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ORIGINAL RESEARCH

Association Between Multidrug-Resistant Bacteria and Mortality in Critically Ill Patients

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ABSTRACT

Introduction: Multidrug-resistant bacteria (MDRB) carriage may impact the outcomes of intensive care unit (ICU) patients. In this study, we aimed to assess the effect of MDRB-related infection and colonization on the day 60 mortality rate.

Methods: We conducted a retrospective, observational study in a single university hospital ICU. From January 2017 to December 2018, we screened all patients admitted to the ICU for at least 48 h for MDRB carriage. The primary outcome was the mortality rate on day 60 after MDRB-related infection. The secondary outcome was the mortality rate on day 60 of non-infected but colonized patients with MDRB. We considered the effect of potential confounders, such as the occurrence of septic shock, inadequate antibiotic therapy, Charlson score, and life-sustaining limitation order.

Results: We included 719 patients during the aforementioned period; of this number, 281 (39%) had a microbiologically documented infection. MDRB was found in 40 (14%) patients. The crude mortality rate in the MDRB-related infection group was 35% vs. 32% in the non-MDRB-related infection group ($p = 0.1$). Logistic regression showed that MDRB-related infection was not associated with excess

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mortality, with an odds ratio of 0.52 and a 95% confidence interval from 0.17 to 1.39 ($p = 0.2$). Charlson score, septic shock, and life-sustaining limitation order were significantly associated with an increased mortality rate on day 60. No effect of MDRB colonization on mortality rate on day 60 was highlighted.

Conclusion: MDRB-related infection or colonization was not associated with an increased mortality rate on day 60. Other confounders, such as comorbidities, may account for a higher mortality rate.

Keywords: Intensive care; Multidrug-resistant bacteria; Colonization; Infection; Sepsis; Outcomes

Key Summary Points

Multidrug-resistant bacteria incidence is increasing worldwide.

The effect of multidrug-resistant bacteria on intensive care unit patients is controversial because potential confounders remain unexplored.

We explored the effect of multidrug-resistant bacteria when an appropriate antibiotic therapy was administered to patients with sepsis.

We found no association between multidrug-resistant bacteria and 60-day mortality when an appropriate therapy was administered.

INTRODUCTION

The incidence of infections caused by multidrug-resistant bacteria (MDRB) is increasing worldwide [1]. Notably, despite the surge in healthcare-associated costs, the relationship between MDRB and hospital mortality rates remains controversial, particularly in intensive care units (ICUs) [2]. A meta-analysis of 15 cohort studies reported an association between increased in-hospital mortality rates and patients diagnosed with bacteremia due to extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae compared with the absence of beta-lactamase-producing Enterobacteriaceae [3]. This meta-analysis showed that adjustment for inappropriate empirical therapy reduces this association [3]. However, this meta-analysis included a heterogeneous population from a pediatric and adult general hospital and only one ICU setting [3]. Meanwhile, two large cohort studies found excess mortality in ICU patients with pneumonia related to a restricted kind of highly resistant bacteria, but these results were not adjusted for the adequacy of empirical antibiotic therapy, the occurrence of septic shock, or patient comorbidity [4, 5]. Furthermore, Paramythiotou et al. did not conclude a direct association between MDRB and ICU mortality rates from a review of 24 studies from ICU settings [6]. The association between MDRB infection and excess ICU mortality may be a confounding bias related to the length of ICU stay of patients with the most severe conditions or those with comorbidities, a topic that warrants further exploration.

As with infections, the consequences of MDRB colonization remain controversial [7, 8]. To date, there is no strong evidence of the influence of bacterial colonization on the prognosis of ICU patients. It should be reiterated that the colonization of MDRB may be confounded by a longer duration of mechanical ventilation or severity [7, 9]. Therefore, our objective was to describe the relationship between mortality and MDRB identification during an ICU stay. The first aim of our study was to compare the mortality rate on day 60 in ICU patients with sepsis in relation to the MDRB status of the infection. The second aim was to compare the mortality rate on day 60 of non-infected patients in relation to their MDRB colonization status.

METHODS

Study Design and Population

From January 2017 to December 2018, we conducted a retrospective, observational, monocentric study in a 15-bed ICU of a university hospital (Hôpital Nord, Marseille, France). All adult patients admitted for more than 48 h with at least one systematic research of MDRB colonization using rectal swabs were included. Research of MDRB colonization was protocolized to be performed at ICU admission and once a week.

The patients were classified into two groups: infected and non-infected. Infections were determined as clinical suspicions of infection associated with a positive microbiology sample, leading to the introduction of antibiotics based on our institutional protocols. The infection type was then defined according to recent guidelines [10].

In the infected group, patients were classified under MDRB-related infection or non-MDRB-related infection. The MDRB-infected group was defined by any microbiological sample positive for MDRB associated with signs of infection and requiring antibiotic treatment during their ICU stay. Meanwhile, the non-infected patients were classified under the categories MDRB colonized and non-MDRB colonized. The MDRB-colonized group was defined by any rectal swab or other microbiological sample showing the presence of any MDRB but not related to infection and, thus, not requiring treatment during their ICU stay. All included patients were followed up until day 60. The data were collected through the network of the central infection control committee (Comité de Lutte contre les Infections Nosocomiales).

This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments and was approved by the Committee for Research Ethics of the French Society of Anesthesia & Intensive Care Medicine (CERAR No. IRB 00010254-2021-079) and the French Commission Nationale Informatique et Liberté (CNIL PADS 21-129). Written informed consent was waived because of the retrospective character of the study in accordance with French law [11]. We adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) requirements for observational studies [12].

Definitions

Patients whose rectal swabs or other microbiological samples were positive for MDRB, without clinical evidence of infection, as previously defined, were considered colonized by MDRB.

MDRB were defined according to international definitions [13] and classified into three groups: multidrug-resistant (MDR), extensively drug-resistant (XDR), and pandrug-resistant (PDR). MDRB were classified as MDR if they were non-susceptible to at least one agent in three or more antimicrobial categories, XDR if they were non-susceptible to at least one agent in all but two or fewer antimicrobial categories, and PDR if they were non-susceptible to all agents in all antimicrobial categories [13].

For their immune profile, the patients were classified into three categories: aplasia, immunocompromised, and immunocompetent. Aplasia was defined as a blood level of polymorphonuclear neutrophils inferior to 0.5×10^9/L. Immunocompromised patients were patients who had received recent chemotherapy or radiotherapy for malignancies (cancer, malignant hemopathy, and lymphoma) or immunosuppressant drugs (e.g., steroids) and those with acquired immunodeficiency syndrome disease. All other patients were classified as immunocompetent.

Sepsis and septic shock were defined according to the Third International Consensus and Definitions for Sepsis and Septic Shock [14].

The empirical antimicrobial treatment was considered appropriate if it included at least one drug displaying in vitro activity against the isolated germ and was administered according to the breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

We computed the number of ICU-free days from admission to ICU discharge within the first 28 days. To address any cases of death

during this period and to reduce the effect of early death, ICU-free days on day 28 were considered zero.

Microbiology Considerations

The suspension of samples in Sigma Transwab® medium was seeded in selective media: methicillin-resistant *Staphylococcus aureus* (MRSA) on ChromID MRSA (Biomérieux, Marcy l'Etoile, France); cephalosporin resistance, including ESBL-E and cephalosporin-resistant *Pseudomonas aeruginosa*, on ChromID BLSE (Biomérieux); carbapenem resistance, including carbapenemase-producing Enterobacteriaceae (CPE) and imipenem-resistant *Acinetobacter baumannii*, on ChromID CarbaSmart (Biomérieux); and glycopeptide-resistant *Enterococcus* spp. (GRE) on ChromID VRE (Biomérieux). Species identification was performed using matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (Microflex LT, Bruker Daltonik, Bremen, Germany). The resistance phenotype of the isolated strains was then confirmed through antibiotic susceptibility testing performed on isolates using the Kirby-Bauer disk diffusion method. The results were interpreted according to the EUCAST guidelines 2021 or EUCAST 2013 if a diameter was not available [15]. Enterobacterial isolates were tested against 13 antibiotics (amoxicillin, amoxicillin-clavulanic acid, piperacillin tazobactam, cefepime, ceftriaxone, ertapenem, imipenem, fosfomycin, sulfamethoxazole trimethoprim, gentamicin, ciprofloxacin, doxycycline, and amikacine). *S. aureus* isolates were tested against 16 antibiotics (benzylpenicillin, cefoxitin, oxacillin, rifampicin, clindamycin, erythromycin, pristinamycin, gentamicin, vancomycin, teicoplanin, ciprofloxacin, doxycycline, fosfomycin, fusidic acid, linezolid, and sulfamethoxazole-trimethoprim). Non-fermenting gram-negative bacteria were tested against 11 antibiotics (ticarcillin, ticarcillin-clavulanic acid, piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, imipenem, meropenem, amikacin, gentamicin, ciprofloxacin). Enterococci were tested against 11 antibiotics (penicillin G, amoxicillin, erythromycin, pristinamycin, gentamicin, vancomycin, teicoplanin, nitrofurantoin, fosfomycin, linezolid, doxycycline).

An ESBL profile was confirmed through the visualization of a champagne cork between a beta-lactamase inhibitor and a third- or fourth-generation cephalosporin. Carbapenem resistance was confirmed by performing a β-Carbatest (MAST Diagnostics, Liverpool, UK), and minimal inhibitory concentration (MIC) of ertapenem and/or imipenem was performed by E-test (Biomérieux) if the disk result was intermediate or resistant.

Molecular characterization of the carbapenemase genes was performed using EZ1 DNA extraction kits (Qiagen, Courtaboeuf, France) with the EZ1 Advanced XL biorobot according to the manufacturer's instructions. A real-time polymerase chain reaction (PCR) was performed to detect the genes bla_{Oxa48}, bla_{NDM}, and bla_{KPC} for CPE and $bla_{\text{OXA-23}}$, $bla_{\text{OXA-24}}$, and bla_{NDM} for carbapenem-resistant *Acinetobacter* [16].

Data Collection

Demographic and clinical data, including clinical and microbiological assessments from the electronic medical charts, were analyzed. We extracted age, gender, comorbidities (extracted as the age-adjusted Charlson comorbidity index (ACCI) score for each patient) [17–19], the reason for ICU admission, the origin of the patient (home, other hospital wards, other ICUs, or long-term medical care centers), Simplified Acute Physiology Score (SAPS) 2 at ICU admission, use of antibiotics in the 48 h before ICU admission, duration of invasive mechanical ventilation (days), duration of urinary catheterization (days), the need for extracorporeal membrane oxygenation support, immune profile, and limitation of life-sustaining care. For each patient, we collected the number of rectal swabs undergone during their ICU stay, prior MDRB acquisition history, MDRB acquisition time, and type of MDRB (MDR, XDR, or PDR). We also collected the sites of infection acquired during the ICU stay as defined above (Appendix B) and the occurrence of sepsis and septic shock.

Outcome Measures

The first aim of our study was to compare the mortality rate on day 60 between patients admitted to the ICU with MDRB-related infection and those with non-MDRB-related infection. The second aim was to compare the mortality rate on day 60 between patients not infected but colonized with MDRB and those not colonized with MDRB.

Analysis

The statistical analyses were performed using IBM SPSS V24.0 (IBM Corp., Armonk, NY, USA).

Primary Outcome Analysis

We conducted a multivariate binary logistic regression to research the factors associated with the 60-day mortality rate of patients with proven infection during their ICU stay. The regression model included the MDR status of the bacteria responsible for the infection. The other variables used in the model were the administration of inappropriate antibiotic treatment, the occurrence of septic shock, male gender, ACCI score, admission for trauma, and the application of the limitation of life-sustaining care order. Parameters achieving p values less than 0.05 were considered statistically significant, and odds ratios (ORs) were derived with a 95% confidence interval (CI).

To avoid immortal time bias when analyzing the association between MDRB status of infection and survival, we conducted a time-dependent Cox regression model. This design eliminates immortal time bias by using MDRB status of infection as a time-dependent covariate. The subjects are classified as unexposed until the occurrence of an MDRB-related infection and exposed thereafter [20–22]. The global assessment was evaluated through the use of the concordance index (i.e., c statistic). In this process, the model is graded on its ability to differentiate between all possible discordant pairs of patients. Concordance indexes can vary between 0.5 (chance) and 1.0 (perfect prediction).

Secondary Outcome Analysis

An analysis using a multivariate binary logistic regression was conducted to identify the factors associated with the 60-day mortality rate between patients with proven MDRB colonization during their ICU stay and the population without any infection during their ICU stay. The regression model included MDRB colonization, gender, ACCI score, admission for trauma, and a limitation of life-sustaining care order. The same time-dependent Cox regression model (as described before) was used to avoid the immortal bias.

RESULTS

During the study period, 994 patients were screened, while 266 were excluded. Of the 728 remaining patients, nine were excluded from the analysis because MDRB acquisition occurred before ICU admission. Thus, 719 patients were included in the analysis. Among them, 281 patients had at least one infection, while 438 patients had no infection (Fig. 1: flowchart, Supplementary Material Table 1).

Descriptive Analysis

The description of the univariate analysis is presented in Tables 1 and 2.

Regarding the population of patients with infection (n = 281), 40 (14%) had MDRB-related infections, with a mean MDRB acquisition time of 2 ± 1 week. Previous MDRB colonization occurred more frequently in the MDRB-related infection group than in the non-MDRB-related infection group (16% vs. 30%, $p = 0.04$). The MDRB-related infection group experienced more infection episodes and more septic shock during their ICU stay than the non-MDRB-related infection group (Table 1). The number of ICU-free days on day 28 was 4.2 ± 7.7 days in the MDRB-related infection group and 11.5 ± 10.5 days in the non-MDRB-related infection group ($p = 0.001$). The 60-day crude mortality rate was 35% in the MDRB-related

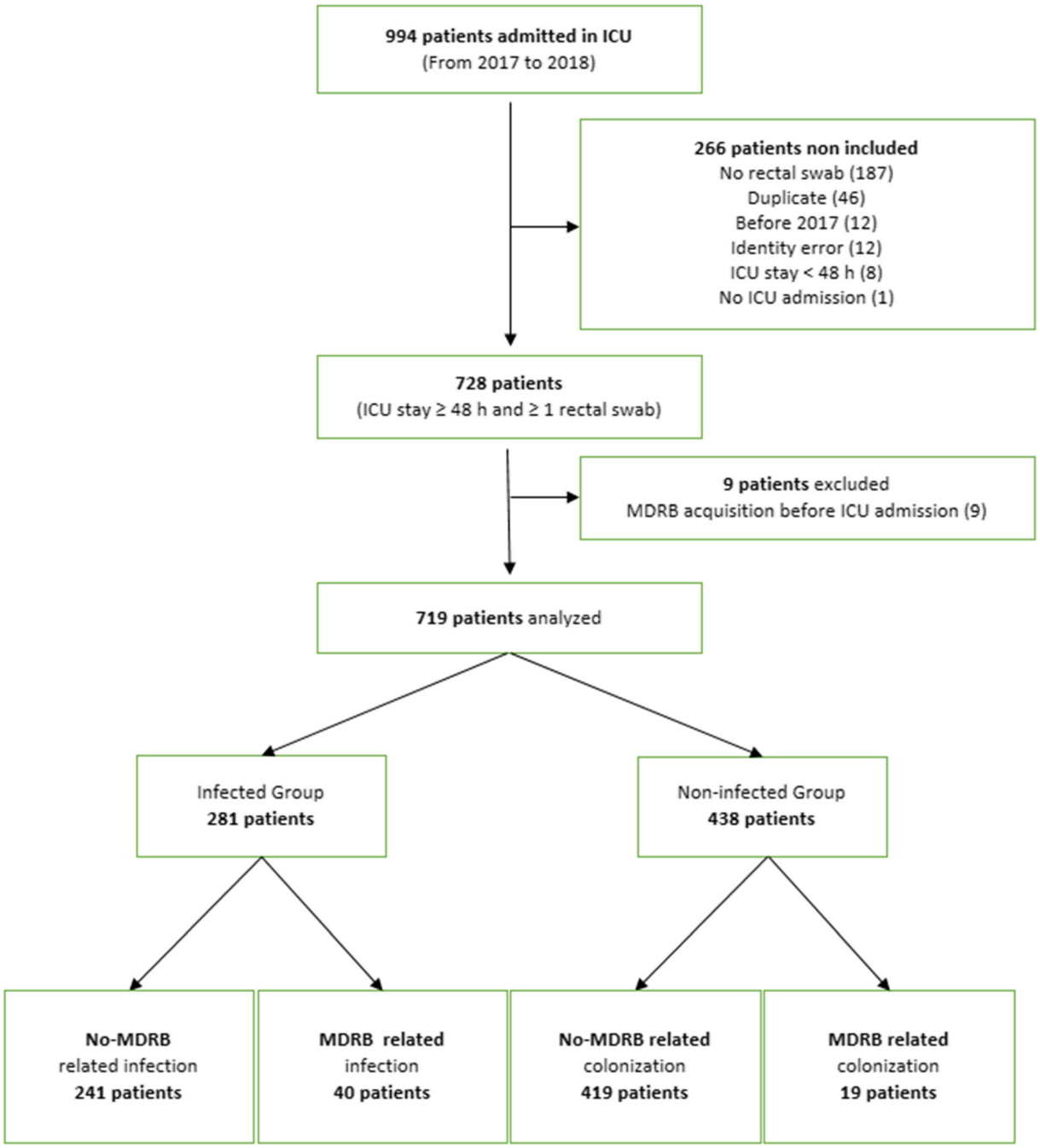

Fig. 1 Flowchart. *ICU* intensive care unit, *MDRB* multidrug-resistant bacteria

infection group vs. 32% in the non-MDRB-related infection group ($p = 0.10$).

The non-infected population is described in Table 2. In this population, 19 (4.5%) patients presented with MDRB colonization. The number of ICU-free days on day 28 was 19.5 ± 9.1 days in the non-MDRB-colonized group and 14.7 ± 9.7 days in the MDRB-colonized group ($p = 0.01$). The 60-day mortality rate was 19% in the non-MDRB-colonized group and 32% in the MDRB-colonized group ($p = 0.12$).

Table 1 Comparative analysis between the MDRB-related infection group and the non-MDRB-related infection group

	Non-MDRB infection (*n* = 241)	**MDRB infection (*n* = 40)**	***P* value**
Male, *n* (%)	170 (70.5)	32 (80.0)	0.22
SAPS2	52.2 ± 18.6	49.5 ± 17.5	0.38
Age (years)	59 ± 18	54.9 ± 20.4	0.38
ACCI	3.4 ± 2.7	3.1 ± 2.6	0.57
Admission for trauma, *n* (%)	60 (24.9)	12 (30.0)	0.49
Provenance, *n* (%)			
Home	123 (51.0)	25 (62.5)	0.44
Nursing home	4 (1.7)	1 (2.5)	
Rehabilitation care center	6 (2.5)	1 (2.5)	
Hospital	77 (32.0)	11 (27.5)	
ICU	31 (12.9)	2 (5.0)	
Category, *n* (%)			
Scheduled surgery	19 (7.9)	8 (20.0)	**< 0.01**
Urgent surgery	123 (51.0)	26 (65.0)	
Medical	99 (41.1)	6 (15.0)	
Immune profile, *n* (%)			
Non-immunocompromised	170 (70.5)	27 (67.5)	0.77
Immunocompromised	66 (27.4)	12 (30)	
Aplasia	5 (2.1)	1 (2.5)	
Origin of infection (1st event)			
Pulmonary	126 (52.3)	17 (42.5)	0.45
Digestive	52 (21.6)	14 (35)	
Urinary	23 (9.5)	5 (12.5)	
Central nervous system	10 (4.1)	1 (2.5)	
Catheters	7 (2.9)	0 (0)	
Others	23 (9.5)	3 (7.5)	
≥ 2 infection, *n* (%)	36 (14.9)	21 (52.5)	**< 0.01**
n = 2 infections, *n* (%)	28 (11.6)	11 (27.5)	**< 0.01**
n = 3 infections, *n* (%)	5 (2.1)	9 (22.5)	**< 0.01**
n = 4 infections, *n* (%)	3 (1.2)	1 (2.5)	0.07
Septic shock, *n* (%)	130 (54)	32 (80.0)	**< 0.01**
Inadequate probabilistic antibiotic therapy, *n* (%)	4 (1.6)	7 (17.5)	**< 0.01**

Table 1 continued

	Non-MDRB infection (n = 241)	MDRB infection (n = 40)	P value
Number of rectal swabs	1.7 ± 1.4	2.9 ± 3.0	< **0.01**
Number of microbiologic samplings	5.2 ± 3.3	8.3 ± 4.7	< **0.01**
MDRB colonization before infection occurrence, n (%)	39 (16.2)	12 (30.0)	**0.04**
Mean MDRB acquisition (days)	12.4 ± 14.7	8.8 ± 10.6	0.55
Mechanical ventilation, n (%)	196 (81.3)	35 (87.5)	0.35
Duration of MV (days)	9.4 ± 14.7	27.6 ± 37.5	< **0.01**
Urinary catheterization, n (%)	225 (93.4)	40 (100)	0.14
Duration of UC (days)	10.8 ± 14.1	30.1 ± 36.6	< 0.01
Limitation of life-sustaining care, n (%)	46 (19.1)	16 (40.0)	< **0.01**
Use of ECMO, n (%)	60 (24.9)	12 (30.0)	0.49
IFD-28 (days)	11.5 ± 10.5	4.2 ± 7.7	< **0.01**
Mortality rate at day 60, n (%)	77 (32.0)	14 (35.0)	< **0.01**

Bolded p values are statistically significant

MDRB multidrug-resistant bacteria, *SAPS2* Simplified Acute Physiology Score 2, *ACCI* age-adjusted Charlson comorbidity index, *ECMO* extracorporeal membrane oxygenation, *ICU* intensive care unit, *IFD-28* ICU-free days at 28 days, *MV* mechanical ventilation, *UC* urinary catheterization

Primary Outcome

Multivariate analysis showed that MDRB-related infection was not associated with the day 60 mortality rate (OR 0.52, 95% CI 0.17–1.39; $p = 0.20$) (Table 3). Moreover, admission for trauma, gender, and inappropriate first-line antibiotic treatment were not associated with the 60-day mortality rate (Table 3). The 60-day mortality rate was significantly associated with the ACCI score (OR 1.16, 95% CI 1.03–1.33; $p = 0.016$) and the limitation of life-sustaining care order (OR 20.19, 95% CI 9.49–47.32; $p < 0.001$) (Table 3).

The time-dependent analysis with the Cox regression model showed that MDRB-related infection was not associated with 60-day mortality rate (hazard ratio = 0.77, 95% CI 0.41–1.48; $p = 0.43$) (Fig. 2, Supplementary Material Table 2). In this model, ACCI score, occurrence of septic shock and limitation of life-sustaining care order were still significantly associated with an increased 60-day mortality rate (Supplementary Material Table 2).

Secondary Outcome

Multivariate analysis showed that MDRB colonization was not associated with the day 60 mortality rate (OR 3.22, 95% CI 0.65–11.57; $p = 0.13$) (Table 3). The 60-day mortality rate was significantly associated with the ACCI score (OR 1.15, 95% CI 1.03–1.27; $p = 0.01$) and the limitation of life-sustaining care (OR 16.93, 95% CI 10.58–27.10; $p < 0.001$). Trauma admission was a protective factor against death on day 60 (Table 3).

The effect of time analysis with the Cox regression model showed no association with MDRB-related colonization and 60-day mortality rate (OR 1.82, 95% CI 0.77–4.30; $p = 0.33$) in

Table 2 Comparative analysis between the MDRB colonized group and the non-MDRB colonized group

	Non-MDRB colonization (n = 419)	MDRB colonization (n = 19)	P value
Male, n (%)	310 (74)	10 (52.6)	**0.04**
SAPS2	45.1 ± 21.7	51.5 ± 14.8	**0.05**
Age (years)	51.1 ± 20.2	58.6 ± 16.5	0.11
ACCI	2.1 ± 2.37	3 ± 2.8	0.12
Admission for trauma, n (%)	228 (54.4)	9 (47.4)	0.55
Provenance, n (%)			
Home	318 (75.9)	12 (63.2)	**0.05**
Nursing home	6 (1.4)	0 (0)	
Rehabilitation care center	11 (2.6)	0 (0)	
Hospital	76 (18.1)	4 (21.1)	
ICU	8 (1.9)	3 (15.8)	
Category, n (%)			
Scheduled surgery	43 (10.3)	1 (5.3)	0.69
Urgent surgery	224 (53.5)	9 (47.4)	
Medical	152 (36.3)	9 (47.4)	
Immune profile, n (%)			
Non-immunocompromised	368 (87.8)	15 (78.9)	0.33
Immunocompromised	49 (11.7)	4 (21.1)	
Aplasia	2 (0.5)	0 (0)	
Number of rectal swabs	1.3 ± 0.56	2.7 ± 5.2	**0.03**
Number of microbiologic samplings	2.2 ± 1.2	3.4 ± 1.8	0.06
Mean MDRB acquisition (days)	–	3 ± 3.1	–
Type of MDRB, n (%)			
MDR	–	17 (90.0)	–
XDR	–	1 (5.0)	
PDR	–	1 (5.0)	
Mechanical ventilation, n (%)	275 (65.6)	15 (78.9)	0.23
Duration of MV (days)	2.4 ± 3.9	4.7 ± 5.8	**0.01**
Urinary catheterization, n (%)	349 (83.3)	16 (84.2)	1
Duration of UC (days)	3.4 ± 3.9	6.3 ± 6.2	**0.03**
Limitation of life-sustaining care, n (%)	50 (11.9)	2 (10.5)	1
Use of ECMO, n (%)	3 (0.7)	0 (0)	1
IFD-28 (days)	19.5 ± 9.1	14.7 ± 9.7	**< 0.01**

Table 2 continued

	Non-MDRB colonization (n = 419)	MDRB colonization (n = 19)	P value
Mortality rate at day-60, n (%)	80 (19.0)	6 (31.5)	0.12

Bolded p values are statistically significant
MDRB multidrug-resistant bacteria, *SAPS2* Simplified Acute Physiology Score 2, *ACCI* age-adjusted Charlson comorbidities index, *ECMO* extracorporeal membrane oxygenation, *ICU* intensive care unit, *IFD-28* ICU-free days at 28 days, *MV* mechanical ventilation, *UC* urinary catheterization

Table 3 Multivariate binary logistic regression of variables associated with occurrence of death before day 60

	OR	Lower 95%	Upper 95%	P value
Infected patients (n = 281)				
MDRB-related infection	0.52	0.17	1.39	0.20
Occurrence of septic shock	1.59	1.01	1.99	**0.04**
Inadequate antibiotic therapy	0.98	0.17	5.24	0.98
Male gender	1.01	0.51	2.04	0.96
Limitation of life-sustaining care	20.19	9.49	47.32	**0.001**
Trauma admission	0.67	0.27	1.60	0.38
ACCI	1.16	1.03	1.33	**0.016**
Non-infected patients (n = 438)				
MDRB colonization	3.22	0.65	11.57	0.13
Male gender	0.82	0.39	1.75	0.59
Limitation of life-sustaining care	16.93	10.58	27.10	**0.001**
Trauma admission	0.39	0.17	0.88	**0.02**
ACCI	1.15	1.03	1.27	**0.01**

Bolded p values are statistically significant
MDRB multidrug-resistant bacteria, *ACCI* age-adjusted Charlson comorbidities index

non-infected patients (Supplementary Material Table 2).

DISCUSSION

In our study, neither MDRB-related infection nor colonization was significantly associated with the mortality rate on day 60 after ICU admission. By contrast, the excess mortality was associated with ACCI and limitations of life-sustaining care. Furthermore, when the effect of time was taken into account, no association was found between MDRB status and mortality rate on day 60 after ICU admission either. These results suggest that crude excess mortality was not associated with the MDRB status.

Our hypothesis was that the excess mortality found among ICU patients with MDRB-related infection that was reported in previous observational studies was due to patient comorbidities, challenges in the administration of an appropriate antibiotic, and the limitation of life-sustaining care of long-stay patients.

To date, this subject has presented conflicting results. In a systematic review of 24 studies involving ICU patients, Paramythiotou et al. concluded that there was no association between infections due to gram-negative MDRB and mortality in ICU patients because of the great heterogeneity of the studies on the subject [6]. Meanwhile, in a multicentric observational study, Denis et al. found no increase in the day 30 mortality rate among patients with ventilator-associated pneumonia due to multidrug-resistant *P. aeruginosa* [23]. In a large prospective European study of 119,699 ICU patients, Lambert et al. found that the antimicrobial resistance profile was associated with an increased ICU mortality rate in the case of drug-resistant bacteria-related pneumonia with an OR of 1.2 [1.1–1.4] but not in the case of bloodstream infections with an OR of 1.1 [0.9–1.3] [5]. In this study, only four bacteria

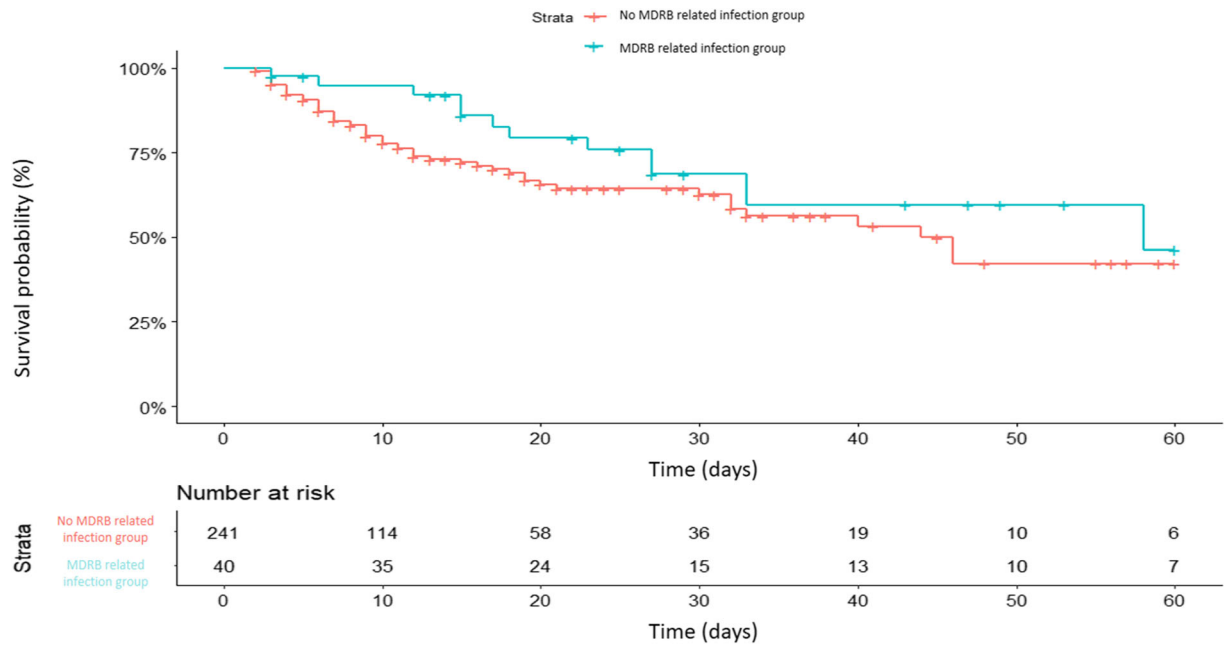

Fig. 2 Kaplan–Meier curves presenting the probability of survival of patients presenting an MDRB related or not infection during their ICU stay. *ICU* intensive care unit, *MDRB* multidrug resistant bacteria

were considered (*S. aureus, A. baumannii, Escherichia coli*, and *P. aeruginosa*), and there was no adjustment on comorbidity [5]. Recently, a French retrospective multicentric study documented a 10% increase in mortality in patients diagnosed with ICU-acquired pneumonia caused by highly resistant bacteria (including *S. aureus*, Enterobacteriaceae, *P. aeruginosa*, or *A. baumannii*) but without consideration for features of antibiotic treatment, occurrence of septic shock, and comorbidities [4]. The discrepancy between these cohort studies may be explained by the heterogeneity of the definitions of resistance and unmatched co-factors, which may represent potential bias.

Notably, a major bias is that patients infected by MDRB may receive inadequate empirical antimicrobial treatment more frequently [3]. Most studies in the field do not assess antimicrobial therapy and its adequacy regarding the MDRB implicated in the infection [3–5, 24]. In our study, this criterion was explored and included in the multivariate analysis of infected patients. Although it occurred more frequently in the MDRB-related infection group (17.5% vs. 1.6%), the inadequate choice of initial probabilistic antimicrobial therapy was not associated with the excess mortality in the multivariate analysis.

Another major source of bias in the interpretation of the association between MDRB-related infection and mortality is the lack of matching for comorbidities. Our results were matched on the ACCI score, ruling out most host factors that could be associated with frailty. In a prospective translational study, Flaatten et al. showed that frailty was independently associated with day 30 survival [25], which was confirmed by a meta-analysis of 10 studies reporting an association between frailty and ICU mortality (OR 1.53, 95% CI 1.40–1.68, I^2 = 0%) [26]. Moreover, frail elderly patients may have an increased risk of MDRB colonization and infection [9]. Indeed, Giarratano et al. found that patients older than 65 years were more likely to present with MDRB infection than younger patients [9]. The authors hypothesized the role of the more frequent use of antibiotics in this population to explain this association with MDRB carriage [9]. Therefore, comorbidities may partially account for the excess mortality in other studies.

The effect of time may also be an important source of bias. In our study, no association was found between mortality rate and MDRB status of infection or colonization when the effect of time was taken into account. Most studies have shown an association between MDRB carriage and increased length of ICU stay [2, 7]. It remains challenging to determine the primary causative effect. Indeed, in the case of more severely ill or frailer patients, the duration of ICU stay may increase independently [9, 25, 26]. In this case, the increased exposure to invasive procedures and repeated nosocomial infections with their associated antibiotic prescription may lead to the emergence of MDRB-related infections or colonization.

Our results have several limitations. First, the reported effect may be due to a lack of power: our study was retrospective, observational, and conducted in one French ICU only. Second, the assessment on MDRB carriage was more frequently performed in the MDRB group with more weekly rectal swabs (3.0 vs. 1.3, $p < 0.001$) and the longest duration of ICU stay. Third, more than 40% of the patients included in our study were admitted for trauma, with an average age of 54 years. We assume that these patients were younger and had fewer comorbidities than the general ICU population [27]. Finally, 170 patients were not included in the analysis because of missing rectal sampling at admission and removal from the unit (dead or alive) before the weekly sampling, thus generating a potential bias.

CONCLUSION

In this study, MDRB-related infection and colonization were not associated with an increase in mortality rate on day 60. However, we found that confounders, such as comorbidities and occurrence of septic shock, were associated with excess mortality. Further large cohort studies considering those confounders are warranted to confirm these observations.

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Data Availability. The results of this study have never been presented or published elsewhere. The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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