



Risk factors for ventilator-associated lower respiratory tract infection in COVID-19, a retrospective multicenter cohort study in Sweden

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Abstract

Background: Ventilator-associated lower respiratory tract infections (VA-LRTI) increase morbidity and mortality in intensive care unit (ICU) patients. Higher incidences of VA-LRTI have been reported among COVID-19 patients requiring invasive mechanical ventilation (IMV). The primary objectives of this study were to describe clinical characteristics, incidence, and risk factors comparing patients who developed VA-LRTI to patients who did not, in a cohort of Swedish ICU patients with acute hypoxemic respiratory failure due to COVID-19. Secondary objectives were to decipher changes over the three initial pandemic waves, common microbiology and the effect of VA-LRTI on morbidity and mortality.

Methods: We conducted a multicenter, retrospective cohort study of all patients admitted to 10 ICUs in southeast Sweden between March 1, 2020 and May 31, 2021 because of acute hypoxemic respiratory failure due to COVID-19 and were mechanically ventilated for at least 48 h. The primary outcome was culture verified VA-LRTI. Patient characteristics, ICU management, clinical course, treatments, microbiological findings, and mortality were registered. Logistic regression analysis was conducted to determine risk factors for first VA-LRTI.

Results: Of a total of 536 included patients, 153 (28.5%) developed VA-LRTI. Incidence rate of first VA-LRTI was 20.8 per 1000 days of IMV. Comparing patients with VA-LRTI to those without, no differences in mortality, age, sex, or number of comorbidities were found. Patients with VA-LRTI had fewer ventilator-free days, longer ICU stay, were more frequently ventilated in prone position, received corticosteroids more often and were more frequently on antibiotics at intubation. Regression analysis revealed increased adjusted odds-ratio (aOR) for first VA-LRTI in patients treated with corticosteroids (aOR 2.64 [95% confidence interval [CI]] [1.31–5.74]), antibiotics at intubation (aOR 2.01 95% CI [1.14–3.66]), and days of IMV (aOR 1.05 per day of

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IMV, 95% CI [1.03–1.07]). Few multidrug-resistant pathogens were identified. Incidence of VA-LRTI increased from 14.5 per 1000 days of IMV during the first wave to 24.8 per 1000 days of IMV during the subsequent waves.

Conclusion: We report a high incidence of culture-verified VA-LRTI in a cohort of critically ill COVID-19 patients from the first three pandemic waves. VA-LRTI was associated with increased morbidity but not 30-, 60-, or 90-day mortality. Corticosteroid treatment, antibiotics at intubation and time on IMV were associated with increased aOR of first VA-LRTI.

KEYWORDS

acute respiratory distress syndrome (ARDS), COVID-19, intensive care, multicenter, SARS-CoV-2, Sweden, ventilator-associated lower respiratory tract infection (VA-LRTI), ventilator-associated pneumonia (VAP), ventilator-associated respiratory infection (VARI)

Editorial Comment

This cohort study presents incidences and comparisons of COVID-19 different subtype waves for intensive care unit (ICU) cases requiring mechanical ventilation, and where microbiological aspects, treatments, and mortalities are described. Data were collected from cases and hospitalizations in selected hospitals in the southern part of Sweden and the Swedish national ICU registry.

1 | BACKGROUND

Ventilator-associated pneumonia (VAP) and ventilator-associated tracheobronchitis (VAT), collectively referred to as ventilator-associated lower respiratory tract infection (VA-LRTI), is a common and serious complication in patients requiring invasive mechanical ventilation (IMV) due to coronavirus disease 2019 (COVID-19).^{1,2} Both inherent and external factors may lead to an increased risk of VA-LRTI in COVID-19. Inherently, SARS-CoV-2 induce immunoparalysis,³ lung thrombosis and pulmonary embolism,⁴ and a shift in lung microbiome,⁵ in addition to long durations of IMV. Recent reports suggest that standard-of-care corticosteroid treatment of COVID-19 may be associated with an increased risk of VA-LRTI.^{6–10} Other factors previously known to increase risk of VA-LRTI are old age, comorbidity, reintubation, burns, long duration of IMV and affected consciousness (neurological disorders).¹¹ VA-LRTI contributes to morbidity and mortality in both non-COVID and COVID patients.^{12–15} Before COVID-19, incidence rates of VA-LRTI between 2 and 20 episodes per 1000 ventilator-days were reported across countries.^{16–18} Reports suggest an increased incidence of VA-LRTI in COVID-19 patients.^{1,2} A retrospective registry study including 20,223 intensive care unit (ICU) episodes (479 COVID) from Swedish ICU patients found an increased prevalence of VA-LRTI in COVID-19 (39 vs. 18%). However, no difference was seen in incidence rate of VA-LRTI per 1000 days of IMV (31 vs. 34 per 1000 days of IMV) as COVID-19 patients needed IMV for longer durations. The incidence rate of VA-LRTI was higher in the second pandemic wave compared with the first and the proportion of COVID-19 patients developing VA-LRTI was higher, but as COVID-19 patients were ventilated for longer durations

compared with all other included diagnoses, this proportional difference resulted in a similar incidence rate.¹⁹

Thus, the current literature indicates a higher risk for VA-LRTI in intubated COVID-19 patients albeit conflicting reports exist.¹⁹ The primary aims of the present study were to determine the characteristics, incidence of and risk factors for first VA-LRTI in a Swedish cohort with acute hypoxemic respiratory failure due to COVID-19. Further, we aimed to explore how first VA-LRTI incidence changed through the pandemic waves, investigate the common microbiology and the effect of VA-LRTI on morbidity and mortality.

2 | METHODS

2.1 | Setting and study design

A retrospective multicenter cohort study of three Swedish healthcare regions, encompassing a total population of 1 million served by one-third-level hospital, three second-level hospitals and five first-level hospitals. All patients above 18 years old admitted to an ICU with acute hypoxemic respiratory failure due to COVID-19 between March 1, 2020 and May 31, 2021, that were in IMV for at least 48 h, were included. Reporting is in accordance with the Strengthening of Reporting Observational Studies in Epidemiology guidelines.²⁰

2.2 | Data collection

Clinical data were obtained retrospectively from hospital medical records and complementary data (disease severity scores) were

retrieved from the Swedish Intensive Care Registry. Patients were identified through the Swedish Intensive Care Registry by filtering on ICU admitted patients with a COVID-19 diagnosis. Primary outcome was the proportion of patients experiencing a first VA-LRTI and the incidence rate of first VA-LRTI per 1000 ventilator-days. The incidence rate of first VA-LRTI was calculated by dividing the number of first VA-LRTI with days at risk (all days of IMV in patients with no VA-LRTI added with all days of IMV up to diagnosis of first VA-LRTI in the remaining patients). Patient characteristics, ICU management, clinical course, treatments, microbiological findings and 30-, 60-, and 90-day mortality were registered. All VA-LRTI diagnoses were set retrospectively by the authors and were confirmed by a senior consultant in infectious diseases or senior consultant in intensive care medicine. The study group jointly discussed ambiguities in recorded data. Spot checks of data collection quality and adherence to definitions were made by GF regarding hospitals in region Östergötland, by FH regarding hospitals in region Jönköping and by JI regarding hospitals in region Kalmar.

2.3 | Definitions

VAP and VAT were presented together as VA-LRTI. VAP was defined as fulfilling the criteria. (1) Intubated for more than 48 h. (2) A clinical condition with one of the following: Fever $>38.5^{\circ}\text{C}$ or $<36.5^{\circ}\text{C}$; total leukocyte count <4 or $>12 \times 10^9/\text{L}$; pulmonary symptoms (increased oxygen demand, changed breathing sounds or debut of purulent sputum, or changed characteristics). (3) Microbiological finding: positive quantitative culture or positive PCR from lower airways using BAL or protected brush specimen.²¹ The radiology criterion of a pulmonary infiltrate was excluded due to the nature of COVID-19. Patients fulfilling the criteria but lacking a positive distal quantitative sample but presenting a positive culture from more proximal airways (i.e., tracheal secretion) were defined as VAT.²² Early VAP was defined as onset within 4 days from intubation and late-VAP as onset after more than 4 days.²³ Antibiotics at intubation were defined as antibiotic treatment started upon or before intubation, and still ongoing at intubation. The three included pandemic waves were based on local COVID-19 incidence peaks, and defined according to the following dates, respectively: Admitted before 2020-07-01, between July 1, 2020 and February 15, 2021 and between February 16, 2021 and May 31, 2021. Ventilator-free days were defined as days alive and out of IMV within 60 days from intubation, with deceased individuals contributing zero ventilator-free days. Corticosteroid treatment was defined as any started treatment with dexamethasone, betamethasone, prednisolone, hydrocortisone, or methylprednisolone for a duration of at least 48 h during hospital care. For additional definitions, see Supplementary.

2.4 | Statistics

Missing data were handled through listwise deletion. No analysis of missing data were performed. Normality was assessed using Shapiro-

Wilk test, histograms, and test of skewness. Independent *t* test, Mann-Whitney *U*, χ^2 , Fisher's exact test, one-way ANOVA, and Kruskal-Wallis tests were used as appropriate. Normal continuous data are presented as mean (SD), non-normal continuous and ordinal data are presented as median (IQR) and categorical data are presented as a percentage ($100 \times n/\text{total}$). A *p*-value of $<.05$ was considered significant. Statistical analysis was made using IBM SPSS (IBM Corp., released 2021, version 28.0 for Macintosh, Armonk, New York) and GraphPad Prism (GraphPad Software, released 2022, version 9.5.0 for Macintosh, www.graphpad.com, San Diego, California).

2.5 | Regression analysis

A multiple logistic regression model was built to estimate the effects of certain variables on the likelihood of first VA-LRTI. Covariates included were based on previous experience, results from descriptive statistics and current literature. These variables were then analyzed through univariable logistic regression, from which each variable with a *p*-value $<.2$ was included in the multivariable model. The variable age was also included in the model. At most one variable per 10 VA-LRTI events was used. Results are presented as adjusted odds ratio (aOR) (95% confidence interval [CI]).

3 | RESULTS

3.1 | Cohort characteristics

A total of 536 patients were included after exclusion (73.8%), see Figure 1. Table 1 presents the baseline characteristics of the cohort

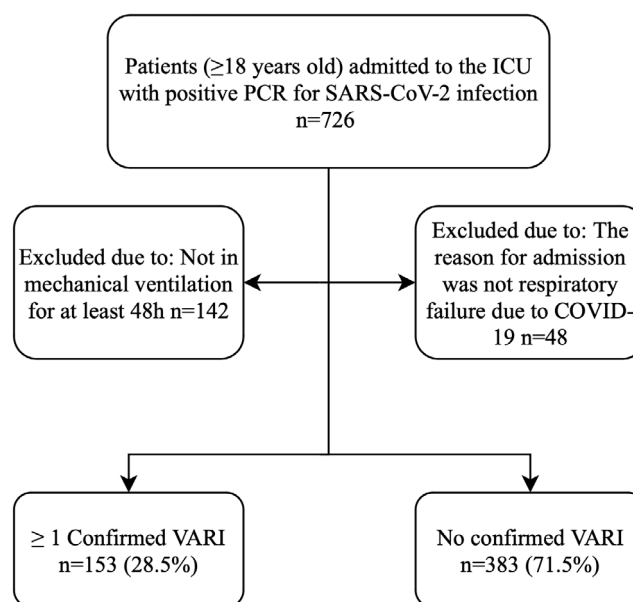


FIGURE 1 Study flowchart of included and excluded patients. In total, 536 patients were included.

and Table 2 presents the ICU management and outcomes. The patients were predominantly male with a mean age of 62.7 (SD 12.9) and a median of 2 (1–3) comorbidities. Mortality at 30, 60, and 90-days was 16.2, 21.0, and 22.5%, respectively (Table 2).

3.2 | Ventilator-associated respiratory infection

Then, 153 patients (28.5%) had at least one VA-LRTI, of which 134 (87.6%) had VAP and 19 (12.4%) had VAT with an incidence rate of first VA-LRTI of 20.8 per 1000 days of IMV (Table 2). Median days from intubation to first VA-LRTI was 9 (IQR 4–14). Patients with a VA-LRTI had fewer ventilator-free days, longer ICU and hospital stay, were treated with neuromuscular relaxants for oxygenation purposes at a higher degree, were more frequently ventilated in prone position, received more corticosteroids and a higher maximum dose of norepinephrine, were more frequently on antibiotic treatments upon intubation, and had deep airway cultures taken more

often when on IMV (Table 2). No difference in age, comorbidities, admission sequential organ failure assessment (SOFA) score or simplified acute physiology score 3 (SAPS3) score were seen. Patients with VA-LRTI had a 90-day mortality of 28.1% compared to 20.4% among the non-VA-LRTI patients ($p = .053$) (Table 1). Additionally, VA-LRTI patients had a higher acute respiratory distress syndrome (ARDS) grade, more complications due to IMV (tracheal recannulations, reintubations, pneumothorax, or pneumomediastinum), more ICU delirium and were more often on renal replacement therapy (RRT).

3.3 | Risk factors

Please see Supplementary Table S1 for results from the univariable logistic regression analysis. A multiple logistic regression model was built using the first VA-LRTI as outcome. Included variables were male sex, body mass index (BMI), days of IMV, ARDS-grade, age,

TABLE 1 Patient characteristics.

Variable	n	All patients (n = 536)	VA-LRTI patients (n = 153)	Non-VA-LRTI patients (n = 383)	p
Male sex	536	72.0% (386/536)	77.8% (119/153)	69.7% (267/383)	.060
Age	536	62.7 (SD 12.9)	62.2 (SD 11.9)	63.0 (SD 13.2)	.620
BMI	520	30.7 (SD 6.0)	31.2 (SD 5.9) n = 150	30.5 (SD 6.1) n = 370	.152
No. of comorbidities	534	2 (1–3)	2 (1–3)	2 (1–3) n = 381	.167
Any comorbidity	534	76.8% (410/534)	79.7% (122/153)	75.6% (288/381)	.365
Asthma	536	14.0% (75/536)	12.4% (19/153)	14.6% (56/383)	.507
Chronic obstructive pulmonary disease	536	6.9% (37/536)	7.2% (11/153)	6.8% (26/383)	.869
Ischemic heart disease	536	17.5% (94/536)	22.2% (34/153)	15.7% (60/383)	.071
Hypertension	536	53.3% (286/536)	56.9% (87/153)	51.7% (198/383)	.279
CKD	534	24.7% (132/534)	28.1% (43/153)	23.4% (89/381)	.250
CKD grade 3 or worse	534	9.9% (53/534)	11.8% (18/153)	9.2% (35/381)	.929
Habitual creatinine	476	81 (67–90)	80 (68–90) n = 143	82 (67–90) n = 333	.492
Diabetes mellitus	536	26.9% (144/536)	29.4% (45/153)	25.9% (99/383)	.401
Diabetes mellitus type 2	536	25.2% (135/536)	26.8% (41/153)	24.5% (94/383)	.501
Liver cirrhosis	536	0.9% (5/536)	2.0% (3/153)	0.5% (2/383)	.143
Neuromuscular disease	536	3.0% (16/536)	5.9% (9/153)	1.8% (7/383)	.013
Cancer	536	9.0% (48/536)	11.1% (17/153)	8.1% (31/383)	.269
Metastatic cancer	536	2.4% (13/536)	5.9% (9/153)	1.0% (4/383)	.006
Hematological cancer	536	3.2% (17/536)	2.0% (3/153)	3.7% (14/383)	.419
Immunodeficient	536	12.3% (66/536)	13.1% (20/153)	12.0% (46/383)	.736
SOFA upon ICU admission	424	4 (3–5) n = 128	4 (3–5) n = 128	4 (3–5) n = 296	.584
SAPS3 upon ICU admission	482	56 (49–62) n = 143	56 (49–62) n = 143	56 (50–62) n = 339	.735
Days in hospital	523	31 (20–50)	41 (29–68) n = 152	27 (18–41) n = 371	<.001
Days in ICU	529	15 (10–25)	25 (17–36) n = 152	13 (8–20) n = 377	<.001

Note: Patient characteristics of all patients on invasive mechanical ventilation for respiratory failure due to COVID-19, divided into two groups of VA-LRTI and no VA-LRTI. Total number of cases with data for each row is presented in column n. In cases of missing data, the number of cases with available data is specified under each column (n). Bold p values highlight significance.

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; ICU, intensive care unit; VA-LRTI, ventilator-associated lower respiratory tract infection.

corticosteroid treatment, prone position, neuromuscular relaxation, antibiotics upon intubation and number of comorbidities, with a total of 12 events (first VA-LRTI) per included variable. A total of 422 cases was included in the model (after exclusions due to missing data), of which 132 VA-LRTI and 290 non-VA-LRTI patients. A significantly increased aOR for first VA-LRTI was observed for corticosteroid treatment (aOR 2.27 95% CI [1.16–4.76]), antibiotics at intubation (aOR 2.17 95% CI [1.23–3.98]) and days of IMV (aOR 1.03 per day of IMV, 95% CI [1.01–1.05]) (Figure 2).

Further, an additional model was built using late-VAP as outcome for the 474 patients on IMV for more than 4 days. Included variables were male sex, days of IMV, corticosteroid treatment, prone position, neuromuscular relaxation, number of comorbidities, and antibiotics upon intubation, with a total of 10.8 events per included variable. A significantly increased aOR for late-VAP was observed for corticosteroid treatment (aOR 2.37 95% CI [1.10–5.73]), antibiotics at intubation (aOR 2.68 95% CI [1.33–5.90]), and days of IMV (aOR 1.03 per day of IMV, 95% CI [1.01–1.04]).

TABLE 2 ICU management and outcomes.

Variable	n	All patients (n = 536)	VA-LRTI patients (n = 153)	Non-VA-LRTI patients (n = 383)	p
Ventilator-free days within 60 days	529	43 (7–52)	32 (0–43)	47 (30–53) n = 376	<.001
Days of mechanical ventilation	528	14 (8–22)	22 (15–33)	10 (6–18) n = 375	<.001
Tracheostomy	536	58.6% (314/536)	83.0% (127/153)	48.8% (187/383)	<.001
Days from hospital admission to intubation	533	3 (1–5)	2 (1–5) n = 152	3 (1–5) n = 381	.408
Days to tracheostomy	285	7 (4–11)	8 (6–13) n = 112	7 (3–10) n = 173	.001
Noninvasive ventilation before intubation	530	35.1% (186/530)	39.9% (61/153)	33.2% (125/377)	.112
High-flow nasal cannula before intubation	534	68.8% (369/534)	67.3% (103/153)	69.8% (266/381)	.630
ECMO	536	0.9% (5/536)	1.3% (2/153)	0.8% (3/383)	1.000
Prone position	477	70.7% (337/477)	78.0% (110/141)	67.6% (227/336)	.022
Neuromuscular relax ^a	523	50.5% (264/523)	62.9% (95/151)	45.4% (169/372)	<.001
Antibiotics upon intubation	513	75.4% (387/513)	82.0% (123/150)	72.7% (264/363)	.026
Corticosteroid treatment	536	82.7% (443/536)	90.2% (138/153)	79.6% (305/383)	.004
Max. norepinephrine dose (µg/kg/min)	493	<0.1 (<0.1–0.2)	0.1–0.2 (<0.1–0.2) n = 146	<0.1 (<0.1–0.2) n = 347	<0.001
Culture within 48 h ^b	536	65.1% (349/536)	71.9% (110/153)	62.4% (239/383)	.009
Cultures per day in invasive ventilation	527	0.16 (0.07–0.23)	0.19 (0.13–0.25)	0.14 (0.04–0.21) n = 374	<.001
Treatment restrictions	536	18.8% (101/536)	23.5% (36/153)	17.0% (65/383)	.080
Remdesivir	533	14.4% (77/533)	17.0% (26/153)	13.4% (51/380)	.289
Tocilizumab	533	11.1% (59/533)	9.8% (15/153)	11.6% (44/380)	.555
Worst ARDS grade	509 ^c	3 (2–3)	3 (2–3) n = 152	2 (2–3) n = 357	.014
Pneumomediastinum or Pneumothorax	536	7.1% (38/536)	11.6% (17/153)	5.5% (21/383)	.022
Reintubation	365	17.0% (62/365)	25.3% (24/95)	14.1% (38/270)	.012
Tracheal recannulation	181	9.2% (24/262)	13.2% (14/106)	6.4% (10/156)	.006
Cardiopulmonary Resuscitation	531	2.8% (15/531)	4.0% (6/153)	2.4% (9/378)	.332
Septic shock	532	11.3% (60/532)	13.7% (21/153)	10.3% (39/379)	.257
Delirium	526	30.6% (161/526)	40.8% (62/152)	26.5% (99/374)	<.001
RRT	533	21.0% (112/533)	26.8% (41/153)	18.7% (71/380)	.038
Dialysis 30 days after ICU discharge	529	4.7% (25/529)	5.3% (8/152)	4.5% (17/377)	.712
30-day mortality	536	16.2%	15.7%	16.4%	.829
60-day mortality	536	21.0%	24.8%	19.6%	.178
90-day mortality	536	22.5%	28.1%	20.4%	.053

Note: ICU management and outcomes of all patients on invasive mechanical ventilation for respiratory failure due to COVID-19, divided into two groups of VA-LRTI and no VA-LRTI. Total number of cases with data for each row is presented in column n. In cases of missing data, the number of cases with available data is specified under each column as (n). Bold p values highlight significance.

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; ICU, intensive care unit; VA-LRTI, ventilator-associated lower respiratory tract infection.

^aNeuromuscular relax used to improve ventilation and/or oxygenation.

^bDeep airway culture within 48 h from intubation.

^cFor the remaining 27 patients with missing data, ARDS grade was not available.

3.4 | Microbiology and antibiotics

In all VA-LRTI cultures, the proportion of gram-positive pathogens was 31.2%, gram-negative 60.7%, and fungal/undefined 8.1%. In early VAP and late VAP, the proportion gram-positive pathogens were 42.9 and 26.4%, gram-negative 50.0 and 63.6%, fungal/undefined 7.1 and 10.0%, respectively, with a significantly higher proportion of gram-negative pathogens in late VAP ($p = .044$). Two extended-spectrum beta-lactamase-producing bacteria and one methicillin-resistant *Staphylococcus aureus* were identified. For a detailed description of VA-LRTI microbiology, see Figure 3 and Supplementary Table S2.

The proportion of late VAP was 70.7% (94/133) (Supplementary Table S3). Patients with late VAP had fewer ventilator-free days (28 [IQR 0–41] vs. 43 [2–50], $p < .001$), had more often antibiotics at intubation (84.0 vs. 69.2%, $p = .027$), had worse ARDS grade (3 [2–3] vs. 2 [2–3], $p = .031$), higher maximum doses of norepinephrine (0.1–0.2 $\mu\text{g}/\text{kg}/\text{min}$ [<0.1 –0.2] vs. <0.1 $\mu\text{g}/\text{kg}/\text{min}$ [<0.1 –0.2], $p = .018$) and were cultured less per day of IMV (0.18 [0.12–0.23] vs. 0.22 [0.18–0.27], $p = .003$) compared to those with early VAP. No

difference was seen in mortality, age, initial SOFA, or SAPS3 score (Supplementary Table S3).

Antibiotics used at intubation were in 69.8% of cases cefotaxime, 20.7% piperacillin/tazobactam, 6.2% erythromycin, and 3.1% meropenem. No difference was found in type of initial antibiotics administered when comparing those that developed VA-LRTI with those that did not (data not shown).

3.5 | Pandemic wave characteristics

Of the total 536 patients, 180 were included from the first pandemic wave, 182 from the second, and 174 from the third (Table 3). Incidence rate of first VA-LRTI per 1000 days of IMV was 14.5, 24.7, and 25.8 for the first, second, and third pandemic wave, respectively. The percentage of patients with at least one VA-LRTI was 22.8, 32.4, and 30.5%, respectively ($p = .101$). Comparing the initial pandemic wave with the combined second and third revealed a significant increase from 22.8 to 31.5% ($p = .036$), with an incidence rate of 14.5 per 1000 days of IMV during the first wave and 24.8 per 1000 days of IMV during the following two ($p = .005$). Comparing the first, second, and third pandemic waves revealed progressively shorter times to first VA-LRTI (12 [8–17], 9 [6–12], and 6 [3–12] days, respectively, $p = .008$), declining frequency of tracheostomy (66.1, 61.0, and 48.3%, $p = .002$), fewer patients on antibiotics upon intubation (82.5, 74.2, and 60.9%, $p = .007$). Age varied between the waves (62.1 [SD 13.1], 65.1 [SD 12.6], and 60.6 [SD 12.6], $p = .004$), as did corticosteroid treatment (48.9, 99.5, and 100%, $p < .001$). Neuromuscular relaxation for oxygenation purposes decreased (68.4, 42.3, and 37.9%, $p < .001$) and ventilator-free days increased (41 [7–49], 45 [0–52], and 47 [23–54], $p = .001$). The number of patients with treatment restrictions was higher in the first two waves as compared to the third (22.8, 23.6, and 9.8%, $p < .001$). No difference was seen in 30-, 60-, or 90-day mortality, sex, prone position ventilation, admission SOFA score, number of comorbidities, or in gram-negative/gram-positive VA-LRTI culture proportions between the three waves.

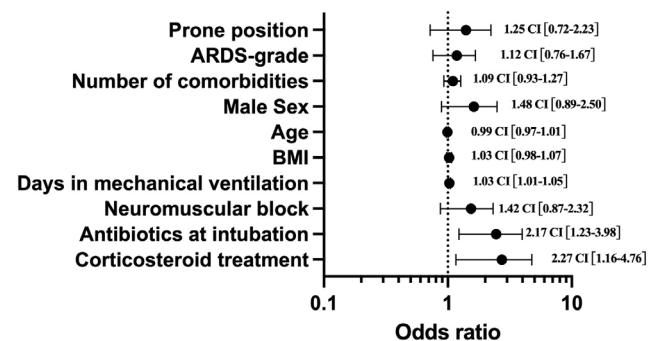


FIGURE 2 Multivariable logistic regression analysis using first ventilator-associated lower respiratory tract infection (VA-LRTI) as outcome. Results presented as adjusted odds-ratio (aOR) (95% confidence interval [CI]).

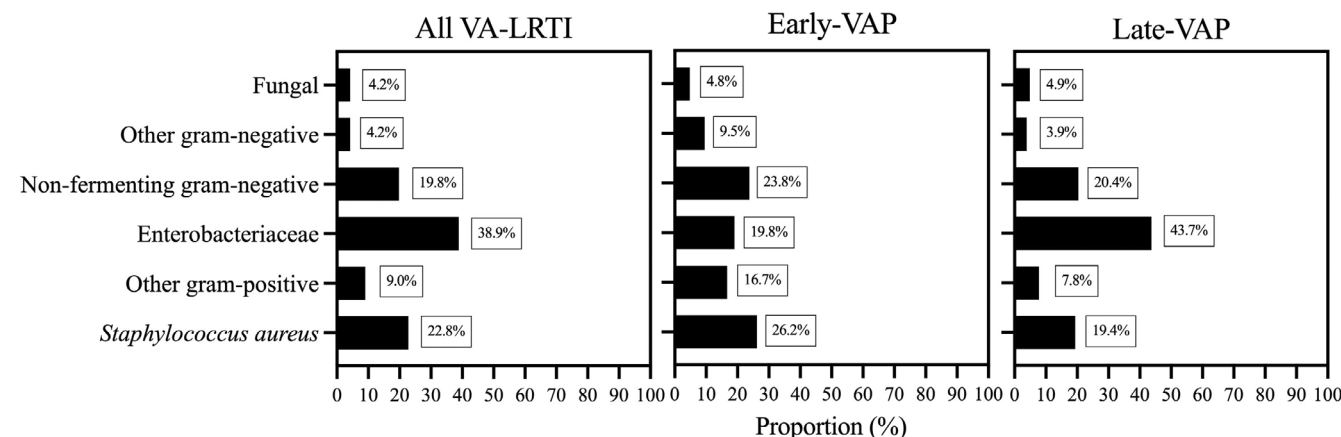


FIGURE 3 Microorganisms found in the airway in ventilator-associated lower respiratory tract infection (VA-LRTI), early and late VAP patients, respectively.

TABLE 3 Pandemic waves comparison.

	N	Wave 1 (n = 180)	Wave 2 (n = 182)	Wave 3 (n = 174)	p
Age	536	62.1 (SD 13.1)	65.1 (SD 12.6)	60.6 (SD 12.6)	.004
Male sex	536	70.0% (126/180)	75.8% (138/182)	70.1% (122/174)	.371
No. comorbidities	534	2 (1-3)	2 (1-3) n = 180	2 (0-3)	.094
SOFA upon ICU admission	424	4 (3-5) n = 156	4 (3-5) n = 161	4 (4-5) n = 107	.679
SAPS3 upon ICU admission	482	55 (49-61) n = 160	58 (53-63) n = 165	55 (49-61) n = 157	.006
Worst ARDS grade	509	2 (2-3) n = 170	3 (2-3) n = 176	3 (2-3) n = 163	.624
Days in hospital	524	33 (19-52) n = 178	31 (21-48) n = 180	30 (19-51) n = 166	.778
Days in ICU	529	17 (11-26) n = 178	16 (10-24) n = 180	13 (8-22) n = 171	.007
Days from hospital admission to intubation	532	2 (1-5) n = 178	3 (1-5) n = 181	4 (1-6) n = 173	.003
Days of mechanical ventilation	528	16 (10-24) n = 178	13 (7-21) n = 182	11 (6-20) n = 168	<.001
Tracheostomy	536	66.1% (119/356)	61.0% (111/182)	48.3% (84/174)	.002
Noninvasive ventilation before intubation	530	13.8% (25/178)	37.4% (68/182)	53.5% (93/174)	<.001
High-flow nasal cannula before intubation	534	54.7% (98/180)	72.5% (132/182)	79.9% (139/174)	<.001
ICU transfer	536	18.8% (34/180)	18.7% (34/182)	37.9% (66/174)	<.001
Prone position	477	74.4% (116/156)	63.7% (116/170)	60.3% (105/151)	.449
Neuromuscular relax	523	68.4% (121/177)	42.3% (77/180)	37.9% (66/166)	<.001
Antibiotics upon intubation	513	82.5% (146/177)	74.2% (135/179)	60.9% (106/157)	.007
Corticosteroid treatment	536	48.9% (88/180)	99.5% (181/182)	100% (174/174)	<.001
Cultures per day in invasive ventilation	527	0.11 (0.05-0.19) n = 178	0.17 (0.11-0.24) n = 181	0.18 (0.08-0.25) n = 168	<.001
Remdesivir	533	0.6% (1/178)	24.2% (44/182)	18.4% (32/173)	<.001
Hydroxychloroquine	533	7.3% (13/178)	0 n = 182	0 n = 173	<.001
Tocilizumab	533	1.1% (2/178)	0 n = 182	32.8% (57/173)	<.001
RRT	533	29.8% (53/178)	18.7% (34/182)	14.4% (25/173)	.001
Ventilator-free days	529	41 (7-49) n = 179	45 (0-52) n = 182	47 (23-54) n = 168	.001
30-day mortality	536	16.6%	17.0%	14.9%	.851
60-day mortality	536	20.0%	23.6%	19.5%	.582
90-day mortality	536	21.1%	26.4%	20.1%	.313
First VA-LRTI	536	22.8% (41/180)	32.4% (59/182)	30.5% (53/174)	.101
Days to first VA-LRTI	153	12 (8-17)	9 (6-12)	6 (3-12)	.008
Treatment restrictions	536	22.8% (41/180)	23.6% (43/182)	9.8% (17/174)	<.001

Note: Characteristics, treatments, and outcomes of all patients on invasive mechanical ventilation for respiratory failure due to COVID-19, divided into the initial three pandemic waves. Total number of cases with data for each row is presented in column n. In cases of missing data, the number of cases with available data is specified under each column as (n). Bold p values highlight significance.

Abbreviations: ARDS, acute respiratory distress syndrome; ICU, intensive care unit; RRT, renal replacement therapy; SOFA, sequential organ failure assessment; VA-LRTI, ventilator-associated lower respiratory tract infection.

4 | DISCUSSION

In this Swedish cohort of patients requiring IMV due to Covid-19 respiratory failure during the initial three pandemic waves, we found a high incidence of VA-LRTI that increased in subsequent pandemic waves. The risk of VA-LRTI was higher in patients treated with antibiotics at intubation or receiving corticosteroids during hospital stay. Further, there was an increased morbidity with fewer ventilator-free days and a higher ARDS grade in patients with a VA-LRTI, but no increase in 30-, 60-, or 90-day mortality. Compared with other European publications, we present a low level of MDR bacteria^{5,24} and as previously presented a correlation between corticosteroid treatment and VA-LRTI.⁸

Corticosteroid treatment was significantly associated with increased odds ratio of VA-LRTI. Following the RECOVERY study,²⁵ which presented a reduced 28-day mortality from corticosteroid treatment in hospitalized COVID-19 patients, corticosteroids has become standard of care. This is evident considering that all but one patient was treated with corticosteroids in wave two and three in the present study. This could possibly explain some of the less pronounced organ failure, such as significantly more ventilator-free days, less RRT and fewer tracheostomies, in these waves. Furthermore, additional changes in clinical management throughout the pandemic may confound our findings regarding corticosteroids and VA-LRTI. Any changes in clinical management that may have occurred after the

initial pandemic wave were not adjusted for in the multivariate regression analysis. For example, development of and adherence to routines, personnel experience and staffing levels, which was recently shown by Taxbro et al. to have contributed to hard end-point outcomes during the pandemic.²⁶ Further, doses, duration and timepoint of treatment start regarding corticosteroids were not possible to retrieve. Hence, corticosteroids may have been administered even after VA-LRTI diagnosis. However, following the initial results of RECOVERY²⁵ corticosteroids were quickly incorporated to standard of care and most likely were started shortly after hospital admission.

Corticosteroid use in the ICU was recently discussed in critical care, as it could be increasing following the pandemic but may come at a cost of increased infectious complications.^{27,28} Our results could support that for patients with severe COVID-19 requiring at least 48 h of IMV, corticosteroids may contribute to the risk of VA-LRTI development. This was also recently presented in a French retrospective cohort study showing a threefold increase in risk for VAP in patients that received dexamethasone, with a VAP incidence of 51%.²⁹ The RECOVERY study group recently reported results of high-dose dexamethasone versus standard of care (including regular dose dexamethasone), demonstrating increased mortality and bacterial pneumonia in the treatment group compared to standard of care among hypoxic patients not requiring ventilatory support.³⁰ Thus, also among COVID-19 patients there is a need to weigh the anti-inflammatory benefits of corticosteroid treatment against potential effects in promoting secondary infection.

Previous publications regarding VAP in non-COVID cases have demonstrated that early antibiotic treatment reduces the risk of VAP^{31,32} and early-onset VAP.³³ In contrast, our results showed that antibiotic treatment at the time of intubation was associated with significantly increased aOR for first VA-LRTI. Subgroup analysis revealed a higher aOR of antibiotics upon intubation for developing late VAP. Further, early VAP patients received a similar amount of antibiotics upon intubation as non-VA-LRTI patients. Hence, early antibiotics primarily seem to be correlated to increased risk of late VAP. Possibly, patients treated with antibiotics upon intubation were in a worse condition than those who were not. They may have been superinfected already at intubation, with a positive culture developing only after antibiotics were discontinued. Additionally, pathogens not covered by the initial antibiotics, such as *Acinetobacter* spp., *Stenotrophomonas maltophilia*, *Pseudomonas aeruginosa*, *Serratia marcescens*, and *Enterococcus* spp., may have been selected by the initial antibiotic treatment. Still, although statistically significant, the clinical relevance of the increased aOR of late VAP in patients treated with antibiotics at intubation may be questionable.

Longer duration of IMV is a well-known risk factor for VA-LRTI¹¹ and was strongly associated with VA-LRTI in our material. In a previously mentioned Swedish registry study comparing non-COVID and COVID-19 patients with regards to VA-LRTI,¹⁹ there was an increased prevalence of VA-LRTI in COVID-19 (30 vs. 18%). However, no difference was seen in incidence rate (31 vs. 34 per 1000 days of IMV) as COVID-19 patients needed IMV for longer durations. Additionally, an increase in incidence rate was observed in the second pandemic wave

(28 vs. 52 per 1000 days of IMV). We present a slightly lower incidence rate of VA-LRTI but a similar increase from the first pandemic wave to the following ones. A possible factor behind this increase could be the rise in corticosteroid treatment. However, additional factors of logistic and structural character that changed throughout the pandemic waves most likely played a part as well, which was not adjusted for in our study. Additionally, in the present study, there was a significant increase in the amount of lower airway cultures in pandemic wave two and three, which could explain an increase in diagnosis.

Differences in VA-LRTI definitions make the entity difficult to compare across studies and countries.³⁴ In the above-mentioned study,¹⁹ VA-LRTI was based on clinician's report to the Swedish Intensive Care Registry. This could explain the difference in incidence as compared to our results, as all VA-LRTIs in our study were verified by culture. Requiring a positive lower airway culture for diagnosis likely leads to an underdiagnosis, depending on local culturing routines. Incidence rates of VA-LRTI in COVID do vary substantially between publications, as shown in a review by Fumagalli et al., where the incidence of VA-LRTI in COVID-19 patients ranged from 18 to 45 episodes per 1000 ventilator-days.¹ Further, in a meta-analysis including 20 studies of VAP in COVID-19 the pooled estimated prevalence of VAP was 45.4%.² Out of five studies in the meta-analysis that included a non-COVID cohort for comparison, the odds ratio of developing VAP in COVID-19 were 3.24 times higher (95% CI [2.2–4.7]). Only one included study from these two systematic reviews is of Scandinavian origin, and as microbiology, resistance patterns, cohort characteristics and local routines differ between countries this impairs generalizability and comparability of our results outside of Swedish hospitals and ICUs.

There are several limitations of the current study, due to the retrospective design, relying on data registered in patient records. As the patients were predominantly hospitalized before routine vaccinations were started, generalizability to the current situation with vaccine coverage and different viral mutations is difficult. Additionally, a larger sample size would have provided additional power to the risk factor analysis. Furthermore, since our study was not designed to evaluate corticosteroid or any other treatment only associations can be presented, and no causative conclusions can be drawn. Possibly, VA-LRTI is simply an indicator of a more severe COVID-19 course, and not the cause of described morbidity differences. A number of factors changed in the course of the pandemic. As the use of corticosteroids is so strongly connected to the two later pandemic waves, the correlation to VA-LRTI could be attributed to other changes in subsequent waves. Lastly, because our definition for VA-LRTI depends on lower airway cultures, the true incidence rate of VA-LRTI is likely to be higher. VA-LRTI events may have been overlooked since less cultures were obtained during the first wave, which could in part explain the incidence rate increase through the pandemic waves.

5 | CONCLUSION

This study shows a low incidence rate of VA-LRTI among critically ill COVID-19 patients compared with reported rates in Sweden for

mechanically ventilated patients both with and without COVID-19.¹⁹ The lower incidence rate could in part be explained by different diagnostic criteria and the present study reports only culture-verified VA-LRTI. Risk factors of potential clinical relevance for VA-LRTI identified in the current study were corticosteroid treatment and days of mechanical ventilation. These results support previous findings pointing out the possible increased risk of VA-LRTI associated to corticosteroid treatment used for COVID-19, and illustrate the need to optimize this potent and essential anti-inflammatory treatment of COVID-19.

AUTHOR CONTRIBUTIONS

All authors contributed to study design. Gustaf Forsberg, Åse Östholm Balkhed, Katarina Niward, and Louise Elander collected data from region Östergötland. Knut Taxbro and Fredrik Hammarskjöld collected data from region Jönköping. Jonna Idh, Johan Berkus, and Andreas Ekman collected data from region Kalmar. Gustaf Forsberg wrote the initial draft after which all authors contributed to subsequent versions and revisions. Gustaf Forsberg conducted the statistical analysis with help from Knut Taxbro, Sören Berg and guidance from a university statistician. All authors contributed to data analysis. All authors have read and approved of the published version of the manuscript.

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DATA AVAILABILITY STATEMENT

Upon reasonable request, limited datasets used during the current study are available via the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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