Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Integrated Epidemiologic and Genomic Surveillance of Carbapenemase-Producing Enterobacterales in a Regional Healthcare Network

Yujin Sohn
Wonju Severance Christian Hospital
Imchang Lee
Hallym University Chuncheon Sacred Heart Hospital
Won Sup Oh
Kangwon National University Hospital
Seungmin Jeong
Hallym University
Dong-Hyun Kim
Hallym University
Eun Hee Song
Gangneung Asan Hospital
Young Keun Kim
Wonju Severance Christian Hospital
Seung Soon Lee
hushh93@hallym.ac.kr

Hallym University Chuncheon Sacred Heart Hospital

Research Article

Keywords: Carbapenemase-producing Enterobacterales, Genomic surveillance, Regional surveillance, Interfacility connectivity, Long-term care facilities, Antimicrobial resistance

Posted Date: July 16th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10203181/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background

Carbapenemase-producing Enterobacterales (CPE) pose a persistent challenge across interconnected healthcare networks. Although epidemiologic risk factors for CPE colonization are well described, evidence integrating patient-level risk profiling with regional genomic surveillance remains limited.

Methods

We conducted a multicenter study integrating epidemiologic risk factor analysis with regional genomic surveillance across three acute-care hospitals and six long-term care facilities in Gangwon Province, Korea. A matched case-control study of 908 patients screened for CPE at admission between August 2024 and June 2025, including 445 CPE-colonized patients and 463 non-colonized controls, identified independent predictors of CPE colonization using multivariable logistic regression. Whole-genome sequencing of 242 CPE isolates collected across the regional healthcare network was performed to characterize circulating lineages, resistance determinants, and genetic connectivity among facilities.

Results

Significant predictors of CPE colonization included prior hospitalization, prior CPE colonization or infection, and prior room sharing with a CPE-colonized or infected patient within the previous year; recent exposure to carbapenems, glycopeptides, penicillins, or proton pump inhibitors; recent indwelling device use; and the presence of wound drainage or respiratory secretions at the time of screening. Genomic surveillance revealed a regionally structured CPE population dominated by *Klebsiella pneumoniae*. The KPC-producing ST307 clone was widely distributed across multiple facilities, while additional lower-frequency lineages, including ST11 and ST16, highlighted the genomic diversity of the regional CPE population. A single ST23-1LV isolate carrying *blaKPC* and multiple hypervirulence-associated loci was identified, representing a potential convergence of carbapenem resistance and hypervirulence. Regional variation in lineage composition suggested heterogeneous dissemination dynamics, whereas SNP-based genetic linkage patterns indicated putative interfacility circulation across the healthcare network.

Conclusions

CPE dissemination within this regional healthcare network was associated with both identifiable high-risk patient populations and persistent circulation of KPC-producing *Klebsiella pneumoniae* ST307. These findings support coordinated regional approaches integrating risk-based screening, interfacility information sharing, and genomics-informed surveillance to strengthen future CPE prevention and control efforts.

Background

Carbapenemase-producing Enterobacterales (CPE) have become a major global threat to healthcare-associated infection prevention because they are associated with extensive antimicrobial resistance, limited therapeutic options, and the capacity for both clonal expansion and horizontal dissemination of carbapenemase genes [1, 2]. In healthcare settings, CPE control is complicated by intestinal colonization, which may remain clinically silent while enabling persistence and onward transmission among vulnerable patients [2, 3]. Importantly, CPE dissemination is not confined to individual hospitals. Patients frequently move between acute-care hospitals (ACHs) and long-term care facilities (LTCFs), creating interconnected healthcare networks in which high-risk patients, prolonged healthcare exposure, antimicrobial use, and invasive device care may converge [4, 5]. Such connectivity creates substantial challenges for coordinated regional CPE prevention and control.

Epidemiologic risk factor analysis is essential for identifying patients who may benefit from targeted CPE screening and prevention measures. Recent multicenter studies have shown that prior colonization, healthcare exposure, antimicrobial use, indwelling device use, invasive procedures, and severe underlying illness are important factors associated with carbapenem-resistant Enterobacterales infection or bloodstream infection [6, 7]. These findings support the use of targeted screening and infection prevention measures for high-risk patients. However, epidemiologic risk factor analysis alone cannot determine whether CPE colonization events within a region represent unrelated acquisitions, persistent facility-level circulation, or dissemination of shared high-risk clones across institutions. This limitation is particularly relevant in healthcare networks where asymptomatic colonization, prolonged carriage, and complex patient movement can obscure transmission pathways and delay recognition of local or interfacility spread [8, 9].

Whole-genome sequencing-based surveillance can complement epidemiologic risk assessment by providing higher-resolution information on CPE population structure, circulating lineages, and potential transmission links. Previous studies have shown that integrating genomic and epidemiologic data can improve understanding of CPE dissemination within healthcare networks and provide insights beyond conventional epidemiologic surveillance alone [8, 9]. Therefore, combining patient-level risk factor analysis with regional genomic surveillance may help characterize high-risk populations, circulating lineages, and regional dissemination patterns of CPE.

Therefore, we conducted a multicenter study integrating epidemiologic risk factor analysis with regional genomic surveillance across ACHs and LTCFs. We aimed to identify factors associated with CPE colonization and characterize regional dissemination patterns and circulating CPE lineages.

Methods

Study setting and regional healthcare network

This multicenter study was conducted as part of the Co-ordinated Regional Intervention to Stop Interfacility Spread of CPE (CRISIS-CPE) project, which established a regional surveillance network involving interconnected ACHs and LTCFs in Gangwon Province, Korea. The participating facilities were located across the Chuncheon, Wonju, and Yeongdong regions and were linked through routine patient referral and transfer pathways.

Study population and admission screening

Between August 1, 2024, and June 30, 2025, we conducted a matched case–control study among hospitalized adult patients (≥ 19 years) across participating facilities. Participating facilities applied harmonized admission active surveillance culture protocols for patients considered at high risk for CPE colonization. High-risk patients were defined according to the participating facilities' CRE-focused admission screening criteria and included those with a history of hospitalization in a long-term care hospital or other healthcare facility within the past year, those transferred from another healthcare facility, or those with a prior history of CRE colonization within the past year. Patients younger than 19 years, those not meeting high-risk criteria, those who declined participation, patients at end-of-life, and those unable to undergo rectal swab (anal swab) sampling were excluded.

A matching strategy was applied to construct the control group. For each CPE-colonized patient, eligible controls were identified based on the following matching variables: (1) month of admission, (2) sex, and (3) age group (10-year intervals). Controls were randomly selected from eligible non-colonized patients who met all matching criteria. Because additional eligible controls with complete clinical data were included following review of clinical records, the final study population included slightly more controls than cases.

Epidemiologic analysis

Epidemiologic analyses were performed to identify patient-level factors associated with CPE colonization relevant to targeted surveillance and infection prevention strategies. Baseline characteristics and potential risk factors were compared between colonized and non-colonized groups.

For statistical analysis, categorical variables were compared using the chi-square test or Fisher's exact test, and continuous variables were analyzed using the independent t-test. To identify independent risk factors for CPE colonization, univariable and multivariable logistic regression analyses were performed. Adjusted odds ratios (aORs) with corresponding 95% confidence intervals (CIs) were calculated to estimate the strength of association between candidate variables and CPE colonization. Variables with P values < 0.10 in the univariable analysis were included in the multivariable logistic regression model. A two-sided P value < 0.05 was considered statistically significant. All analyses were conducted using IBM SPSS Statistics for Windows, version 29.0 (IBM Corp., Armonk, NY, USA).

Whole-genome sequencing and genome assembly

Genomic DNA was extracted from 242 CPE isolates collected through the regional surveillance network using a QIAGEN DNA extraction kit. Sequencing libraries were prepared using the TruSeq Nano DNA kit, followed by 150-bp paired-end sequencing on an Illumina platform. Raw reads were trimmed using Trimmomatic v0.39 [10], and de novo genome assembly was performed using Unicycler v0.5.1 [11]. Assembly quality was assessed using CheckM v1.1.3 [12], and genomes with estimated completeness ≥ 90% and contamination ≤ 5% were retained for downstream genomic analyses. A total of 107 assemblies met these criteria.

Genome-based species identification and AMR gene classification

Genome-based species identification was conducted using GTDB-Tk v1.7.0 [13]. For isolates with available clinical species identification results, genome-based and clinical species assignments were compared. For AMR gene profiling, the 107 genome assemblies were screened for antimicrobial resistance determinants using NCBI AMRFinderPlus v4.2.7 [14]. Detected resistance determinants were assigned to predefined antimicrobial resistance categories, including carbapenemase, extended-spectrum beta-lactamase (ESBL), AmpC beta-lactamase, colistin, fosfomycin, fluoroquinolone, plasmid-mediated quinolone resistance, aminoglycoside, tetracycline, sulfonamide, trimethoprim, phenicol, efflux pump, and outer membrane porin-related categories. The AMR category classification scheme is summarized in Supplementary Fig. 1. Carbapenemase genes were further grouped by enzyme family, including KPC, NDM, OXA-48 variant, and VIM.

Klebsiella pneumoniae genotyping and K/O locus diversity analysis

Klebsiella pneumoniae complex isolates were further characterized using Kleborate [15] to determine sequence type, K-locus and O-locus profiles, virulence-associated loci, and virulence scores. Regional K- and O-locus diversity was evaluated after grouping facilities into Chuncheon, Wonju, Gangneung, Donghae, and Sokcho. For each region, K- and O-locus profiles were ranked in descending order of frequency. Cumulative prevalence curves were generated for each region and for the overall *K. pneumoniae* population based on the cumulative proportion of isolates covered by ranked K- or O-locus profiles.

Core-genome SNP-based phylogenetic analysis

Core-genome SNP-based phylogenetic analysis was performed using PhaME [16]. For the broad Enterobacterales phylogenetic analysis, *Salmonella enterica* subsp. *enterica* serovar Typhimurium str. LT2 (NC_003197.2) was used as the reference genome. For *K. pneumoniae*-focused SNP analysis, *K. pneumoniae* subsp. *pneumoniae* HS11286 (NC_016845.1) was used as the reference genome. Isolates assigned to the *Klebsiella* spp. and *E. coli* with available typing annotations were included in the integrated phylogenetic visualization. Phylogenetic metadata, including year, region, lineage, serotype or K/O locus, virulence-associated loci, carbapenemase type, and antimicrobial resistance categories, were annotated alongside the phylogeny.

SNP-distance-based genetic linkage mapping

Putative genetic linkage among *K. pneumoniae* isolates was assessed using pairwise core-genome SNP distances. Isolate pairs differing by fewer than 21 SNPs were considered genetically linked based on a previously reported threshold for carbapenem-resistant *K. pneumoniae* genomic epidemiology [17]. Pairwise links were summarized by sequence type and facility. Within-facility links were defined as genetically linked isolate pairs collected from the same facility, whereas between-facility links were defined as genetically linked isolate pairs collected from different facilities. Directionality was assigned from the earlier to the later collection date for visualization only and was not interpreted as confirmed patient-to-patient transmission.

Results

Regional surveillance network and study population overview

A total of 908 patients who underwent admission CPE surveillance across the regional healthcare network were included in the analysis, comprising 445 CPE-colonized patients and 463 non-colonized controls. Baseline characteristics of the study population are summarized in Table 1.

Table 1
Baseline characteristics and potential risk factors for CPE colonization among patients undergoing admission surveillance

Factors	Overall			ACH			LTCF		
	No CPE (N = 463)	CPE (N = 445)	*P* value	No CPE (N = 362)	CPE (N = 362)	*P* value	No CPE (N = 101)	CPE (N = 83)	*P* value
Demographics									
Age(yr) [a]	73.8 ± 12.9	74.0 ± 12.9	0.965	73.1 ± 13.1	73.5 ± 13.0	0.664	76.4 ± 11.4	76.0 ± 12.3	0.855
Male gender	267 (57.7)	259 (58.2)	0.893	216 (59.7)	218 (60.2)	0.879	51 (50.5)	41 (49.4)	0.882
Prior Healthcare exposure									
ICU Admission	230 (49.7)	200 (44.9)	0.153	230 (63.5)	200 (55.2)	0.023	0 (0.0)	0 (0.0)	-
Hospitalization within 1yr	255 (55.1)	343 (77.1)	< 0.001	174 (48.1)	269 (74.3)	< 0.001	81 (80.2)	74 (89.2)	0.097
ICU admission within 1yr	45 (9.7)	125 (28.1)	< 0.001	28 (7.7)	104 (28.7)	< 0.001	17 (16.8)	21 (25.3)	0.158
Prior CPE colonization/infection within 1yr	3 (0.6)	54 (12.1)	< 0.001	3 (0.8)	27 (7.5)	< 0.001	0 (0.0)	27 (32.5)	< 0.001
Room sharing with CPE pt. within 1yr	7 (1.5)	51 (11.5)	< 0.001	6 (1.7)	45 (12.4)	< 0.001	1 (1.0)	6 (7.2)	0.047
Residence in LTCF within 1yr	70 (15.1)	66 (14.8)	0.903	62 (17.1)	55 (15.2)	0.480	62 (17.1)	55 (15.2)	0.480
Prior non-CRE MDRO infection within 1yr	11 (2.4)	97 (21.8)	< 0.001	9 (2.5)	84 (23.2)	< 0.001	2 (2.0)	13 (15.7)	< 0.001
Colonization with non-CRE MDRO	11 (2.4)	99 (22.2)	< 0.001	9 (2.5)	86 (23.8)	< 0.001	2 (2.0)	13 (15.7)	< 0.001

ACH, acute care hospital; LTCF, long-term care facility; CPE, carbapenemase-producing Enterobacterales; CRE, carbapenem-resistant Enterobacterales; ICU, intensive care unit; MDRO, multi-drug resistant organism; MRAB, multidrug-resistant *Acinetobacter baumannii*; MRPA multidrug-resistant *Pseudomonas aeruginosa*; MRSA, methicillin-resistant *Staphylococcus aureus*; PPI, proton pump inhibitor; SD, standard deviation; VRE, vancomycin-resistant Enterococci

[a]Values are means ± SD

Data are presented as No. (%) unless indicated otherwise

Factors	Overall			ACH			LTCF		
	No CPE (N = 463)	CPE (N = 445)	*P* value	No CPE (N = 362)	CPE (N = 362)	*P* value	No CPE (N = 101)	CPE (N = 83)	*P* value
Demographics									
MRAB	3 (0.6)	49 (11.0)	< 0.001	3 (0.8)	48 (13.3)	< 0.001	0 (0.0)	1 (1.2)	0.451
MRPA	3 (0.6)	34 (7.6)	< 0.001	3 (0.8)	27 (7.5)	< 0.001	0 (0.0)	7 (8.4)	0.003
MRSA	6 (1.3)	24 (5.4)	< 0.001	4 (1.1)	19 (5.2)	< 0.001	2 (2.0)	5 (6.0)	0.247
VRE	2 (0.4)	28 (6.3)	< 0.001	2 (0.6)	24 (6.6)	< 0.001	0 (0.0)	4 (4.8)	0.040
Previous antibiotic exposure within 3mon	82 (17.7)	268 (60.2)	< 0.001	36 (9.9)	219 (60.5)	< 0.001	46 (45.5)	48 (59.0)	0.068
Cephalosporins	54 (11,7)	161 (36.2)	< 0.001	36 (9.9)	219 (60.5)	< 0.001	28 (27.7)	30 (36.1)	0.221
Penicillins	25 (5.4)	130 (29.2)	< 0.001	9 (2.5)	108 (29.8)	< 0.001	16 (15.8)	22 (26.5)	0.075
Quinolones	26 (5.6)	97 (21.8)	< 0.001	12 (3.3)	84 (23.2)	< 0.001	14 (13.9)	13 (15.7)	0.731
Carbapenems	14 (3.0)	101 (22.7)	< 0.001	10 (2.8)	94 (26.0)	< 0.001	4 (4.0)	7 (8.4)	0.227
Glycopeptides	2 (0.4)	55 (12.4)	< 0.001	1 (0.3)	48 (13.3)	< 0.001	1 (1.0)	7 (8.4)	0.024
Polymixin E	0 (0.0)	16 (3.6)	< 0.001	0 (0.0)	13 (3.6)	< 0.001	16 (15.8)	22 (26.5)	0.075
Others	28 (6.0)	107 (24.0)	< 0.001	19 (5.2)	100 (27.6)	< 0.001	9 (8.9)	7 (8.4)	0.909

ACH, acute care hospital; LTCF, long-term care facility; CPE, carbapenemase-producing Enterobacterales; CRE, carbapenem-resistant Enterobacterales; ICU, intensive care unit; MDRO, multi-drug resistant organism; MRAB, multidrug-resistant *Acinetobacter baumannii*; MRPA multidrug-resistant *Pseudomonas aeruginosa*; MRSA, methicillin-resistant *Staphylococcus aureus*; PPI, proton pump inhibitor; SD, standard deviation; VRE, vancomycin-resistant Enterococci

[a]Values are means ± SD

Data are presented as No. (%) unless indicated otherwise

Factors	Overall			ACH			LTCF		
	No CPE (N = 463)	**CPE (N = 445)**	***P* value**	**No CPE (N = 362)**	**CPE (N = 362)**	***P* value**	**No CPE (N = 101)**	**CPE (N = 83)**	***P* value**
Demographics									
Previous gastric acid suppressant use (≥ 3d)	74 (16.0)	233 (52.4)	< 0.001	32 (8.8)	184 (50.8)	< 0.001	42 (41.6)	49 (59.0)	0.018
PPIs	44 (9.5)	147 (33.0)	< 0.001	18 (5.0)	123 (34.0)	< 0.001	26 (25.7)	24 (28.9)	0.630
H2 receptor blockers	19 (4.1)	81 (18.2)	< 0.001	7 (1.9)	65 (18.0)	< 0.001	12 (11.9)	16 (19.3)	0.165
Antacids	18 (3.9)	45 (10.1)	< 0.001	11 (3.0)	36 (9.9)	< 0.001	7 (6.9)	9 (10.8)	0.349
P-CABs	11 (2.4)	26 (5.8)	0.008	8 (2.2)	21 (5.8)	0.014	3 (3.0)	5 (6.0)	0.471
Immunosuppressant use	16 (3.5)	42 (9.4)	< 0.001	12 (3.3)	33 (9.1)	0.001	4 (4.0)	9 (10.8)	0.070
Systemic steroid	7 (1.5)	31 (7.0)	< 0.001	5 (1.4)	25 (6.9)	< 0.001	2 (2.0)	6 (7.2)	0.143
Chemotherapy	13 (2.8)	16 (3.6)	0.500	10 (2.8)	14 (3.9)	0.406	3 (3.0)	2 (2.4)	1.000
Immunosuppressant	0 (0.0)	2 (0.4)	0.240	0 (0.0)	0 (0.0)	-	0 (0.0)	2 (2.4)	0.202
Use of indwelling device	77 (16.6)	251 (56.4)	< 0.001	30 (8.3)	201 (55.5)	< 0.001	47 (46.5)	50 (60.2)	0.064
Surgery within 3mon	40 (8.6)	93 (20.9)	< 0.001	12 (3.3)	67 (18.5)	< 0.001	28 (27.7)	26 (31.3)	0.593
Current symptoms	218 (47.1)	241 (54.2)	0.033	198 (54.7)	216 (59.7)	0.176	20 (19.8)	25 (30.1)	0.105
Respiratory secretions	18 (3.9)	44 (9.9)	< 0.001	12 (3.3)	33 (9.1)	0.001	6 (5.9)	11 (13.3)	0.088

ACH, acute care hospital; LTCF, long-term care facility; CPE, carbapenemase-producing Enterobacterales; CRE, carbapenem-resistant Enterobacterales; ICU, intensive care unit; MDRO, multi-drug resistant organism; MRAB, multidrug-resistant *Acinetobacter baumannii*; MRPA multidrug-resistant *Pseudomonas aeruginosa*; MRSA, methicillin-resistant *Staphylococcus aureus*; PPI, proton pump inhibitor; SD, standard deviation; VRE, vancomycin-resistant Enterococci

[a]Values are means ± SD

Data are presented as No. (%) unless indicated otherwise

Factors	Overall			ACH			LTCF		
	No CPE (N = 463)	CPE (N = 445)	*P* value	No CPE (N = 362)	CPE (N = 362)	*P* value	No CPE (N = 101)	CPE (N = 83)	*P* value
Demographics									
Diarrhea	12 (2.6)	28 (6.3)	0.007	9 (2.5)	23 (6.4)	0.011	3 (3.0)	5 (6.0)	0.471
Wound drainage	5 (1.1)	21 (4.7)	0.001	3 (0.8)	20 (5.5)	< 0.001	2 (2.0)	1 (1.2%)	1.000
Urinary or fecal incontinence	11 (2.4)	8 (1.8)	0.543	2 (0.6)	6 (1.7)	0.286	9 (8.9)	2 (2.4)	0.115
Others	176 (38.0)	153 (34.4)	0.255	173 (47.8)	145 (40.1)	0.036	3 (3.0)	8 (9.6)	0.068
Underlying comorbidities	411 (88.8)	413 (92.8)	0.036	323 (89.2)	337 (93.1)	0.067	88 (87.1)	76 (91.6)	0.336
Cardiovascular disease	293 (63.3)	303 (68.1)	0.127	233 (64.4)	250 (69.1)	0.180	60 (59.4)	53 (63.9)	0.537
Diabetes mellitus	188 (40.6)	188 (42.2)	0.615	146 (40.3)	153 (42.3)	0.597	42 (41.6)	35 (42.2)	0.936
Malignancy	55 (11.9)	95 (21.3)	< 0.001	44 (12.2)	84 (23.2)	< 0.001	11 (10.9)	11 (13.3)	0.623
Kidney disease	55 (11.9)	66 (14.8)	0.191	45 (12.4)	59 (16.3)	0.138	10 (9.9)	7 (8.4)	0.732
Respiratory disease	40 (8.6)	68 (15.3)	0.002	33 (9.1)	57 (15.7)	0.007	7 (6.9)	11 (13.3)	0.151
Liver disease	24 (5.2)	31 (7.0)	0.260	22 (6.1)	21 (5.8)	0.875	2 (2.0)	10 (12.0)	0.006
Immunosuppressant	2 (0.4)	14 (3.1)	0.002	1 (0.3)	14 (3.9)	< 0.001	1 (1.0)	0 (0.0)	1.000
Others	158 (34.1)	88 (19.8)	< 0.001	122 (33.7)	68 (18.8)	< 0.001	36 (35.6)	20 (24.1)	0.090

ACH, acute care hospital; LTCF, long-term care facility; CPE, carbapenemase-producing Enterobacterales; CRE, carbapenem-resistant Enterobacterales; ICU, intensive care unit; MDRO, multi-drug resistant organism; MRAB, multidrug-resistant *Acinetobacter baumannii*; MRPA multidrug-resistant *Pseudomonas aeruginosa*; MRSA, methicillin-resistant *Staphylococcus aureus*; PPI, proton pump inhibitor; SD, standard deviation; VRE, vancomycin-resistant Enterococci

[a]Values are means ± SD

Data are presented as No. (%) unless indicated otherwise

Patient-level epidemiologic risk profile for CPE colonization

Compared with non-colonized controls, CPE-colonized patients had more frequent healthcare exposure within the preceding year, including prior hospitalization (77.1% vs. 55.1%), ICU admission (28.1% vs. 9.7%), prior CPE colonization or infection (12.1% vs. 0.6%), and prior room sharing with a CPE-colonized or infected patient (11.5% vs. 1.5%) (all $P < 0.001$). Recent antimicrobial exposure within the previous 3 months was more common among colonized patients (60.2% vs. 17.7%, $P < 0.001$), including exposure to carbapenems, glycopeptides, cephalosporins, and penicillins. Use of gastric acid suppressants for ≥ 3 days within the previous 3 months was also more frequent among colonized patients (52.4% vs. 16.0%, $P < 0.001$). Indwelling device use and surgery within the previous 3 months were both more common among colonized patients than among non-colonized controls (56.4% vs. 16.6% and 20.9% vs. 8.6%, respectively; both $P < 0.001$). Respiratory secretions, wound drainage, and diarrhea were more common among colonized patients. Malignancy and chronic respiratory disease were also more prevalent in the CPE-colonized group, (Table 1).

In multivariable logistic regression analysis (Table 2), prior CPE colonization or infection within the past year (aOR 14.16, 95% CI 4.02–49.84, $P < 0.001$), prior room sharing with a CPE-colonized or infected patient (aOR 3.38, 95% CI 1.24–9.20, $P = 0.017$), and prior hospitalization within 1 year (aOR 1.57, 95% CI 1.08–2.29, $P = 0.018$) were independently associated with CPE colonization. Antimicrobial- and medication-related predictors included recent exposure to carbapenems (aOR 2.60, 95% CI 1.25–5.42), glycopeptides (aOR 6.79, 95% CI 1.44–31.97), penicillins (aOR 1.90, 95% CI 1.04–3.41), and PPIs (aOR 1.81, 95% CI 1.09–3.00). Additionally, clinical factors independently associated with colonization included recent indwelling device use (aOR 2.35, 95% CI 1.47–3.74, $P < 0.001$), and the presence of wound drainage (aOR 3.56, 95% CI 1.11–11.37, $P = 0.032$) or respiratory secretions (aOR 2.35, 95% CI 1.18–4.66, $P = 0.015$) at screening. In ACH-specific analyses, independent predictors of CPE colonization included hospitalization within the previous year (aOR 1.85, 95% CI 1.21–2.82, $P = 0.004$), recent PPI use (aOR 3.01, 95% CI 1.39–6.49, $P = 0.005$), recent indwelling device use (aOR 3.51, 95% CI 1.85–6.65, $P < 0.001$), and respiratory secretions at screening (aOR 3.32, 95% CI 1.41–7.73, $P = 0.006$) (Table 2; Fig. 1).

Table 2
Multivariable logistic regression analysis of factors associated with CPE colonization

Factors[a]	**Overall**		**ACH**		**LTCF**	
	aOR (95% CI)	***P* value**	**aOR (95% CI)**	***P* value**	**aOR (95% CI)**	***P* value**
Age[a]	1.01 (0.99–1.02)	0.277	1.01 (1.00-1.03)	0.088	0.99 (0.96–1.02)	0.514
Male gender	0.86 (0.91–1.20)	0.367	0.94 (0.63–1.40)	0.769	0.47 (0.21–1.03)	0.058
Hospitalization within 1yr	1.57 (1.08–2.29)	**0.018**	1.85 (1.21–2.82)	**0.004**	1.29 (0.36–4.63)	0.692
ICU admission within 1yr	0.73 (0.3–1.24)	0.242	0.74 (0.37–1.44)	0.370	-	-
Prior CPE colonization within 1yr	14.16 (4.02–49.84)	**< 0.001**	3.58 (0.86–14.98)	0.080	-	-
Room-sharing with CPE pt. within 1yr	3.38 (1.24–9.20)	0.017	2.55 (0.79–8.24)	0.117	-	-
Prior non-CRE MDRO infection within 1yr	1.62 (0.23–11.63)	0.632	2.54 (0.27–24.34)	0.419	-	-
Colonization with non-CRE MDRO						
MRAB	2.69 (0.35–20.48)	0.338	1.38 (0.16–12.04)	0.773	-	-
MRPA	1.97 (0.29–13.19)	0.485	1.29 (0.17–10.08)	0.809	-	-
MRSA	0.81 (0.12–5.58)	0.834	0.89 (0.09–9.07)	0.922	-	-
VRE	4.33 (0.53–35.19)	0.170	3.04 (0.33–27.91)	0.325	-	-
Previous antibiotic exposure						

aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio

[a] All variables with *P* value < 0.1 on univariable analysis were included in a multivariable logistic regression model.

Factors[a]	Overall		ACH		LTCF	
	aOR (95% CI)	*P* value	aOR (95% CI)	*P* value	aOR (95% CI)	*P* value
Cephalosporins	1.07 (0.65–1.76)	0.800	0.99 (0.48–2.05)	0.979	-	-
Penicillins	1.90 (1.04–3.41)	0.036	2.22 (0.90–5.46)	0.082	-	-
Quinolones	0.79 (0.41–1.50)	0.467	0.79 (0.31–1.98)	0.608	-	-
Carbapenems	2.60 (1.25–5.42)	**0.011**	2.31 (0.91–5.87)	0.080	-	-
Glycopeptides	6.79 (1.4-31.97)	**0.015**	6.16 (0.71–53.80)	0.100	-	-
Polymixin E	-	-	-	-	-	-
Others	1.44 (0.76–2.74)	0.267	1.41 (0.59–3.36)	0.438	-	-
Gastric acid suppressant use within 3mon (≥ 3d)						
PPIs	1.81 (1.09-3.00)	0.021	3.01 (1.39–6.49)	**0.005**	-	-
H2 receptor blockers	1.29 (0.64–2.59)	0.474	1.81 (0.65–5.04)	0.256	-	-
Antacids	1.00 (0.46–2.17)	0.995	0.62 (0.22–1.76)	0.368	-	-
P-CABs	0.80 (0.30–2.13)	0.659	0.50 (0.14–1.74)	0.276	-	-
Use of systemic steroid	1.31 (0.45–3.79)	0.625	0.61 (0.15–2.48)	0.494	2.06 (0.42–9.98)	0.370

aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio

[a] All variables with *P* value < 0.1 on univariable analysis were included in a multivariable logistic regression model.

Factors[a]	Overall		ACH		LTCF	
	aOR (95% CI)	*P* value	aOR (95% CI)	*P* value	aOR (95% CI)	*P* value
Use of indwelling device	2.35 (1.47–3.74)	**< 0.001**	3.51 (1.85–6.65)	**< 0.001**	2.07 (0.78–5.46)	0.143
Surgery within 3mon	0.82 (0.47–1.44)	0.494	1.58 (0.66–3.78)	0.300	-	-
Current symptoms						
Diarrhea	2.12 (0.91–4.94)	0.083	1.73 (0.65–4.57)	0.274	-	-
Wound drainage	3.56 (1.11–11.37)	**0.032**	3.64 (0.85–15.51)	0.081	-	-
Respiratory secretion	2.35 (1.18–4.66)	**0.015**	3.32 (1.41–7.73)	0.006	2.35 (0.67–8.30)	0.184
Underlying comorbidities						
Respiratory disease	1.22 (0.71–2.09)	0.465	0.99 (0.54–1.84)	0.980	-	-
Liver diseases	-	-	-	-	13.43 (2.22–81.14)	**0.005**
Other comorbidities, excluding major chronic diseases	0.29 (0.19–0.43)	**< 0.001**	0.28 (0.17–0.45)	**< 0.001**	0.27 (0.10–0.74)	**0.010**

aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio

[a] All variables with *P* value < 0.1 on univariable analysis were included in a multivariable logistic regression model.

Regional genomic epidemiology of CPE isolates

Among 242 genome-sequenced CPE isolates, genome-based species assignment demonstrated predominance of *K. pneumoniae*, followed by *E. coli*, whereas other Enterobacterales species were detected at substantially lower frequencies across participating facilities (Supplementary Fig. 2). Clinical and genome-based species assignments were largely concordant, with discrepancies occurring primarily within the *K. oxytoca* complex, particularly the reclassification of clinically identified *K. oxytoca* isolates as *K. michiganensis* (Supplementary Fig. 3). AMR profiling of 107 high-quality genome assemblies demonstrated

widespread multidrug resistance, with ESBL and carbapenemase determinants detected in nearly all *K. pneumoniae* assemblies (Supplementary Fig. 4).

Genome-wide phylogenetic analysis of *Klebsiella* spp. and *E. coli* isolates revealed clear species-level clustering across the regional surveillance network (Fig. 2). The analyzed genomes separated into major *E. coli* and *Klebsiella* clades, with *K. pneumoniae* representing the dominant species within the *Klebsiella* group. Multiple sequence types, K/O-locus profiles, virulence-associated loci, and AMR gene categories were distributed throughout the phylogeny, indicating genomic diversity among circulating CPE isolates.

Regional dissemination patterns and genetic connectivity of K. pneumoniae

Genome-based typing of 155 *K. pneumoniae* isolates identified multiple sequence types across facilities and regions (Fig. 3a). ST307 was the predominant lineage, accounting for 106 isolates (68.4%), and was detected in CCH, CCN, CCT, DHN, GNA, SCW, and WJC. Its distribution spanned multiple regions and was detected in both ACH and LTCF settings. Additional sequence types, including ST16, ST11, ST15, ST256, ST48, ST12, ST17, and ST23-1LV, were observed at lower frequencies. Carbapenemase profiling demonstrated marked predominance of KPC, which was detected in 134 of 155 isolates (86.5%), whereas OXA-, NDM-, and VIM-producing isolates were identified less frequently. ST307 and ST11 were predominantly associated with KPC production, whereas ST16 was primarily associated with OXA-48 variant (Fig. 3a). A single ST23-1LV isolate carrying *blaKPC* and multiple hypervirulence-associated loci was identified in SCW.

Capsular and O-antigen locus distributions were examined among *K. pneumoniae* isolates grouped by geographic region (Fig. 3b, c). K-locus profiles demonstrated broader diversity than O-locus profiles across all regions. Gangneung, Donghae, and Sokcho reached high cumulative prevalence after relatively few K and O loci, whereas Chuncheon and Wonju showed more gradual cumulative prevalence curves, indicating greater locus diversity. Overall, O-locus distributions were more restricted than K-locus distributions throughout the regional network.

Genetically linked *K. pneumoniae* isolate pairs were identified using the predefined SNP-distance threshold (Fig. 4). Six sequence types met the linkage criterion, with ST307 accounting for the largest number of within-facility and between-facility connections. Between-facility ST307 links were observed primarily among CCH, GNA, and DHN, whereas additional links involved several other facilities. ST16 also demonstrated interfacility connectivity across western and eastern Gangwon.

Discussion

In this multicenter study integrating epidemiologic analysis with regional genomic surveillance across interconnected ACHs and LTCFs, we identified patient-level factors independently associated with CPE colonization and demonstrated that regional CPE dissemination was characterized by predominance of KPC-producing *K. pneumoniae* ST307 and interfacility genetic connectivity. Epidemiologic analyses defined a risk profile relevant to targeted admission screening, whereas genomic analyses revealed a regionally distributed CPE population dominated by *K. pneumoniae* and widespread circulation of a major high-risk clone across multiple institutions. Together, these findings highlight the complementary value of epidemiologic and

genomic surveillance for understanding CPE dissemination within regional healthcare networks and informing coordinated prevention strategies.

Our epidemiologic findings provide a basis for risk-based admission screening within regional CPE surveillance programs. Prior CRE colonization or infection, prior room sharing with a CPE-colonized or infected patient, recent antimicrobial or PPI exposure, recent indwelling device use, and the presence of wound drainage or respiratory secretions at the time of screening were independently associated with CPE colonization, indicating that colonization is concentrated among patients with substantial healthcare exposure and ongoing care needs. Because several of these risk factors may only be identifiable through information originating from other healthcare facilities, effective implementation of targeted screening strategies requires interfacility information sharing within regional healthcare networks [18, 19].

Recent exposure to carbapenems, glycopeptides, penicillins, and PPIs was independently associated with CPE colonization. The associations observed with antimicrobial exposure are consistent with the concept that disruption of the intestinal microbiota may reduce colonization resistance and facilitate expansion of resistant Enterobacterales [20]. Notably, PPI use remained independently associated with CPE colonization after adjustment for other healthcare-associated factors. Beyond gastric acid suppression, PPIs have been associated with alterations in gut microbial composition and diversity, which may further impair colonization resistance and promote intestinal persistence of multidrug-resistant organisms [21, 22]. Given the widespread use of both antimicrobials and acid-suppressive therapy in ACHs and LTCFs, these findings support antimicrobial stewardship and more judicious use of PPIs as potentially modifiable components of CPE prevention strategies.

Genome-based species assignment provided additional taxonomic resolution beyond routine clinical identification and improved characterization of circulating CPE populations within the regional healthcare network. Consistent with previous studies, discordant assignments were observed among closely related *Klebsiella* taxa, highlighting the limitations of conventional species identification for genomic surveillance applications [23, 24].These findings support the complementary role of genome-based species assignment in improving interpretation of species distribution and population structure during regional CPE surveillance [13].

Genomic surveillance provided insights into regional CPE dissemination beyond those obtainable through conventional epidemiologic surveillance alone. The predominance of KPC-producing *K. pneumoniae* ST307 across multiple healthcare facilities, together with the observed interfacility SNP-based genetic linkage patterns, suggests that dissemination of a successful high-risk lineage contributed substantially to the regional CPE burden. ST307 has emerged as a globally disseminated multidrug-resistant clone associated with healthcare-associated transmission [25–27], and its widespread distribution across geographically separated facilities in the present study supports its importance within the regional epidemiology of CPE. The concentration of genetically linked isolates and comparatively restricted K-locus diversity in the Yeongdong region further suggest that a limited number of successful lineages may have contributed disproportionately to local dissemination [27, 28]. Notably, genetically linked isolate pairs were also identified between facilities in eastern and western Gangwon, indicating that regional circulation extended beyond geographically localized clusters. Although direct transmission pathways could not be established, these findings are

consistent with previous studies demonstrating that interconnected healthcare networks and patient sharing may facilitate dissemination of carbapenem-resistant *K. pneumoniae* across institutional boundaries [29–31]. Collectively, these observations highlight the value of genomic surveillance for identifying dominant regional lineages and characterizing dissemination patterns that may not be readily apparent through facility-level surveillance alone.

A notable finding was the identification of a KPC-producing ST23-1LV isolate carrying multiple virulence-associated loci. Although detected in only a single isolate, this observation is epidemiologically important because ST23-related lineages are strongly associated with hypervirulent *K. pneumoniae* and have increasingly been implicated in convergence events involving both antimicrobial resistance and hypervirulence determinants [32]. Such strains are of particular concern because they combine enhanced pathogenic potential with limited therapeutic options. While no evidence of regional dissemination was observed in the present study, detection of this isolate demonstrates the additional value of genomic surveillance beyond tracking dominant epidemic clones. Continued genomic monitoring may facilitate early recognition of uncommon but potentially high-consequence lineages before wider dissemination occurs within regional healthcare networks.

Taken together, our findings support the value of regional surveillance frameworks that integrate patient-level risk assessment with genomic surveillance across interconnected ACHs and LTCFs. Epidemiologic analyses identified risk factors that may inform targeted admission screening, whereas genomic analyses revealed dominant circulating lineages and interfacility genetic connectivity that would not have been apparent through institution-based surveillance alone. Because key risk factors such as prior CPE colonization and healthcare exposure often span multiple facilities, effective regional CPE prevention is likely to depend on interfacility communication and standardized sharing of colonization-related information. Although the present study was not designed to quantify LTCF-to-ACH transmission, inclusion of LTCFs within the surveillance network provided a broader perspective on regional CPE circulation and highlights the importance of coordinated surveillance strategies that extend beyond individual healthcare institutions.

Several limitations should be considered. First, the epidemiologic analyses were based on admission screening data collected within participating ACHs and LTCFs and may not be fully generalizable to other healthcare settings or regions. Second, genomic analyses were performed using analysis-specific subsets, and therefore findings related to AMR determinants, lineage distribution, and genetic linkage should be interpreted within the context of the analyzed populations rather than extrapolated to all CPE isolates. Third, although SNP-based genetic linkage analysis identified closely related isolates across facilities, available patient-transfer and healthcare-network data were insufficient for comprehensive integration with genomic findings. Consequently, transmission pathways and the relative contribution of individual facilities to regional dissemination could not be formally evaluated [29, 30, 33]. Future studies integrating genomic surveillance with detailed patient-transfer and healthcare-network analyses may provide a more comprehensive understanding of regional CPE dissemination dynamics. Finally, the KPC-producing ST23-1LV isolate carrying virulence-associated loci represented a single observation and should be interpreted as a surveillance finding rather than evidence of regional emergence.

Conclusions

Integrated epidemiologic and genomic surveillance across interconnected ACHs and LTCFs identified both patient-level risk factors and dominant circulating lineages associated with regional CPE dissemination. Risk-based admission screening identified patient populations most likely to benefit from targeted surveillance, whereas genomic analyses revealed regional dissemination patterns and interfacility genetic connectivity that would not have been apparent through institution-based surveillance alone. Together, these findings suggest that effective regional CPE prevention requires approaches that extend beyond individual healthcare institutions. Coordinated surveillance strategies integrating risk-based screening, interfacility information sharing, and ongoing genomic surveillance may strengthen regional CPE prevention and support broader antimicrobial resistance control efforts.

Abbreviations

ACH
acute-care hospital
AMR
antimicrobial resistance
aOR
adjusted odds ratio
CI
confidence interval
CPE
carbapenemase-producing Enterobacterales
CRE
carbapenem-resistant Enterobacterales
ESBL
extended-spectrum beta-lactamase
KPC
Klebsiella pneumoniae carbapenemase
LTCF
long-term care facility
NDM
New Delhi metallo-β-lactamase
OXA
oxacillinase
PPI
proton pump inhibitor
SNP
single-nucleotide polymorphism
ST
sequence type
VIM
Verona integron-encoded metallo-β-lactamase

WGS
whole-genome sequencing

Declarations

Ethics approval and consent to participate

This study was reviewed and approved by the Institutional Review Board of Hallym University Chuncheon Sacred Heart Hospital (CHUNCHEON IRB 2024-05-005). Written informed consent was waived because the study involved minimal risk.

Consent for publication

Not applicable.

Availability of data and materials

The genome sequence data generated in this study have been deposited in the National Center for Biotechnology Information (NCBI) under BioProject accession number PRJNA1465574. The corresponding BioSample accession numbers and isolate-level metadata are provided in Supplementary Table 1. The datasets supporting the genomic analyses, including genome-based species assignment, antimicrobial resistance gene classification, sequence type, carbapenemase type, K/O locus profiles, and genetic linkage summary data, are included within the article and its supplementary information files. De-identified epidemiologic summary data supporting the findings of this study are included in the article and supplementary information files. Individual-level clinical data are not publicly available because of patient privacy and institutional ethical restrictions, but may be available from the corresponding author upon reasonable request and subject to institutional approval.

Competing interests

The authors have no potential conflicts of interest to disclose.

Funding

This research was supported by the Hallym University Research Fund and the Korea National Institute of Infectious Diseases, Korea National Institute of Health [2024-ER2208-01].

Authors' contributions

YKK, EHS, and SSL conceived and designed the study. YS, WSO, EHS, YKK, and SSL coordinated the multicenter surveillance network and clinical data collection. YS, YKK, SJ, and DHK performed the epidemiologic and statistical analyses. IL performed the genomic and bioinformatic analyses, data visualization, and interpretation of genomic surveillance findings. YS and IL drafted the manuscript. All authors contributed to data interpretation, critically revised the manuscript, and read and approved the final version. SSL supervised the study. YKK, EHS, and SSL provided overall project oversight.

Acknowledgements

We thank the infection prevention and control teams and healthcare personnel at all participating ACHs and LTCFs for their contributions to patient screening, surveillance activities, and clinical data collection throughout the CRISIS-CPE project. We are particularly grateful to Soyoung Park, RN, for her assistance with isolate collection, data management, and coordination of whole-genome sequencing–based genomic surveillance across participating institutions.

The authors used ChatGPT (OpenAI, San Francisco, CA, USA) to assist with language editing and improvement of manuscript readability. The authors reviewed, revised, and approved all content and take full responsibility for the accuracy and integrity of the final manuscript.

This work was presented in part as a poster presentation at ASM Microbe 2026.

References

1. Nordmann P, Cuzon G, Naas T. The real threat of Klebsiella pneumoniae carbapenemase-producing bacteria. Lancet Infect Dis. 2009;9:228–36.
2. Temkin E, Adler A, Lerner A, Carmeli Y. Carbapenem-resistant Enterobacteriaceae: biology, epidemiology, and management. Ann N Y Acad Sci. 2014;1323:22–42.
3. van Loon K, Voor in 't holt AF, Vos MC. A systematic review and meta-analyses of the clinical epidemiology of carbapenem-resistant Enterobacteriaceae. Antimicrob Agents Chemother. 2018;62:e01730-17.
4. Lin MY, Lyles-Banks RD, Lolans K, Hines DW, Spear JB, Petrak R, et al. The importance of long-term acute care hospitals in the regional epidemiology of Klebsiella pneumoniae carbapenemase–producing Enterobacteriaceae. Clin Infect Dis. 2013;57:1246–52.
5. Won SY, Munoz-Price LS, Lolans K, Hota B, Weinstein RA, Hayden MK, et al. Emergence and rapid regional spread of Klebsiella pneumoniae carbapenemase–producing Enterobacteriaceae. Clin Infect Dis. 2011;53:532–40.
6. Pérez-Galera S, Bravo-Ferrer JM, Paniagua M, Kostyanev T, de Kraker MEA, Feifel J, et al. Risk factors for infections caused by carbapenem-resistant Enterobacterales: an international matched case-control-control study (EURECA). EClinicalMedicine. 2023;57:101871.
7. Zhou H, Buetti N, Pérez-Galera S, Bravo-Ferrer J, Gutiérrez-Gutiérrez B, Paniagua-García M, et al. Risk factors for bloodstream infections due to carbapenem-resistant Enterobacterales: a nested case-control-control study. J Antimicrob Chemother. 2024;79:2132–41.
8. Lane CR, Brett J, Schultz M, Gorrie CL, Stevens K, Cameron DR, et al. Search and contain: impact of an integrated genomic and epidemiological surveillance and response program for control of carbapenemase-producing Enterobacterales. Clin Infect Dis. 2021;73:e3912–20.
9. Marimuthu K, Venkatachalam I, Koh V, Harbarth S, Perencevich E, Cherng BPZ, et al. Whole genome sequencing reveals hidden transmission of carbapenemase-producing Enterobacterales. Nat Commun. 2022;13:3052.

10. Bolger AM, Lohse M, Usadel B. Trimmomatic: a flexible trimmer for Illumina sequence data. Bioinformatics. 2014;30:2114–20.
11. Wick RR, Judd LM, Gorrie CL, Holt KE. Unicycler: resolving bacterial genome assemblies from short and long sequencing reads. PLoS Comput Biol. 2017;13:e1005595.
12. Parks DH, Imelfort M, Skennerton CT, Hugenholtz P, Tyson GW. CheckM: assessing the quality of microbial genomes recovered from isolates, single cells, and metagenomes. Genome Res. 2015;25:1043–55.
13. Chaumeil P-A, Mussig AJ, Hugenholtz P, Parks DH. GTDB-Tk: a toolkit to classify genomes with the Genome Taxonomy Database. Bioinformatics. 2020;36:1925–7.
14. Feldgarden M, Brover V, Gonzalez-Escalona N, Frye JG, Haendiges J, Haft DH, et al. AMRFinderPlus and the Reference Gene Catalog facilitate examination of the genomic links among antimicrobial resistance, stress response, and virulence. Sci Rep. 2021;11:12728.
15. Lam MMC, Wick RR, Watts SC, Cerdeira LT, Wyres KL, Holt KE. A genomic surveillance framework and genotyping tool for Klebsiella pneumoniae and its related species complex. Nat Commun. 2021;12:4188.
16. Shakya M, Ahmed SA, Davenport KW, Flynn MC, Lo C-C, Chain PSG. Standardized phylogenetic and molecular evolutionary analysis applied to species across the microbial tree of life. Sci Rep. 2020;10:1723.
17. David S, Reuter S, Harris SR, Glasner C, Feltwell T, Argimon S, et al. Epidemic of carbapenem-resistant Klebsiella pneumoniae in Europe is driven by nosocomial spread. Nat Microbiol. 2019;4:1919–29.
18. Magiorakos A, Burns K, Rodríguez Baño J, Borg M, Daikos G, Dumpis U, et al. Infection prevention and control measures and tools for the prevention of entry of carbapenem-resistant Enterobacteriaceae into healthcare settings: guidance from the European Centre for Disease Prevention and Control. Antimicrob Resist Infect Control. 2017;6:113.
19. World Health Organization. Guidelines for the prevention and control of carbapenem-resistant Enterobacteriaceae, Acinetobacter baumannii and Pseudomonas aeruginosa in health care facilities. Geneva: World Health Organization; 2017.
20. Palacios-Baena ZR, Giannella M, Manissero D, Rodríguez-Baño J, Viale P, Lopes S, et al. Risk factors for carbapenem-resistant Gram-negative bacterial infections: a systematic review. Clin Microbiol Infect. 2021;27:228–35.
21. Lee I, Jo J-W, Woo H-J, Suk KT, Lee SS, Kim B-S. Proton pump inhibitors increase the risk of carbapenem-resistant Enterobacteriaceae colonization by facilitating the transfer of antibiotic resistance genes among bacteria in the gut microbiome. Gut Microbes. 2024;16:2341635.
22. Willems RP, van Dijk K, Ket JC, Vandenbroucke-Grauls CM. Evaluation of the association between gastric acid suppression and risk of intestinal colonization with multidrug-resistant microorganisms: a systematic review and meta-analysis. JAMA Intern Med. 2020;180:561–71.
23. Long SW, Linson SE, Ojeda Saavedra M, Cantu C, Davis JJ, Brettin T, et al. Whole-genome sequencing of human clinical Klebsiella pneumoniae isolates reveals misidentification and misunderstandings of Klebsiella pneumoniae, Klebsiella variicola, and Klebsiella quasipneumoniae. mSphere. 2017;2:e00290–17.

24. Yang J, Long H, Hu Y, Feng Y, McNally A, Zong Z. Klebsiella oxytoca complex: update on taxonomy, antimicrobial resistance, and virulence. Clin Microbiol Rev. 2022;35:e00006–21.
25. Logan LK, Weinstein RA. The epidemiology of carbapenem-resistant Enterobacteriaceae: the impact and evolution of a global menace. J Infect Dis. 2017;215:S28–36.
26. Pitout JD, Nordmann P, Poirel L. Carbapenemase-producing Klebsiella pneumoniae, a key pathogen set for global nosocomial dominance. Antimicrob Agents Chemother. 2015;59:5873–84.
27. Wyres KL, Lam MMC, Holt KE. Population genomics of Klebsiella pneumoniae. Nat Rev Microbiol. 2020;18:344–59.
28. Lam MMC, Wick RR, Judd LM, Holt KE, Wyres KL. Kaptive 2.0: updated capsule and lipopolysaccharide locus typing for the Klebsiella pneumoniae species complex. Microb Genom. 2022;8:e000800.
29. Luterbach CL, Chen L, Komarow L, Ostrowsky B, Kaye KS, Hanson B, et al. Transmission of carbapenem-resistant Klebsiella pneumoniae in US hospitals. Clin Infect Dis. 2023;76:229–37.
30. Spencer MD, Winglee K, Passaretti C, Earl AM, Manson AL, Mulder HP, et al. Whole genome sequencing detects inter-facility transmission of carbapenem-resistant Klebsiella pneumoniae. J Infect. 2019;78:187–99.
31. Tadese BK, Fujimoto K, DeSantis SM, Mgbere O, Darkoh C. Regional transmission patterns of carbapenemase-producing Enterobacterales: a healthcare network analysis. Infect Control Hosp Epidemiol. 2023;44:453–9.
32. Lam MMC, Wyres KL, Duchêne S, Wick RR, Judd LM, Gan Y-H, et al. Population genomics of hypervirulent Klebsiella pneumoniae clonal-group 23 reveals early emergence and rapid global dissemination. Nat Commun. 2018;9:2703.
33. Lee AS, Dolan L, Jenkins F, Crawford B, van Hal SJ. Active surveillance of carbapenemase-producing Enterobacterales using genomic sequencing for hospital-based infection control interventions. Infect Control Hosp Epidemiol. 2024;45:137–43.

Figures

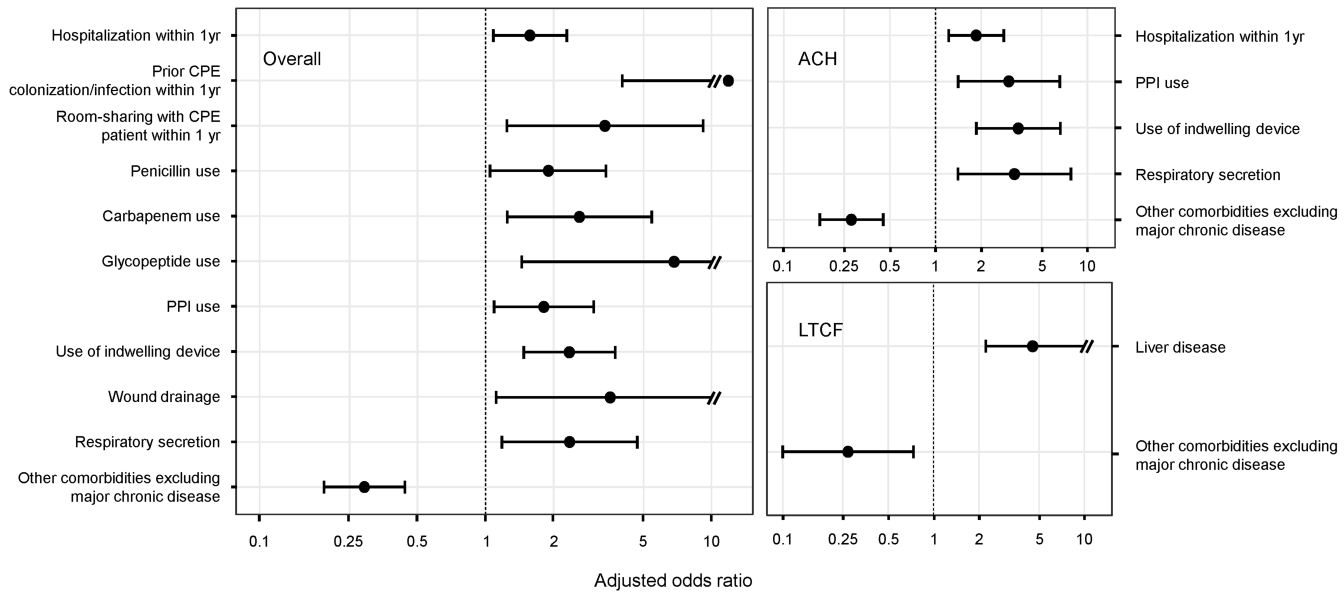


Figure 1

Adjusted risk factors for CPE colonization overall and by facility type. Forest plots show adjusted odds ratios and corresponding 95% confidence intervals derived from *multivariable logistic regression analyses* for the overall study population, acute-care hospitals, and long-term care facilities. Black dots indicate adjusted odds ratios, and horizontal lines indicate 95% confidence intervals. The vertical dotted line indicates an adjusted odds ratio of 1. The x-axis is presented on a logarithmic scale and is displayed up to an adjusted odds ratio of 10. Diagonal double-slash marks indicate point estimates or upper confidence limits exceeding the displayed upper x-axis limit. ACH, acute-care hospital; CPE, carbapenemase-producing Enterobacterales; CRE, carbapenem-resistant Enterobacterales; LTCF, long-term care facility; PPI, proton pump inhibitor.

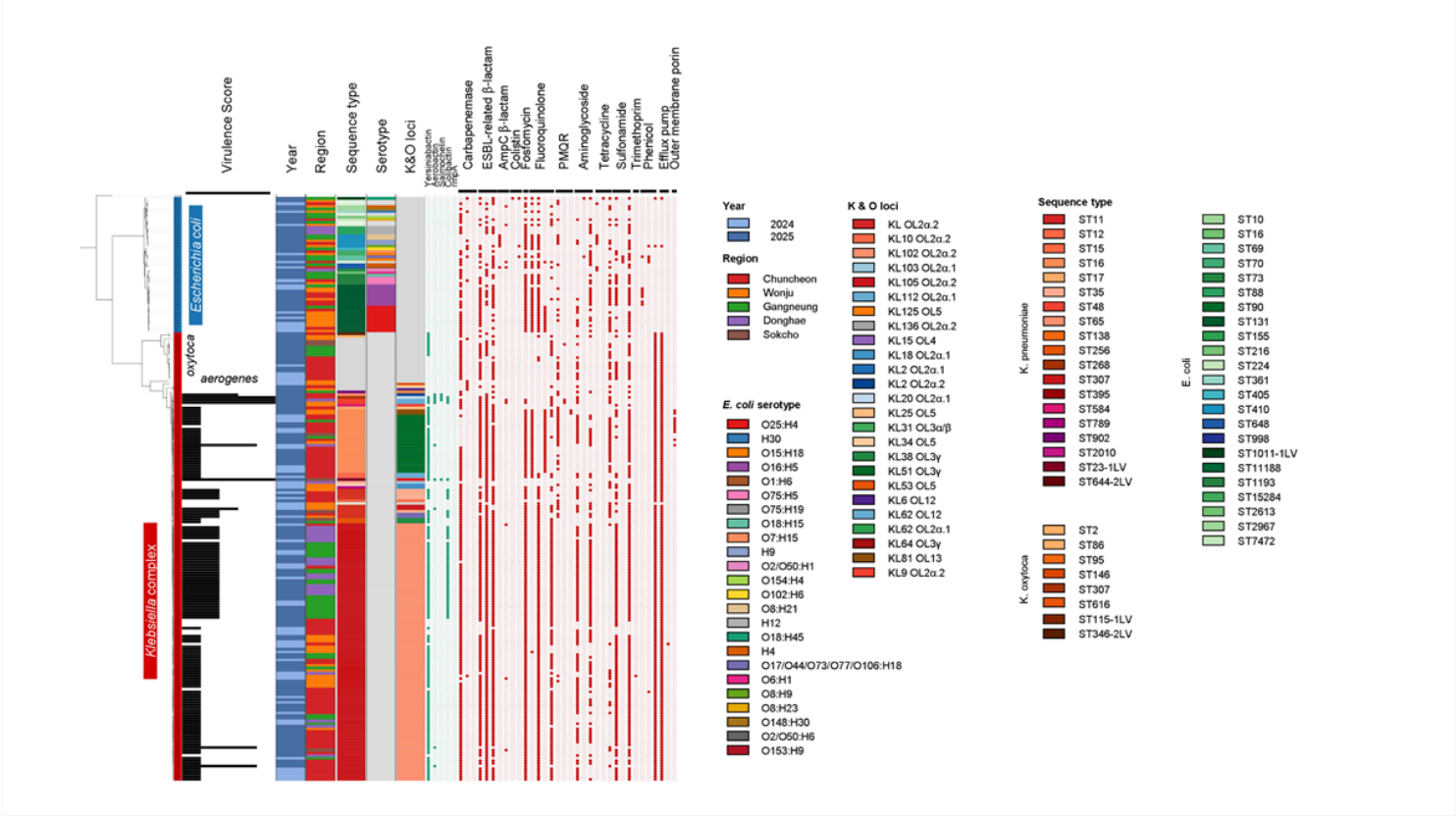


Figure 2

Integrated phylogenetic and genomic profiles of *Klebsiella* isolates and *E. coli* isolates. A core-genome single-nucleotide polymorphism phylogeny is shown on the left, with isolates grouped into *Klebsiella* and *E. coli*, indicated by the adjacent taxonomic strip. Horizontal black bars indicate virulence scores. Annotation tracks display, from left to right, year of isolation, geographic region, sequence type, serotype for *E. coli*or K and O loci for *Klebsiella*isolates, virulence-associated loci, carbapenemase and antimicrobial resistance categories. Colored tiles indicate the corresponding annotation category for each isolate, as defined in the figure keys. Turquoise tiles indicate the presence of virulence-associated loci, including yersiniabactin, aerobactin, salmochelin, colibactin, and *rmpA*. Red tiles indicate the presence of one or more determinants belonging to the indicated carbapenemase or antimicrobial resistance category. Grey tiles indicate unavailable or undetermined information. AMR, antimicrobial resistance; ESBL, extended-spectrum beta-lactamase.

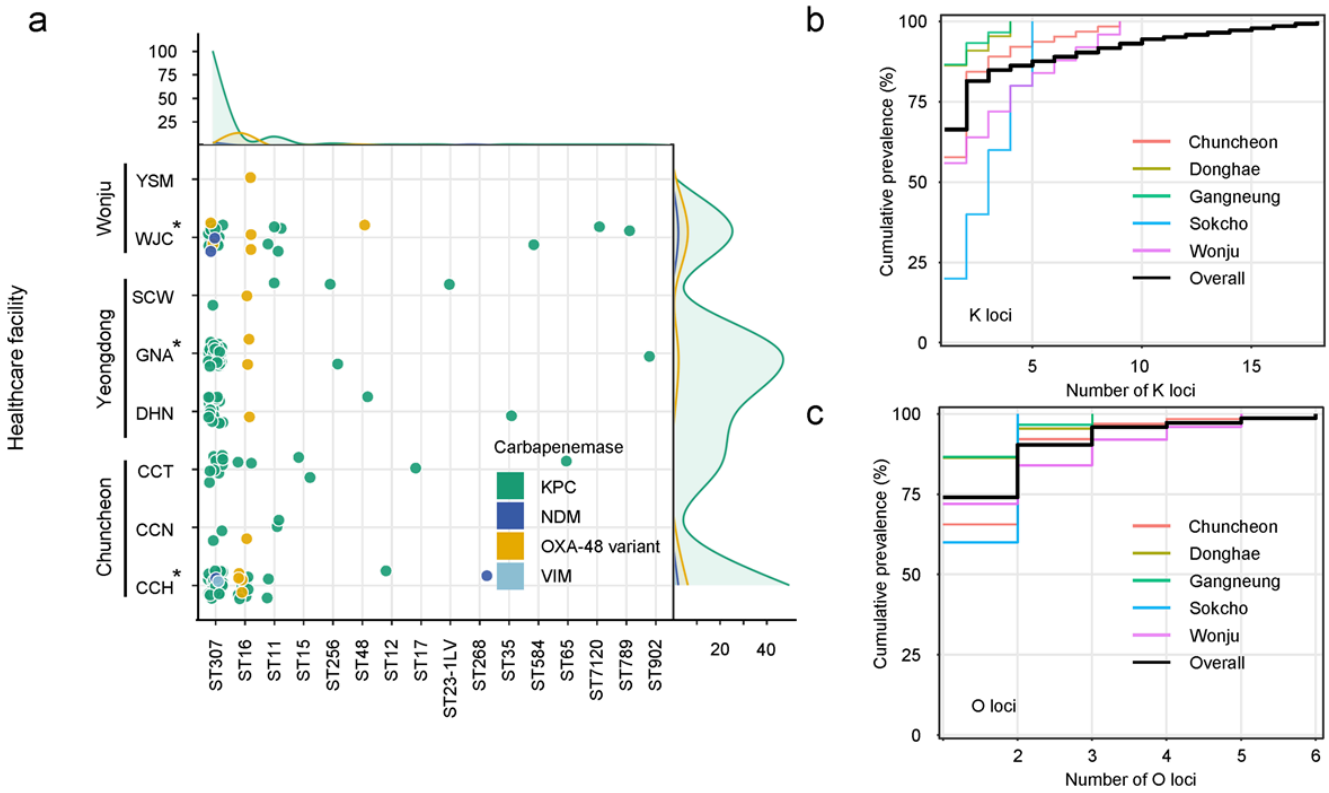


Figure 3

Regional distribution, carbapenemase profiles, and K/O locus diversity of *K. pneumoniae* isolates. a. Distribution of *K. pneumoniae* isolates according to healthcare facility and sequence type. Each dot represents an individual isolate, and dot colors indicate the detected carbapenemase family. Facilities are grouped by geographic region. The upper and right marginal curves show isolate counts across sequence types and healthcare facilities, respectively, stratified by carbapenemase family. b. Regional cumulative prevalence curves for K loci. c. Regional cumulative prevalence curves for O loci. For each region, K and O loci were ranked in descending order of frequency, and the curves indicate the cumulative proportion of isolates covered as successive loci were added. Black curves indicate cumulative prevalence calculated across all included *K. pneumoniae* isolates. Isolates with undetermined K or O loci were excluded from the corresponding cumulative prevalence analysis. NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; ST, sequence type; VIM, Verona integron-encoded metallo-β-lactamase. CCH, Hallym University Chuncheon Sacred Heart Hospital; CCN, Chuncheon Recuperation Hospital, CCT, Chuncheon Thomas Convalescent Hospital; GNA, Gangneung Asan Hospital; WJC, Wonju Severance Christian Hospital. Asterisks indicate ACHs.

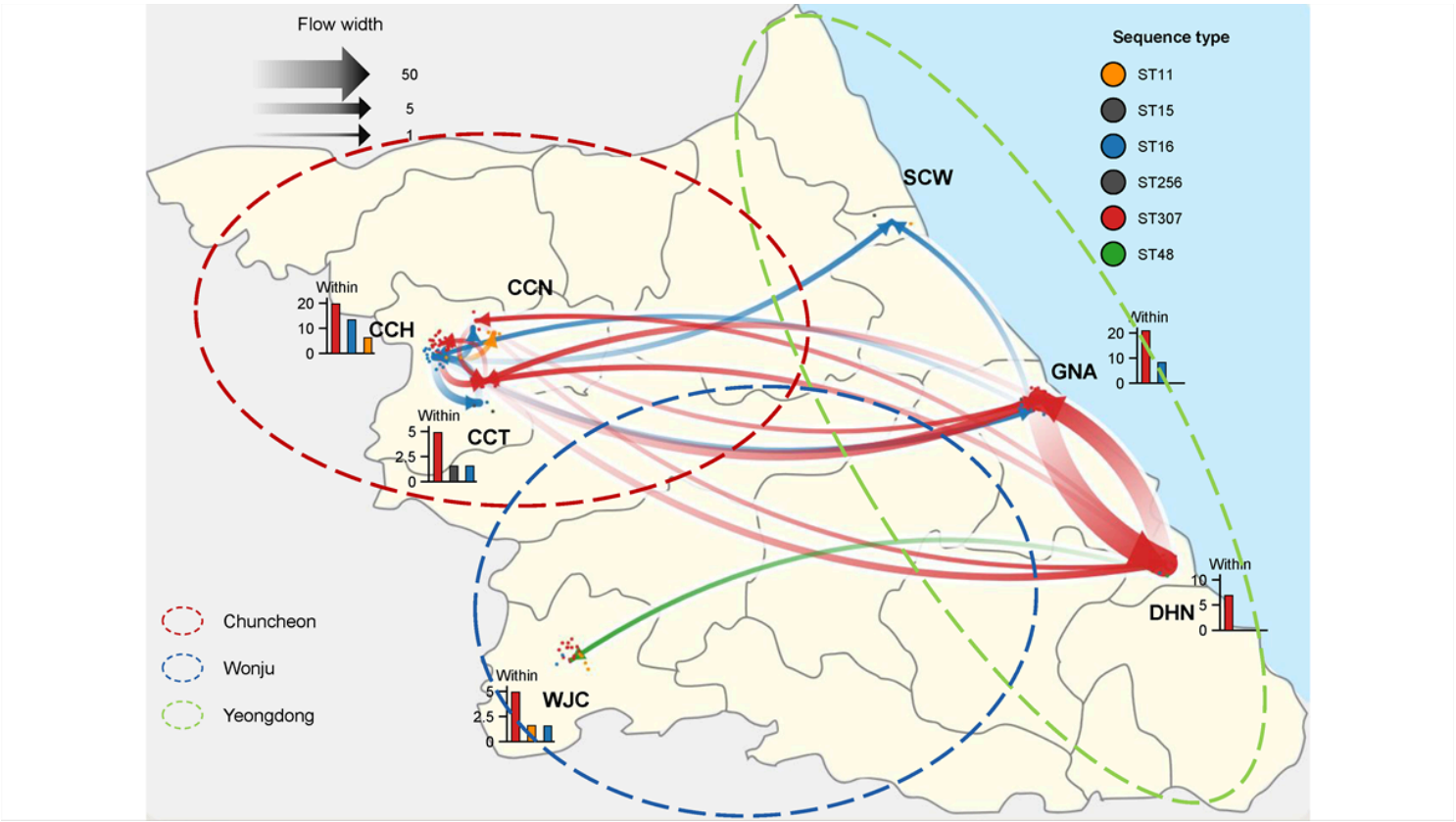


Figure 4

Regional map of genetic linkage among *K. pneumoniae* isolates.Colored points indicate individual *K. pneumoniae* isolates at each healthcare facility, with point colors representing sequence type. Curved arrows indicate genetically linked isolate pairs between facilities, grouped by sequence type, and arrow width is proportional to the number of linked isolate pairs. Arrow direction follows collection-date order and is shown for temporal ordering only; it should not be interpreted as evidence of transmission direction. Insets labeled "Within" show the numbers of genetically linked isolate pairs identified within each facility, stratified by sequence type. Healthcare facilities are positioned approximately according to geographic location. Dashed ellipses indicate the Chuncheon, Wonju, and Yeongdong regional groups. CCH, Hallym University Chuncheon Sacred Heart Hospital; CCN, Chuncheon Recuperation Hospital, CCT, Chuncheon Thomas Convalescent Hospital; GNA, Gangneung Asan Hospital; WJC, Wonju Severance Christian Hospital; ST, sequence type.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementary.docx
- SupplementaryTable11.xlsx
- FigureS1.tiff
- FigureS2.tiff
- FigureS3.tiff

- FigureS4.tiff