscore the importance of implementing stricter infection control measures, optimizing antibiotic use, and investing in research to develop alternative treatment options. Recent recommendations from global health organizations emphasize the need for multidisciplinary approaches, including the integration of rapid diagnostic tools, antimicrobial stewardship programs, and ongoing surveillance to monitor resistance trends[20-22]. Future studies should aim to expand the sample size, include multiple regions for comparative analysis, and explore the use of novel antibiotics or combination therapies to combat resistant infections.

5. Conclusion

This study provides important insights into the prevalence of vancomycin resistance among *Staphylococcus aureus* and *Enterococcus* species in clinical isolates from hospitalized patients in Mashhad, Iran. Out of 98 isolates analyzed, 7 (7.1%) were found to harbor vancomycin resistance genes. Specifically, 7.8% of *Staphylococcus aureus* isolates were resistant, while a notable 28.6% of *Enterococcus faecium* isolates exhibited resistance, highlighting the particularly high risk posed by *Enterococcus faecium* in clinical settings. The findings underscore the urgent need for ongoing surveillance, research, and tailored intervention strategies to combat the spread of vancomycin-resistant bacteria. As resistance patterns continue to evolve, healthcare systems must remain vigilant, ensuring that treatment protocols are consistently updated with the latest evidence. This vigilance is crucial for safeguarding patient outcomes and effectively managing infections caused by these increasingly resistant pathogens.

Declarations

Competing interests

The authors declare that they have not competing interests.

Authors' contributions

All authors conceived and designed the study. All authors read and approved the final manuscript.

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Availability of data and materials

The authors are ready to send all necessary data of this study upon the reasonable requests.

Ethical considerations

The authors have made necessary ethical considerations (e.g., plagiarism, consent to publish, misconduct, datafabrication, and/or falsification, double publication and/or submission, and redundancy).

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