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Clinical Outcomes Associated with Co-infection of Carbapenem-Resistant Enterobacterales and other Multidrug-Resistant Organisms

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SUMMARY

Background: Infections with carbapenem-resistant Enterobacterales (CRE) are associated with increased risk of death. Polymicrobial infections with antimicrobial-resistance may add to the burden of clinical care and patients' clinical prognosis.
Aim: To examine the impact of CRE co-infection with other multi-drug resistant organisms (MDRO) on patient clinical outcomes.
Study Design: A retrospective observational study was conducted to compare the clinical outcomes of CRE patients who were co-infected with carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), multidrug-resistant *Acinetobacter baumannii* (MDRA) and Methicillin-resistant *Staphylococcus aureus* (MRSA).
Results: A total of 224 CRPA and 209 MDRA co-infections with CRE were identified from 4,236 cases from 2015-2020. The overall 90-day all-cause mortality was 21.6% but increased to 35.0% and 33.5% among patients who were co-infected with CRPA and MDRA, respectively. The odds of all-cause mortality among CRE patients who were co-infected with CRPA was twice that of patients identified with CRE alone [adjusted odds ratio (AOR) = 2.02, 95% confidence interval (CI): 1.18—3.46]. Further, the odds of all-cause mortality among CRE patients who were concomitantly identified with MRSA was more than twice that of patients who were not identified with MRSA [AOR = 2.16, 95%CI:1.31—3.56]. The clinical outcome of patients with CRE did not differ significantly depending on the presence of carbapenemase genes.
Conclusion: The results show that CRPA and CRE co-infections have synergistic effects on clinical outcomes. Further investigation is necessary to understand the mechanism. Screening high risk patients for concomitant antimicrobial-resistant infections may have a

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significant clinical impact, including effective therapies, antibiotic stewardship, and infection control policies.

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Background

Infections with carbapenem-resistant Enterobacterales (CRE) are associated with increased patient mortality [1,2]. Patients identified with CRE often have underlying acute or chronic medical illnesses and may be infected with other Gram-negative multidrug-resistant organisms (MDROs) such as carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), and carbapenem-resistant *Acinetobacter baumannii* (CRAB) or multidrug-resistant *Acinetobacter baumannii* (MDRA). About 40% of patients infected with CRE are co-colonized with either CRPA and/or CRAB [3]. Particularly, critically ill patients, with history of multiple antibiotic exposure, and presence of indwelling medical devices are at risk of MDROs and CRE infection [3,4]. Further, CRE infected patients have 10-fold greater risk of co-infection with other carbapenem-resistant pathogens [5].

Heterogeneity in MDRO co-infections may add to the burden of infection control management, clinical care, and poor patient outcomes [6]. Polymicrobial infections and their synergistic interactions may also lead to increased antibiotic resistance, delayed wound healing, and increased risk of amputation among diabetic patients [7,8]. Moreover, polymicrobial infections may facilitate cross-transfer of resistant genes between different species and this could increase the risk of poor clinical outcomes in patients [6,9,10].

A prospective cohort study conducted in the U.S. found that about 9% of patients had at least two different CRE species [11], with 36% showing different mechanisms of resistance. Further, patients isolated with carbapenemase-producing Enterobacterales (CPE) had nearly five times the odds of dying compared to patients with non-CP CRE [12]. Because CRE infection can be acquired and spread via both endogenous and exogenous transmission, high risk patients may be at higher risk of co-infection with multiple MDROs [6]. Co-infections with MDROs are associated with higher antibiotic resistance [3]. While polymicrobial infections are increasingly diagnosed in critically ill patients, most MDRO infection prevention policies and antibiotics stewardship are generally based on the assumptions of a single microorganism [6]. The impact of CRE co-infections with other MDROs on patient clinical prognosis is largely unexplored. Understanding the burden of antimicrobial-resistant co-infections may also have significant implications in antimicrobial stewardship. The primary aim of this study was to examine the impact of CRE co-infection with other MDROs (CRPA and CRAB/MDRA) on patient clinical outcomes.

Methods

Study design and data source

The study was a retrospective cohort study consisting of 4,236 laboratory confirmed CRE cases that were collected from the Greater Houston region of Texas from January 2015 to December 2020. The study utilized CRE surveillance data obtained from the Houston Health Department and the adjacent county, Fort Bend County Health and Human Services. Infections caused by MDROs are reportable in the state of Texas. Our cohort includes verified cases with a clinical diagnosis in addition to the isolation of a CPE organisms.

The surveillance data was originally collected from electronic medical records (EMRs), and electronic clinical laboratories (ELRs) obtained from several different healthcare facilities throughout the region, including acute care hospitals, long-term acute care hospitals, long-term care facilities or skilled nursing facilities, and public health laboratories.

The surveillance data contained patient demographics, microbiology laboratory reports (including antibiotic susceptibility reports), molecular tests for resistance mechanisms, clinical history, patient disposition, and clinical outcomes. Patient disposition included clinical outcome at discharge, post-discharge patient location or place of transfer, and patient outcome at the completion of CRE case investigation. To minimize missing information in the surveillance database, a repeated review and extraction of available medical records, laboratory reports, susceptibility reports, molecular test results, and surveillance documentation forms were conducted for approximately 2,000 of all the 4236 cases. Patients identified with CRE were followed from the time of specimen collection for case to clinical outcome.

Definitions of study variables

The outcome variable of the study was all-cause mortality, which is a composite outcome of infection or non-infection-related mortality that occurred within 90 days of the initial CRE isolation. For the purpose of analyses, discharge to hospice for lack of improvement and functional deterioration including prolonged admission to ICU, were classified as deceased at the time of patient disposition or at the time of completion of case investigation. Patients' clinical outcomes were ascertained using EMR. Patient outcome was classified as 'survived' if the patient disposition was discharged in a stable condition to home or a facility of residence or if the patient's condition was stable and did not require admission. Patients who were documented as death at the time the CRE case investigation was completed were included as all-cause mortality if the documentation of death was within 90-day of the initial CRE isolation.

The primary exposure variable was the presence of CRPA, MDRA or CRAB co-infection with CRE. Co-infection was defined as laboratory-based identification of MDROs from the same clinical specimen as CRE or from a different specimen during the same period of patient admission, or that the MDRO co-infection was identified within seven days of CRE isolation or after seven days of CRE identification. The MDRO cases (CRE, CRPA, and CRAB/MDRA) were ascertained based on the clinical

microbiology laboratory, electronic medical records, antibiotic susceptibility reports, and phenotypic and genotypic tests reported by both clinical and public health laboratories.

The independent variables considered as potential confounders in the association between the co-infections and all-cause mortality were demographic variables that included age, race/ethnicity (Asian, Black, Hispanic, White, other race or multiracial, and unknown race), sex (male or female), microbiological variables included the species of CRE organism (*K. pneumoniae, E. coli* or other Enterobacterales), carbapenemase enzyme production (positive, negative, unknown), types of carbapenemase genes (KPC, NDM, and others), presence of concomitant infection with MRSA, presence of concomitant infection with vancomycin-resistant *enterococcus* (VRE), clinical syndromes, and background comorbid conditions or underlying diseases.

Statistical analysis

All data management and analysis were performed using SAS 9.4 (SAS Institute, Cary, NC, USA). Continuous variables were compared using Wilcoxon rank-sum test or Kruskal-Wallis test as appropriate. Categorical variables were compared using the Chi-square test or Fisher's exact test (when expected cell counts were less than or equal to 5). All tests were two-sided with a 5% level of significance. Stratified analyses using Cochran-Mantel Haenszel tests were conducted to examine the heterogeneity of the effects of certain covariates on the association between co-infection and all-cause mortality.

Univariate logistic regression analysis was performed to investigate the relationship between covariates and all-cause mortality. Variables with a *P*-value <0.1 in the univariate analysis were included in the multivariable model. Each variable was also assessed for biological and clinical relevance and direction of effect on the association between co-infection and all-cause mortality.

The multivariable logistic regression model was constructed using a stepwise variable selection method to estimate the effect of the exposure variable on all-cause mortality while controlling for potential confounding variables in the model. The Hosmer-Lemeshow Chi-square test was used to determine the model goodness of fit. Adjusted odds ratios (AOR) were computed along with 95% confidence intervals (95% CI). Variables with a *P*-value <0.05 were considered statistically significant.

The study was reviewed and approved as exempt by the Institutional Review Board of the University of Texas Health Sciences Center.

Results

Demographic characteristics of patients

A total of 4,236 CRE infections were analyzed, of which Black or African American (31.7%) and White (32.4%) patients accounted for more than 60% of the cases. Patients were older, with median age (IQR, interquartile range) of 62 years [52—75], and about half of them were female (Table I).

Approximately 18% of patients were existing residents of healthcare facilities, whereas 82% of patients were admitted to a healthcare facility at the time of diagnosis with CRE infection. *K. pneumoniae* was the most commonly identified CRE species (84.8%), and 77.2% (525/680) of all carbapenemase gene positive cases were KPC-producers. Urine sample was the

Table I
Demographic and microbiological characteristics of CRE cases identified from 2015—2020 in Greater Houston, Texas.

Variables	Total	Percent	*P* value
Age in years [median, IQR]	62 [52,75]		0.001
Gender			0.601
Female	2142	50.6	
Male	2092	49.4	
Race			0.061
Asian	208	4.9	
Black	1174	31.7	
White	1199	32.4	
Hispanic	660	17.8	
Others/multiracial	123	3.3	
Unknown	336	9.2	
Healthcare facility resident			<0.001
Yes	798	18.8	
No	3438	81.2	
Organism			0.988
K. pneumoniae	3595	84.8	
E. coli	468	11.1	
Other Enterobacterales Φ	154	3.7	
Specimen type			<0.001
Blood	319	7.5	
Respiratory	566	13.4	
Wound/tissue	598	14.1	
Urine	2038	48.1	
Other body fluid	108	2.6	
Medical devices	11	0.3	
Swabs	48	1.1	
Other	548	12.9	
Clinical syndrome			<0.001
Urinary tract infection	1997	47.2	
Pneumonia	589	13.9	
Bloodstream infection	321	7.6	
Surgical site or wound infection	601	14.2	
Other infections	655	15.5	
Colonization	69	1.6	
Carbapenemase production			<0.001
Positive	680	16.1	
Negative	184	4.3	
Unknown	3372	79.6	
Types of Carbapenemase identified			0.588
KPC	525	77.2	
NDM	45	6.7	
Other genes	8	1.4	
Admitted			<0.001
Yes	3425	81.7	
No	768	18.3	
Case admitting facility type			<0.001
Acute care hospital	2889	85.6	
Long-term acute hospital	438	13.0	
Long-term care facility	47	1.4	

*The other Enterobacterales included *K. oxytoca*, Enterobacter, *K. aerogenes*. KPC-*Klebsiella pneumoniae* carbapenemase; NDM-New Delhi metallo-beta-lactamase; IQR- Inter quartile range.

Table. II
Univariate analysis of demographic, microbiological, and clinical characteristics of CRE cases and all-cause mortality, Greater Houston, Texas, 2015—2020.

Variables	N (%)	All-cause mortality	Survived	Unadjusted odds ratio	*P* value
Age in years, median [IQR]	62 [53,75]	67	64	1.05	0.03
Gender					0.58
Female	2142 (50.6)	470 (21.9)	1672 (78.1)	1.04	
Male (ref.)	2091 (49.4)	444 (21.2)	1647 (78.8)		
Race/Ethnicity					0.06
Asian (ref.)	208 (5.6)	44 (21.2)	164 (78.8)		
Black	1174 (31.7)	299 (25.5)	875 (74.5)	1.27	
White	1199 (32.4)	302 (25.2)	897 (74.8)	1.26	
Hispanic	660 (17.8)	142 (21.5)	518 (78.5)	1.02	
Others/multiracial	123 (3.3)	33 (26.8)	90 (73.2)	1.37	
Unknown	336 (9.2)	64 (19.1)	272 (80.9)	0.88	
Healthcare facility of residence					<0.01
Yes	798 (18.8)	371 (46.5)	427 (12.9)	4.62	
No (ref.)	3438 (81.2)	544 (15.8)	2894 (84.2)		
Organisms					0.98
K. pneumoniae	3595 (84.8)	765 (21.3)	2830 (78.7)	1.03	
E. coli	468 (11.1)	99 (21.2)	369 (78.8)	1.02	
Other *Enterobacterales** (ref.)	154 (3.7)	32 (20.8)	122 (79.2)		
Carbapenemase production					0.03
Positive	680 (16.1)	176 (25.9)	504 (74.1)	0.78	
Negative (ref.)	184 (4.3)	46 (25.0)	138 (75.0)		
Unknown	3372 (79.6)	693 (20.6)	2679 (79.4)	1.05	
Types of carbapenemase identified					0.59
KPC	525 (77.2)	127 (24.2)	398 (75.8)	2.23	
NDM	53 (6.6)	15 (28.3)	38 (71.7)	2.76	
Other genes (ref.)	8 (1.2)	1 (0.7)	7 (87.5)		
Admitted					<0.01
Yes	3425 (81.7)	889 (98.5)	2536 (77.1)	18.88	
No (ref.)	768 (18.3)	14 (1.8)	754 (98.2)		
Case admitting facility type					<0.01
Acute care hospital	2889 (85.6)	716 (24.8)	2173 (75.2)	0.86	
Long-term acute	438 (13.0)	152 (34.7)	286 (65.3)	1.39	
Long-term care facilities (ref.)	47 (1.4)	13 (27.7)	34 (72.3)		
Admitted to ICU					<0.01
Yes	690 (16.4)	411 (59.6)	279 (40.4)	23.88	
No (ref.)	1394 (33.2)	81 (5.8)	1313 (94.2)		
Unknown	2113 (50.4)	414 (19.6)	1699 (80.4)	3.95	
Clinical syndrome					<0.01
Urinary tract infection	1997 (47.2)	281 (14.1)	1716 (85.9)	0.40	
Pneumonia or respiratory illness	589 (13.9)	198 (33.6)	391 (66.4)	1.24	
bloodstream infection	321 (7.6)	229 (71.3)	92 (28.7)	6.09	
Surgical site or wound infection	601 (14.2)	132 (22.0)	469 (78.0)	0.69	
Other infections	655 (15.5)	52 (7.9)	603 (92.1)	0.21	
Colonization (ref.)	69 (1.6)	20 (29.0)	49 (71.0)		
Indwelling medical devices					<0.01
Yes	1331 (32.4)	504 (56.6)	827 (25.7)	3.76	
No (ref.)	2778 (67.6)	387 (13.9)	2391 (86.1)		
Surgery in the past month					0.47
Yes	217 (27.4)	97 (44.7)	120 (55.3)	1.12	
No (ref.)	576 (72.6)	241 (41.8)	335 (58.2)		
Presence of underlying disease					<0.01
Yes	1631 (38.5)	487 (29.9)	1144 (70.1)	2.17	
No or unknown (ref)	2605 (61.5)	428 (16.4)	2177 (83.6)		
Types of underlying diseases*					0.01
Cardiovascular disease	52 (5.4)	19 (36.5)	33 (63.5)	6.04	
Cerebrovascular disease	115 (12.0)	34 (29.6)	81 (70.4)	4.41	

Table. II (*continued*)

Variables	N (%)	All-cause mortality	Survived	Unadjusted odds ratio	*P* value
Chronic respiratory disease	17 (1.8)	4 (23.5)	13 (76.5)	3.23	
Diabetes and complications	196 (20.4)	56 (28.6)	140 (71.4)	4.20	
Morbid obesity	25 (2.6)	9 (36.0)	16 (64.0)	5.91	
Chronic kidney disease (CKD or ESRD)	184 (19.1)	77 (41.8)	107 (58.2)	7.65	
Bedbound or chronic ulcer	85 (8.8)	26 (30.6)	59 (69.4)	4.63	
Gastrointestinal and liver diseases	85 (8.8)	28 (32.9)	57 (67.1)	5.16	
Cancer or malignancy	86 (8.9)	30 (34.9)	56 (65.1)	5.62	
Mental disorder	46 (3.8)	4 (8.7)	42 (91.3)	1.0	
Chronic infectious diseases	71 (7.4)	35 (49.3)	36 (50.7)	10.21	
Co-infections and clinical outcome					
MDRO co-infections					
CRAB or MDRA	224 (5.3)	75 (33.5)	149 (66.5)	1.99	<0.01
CRPA	209 (4.9)	73 (34.9)	136 (65.1)	2.13	
CRE only (ref.)	3803 (89.8)	767 (20.2)	3036 (79.8		
Other infections					
MRSA infection					<0.01
Yes	149 (3.5)	74 (49.7)	75 (50.3)	3.81	
No					
VRE infection					<0.01
Yes	78 (1.8)	40 (51.3)	38 (48.7)	3.97	
No (ref.)	4140 (98.2)	867 (20.9)	3273 (79.1)		
Disposition					
Hospice	602 (14.2)				
Died	313 (7.4)				
Survived	3321 (78.4)				

IQR- Interquartile range; *The other *Enterobacterales* include *K. oxytoca, Enterobacter, K.erogenes;* # the sum does not add up to 100 due to missing data to categorize the source of onset; ICU-Intensive care unit. CKD-chronic kidney disease; ESRD-End stage renal disease. ** included functional deterioration and admission to ICU and prolonged ICU admission (>15 days) and or transfer to high acuity care due to lack of deterioration. # Patient transferred to hospice care due to lack of clinical improvement. Odds ratios were based on logistic regression.

most common specimen type of organism identification, followed by wound or surgical site (14.1%) and respiratory specimens (13.4%). Although urinary tract infections accounted for majority of the primary clinical syndromes (47.2%), surgical site or wound infections (14.2%) and respiratory infections or pneumonia (13.9%) were also of significant proportions. At the time CRE was identified, over 85% and 13% of the cases were admitted to acute care hospitals (ACH) and long-term acute care hospitals (LTAC), respectively.

MDRO Co-infections and patient clinical outcome

Of the total of 4236 CRE infections, 224 (5.3%) were co-infected with MDRA or CRAB and 209 (4.9%) with CRPA. Furthermore, Gram-positive co-infections were also documented that included MRSA in 149/4236 (3.5%) and VRE in 78/4236 (1.8%) of the cases. Although the majority of CRE cases, 3,321/4236 (78.4%) survived or were discharged in stable condition, the overall 90-day all-cause mortality accounted for 915 (21.6%). However, the attributable mortality of CRE infection was not well documented to report (Table II). All-cause mortality was 35.0%, 33.5%, and 20.2% among patients with CRE who had CRPA, MDRA co-infections, and CRE alone, respectively. The proportion of all-cause mortality was not significantly different based on race or ethnicity (P=0.06). All-cause mortality was significantly different based on clinical syndrome of CRE; 73.4% (229/321) for CRE with central line-associated or bloodstream infections, 14.1% (281/1997) among those presented with urinary tract infections, and 33.6% (198/589) among patients presented with respiratory syndromes (primarily pneumonia). Furthermore, the proportion of all-cause mortality was not significantly different based on carbapenemase gene production; 25.9% (176/680) for carbapenemase gene positive CRE versus 25.0% (46/184) among the carbapenemase negative CRE.

Predictors of all-cause mortality

In the bivariate analysis, the odds of all-cause mortality were significantly associated (P <0.05) with age, healthcare facility residence, production of carbapenemase, type of patient admitting healthcare facility, clinical syndrome, presence of indwelling medical devices, presence of underlying disease, co-infections with MRSA, VRE, CRAB/MDRA, and CRPA (Table II). The odds of all-cause mortality among patients who had CRE infection and were co-infected with CRAB/MDRA and CRPA was about 2 times and more than 3 times that of patients who were identified with CRE only, respectively. However, there was no significant difference in clinical outcome based on gender (P= 0.58), species of organism (P= 0.98), and history of surgery in the past month (P= 0.47). The presence of a carbapenemase gene was associated with 22% lower odds of all-cause mortality (unadjusted OR=0.78) compared to carbapenemase negative CRE in the bivariate analysis (Table II). However, patient clinical outcomes were not significantly different based on the types of carbapenemase-encoding genes (P=

Table III
Multivariable model of predictors of all-cause mortality among CRE, CRPA, and CRAB/MDRA co-infected patients, from 2015–2020,Greater Houston, Texas

Effect	Adjusted OR	95% C. I.	*P* value
CRAB/MDRA	1.15	0.687–1.925	0.590
CRPA	2.024	1.182–3.466	**0.010**
CRE ((referent)	1.00		
Age in years (unit=10 years)	1.12	1.007–1.239	**0.036**
Admitting/reporting facility			
Acute care hospital	0.27	0.023–3.033	0.286
Long-term acute	0.45	0.038–5.197	0.518
Long-term care facilities (referent)	1.0		
Indwelling medical device (yes Vs. no)	2.48	1.602–3.844	**<0.001**
MRSA (yes Vs. no)	2.16	1.311–3.565	**0.003**
Underlying (chronic) diseases			
Bedbound/chronic ulcer	3.78	1.195 –11.951	**0.024**
Cancer or malignancy	4.76	1.510 –14.988	**0.008**
Cardiovascular disease	5.02	1.478 –17.060	**0.009**
Cerebrovascular disease	4.07	1.322 –12.550	**0.014**
Chronic infectious disease#	7.96	2.491 –25.435	**0.001**
Chronic kidney disease (CKD or ESRD)	6.35	2.138 –18.872	**0.001**
Chronic respiratory disease	3.22	0.648 –15.955	0.152
Diabetes	3.98	1.327 –11.919	**0.014**
Liver and gastrointestinal disease	3.29	1.026 –10.522	**0.045**
Morbid obesity	3.69	0.955 –14.237	**0.058**
Mental disorder (referent)	1.00		

CRAB-Carbapenem-resistant Acinetobacter baumannii; MDRA-Multidrug-resistant Acinetobacter baumannii; CRPA- Carbapenem-resistant Pseudomonas aeruginosa; MRSA- Methicillin-resistant Staphylococcus aureus; Model goodness fit Hosmer-Lemeshow Chi-square test *P* value (0.6). *The model is based on multivariable logistic regression analysis. #Chronic infectious diseases included like HIV and TB. OR; Odds ratios.

0.59) Additionally, exploratory stratified analysis using the Cochran-Mantel Haenszel test also indicated that there was no heterogeneity of effect on the patient mortality based on carbapenemase production.

Based on multivariable analyses (Table III), the odds of all-cause mortality among patients identified with CRE who were co-infected with CRPA was more than 2 times [AOR=2.02, 95% CI: 1.18–3.46] that of patients identified with CRE alone, after controlling for potential confounding factors in the model. Furthermore, CRE patients who were co-infected with MDRA, or CRAB had 15% higher odds of death when compared to patients identified with CRE alone, however, this was not statistically significant (*P*=0.59).

On the other hand, the odds of all-cause mortality among CRE patients identified with MRSA co-infection was more than twice [AOR=2.16, 95%CI:1.31–3.56] the odds of all-cause mortality among patients without MRSA. Although CRE patients who were co-infected with VRE had about 4 times the odds of death as that of patients without VRE (in the binary analysis), this association did not remain statistically significant in the multivariable model.

Furthermore, when compared to CRE patients with no documented presence of indwelling medical devices, odds of all-cause mortality among CRE patients with indwelling medical devices was about 2.5 times higher [AOR=2.5 95% CI: 1.60–3.84].

For every 10-year increase in patient age, the odds of all-cause mortality increased by 12% [AOR=1.12, 95% CI:1.01–1.24], which was statistically significant (*P*= 0.036). The odds of all-cause mortality were positively associated with the different types of background diseases, as detailed in Table III. Potential interaction effects analysis was conducted with variables including MRSA, VRE, and CPE, but none of them was significant.

Discussion

In this study, a significant number of patients infected with CRE were concomitantly identified with CRPA, MDRA or CRAB infection. Although the incidence of co-infections identified in this study may be underestimated due to the source of the data, previous studies have estimated that CRE cases were up to 10-fold higher risk of co-infection with other carbapenem-resistant pathogens compared to non-CRE [5]. Among patients identified with CRE, co-infections with CRPA was an independent prognostic factor of clinical outcome. While all-cause mortality was 20% among patients identified with CRE alone, all-cause mortality was 35% among patients who were identified with CRPA co-infection. This finding is much lower than previous studies [1,3,13] for several possible reasons. One study which was based on a smaller sample (n=86) found that the 90-day mortality among patients identified with CRE was 24%, and the 90-day mortality among patients co-colonized with CRPA and/or CRAB was 53%. This may be due to the fact that the study population was acutely ill or hospitalized (79% were debilitated and the majority were residents of long-term care facilities) and 80% African Americans. In addition, co-infections were combined with CRPA and CRAB, which may have had a greater impact on the patient outcome than effects of individual co-infections [3]. The finding in the present study is more generalizable in terms of the diversity of patient sample as well as larger sample size. Other studies have documented much higher mortality and high infection-related mortality associated with CRE among hospitalised patients [1,2,13,14]. However, most of these studies have focused on the effect of CRE bacteremia, by excluding other infections caused by CRE. A study by Hauck *et al.* [13] found high mortality among patients with carbapenem-resistant *K. pneumoniae* bloodstream infection, however, the study was exclusively CRE (*K. pneumoniae* only) bloodstream infection and did not control for the impact of co-infections with CRPA or other co-infections. In our study, all CRE infections including both nosocomial and community-acquired infections were included, which may have underestimated the incidence of mortality

unlike the previous studies [1,13]. Additionally, most previous studies were based on either a small sample size or patients who were critically ill.

In multivariable analyses, the odds of all-cause mortality among patients with CRE who were identified with CRPA coinfection were twice that of patients identified with CRE alone.

The molecular or genetic mechanisms of this association may be difficult to explain because the association remained statistically significant, even after controlling for the effects of age, underlying illness or comorbid conditions, co-colonization or co-infection with MRSA, the type of facility, surgery in the past month, and presence of indwelling medical devices. One possible explanation is that co-infections with multiple MDROs may have synergistic effect that led to increased resistance against antibiotics, and therefore lack of effective therapeutic agents leading to poor prognosis. A previous study documented that co-colonization with MDROs was associated with greater antibiotic resistance and elevated MICs in CRE isolates among patients [3]. Also, co-infections were associated with increased risk of mortality in that study, even though CRPA and CRAB were not treated as separate co-infections. In another study, co-infections with CRPA and/or CRAB were associated with isolation of colistin-resistant CRE [15], indicating the development of greater resistance in co-infected cases. Furthermore, Marchaim and colleagues [16] also found a positive association between CRE infection and co-colonization with *P. aeruginosa* and *A. baumannii* and mortality, though the study did not distinguish whether the co-colonization was carbapenem-resistant or MDROs.

This study is one of the first studies to assess the impact of CRE co-infections with Gram-positive infections, besides non-lactose-fermenters, that included MRSA and VRE. Patients with MRSA co-colonization or co-infection with CRE had greater odds of all-cause mortality when compared with CRE patients without MRSA. The odds of all-cause mortality among patients with CRE patients who were identified with MRSA co-infection were more than twice as many patients without MRSA. This effect may be due to either presence of underlying severe acute illness or the absence of antibiotic coverage. If the patient had MRSA infection prior to identifying CRE and the patient had been on antibiotic coverage for the MRSA, there may be a delay in appropriate antibiotics intervention for the CRE. However, this study cannot determine whether the lack of appropriate antimicrobial therapy covering for both organisms may have resulted in a higher proportion of poor clinical outcome. This finding corroborates a recent study by Marchaim *et al.* who reported that prior infection with MRSA was associated with risk of co-colonization with CRE and CRPA. According to that study, MRSA infection in the past six months was associated with increased risk of co-colonization of CRE with CRPA or CRAB [3], yet the investigators did not assess MRSA concomitant infection with CRE in their analysis. In the present study, MRSA co-infection with CRE stood out as a strong and independent predictor of mortality among patients infected with CRE.

There are inherent limitations to this study due to the nature of the study design. CRPA is a non-reportable MDRO in Texas, thus, underestimation of CRPA is possible in this study. As a result, the proportion of CRPA presented in this study may not accurately reflect the true incidence of co-infection in this population. Second, data were collected retrospectively; therefore, this study is prone to information bias. Additionally, there may be potential surveillance bias, if surveillance was variable based on the presence of carbapenemase. Moreover, most CRE carbapenemase production was unknown, hence cases with unknown carbapenemase status may have been misclassified. This potential bias unlikely impacted the identified association.

Conclusion

The results show that MDRO (including CRPA and MRSA) and CRE co-infections have synergistic effects on clinical outcomes. This study represents the largest cohort of patients identified with CRE from multiple healthcare institutions and explored the effect of co-infections with multidrug-resistant organisms on patients' clinical prognosis. The findings from this study are important in infection control policy and clinical patient management. Screening high risk patients with CRE infection for MDRO co-infections may guide clinicians to an appropriate antibiotic choice which could potentially reduce therapeutic failure. Moreover, identifying patients with co-infections may have a greater implication in infection control; including patient cohorting or isolation based on the identified pathogens. Furthermore, concomitant MDRO infections, aside from the CRE surveillance, may need to be considered in the current infection control policy including antibiotic stewardship.

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Conflict of interest

No reported conflict of interest.

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Author contributions

BKT performed the literature searches, managed the data, abstracted medical and laboratory records, analyzed the data, and drafted the manuscript. CD supervised BKT, reviewed the research protocol and results, and made critical revisions to the manuscript. KF reviewed the study protocol and methods and the results and made necessary revisions to the manuscript. SD reviewed the study protocol and statistical analysis, the results, and the manuscript. OM reviewed the study protocol and the results and made critical revisions to the manuscript.

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