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Whole-genome characterization of clinical *Enterococcus faecalis* and *Staphylococcus epidermidis* Isolates reveals *mecA*-positive *E. faecalis* and a shared *Inu(A)*–*rep7a* resistance plasmid in Türkiye

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Abstract

Background This study aimed to genomically characterize clinical *Enterococcus faecalis* and *Staphylococcus epidermidis* isolates obtained from aspirate and sputum samples at Bayburt State Hospital, focusing on antimicrobial resistance genes, virulence factors, and mobile genetic elements.

Methods Whole-genome sequencing (WGS) was performed on the isolates, and antimicrobial resistance genes, virulence determinants, multilocus sequence types (MLST), plasmid replicons, and mobile genetic elements were identified using bioinformatics tools.

Results The *E. faecalis* E5 (ST64) isolate, recovered from an aspirate sample, carried multiple antimicrobial resistance genes, including *mecA*, *vanT*, *erm(B)*, *tet(M)*, and *qacA*, along with a diverse virulence gene repertoire (*cyl*, *ebp*, *ace*, and *agg*), mobile genetic elements (*Tn6009*, *ISL1a3*), and four plasmid replicons (*rep19C*, *rep9C*, *repUS43*, and *rep7a*). The *E. faecalis* E184 and E187 isolates (ST124), obtained from sputum samples, harbored fewer acquired resistance genes but shared *gyrA* (T672A) and *parC* (V307I) mutations associated with fluoroquinolone resistance. The *S. epidermidis* ST59 isolate carried resistance genes *Inu(A)*, *fosB*, and *qacD*, together with the plasmid replicon *rep7a* and insertion sequence *ISSau4*. The co-occurrence of *Inu(A)* and the *rep7a* plasmid in both species suggests a potential pathway for interspecies transmission of resistance determinants.

Conclusions This study reports the genomic detection of *mecA* in an *E. faecalis* isolate from Türkiye based on WGS analysis. However, this finding is based solely on genomic data and lacks phenotypic or experimental validation. The detection of a shared plasmid-associated resistance element (*Inu(A)*–*rep7a*) in both *E. faecalis* and *S. epidermidis* highlights the potential for interspecies resistance gene flow within the hospital environment.

Keywords *Enterococcus faecalis*, *Staphylococcus epidermidis*, Whole-genome sequencing, Antimicrobial resistance, Resistance plasmid, *mecA*, Interspecies gene transfer

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Introduction

Staphylococcus epidermidis and *Enterococcus faecalis* are opportunistic Gram-positive pathogens that frequently cause healthcare-associated infections, particularly bloodstream, urinary tract, and device-related infections. *S. epidermidis* commonly causes catheter-related bacteraemia and prosthetic joint infections, whereas *E. faecalis* is a leading cause of surgical site and urinary tract infections and displays high intrinsic and acquired antimicrobial resistance [1–3]. Both species have a strong capacity for biofilm formation on indwelling medical devices, contributing to persistence and tolerance to antimicrobial agents, which makes the treatment of healthcare-associated infections (HAIs) increasingly challenging [4–6].

The pathogenic potential of *S. epidermidis* largely stems from its ability to form biofilms, which facilitate persistent colonization and confer antibiotic tolerance [2, 5]. Community-associated *S. epidermidis* isolates exhibit substantial genomic diversity and are predominantly methicillin-susceptible, whereas hospital-adapted strains are typically methicillin-resistant and belong to distinct evolutionary lineages [7]. Whole-genome sequencing studies have revealed that multidrug-resistant *S. epidermidis* strains commonly possess mobile genetic elements and plasmid replicons that contribute to genomic plasticity and persistence in clinical environments [8, 9].

E. faecalis has emerged as a prominent nosocomial pathogen with remarkable genomic plasticity, facilitating the acquisition and dissemination of antimicrobial resistance determinants. It is commonly associated with bloodstream, surgical site, and urinary tract infections, particularly in hospital environments [10]. Genomic analyses have revealed that *E. faecalis* possesses an extensive set of intrinsic and horizontally acquired resistance determinants, allowing survival against a wide spectrum of antimicrobials such as β -lactams, macrolides, aminoglycosides, and fluoroquinolones [11]. Fluoroquinolone resistance is commonly linked to mutations within the quinolone-resistance-determining regions (QRDRs) of *gyrA* and *parC*, accompanied by active efflux mechanisms that enhance bacterial persistence under antibiotic stress [12]. In addition to its extensive resistance profile, *E. faecalis* possesses a diverse set of virulence factors that promote adhesion, colonization, and biofilm development. Major determinants include surface adhesins such as *Ace* and *EbpABC*, aggregation substances (*Agg*), and secreted enzymes like gelatinase (*GelE*), all of which contribute to persistent infection and facilitate evasion of host immune defenses [13]. Collectively, these genetic and phenotypic traits underpin the dual lifestyle of *E. faecalis* as both a commensal organism and a significant opportunistic pathogen in healthcare-associated environments.

Recent genomic epidemiology studies have revealed that both *S. epidermidis* and *E. faecalis* can serve as

reservoirs for antimicrobial resistance genes, facilitating horizontal gene transfer across species within the hospital microbiome [14, 15]. The frequent co-occurrence of *S. epidermidis* and *E. faecalis* in nosocomial infections accentuates the urgent need for high-resolution genomic surveillance to elucidate the evolution and dissemination of multidrug-resistant (MDR) lineages [16, 17].

This study characterized clinical *Enterococcus faecalis* and *Staphylococcus epidermidis* isolates obtained from a hospital in Türkiye using whole-genome sequencing, and investigated them in terms of antibiotic resistance genes, virulence factors, and mobile genetic elements.

Materials and methods

Bacterial isolates and antibiotic susceptibility

The clinical strains *S. epidermidis* (S5) and *E. faecalis* (E5, E184, and E187) were isolated from sputum and aspirate specimens at Bayburt State Hospital (Türkiye) in 2021. These isolates were selected for whole-genome sequencing based on their clinical origin and distinct antimicrobial resistance profiles observed during routine laboratory testing. Antimicrobial susceptibility testing (AST) was performed according to the Clinical and Laboratory Standards Institute (CLSI) guidelines using the disk diffusion method (CLSI, M100). The isolates were tested against the following antimicrobial agents: cefepime, amoxicillin/clavulanic acid, nitrofurantoin, cefixime, cefotaxime, cefoxitin, cefuroxime, piperacillin/tazobactam, ampicillin, ceftriaxone, ciprofloxacin, levofloxacin, sulfamethoxazole/trimethoprim, ampicillin/sulbactam, meropenem, ertapenem, imipenem, and piperacillin. Genotypic resistance determinants identified through whole-genome sequencing were systematically compared with phenotypic AST results to assess concordance and identify potential discrepancies. Ethical approval was obtained from the Recep Tayyip Erdoğan University Ethics Committee (Approval No: E-40465587-050-1676; Date: 29.07.2025).

DNA isolation and sequencing

In this study, genomic DNA was isolated from 4 bacterial isolates and whole genome sequencing (WGS) analysis was performed using paired-end Illumina sequencing technology. The resulting raw sequencing data were analyzed with FastQC v0.12.1. software to assess quality control parameters [18].

Data preprocessing and quality control

To improve the quality of the raw sequencing data, Cutadapt 5.1 [19] software was used to remove adapter sequences and filter low-quality reads. After trimming, BUSCO 5.6.1 [20] analysis was applied to assess genome integrity and completeness.

De novo genome assembly

De novo genome assembly was performed using data that had undergone quality control using SPAdes genome assembler v4.1.0 [21]. Assembly quality was assessed using N50 value, total length, and number of contigs. Gene annotation was performed on the assembled genomes using Prokka 1.14.6 [22].

Antibiotic resistance genes, mobile genetic elements, virulence genes and plasmid replicon types analysis

Resistance Gene Identifier (RGI) 6.0.3 [23] software and the Comprehensive Antibiotic Resistance Database (CARD) database were used to identify antimicrobial resistance genes. RGI analysis was performed at three different stringency levels: Perfect, Strict, and Loose and ResFinder. The virulence factors, plasmid replicon type and mobile genetic elements (MGEs) were identified using Virulencefinder_db, PlasmidFinder and MobileElementFinder, respectively (CGE server5).

Phage region analysis and multilocus sequence typing (MLST)

PHASTEST 3.0 (DB-2020) [24] analysis was performed on the Proksee 1.01 platform to identify prophage regions in bacterial genomes. MLST analysis was performed for the molecular typing of bacterial isolates using mlst 2.23.0 [25].

Statistical analysis and data visualization

All data analyses, statistical evaluations, and visualizations were performed using the R programming language v4.5.1. The dplyr and tidyverse packages were used for data manipulation, and the ggplot2 and plotly packages were used for visualization. All analyses were documented in R Markdown, following the principles of reproducible research.

Results

In this study, whole-genome sequencing was performed on one *S. epidermidis* (S5) and three *E. faecalis* (E5, E184, and E187) isolates obtained from Bayburt State Hospital. Genome quality metrics, antibiotic resistance genes, virulence factors, plasmid replicons, and mobile genetic elements were characterized (Figs. 1, 2, 3 and 4).

De novo genome assembly and BUSCO analyses revealed differences in the genome structure and quality of the isolates.

BUSCO analysis of *S. epidermidis* S5 (ST59) and *E. faecalis* E5 (ST64) isolates showed 100% complete and (98.4% Complete, 0% Incomplete, 2.4% Duplication) respectively. *E. faecalis* isolates E184 and E187, which share the same MLST type (ST124), had the highest quality metrics for both assembly and genome integrity. BUSCO results also showed that the genomes of these

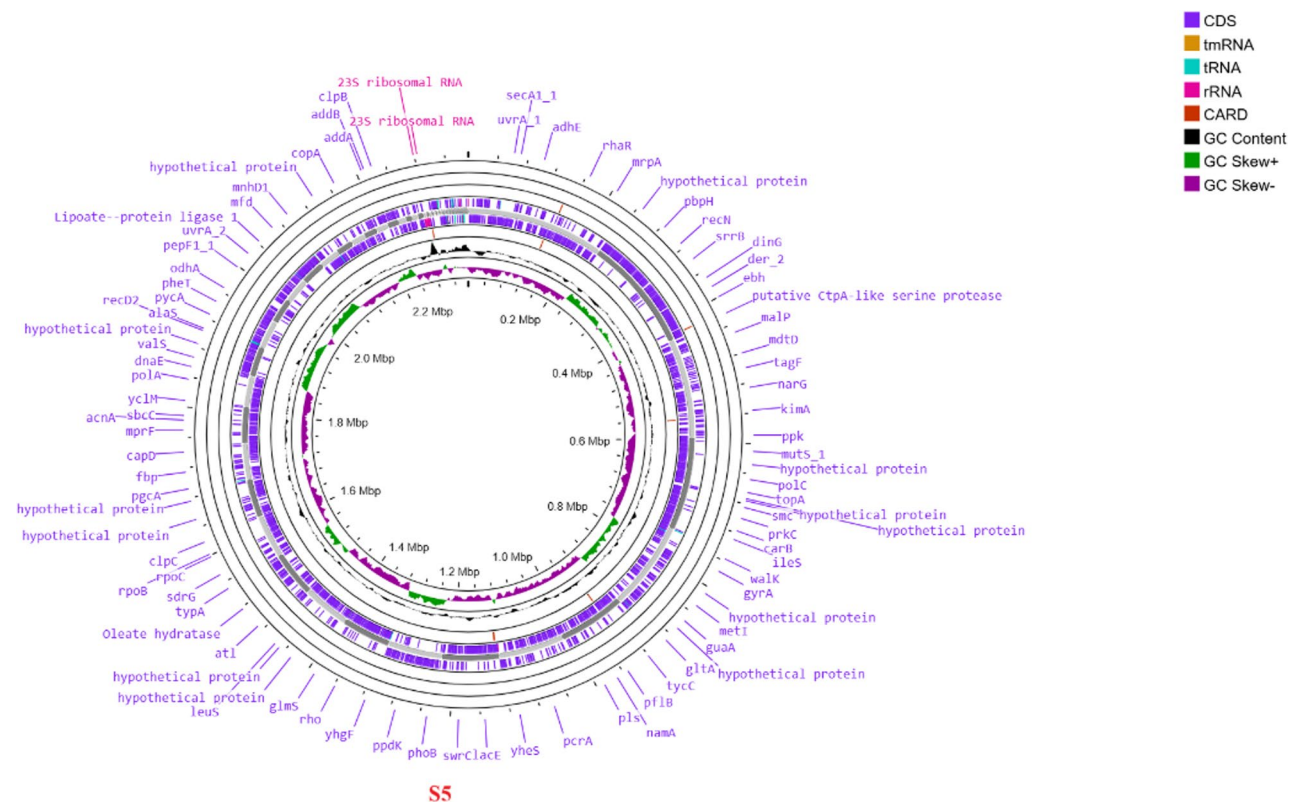


Fig. 1 Circular visualisation of the complete genome of strain S5



De novo genome assembly of the isolates revealed significant differences in their genomic structures (Table 1). The genome of *S. epidermidis* isolate S5 was 2,351,853 bp long and comprised 119 contigs. *E. faecalis* isolate E5 was found to have the longest genome length

with 3,162,919 bp and 174 contigs. The genomes of isolates E184 and E187, which share the same MLST type (ST124), were assembled with 33 and 34 contigs, respectively. The much higher average contig lengths of these isolates (49,874 bp and 56,875 bp, respectively) compared to isolate E5 (3,537 bp) suggest that their genomes

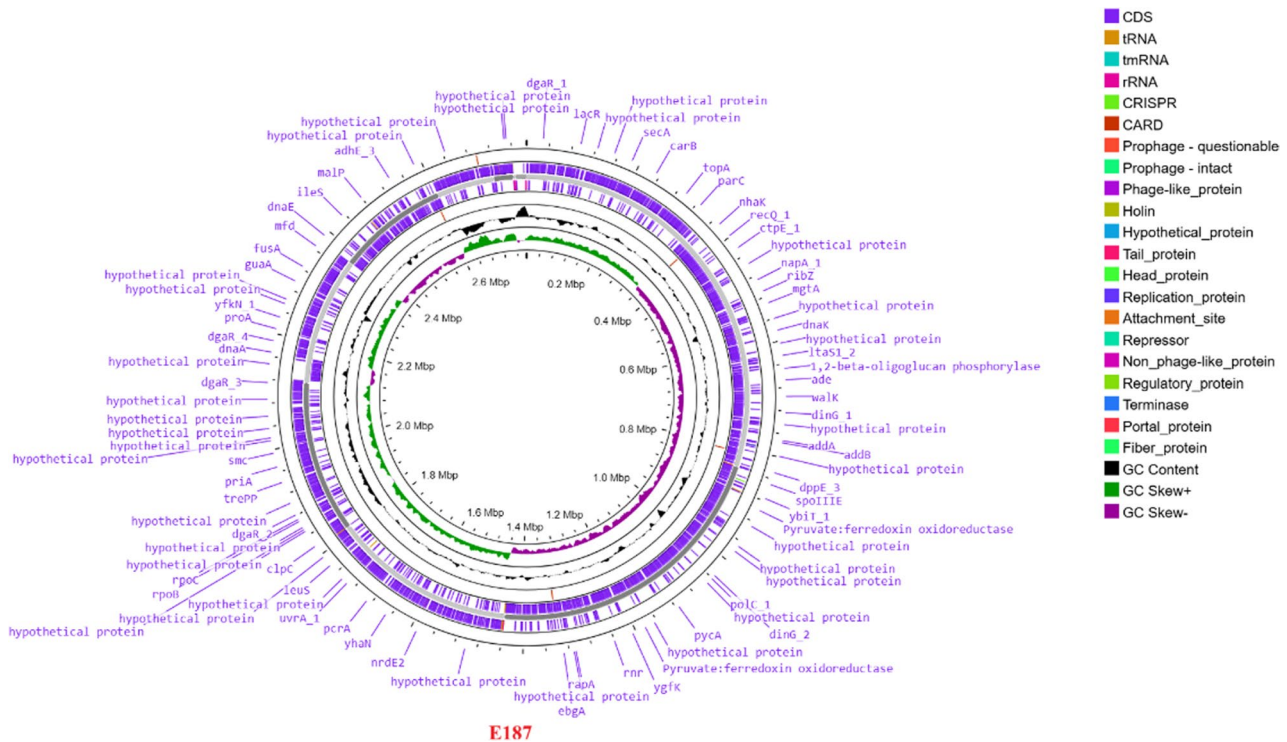


Fig. 4 Circular visualisation of the complete genome of strain E187

Table 1 Genome and assembly characteristics of sequenced

Isolate ID	Species	Source	AST profile	Genome size (bp)	Contigs (n)	Avg contig length (bp)	GC content (%)
S5	<i>S. epidermidis</i>	Aspirate	TOB, AK, FOX, CXM, TPZ, CRO, CN, CTX, FEB, AMC, CAZ, F100	2,351,853	119	19,763	32.2
E5	<i>E. faecalis</i>	Aspirate	TOB, AK, FOX, CXM, TPZ, CRO, CN, CTX, FEB, AMC, CAZ, F100	3,162,919	174	3,537	37.04
E184	<i>E. faecalis</i>	Sputum	ETP, CIP, LEV, MEM, AMC, CAZ, F100, CFM, CN, CTX, AK, FOX, CXM, TPZ, AM, CRO, TOB	2,767,069	33	49,874	37.51
E187	<i>E. faecalis</i>	Sputum	ETP, CIP, LEV, AMC, CAZ, F100, CFM, CN, CTX, AK, FOX, CXM, TPZ, AM, CRO, TOB	2,765,750	34	56,875	37.50

TOB tobramycin, AK amikacin, FOX cefoxitin, CXM cefuroxime, TPZ piperacillin/tazobactam, CRO ceftriaxone, CN gentamicin, CTX cefotaxime, FEB cefepime, AMC amoxicillin/clavulanic acid, CAZ ceftazidime, F100 nitrofurantoin, ETP ertapenem, CIP ciprofloxacin, LEV levofloxacin, MEM meropenem, CFM cefixime, AM ampicillin

are more stable and less complex in terms of repetitive elements.

The *S. epidermidis* S5 isolate was assigned to sequence type ST59 and carried a multidrug resistance profile, including genes encoding β -lactamase (PC1), trimethoprim resistance (*dfrC*), multiple efflux pumps (*mgrA*, *norA*, *sdrM* and *sepA*), the lincosamide resistance gene *lnu(A)*, the fosfomycin resistance gene (*fosB*) and the biocide resistance determinant *qacD*. Plasmid analysis identified the replicon types *rep39* and *rep7a*, while the insertion sequence *ISSau4* was detected as a mobile genetic element.

The *E. faecalis* ST64 isolate E5 harbored an extensive repertoire of antimicrobial resistance genes, including

erm(B), *dfrE*, *efrA*, *emeA*, *lnu(A)*, *isaA*, *mecA*, *mphC*, *msrA*, *qacA*, *tet(M)* and *clpL*, together with the glycopeptide-associated gene *vanT* and point mutations in *gyrA* and *parC* associated with fluoroquinolone resistance. This isolate also carried multiple virulence determinants, including *elrA*, *srtA*, *ace*, *agg*, *ebpABC*, and the complete cytolysin operon. In addition, several plasmid replicons (*rep19C*, *rep9C*, *repUs43*, and *rep7a*) and mobile genetic elements such as Tn6009 and ISL1a3 were identified. Notably, both *S. epidermidis* S5 and *E. faecalis* E5 carried the *lnu(A)* resistance gene together with the *rep7a* plasmid replicon based on WGS analysis (Table 2).

In contrast, the ST124 isolates E184 and E187 contained a narrower set of acquired resistance genes (*dfrE*,

Table 2 Summary of genomic features of the isolates based on whole-genome sequencing

Isolate (MLST)	Resistance genes	Plasmid replicons	Virulence genes	MGEs
S5 (ST59)	<i>fosB</i> , <i>lnu(A)</i> , <i>blaZ</i>	rep7a, rep39	–	ISSau4
E5 (ST64)	<i>erm(B)</i> , <i>tet(M)</i> , <i>dfrE</i> , <i>lnu(A)</i> , <i>msr(A)</i> , <i>mph(C)</i> , <i>qacA</i> , <i>mecA</i> , <i>clpL</i> , <i>isaA</i>	rep19C, rep9C, repUS43, rep7a	<i>ebpABC</i> , <i>srtA</i> , <i>ace</i> , <i>agg</i> , <i>cyl operon</i> , <i>elrA</i> , <i>efaAfs</i> , <i>gelE</i> , <i>tpx</i>	Tn6009, Tn917, ISL1a3
E184 (ST124)	<i>lsa(A)</i>	–	<i>fsrB</i> , <i>hylA</i> , <i>hylB</i> , <i>gelE</i> , <i>tpx</i> , <i>ebpABC</i> , <i>srtA</i> , <i>ace</i>	–
E187 (ST124)	<i>lsa(A)</i>	–	<i>fsrB</i> , <i>hylA</i> , <i>hylB</i> , <i>gelE</i> , <i>tpx</i> , <i>ebpABC</i> , <i>srtA</i> , <i>ace</i>	–

efrA, *emeA*, *isaA*), but shared the same *gyrA* (T672A) and *parC* (V3071) mutations with E5. The antimicrobial resistance genes detected through WGS were systematically compared with the phenotypic AST results to assess genotype–phenotype concordance. A high level of agreement was observed for several resistance determinants, including *erm(B)* with macrolide resistance, *tet(M)* with tetracycline resistance, and *gyrA/parC* mutations with fluoroquinolone resistance. However, the presence of *mecA* could not be correlated with phenotypic resistance, indicating a discrepancy between genotypic detection and phenotypic expression.

Virulence profiling revealed that the isolates carried multiple genes associated with adhesion, biofilm formation, and pathogenicity, including *fsrB*, *hylA*, *hylB*, *gelE*, and *tpx*, together with core adhesion-related genes (*ebpABC*, *srtA*, *ace*, and *agg*).

A comparative analysis was performed to assess the correlation between genotypic resistance determinants identified by whole-genome sequencing and phenotypic antimicrobial susceptibility testing (AST) results. A high level of concordance was observed for several resistance determinants. Specifically, the presence of *erm(B)* and *tet(M)* genes was consistent with resistance to macrolides and tetracycline, respectively. In addition, mutations in *gyrA* and *parC* were associated with resistance to fluoroquinolones. However, the detection of *mecA* in *E. faecalis* E5 did not correspond to phenotypic resistance, indicating a discrepancy between genotypic detection and phenotypic expression.

Discussion

Antimicrobial resistance among Gram-positive bacteria represents a major challenge to global public health, particularly in healthcare-associated infections caused by *Staphylococcus aureus*, *Enterococcus faecium* and *Enterococcus faecalis*, and *Staphylococcus epidermidis* [26, 27]. Although *E. faecalis* and *S. epidermidis* are part of the normal microbiota, both species have emerged as important opportunistic pathogens in hospital settings due to their ability to acquire antimicrobial resistance and express virulence traits such as biofilm formation and host tissue adhesion [28–30].

Whole-genome sequencing (WGS) in this study provided detailed insight into the resistance and virulence

profiles of *S. epidermidis* and *E. faecalis* isolates obtained from the same hospital environment. The *S. epidermidis* isolate belonged to sequence type ST59, a lineage frequently associated with nosocomial infections [31], and carried multiple resistance determinants, including *dfrC*, *lnu(A)*, and multidrug efflux systems (*mgrA*, *norA*, *sdrM*, and *sepA*). These findings are consistent with previous genomic studies highlighting *S. epidermidis* as an important reservoir of antimicrobial resistance [32–35], and suggest that this species may act as a stable reservoir of resistance genes in hospital environments.

The *E. faecalis* isolates represented two distinct clones (ST64 and ST124) with different resistance profiles. The ST64 isolate exhibited a comprehensive set of resistance mechanisms, including *erm(B)*, *tet(M)*, *dfrE*, and *qacA*, indicating adaptation to both antibiotic and disinfectant pressures [36–39]. The presence of resistance-associated plasmid elements further supports the role of horizontal gene transfer in the dissemination of resistance [38–39]. In contrast, ST124 isolates carried fewer acquired resistance genes but shared chromosomal mutations in *gyrA* and *parC*, indicating alternative resistance mechanisms. These findings highlight clone-specific adaptation strategies and are consistent with previous genomic studies on enterococci [40–46].

Notably, the detection of *mecA* in *E. faecalis* is a rare finding and may indicate potential interspecies gene transfer. However, this result should be interpreted with caution, as *mecA* was identified solely based on whole-genome sequencing without PCR confirmation or functional validation. Moreover, the presence of *mecA* did not correlate with phenotypic resistance, suggesting possible genotype–phenotype discordance.

Virulence gene analysis revealed both conserved and variable elements. All isolates carried biofilm-associated genes such as *ebpABC*, *srtA*, *ace*, *agg*, and *efaA*, whereas clone-specific differences were observed in other virulence determinants. The ST64 isolate carried the cytolysin operon (*cylA*, *cylB*, *cylL*, and *cylM*), while ST124 isolates possessed invasion-associated genes (*hylA*, *hylB*, and *fsrB* genes). This suggests that different clones may employ distinct pathogenicity strategies.

Furthermore, the identification of shared resistance-associated elements, including *lnu(A)* linked with plasmid replicons across *S. epidermidis* and *E. faecalis*,

indicates that mobile genetic elements may facilitate horizontal gene transfer within the hospital environment. This observation is supported by previous studies emphasizing the role of mobile genetic elements in antimicrobial resistance dissemination [40–42]. Collectively, these findings highlight the dynamic role of hospital environments as reservoirs and exchange hubs for resistance determinants.

From a clinical perspective, these findings underscore the importance of strict infection control strategies, including hand hygiene, environmental cleaning, sterilization of medical devices, and antimicrobial stewardship programs. In addition, the integration of genomic surveillance into routine hospital practice may help identify transmission pathways and enable early intervention to control potential outbreaks.

This study has several limitations. The relatively small number of isolates and the single-center design limit generalizability. In addition, resistance gene detection was based on genomic data without PCR confirmation or functional validation, particularly for *mecA*. The lack of phenotypic correlation for certain resistance determinants further indicates possible genotype–phenotype discordance. Moreover, contig-level sequencing limits the ability to confirm direct horizontal gene transfer events. Future multicenter studies incorporating long-read sequencing and functional analyses are needed to better understand the genomic epidemiology of antimicrobial resistance.

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None.

Authors' contributions

All authors contributed to the study conception and design. AÖD and NE wrote the paper.

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Data availability

The genome assemblies of isolates were deposited in GenBank and registered with the BioProject number PRJNA1366064 (E187 (SAMN53301940, JBTHHD000000000), E184 (SAMN53301939, JBTHHE000000000), E5 (SAMN53301938, JBTHHF000000000), S5 (SAMN53301937, JBTHHG000000000)).

Declarations

Ethics approval and consent to participate

This study was reviewed by the Recep Tayyip Erdoğan University Non-Interventional Clinical Research Ethics Committee (Recep Tayyip Erdoğan Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu) (decision No E-40465587-050-1676, date 29.07.2025). The Committee waived the requirement for informed consent to participate, as the research used fully de-identified residual bacterial isolates and routine laboratory data with no patient contact and no access to identifiable personal information. This waiver was granted in accordance with applicable national regulations for non-

interventional research on anonymized data and institutional policy. The study was conducted in accordance with the Declaration of Helsinki and relevant institutional/national guidelines and regulations.

Consent for publication

Not applicable. No individual person's data are included.

Competing interests

The authors declare no competing interests.

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