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Risk of death in *Klebsiella pneumoniae* bloodstream infections is associated with specific phylogenetic lineages

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SUMMARY

Background: Klebsiella pneumoniae species complex (KpSC) bloodstream infections (BSIs) are associated with considerable morbidity and mortality, particularly in elderly and multimorbid patients. Multidrug-resistant (MDR) strains have been associated with poorer outcome. However, the clinical impact of KpSC phylogenetic lineages on BSI outcome is unclear.

Methods: In an 18-month nationwide Norwegian prospective study of KpSC BSI episodes in adults, we used whole-genome sequencing to describe the molecular epidemiology of KpSC, and multivariable Cox regression analysis including clinical data to determine adjusted hazard ratios (aHR) for death associated with specific genomic lineages.

Findings: We included 1078 BSI episodes and 1082 bacterial isolates from 1055 patients. The overall 30-day case-fatality rate (CFR) was 12.5%. Median patient age was 73.4, 61.7% of patients were male. Median

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Cohort
Multi-centre
Variicola

Charlson comorbidity score was 3. Klebsiella pneumoniae sensu stricto (Kp) (79.3%, n = 858/1082) and K. variicola (15.7%, n = 170/1082) were the dominating phylogroups. Global MDR-associated Kp clonal groups (CGs) were prevalent (25.0%, n = 270/1082) but 78.9% (n = 213/270) were not MDR, and 53.7% (n = 145/270) were community acquired. The major findings were increased risk for death within 30 days in monomicrobial BSIs caused by K. variicola (CFR 16.9%, n = 21; aHR 1.86, CI 1.10–3.17, p = 0.02), and global MDR-associated Kp CGs (CFR 17.0%, n = 36; aHR 1.52, CI 0.98–2.38, p = 0.06) compared to Kp CGs not associated with MDR (CFR 10.1%, n = 46).

Conclusion: Bacterial traits, beyond antimicrobial resistance, have a major impact on the clinical outcome of KpSC BSIs. The global spread of MDR-associated Kp CGs is driven by other mechanisms than antibiotic selection alone. Further insights into virulence determinants, and their association with phylogenetic lineages are needed to better understand the epidemiology of KpSC infection and clinical outcome.

Introduction

Klebsiella pneumoniae is a frequent cause of bloodstream infections (BSIs) in adults, particularly elderly with comorbidities. The 30-day case-fatality rate range between 10 and 20% in unselected cohorts.[1–5] Poor outcome is associated with increased age, comorbidities, and clinical presentations of pneumonia, neutropenic fever, or severe systemic inflammatory response (sepsis).[1,6,7]

Several virulence factors have been described for *K. pneumoniae*. Siderophores, colibactin, and capsule hyperexpression have been linked to hypervirulence (HV), which is associated with invasive disease, abscess development and metastatic infection.[8] However, most invasive isolates have few of these defined virulence determinants.[9–12] Although multiple bacterial genetic determinants have been linked to the progression from carriage to infection, as well as to clinical outcome, the underlying causal relationship is complex and not well understood.[6,13] Furthermore, infections with strains producing extended-spectrum β-lactamase- (ESBL) and carbapenemase have been associated with increased mortality in critically ill patients,[14,15] which is assumed to be caused by delayed appropriate antibiotic treatment.[14]

The *K. pneumoniae* species complex (KpSC) is comprised of seven phylogroups,[9] where the most prevalent in human clinical samples are *K. pneumoniae* sensu stricto (Kp) and *Klebsiella variicola*[3,10] where HV and multidrug resistance (MDR) are associated with specific Kp clonal groups (CGs).[8,9]

However, the clinical impact of KpSC phylogenetic lineage on invasive infections has not been thoroughly investigated, as bacterial identification methods in most studies have not reliably discerned between the phylogroups nor determined CGs.[16] Furthermore, most KpSC BSI studies have been either single centre studies or from selected populations, e.g., ESBL-producing strains. Previous unselected cohort studies employing genomic identification of KpSC phylogroups have produced conflicting estimates of the effect on 30-day case-fatality.[3,4] To our knowledge, no study has integrated clinical data and KpSC genomics in a large, unselected national cohort to investigate the clinical significance of bacterial phylogeny in KpSC BSIs.

We have conducted a nationwide, prospective investigation of adult KpSC BSI episodes over an 18-month period, gathering both clinical and bacterial genomic data. The aims of the study were to explore the clinical and genomic epidemiology of KpSC BSIs in an unselected large cohort and determine the risk for death within 30 days associated with KpSC phylogenetic lineages.

Material and methods

Setting, study population, and bacterial isolates

Eighteen out of 22 Norwegian health trusts participated in the study from 01.03.2017 to 31.08.2018. Episodes were eligible if the patient was ≥18 years of age and had blood culture growth of a *Klebsiella* spp. identified with MALDI-TOF MS (Bruker Daltonics, Bremen), excluding *Klebsiella oxytoca* and *Klebsiella aerogenes*. Repeated findings within eight weeks of the same *Klebsiella* species, with identical antibiotic susceptibility were disregarded. Antibiotic susceptibility testing (AST) was performed, either by EUCAST disc diffusion or Vitek 2 (bioMérieux, Durham NC) and categorised according to 2023 EUCAST breakpoints (https://eucast.org/). ESBL phenotype was resolved using the combined disc method (Becton Dickinson, New Jersey, USA).

Clinical data

Relevant clinical variables were selected a priori based on clinical experience and literature and retrieved from patient records. The data included age, sex, statin use, length of stay, survival up to 30 days, place of acquisition, admission to high dependency units (HDUs) or intensive care units (ICUs), admission date and duration of stay, infection focus, presence of abscess, Charlson comorbidity score,[17] quick Sequential Organ Failure Assessment (qSOFA) score,[18] and antibiotic treatment.

Definitions

For the full set of definitions see the Supplementary Methods. Survival time—number of days surviving from blood culture sampling up to 90 days. Infection focus—as specified in patient record. Polymicrobial case—growth of other bacteria or fungi, excluding microbes clinically assessed as contaminants. MDR was defined according to Magiorakos et al.[19] HV was defined as Kleborate virulence score ≥3, which includes all strains possessing aerobactin (*iuc*) as this is considered a strong predictor for HV phenotype[8,20] CGs were considered as global MDR-associated or HV-associated CGs according to Wyres et al.[9] Appropriate antimicrobial treatment was defined as intravenous administration of a drug categorised as susceptible according to the EUCAST breakpoints for Enterobacterales, disregarding any ESBL phenotype or genotypic resistance mechanisms. Susceptible, increased exposure (I) was considered active, in case of high dosage or concentration at the infection site (https://eucast.org/). Aminoglycosides were considered inappropriate for unknown infection foci or foci outside of the urinary tract.

Genomic analyses

We did whole-genome sequencing and genomic analyses as detailed in the Supplementary Methods. Briefly, Illumina MiSeq short-reads were assembled using Unicycler v.0.4.8[21] and analysed with Kleborate v.2.2.0.[20] Single nucleotide polymorphisms (SNPs), phylogeny, and CGs were identified as described in Fostervold et al.,[12] where CGs were assigned based on patristic distances as in Wyres

et al.[22] The CGs dominated by sequence types (STs) 107, 14 and 340 were named CG101, CG15 and CG258 to be consistent with current nomenclature.[9]

Statistical analyses

Population and hospital statistics were retrieved from Statistics Norway (https://www.ssb.no/en) and the Norwegian Directorate of Health (https://www.helsedirektoratet.no/english). Incidence data were calculated using the number of eligible episodes and the adult population at the end of 2017. All isolates were used for genomic analyses. The primary research question:"Does the sequence type, clonal group, or phylogroup of the KpSC blood culture isolate have an association with all-cause mortality within 30 days for KpSC bacteremia" was assessed with a multivariable Cox-regression model. The primary per-protocol phylogenetic exposure variable was defined as Kp, *K. variicola*, or *Klebsiella quasipneumoniae.* As many Kp isolates became assigned to global MDR-associated CGs,[9] we post-hoc subdivided Kp into 'global MDR-associated Kp CGs' and Kp CGs with no global MDR-association, termed 'other Kp CGs', since the former has been associated with poorer outcome.[14,23] The multivariable Cox-regression model with per-protocol exposure groups is shown in Supplementary Fig. S1.

Relevant clinical variables for descriptive epidemiology and survival analyses were chosen a priori according to clinical experience. The clinical variables were evaluated per protocol in a causal diagram (Fig. S2) before analysing data. qSOFA, admittance to ICU or HDU, presence of an abscess, and time to and type of antibiotic treatment were considered mediating co-variables, and therefore omitted from the multivariable Cox regression model. Power calculation for the Cox multivariable regression model was considered unfeasible, so a simplified solution was done using z-test for difference I proportions was done. With power to detect a difference in mortality of 10% between Kp and *K. variicola* BSIs and a significance level of α = 5% and a desired power of 1-β = 80%, the expected 25% mortality rate and 25% prevalence of *K. variicola* resulted in a required study size of 1000 BSI episodes.

The primary outcome was time to death within 30 days of positive blood culture sampling time.

Baseline characteristics between groups were compared using Fisher's exact and Kruskal-Wallis tests as appropriate. A p-value < 0.05 was considered significant. Confidence intervals (CIs) were reported as 95%. The effect of the exposure variable was investigated

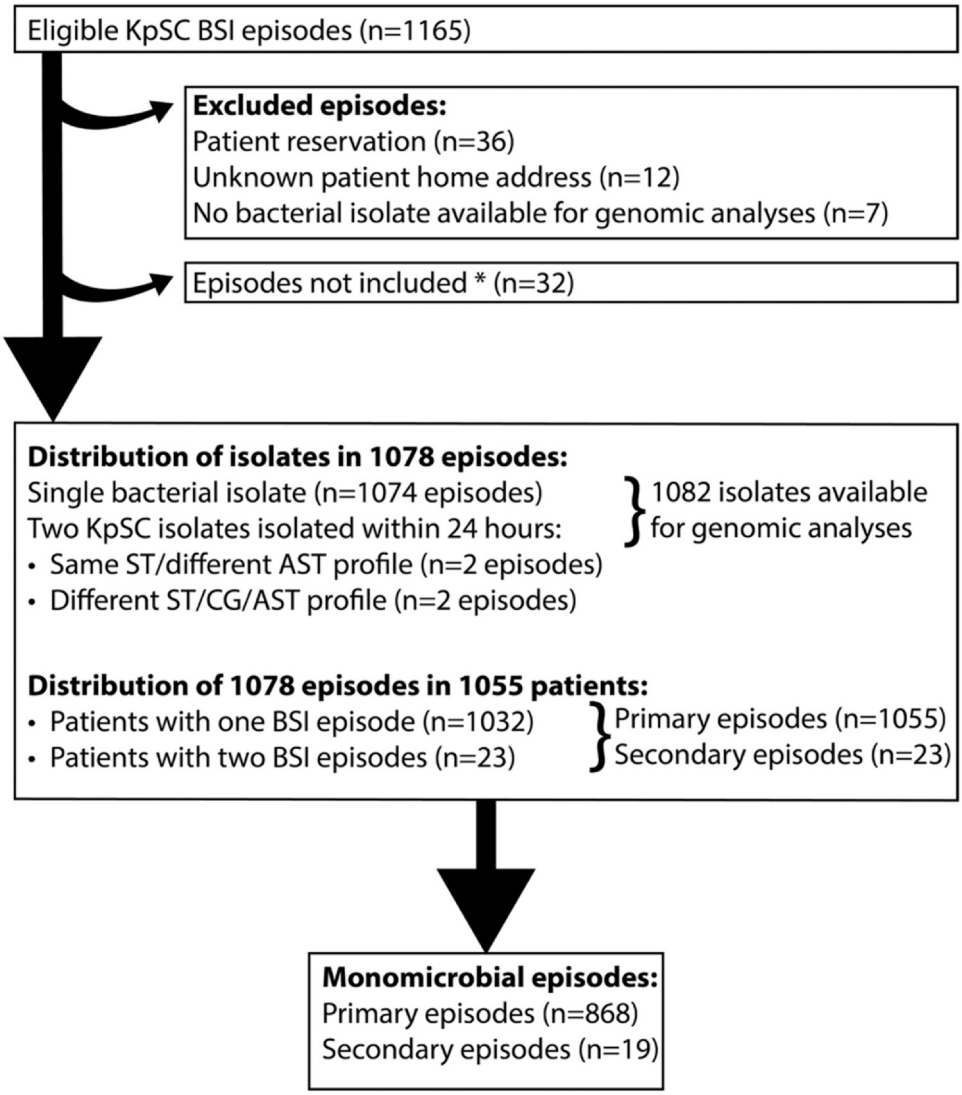

Fig. 1. Inclusion of *Klebsiella pneumoniae* species complex (KpSC) bloodstream infection (BSI) episodes. ST, sequence type; CG, clonal group; AST, antibiotic susceptibility testing. *Episodes not included were overlooked due to a miscommunication (all eligible episodes that occurred between March and August 2018 in one hospital trust). Primary episode—Patient´s first KpSC BSI during the study period. Secondary episode—Patient´s second KpSC BSI during the study period.

in the primary (first) monomicrobial BSI episode for each patient using Kaplan–Meier plots, and uni- and multivariable Cox-regression models. Missing data were not imputed. Assessment of the Cox model is shown in Supplementary Methods, Tables S1, S2 and Figs. S3, S4. Statistical analyses were done using R version v.4.2.2 (https://www.r-project.org/), with the survminer v.0.4.9 and survival v.3.5–7 packages.

Ethics

The regional ethics committee (REK Vest, 2016/1093) approved the study. Patients were included in the study consecutively and notified by letter after hospital discharge with the option to withdraw. Clinical data were obtained after three weeks' notice or if the patient died. Patients with unknown home addresses were excluded (Fig. 1).

Data availability statement

The 1082 KpSC short-read sequences are deposited in the European Nucleotide Archive (BioProject PRJEB48268, see Table S3 for details). Genotyping and antimicrobial susceptibility data are shown in Table S4. Clinical data sharing requires approval by the regional ethics committee and data protection officer and must align with the original purpose for data collection and use. The study protocol can be found as a supplementary document.

Results

We included 1078 (92.5% of 1165 eligible episodes) BSI episodes in 1055 patients, with 1082 corresponding KpSC isolates available for genomic analyses (Fig. 1), from 18 Norwegian health trusts with a primary catchment area covering 87.5% (n = 3,609,906) of the adult Norwegian population (Fig. S5). The national incidences of KpSC BSI in adults in the study period were 30.8 per 100,000 adult bed-days per year and 21.6 per 100,000 adult inhabitants per year (Table S5).

Bacterial population structure and antimicrobial resistance

Kp (79.3%, n = 858/1082) was the dominant phylogroup, followed by *K. variicola* (15.7%, n = 170/1082), *K. quasipneumoniae* subsp. *similipneumoniae* (3.0%, n = 33/1082), *K. quasipneumoniae* subsp. *quasipneumoniae* (1.8%, n = 20/1082), and '*K. quasivariicola*' (0.1%, n = 1/1082) (Fig. 2). The genomic population structure was highly diverse with 522 sequence types (STs) assigned to 303 CGs, where 384 (73.6%) STs and 154 (50.8%) CGs were singletons. There were no apparent differences in diversity between the species. The threshold for high prevalent CGs was arbitrarily set to 1.5%, which included nine CGs (Table 1, Fig. 2). CG101 (8.7%, n = 94 isolates) was the most prevalent.

Five of the global MDR-associated Kp CGs (CG101, CG20, CG37, CG307, and CG15) were among the most prevalent in our dataset (Table 1). The predominant STs in CG307 (ST307, n = 26) and CG101 (ST107, n = 88), were widely distributed and displayed lower median pairwise SNP distances of 13 and 34, respectively, compared to the

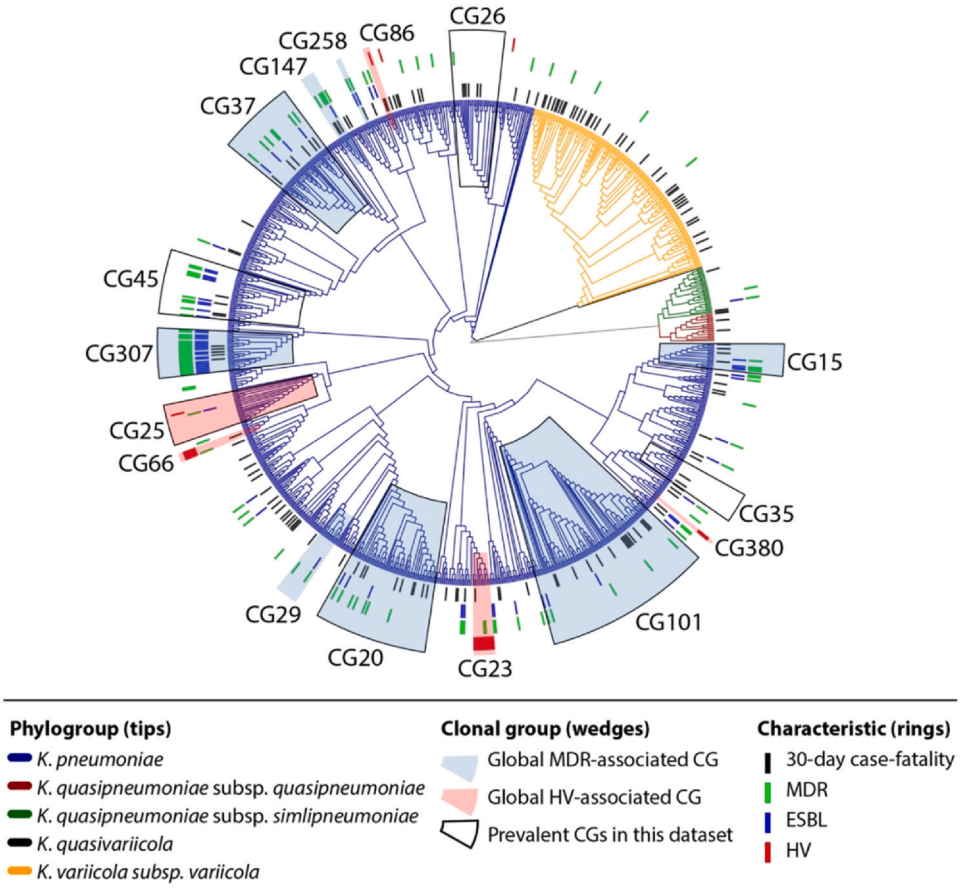

Fig. 2. Spatial relationships between 1082 *Klebsiella pneumoniae* species complex genomes, based on a maximum likelihood tree. The tips are coloured according to phylogroup. Prevalent clonal groups (CGs) representing > 1.5% of isolates are shown in black-framed wedges. Wedges coloured blue and red represent global clonal groups (CGs) associated with multidrug resistance (MDR) or hypervirulence (HV). Wedges include all genomes on the most recent common ancestor node of the indicated CG. The rings from inner to outer show associated case-fatality (black bars), phenotypic MDR (green bars), phenotypic ESBL (blue bars) and genomes meeting the study definition of HV (red bars).

Table 1
Characteristics of *Klebsiella pneumoniae* species complex clonal groups (CGs) representing more than 1.5% of all isolates.

Global MDR-associated Kp clonal group	Clonal group	Prevalence,% of all isolates (n)	MDR phenotype % (n)	ESBL phenotype % (n)	Community acquired % (n)	Presence among 18 trusts % (n)	ST	Prevalence,% of all isolates (n)	MDR phenotype % (n)	ESBL phenotype % (n)	Community acquired % (n)	Presence among the 18 trusts % (n)	Pairwise SNP distance within ST - Median value [IQR]
+	CG101	8.7 (94)	5.3 (5)	3.2 (3)	47.9 (45)	83.3 (15)	ST107	8.1 (88)	3.4 (3)	1.1 (1)	48.9 (43)	83.3 (15)	13 [9–18]
							ST101	0.3 (3)	33.3 (1)	33.3 (1)	33.3 (1)	11.1 (2)	299 [270–311.5]
							Other STs*	0.3 (3)	33.3 (1)	33.3 (1)	33.3 (1)	16.7 (3)	
+	CG20	5.8 (63)	11.1 (7)	4.8 (3)	63.5 (40)	100 (18)	ST20	3.3 (36)	2.8 (1)		63.9 (23)	94.4 (17)	444 [347–528.5]
							ST17	1.4 (15)	20 (3)	6.7 (1)	73.3 (11)	44.4 (8)	4756 [292–5559]
							ST636	0.3 (3)			33.3 (1)	11.1 (2)	2650 [2438.5–2763]
							Other STs*	0.8 (9)	33.3 (3)	22.2 (2)	55.6 (5)	44.4 (8)	
+	CG37	4 (43)	16.3 (7)	9.3 (4)	44.2 (19)	88.9 (16)	ST37	3.2 (35)	17.1 (6)	8.6 (3)	48.6 (17)	77.8 (14)	8730 [4133–12185.5]
							Other STs*	0.7 (8)	12.5 (1)	12.5 (1)	25 (2)	44.4 (8)	
	CG45	3.3 (36)	27.8 (10)	27.8 (10)	61.1 (22)	77.8 (14)	ST45	2.5 (27)	29.6 (8)	29.6 (8)	63 (17)	66.7 (12)	2277 [1314.5–3084.5]
							ST485	0.4 (4)			75 (3)	22.2 (4)	22,580 [7223–24970.5]
							Other STs*	0.5 (5)	40 (2)	40 (2)	40 (2)	16.7 (3)	
	CG26	2.9 (31)	3.2 (1)		51.6 (16)	77.8 (14)	ST26	1.7 (18)	5.6 (1)		61.1 (11)	44.4 (8)	163 [126–4807]
							ST253	0.5 (5)			60 (3)	27.8 (5)	6897.5 [404.75–7168.5]
							ST2800	0.3 (3)				11.1 (2)	4776 [2388.5–4777]
							Other STs*	0.5 (5)			40 (2)	22.2 (4)	
+	CG307	2.6 (28)	92.9 (26)	82.1 (23)	35.7 (10)	66.7 (12)	ST307	2.4 (26)	92.3 (24)	80.8 (21)	30.8 (8)	66.7 (12)	34 [19–82]
							Other STs*	0.2 (2)	100 (2)	100 (2)	100 (2)	5.6 (1)	
	CG25	2.1 (23)	4.3 (1)	4.3 (1)	60.9 (14)	66.7 (12)	ST25	1.9 (21)	4.8 (1)	4.8 (1)	61.9 (13)	66.7 (12)	104 [37–1779]
							Other STs*	0.2 (2)			50 (1)	11.1 (2)	
+	CG15	1.7 (18)	22.2 (4)	22.2 (4)	83.3 (15)	66.7 (12)	ST14	1 (11)	9.1 (1)	9.1 (1)	90.9 (10)	44.4 (8)	327 [240.5–2009]
							ST15	0.4 (4)	75 (3)	75 (3)	75 (3)	16.7 (3)	6547 [255–12842]
							Other STs*	0.3 (3)			66.7 (2)	16.7 (3)	
	CG35	1.6 (17)			47.1 (8)	61.1 (11)	ST35	1.4 (15)			46.7 (7)	55.6 (10)	354 [281–1702]
							Other STs*	0.2 (2)			50 (1)	11.1 (2)	

*Sequence types (STs) represented with a single isolate.
MDR, multidrug resistance; CG, clonal group; SNP, single nucleotide polymorphism; IQR, inter quartile range.

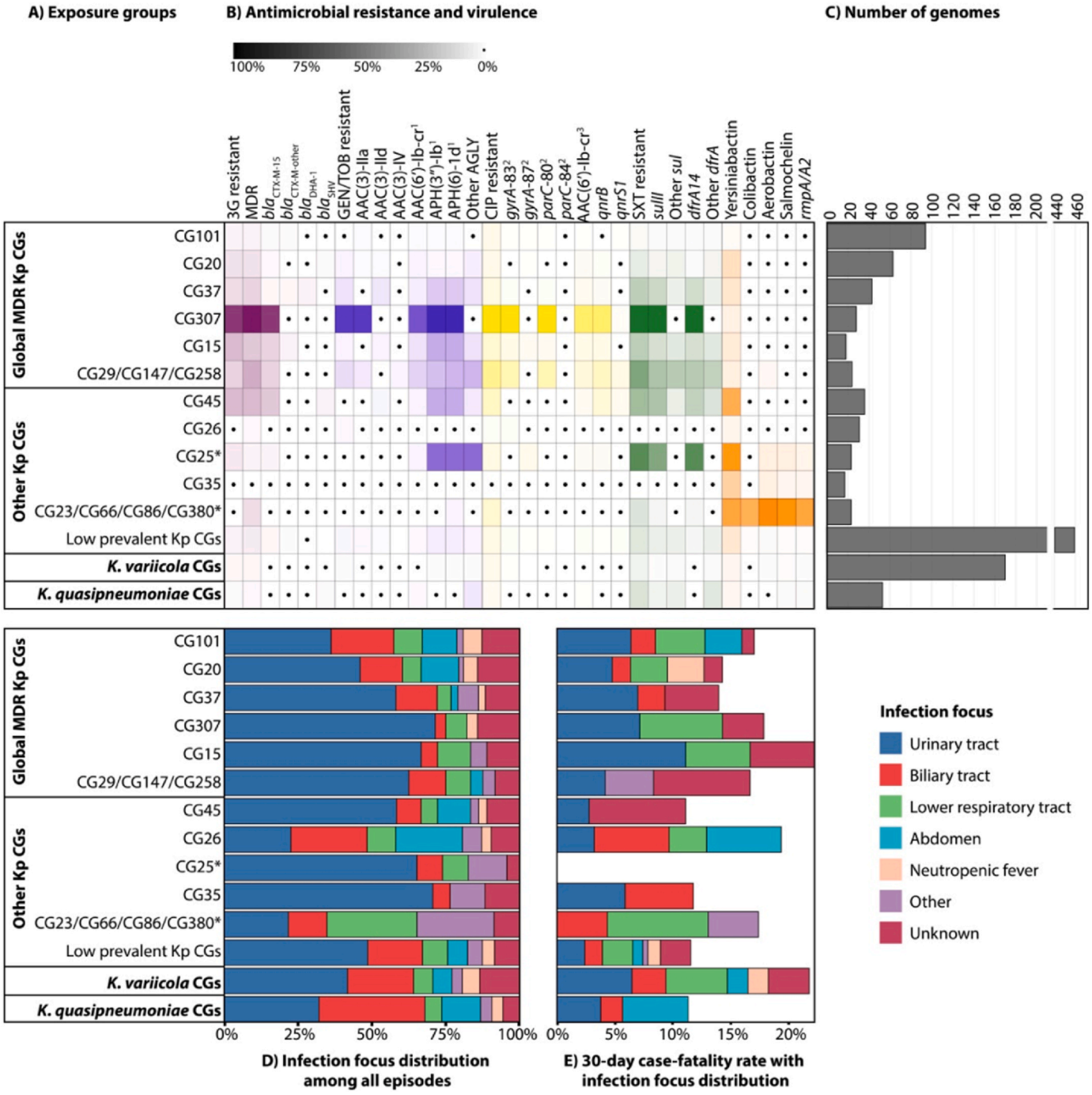

Fig. 3. Distribution of phenotypic resistance, resistance determinants, virulence factors, infection foci and case-fatalities in 1078 *Klebsiella pneumoniae* species complex (KpSC) bloodstream infection episodes, shown by exposure groups. For episodes that had two isolates (N = 4), only the most resistant is shown. A) Prevalent clonal groups (CGs) (> 1.5% of isolates) shown separately. *Global hypervirulence-associated CG; Kp, *Klebsiella pneumoniae* sensu stricto; Other Kp CGs, Kp CGs without global multidrug resistance (MDR) association. B) The box shading intensity corresponds to the percentage of isolates harbouring the respective traits. A black dot indicates no isolates. For each antibiotic class, the presence of a resistant phenotype and resistance determinants are indicated. C) Number of genomes. D) Distribution of infection foci. E) Thirty-day case-fatality rate coloured by infection focus. 3G, 3rd generation cephalosporin; GEN, gentamicin; TOB, tobramycin; CIP, ciprofloxacin; SXT, trimethoprim/sulfamethoxazole; AGLY, acquired aminoglycoside resistance genes; [1] does not confer resistance to gentamicin; [2] chromosomal mutation position; [3] may reduce susceptibility to both aminoglycosides and fluoroquinolones. See Fig. S6 for the subset of 868 primary, monomicrobial KpSC bloodstream infection episodes.

other dominant STs (Table 1). In total, 25.0% (n = 270/1082) of the isolates belonged to a global MDR-associated Kp CG where only 21.1% (n = 57) were phenotypically MDR.

Overall, 10.4% (n = 112/1082) of isolates were phenotypically MDR (Fig. 3). Of the 74 cefotaxime and/or ceftazidime-resistant isolates, 72 were phenotypically confirmed ESBL- (n = 70) or pAmpC-producing (n = 2), and 69 of those had a corresponding resistance genotype ($bla_{\text{CTX-M-15}}$, n = 57; $bla_{\text{CTX-M-1/3/14/24}}$, n = 7; $bla_{\text{SHV-2/2A/12}}$, n = 3; $bla_{\text{DHA-1}}$, n = 2). Clinical resistance to meropenem was not observed, but one $bla_{\text{CTX-M-15}}$ ESBL-producing isolate (CG147, ST392) harboured the carbapenemase gene $bla_{\text{OXA-48}}$., reflecting the low prevalence of carbapenemase-producing Kp in Norway.[24]

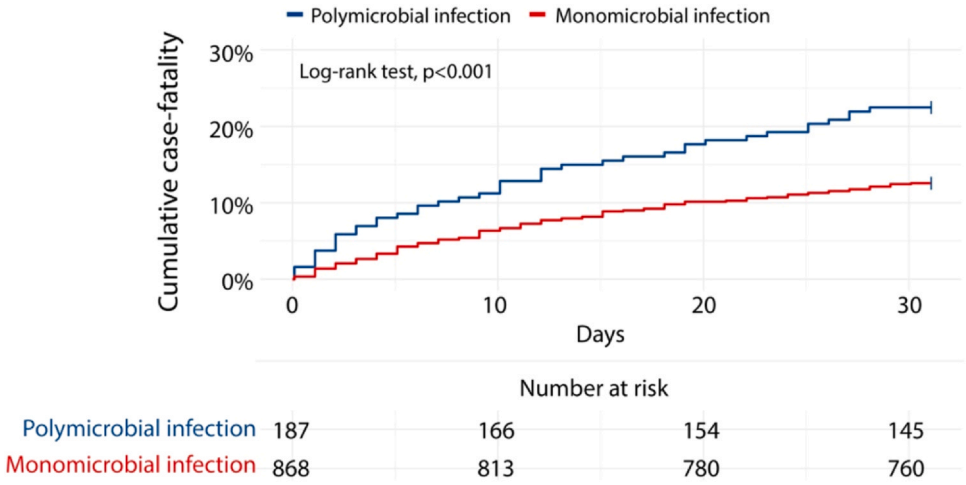

Fig. 4. Kaplan-Meier plot with log-rank test and at-risk table, showing cumulative case-fatality in primary *Klebsiella pneumoniae* species complex bloodstream infection episodes comparing monomicrobial (red) and polymicrobial (blue) episodes.

Bacterial virulence

The majority (79.0%, n = 855/1082) of isolates had no acquired virulence determinants as examined by Kleborate (Fig. 3). A HV genotype was found in 3.4% (n = 37) of the isolates, whereof 70.3% (n = 26/37) belonged to global HV-associated CGs. None of the HV isolates had an ESBL pheno- or genotype, however, one CG66 (ST66) and two CG23 (ST23) isolates were phenotypically MDR.

Clinical characteristics

The median patient age was 73.4 years (IQR 65.2–82.2), and 61.7% (n = 651/1055) of patients were male (Table S6). The median weighted Charlson comorbidity score was 3 (IQR 2–6), where cancer was the most common comorbidity (44.0%, n = 470). Upon admission to the hospital, 26.4% (n = 279) of the patients were on statins, while data were missing for 4.2% (n = 44) of the patients.

Only 15.8% (n = 170/1078) of episodes were hospital acquired, while 27.5% (n = 298) were health care associated and 56.6% (n = 609) community acquired. An MDR phenotype (n = 112) was more frequent in hospital acquired (15.2%, n = 26) and health care associated isolates (13.2%, n = 41), compared to community acquired ones (7.4%, n = 45) (p < 0.001). However, the global MDR-associated CGs, irrespective of phenotype, were neither associated with community nor hospital acquisition (p = 0.6).

Urinary tract (46.8%, n = 504/1078) and biliary tract (18.4%, n = 198) were the most common infection foci, while the infection focus was unknown in 10.3% (n = 111) of episodes (Fig. 3, and Table S6). Abscess formation was more common in patients with an HV isolate (24.3%, n = 9/37), compared to patients with non-HV isolates (3.8%, n = 40/1041, p < 0.001). Polymicrobial episodes accounted for 17.7% (n = 191/1078) of all episodes, and patients in this group differed from patients with monomicrobial BSI primarily in terms of less statin use (16.0% vs. 28.7%, p < 0.001) and distribution of infection foci (p < 0.001) (Table S6).

Clinical outcomes

Patients with polymicrobial infection had a higher 30-day case-fatality rate (23.6%, n = 45) compared to those with monomicrobial infection (12.6%, n = 109, p < 0.001) (Fig. 4). To assess the effect of KpSC lineages on clinical outcomes, we looked at the 868 primary monomicrobial episodes with a 30-day case-fatality rate of 12.6% (n = 109/868), ranging from 7.5% (n = 3) in *K. quasipneumoniae* to 16.1% (n = 36) in global MDR-associated Kp CGs (Table 2). In monomicrobial infections, the 30-day case-fatality rate was 10.6% (n = 7/66) in patients with ESBL-producing Kp and 18.8%(n = 6/32) in patients with HV-genotype Kp. In-hospital mortality rates are shown in Table 2.

qSOFA scores ≥2 were observed in 26.7% (n = 232/868) of episodes. Within 48 h after blood culture sampling, 8.5% (n = 74/868) of the patients were admitted to high dependency units (HDUs) and 11.6% (n = 101/868) were admitted to intensive care units (ICUs). Only 1.0% (n = 9/868) were patients who had stayed two or more days in either an HDU or ICU at time of blood culture sampling (Table 2). The median length of stay among patients surviving to discharge ranged from six days in `other Kp CGs` to eight days in global MDR-associated Kp CG. Clinical characteristics of the 109 case fatalities, according to exposure group is shown in Table S7.

Clinical characteristics in patients with monomicrobial BSI

Median patient age differed slightly (p = 0.04) among groups, ranging from 73.1 years in Kp other CGs to 76.4 years in *K. variicola* (Table 2). There were no significant differences between the groups in statin use, infection types, infection foci or type/timing of first appropriate antibiotic treatment. Global MDR-associated Kp CGs had a higher ESBL prevalence (12.9%, n = 29, p < 0.001) (Table 2). Appropriate antibiotic treatment was administered in 91.2% (n = 786/862) of primary monomicrobial episodes where data was missing for six patients. Six patients were not given any treatment. Median time to treatment in 684 patients with complete treatment data was 2.0 h, (IQR 0.5–15.0). Most patients received second- or third-generation cephalosporins (36.9%, n = 318), aminoglycosides (22.6%, n = 195), or piperacillin-tazobactam (19.1%, n = 165) as first appropriate treatment (Table S8). Three patients with ESBL received piperacillin-tazobactam as their first active medication, and all survived. Among the 70 patients that did not receive appropriate intravenous treatment, 48.6% (n = 34) were given aminoglycosides for susceptible isolates originating from outside the urinary tract.

Survival analyses

In univariable Cox-regression analysis (Table S9), the hazard ratio (HR) for global MDR-associated Kp CGs was significantly increased (HR 1.58, CI 1.02–2.42, p = 0.04). For *K. variicola* the HR was increased although not significantly, when compared to other Kp CGs (HR 1.60, CI 0.96–2.67, p = 0.07).

For the 829 monomicrobial episodes with complete data, the multivariable Cox-regression model showed a significantly higher

Table 2
Baseline characteristics of 868 primary monomicrobial *Klebsiella pneumoniae* species complex bloodstream infection episodes according to phylogenetic exposure group.

		Exposure groups				
	Overall	Other Kp CGs	Klebsiella quasipneumoniae	Klebsiella variicola	Global MDR Kp CGs	p
	% (n), median [IQR]					
Number of episodes	868	473	40	131	224	
Case-fatality rate day 30	12.6 (109)	10.4 (49)	7.5 (3)	15.9 (21)	16.1 (36)	0.08
In hospital mortality	8.3 (72)	7.4 (35)	5.0 (2*)	9.8 (13)	9.8 (22)	0.57
Data missing	(3)	(1)	(2)			
Sex Male	61.6 (535)	61.9 (292)	57.5 (23)	63.6 (84)	60.7 (136)	0.90
Age (years)	73.5 [65.2-81.9]	73.1 [64.5-81.7]	74.3 [66.0-80.3]	76.4 [69.5-83.8]	73.0 [65.1-81.8]	0.04
Charlson comorbidity score	2.0 [1.0-5.0]	2.0 [1.0-5.0]	1.50 [0.0-5.3]	2.0 [1.00-5.00]	2.0 [1.0-5.23]	0.18
Statin use	30.0 (249)	31.8 (145)	21.6 (8)	33.1 (41)	25.9 (55)	0.25
Data missing	(39)	(16)	(3)	(8)	(12)	
Infection type						
Community acquired	58.6 (508)	59.5 (281)	66.7 (26)	53.8 (71)	58.0 (130)	0.73
Health care associated	25.5 (221)	25.4 (120)	23.1 (9)	28.8 (38)	24.1 (54)	
Hospital acquired	15.9 (138)	15.0 (71)	10.3 (4)	17.4 (23)	17.9 (40)	
Data missing	(1)		(1)			
Infection focus						
Urinary tract	51.4 (446)	52.3 (247)	40.0 (16)	48.5 (64)	53.1 (119)	0.23
Biliary tract	16.0 (139)	14.4 (68)	27.5 (11)	19.7 (26)	15.2 (34)	
Unknown	9.7 (84)	8.3 (39)	7.5 (3)	10.6 (14)	12.5 (28)	
Lower respiratory tract	8.9 (77)	10.2 (48)	7.5 (3)	6.1 (8)	8.0 (18)	
Abdomen	6.0 (52)	6.4 (30)	7.5 (3)	4.5 (6)	5.8 (13)	
Neutropenic fever	3.6 (31)	2.8 (13)	5.0 (2)	5.3 (7)	4.0 (9)	
Other	4.5 (39)	5.7 (27)	5.0 (2)	5.3 (7)	1.3 (3)	
ESBL phenotype	6.3 (55)	5.3 (25)	2.5 (1)	0.0 (0)	12.9 (29)	< 0.001
MDR phenotype	10.1 (88)	8.5 (40)	5.0 (2)	3.0 (4)	18.8 (42)	< 0.001
qSOFA score						
0	39.9 (346)	38.6 (182)	47.5 (19)	42.0 (55)	40.2 (90)	0.51
1	33.3 (289)	33.3 (157)	22.5 (9)	33.6 (44)	35.3 (79)	
2	19.8 (172)	21.2 (100)	25.0 (10)	14.5 (19)	19.2 (43)	
3	6.9 (60)	7.0 (33)	5.0 (2)	9.9 (13)	5.4 (12)	
Data missing	(1)			(1)		
First appropriate antibiotic treatment						
2nd- or 3rd generation cephalosporins[1]	36.9 (318)	39.1 (184)	38.5 (15)	36.9 (48)	32.3 (71)	0.61
Aminoglycosids[2]	22.6 (195)	23.6 (111)	23.1 (9)	20.8 (27)	21.5 (48)	
Piperacillin-tazobactam	19.1 (165)	18.7 (87)	20.5 (8)	21.5 (28)	18.4 (42)	
Carbapenems[3]	9.5 (82)	8.1 (39)	7.7 (3)	6.2 (8)	14.3 (32)	
Other[4]	3.0 (26)	2.1 (10)	5.1 (2)	4.6 (6)	3.6 (8)	
No appropriate IV treatment	8.1 (70)	7.7 (36)	5.1 (2)	9.2 (12)	9.0 (20)	
No antibiotic treatment	0.7 (6)	0.6 (3)		0.8 (1)	0.9 (2)	
Data missing	(6)	(2)	(1)	(2)	(1)	
Time to appropriate antibiotic treatment (hours)	2.0 [−0.5 to 15.0]	1.9 [−0.4 to 14.9]	2.0 [0.6-9.1]	1.9 [−1.4 to 12.6]	3.0 [−0.1 to 19.0]	0.56
Data missing	(183)	(85)	(6)	(35)	(57)	
Admitted to HDU within 2 days[5]	8.5 (74)	7.6 (36)	10.0 (4)	9.1 (12)	9.8 (22)	0.82
Blood culture sampled during HDU stay[6]	0.2 (2)	0.4 (2)				
Admitted to ICU within 2 days[5]	11.6 (101)	12.5 (59)	10.0 (4)	13.6 (18)	8.9 (20)	0.39
Blood culture sampled during ICU stay[6]	0.8 (7)	0.6 (3)	2.5 (1)	1.5 (2)	0.4 (1)	
Length of stay (days)[7]	7.0 [4.0-12.0]	6.0 [4.0- 11.0]	7.5 [5.0-16.8]	7.0 [4.0-13.0]	8.0 [4.0-12.0]	0.05

Kp, Klebsiella pneumoniae sensu stricto; MDR, multidrug-resistant; CG, clonal group; Other Kp CGs, Kp CGs without global MDR-association; qSOFA, quick sequential organ failure assessment; IV, intravenous; HDU, high dependency unit; ICU, intensive care unit. *One patient died in-hospital after 30 days. 1cefuroxime, cefotaxime, ceftriaxone or, ceftazidime; 2gentamicin or tobramycin; 3ertapenem, meropenem, or imipenem; 4ciprofloxacin, trimethoprim-sulfamethoxazole; 5within 2 days of positive blood culture sampled; 6admitted to HDU or ICU at least 2 days before blood culture was sampled; 7calculated among patients discharged alive. P-test for comparison between exposure groups—Kruskal-Wallis test for continuous variables, Fisher exact test for categorical variables.

adjusted hazard ratio (aHR) for *K. variicola* (aHR 1.86, CI 1.10–3.17, p = 0.02) compared to other Kp CGs (Figs. 5 and 6), whereas aHR for global MDR-associated Kp CGs remained unchanged from the univariable estimate but not significant compared to other Kp CGs (aHR 1.52, CI 0.98–2.38, p = 0.06).

Other significant variables were age (aHR 1.02, CI 1.00–1.04, p < 0.02), Charlson comorbidity score (aHR 1.21, CI 1.13–1.31, p < 0.001), and statin use (aHR 0.55, CI 0.34–0.89, p = 0.02). Infections of the lower respiratory tract (aHR 5.02, CI 2.98–8.47, p < 0.001), unknown focus (aHR 2.56, CI 1.45–4.52, p < 0.001), and neutropenic fever (aHR 2.59, CI 1.10–6.11, p = 0.03) were associated with increased aHRs when compared to urinary tract infections.

Discussion

We have prospectively examined the epidemiology and outcomes of KpSC BSI in a nationwide adult Norwegian population, a country with low prevalence of antimicrobial resistance.[24] The major finding is the significantly increased aHR for death in BSIs caused by *K. variicola* compared to other Kp CGs. The aHR was also increased in global MDR-associated Kp CGs, although not significantly (p = 0.06). The mechanisms behind these associations are unclear, and whether they are microbe and/or host related. There is some experimental support for increased pathogenicity in global MDR-associated CGs in a recent study by Örmälä-Tiznado et al. who studied 30 whole-

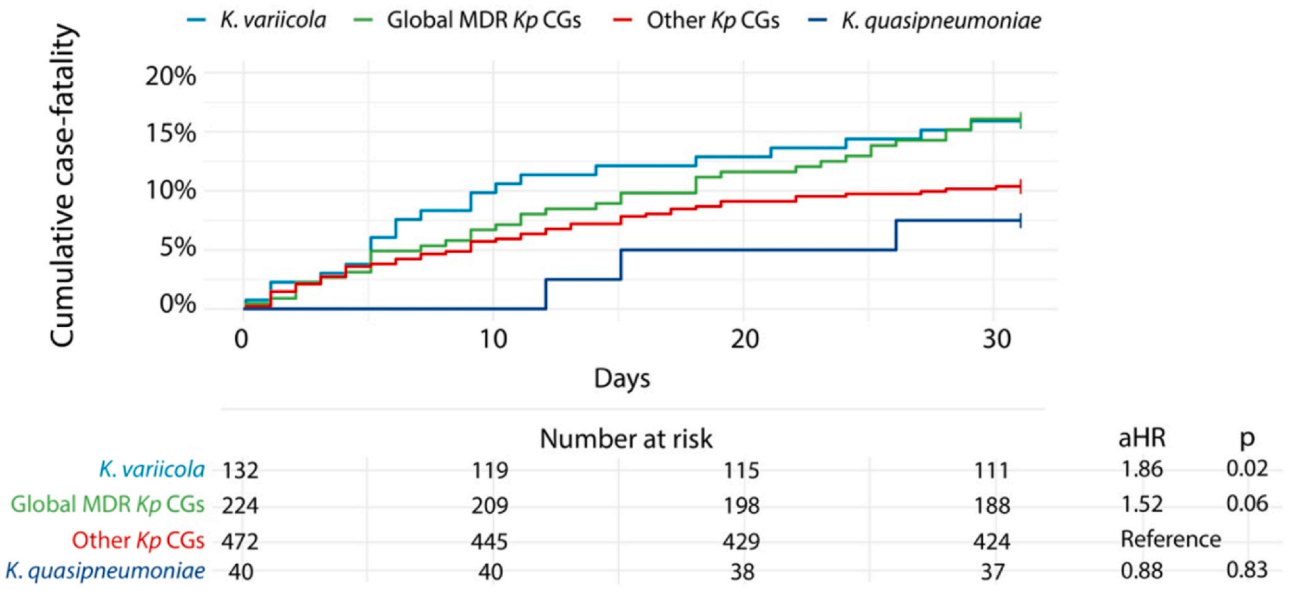

Fig. 5. Kaplan-Meier plot with at-risk table and adjusted hazard ratios (aHR) from a multivariable Cox-regression model, showing cumulative case-fatality in primary monomicrobial *Klebsiella pneumoniae* species complex bloodstream infection episodes according to the exposure groups; *K. variicola*—turquoise, global multidrug resistance (MDR)-associated *K. pneumoniae* sensu stricto (Kp) clonal groups (CGs)—green, other Kp CGs - red, and *K. quasipneumoniae*—blue. Other Kp CGs—Kp CGs without global MDR-association.

genome-sequenced carbapenemase-producing Kp strains in a Galleria mellonella insect model. They found that the global multidrug-resistant-associated CGs were associated with higher mortality than the other CGs but did not find any clear in-silico support for virulence.[25]

Our findings imply that KpSC pathogenicity differs between different phylogenetic lineages and affects patient outcome. Although the phylogenetic classification is crude, it disclosed associations between phylogenetic lineages and clinical outcomes. This highlights that both clinical and microbiological research needs to delve deeper into phylogenetic characteristics and traits beyond established virulence determinants to identify strains that pose a heightened risk to patients.

While the MDR isolates in general were associated with hospital and health-care environments, the prevalent and mainly antimicrobial susceptible global MDR-associated CGs were not. This implies that the MDR associated CGs carry traits making them successful both in the hospital environments and the community. It could be argued that the definition of community acquired infection (no hospitalisation in the last 30 days) is less suited to discern association to hospital environments in KpSC BSI, as KpSC gut carriage can endure for many months.[26] On the other hand, the lack of antimicrobial resistance in the majority of MDR-associated CGs suggests that the success of these strains is less associated with antimicrobial selection primarily occurring in the hospital setting. Notably, the most prevalent and largely antimicrobial susceptible CG in our dataset (CG101), was the fourth most prevalent carbapenemase-carrying CG in a large European study.[27] The close genetic relatedness of the ST107 isolates (the dominating ST in CG101) and their wide distribution across 15 health trusts in this study, suggests an association with increased risk of dissemination and/or infection. This is worryingly as CG101 has shown a propensity to acquire carbapenemase-encoding genes in other settings.[27]

The 30-day case-fatality rate of 12.5% is within the range (10–20%) of previous studies.[1–5] Also consistent with previous studies, the typical KpSC BSI patient was elderly with comorbidities, including cancer, and with the urinary and biliary tracts as the most common infection foci.[1–4] The overall impact of increasing age and comorbidity on KpSC BSIs, as well as poor outcome in polymicrobial infection, neutropenic fever, lower respiratory tract infection and infection of unknown focus, is likewise well documented.[1–4] The observed benefit of statin use has been described previously, but it is unclear if statin use offers a true protective effect or if it is just a marker for lower comorbidity.[28]

We found a higher annual incidence of KpSC BSIs than other studies.[1,5,29] However, incidence rates based on the total population are likely to be lower, as the KpSC BSI rate in children, excluding neonates, is typically much lower than in adults.[1] Furthermore, over the last decades there has been a general increase in the incidence of gram-negative BSIs in several countries, which may contribute to the incidence disparity.[10,24,29]

The dominance of Kp and *K. variicola*, and a high CG diversity, is in line with other national and international observations.[3,10,12] Likewise, low rates of antimicrobial resistance, including ESBLs and carbapenemases are aligned with population-based studies and national surveillance data.[11,24] Virtually all ESBL-producing strains were Kp carrying $bla_{\text{CTX-M-15}}$, with CG307 being the most prevalent. CG307 seems now to be established as the major ESBL-carrying CG in Norway since its emergence in 2015.[12,24] As observed in previous studies, all *K. variicola* were non-ESBL.[11,12,30,31] As *K. variicola* is found both in human gut carriage, animal and environmental sources[11,32], the scarcity of ESBL in comparison to Kp is interesting and warrants further investigation into factors influencing the acquisition of AMR. As expected, hypervirulent isolates were rare.[9–12]

The low rate of hospital acquired infections compared to other studies[1–5] might in part be explained by the increasing trend of outpatient care and shorter hospital stays. While less than 1% of BSIs occurred in ICU or HDU patients, one in five patients were admitted to an ICU or HDU within two days after blood cultures were taken, indicating that the KpSC BSIs were associated with significant morbidity.

The major strength of this study is the large and unselected patient population encompassing both secondary and tertiary care hospitals, nationwide coverage, high participation rate and no loss of follow-up. By combining curated clinical data with bacterial genomic and antimicrobial susceptibility data, we were able to conduct detailed analyses of the clinical and microbial epidemiology of KpSC BSI episodes. The limitations of the study include the retrospective retrieval of clinical data, which meant that some data were unavailable. The post-hoc modification of the exposure variable into

Variable		case-fatality/N	Adjusted hazard ratio	p
Exposure group	Other Kp CGs	46/456	Reference	
	K. quasipneumoniae	3/37	0.88 (0.27 - 2.84)	0.83
	K. variicola	21/124	1.86 (1.10 - 3.17)	0.02
	Global MDR Kp CGs	36/212	1.52 (0.98 - 2.38)	0.06
Sex	Female	40/318	Reference	
	Male	66/511	0.87 (0.58 - 1.30)	0.51
Age		106/829	1.02 (1.00 - 1.04)	0.015
Charlson comorbidity score		106/829	1.21 (1.13 - 1.31)	<0.001
Statin use	No statin use	84/580	Reference	
	Statin use	22/249	0.55 (0.34 - 0.89)	0.015
Infection type	Community acquired	48/478	Reference	
	Health care associated	37/216	1.30 (0.83 - 2.03)	0.25
	Hospital acquired	21/135	1.20 (0.70 - 2.08)	0.51
Infection focus	Urinary tract	36/424	Reference	
	Biliary tract	10/131	0.75 (0.37 - 1.52)	0.42
	Unknown	19/79	2.56 (1.45 - 4.52)	0.001
	Lower respiratory tract	25/74	5.02 (2.98 - 8.47)	<0.001
	Abdomen	6/52	0.99 (0.41 - 2.39)	0.98
	Neutropenic fever	7/31	2.59 (1.10 - 6.11)	0.03
	Other	3/38	1.14 (0.35 - 3.75)	0.83

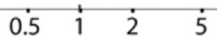

Fig. 6. Multivariable Cox regression model of 829 monomicrobial *Klebsiella pneumoniae* species complex (KpSC) bloodstream infection episodes with KpSC exposure group. Kp—*K. pneumoniae* sensu stricto. CG, clonal group; MDR, multidrug resistance. Other Kp CGs—Kp CGs without global MDR-association.

globally MDR-associated Kp-, other Kp CGs resulted in some loss of statistical power and may increase the risk of committing a Type I error. Further we did not measure the time it took to correct any organ dysfunction, a factor critical for survival.[33] However, since neither qSOFA, ICU admission, nor time to appropriate antibiotic treatment differed significantly between exposure groups, we assume the time to correct organ dysfunction are evenly distributed in the exposure groups. While the study design allowed for risk of unrecognised bias, we believe this is at least partially alleviated by the size and multi-centre design of the study. Most general findings align well with previous studies, so all in all, we find the risk of systematic bias to be limited and directed towards null.

In conclusion, *K. variicola* and global MDR-associated Kp CGs were associated with a higher 30-days fatality rate. Global MDR-associated Kp CGs were frequent, often community acquired, and mainly non-MDR, suggesting that traits beyond antimicrobial resistance are important drivers in the global dissemination of these CGs. This warrants further efforts to identify additional genetic markers to understand the pathogenicity of KpSC.

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CRediT authorship contribution statement

Study conception: A.F, Ø. S, A.S, J.V.B, I.H.L; study administration: A.F; whole-genome sequencing: R.B and E.B.; data analysis: A.F, N.R, M.A.K.H, J.V.B; Figures A.F and M.A.K.H; manuscript: A.F and N.R.; isolate and data collection: A.F, N.R, J.E.A, C.F.B, M.H.E, K.W.G, N.H, A.J, R.B.J, S.K.J, A.N, R.A.S, S.T, J.V.B, A.B, Y.T, A.D.G, R.H and Å.M.

All authors contributed to data interpretation, reading, and commenting on the manuscript. Statistical analyses were performed by A.F, and quality controlled by N.R. Study group members provided isolates, clinical data and commented on the final manuscript.

Declaration of Competing Interest

We declare no conflict of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106155.

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