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Association between rectal colonisation by *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* and mortality: a prospective, observational study

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ABSTRACT

Objectives: We evaluated the association of *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* (KPC-Kp) rectal colonisation with crude mortality and whether this association is independent of the risk of KPC-Kp infection.

Methods: This was a prospective cohort study of patients followed-up 90 days after a study of rectal colonisation. Cox regression was used to study the variables associated with crude mortality. Sensitivity analyses for 90-day crude mortality in different subcohorts were performed.

Results: A total of 1244 patients (1078 non-colonised and 166 colonised) were included. None of the non-colonised patients and 78 (47.0%) of the colonised patients developed KPC-Kp infection. The 90-day crude mortality was 18.0% (194/1078) in non-colonised patients and 41.6% (69/166) in colonised patients. Rectal colonisation was not associated with crude mortality [hazard ratio (HR) = 1.03, 95% confidence interval (CI) 0.69–1.54; $P = 0.85$] when the model was adjusted for severe KPC-Kp infection [INCREMENT-CPE score (ICS) > 7]. KPC-Kp infection with ICS > 7 was associated with an increased risk of all-cause mortality (HR = 2.21, 95% CI 1.35–3.63; $P = 0.002$). In the sensitivity analyses, KPC-Kp colonisation was not associated with mortality in any of the analysed subcohorts, including patients who did not develop KPC-Kp infection (HR = 0.93, 95% CI 0.60–1.43; $P = 0.74$).

Conclusion: KPC-Kp rectal colonisation was not associated with crude mortality. Mortality increased when colonised patients developed severe KPC-Kp infection (ICS > 7). Rectal colonisation was a necessary although insufficient condition to die from a KPC-Kp infection.

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1. Introduction

Klebsiella pneumoniae carbapenemase-producing *K. pneumoniae* (KPC-Kp) strains have spread worldwide [1,2]. These strains can acquire different resistance mechanisms that preclude the use not only of carbapenems and other β-lactam antibiotics, but also fluoroquinolones, aminoglycosides and even colistin [3,4]. Consequently, invasive infections are difficult to treat and are associated with high mortality [5–10].

It is accepted that colonisation often precedes infection [11,12]. Empirical treatment is indicated based on the detection of colonisation [13]. Predictive models that combine the risk of infection in colonised patients and the risk of mortality in infected patients have been developed to determine the best clinical management [13–16]. Therefore, it would seem obvious that colonisation, infection and mortality are related variables.

Colonisation by carbapenemase-producing Enterobacterales (CPE) alone has been reported to increase the crude mortality of critical patients owing to the length of stay in the intensive care unit (ICU) [2]. This has important implications for infection control and patient management. It seems logical to assume that colonisation by KPC-Kp would be associated with mortality by increasing the risk of developing KPC-Kp infection, since this variable is on the pathogenic pathway from colonisation to mortality. It is critical to clarify whether mortality is associated only with colonisation or also with infection in colonised patients.

Unequivocally demonstrating the association between colonisation/infection and mortality in cohort studies is very difficult due to the multiple confounding variables and competing events that need to be controlled. The aim of this study was to determine whether colonisation is associated with crude mortality in hospitalised patients and to test whether this association is independent of the risk of KPC-Kp infection.

2. Materials and methods

2.1. Study design

We conducted an observational, prospective, longitudinal cohort study. We recruited patients aged ≥18 years undergoing rectal colonisation screening for KPC-Kp from July 2012 to November 2017 in the context of an outbreak of KPC-Kp infections that began in July 2012 with subsequent endemicity. Screening was performed by means of a rectal swab culture in patients admitted to the ICU or haematology unit, those undergoing abdominal surgery or transplants, those previously admitted to units affected by the outbreak and those who shared a room with colonised patients. Rectal colonisation by KPC-Kp was defined as the isolation of KPC-Kp from a rectal swab in the absence of clinical signs and symptoms of infection. The start date of follow-up was considered to be the day the first rectal swab was taken. Colonised patients were studied for additional colonisation sites (urine, respiratory tract and skin ulcers). Non-colonised patients included in the cohort were excluded from the analysis if they did not have, at least, a second negative rectal swab culture between 30 days and 90 days after the first swab. If the second rectal swab was positive, colonisation was considered during follow-up. Patients with active infection at the time of the first rectal swab and those who received intestinal decolonisation with oral non-absorbable antibiotics were excluded.

All included patients were followed according to the clinical protocols. For the analysis, follow-up was censored at Day 90 or after death. When necessary, patients or family members were contacted by telephone to determine their status. The Ethics Committee of the Reina Sofia University Hospital–IMIBIC approved the study. All data were anonymised. This report follows STROBE recommendations (Supplementary Table S1).

2.2. Variables

The primary outcome variable was crude mortality at 90 days. All KPC-Kp infections were microbiologically tested and were defined according to the US Centers for Disease Control and Prevention (CDC) criteria [17]. The date of the index culture extraction was considered the date of infection.

Data were collected using a standardised form. The explanatory variables included: (i) demographics: age, sex; (ii) related to hospitalisation: admission in the previous 6 months, ICU stay, admission to high-risk services and in the high-risk period, institutionalisation; (iii) invasive procedures performed: urological manipulation, central venous catheterisation, invasive mechanical ventilation during follow-up, major surgery during follow-up or in the previous 3 months, upper endoscopy or nasogastric intubation during follow-up; (iv) co-morbidities: diabetes mellitus, heart failure, chronic obstructive pulmonary disease, kidney disease, neoplasm, neutropenia, Charlson comorbidity index (CCI), human immunodeficiency virus (HIV) infection, arterial hypertension, solid organ transplantation, dialysis, parenteral drug use; (v) concomitant treatments: steroids, administration of antibiotics active against Gram-negative bacilli or carbapenems for ≥48 h in the previous month, chemotherapy/radiation in the previous 3 months; (vi) related to the KPC-Kp infection episode: Giannella risk score (a predictive score for developing bloodstream infection in colonised patients) [14], all-site KPC-Kp infection, INCREMENT-CPE score (ICS) calculated on a 17-point scale to take into account the administration of appropriate early treatment [15], development of bacteraemia; and (vii) 90-day crude mortality.

2.3. Microbiological studies

Strains were isolated and characterised in accordance with the usual protocols of the centre. Plates with selective medium for carbapenemase-producing strains were used for rectal swab cultures. Specifically, SuperCarba® plates (Francisco Soria Melguizo S.A.) were used. Isolates were identified as *K. pneumoniae* using the WIDER system (Francisco Soria Melguizo S.A.) and NC54 panels. In some cases identification was confirmed by matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF/MS) using a MALDI Biotyper® (Bruker Daltonik GmbH). KPC production was confirmed from July 2012 to March 2017 by commercial PCR (Xpert® Carba-R; Cepheid Inc., Sunnyvale, CA, USA) and from March 2017 by immunochromatography (NG-Test CARBA 5).

The index isolate of KPC-Kp in our centre and some other initial isolates of this outbreak had been previously characterised by multilocus sequence typing (MLST) as corresponding to the same clone (ST512) (reference laboratory, Virgen Macarena University Hospital, Seville, Spain) [18]. These isolates were found to be KPC-3 producers and to contain the $bla_{\text{SHV-11}}$ and $bla_{\text{TEM-1}}$ genes using specific PCR primers for class A, B and D carbapenemases with subsequent sequencing of the obtained amplicons. The results were interpreted following the recommendations of the Clinical and Laboratory Standards Institute (CLSI) [19]. The isolates showed resistance to ampicillin, cephalosporins, aztreonam, quinolones, amikacin,

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tobramycin, trimethoprim/sulfamethoxazole, chloramphenicol, ertapenem, imipenem and meropenem (>32 mg/L). Susceptibility to fosfomycin, amikacin, tigecycline and colistin was variable. All of the isolates tested susceptible to ceftazidime/avibactam.

2.4. Statistical analysis

The results were expressed as the median and interquartile range for quantitative variables and as percentages for qualitative variables. Continuous variables were analysed using the Mann–Whitney *U*-test. Categorical variables were compared using the χ^2 test or Fisher's exact test when indicated. TreeNet was used to categorise hospital services as being at high/low risk of mortality. A classification and regression tree (CART) analysis was performed to study differences in 90-day crude mortality in different time periods. The variables associated with 90-day crude mortality were analysed using Cox regression. Kaplan–Meier survival curves were compared using the log-rank test. A sensitivity analysis was performed to analyse the association between colonisation by KPC-Kp and/or severe KPC-Kp infection (ICS > 7) with crude mortality in different subgroups of interest: (i) not developing KPC-Kp infection; (ii) KPC-Kp colonised; (iii) with CCI > 2; (iv) with CCI ≤ 2; (v) age > 60 years; (vi) age ≤ 60 years; (vii) belonging to a high-mortality risk service; and (viii) belonging to a low-mortality risk service. R software v.3.0.1, IBM SPSS Statistics v.25.0 (IBM Corp., Armonk, NY, USA) and Salford Predictive Modeller software 8.2 (includes CART and TreeNet) were used for statistical analysis.

3. Results

3.1. Characteristics of the groups

A total of 1310 patients were followed during the study period. Of these, 47 non-colonised patients were excluded because they did not have a second rectal swab culture, 14 because they presented active infection at the time of the colonisation study and 5 because they had received decolonisation treatment. Finally, 1244 patients were analysed: 1078 patients did not have rectal colonisation and 166 patients were colonised by KPC-Kp (Supplementary Fig. S1). The clinical characteristics of both groups were different in many variables (Table 1).

Of the 166 colonised patients, 78 (47.0%) developed KPC-Kp infection, of whom 70.5% (55/78) had a high risk of mortality (ICS > 7) and 39.7% (31/78) had bacteraemia. None of the non-colonised patients developed KPC-Kp infection. Crude mortality was higher in colonised patients [41.6% (69/166) vs. 18.0% (194/1078); $P < 0.001$].

3.2. Variables associated with crude mortality

Hospital services (TreeNet analysis; Supplementary Fig. S2) and follow-up period (CART analysis; Supplementary Fig. S3) were classified as high/low risk for mortality. Table 2 shows the Cox regression analysis of the variables associated with crude mortality. Colonisation was associated with higher crude mortality [hazard ratio (HR) = 1.41, 95% confidence interval (CI) 1.04–1.92; $P < 0.001$] in model 1 (not adjusted for KPC-Kp infection). Fig. 1A shows the Kaplan–Meier survival curves according to whether the patient was colonised or not during follow-up (log-rank test, $P < 0.001$). Nevertheless, colonisation was not associated with crude mortality (HR = 1.04, 95% CI 0.61–1.77; $P = 0.88$) when the model was adjusted for KPC-Kp infection (Table 2, model 2). As can be seen in Fig. 1B, mortality was lower in non-colonised patients (194/1078; 18.0%), intermediate in colonised patients with no KPC-Kp infection (26/88; 29.5%) and higher in colonised patients who developed KPC-Kp infection (43/78; 55.1%) (log-rank test, $P < 0.0001$). In a third model (Table 2, model 3) adjusted for severe KPC-Kp infection (ICS > 7), colonisation continued without being associated with higher crude mortality (HR = 1.03, 95% CI 0.69–1.54; $P = 0.85$), while developing a severe KPC-Kp infection was associated with increased risk of all-cause mortality (HR = 2.21, 95% CI 1.35–3.63; $P = 0.002$). The same result was observed when the variable KPC-Kp colonisation was classified into three time categories: non-colonised during follow-up; colonised at baseline; and colonised during follow-up (Supplementary Table S2). Fig. 1C shows how mortality was even higher in colonised patients who developed severe KPC-Kp infection (39/55; 70.9%) in comparison to colonised patients with either no KPC-Kp infection or non-severe (ICS ≤ 7) KPC-Kp infection (30/111; 27.0%; log rank test, $P < 0.0001$).

3.3. Sensitivity analysis

The sensitivity analysis showed that KPC-Kp colonisation was not associated with increased risk of crude mortality in any of the subgroups of interest analysed (Fig. 2A) when the multivariate models were adjusted for other covariates. Specifically, in the subgroup of patients who did not develop KPC-Kp infection, colonisation by KPC-Kp, once the model was adjusted for other covariates such as age, CCI, neutropenia, mechanical ventilation and high-risk service, presented an adjusted HR of 0.93 (95% CI 0.60–1.43; $P = 0.74$) (Supplementary Table S3). However, a severe KPC-Kp infection was always significantly associated with higher crude mortality (Supplementary Fig. 2B).

4. Discussion

Our study shows that KPC-Kp colonisation in hospitalised patients is associated with higher crude mortality at 90 days of follow-up when (severe) KPC-Kp infection is not included in the multivariable model. When it is included, the association between colonisation and crude mortality disappears, while severe KPC-Kp infection (ICS > 7) remains in the model assessed. Similar results were obtained in the sensitivity analysis that was performed. Our interpretation is that in hospitalised patients (critical and non-critical) colonisation may lead to KPC-Kp infection, which in turn would be associated with mortality depending on the patient's risk (based on severity and origin of infection, co-morbidity or having received appropriate early treatment that includes the ICS [15] at time of presentation). Besides, as can be seen in our analysis (including the analysis in the subgroup with no KPC-Kp infection), colonisation alone would not imply higher mortality in colonised patients when the models were adjusted for other covariates.

A previous study in critically ill patients [2] demonstrated the association between CPE colonisation and crude mortality because of an increased length of stay. This made it necessary to propose a strategy to reduce this risk (detection of carriers, intestinal decolonisation, generalised empirical treatment). Unfortunately, the variable CPE infection was not available in that study for analysis. Our study demonstrates that the association between colonisation and mortality in hospitalised patient depends on the risk of severe infection in colonised patients.

It is well known that the main risk factor for KPC-Kp infection is colonisation, especially intestinal colonisation [11,12,14]. Moreover, colonisation is considered the first step for a patient to develop infection. In our study, 47.0% of colonised patients developed KPC-Kp infection. None of the non-colonised patients in our study developed infection. Other studies have reported only very low KPC-Kp infection rates in non-colonised patients (<1%) [20–22].

These data indicate that in our cohort colonisation was a necessary (although insufficient) cause of KPC-Kp infection. It is gen-

Table 1
Characteristics of 1244 patients studied for rectal *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* (KPC-Kp) colonisation and prospectively followed during 90 days

Characteristic	No rectal colonisation (n = 1078)	Rectal colonisation (n = 166)	P-value [a]
Demographics and others			
Age (years) [median (IQR)]	61 (18–71)	68 (19–77)	<0.001 *
Sex female	412 (38.2)	59 (35.5)	0.51
Hospitalisation in previous 6 months	300 (27.8)	134 (80.7)	<0.001
ICU admission during follow-up	444 (41.2)	62 (37.3)	0.08
ICU admission in previous 3 months	101 (9.4)	79 (47.6)	<0.001
High-risk service	540 (50.1)	110 (66.3)	<0.001 **
High-risk period (July 2012–August 2014)	216 (20.0)	74 (44.6)	<0.001
Institutionalisation	206 (19.1)	20 (12.0)	0.03
Invasive procedures			
Urological manipulation during follow-up	484 (44.9)	134 (80.7)	<0.001
Central venous catheterisation during follow-up	382 (35.4)	90 (54.2)	<0.001
Mechanical ventilation during follow-up	292 (27.1)	61 (36.7)	0.01
Major surgery during follow-up	184 (17.1)	36 (21.7)	0.15
Major surgery in previous 3 months	136 (12.6)	80 (48.2)	<0.001
Upper gastrointestinal endoscopy during follow-up	36 (3.3)	12 (7.2)	0.02
Nasogastric intubation during follow-up	95 (8.8)	35 (21.1)	<0.001
Underlying disease			
Diabetes mellitus	268 (24.9)	58 (34.9)	0.006
Heart failure	199 (18.5)	51 (30.7)	0.002
COPD	184 (17.1)	43 (25.9)	0.006
Kidney disease	109 (10.1)	34 (20.5)	<0.001
Neoplasia	238 (22.1)	50 (30.1)	0.02
Neutropenia	19 (1.8)	22 (13.3)	<0.001
Charlson comorbidity index [median (IQR)]	2 (1–3)	3 (2–5)	<0.001***
HIV infection	12 (1.1)	3 (1.8)	0.45
Arterial hypertension	490 (45.5)	94 (56.6)	0.007
Solid organ transplantation	92 (8.5)	17 (10.2)	0.47
Dialysis	35 (3.2)	16 (9.6)	<0.001
Parenteral drug use	32 (3.0)	4 (2.4)	0.69
Concomitant treatments			
Steroids	144 (13.4)	99 (59.6)	<0.001
Antibiotics active against Gram-negative bacilli in previous month	296 (27.5)	156 (94.0)	<0.001
Carbapenem treatment in previous month	37 (3.4)	65 (39.2)	<0.001
Chemotherapy/radiation in previous 3 months	72 (6.7)	12 (7.2)	0.79
KPC-Kp infection			
Risk of infection in colonised patients (Giannella risk score) [median (IQR)]	NA	5 (5–10)	NA
All-site KPC-Kp infection	0	78 (47.0)	NA
Severe KPC-Kp infection (INCREMENT-CPE score > 7)	0	55 (33.1)	NA
KPC-Kp bacteraemia	0	31 (18.7)	NA
Mortality			
Crude mortality	194 (18.0)	69 (41.6)	<0.001

NOTE: Data presented as number (%) of patients except where specified otherwise.
IQR, interquartile range; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; NA, not applicable.
[a] P-values were calculated by the χ^2 test, except where specified otherwise: * Mann–Whitney U-test; ** TreeNet; *** Student's t-test.

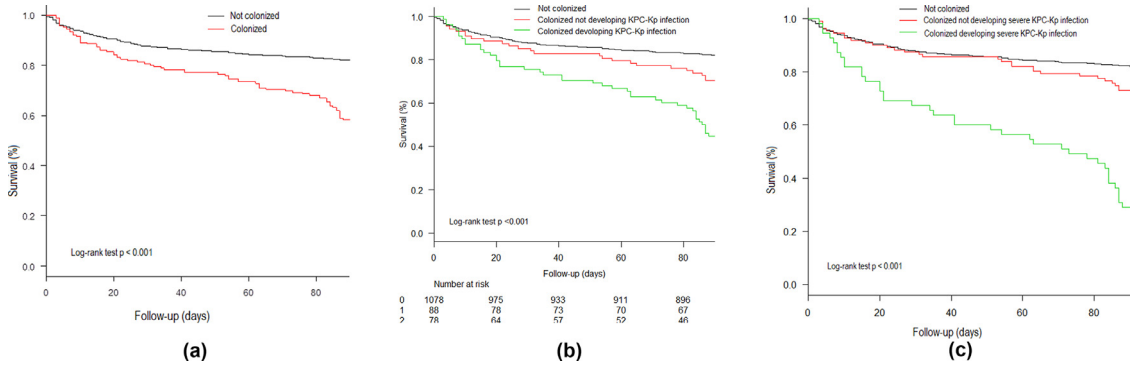

Fig. 1. (A) Survival at Day 90 of follow-up according to KPC-Kp colonisation or no colonisation. Black curve, non-colonised patients; red curve, colonised patients. (B) Survival at Day 90 of follow-up according to no KPC-Kp colonisation, KPC-Kp colonisation and KPC-Kp infection. Black curve, non-colonised patients; red curve, colonised patients who did not develop KPC-Kp infection; green curve, colonised patients who developed KPC-Kp infection. (C) Survival at Day 90 of follow-up according to no KPC-Kp colonisation, KPC-Kp colonisation and severe KPC-Kp infection (INCREMENT-CPE score). Black curve, non-colonised patients; red curve, colonised patients who did not develop KPC-Kp infection or are at low risk of mortality if they developed infection (INCREMENT-CPE score ≤ 7); green curve, colonised patients who developed KPC-Kp infection with high risk of mortality (INCREMENT-CPE score > 7). KPC-Kp, *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*.

Table 2
Adjusted Cox regression analysis of variables associated with 90-day crude mortality

Variable	Univariate analysis		Multivariable model 1		Multivariable model 2		Multivariable model 3	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age, per unit	1.03 (1.02–1.04)	<0.001	1.02 (1.01–1.03)	<0.001	1.02 (1.01–1.03)	0.0007	1.02 (1.01–1.03)	<0.001
Female sex	1.00 (0.78–1.29)	0.97						
ICU admission in previous 3 months	2.06 (1.55–2.73)	<0.001						
High-risk service	4.19 (3.10–5.66)	<0.001	3.10 (2.26–4.26)	<0.001	3.16 (1.98–5.02)	<0.0001	3.07 (2.24–4.21)	<0.001
High-risk period (July 2012–August 2014)	1.24 (0.95–1.63)	0.12						
Institutionalised	0.90 (0.65–1.25)	0.53						
Urological manipulation during follow-up	3.47 (2.62–4.59)	<0.001			1.94 (1.13–3.31)	0.02		
Central venous catheterisation during follow-up	1.91 (1.5–2.4)	<0.001						
Mechanical ventilation during follow-up	2.93 (2.30–3.73)	<0.001	2.48 (1.92–3.20)	<0.001	2.08 (1.42–3.04)	0.0002	2.38 (1.84–3.07)	<0.001
Major surgery during follow-up	0.78 (0.56–1.1)	0.15						
Major surgery 3 months prior to start of follow-up	1.40 (1.05–1.87)	0.02						
Upper gastrointestinal endoscopy during follow-up	1.12 (0.64–1.96)	0.68						
Nasogastric intubation during follow-up	2.02 (1.47–2.76)	<0.001						
Diabetes mellitus	1.44 (1.11–1.86)	0.005						
Heart failure	1.80 (1.38–2.34)	<0.001						
COPD	1.37 (1.03–1.82)	0.03						
Kidney disease	1.94 (1.43–2.64)	<0.001	1.56 (1.14–2.14)	0.005	1.87 (1.23–2.84)	0.003	1.53 (1.12–2.10)	0.008
Neoplasia	1.48 (1.14–1.93)	0.003	1.43 (1.08–1.88)	0.01	1.73 (1.20–2.50)	0.003	1.40 (1.06–1.84)	0.01
Neutropenia	3.58 (2.37–5.41)	<0.001	2.60 (1.64–4.18)	<0.001			2.28 (1.42–3.64)	<0.001
HIV infection	1.34 (0.50–3.60)	0.56						
Arterial hypertension	1.30 (1.02–1.66)	0.03						
Solid organ transplantation	0.70 (0.43–1.14)	0.15						
Dialysis	2.04 (1.28–3.25)	0.002						
Chemotherapy/radiation in previous 3 months	1.26 (0.81–1.95)	0.30						
KPC-Kp colonisation	2.50 (1.90–3.29)	<0.001	1.41 (1.04–1.92)	<0.001	1.04 (0.61–1.77)	0.88	1.03 (0.69–1.54)	0.85
KPC-Kp infection	3.38 (2.44–4.67)	<0.001	Not included in the model		1.62 (0.93–2.83)	0.08		
Severe KPC-Kp infection (INCREMENT-CPE score > 7)	4.71 (3.35–6.63)	<0.001	Not included in the model		Not included in the model		2.21 (1.35–3.63)	0.002

HR, hazard ratio; CI, confidence interval; ICU, intensive cade unit; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; KPC-Kp, *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*.
NOTE: The INCREMENT-CPE score has been calculated on a 17-point scale to take into account the administration of appropriate early treatment or not.

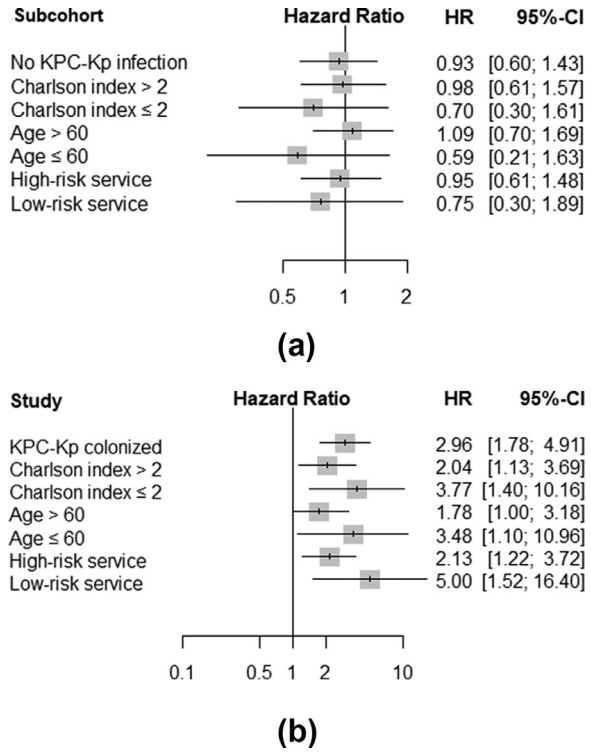

Fig. 2. (A) Sensitivity analysis. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for 90-day crude mortality for KPC-Kp colonisation in different subcohorts [a]. [a] Subcohort including only patients who developed KPC-Kp infection was not included in the analysis since all the cases were colonised. (B) Sensitivity analysis. Adjusted HRs and 95% CIs for 90-day crude mortality for severe KPC-Kp infection (INCREMENT-CPE score > 7) in different subcohorts [b]. [b] Subcohort including only not KPC-Kp colonised patients was not included in the analysis since no case developed KPC-Kp infection. KPC-Kp, *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*.

erally accepted that KPC-Kp infections increase mortality, and observational studies and meta-analyses show this to be true [23]. Other studies, however, have not found such an association, usually in critically ill patients where mortality depends on the baseline severity of the patients [24]. These discrepancies highlight the difficulty of controlling for bias in observational studies conducted in the setting of multidrug-resistant bacterial infections. We have attempted to analyse the variables associated with mortality in greater depth, both conducting sensitivity analysis as well as using advanced software tools to control the 'centre effect' of the different hospital services and possible temporal differences in the clinical management of these patients.

It was expected that infections with an ICS > 7 would be associated with higher mortality. The predictive capacity of this score is well known [15] and is applicable to our cohort of infected patients [4].

This study confirms the importance of determining the carriage status of patients when a centre is suffering an outbreak or endemic situation as well as the importance of managing colonised patients on an individual basis. Therefore, it is also important to administer appropriate empirical treatment and even use newly available drugs (ceftazidime/avibactam, meropenem/vaborbactam) when there is an objective situation that justifies it. Clinical management algorithms are available to make objective treatment decisions [13,25]. However, these results would also require further analysis of the factors that could predispose colonised patients to develop infection and the severity of the infection.

Our study has limitations. When a patient was not colonised, there was no protocolised follow-up for rectal swab cultures. For this reason, we required that non-colonised patients have, in addition to the baseline culture, at least one negative rectal swab culture between Days 30 and 90. We did not include short-admission patients with milder symptoms who did not return to the hospital. Therefore, including only the most severe non-colonised patients can be considered a bias. This bias would have influenced the conclusions if the crude mortality of non-colonised patients had been similar to or higher than that of colonised patients, which evidently did not occur.

In conclusion, colonisation was a necessary although insufficient cause of KPC-Kp infection. The risk of mortality of a colonised patient depended on whether the patient developed a severe KPC-Kp infection. Colonisation does not increase crude mortality per se.

Declaration of Competing Interests

JRB has served as a scientific advisor for a research project for AstraZeneca, Pfizer and InfectoPharm, as a speaker in unrestricted accredited educational activities funded by Merck and has obtained funding from the Spanish Ministry of Economy and Competitiveness, the Carlos III Health Institute (ISCIII); BGG has a contract to intensify the research activity associated with the project P18/01849 (Carlos III Health Institute); JTC has served as scientific advisor for a research/consensus project for Pfizer, as an expert in a consensus document for InfectoPharm and has received payment for lectures including service on speakers bureaus and for the development of educational presentations for Pfizer, AstraZeneca, Shionogi and Merck; AC has received honoraria for the development of educational presentations for Pfizer and Shionogi. All other authors declare no competing interests.

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Ethical approval

The Ethics Committee of the Reina Sofia University Hospital–IMIBIC [code MOR-ANG-2018-09] approved the study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jgar.2021.10.024.

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