Bacteraemia due to non-ESBL-producing *Escherichia coli* O25b:H4 sequence type 131: insights into risk factors, clinical features and outcomes

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ABSTRACT

The epidemiology and outcomes of bloodstream infections (BSIs) caused by *Escherichia coli* ST131 isolates not producing extended-spectrum β-lactamases (ESBLs) are not well defined despite being more prevalent than ESBL-producers. In this study, risk factors and the impact on outcome of BSIs caused by non-ESBL-producing ST131 *E. coli* versus non-ST131 *E. coli* were investigated. A case–control study was performed in two tertiary centres to identify risk factors for ST131. Molecular methods were used to investigate all *E. coli* isolates from blood cultures for belonging to O25b:H4-ST131 clonal group. *fimH* alleles were characterised in ST131 isolates. Multivariate analysis was performed by logistic regression or Cox regression as appropriate. A total of 33 ST131 *E. coli* cases and 56 controls were studied. ST131 isolates showed higher rates of resistance to ampicillin and ciprofloxacin; *fimH* alleles were *H*30 in 14 isolates (42.4%) and *H*22 in 12 isolates (36.3%). Only recent surgery (OR = 7.03, 95% CI 1.71–28.84; *P* = 0.007) and unknown source of bacteraemia (OR = 5.37, 95% CI 0.93–30.81; *P* = 0.05) were associated with ST131. ST131 isolates showed no association with 30-day mortality, therapeutic failure, presentation with severe sepsis/shock or length of stay. Bacteraemia due to non-ESBL-producing O25b:H4-ST131 *E. coli* showed few differences in terms of risk factors as well as similar outcome to non-ST131 *E. coli*. These data support the notion that ST131 strains are not less clinically virulent despite showing increased antimicrobial resistance, but also are not more virulent than other clonal groups causing BSI.

Highlights

- A case–control study on *Escherichia coli* ST131 bacteraemia was performed.
- Resistance to ampicillin and ciprofloxacin was more frequent in ST131 isolates.
- Previous surgery and unknown source of bacteraemia were associated with ST131.
- Outcomes of ST131 and non-ST131 bacteraemia were not significantly different.
- ST131, although more resistant, showed similar clinical behaviour to non-ST131 isolates.

1. Introduction

Escherichia coli sequence type 131 (ST131) has spread rapidly worldwide in recent decades and is considered an important driver of the increase in antimicrobial resistance in *E. coli* [1]. Because all *E. coli* ST131 harbour type 1 fimbrial adhesins encoded by *fimH*, the allelic diversity of this gene has been used for subtyping. The so-called *H*30 subclone is now predominant among ST131 isolates; its derivatives, *H*30-R and *H*30-Rx, are associated with fluoroquinolone resistance and the production of CTX-M-15 extended-spectrum β-lactamase (ESBL), respectively [2,3]. However, the predominance of *H*30-R and *H*30-Rx may be overestimated when only quinolone-resistant and/or ESBL-producing isolates are studied.

ST131 is important because it combines the ability for successful spread, antibiotic resistance and virulence; in fact, ST131 isolates usually exhibit the virulence factors associated with extraintestinal pathogenic *E. coli* (ExPEC) strains [1]. Clinical studies of ST131 isolates are challenging because molecular techniques are needed for their identification. As a consequence, previous studies investigating the risk factors and clinical impact of ST131 isolates causing bloodstream infections (BSIs) have mostly focused on ESBL-producers [4–7]. However, ESBL production may be an important confounder for risk factors and outcomes. To the best of our knowledge, data on non-ESBL-producing ST131 are limited to one retrospective study including only 20 patients [8].

The objectives of this study were to investigate the clinical features, risk factors and outcomes of BSI caused by ST131 *E. coli* not producing ESBLs.

2. Methods

2.1. Study design, sites and patients

A case–control study to investigate risk factors and a cohort study to investigate the outcome of BSI due to non-ESBL-producing *E. coli* O25b:H4-ST131 was conducted from January 2010 to October 2012 at Hospital Universitario Virgen Macarena and Hospital Universitario Virgen del Rocío, two tertiary hospitals serving a population of 1 100 000 in Seville, Spain. Adult patients with monomicrobial bacteraemia due to *E. coli* were eligible. Episodes caused by ESBL-producers were excluded but AmpC-producers were not as these are not so clearly linked to ST131. The case group was formed of all consecutive patients with bacteraemia due to O25b:H4-ST131 *E. coli*. The next two patients with bacteraemia due to non-O25b:H4-ST131 *E. coli* from the same centre were selected as controls.

Cases and control patients were prospectively recruited by daily review of blood cultures; all *E. coli* isolates were checked for belonging to O25b:H4-ST131 by real-time PCR (see below). For the outcome investigation, the cohort made up of all cases and controls was studied. All patients were followed for 30 days. The study was approved by the local Ethics Committee.

2.2. Variables and definitions

The following variables were collected: demographics; acquisition type (nosocomial, community or healthcare-associated); chronic underlying conditions and severity according to the Charlson comorbidity index [9] and McCabe classification [10]; antibiotic use (previous 2 months); invasive procedures (previous week; 1 month for surgery); and source of bacteraemia according to clinical and microbiological criteria. The main outcome variables were 30-day all-cause mortality and clinical failure at Day 14, defined as the persistence or worsening of signs or symptoms of infection. Secondary outcome variables were occurrence of severe sepsis or septic shock [11] in the first 24 h and length of stay after infection in survivors.

2.3. Microbiological studies

All isolates were screened by real-time PCR for the O25b:H4-ST131 clonal group using primers for O25b *rfb* and allele 3 of the *pabB* gene [12], and by multiplex PCR for phylogroup $B2_3$ typing using two different sets of primers [13]. All isolates showing cefotaxime or ceftazidime minimum inhibitory concentrations (MICs) ≥1 mg/L were screened for ESBL production and AmpC hyperproduction by the double-disk method (third-generation cephalosporin with and without clavulanic acid) on Mueller–Hinton agar and on cloxacillin (200 mg/L)-containing Mueller–Hinton agar. *fimH* allele types were determined using previously designed primers [14] and were designated using FimTyper 1.0 (https://cge.cbs.dtu.dk/services/FimTyper-1.0/). Antibiotic susceptibility was studied using commercial panels (MicroScan; Beckman, Brea, CA, USA) and was interpreted according to Clinical and Laboratory Standards Institute (CLSI)

recommendations [15]. Isolates showing resistance to at least one drug from three or more families with intrinsic activity against Enterobacteriaceae were considered multidrug-resistant.

2.4. Statistical analysis

Univariate comparisons were performed using the χ^2 test or the Fisher's exact test and Mann–Whitney *U*-test as appropriate. Multivariate analyses were performed using logistic regression, except for mortality when Cox regression analysis was used. Variables with a *P*-value of ≤0.2 in the univariate analysis and interactions of interest were introduced and selected using a stepwise backward method. Adjusted hazard ratios and odds ratios (ORs) were calculated with their 95% confidence interval (CI). Analyses were performed with the statistical software package SPSS v.15 (SPSS Inc., Chicago, IL).

3. Results

Non-ESBL-producing O25b:H4-ST131 *E. coli* were isolated from blood cultures of 33 patients during the study period; 56 control patients with non-O25b:H4-ST131 non-ESBL-producing *E. coli* were included (only 1 control could be found for 10 cases).

3.1. Antimicrobial susceptibility and fimH alleles

O25b:H4-ST131 *E. coli* showed higher rates of resistance to ampicillin and ciprofloxacin than non-ST131 isolates (29% vs. 38%, *P* = 0.04; and 16% vs. 14%, *P* = 0.02),

respectively, and were more frequently multidrug-resistant (78.8% vs. 41%; $P < 0.001$). The *fimH* alleles of ST131 isolates were *H*30 in 14 isolates (41.2%), *H*22 in 12 isolates (36.6%), other variants in 6 isolates and 1 isolates lacked *fimH*. Compared with all other ST131 isolates, *H*30 isolates were more frequently resistant to ciprofloxacin [12/14 (85.7%) vs. 4/19 (21.1%); $P < 0.001$] and less frequently to resistant trimethoprim/sulfamethoxazole [2/14 (14.3%) vs. 11/19 (57.9%); $P = 0.1$]. Three ceftazidime-resistant ST131 isolates were shown to be AmpC-hyperproducers, and all were *H*22.

3.2. Risk factors for ST131: case–control study

The features of cases and controls are shown in Table 1. Variables included in the multivariate analysis were chronic pulmonary disease, recent surgery, unknown source of bacteraemia and urinary tract source. The final multivariate model showed that the two variables independently associated with ST131 were recent surgery (OR = 7.03, 95% CI 1.71–28.84; $P = 0.007$) and unknown source of bacteraemia (OR = 5.37, 95% CI 0.93–30.81; $P = 0.05$). Inclusion of previous antimicrobials did not change the results. The *P*-value of the Hosmer–Lemeshow goodness-of-fit test for the model was 0.95.

Compared with all other ST131 isolates, *H*30 isolates tended to be less frequently nosocomially acquired [3/14 (21.4%) vs. 10/19 (52.6%); $P = 0.07$] and to more frequently affect patients aged >65 years [12/14 (85.7%) vs. 10/19 (52.6%); $P = 0.06$ by Fisher's exact test]. No other differences in exposure to predisposing factors were shown.

3.3. Outcome analysis

No significant differences were found for mortality rates, presentation with severe sepsis or septic shock, clinical failure at Day 14 or median length of stay after infection in survivors between patients with ST131 and non-ST131 isolates (Table 1; Fig. 1). A stratified analysis according to fluoroquinolone susceptibility did not change the results (data not shown).

Univariate and multivariate analyses of factors associated with 30-day mortality and clinical failure at Day 14 are shown in Table 2. Non-fatal underlying disease and sources of bacteraemia other than the urinary and biliary tracts were associated with a higher risk of death and clinical failure. O25b:H4-ST131 *E. coli* was not shown to be associated with either of these two outcome variables.

The only variable associated with increased risk of presentation of severe sepsis or shock in the univariate analysis was strict community acquisition of the infection (OR = 2.67, 95% CI 1.03–6.87; $P = 0.04$). The results did not change after multivariate analysis. Again, O25b:H4-ST131 *E. coli* showed no associations (adjusted OR = 0.81, 95% CI 0.30–2.15; $P = 0.67$).

A comparison of *H*30 with other O25b:H4-ST131 isolates showed no differences for source [urinary tract, 6/14 (42.9%) vs. 6/19 (31.6%); $P = 0.5$], presentation with severe

sepsis or shock [4/14 (28.6%) vs. 5/19 (26.3%); *P* = 1.0], therapeutic failure [3/14 (21.4%) vs. 2/19 (10.5%); *P* = 0.6] or mortality [3/14 (21.4%) vs. 3/19 (15.8%); *P* = 1.0].

4. Discussion

The main finding of this study was that we were unable to find many significant differences in risk factors or prognosis between bacteraemic infections caused by non-ESBL-producing O25b:H4-ST131 and non-O25b:H4-ST131 *E. coli* isolates, even though O25b:H4-ST131 isolates were more frequently multidrug-resistant.

Previous surgery and an unknown source of bacteraemia were identified as the only predictors for O25b:H4-ST131. Previous surgery was also identified as a risk factor in a previous study including BSI caused by ESBL-producing *E. coli* [6]. Our interpretation is that surgery may be a surrogate marker integrating various exposures, including co-morbidities, nosocomial acquisition and exposure to antibiotics. Unknown source of BSI among ST131 cases was also found in a population-based study in Canada that included fluoroquinolone-resistant bacteraemic strains only, in which ST131 was associated with primary sepsis (but also with upper urinary tract infection) [7].

Nevertheless, it is remarkable that there were no important differences in demographic features, type of acquisition, underlying conditions, other invasive procedures or previous antibiotic use. Similarly, no predictors for ST131 were found in the only study performed on BSI due to non-ESBL-producing *E. coli*, which included only community-onset episodes [8], and few predictors were identified in two previous studies in ESBL-

producers [4,6]. This contrasts with previous studies investigating the risk factors associated with ST131 isolated in any sample (mostly urine), in which several risk factors were found including older age, long-term care facility, previous urinary tract infection, complex infection and previous exposure to antibiotics in a study in Minnesota, USA [16], and female sex, diabetes mellitus, bedridden status and previous exposure to antibiotics in Seville, Spain [17], and suggest that the ability to cause bacteraemia of ST131 strains is similar to that of other clonal groups of *E. coli*.

The second objective of this study was to investigate whether the outcomes of BSI due to ST131 is different from other *E. coli* clonal groups. We did not find O25b:H4-ST131 to be associated with different outcomes, which may be interpreted as meaning that ST131 strains are not more clinically virulent than other strains, but also that they are not less virulent, even though they are more frequently multidrug-resistant. Early anecdotal reports of severe infections caused by ST131 isolates transmitted between households suggested high clinical virulence [18,19]. In previous studies on bacteraemic infections, ST131 isolates did not show an increase in mortality or incidence of shock [4–6,8], which is similar to the findings in the current study. ST131 strains were not associated with bacteraemia, shock or mortality in a study including all-source (mainly urine) *E. coli* isolates in Seville [17], but were independently associated with persistent or recurrent infections in the Minnesota study [16].

Interestingly, there was a lower proportion of ST131 isolates belonging to the *H*30 subclone in this study than in previous studies (mostly not performed in bacteraemic

isolates), where *H*30 was the most frequent subclone overall [3]. In Minnesota, *H*30 was shown to be specifically associated with healthcare-associated infections, mostly among older patients in long-term care facilities [20], which is similar to the current findings.

This study has some limitations. First, statistical power was limited and some associations may therefore not have been detected. Second, virulence-associated genes and clonal groups in control patients were not investigated. Third, the data would apply to areas with a similar epidemiology of *E. coli* bacteraemic infection. Strengths include the fact that detection of O25b:H4-ST131 was performed prospectively. In addition, only non-ESBL-producing isolates were included to avoid the potential effects of confounding caused by ESBL production.

In conclusion, bacteraemia due to non-*H*30, O25b:H4-ST131 *E. coli* showed limited differences in terms of risk factors and no differences in terms of outcome in comparison with non-ST131 isolates among non-ESBL-producing isolates. These data support the notion that despite showing increased antimicrobial resistance, ST131 strains are not less clinically virulent, but also not more virulent than other clonal groups causing bacteraemia.

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Competing interests: JR-B has been a scientific advisor for AstraZeneca, Merck, Pfizer, Achaogen, InfectoPharm, Basilea and Vifor Pharma, and has been a speaker for AstraZeneca, Merck, Astellas and Pfizer. All other authors declare no competing interests.

Ethical approval: The Institutional Review Board of Hospital Universitario Virgen Macarena (Seville, Spain) approved the study.

References

[1] Nicolas-Chanoine MH, Bertrand X, Madec JY. *Escherichia coli* ST131, an intriguing clonal group. Clin Microbiol Rev 2014;27:543–74.

[2] Johnson JR, Johnston B, Clabots C, Kuskowski MA, Castanheira M. *Escherichia coli* sequence type ST131 as the major cause of serious multidrug-resistant *E. coli* infections in the United States. Clin Infect Dis 2010;51:286–94.

[3] Olesen B, Frimodt-Møller J, Fleron Leihof R, Struve C, Johnston B, Hansen DS, et al. Temporal trends in antimicrobial resistance and virulence-associated traits within the *Escherichia coli* sequence type 131 clonal group and its *H*30 and *H*30-Rx subclones, 1968 to 2012. Antimicrob Agents Chemother 2014;58:6886–95.

[4] Chung HC, Lai CH, Lin JN, Huang CK, Liang SH, Chen WF, et al. Bacteremia caused by extended-spectrum-β-lactamase-producing *Escherichia coli* sequence type ST131 and non-ST131 clones: comparison of demographic data, clinical features, and mortality. Antimicrob Agents Chemother 2012;56:618–22.

[5] Rodríguez-Baño J, Mingorance J, Fernández-Romero N, Serrano L, López-Cerero L, Pascual A, et al. Outcome of bacteraemia due to extended-spectrum β-lactamase-producing *Escherichia coli*: impact of microbiological determinants. J Infect 2013;67:27–34.

[6] Cho SY, Kang CI, Cha MK, Wi YM, Ha YE, Chung DR, et al. Clinical features and treatment outcomes of bloodstream infections caused by extended-spectrum β-lactamase-producing *Escherichia coli* sequence type 131. Microb Drug Resist 2015;21:463–9.

[7] Peirano G, Pitout JD. Fluoroquinolone-resistant *Escherichia coli* sequence type 131 isolates causing bloodstream infections in a Canadian region with a centralised laboratory system: rapid emergence of the *H*30-Rx sublineage. Antimicrob Agents Chemother 2014;58:2699–703.

[8] Wu YH, Cheng MF, Lai CH, Lin HH, Hung CH, Wang JL. The role of sequence type (ST) 131 in adult community-onset non-ESBL-producing *Escherichia coli* bacteraemia. BMC Infect Dis 2014;14:579.

[9] Charlson ME, Pompei P, Ales KL, McKenie CR. A new method of classifying prognostic co-morbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.

[10] McCabe WR, Jackson GG. Gram-negative bacteremia I. Etiology and ecology. Arch Intern Med 1962;110:845–55.

[11] Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definition Conference. Crit Care Med 2003;31:1250–6.

[12] Doumith M, Day MJ, Hope R, Wain J, Woodford N. Improved multiplex PCR strategy for rapid assignment of the four major *Escherichia coli* phylogenetic groups. J Clin Microbiol 2012;50:3108–10.

[13] Clermont O, Christenson JK, Denamur E, Gordon DM. The Clermont *Escherichia coli* phylo-typing method revisited: improvement of specificity and detection of new phylo-groups. Environ Microbiol Rep 2013;5:58–65.

[14] Weissman SJ, Johnson JR, Tchesnokova V, Billig M, Dykhuizen D, Riddell K, et al. High-resolution two-locus clonal typing of extraintestinal pathogenic *Escherichia coli*. Appl Environ Microbiol 2012;78:1353–60.

[15] Clinical and Laboratory Standards Institute. *Performance standards for antimicrobial susceptibility testing; twenty-second informational supplement.* Document M100-S22. Wayne, PA: CLSI; 2012.

[16] Banerjee R, Johnston B, Lohse C, Porter SB, Clabots C, Johnson JR. *Escherichia coli* sequence type 131 is a dominant, antimicrobial-resistant clonal group associated with healthcare and elderly hosts. Infect Control Hosp Epidemiol 2013;34:361–9.

[17] López-Cerero L, Navarro MD, Bellido M, Martín-Peña A, Viñas L, Cisneros JM, et al. *Escherichia coli* belonging to the worldwide emerging epidemic clonal group O25b/ST131: risk factors and clinical implications. J Antimicrob Chemother 2014;69:809–14.

[18] Ender PT, Gajanana D, Johnston B, Clabots C, Tamarkin FJ, Johnson JR. Transmission of an extended-spectrum-β-lactamase-producing *Escherichia coli* (sequence type ST131) strain between a father and daughter resulting in septic shock and emphysematous pyelonephritis. J Clin Microbiol 2009;47:3780–2.

[19] Owens RC, Johnson JR, Stogsdill P, Yarmus L, Lolans K, Quinn J. Community transmission in the United States of a CTX-M-15-producing sequence type ST131 *Escherichia coli* strain resulting in death. J Clin Microbiol 2011;49:3406–8.

[20] Banerjee R, Johnston B, Lohse C, Chattopadhyay S, Tchesnokova V, Sokurenko EV, et al. The clonal distribution and diversity of extraintestinal *Escherichia coli* isolates vary according to patient characteristics. Antimicrob Agents Chemother 2013;57:5912–7.

Fig. 1. Kaplan–Meier curves showing survival of patients with bacteraemia due to ST131 and non-ST131 *Escherichia coli* not producing extended-spectrum β-lactamases (ESBLs).

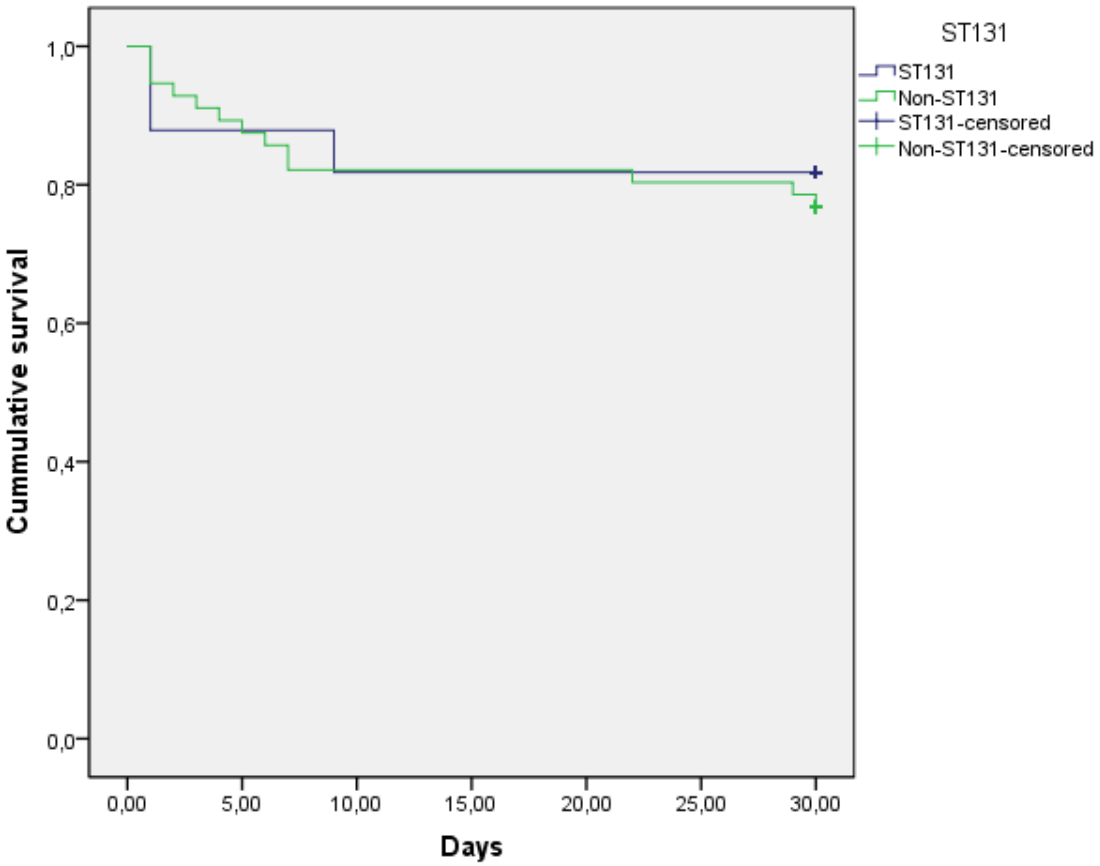

Table 1

Features of patients with bacteraemia due to O25b:H4-T131 *Escherichia coli* (cases) and non-O25b:H4-ST131 *E. coli* (controls) not producing extended-spectrum β-lactamases (ESBLs) [a]

Characteristic	O25b:H4-ST131 (*n* = 33)	Non-O25b:H4-ST131 (*n* = 56)	OR (95% CI)	*P*-value [b]
Age (years) [median (IQR)]	70 (58.5–77.0)	71 (56.75–80)	–	0.98 [c]
Male sex	23 (69.7)	32 (57.1)	1.72 (0.69–4.29)	0.23
Acquisition type				
Community	10 (30.3)	19 (33.9)	0.84 (0.33–2.13)	0.72
Healthcare-associated	10 (30.3)	16 (28.6)	1.08 (0.42–2.78)	0.86
Nosocomial	13 (39.4)	21 (37.5)	1.08 (0.44–2.62)	0.85
Nursing home resident	1 (3.0)	2 (3.6)	0.84 (0.07–9.68)	1 [d]
Recent hospital admission (1 year)	8 (24.2)	11 (19.6)	1.3 (0.46–3.68)	0.6

Charlson comorbidity index [median (IQR)]	2 (0–3)	2 (0–3)	–	0.52 [c]
McCabe classification				
Non-fatal	22 (66.7)	31 (55.4)	1.61 (0.65–3.94)	0.29
Ultimately fatal	7 (21.2)	19 (33.9)	0.52 (0.19–1.42)	0.20
Rapidly fatal	4 (12.1)	6 (10.7)	1.14 (0.29–4.41)	1 [d]
Diabetes mellitus	11 (33.3)	21 (37.5)	0.83 (0.33–2.05)	0.69
Chronic pulmonary disease	2 (6.1)	10 (17.9)	0.29 (0.06–1.44)	0.19 [d]
Cancer	10 (30.3)	16 (28.6)	1.08 (0.42–2.78)	0.86
Liver cirrhosis	2 (6.1)	3 (5.4)	1.14 (0.18–7.20)	1 [d]
Chronic renal insufficiency	1 (3.0)	6 (10.7)	0.26 (0.03–2.26)	0.25 [d]
Neutropenia	3 (9.1)	3 (5.4)	1.76 (0.33–9.30)	0.66 [d]
Solid organ transplantation	0 (0)	3 (5.4)	–	0.29 [d]

Stem cell transplantation	0 (0)	2 (3.6)	–	0.52 [d]
Dependent for basic activities	5 (15.2)	11 (19.6)	0.73 (0.23–2.32)	0.59 [d]
Bedridden	1 (3.0)	3 (5.4)	0.55 (0.05–5.53)	1 [d]
Recurrent UTI	5 (15.2)	4 (7.1)	2.32 (0.57–9.34)	0.28 [d]
Recent surgery	9 (27.3)	3 (5.4)	6.62 (1.64–26.67)	0.008
Recent transrectal prostate biopsy	0	0	–	–
Mechanical ventilation	0	2 (3.6)	–	0.52 [d]
Urinary catheter	8 (24.2)	16 (28.6)	0.78 (0.29–2.09)	0.62 [d]
Endoscopy	3 (9.1)	6 (10.7)	0.83 (0.19–3.58)	1 [d]
Central venous catheter	2 (6.1)	8 (14.3)	0.38 (0.07–1.94)	0.31 [d]
Immunosuppressive drugs	1 (3.0)	6 (10.7)	0.26 (0.03–2.26)	0.25 [d]
Any recent antimicrobial use	15 (45.5)	22 (39.3)	1.28 (0.53–3.07)	0.56

Fluoroquinolones	7 (21.2)	8 (14.3)	1.61 (0.52–4.95)	0.39
Amoxicillin/clavulanic acid	10 (30.3)	14 (25.0)	1.3 (0.50–3.39)	0.58
Piperacillin/tazobactam	4 (12.1)	3 (5.4)	2.43 (0.51–11.64)	0.41 [d]
Carbapenems	2 (6.1)	2 (3.6)	1.74 (0.23–12.98)	0.62 [d]
Cephalosporins	2 (6.1)	1 (1.8)	3.54 (0.30–40.73)	0.55
Source of bacteraemia				
Unknown	5 (15.2)	2 (3.6)	4.82 (0.87–26.44)	0.09 [d]
UTI	12 (36.4)	29 (51.8)	0.53 (0.22–1.28)	0.15
Biliary tract	7 (21.2)	14 (25.0)	0.81 (0.28–2.27)	0.68
Other intra-abdominal infection	4 (12.1)	3 (5.4)	2.43 (0.51–12.5)	0.41 [d]
Respiratory tract	3 (9.1)	3 (5.4)	1.76 (0.33–9.30)	0.66 [d]

Skin and soft-tissue infection	2 (6.1)	3 (5.4)	0.55	1 [d]
Others	0	2 (3.5)	–	0.53 [d]
Pitt bacteraemia score [median (IQR)]	2 (2–3)	2 (2–3.75)	–	0.32 [c]
Active empirical therapy	28 (84.8)	46 (82.1)	1.21 (0.37–3.93)	0.74
Active definitive therapy [e]	26/29 (89.7)	47/51 (92.2)	0.73 (0.15–3.55)	0.70 [d]
Inflammatory response syndrome				
Sepsis	24 (72.7)	38 (67.9)	1.26 (0.48–3.26)	0.62
Severe sepsis	5 (15.2)	8 (14.3)	1.07 (0.31–3.59)	1 [d]
Septic shock	4 (12.1)	10 (17.9)	0.63 (0.18–2.21)	0.47
Mortality at Day 30	6 (18.2)	12 (21.4)	0.81 (0.27–2.42)	0.71
Clinical failure at Day 14	5 (15.2)	10 (17.9)	0.82 (0.25–2.65)	0.74
Duration of hospital stay after infection [median (IQR)] [f]	10 (5–16)	10 (6–17)	–	0.44 [c]

OR, odds ratio; CI, confidence interval; IQR, interquartile range; UTI, urinary tract infection.

[a] Data are expressed as number (%) of exposed patients except where specified.

[b] *P*-values were calculated by χ^2 test except where specified.

[c] Mann–Whitney *U*-test.

[d] Fisher's exact test.

[e] Only patients who survived until Day 3 were included (29 among ST131 and 51 among non-ST131).

[f] Only patients discharged alive were included.

Table 2

Univariate and multivariate analyses of factors associated with 30-day mortality and clinical failure at Day 14

Factor	30-day mortality				Clinical failure at Day 14			
	Crude HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value	Crude OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Age	1.03 (0.99–1.06)	0.08	–		1.02 (0.99–1.07)	0.14		
Male sex	1.46 (0.59–3.60)	0.40	–		0.65 (0.21–2.01)	0.46	–	
Nosocomial acquisition	1.80 (0.64–4.99)	0.25	–		1.87 (0.54–6.44)	0.31	–	
Non-fatal underlying disease [a]	0.27 (0.10–0.72)	0.09	0.21 (0.07–0.60)	0.003	0.27 (0.08–0.87)	0.02	0.21 (0.07–0.60)	0.01
Charlson comorbidity index	1.00 (0.83–1.21)	0.94	–		1.17 (0.89–1.56)	0.25	–	

Immunosuppression [b]					0.80 (0.15–4.0)	0.70	–	
Pitt bacteraemia score	1.08 (0.86–1.35)	0.49	–		1.11 (0.83–1.49)	0.47	–	
Active empirical therapy	0.88 (0.25–3.04)	0.84	–		0.85 (0.21–3.57)	0.82	–	
High-risk source [c]	2.28 (0.88–5.82)	0.08	3.94 (1.36–11.40)	0.01	2.85 (0.87–4.75)	0.08	4.80 (1.17–19.63)	0.02
ST131 *E. coli* [d]	0.78 (0.29–2.06)	0.62	0.53 (0.18–1.57)	0.26	0.28 (0.25–2.65)	0.74	0.60 (0.15–2.33)	0.46
Resistance to ampicillin	0.95 (0.57–1.58)	0.84	–		0.95 (0.57–1.58)	0.84	–	
Resistance to AMC	1.51 (0.87–2.63)	0.13	–		1.51 (0.87–2.63)	0.13	–	
Resistance to ciprofloxacin	1.11 (0.42–2.94)	0.82	–		1.11 (0.42–2.94)	0.82	–	

HR, hazard ratio; CI, confidence interval; OR, odds ratio; AMC, amoxicillin/clavulanic acid.

[a] According to McCabe classification.

[b] Includes neutropenia and use of immunosuppressive drugs.

[c] Includes sources other than the urinary and biliary tracts.

[d] ST131 *Escherichia coli* was forced into the multivariate models.