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ORIGINAL

Relationship between COVID-19 and ICU-acquired colonization and infection related to multidrug-resistant bacteria: a prospective multicenter before-after study

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Abstract

Purpose: Patients presenting the most severe form of coronavirus disease 2019 (COVID-19) pneumonia, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), have a prolonged intensive care unit (ICU) stay and are exposed to broad-spectrum antibiotics, but the impact of COVID-19 on antimicrobial resistance is unknown.

Methods: Observational prospective before-after study in 7 ICUs in France. All consecutive patients with an ICU stay > 48 h and a confirmed SARS-CoV-2 infection were included prospectively and followed for 28 days. Patients underwent systematic screening for colonization with multidrug-resistant (MDR) bacteria upon admission and every week subsequently. COVID-19 patients were compared to a recent prospective cohort of control patients from the same ICUs. The primary objective was to investigate the association of COVID-19 with the cumulative incidence of a composite outcome including ICU-acquired colonization and/or infection related to MDR bacteria (ICU-MDR-col and ICU-MDR-inf, respectively).

Results: From February 27th, 2020 to June 2nd, 2021, 367 COVID-19 patients were included, and compared to 680 controls. After adjustment for prespecified baseline confounders, the cumulative incidence of ICU-MDR-col and/or ICU-MDR-inf was not significantly different between groups (adjusted sub-hazard ratio [sHR] 1.39, 95% confidence interval [CI] 0.91–2.09). When considering both outcomes separately, COVID-19 patients had a higher incidence of ICU-MDR-inf than controls (adjusted sHR 2.50, 95% CI 1.90–3.28), but the incidence of ICU-MDR-col was not significantly different between groups (adjusted sHR 1.27, 95% CI 0.85–1.88).

Conclusion: COVID-19 patients had an increased incidence of ICU-MDR-inf compared to controls, but the difference was not significant when considering a composite outcome including ICU-MDR-col and/or ICU-MDR-inf.

Keywords: Antimicrobial resistance, COVID-19, Intensive care unit, Cross infection, Patient isolation

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic reached Europe in February 2020, leading to a surge in intensive care unit (ICU) admissions and profound changes in the delivery of care to the critically ill. Patients presenting with the most severe form of coronavirus disease 2019 (COVID-19) pneumonia require an extended duration of invasive mechanical ventilation (IMV) and have a prolonged ICU stay [1]. These patients have been repeatedly shown to present a high incidence of ICU-acquired infections [2, 3], and are frequently exposed to broad-spectrum antimicrobials [4], leading to a sustained antibiotic selection pressure. Furthermore, limited adherence to infection prevention and control (IPC) policies due to shortages of staff and over-crowding of patients may have facilitated the cross-transmission of multi-drug resistant (MDR) strains between patients. Consequently, there have been major concerns about the potential impact of the COVID-19 pandemic on the emergence and spread of antimicrobial resistance (AMR) [5].

AMR is an emerging threat to human health that has been referred to as a "silent pandemic" [6]. Its burden is critical in ICUs, where a significant proportion of secondary infections are attributed to MDR strains [7]. ICU-acquired colonization with MDR bacteria (ICU-MDR-col) often precedes infection, and has been associated with a prolonged ICU stay [8]. Moreover, ICU-acquired infection with MDR bacteria (ICU-MDR-inf) has been linked to a longer IMV duration [9], a higher mortality [7, 10] and increased healthcare costs. Finally, because carriage of MDR bacteria can persist for several months, resistant strains acquired during ICU stay could be carried over outside of the hospital after patient discharge, further aggravating the spread of AMR globally [11, 12].

Several studies have aimed to investigate the burden of AMR among COVID-19 patients [13–15], but most present important methodological limitations. These include a limited sample size, a retrospective and monocentric design, the lack of a formal comparison between COVID-19 patients and controls, and the failure to account for sampling biases and confounding variables. To provide a precise understanding of AMR epidemiology in critically-ill COVID-19 patients, we conducted the COVID-BMR study. In this observational prospective before-after study in 7 French ICUs, COVID-19 patients were compared to a recent prospective cohort of control patients recruited before the pandemic in the same ICUs [16].

The primary objective was to investigate the association of COVID-19 with the 28-day cumulative incidence of a composite outcome including ICU-MDR-col and/or ICU-MDR-inf. Secondary objectives were to investigate the association of COVID-19 with the 28-day cumulative incidence of ICU-MDR-col and ICU-MDR-inf (considered separately) and with the incidence rate of ICU-MDR-col and ICU-MDR-inf (combined and separately); to describe the microbiology of ICU-MDR-col and ICU-MDR-inf in COVID-19 patients; and to determine whether COVID-19 modifies the impact of ICU-MDR-col and ICU-MDR-inf on patient prognosis.

Take-home message

In this prospective multicenter before-after study, COVID-19 patients have a higher incidence of ICU-acquired infection with MDR bacteria than control patients recruited in the same ICUs before the pandemic, despite a similar incidence of ICU-acquired colonization with MDR bacteria.

Methods

Design, setting and patients

COVID-BMR was an observational prospective multicenter before-after study conducted in the ICUs of Lille, Croix-Rousse (Lyon), Lyon-Sud and Amiens University-affiliated hospitals, and Marne-La-Vallée, Lens and Béthune hospitals from February 27th, 2020 to June 2nd, 2021. All participating centers had single-bed rooms and shared similar organizational characteristics (see Supplementary Table 1).

All adult patients hospitalized for > 48 h in the participating ICUs were eligible. Patients were included consecutively if they fulfilled the following criteria: polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infection; MDR bacteria screening by rectal and nasal swabbing < 48 h following ICU admission; at least one MDR bacteria screening by rectal or nasal swabbing after the 48th hour in the ICU and before ICU discharge; non-opposition to participate. Exclusion criteria included: ICU stay ≤ 48 h, rectal/nasal swabs not collected within 48 h following ICU admission or subsequently, opposition to participate, and other exclusion criteria (adult subject to guardianship, jailed patient, child-bearing or breastfeeding woman, major cognitive impairment or severe psychiatric disorder, impossibility to communicate in French, limitation of active therapies).

COVID-19 patients were compared with those (hereafter named controls) hospitalized in the same ICUs, and included in the CIMDREA study [16]. Briefly, the CIMDREA study was an observational prospective cohort study conducted from May 5th, 2019 to January 31st, 2020 to investigate the relationship between immunosuppression and ICU-MDR-col/inf. Screening for MDR bacteria was similar in COVID-19 and control patients.

Microbiology

In the participating ICUs, patients underwent rectal and nasal swabbing upon admission (at the latest on the 48th hour following admission) and every week until ICU discharge (or until day 28, whichever came first). Colonization with MDR bacteria was detected by streaking swabs onto selective culture media, followed by species identification.

Routine microbiology data, i.e. the results of bacterial cultures ordered by attending physicians as part of routine care, were also collected. Antibiotic susceptibility was defined according to breaking points recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [17]. MDR bacteria were defined as: third generation cephalosporins (3GC)-resistant Enterobacterales, including through expression of an extended spectrum beta-lactamase (ESBL); carbapenem-resistant Enterobacterales; methicillin-resistant *Staphylococcus aureus* (MRSA); vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium* (VRE); *Pseudomonas aeruginosa* resistant to imipenem and ceftazidime; and carbapenem-resistant *Acinetobacter baumannii* (CRAB) [16, 18]. No molecular technique was used during the study for species identification or antibiotic susceptibility testing.

Clinical variables and outcomes

ICU-MDR-col was defined as the colonization by MDR bacteria isolated on a rectal or nasal swab collected > 48 h following admission, or on any other sample if it was not considered to be related to an infection. In patients colonized with MDR bacteria at ICU admission (i.e., patients with a positive rectal or nasal swab within 48 h of ICU admission), only ICU-acquired colonization related to other MDR bacterial species were taken into account. ICU-MDR-inf was defined as an infection related to MDR bacteria occurring > 48 h following ICU admission. As opposed to colonization (asymptomatic carrier state), infections were defined by clinical, biological and imaging characteristics compatible with the definitions published by international societies on healthcare- and ventilator-associated pneumonia (HAP, VAP) [19], bloodstream and catheter-related infections [20], and other healthcare-associated infections [21–25]. Colonization vs. infection status was established through assessment made by attending physicians, with no involvement of an independent adjudication committee.

Clinical variables potentially associated with MDR-ICU-col and MDR-ICU-inf were recorded: demographics, co-morbidities, immunosuppression [16], recent hospitalization and antibiotic exposure (< 3 months before ICU admission), organ failures at admission, exposure to invasive devices and antibiotics during ICU stay. When recording antibiotic exposure, we did not consider antimycobacterial drugs, fidaxomicine, erythromycin, low-dose trimethoprim-sulfamethoxazole. When recording steroids, we did not consider hydrocortisone (often prescribed as substitutive hormonotherapy for refractory shock). After the publication of the RECOVERY trial in July 2020 [26], all participating centers started treating COVID-19 patients with dexamethasone according to the published study protocol (dexamethasone IV, 6 mg q.d.; see Supplementary Table 1 for further details on prescription patterns of steroids in each center).

Patients were followed and data were collected on an electronic Case Report Form (eCRF) until ICU discharge or until day 28, whichever came first.

Statistical analysis

Patient characteristics were described according to COVID-19 status without statistical comparisons. Categorical variables were reported as number and percentage, whereas quantitative variables were expressed as median with interquartile range (25th–75th percentile).

We estimated the 28-day cumulative incidence of ICU-MDR-col and ICU-MDR-inf (combined and separately), using the Kalbfleisch and Prentice method [27], considering ICU discharge (alive or dead) as a competing event. The association of COVID-19 status with ICU-MDR-col and ICU-MDR-inf was assessed by modeling the subdistribution hazard function (Fine and Gray models) and the cause-specific hazard function (cause-specific Cox models). The association of COVID-19 status with the incidence of ICU-MDR-col and ICU-MDR-inf was further investigated after adjustment for prespecified baseline confounders [28], including age, gender, Simplified Acute Physiology Score II (SAPS-II), baseline immunosuppression, recent (< 3 months) ICU hospitalization, recent colonization or infection with MDR bacteria, and recent antibiotic treatment. Additional adjustments on IMV and antibiotic treatment during ICU stay (treated as time-dependent covariates) were done in Cox models. Because patients colonized with MDR bacteria.

We investigated the association between occurrence of ICU-MDR-col/ICU-MDR-inf and 28-day prognostic outcomes (28-day mortality, ICU length-of-stay and duration of IMV) by using Cox regression models, treating ICU-MDR-col/ICU-MDR-inf as a time-varying covariate. These models were further adjusted for prespecified confounders, including age, gender, SAPS-II, diabetes mellitus, heart disease, lung disease, cerebrovascular disease, chronic kidney disease and liver cirrhosis. Given the strong deviation from the proportional hazard assumption for the association of COVID-19 with ICU length-of-stay and duration of IMV, all subgroup analyses according to COVID-19 status were done by performing

separate Cox regressions models. Heterogeneity of association between occurrence of ICU-MDR-col/ICU-MDR-inf and 28-day prognostic outcomes, according to COVID-19 status, was tested using the chi-square heterogeneity test.

Statistical testing was performed with a two-tailed α level of 0.05. Data were analyzed using the SAS software package, release 9.4 (SAS Institute, Cary, NC).

Full details on statistical analysis (including sample size calculation) and ethics are provided in the supplementary material.

Results

Patient characteristics

From February 27th, 2020 to June 2nd, 2021, 367 COVID-19 patients were included (see Supplementary Table 2 for a detailed timeframe of patients' enrollment). As presented in Supplementary Fig. 1, 846 patients were screened but excluded during the study period. Reasons for non-inclusion were: ICU length-of-stay ≤ 48 h ($n=114$), rectal/nasal swabs not collected on admission ($n=376$) or subsequently ($n=154$), opposition to participate ($n=34$) and other exclusion criteria ($n=168$). COVID-19 patients were compared with 680 controls recruited in the same centers between May 5th, 2019 and January 31st, 2020 as part of the CIMDREA study [16].

Patients were mostly males (68.2%), with a median age of 65 years (Table 1). In comparison to controls, COVID-19 patients had a higher median body mass index and a higher prevalence of diabetes, but a lower prevalence of heart disease, lung disease, cirrhosis, alcohol intake and active smoking. COVID-19 patients were less likely to live in a nursing home and to be immunocompromised, but more likely to have been exposed to antibiotics prior to ICU admission.

On ICU admission, COVID-19 patients had lower initial severity scores than controls. The proportion of patients exposed to antibiotics and invasive devices while in ICU was similar between groups, but COVID-19 patients had a more frequent exposure to extracorporeal membrane oxygenation (ECMO), arterial catheters and steroids than controls (Table 2). The median duration of exposure to invasive devices was higher in COVID-19 patients (by a factor ~ 1.4 to ~ 1.8).

Relationship between COVID-19 on ICU-acquired colonization and infection with MDR bacteria

When considering the composite outcome of ICU-MDR-col and/or ICU-MDR-inf, a total of 206 events occurred among 147 COVID-19 patients (incidence rate [IR] 32, 95% confidence interval [CI] 28–36.8 per 1000 patients·ICU days), in comparison to 261 events among 209 controls (IR 26.5, 95% CI 23.4–30; Tables 3 and 4). Among patients with ICU-MDR-col and/or ICU-MDR-inf, the first event occurred with a median delay of 8 days (interquartile range [IQR] 5–13) following ICU admission, and colonization was the first event in the majority of cases in both groups. After adjustment for baseline confounders, the incidence rate of the ICU-MDR-col and/or ICU-MDR-inf was not significantly different in COVID-19 patients compared with controls (Table 4).

The cumulative incidence of ICU-MDR-col and ICU-MDR-inf in COVID-19 patients and controls is presented in Fig. 1. After adjustment for baseline confounders, the cumulative incidence of the composite outcome including ICU-MDR-col and/or ICU-MDR-inf (primary endpoint) was not significantly different between groups (adjusted sub-hazard ratio (sHR) 1.39, 95% CI 0.91–2.09; Table 4 and Supplementary Table 3).

When considering ICU-MDR-col and ICU-MDR-inf separately, the incidence rate of ICU-MDR-inf was higher in COVID-19 patients than in controls, both before and after adjustment for baseline confounders. There was also a clear association between COVID-19 status and the cumulative incidence of ICU-MDR-inf, both by modeling the sub-distribution hazard function (Fine and Gray models, adjusted sHR 2.50, 95% CI 1.90–3.28; Table 4) and the cause-specific sub-hazard function (Cox models, adjusted cause-specific hazard ratio (cHR) 1.95, 95% CI 1.43–2.66, Supplementary Table 3). The association between COVID-19 and ICU-MDR-inf remained significant after additional adjustment for IMV and antibiotic treatment during ICU.

The incidence rate and cumulative incidence of ICU-MDR-col were not significantly different between groups.

As shown in Supplementary Table 4, similar results were obtained when conducting a sensitivity analysis excluding patients with baseline colonization and/or infection with MDR bacteria (sub-analysis on 352 COVID-19 patients vs. 601 controls).

Microbiology

Among MDR bacteria responsible for ICU-MDR-col and ICU-MDR-inf, third generation cephalosporins (3GC)-resistant Enterobacterales were the most frequently isolated organisms (~ 75% in the overall cohort), followed by carbapenems-resistant Enterobacterales and methicillin-resistant *Staphylococcus aureus* (MRSA) (Table 3). The distribution of MDR bacteria was comparable between groups. Among patients with ICU-MDR-inf, COVID-19 patients had a higher incidence of VAP related to MDR bacteria than controls.

Relationship between ICU-acquired MDR colonization and infection on prognosis

As shown in Supplementary Table 5, a significant heterogeneity was found in the association of ICU-MDR-col and/

Table 1 Patient characteristics on ICU admission

	COVID-19 patients $n = 367$	Controls $n = 680$
Age (years)	65 (57–71)	65 (55–73)
Male gender	265 (72.2)	449 (66)
Body mass index (kg/m^2)	29.7 (26.1–34)[a]	26.2 (22.5–30.8)[b]
Diabetes mellitus	119 (32.4)	180 (26.5)
Heart disease	66 (18)	211 (31)
Heart Failure	10 (2.7)	40 (5.9)
Coronary-artery disease	44 (12)	109 (16)
Lung disease	54 (14.7)	166 (24.4)
COPD	32 (8.7)	108 (15.9)
Chronic respiratory failure	7 (1.9)	42 (6.2)
Syndrome obesity-hypoventilation	19 (5.2)	40 (5.9)
Cerebrovascular disease	23 (6.3)	62 (9.1)
Chronic kidney disease	27 (7.4)	86 (12.6)
Renal replacement therapy	6 (1.6)	28 (4.1)
Liver cirrhosis	1 (0.3)	54 (7.9)
Smoking		
Never	243 (66.2)	368 (54.1)
Former	102 (27.8)	156 (22.9)
Current	22 (6)	156 (22.9)
Alcohol use	35 (9.5)	145 (21.3)
Residing in nursing home or assisted living	3 (0.8)	37 (5.5)[c]
Recent (< 3 months) hospitalization > 48 h	140 (39.5)[d]	332 (49.8)[e]
ICU	63 (17.8)[d]	111 (16.7)[e]
Other wards	96 (27.1)[d]	282 (42.3)[e]
Recent (< 3 months) antibiotic exposure	216 (58.9)	331 (48.7)
Baseline colonization and/or infection with MDR bacteria	15 (1.4)	79 (11.6)
Prior to (< 3 months) ICU admission	6 (1.6)	46 (6.8)
Within 48 h of ICU admission	9 (2.5)	40 (5.9)
Immunocompromised at ICU admission	53 (14.4)	252 (37.1)
SAPS-II	39 (32–52)	51 (40–65)[f]
SOFA	4 (2–7)	7 (4–11)
Type of ICU admission		
Medical	365 (99.5)	633 (93.1)
Scheduled surgical	0 (0)	10 (1.5)
Unscheduled surgical	2 (0.5)	37 (5.4)

Values are as no. (%) or median (interquartile range)

COPD chronic obstructive pulmonary disease, *HIV* human immunodeficiency virus, *ICU* intensive care unit, *SAPS-II* Simplified Acute Physiology Score II, *SOFA* sequential organ failure assessment

[a] 6 missing values

[b] 35 missing values

[c] 3 missing values

[d] 13 missing values

[e] 14 missing values

[f] 1 missing value

or ICU-MDR-inf with overall survival. Both prior to and after adjustment for baseline confounders, the occurrence of ICU-MDR-col and/or ICU-MDR-inf was associated with a decreased survival (adjusted cHR 2.61, 95% CI 1.59–4.27) in COVID-19 patients, but not in controls. There was no impact of the occurrence of ICU-MDR-col and/or ICU-MDR-inf on ICU length-of-stay and on the duration of IMV in the overall cohort, in COVID-19 patients and in controls.

Table 2 Patient characteristics during ICU stay

	COVID-19 patients $n=367$	Controls $n=680$
Invasive devices		
ECMO/ECLS	35 (9.5)	14 (2.1)
Venous catheters	313 (85.3)	562 (82.6)
Duration (days)	16 (10–26)[a]	11 (7–17)[b]
Arterial catheter	358 (97.5)	565 (83.1)
Duration (days)	14 (8–23)[c]	9 (6–14)[d]
Invasive mechanical ventilation	265 (72.2)	461 (67.8)
Duration (days)	15 (9–22)	8 (4–14)
Renal replacement therapy	61 (17.4)[e]	128 (19.1)[f]
Duration (days)	7 (3–13)	5 (2–9)
Urethral catheter	298 (83.2)[g]	612 (90)
Duration (days)	17 (10–27)	10 (6–16)
Nasogastric tube	267 (74.8)[d]	496 (73)[e]
Duration (days)	16 (10–26)	9 (5–14)
Treatments		
Antibiotics	346 (94.3)	629 (92.5)
Duration (days)	9 (4–16)[h]	8 (6–12)[i]
Steroids	276 (75.2)	152 (22.4)
Dexamethasone	214 (58.3)	19 (2.8)
Methylprednisolone	89 (24.3)	119 (17.5)
Prednisolone	6 (1.6)	28 (4.1)
Duration (days)	9 (6–11)[j]	6 (4–11)[k]
COVID-19-specific treatments		
Hydroxychloroquine	12 (3.3)	0 (0)
Remdesivir	28 (7.6)	0 (0)
Lopinavir-ritonavir	23 (6.3)	0 (0)
Convalescent plasma	1 (0.3)	0 (0)
Tocilizumab	2 (0.5)	2 (0.3)
Blood transfusions	104 (28.3)	220 (32.4)

Values are as no. (%) or median (interquartile range)

ECMO extracorporeal membrane oxygenation, *ECLS* extracorporeal life support, *ICU* intensive care unit, *SAPS-II* Simplified Acute Physiology Score II, *SOFA* sequential organ failure assessment, *NA* not applicable

[a] 3 missing values

[b] 4 missing values

[c] 1 missing values

[d] 2 missing value

[e] 16 missing values

[f] 10 missing values

[g] 9 missing values

[h] 6 missing values

[i] 15 missing values

[j] 6 missing values

[k] 34 missing values

Discussion

In this observational prospective multicenter before-after study, we found that after adjustment for prespecified baseline confounders, the 28-day cumulative incidence of a composite outcome including ICU-MDR-col and/or ICU-MDR-inf was not significantly different between COVID-19 patients and controls recruited before the pandemic in the same ICUs. When both outcomes were considered separately, COVID-19 patients had a higher incidence rate and 28-day cumulative incidence of ICU-MDR-inf, but the incidence of ICU-MDR-col was not different between groups.

Several large-scale routine surveillance studies have documented an increased rate of MDR bacteria in COVID-19 patients, both in the community- and healthcare settings [29–31]. Because they have not linked antimicrobial susceptibility testing and patient-related data, these studies provide limited insights into AMR epidemiology in COVID-19 patients. Other studies [13–15] have reported on resistance data in hospitalized COVID-19 patients, albeit with important limitations, such as a small sample size, a retrospective inclusion of patients, and a single-center design. Most studies have not distinguished colonization from infection with MDR bacteria, have not focused on critically-ill patients, have not compared COVID-19 patients with controls recruited in the same centers, and have failed to adjust statistical analyses on confounding factors known to be associated with ICU-MDR-col/ICU-MDR-inf. To our knowledge, COVID-BMR is the first study addressing these methodological limitations simultaneously.

Our results are in line with a monocentric retrospective case–control study where the incidence rate of ICU-MDR-col was not statistically different in COVID-19 patients in comparison to matched controls (respectively 30 vs. 18 per 1000 patients·ICU days, sHR 1.71, 95% CI 0.93–3.12) [32]. In a theoretical framework where ICU-MDR-col is mainly related to cross-transmission of MDR strains between patients via healthcare-workers, several organizational changes triggered by the COVID-19 pandemic could have modified the incidence of ICU-MDR-col in opposite directions [5]. On the one hand, because COVID-19 patients were often treated in dedicated units where strict IPC measures were implemented, it has been hypothesized that enhanced hand hygiene, use of protective personal equipment (PPE) and efforts to decrease patient contacts may have lowered the risk of cross-transmission events. On the other hand, shortages of PPEs (documented in France at the onset on the pandemic [33]), limited adherence to IPC measures due to higher workload of healthcare workers and overcrowding of patients, and disruptions of diagnostic microbiology workflows (leading to delayed isolation of ICU patients colonized with MDR bacteria) could have facilitated the spread of MDR strains between patients. Our study was not designed to investigate the relative contribution of

Table 3 Patient outcomes

	COVID-19 patients $n = 367$	Controls $n = 680$
ICU-acquired colonization and/or infection with MDR bacteria		
At least one event (n, %)	147 (40.1)	209 (30.7)
Type of first event		
ICU-acquired MDR colonization	98/147 (66.7)	176/209 (84.2)
ICU-acquired MDR infection	49/147 (33.3)	33/209 (15.8)
MDR bacteria of first event (n, %)		
Methicillin-resistant *Staphylococcus aureus*	7/147 (4.8)	15/209 (7.2)
Carbapenem-resistant *Enterobacterales*	18/147 (12.2)	20/209 (9.6)
MDR *Pseudomonas aeruginosa*	7/147 (4.8)	10/209 (4.8)
Carbapenem-resistant *Acinetobacter baumannii*	7/147 (4.8)	4/209 (1.9)
Vancomycin-resistant enterococci	0/147 (0)	1/209 (0.5)
3GC-resistant *Enterobacterales* (including ESBL)	108/147 (73.5)	159/209 (76.1)
Mean (SD) number of events per patient	1.4 (0.6)	1.2 (0.6)
ICU-acquired colonization with MDR bacteria		
At least one event (n, %)	125 (34.1)	190 (27.9)
MDR bacteria of first event (n, %)		
Methicillin-resistant *Staphylococcus aureus*	4/125 (3.2)	9/190 (4.7)
Carbapenem-resistant *Enterobacterales*	16/125 (12.8)	20/190 (10.5)
MDR *Pseudomonas aeruginosa*	1/125 (0.8)	4/190 (2.1)
Carbapenem-resistant *Acinetobacter baumannii*	9/125 (7.2)	4/190 (2.1)
Vancomycin-resistant enterococci	0/125 (0)	0/190 (0)
3GC-resistant *Enterobacterales* (including ESBL)	95/125 (76)	153/190 (80.5)
Mean (SD) number of events per patient	1.2 (0.4)	1.1 (0.4)
ICU-acquired infection with MDR bacteria		
At least one event (n, %)	80 (21.8)	63 (9.3)
By MDR bacteria of first event (n, %)		
Methicillin-resistant *Staphylococcus aureus*	3/80 (3.8)	10/63 (15.9)
Carbapenem-resistant *Enterobacterales*	8/80 (10)	4/63 (6.4)
MDR *Pseudomonas aeruginosa*	9/80 (11.3)	6/63 (9.5)
Carbapenem-resistant *Acinetobacter baumannii*	7/80 (8.8)	4/63 (6.4)
Vancomycin-resistant enterococci	0/80 (0)	1/63 (1.6)
3GC-resistant *Enterobacterales* (including ESBL)	53/80 (66.3)	38/63 (60.3)
By infection type[a] (n, %)		
Bloodstream and catheter-related infection	9 (12.9)	13/63 (20.6)
Urinary-tract infection	2/70 (2.9)	4/63 (6.4)
Hospital-associated pneumonia	12/70 (17.1)	15/63 (23.8)
Ventilator-associated pneumonia	46/70 (65.7)	23/63 (36.5)
Intra-abdominal infection	0/70 (0)	2/63 (3.2)
Other	1/70 (1.4)	6/63 (9.5)
Mean (SD) number of events per patient	1.2 (0.4)	1.2 (0.5)
Outcomes		
ICU length-of-stay (days, median [IQR])[b]	15 (8–26)	10 (7–18)
28-day mortality	79 (21.5)	154 (22.7)

Values are no./total no. (%), unless otherwise indicated

ICU intensive care unit, *MDR* multidrug-resistant, *ESBL* extended spectrum betalactamase, *3GC* third-generation cephalosporins

[a] 10 missing values among COVID-19 patients

[b] Calculated among patients discharged alive

Table 4 Unadjusted and adjusted effect size of COVID-19 status on the incidence of ICU-acquired colonization and infection with MDR bacteria

28-day outcomes	COVID-19 patients $n=367$	Controls $n=680$	Unadjusted		Adjusted[a]	
			Effect size (95% CI)	p value	Effect size (95% CI)	p value
ICU-acquired MDR colonization and/or infection						
Cumulative incidence (%)[d]	40 (35–45)	30.7 (27.3–34.2)	1.32 (1.07–1.63)[b]	0.008	1.39 (0.91–2.09)	0.12
Incidence rate per 1000 patients·ICU days	32 (28–36.8)	26.5 (23.4–30)	1.21 (1–1.45)[c]	0.041	1.22 (0.99–1.5)	0.061
ICU-acquired MDR colonization						
Cumulative incidence (%)	34.1 (29.3–38.9)	27.9 (24.6–31.4)	1.22 (0.97–1.52)[b]	0.082	1.27 (0.85–1.88)	0.23
Incidence rate per 1000 patients·ICU days	23.8 (20.3–27.9)	22.2 (19.4–25.3)	1.07 (0.87–1.32)[c]	0.50	1.09 (0.86–1.37)	0.48
ICU-acquired MDR infection						
Cumulative incidence (%)	21.8 (17.7–26.2)	9.3 (7.2–11.6)	2.46 (1.77–3.42)[b]	< 0.001	2.50 (1.9–3.28)	< 0.001
Incidence rate per 1000 patients·ICU days	15.2 (12.4–18.5)	7.9 (6.3–9.9)	1.92 (1.42–2.58)[c]	< 0.001	1.85 (1.32–2.6)	< 0.001

Values are incidence (95% CI), otherwise as indicated

ICU intensive care unit, *MDR* multidrug-resistant

[a] Adjusted for center and prespecified baseline confounders (age, gender, SAPS-II, prior ICU hospitalization, recent (< 3 months) MDR colonization or infection, recent (< 3 months) antibiotic treatment and immunosuppression), calculated after handling missing values by multiple imputation

[b] Sub-hazard ratio

[c] Incidence rate ratio

[d] Primary endpoint

these factors, but our results suggest that their effects are either individually marginal, or balance each other out when assessed in combination.

Despite a similar incidence of ICU-MDR-col between groups, COVID-19 patients presented a higher cumulative incidence of ICU-MDR-inf, both in univariate and multivariate analyses. Several prospective multicenter observational studies have documented that critically-ill COVID-19 patients had an increased risk of healthcare-associated infections [34], especially ventilator-associated pneumonia [2, 35] and bloodstream and catheter-related infections [3]. However, these studies have reported discordant results regarding the proportion of MDR strains isolated in COVID-19 patients and in controls [2, 36]. Our study did not assess the incidence of ICU-acquired infections with non-MDR strains, which would have provided important information to understand the different effect of COVID-19 on ICU-MDR-col and ICU-MDR-inf in our cohort.

Independently from the resistance phenotype, the transition from colonization to infection in individual patients is mostly influenced by the integrity of anatomical barriers and host immune defenses. Regarding anatomical barriers, COVID-19 patients in our study had a longer duration of exposure to invasive devices and IMV. Regarding host defenses, critically-ill COVID-19 patients are known to present features of acquired immunosuppression [37, 38], and the proportion of patients with baseline immunosuppression was different in COVID-19 patients and controls. However, both IMV duration and immunosuppression were included in multivariate models, suggesting that these variables are probably not the sole explanations for the increased incidence of ICU-MDR-inf in COVID-19 patients. It can be speculated that steroids, specifically dexamethasone, might have contributed too [39], but we and others have documented that the increased risk of secondary infections (especially VAP) related to steroids in COVID-19 patients appears mainly on the third week of ICU stay [40, 41], whereas the difference in the incidence of ICU-MDR-inf between COVID-19 patients and controls becomes apparent as early as 1 week post-admission in our cohort. Of note, because most COVID-19 patients were enrolled before January 2021, only 2 of them received tocilizumab (or other immunomodulating agent) as COVID-19-specific treatment.

Antibiotic exposure is a key driver of the occurrence of healthcare-associated infections related to MDR bacteria [42]. Numerous studies have documented increased rates of antibiotic usage (including broad-spectrum regimens) and breakdowns in antibiotic stewardship programs during the COVID-19 pandemic [4, 34]. These prescribing patterns can be explained by initial reports documenting

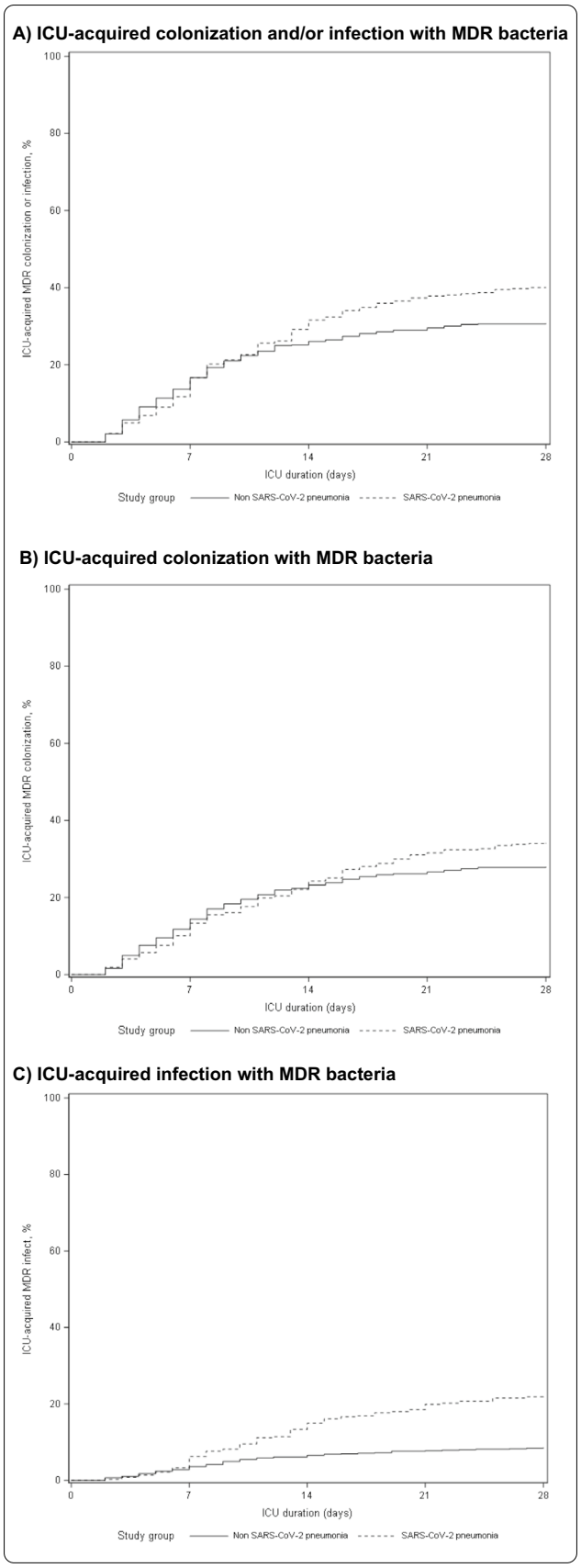

Fig. 1 Cumulative incidence of ICU-acquired colonization and infection with MDR bacteria in COVID-19 patients and controls during the first 28 days of ICU stay

high rates of early bacterial co-infections in COVID-19 patients [43] (even though this was not confirmed in later multicenter studies [44]), the difficulty in differentiating airway colonization from respiratory tract infections in these patients, and the fact that this attitude was supported by guidelines published at the onset of the pandemic [45]. However, antibiotic exposure during ICU stay was comparable (both in proportion and duration) in COVID-19 patients and in controls, and the difference in the proportion of patients receiving antibiotics prior to ICU admission was accounted for in multivariate regression models. It was beyond the scope of our study to fully characterize the effect of antibiotic exposure on the incidence of ICU-MDR-col/inf, and further work is warranted to explore how doses, spectra and administration routes can influence AMR epidemiology in ICU patients [46].

We found that the occurrence of ICU-MDR-col and/or ICU-MDR-inf was associated with a higher mortality in COVID-19 patients, but not in controls. Furthermore, there was no association between the occurrence of ICU-MDR-col and/or ICU-MDR-inf and either ICU length-of-stay or the duration of IMV, in the overall cohort and in both patient subgroups. Previous studies conducted before the COVID-19 pandemic have documented that ICU-MDR-inf was associated with a longer IMV duration [9] and a higher mortality [10, 47, 48], but these findings are not universal [49, 50]. Exploring the association of ICU-MDR-col and/or ICU-MDR-inf with prognostic outcomes was a secondary objective of our study, and dedicated studies would be required to confirm these results.

Prone positioning has been suggested to decrease the incidence of VAP in patients with acute respiratory distress syndrome (ARDS), which could have impacted the occurrence of VAP related to MDR bacteria (and thus ICU-MDR-inf) in our cohort, but this was not confirmed in an ancillary study of the PROSEVA trial [51]. Furthermore, it could be hypothesized that increased contact between patients and healthcare workers during prone positioning sessions could result in higher cross-transmission events, thus increasing the incidence of ICU-MDR-col/inf (even though, to our knowledge, no data has been published on that specific question). Unfortunately, prone positioning sessions were not recorded at the individual patient level as part of the COVID-BMR study, which makes it impossible to study the specific effect of this intervention on the incidence of ICU-MDR-col/inf.

Our study has several limitations. Due to its observational design, our findings only reflect associations between COVID-19 status and the occurrence of ICU-MDR-col/inf, and no causal relationships between these variables can be ascertained. We did not record the incidence of ICU-acquired infections not related to MDR bacteria, which could have enabled an even more detailed epidemiological analysis of AMR in COVID-19 patients. The diagnosis of ICU-acquired infections could be difficult in COVID-19 patients, and our study did not involve an independent adjudication committee. Similarly, the higher prevalence of baseline radiological abnormalities related to ARDS in this patient group could have led to an overestimation of the incidence of VAP related to MDR bacteria, as there was no radiologist assessment to confirm VAP cases. COVID-19 patients were compared to a cohort of patients hospitalized in the same ICUs before the pandemic (in opposition to non-COVID-19 patients hospitalized during the pandemic), which makes it difficult to disentangle the direct effect of COVID-19 from the consequences of organizational changes on the evolution of AMR epidemiology between groups. However, importantly, such study design and the wash-out period between CIMDREA and COVID-BMR studies have prevented any potential direct interaction, such as cross-transmission events, between COVID-19 and controls during the inclusion period, which is an important strength of the study. A total of 530 patients were screened during the study period, but not included because rectal/nasal swabs were not performed at admission or during ICU stay, which could introduce a selection bias. However, this reflects current practices, whereby complete screening of all patients might not be performed despite physician prescription, or in case of a short ICU stay, especially during the COVID-19 surge. Reasons for treatment with steroids and antibiotics, as well as molecules and doses (prior to and during ICU stay) were not recorded. Data on contact precautions and isolation measures were not collected for patients individually, but only at the center level. Similarly, our study was not designed to record detailed data regarding compliance with IPC measures (e.g., hand washing, use of PPEs, etc.). Follow-up was limited to ICU stay, and assessment of colonization through rectal and nasal swabs was not maintained after ICU discharge. Finally, the epidemiology of AMR in ICUs during COVID-19 could be influenced by a variety of factors, such as structural changes triggered by the pandemic, organizational characteristics of ICUs (e.g., single-bed rooms vs. open bays), patterns of antibiotic prescription, etc., all of which may have important variation across centers, and even more so across countries. Consequently, it is possible that the results of our study, which only enrolled patients in a limited number of French centers, could not be entirely transposable to other clinical settings.

Conclusion

In this observational prospective multicenter before-after study, the cumulative incidence of a composite outcome including ICU-MDR-col and/or ICU-MDR-inf was not significantly different between COVID-19 patients and controls recruited before the pandemic in the same centers, after adjustment for baseline confounders. COVID-19 patients had a higher incidence rate and cumulative incidence of ICU-MDR-inf, but the incidence of ICU-MDR-col was not different between groups.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s00134-023-07109-5.

Abbreviations

3GC: Third-generation cephalosporins; AMR: Antimicrobial resistance; CARB: Carbapenem-resistant *Acinetobacter baumannii*; COPD: Chronic obstructive pulmonary disease; COVID-19: Coronavirus disease 2019; ECLS: Extracorporeal life support; ECMO: Extracorporeal membrane oxygenation; ESBL: Extended-spectrum beta-lactamase; EUCAST: European Committee on Antimicrobial Susceptibility Testing; HAI: Healthcare-associated infection; HAP: Healthcare-associated pneumonia; HIV: Human immunodeficiency virus; ICU: Intensive care unit; ICU-MDR-col: ICU-acquired colonization with multidrug-resistant bacteria; ICU-MDR-inf: ICU-acquired infection with multidrug-resistant bacteria; IQR: Interquartile range; IMV: Invasive mechanical ventilation; MDR: Multidrug-resistant; MRSA: Methicillin-resistant *Staphylococcus aureus*; PCR: Polymerase chain reaction; SAPS-II: Simplified Acute Physiology Score II; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SOFA: Sequential organ failure assessment; SOT: Solid organ transplant; VAP: Ventilator-associated pneumonia; VRE: Vancomycin-resistant *Enterococcus* sp..

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Author contributions

Study conception and design: LK, SN. Statistical analysis: AD, JL. Data curation: LK, SJ, MV, MC, EN, JCR, FW, PG, SK, YZ, NVG, CV. Manuscript drafting: LK, JL, SN. Critical revision: all authors.

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Availability of data and materials
Not applicable.

Declarations

Conflicts of interest
LK has received speaking fees and a research scholarship from BioMérieux, and has been employed by Transgene. SN has received speaking fees from MSD, Pfizer, Gilead, BioMérieux, Fischer and Paykel, and BioRad. JCR received a grant from Hamilton Medical for an experimental study. Other authors have no competing interest.

Consent for publication
All authors consent to the publication of the manuscript in Intensive Care Medicine, should the article be accepted by the Editor-in-Chief upon completion of the review process.

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