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Ventilator-associated bacterial pneumonia in coronavirus 2019 disease, a retrospective monocentric cohort study



Marco Moretti ^{a,*}, Johan Van Laethem ^a, Andrea Minini ^{b,c}, Denis Pierard ^{d,e},
Manu L.N.G. Malbrain ^f

^a Department of Internal Medicine and Infectious Diseases, Universitair Ziekenhuis Brussel (UZ Brussel), Brussels, Belgium

^b Faculty of Medicine and Pharmacy, University of Insubria, Como, Italy

^c Department of Intensive Care, Universitair Ziekenhuis Brussel (UZ Brussel), Brussels, Belgium

^d Department of Microbiology and Infection Control, Universitair Ziekenhuis Brussel (UZ Brussel), Brussels, Belgium

^e Faculty of Medicine and Pharmacy, Vrije Universiteit Brussel (VUB), Brussels, Belgium

^f Faculty of Engineering, Department of Electronics and Informatics, Vrije Universiteit Brussel (VUB), Brussels, Belgium

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ABSTRACT

Introduction: Severe coronavirus 2019 disease (CoViD-19) may lead to respiratory failure and mechanical ventilation. Therefore, ventilator associated pneumonia (VAP) may complicate the course of the disease. The aim of the current article was to investigate possible predictive factors for bacterial VAP on a retrospective manner, in a cohort of mechanically ventilated CoViD-19 patients. Additionally, determinant factors of lethality were analyzed.

Methods: Medical records of patients hospitalized in the intensive care units (ICU) at the university hospital UZ Brussel during the epidemic were reviewed. VAP was defined following the National Healthcare Safety Network 2017 criteria. Univariate and multivariate logistic regressions analyses were performed.

Results: Among the 39 patients included in the study, 54% were diagnosed with bacterial VAP. Case fatality rate was 44%, but 59% of the deceased patients had a do-not-resuscitate status. Multivariate logistic regression for prediction of VAP showed significant differences in duration of ICU hospitalization and in minimal lung compliance.

Additional analyses were performed on CoViD-19 patients who were affected by bacterial respiratory superinfection. The responsible pathogens correspond to the commonly found bacteria in VAP. However, 71% of the isolated germs were multi-drug resistant and bacteraemia was reported in 38%. Multivariate analyses for prediction of lethality found significant difference in SOFA score.

Conclusions: Mechanically ventilated CoViD-19 patients might frequently develop VAP. Longer ICU hospitalization was associated with pulmonary superinfection in the current cohort. Moreover, decreased minimal lung compliance was correlated to VAP and higher SOFA score at VAP diagnosis was associated with lethality.

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1. Introduction

A novel zoonotic coronavirus 2019, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), originated in Wuhan in mid-December 2019 and rapidly spread to the rest of the world.

The virus explicitly affects the respiratory system, generating Coronavirus disease 2019 (CoViD-19). Respiratory failure with mechanical ventilation need was reported in 2.3% up to 33% of the affected patients [1,2].

Bacterial ventilator-associated pneumonia (VAP) is a common hospital acquired infection which occurs in 10% up to 33% of the mechanically ventilated patients [3]. Bacterial superinfections were described in 13.5%–44% of the CoViD-19 patients admitted to intensive care unit (ICU), with a case fatality rate of 50–100% [2,4,5]. However, the role of bacterial VAP in CoViD-19 patients has

* Corresponding author.

E-mail addresses: marco.moretti@uzbrussel.be, marco.moretti9@gmail.com (M. Moretti).

Uncommon abbreviations

BIA	Bioelectrical impedance analysis
CDC	Center of Disease and Control
CCI	Charlson comorbidity index
DNR	Do-not-resuscitate
ECDC	European Center of Disease and Control definition
EUCAST	European committee on antimicrobial susceptibility testing
ECMO	Extra corporeal membrane oxygenation
XDR	Extreme-drug resistant
iVAC	Infectious ventilator associated condition
NHSN	National Healthcare Safety Network
SOFA	Sequential organ failure assessment
SAPS	Simplified Acute Physiology Score
spp	Species
VIM	Verona integron-encoded metallo- β -lactamase

not yet been established. Prolonged mechanical ventilation may expose CoViD-19 patients to higher risk of pulmonary superinfection [4,5]. The current monocentric observational study has been designed to describe and investigate predictors of VAP in a cohort of mechanically ventilated CoViD-19 patients. Furthermore, discriminants for lethality in CoViD-19 patients with respiratory bacterial superinfection will be analyzed.

2. Materials and methods

2.1. Ethical considerations

The study was conducted in accordance with the study protocol, the Declaration of Helsinki and applicable regulatory requirements. We applied for approval of the protocol by the local Institutional Review Board and the Ethics Committee of the University Hospital Brussels approved the protocol (EC approval number: B1432020000208). In view of the retrospective nature of the study, which did not demand any deviation from standard clinical ICU care, and the fact that all data was anonymized, a waiver of informed consent was obtained.

2.2. Patient population

Medical records of patients hospitalized in ICU wards in our tertiary care hospital with a confirmed SARS-CoV-2 infection between March 1, 2020 up to May 31, 2020 were reviewed. All confirmed cases of CoViD-19, who were admitted to intensive care unit (ICU) and were mechanically ventilated within the selected period, were enrolled in the current study. All included patients had a positive polymerase chain reaction (PCR) for SARS-CoV-2 in nasopharyngeal swab or bronchial alveolar lavage fluid (BAL).

2.3. Variables definition

National Healthcare Safety Network (NHSN) 2017 criteria were used to define VAP, as these criteria are embraced by the Center of Disease and Control (CDC) [6]. Consequently, infectious ventilator associated condition (iVAC) was diagnosed whenever an oxygenation problem (positive end-expiratory pressure increase more or equal to three cmH₂O or a rise in fraction of inspired oxygen of greater than or equal to 20 points for two or more days) occurred with hypothermia (temperature < 36 °C) or fever (temperature > 38 °C) or leucocytosis (>12,000 white blood cells/

mm³) or leukocytopenia (<4000 white blood cells/mm³). Possible VAP was defined as iVAC combined with a qualitative pulmonary infection (endotracheal aspiration or BAL showing on gram stain >25 neutrophils and <10 epithelial cells per low power field). Finally, probable VAP was delineated as the sum of iVAC and a quantitative pulmonary infection (endotracheal aspiration or BAL growing respectively > 10⁵ CFU/mL and >10⁴ CFU/mL) [6].

Lung compliance was indirectly calculated for all-included patients, who were mechanically ventilated in volume or pressure-controlled modalities [7,8] and who were deeply sedated, with a Richmond agitation-sedation scale ranging between –4 and –5 [9].

Bacteria responsible for VAP were classified as sensitive, multi-drug resistant (MDR) or extreme-drug resistant (XDR), based on European Center of Disease and Control definition (ECDC) [10].

Lethality or case-fatality rate was defined as crude death percentage of CoViD-19 intubated patients during ICU hospitalization.

2.4. Patient data collection

Epidemiological, clinical, biological and microbiological data were collected from the medical records of enrolled patients during ICU admission, and at VAP diagnosis for cases diagnosed with probable VAP. Furthermore, comorbidities were classified using the Charlson comorbidity index (CCI), a validated tool to quantify the burden of comorbidities [11]. Bioelectrical impedance analysis (BIA) assessing the patient's fluid status, obtained the day of VAP diagnosis, was reported to estimate body fluid excess [12]. Average maximal and minimal lung compliance were calculated for all included patients during ICU hospitalization. Furthermore, lung compliance was assessed in patients affected by bacterial VAP at diagnosis. Previously validated prognostic scores (Apache II, Apache III, SAPS 1 and SAPS 2) were calculated for all the included patients at 48 h from ICU admission [13]. Finally, sequential organ failure assessment (SOFA) score was documented for probable bacterial VAP patients at time of diagnosis, in order to estimate the prognosis and the severity of the disease [14].

2.5. Statistical analysis

Positive outcome was defined as development of probable VAP in the first statistical analyses. Secondly, lethality was chosen as endpoint for CoViD-19 patients affected by bacterial probable VAP.

Data are expressed as median and interquartile range for continuous variable, numbers and proportions for categorical variables, as all the analyzed data were non-normal distributed. Mann-Whitney U tests and Chi-square or Fisher exact tests were performed on baseline characteristics respectively for the assessment of continuous and categorical data. Independent predictors of development of VAP were determined using univariate logistic regression analyses. Length of ICU hospitalization, lung compliance and the prognostic scores were chosen as these were previously correlated to onset of pneumonia and/or disease severity [8].

Further assessments were performed through multivariate logistic regression. Two statistical models were computed, the first included the variables age, sex, CCI and duration of ICU hospitalization. The variables age, sex, CCI and minimal lung compliance were chosen to compute the second model.

Additional analyses were performed only in the group of patients affected by bacterial probable VAP in order to predict lethality. Conform to our first analysis, univariate logistic regression was computed to estimate predictive factors. Prognostic scores, positive blood cultures, infection caused by MDR pathogen, need of renal replacement therapy or veno-venous extra corporeal membrane oxygenation (ECMO) were selected as these are related to disease severity or/and mortality [8,14,15]. Subsequently, a

multivariate regression model was performed. The variables age, sex, CCI and SOFA score were used in this last statistical model.

All the analyses were performed with IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp, released in 2011.

3. Results

3.1. Baseline characteristics of the study population

Thirty-nine CoViD-19 mechanically ventilated patients were admitted in the ICU of the university hospital UZ Brussel between March 1, 2020 and May 31, 2020. The median age was 62 (IQR: 55–72) years and 72% (n = 28) were male, the median body mass index (BMI) was 29.0 (IQR: 26.5–36.5) kg/m². The most frequently reported comorbidity was type 2 diabetes mellitus, 59% of the included patients. Three patients were considered to be immunosuppressed, as two patients were treated with tacrolimus and mycophenolate due to renal transplantation and one patient was on high dose hydrocortisone due to IgA nephropathy. These three patients were treated with high dose methylprednisolone during ICU hospitalization. According to local protocol, 30 patients received hydroxychloroquine, among them five patients were concomitantly treated with lopinavir/ritonavir. Moreover, one patient participated to a clinical study and received an interleukin-1 receptor antagonist. Forty-four percent (n = 17) of the included patients died of CoViD-19 or its complications, of which 11 patients affected by VAP and 6 without VAP (Table 1). Among the deceased patients, ten (59%) had do-not-resuscitate (DNR) status.

Thirty-three (85%) of the included cases were treated for bacterial respiratory superinfection. Among them, 27 patients were affected by VAP, fulfilling the criteria of NHSN 2017. One patient met the criteria of iVAC, but did not meet the definition of possible/probable VAP. Five patients fulfilled the criteria of possible VAP and 21 of probable VAP (Fig. 1). Only the latter group (n = 21) was further analyzed.

Baseline characteristics of CoViD 19 patients with probable bacterial VAP are reported in Table 2. The median time at VAP onset was 16 (IQR: 7–22) days from ICU hospitalization and 13 (IQR:

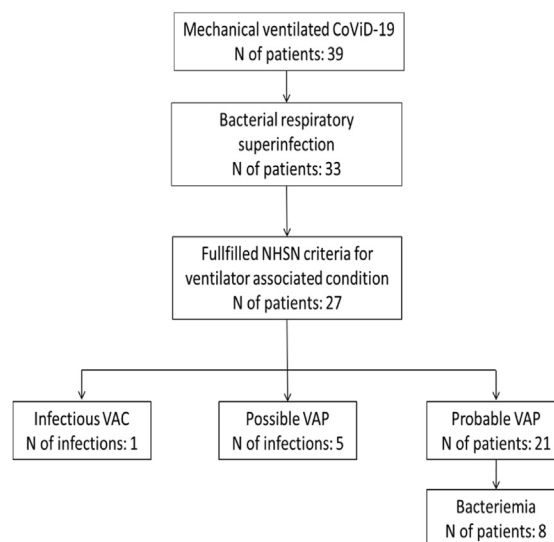


Fig. 1. Study flowchart: CoViD-19: Coronavirus 2019 disease; NHSN: National Healthcare Safety Network; VAC: ventilator associated condition; VAP: ventilator associated pneumonia.

7–21) days from intubation. Ninety percent of the VAP's were acquired five or more days from intubation and thus, were considered as late onset VAP. Twenty-seven bacterial pathogens were cultivated in 21 patients. The most reported pathogen was *Klebsiella* spp (44%). Particularly seven isolated germs were classified as *Klebsiella pneumoniae*, three as *Klebsiella oxytoca* and two as *Klebsiella aerogenes*. *Pseudomonas aeruginosa* was the second most found germ (18%), followed by *Enterobacter* spp. (11%) (Fig. 2). The majority of the superinfections were caused by MDR bacteria (67%) (Fig. 3), of which 29% were identified as *Klebsiella* spp with production of extended spectrum beta lactamase (ESBL). Specifically, five *Klebsiella pneumoniae* and one by *Klebsiella oxytoca* were classified as ESBL following the criteria European committee on antimicrobial

Table 1

Baseline characteristics of mechanically ventilated CoViD-19 patients; Baseline characteristics of mechanically ventilated patients; BMI: body mass index; CCI: Charlson comorbidity index; ICU: intensive care units; SAPS: Simplified Acute Physiology Score; P/F ratio: oxygen partial pressure to fractional inspired oxygen ratio; ACEI: Angiotensin-converting-enzyme inhibitors; Data are expressed as median and interquartile range for continuous variable and numbers and proportions for categorical variables.

Parameters	Overall study populationc (n = 39)	Study characteristics considering probable VAP as primary endpoint		
		VAP patientsc (n = 21)	Non-VAP affected patients (n = 18)	P-value
Age, year	62 (55–72)	62 (58–71)	64 (52–73)	0.865
CCI, index	3 (2–5)	4 (3–6)	3 (1–4)	0.107
BMI, Kg/m ²	29.0 (26.5–36.5)	31.0 (37.0–27.0)	28.0 (25.0–35.0)	0.237
ICU hospitalization length, days	22 (10–34)	29 (21–39)	10 (7–24)	0.004
Intubation length, days	21 (10–31)	27 (18–34)	10 (5–24)	0.008
Apache II, index	17 (13–25)	16 (14–28)	18 (12–24)	0.715
Apache III, index	47 (38–66)	49 (38–70)	47 (38–64)	0.895
SAPS 1, index	9 (7–12)	10 (7.7–14.0)	8.5 (6.0–10.0)	0.056
SAPS 2, index	28 (20–40)	28 (21–40)	27 (18–41)	0.715
Mean lung compliance, ml/cmH ₂ O	36.5 (25.1–55.6)	31.5 (24.0–44.7)	46.5 (36.9–66.5)	0.032
Maximal lung compliance, ml/cmH ₂ O	67.0 (48.0–123.5)	71.0 (44.0–130.5)	63.8 (48.3–97.2)	0.785
Minimal lung compliance, ml/cmH ₂ O	16.1 (12.0–24.7)	14.0 (11.0–17.3)	24.0 (17.5–36.5)	0.001
Mean P/F ratio	172 (153–235)	169 (145–238)	209 (156–233)	0.573
Sex, male (%)	28 (71.8%)	15 (71.4%)	13 (72.2%)	0.725
Active smoker, yes (%)	3 (7.8%)	2 (9.5%)	1 (5.5%)	1.000
ACEI use, yes (%)	18 (46.1%)	13 (61.9%)	5 (27.8%)	0.106
Immunosuppressant use, yes (%)	3 (7.8%)	3 (14.3%)	0 (0.0%)	0.243
Diabetes, yes (%)	23 (59.0%)	15 (71.46%)	8 (44.4%)	0.209
Chronic respiratory disease, yes (%)	3 (7.8%)	2 (9.5%)	1 (5.5%)	1.000
Neoplasms, yes (%)	3 (7.8%)	3 (14.3%)	0 (0.0%)	0.243
Chronic renal disease, yes (%)	7 (17.9%)	7 (33.3%)	0 (0.0%)	0.120
Case fatality rate, yes (%)	17 (43.6%)	11 (52.4%)	6 (33.3%)	0.517

Table 2

Baseline characteristics of mechanically ventilated CoViD-19 patients affected by probable VAP; Baseline characteristics of CoViD-19 patients affected by probable VAP at diagnosis of VAP; BMI: body mass index; CCI: Charlson comorbidity index; ICU: intensive care unit; VAP: ventilator-associated pneumonia; CRP: C reactive protein; WBC: white blood cells; NLR: neutrophil to lymphocyte ratio; IL-6: interleukin 6; SOFA: Sepsis-related Organ Failure Assessment; SAPS: Simplified Acute Physiology Score; P/F ratio: oxygen partial pressure to fractional inspired oxygen ratio; ECMO: Extracorporeal membrane oxygenation; Data are expressed as median and interquartile range for continuous variable and numbers and proportions for categorical variables.

Parameters	CoViD-19 patients affected by VAP (n = 21)	Study characteristics considering all-cause mortality as primary endpoint		
		Deceased patients (n = 10)	Alive patients (n = 11)	P-value
Age, year	62 (57–71)	66 (58–76)	60 (52–64)	0.223
CCI, index	4 (2–6)	4 (2–6)	3 (3–6)	0.705
BMI, Kg/m ²	30.0 (27.0–37.0)	29.5 (28.7–34.7)	33.0 (26.0–39.0)	0.918
ICU days at VAP diagnosis	15 (7–20)	16 (7–22)	13 (7–20)	1.000
Mechanical ventilation days at diagnosis	12 (7–19)	13 (6–20)	12 (7–20)	0.863
CRP, mg/L	244 (137–373)	302 (190–385)	224 (80–248)	0.132
WBC, 10 ³ /μL	13.0 (7.5–19.5)	13.0 (6.0–22.7)	13.0 (9.0–19.0)	1.000
NLR ratio	10.0 (7.5–16.5)	10.5 (7.2–16.2)	9.0 (7.0–18.0)	1.000
D-dimers, ng/mL	3379 (2101–5522)	3344 (1277–5213)	4206 (2245–5654)	0.387
Troponin, mcg/L	0.060 (0.030–0.093)	0.082 (0.039–0.163)	0.060 (0.025–0.078)	0.132
IL-6, pg/mL	92 (39–522)	665 (76–911)	50 (29–220)	0.060
Fluid excess, liter	4.0 (0.0–6.0)	4.5 (1.0–8.7)	2.0 (0.0–6.0)	0.788
SOFA score, score	7 (4–9)	8 (8–10)	6 (3–7)	0.005
Apache II, score	16 (14–29)	16 (16–28)	16 (13–36)	0.809
Apache III, score	48 (37–64)	45 (34–70)	48 (44–58)	0.468
SAPS 1, score	10 (7–14)	11 (7–15)	9 (8–14)	0.918
SAPS 2, score	28 (20–36)	28 (18–40)	29 (21–36)	0.705
P/F ratio	137 (102–162)	119 (97–142)	160 (132–217)	0.051
Lung compliance, ml/cmH ₂ O	30.5 (23.0–38.5)	28.0 (21.0–38.0)	33.0 (27.0–63.0)	0.383
Sex, male, (%)	14 (66.7%)	7 (70.0%)	7 (63.6%)	1.000
Diabetes, yes (%)	14 (66.7%)	6 (60.0%)	8 (72.7%)	0.659
Renal replacement, yes (%)	9 (42.8%)	5 (50.0%)	4 (36.4%)	0.670
ECMO, yes (%)	3 (14.3%)	1 (10.0%)	2 (18.2%)	1.000
Multi-resistant drug VAP pathogen, yes (%)	15 (71.4%)	7 (70.0%)	8 (72.7%)	1.000
Positive blood cultures, yes (%)	8 (38.1%)	2 (20.0%)	6 (54.5%)	0.138

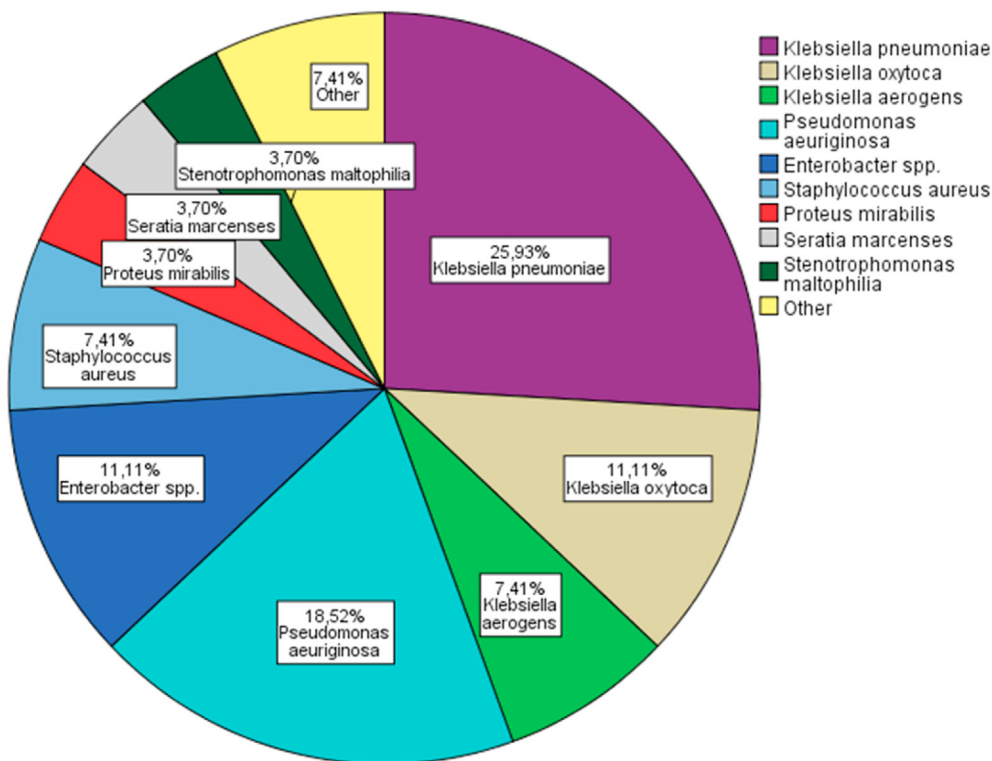


Fig. 2. Bacterial pathogens in probable VAP; VAP: ventilator associated pneumonia; spp: species.

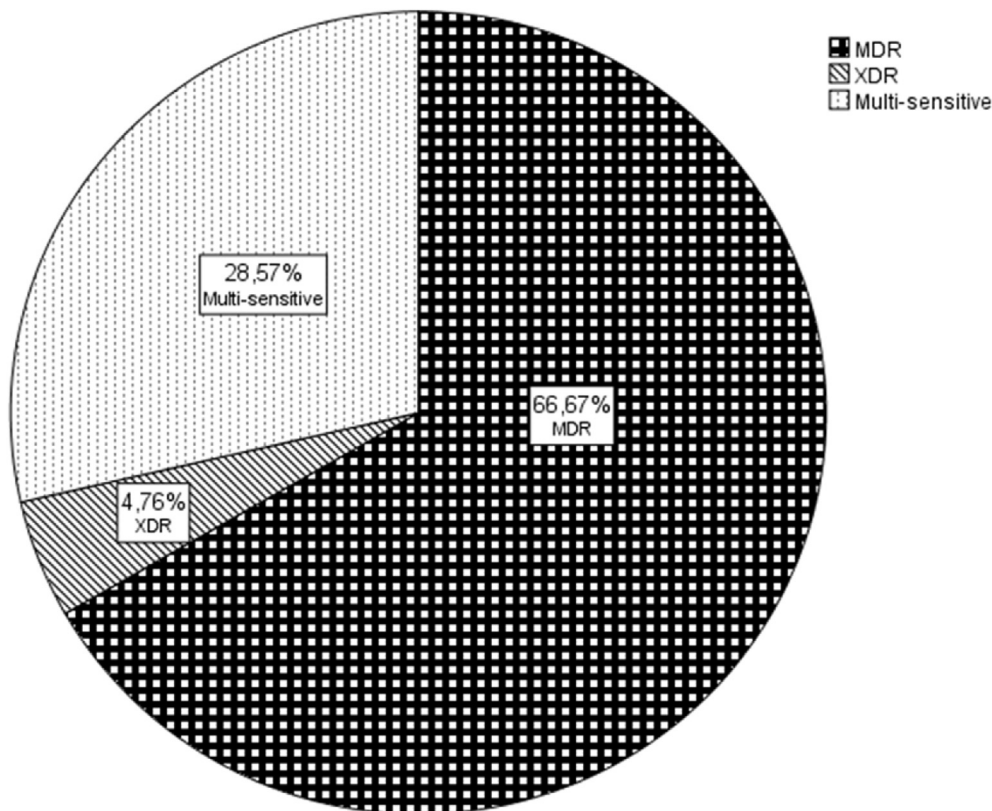


Fig. 3. Bacterial resistance in probable VAP; MDR: multi-drug resistant; XDR: extreme-drug resistant.

susceptibility testing (EUCAST) [16]. Only one germ was defined as XDR: a *Pseudomonas aeruginosa* producer of Verona integron-encoded metallo- β -lactamase (VIM), which was resistant to all tested antibiotics except aztreonam. Thirty-eight percent ($n = 8$) of the affected patients had positive blood cultures. No other source of bacteraemia was found in these patients. During hospitalization or the week previous admission, 81% ($n = 17$) of the patients were exposed to antibiotics before the onset of VAP. In particular, ten patients received two antibiotic courses, seven were exposed to one antibiotic course and only 19% of the selected patients ($n = 4$) were antibiotic naïve. The preferred antibiotic for treatment of bacterial VAP was piperacillin-tazobactam, which was used in 42% ($n = 10$) of the documented infections, mainly in monotherapy. Other used antibiotic regimens were meropenem in 25% ($n = 6$), trimethoprim-sulfamethoxazole in 9% ($n = 2$) and cefepime in 9% ($n = 2$). Three patients had VAP caused by bacteria, which were not sensitive to the initial empiric treatment. A different, appropriate antimicrobial was hence started after two to three days without any impact on lethality. One patient was affected by VAP caused by a *Pseudomonas* XDR, for which a combination of aztreonam and piperacillin-tazobactam was started. However, the pathogen was only sensitive to aztreonam, and the patient eventually died. Only four patients were de-escalated in function of microbiological results. The median antibiotic treatment length was seven (IQR: 4–8) days. Six patients died prematurely, before the termination of the antibiotic course. Nine patients (43%) needed renal replacement therapy as continuous veno-venous hemofiltration and three (14%) were treated with ECMO.

3.2. Predictive factors for probable VAP

The results of the univariate logistic regression for prediction of probable VAP, within the cohort of mechanical ventilated CoViD-19 patients, are reported in Table 3. No significant differences were found in age, sex, BMI and medical history. The duration of ICU hospitalization was significantly longer in CoViD-19 patients, who developed VAP, with an OR (95%CI): 1.04 (1.01–1.09, $p = 0.048$). However, no major differences were found in duration of intubation. Furthermore, significant differences were found in minimal lung compliance between the two groups, with OR (95%CI): 0.86 (0.77–0.96, $p = 0.007$), but insignificant discrepancies were noted in average and maximal lung compliance. Finally, significant differences were appreciated in Simplified Acute Physiology Score 1 (SAPS) score for prediction of VAP development within the current cohort, but none in other severity scores.

Multivariate regression analysis found significant differences in length of ICU hospitalization OR (95%CI): 1.06 (1.01–1.12, $p = 0.044$) and minimal lung compliance OR (95%CI): 0.82 (0.70–0.96, $p = 0.013$) after adjustment for age, sex and CCI.

3.3. Predictive factors for lethality

The results of univariate logistic regression for prediction of lethality within the CoViD-19 patients diagnosed with probable VAP are reported in Table 4. No major discrepancies were noticed for the variables age, sex, BMI and medical history. Furthermore, patients affected by VAP caused by MDR pathogens or with

Table 3

Logistic regression analysis for the prediction of VAP; Logistic regression for prediction of probable VAP; OR: odds ratio; CI: confidence interval; BMI: body mass index; CCI: Charlson comorbidity index; ICU: intensive care units; SAPS: Simplified Acute Physiology Score; P/F ratio: oxygen partial pressure to fractional inspired oxygen ratio; ACEI: Angiotensin-converting-enzyme inhibitors; '-' is used for 'no observation' or 'not applicable'.

Independent variables	Univariate regression analysis for prediction of probable VAP		Multivariate regression analysis for prediction of probable VAP adjusted for age, sex and CCI	
	OR (95%CI)	P-value	OR (95%CI)	P-value
Age	1.01 (0.96–1.06)	0.735	-	-
CCI	1.33 (0.95–1.85)	0.970	-	-
BMI	1.07 (0.96–1.19)	0.233	-	-
ICU hospitalization length	1.04 (1.01–1.09)	0.048	1.06 (1.01–1.12)	0.044
Intubation length	1.04 (0.99–1.09)	0.072	-	-
Apache II	1.03 (0.96–1.10)	0.424	-	-
Apache III	1.00 (0.98–1.03)	0.752	-	-
SAPS 1	1.24 (1.01–1.526)	0.043	-	-
SAPS 2	1.01 (0.96–1.05)	0.701	-	-
Mean lung compliance	0.972 (0.94–1.01)	0.106	-	-
Maximal lung compliance	1.01 (0.99–1.02)	0.300	-	-
Minimal lung compliance	0.86 (0.77–0.96)	0.007	0.82 (0.70–0.96)	0.013
Mean P/F ratio	0.99 (0.98–1.00)	0.305	-	-
Sex	0.66 (0.16–2.77)	0.570	-	-
Active smoker	1.60 (0.13–19.28)	0.711	-	-
ACEI use	3.47 (0.90–13.31)	0.070	-	-
Immunosuppressant use	-	-	-	-
Diabetes	2.41 (0.65–8.92)	0.187	-	-
Chronic respiratory disease	1.60 (0.13–19.28)	0.711	-	-
Neoplasms	-	-	-	-
Chronic renal disease	-	-	-	-

Table 4

Logistic regression analysis for the prediction of lethality; Logistic regression for prediction of lethality within CoViD-19 patients affected by VAP; OR: odds ratio; CI: confidence interval; CCI: Charlson comorbidity index; BMI: body mass index; ICU: intensive care unit; VAP: ventilator-associated pneumonia; CRP: C reactive protein; WBC: white blood cells; ACEI: Angiotensin-converting-enzyme inhibitors; IL-6: interleukin 6; SOFA: Sepsis-related Organ Failure Assessment; SAPS: Simplified Acute Physiology Score; P/F ratio: oxygen partial pressure to fractional inspired oxygen ratio; ECMO: Extracorporeal membrane oxygenation; '-' is used for 'no observation' or 'not applicable'.

Independent variables	Univariate regression analysis for prediction of lethality		Multivariate regression analysis for prediction of lethality adjusted for age, sex and CCI	
	OR (95%CI)	P-value	OR (95%CI)	P-value
Age	1.07 (0.97–1.18)	0.158	-	-
CCI	1.06 (0.72–1.56)	0.759	-	-
BMI	0.96 (0.85–1.08)	0.502	-	-
ICU days at VAP diagnosis	0.99 (0.91–1.08)	0.821	-	-
Mechanical ventilation days at VAP diagnosis	0.98 (0.90–1.07)	0.606	-	-
CRP	1.01 (0.99–1.01)	0.142	-	-
WBC	1.00 (0.93–1.08)	0.988	-	-
D-dimers	1.00 (1.00–1.00)	0.998	-	-
Troponin	1.02 (0.99–1.04)	0.102	-	-
IL-6	1.00 (1.00–1.01)	0.074	-	-
SOFA score	1.86 (1.03–3.36)	0.039	2.70 (1.08–6.73)	0.034
Apache II	0.98 (0.91–1.05)	0.573	-	-
Apache III	0.99 (0.95–1.03)	0.506	-	-
SAPS 1	0.99 (0.84–1.18)	0.940	-	-
SAPS 2	0.99 (0.92–1.06)	0.754	-	-
P/F ratio	0.97 (0.94–1.00)	0.052	-	-
Lung compliance	0.95 (0.87–1.04)	0.282	-	-
Fluid excess	1.14 (0.78–1.67)	0.489	-	-
Sex	1.33 (0.21–8.29)	0.758	-	-
Diabetes	0.56 (0.09–3.52)	0.538	-	-
Renal replacement	1.75 (0.31–10.02)	0.530	-	-
ECMO	0.50 (0.04–6.55)	0.597	-	-
Multi-resistant drug VAP pathogen	0.87 (0.13–5.82)	0.890	-	-
Positive blood cultures	0.21 (0.03–1.47)	0.115	-	-

bacteraemia had no significant higher fatality rate. Deceased patients had a significantly higher SOFA score at VAP diagnosis, with OR (95%CI): 1.86 (1.03–3.36, p = 0.039). In the current cohort, mechanically ventilated patients affected by VAP with a SOFA score higher than seven had a sensitivity of 80% and a specificity of 82% for lethality. No meaningful discrepancies were noted in either

other severity score, or lung mechanics laboratory variables. No significant differences were found in renal replacement therapy or ECMO or body fluid excess at VAP diagnosis.

Finally, multivariate logistic regression for prediction of lethality showed a significantly higher SOFA score after adjustment for age, sex and CCI, with OR (95%CI): 2.70 (1.08–6.73, p = 0.034).

4. Discussion

During a period of three months, 39 CoViD-19 patients required mechanically ventilation at the ICU of the university hospital UZ Brussel. As previously reported, the majority of the inclusions were male patients and the most frequent comorbidity was diabetes mellitus [2,5]. According to different reports, the incidence of VAP roughly ranges between 10% up to 33% of the mechanically ventilated patients [3,6,17]. In our study, more than the half of the examined subjects (54%) developed VAP, following the strict criteria of NHNS for probable VAP. It could be speculated that a protracted ICU hospitalization and a longer intubation period may be responsible for the greater rate of VAP [18]. In this cohort, the duration of ICU hospitalization in mechanically ventilated CoViD-19 patients was associated with VAP development after adjusting for age, sex and comorbidities.

Gattinoni et al. previously reported two different phenotypes of physio-pathological respiratory tract involvement in CoViD-19 patients [19]. SARS-CoV-2 pneumonia type L, which provokes hypoxia, but minimally affects lung compliance, and SARS-CoV-2 pneumonia type H, similar to classic acute respiratory distress syndrome (ARDS), which induces hypoxia and decreases lung compliance. Further hypotheses based on Italian and Spanish experience speculate that vasoconstriction due to hypoxia and pulmonary micro-embolization might be responsible for pneumonia with “normal” compliance (>40 ml/cmH₂O), whereas acute lung injury occurring in later stage of disease and/or bacterial superinfection might lead to pneumonia with reduced compliance [20]. In the current cohort, lower average lung compliance was detected in CoViD-19 patients affected by VAP (31.5 ml/cmH₂O) in comparison with those who did not develop pulmonary superinfection (46.5 ml/cmH₂O). However, this finding was not significant in univariate analyses. Moreover, decreased minimal lung compliance was significantly correlated with VAP occurrence, independently from age, sex and comorbidities. Further investigations are needed to confirm these results.

In the current cohort, univariate analysis showed a greater SAPS 1 score at 48 h from ICU admission in CoViD-19 patients affected by VAP, however the same result could not be found with SAPS 2 or Apache II–III scores.

Case fatality rate was 44%. Fifty-two percent of the VAP patients and 33% of the non-VAP inclusions died. No significant discrepancies in lethality between the two groups were found, possibly due to the small sample size.

As expected, gram negative rods were the most detected VAP associated pathogens [3,17]. *Klebsiella* spp. Was the most involved bacteria, followed by *Pseudomonas* spp., with the large majority of isolated germs being MDR (71%). As previously reported, the higher rate of resistances might be explained by the late onset of VAP [3,17]. Ninety percent of the patients, affected by probable VAP, developed bacterial pulmonary superinfection five or more days after intubation. Moreover, 81% of the patients affected by VAP had previously been exposed to one or more antibiotic regimens before VAP diagnosis. Inappropriate or unnecessary broad antibiotic treatment at hospital admission in hospitalized CoViD-19 patients could result in higher resistance levels and might increase mortality rates [20–22]. Therefore, prompt antibiotic de-escalation or cessation should be considered following microbiologic results and antimicrobial stewardship principles should be respected particularly during the CoViD-19 epidemic [21].

An unexpected high rate of positive blood cultures was found in the current cohort. Thirty-eight percent of the VAP patients developed a significant bacteremia, without any extra pulmonary source of infection identified. Nonetheless, positive blood cultures

were not associated with higher lethality as previously reported, again possibly due to the small sample size [18].

Greater SOFA score at diagnosis may be correlated with higher fatality rate. As observed in the present study, a higher SOFA score was significantly correlated to lethality in VAP affected CoViD-19 patients independently from age, sex and comorbidities. Furthermore, a SOFA score, greater than seven, had a considerable predictive power for lethality.

The strengths of this study are the rigorous study design and structure. Variables were strictly defined. Particularly, the definition of VAP was in accordance with NHNS classification and the bacterial resistances classification followed the ECDC criteria [6,10]. To the best of our knowledge, this is the first cohort study focused on bacterial VAP's in CoViD-19 patients [4,23]. Finally, the current study enforces the evidence-based knowledge on critical ill CoViD-19 patients, affected by bacterial VAP, and provides possible risk factor for lethality in these patients.

This study has several limitations. First, due to the retrospective design of this study, some confounding factors could not have been excluded. Furthermore, the difference between upper respiratory ways colonisation and bacterial VAP is extremely challenging in severe CoViD-19 patients [24]. In the current article, NHNS classification was used to differentiate the two entities. However, this could have under or overestimated the real number of bacterial VAP. Second, a relative low number of patients were included, which may undermine the power of this study. Multicentre large prospective observational trials should be performed to shed more light on this topic.

5. Conclusion

In summary, we found a high number of bacterial VAP's in mechanically ventilated CoViD-19 patients which may be due to the longer ICU hospitalization. Furthermore, decreased minimal lung compliance might be associated with bacterial respiratory superinfection in CoViD-19 mechanically ventilated patients. We believe that the implementation of an antimicrobial stewardship team could enhance judicious antibiotic use, prevent antibiotic overuse, and perhaps reduce ICU hospitalization duration. Restricted antimicrobial use and early de-escalation might lower resistances and airway colonisation with MDR pathogens. Furthermore, preventive measures should be considered to limit decreases in lung compliance. Strict protective ventilation might delay lung damages and lowering of the lung compliance. We observed the expected distribution of bacteria responsible for VAP in these CoViD-19 patients, however a greater number of MDR pathogen and bacteraemia was reported in the current cohort. SOFA score at VAP diagnosis may predict lethality with considerable specificity and sensitivity.

Ethics approval and consent to participate

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was conducted in accordance with the study protocol, the Declaration of Helsinki and applicable regulatory requirements. We applied for approval of the protocol by the local Institutional Review Board and Ethics Committee of the University Hospital Brussels approved the protocol (EC approval number: B143202000208). In view of the retrospective nature of the study, which did not demand a deviation from standard clinical ICU care, and the fact that all data was anonymized, informed consent from the patient or the next of kin was not essential.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MM: concept, study design, data collection, data analysis and interpretation, writing and revision. JVL: study design, writing and revision. AM: data collection and data analysis. DP and MLNGM: writing and revision. All authors have given final approval of the version to be submitted.

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Declaration of competing interest

MLNGM is a member of the medical advisory Board of Pulsion Medical Systems (now fully integrated in Getinge, Solna, Sweden) and Serenno Medical (Tel Aviv, Israel), consults for Baxter, Maltron, ConvaTec, Acelity, Spiegelberg and Holtech Medical.

All other authors declare that they have no competing interests in relation to the content published in this manuscript.

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MLNGM is member of the Executive Committee of the Abdominal Compartment Society, formerly known as the World Society of Abdominal Compartment Syndrome (<https://www.wsacs.org/>). He is co-founder, past-president and current treasurer of WSACS. He is co-founder and president of the International Fluid Academy (IFA). The mission statement of the IFA is to foster education, promote research on fluid management and hemodynamic monitoring, and thereby improve survival of critically ill by bringing together physicians, nurses, and others from throughout the world and from a variety of clinical disciplines. The IFA is integrated within the not-for-profit charitable organization iMERiT, International Medical Education and Research Initiative, under Belgian law. The content of the IFA website (<http://www.fluidacademy.org>) is based on the philosophy of FOAM (Free Open Access Medical education – #FOAMed). The site recently received the HONcode quality label for medical education (<https://www.healthonnet.org/HONcode/Conduct.html?HONConduct519739>).

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