

Ventilator-Associated Lower Respiratory Tract Bacterial Infections in COVID-19 Compared With Non-COVID-19 Patients*

OBJECTIVES: Ventilator-associated lower respiratory tract infections (VA-LRTIs) are associated with prolonged length of stay and increased mortality. We aimed to investigate the occurrence of bacterial VA-LRTI among mechanically ventilated COVID-19 patients and compare these findings to non-COVID-19 cohorts throughout the first and second wave of the pandemic.

DESIGN: Retrospective cohort study.

SETTING: Karolinska University Hospital, Stockholm, Sweden.

PATIENTS: All patients greater than or equal to 18 years treated with mechanical ventilation between January 1, 2011, and December 31, 2020.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: The cohort consisted of 20,223 ICU episodes (479 COVID-19), with a VA-LRTI incidence proportion of 30% (129/426) in COVID-19 and 18% (1,081/5,907) in non-COVID-19 among patients ventilated greater than or equal to 48 hours. The median length of ventilator treatment for COVID-19 patients was 10 days (interquartile range, 5–18 d), which was significantly longer than for all other investigated specific diagnoses. The VA-LRTI incidence rate per 1,000 ventilator days at risk was 31 (95% CI, 26–37) for COVID-19 and 34 (95% CI, 32–36) for non-COVID-19. With COVID-19 as reference, adjusted subdistribution hazard ratios for VA-LRTI was 0.29–0.50 (95% CI, < 1) for influenza, bacterial pneumonia, acute respiratory distress syndrome, and severe sepsis, but 1.38 (95% CI, 1.15–1.65) for specific noninfectious diagnoses. Compared with COVID-19 in the first wave of the pandemic, COVID-19 in the second wave had adjusted subdistribution hazard ratio of 1.85 (95% CI, 1.14–2.99). In early VA-LRTI *Staphylococcus aureus* was more common and *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Escherichia coli* less common in COVID-19 patients, while *Serratia* species was more often identified in late VA-LRTI.

CONCLUSIONS: COVID-19 is associated with exceptionally long durations of mechanical ventilation treatment and high VA-LRTI occurrence proportions. The incidence rate of VA-LRTI was compared with the pooled non-COVID-19 cohort, however, not increased in COVID-19. Significant differences in the incidence of VA-LRTI occurred between the first and second wave of the COVID-19 pandemic.

KEY WORDS: artificial respiration; bacterial infections; COVID-19; critical care; severe acute respiratory syndrome coronavirus 2; ventilator-associated pneumonia

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COVID-19 continues to exert a tremendous pressure on healthcare systems worldwide. The number of COVID-19 patients in need of ICUs varies between countries and time of the pandemic and is estimated to be around 10–30% of hospital-admitted patients, with 15–20% of these receiving ventilatory support (1–4).

Ventilator-associated lower respiratory tract infection (VA-LRTI) encompasses ventilator-associated tracheobronchitis (VAT) and ventilator-associated pneumonia (VAP), where the presence of new or progressive infiltrates on chest radiography distinguishes the two (5, 6). Difficulties preclude accurate diagnosis of VAP, involving subjectivity and interobserver variability with regards to the presence of new or worsening infiltrates and concomitant lung parenchyma invasion (7, 8). In COVID-19, this is further aggravated by the similar clinical presentation, involving fever, leukocytosis, and extensive radiographic infiltrates. Microbiological findings from the lower respiratory tract (LRT) has also been considered the sole reliable criterion to support a VAP diagnosis in COVID-19 patients (9). Previous reports have found an increased risk of VAP and VA-LRTI in critically ill patients with COVID-19, with high reported incidence proportions ranging from 29% to 86% (10–16).

The clinical management of COVID-19 has since the beginning of the pandemic undergone major changes, with use of corticosteroid therapy for severely ill patients and an increased use of prone positioning, noninvasive ventilation, and anticoagulants warranting comparison of VA-LRTI between different stages of the pandemic. The aim of this study was to investigate the occurrence of microbiologically defined bacterial VA-LRTI among mechanically ventilated COVID-19 patients during the first 10 months of the pandemic and compare these findings to mechanically ventilated non-COVID-19 patients during and before the pandemic.

MATERIALS AND METHODS

Patient Population and Study Setting

This was a retrospective study in four ICUs at Karolinska University Hospital in Stockholm, Sweden, a tertiary care hospital at two sites with 1,100 beds and a catchment area of 2.3 million inhabitants. Patients greater than or equal to 18 years admitted to the ICU between January 1, 2011, and December 31, 2020, treated with mechanical ventilation during their ICU stay were included in the study cohort.

The study was approved by the Swedish Ethical Review Board with a waiver of informed consent (Dnr 2018/1030-31, COVID-19 research amendments Dnr 2020-01385 and Dnr 2020-02145).

Data Collection

Data were obtained from a data extraction of the Swedish Intensive Care Registry of all patients admitted to Karolinska University Hospital between January 2010 and February 2021, including demographics, admission reasons, descriptives of the ICU stay, and discharge status. Further, a database of electronic health records (EHRs) was used for extraction of *International Classification of Diseases*, 10th Revision (ICD-10) codes, mortality data, and microbiology. Comorbidities were based on ICD-10 codes recorded from hospital care up to 5 years before admission (**Table S1**, <http://links.lww.com/CCM/G989>). For admission vital signs and laboratory parameters, the most deviating value during the first 24 hours of the ICU stay was registered. Use and duration of mechanical ventilation as well as prone positioning were identified using nationally harmonized procedure codes.

Definitions

Given the extensive bilateral radiographic infiltrates commonly observed in critically ill COVID-19 patients, the presence of new or worsening infiltrates was deemed difficult to assess retrospectively and thus not assessed (9). As such, ascertaining whether the VA-LRTI was a VAP or VAT was not possible, and therefore the outcome was referred to as VA-LRTI only. The definition of VA-LRTI was based strictly on microbiological criteria, with a positive microbiological isolation of at least 10^5 colony-forming units (CFUs) per mL in tracheal and bronchial secretions, 10^4 CFU per mL in bronchoalveolar lavage or 10^3 CFU per mL in protected brush specimens (5, 17). All quantitative microbiological cultures from 48 hours after intubation until extubation were considered. At Karolinska University Hospital, surveillance LRT cultures are not performed, but rather cultures are performed on clinical suspicion of pneumonia. Only significant bacterial pathogens were included in the analyses, excluding organisms rarely causing manifest VA-LRTI (**Table S2**, <http://links.lww.com/CCM/G989>) (18, 19). Only new findings were considered, that is, if the same pathogen was detected at significant levels from the time of hospitalization until 48 hours after intubation, it was not considered a VA-LRTI. In a predefined sensitivity analysis, VA-LRTI was restricted to the presence of fever or a leukocyte count greater than 12,000 or less

than 4,000 cells per μL , 1 day before up to 1 day after the time of the microbiological sampling (10). Given the retrospective study design, we considered the documentation of purulent sputum to be inadequate and therefore excluded this criterion.

Only the first ventilator episode per ICU admission was included, where we considered intubations with more than 48 hours since a preceding extubation as separate ventilator episodes.

Statistical Methods

The incidence of VA-LRTI in COVID-19 was compared with all non-COVID-19 patients as well as to influenza and the 10 most common mutually exclusive specific main diagnoses given by the ICU physician (Table S1, <http://links.lww.com/CCM/G989>). For comparisons of different phases of the COVID-19 pandemic, the study time period March 1, 2020, until July 31, 2020, represented the first wave and October 1, 2020, until December 31, 2020, the second wave.

Continuous variables were summarized as medians and interquartile ranges (IQRs), and categorical variables were summarized as numbers and percentages, with testing of significance using chi-square test and Wilcoxon signed-rank test. Statistical testing was two-sided, with p value of less than 0.05 considered significant.

The incidence of VA-LRTI was studied using a competing-risks analysis, with extubation (dead or alive) as a competing event (10, 20). Follow-up included the entire ICU stay (or up to 30 d for mortality if ICU stay was shorter). Incidence proportions and rates (per 1,000 ventilator days at risk) of first episodes of VA-LRTI were calculated. To avoid immortal time (i.e., the time period where the patient can not develop VA-LRTI), only the time interval from 48 hours after intubation until the occurrence of VA-LRTI or extubation was included in the incidence rate denominator. The cumulative incidence of first episodes of VA-LRTI was estimated using the Aalen and Johansen estimator (21). Cause-specific hazard ratios (CSHRs) were calculated using Cox proportional hazard models for each event (VA-LRTI or extubation), and Fine and Gray models were performed to calculate subdistribution hazard ratios (sHRs) (22). Multivariable analyses were performed adjusting for age, sex, and Charlson Comorbidity Index (CCI) score. For the models comparing VA-LRTI during the first and second wave in COVID-19 episodes, obesity, prone

positioning, and steroid use before ICU admission was also included in the multivariable models. In order to address potential time-related drifts in diagnostic procedures and LRT culture sampling strategies as well as different case-mixes in the non-COVID-19 cohort, as well as the potential biases arising by the use of historical controls, the following predefined sensitivity analyses were performed for the incidence of VA-LRTI, restriction to episodes: 1) admitted from 2017 and onwards, 2) admitted during the pandemic, 3) with a LRT culture sampling performed, 4) with a $\text{PaO}_2/\text{FiO}_2$ ratio less than 13.3 kPa at admission, and 5) with fever or a leukocyte count less than 4,000 or greater than 12,000 cells per μL .

All statistical analyses were performed in R Version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

In total, 28,347 ICU episodes admitted from January 1, 2011, to December 31, 2020, were recorded, with 680 of these being COVID-19 episodes. The final study cohort consisted of 20,223 episodes from 18,674 persons treated with mechanical ventilation, with 19,744 and 479 non-COVID-19 and COVID-19 episodes, respectively.

Patient Characteristics, ICU Admission Status, and Clinical Outcomes

COVID-19 patient were, compared with non-COVID-19 patients, younger, more often male, had lower CCI score, more often had diabetes, hypertension, and chronic respiratory disease, but less often had malignancy and immunosuppression (Table 1). COVID-19 patients more often received antibiotics and steroids prior to ICU admission and presented with a better SAPS III but worse $\text{PaO}_2/\text{FiO}_2$. Among non-COVID-19 episodes, the five most common diagnoses were cardiac arrest, nonintracranial injuries, nontraumatic intracranial hemorrhage, sepsis, and intracranial injuries.

COVID-19 patients had a median length of stay (LOS) in the ICU of 14 days (IQR, 8–22 d) compared with 2 days (IQR, 1–6 d) in non-COVID-19 patients. The ICU and 30-day mortality were 26% (123/479) and 24% (114/479) among COVID-19 patients, compared with 11% (2,176/19,744) and 15% (3,055/19,744) in non-COVID-19 patients, respectively.

TABLE 1.
Baseline Characteristics and Description of ICU Stay

Characteristic	Ventilated			Ventilated \geq 48 hr		
	COVID-19 (n = 479)	Non- COVID-19 (n = 19,744)	p	COVID-19 (n = 426)	Non- COVID-19 (n = 5,907)	p
Age at ICU admission (yr)	60 (52–68)	64 (51–72)	< 0.001	60 (52–68)	62 (49–71)	0.079
18–44	62 (13)	3,315 (17)	< 0.001	47 (11)	1,128 (19)	
45–64	251 (52)	7,054 (36)		230 (54)	2,165 (37)	< 0.001
\geq 65	166 (35)	9,375 (47)		149 (35)	2,614 (44)	
Male sex	370 (77)	13,296 (67)	< 0.001	330 (77)	3,836 (65)	< 0.001
Charlson Comorbidity Index (points)	1 (0–2)	1 (0–2)	< 0.001	1 (0–2)	1 (0–3)	< 0.001
0–1	345 (72)	11,789 (60)	< 0.001	302 (71)	3,088 (52)	
2–4	115 (24)	6,227 (32)		108 (25)	2,114 (36)	< 0.001
\geq 5	19 (4)	1,728 (9)		16 (4)	705 (12)	
Diabetes mellitus	136 (28)	3,369 (17)	< 0.001	125 (29)	986 (17)	< 0.001
Hypertension	221 (46)	7,700 (39)	0.002	201 (47)	2,098 (36)	< 0.001
Chronic lower respiratory disease	79 (16)	1,951 (10)	< 0.001	71 (17)	725 (12)	0.010
Chronic kidney disease	16 (3)	1,128 (6)	0.034	15 (4)	448 (8)	0.003
Malignancy	31 (6)	2,809 (14)	< 0.001	28 (7)	1,081 (18)	< 0.001
Immunosuppression	53 (11)	3,938 (20)	< 0.001	48 (11)	1,540 (26)	< 0.001
Time in hospital before ICU admission (d) ^a	3 (1–6)	1 (0–2)	< 0.001	3 (1–6)	1 (0–4)	< 0.001
Location before ICU admission						
Emergency department	56 (12)	3,495 (18)	< 0.001	45 (11)	1,349 (23)	< 0.001
Ward	299 (62)	3,878 (20)		276 (65)	1,960 (33)	
Surgical	12 (3)	10,609 (54)		6 (1)	1,567 (27)	
Other hospital	9 (2)	622 (3)		8 (2)	308 (5)	
Other ICU	103 (22)	1,140 (6)		91 (21)	723 (12)	
Antibiotic treatment before ICU admission ^b	189 (39)	6,594 (33)	0.006	173 (41)	2,153 (36)	0.095
Steroid treatment before ICU admission ^c	175 (37)	2,695 (14)	< 0.001	163 (38)	998 (17)	< 0.001
Simplified Acute Physiology Score III (points) ^d	57 (50–65)	62 (50–73)	< 0.001	57 (50–65)	66 (55–75)	< 0.001
PaO ₂ /FIO ₂ (kPa) ^e	12 (9–19)	33 (20–50)	< 0.001	12 (10–18)	28 (17–45)	< 0.001
> 40	25 (5)	4,439 (38)	< 0.001	16	1,684	
26.8–40	33 (7)	2,734 (23)		27	1,172	< 0.001
13.4–26.7	151 (32)	3,002 (26)		133	1,657	
\leq 13.3	263 (56)	1,536 (13)		244	900	
Prone positioning	264 (55)	116 (1)	< 0.001	258 (61)	92 (2)	< 0.001
ICU length of stay (d)	14 (8–22)	2 (1–6)	< 0.001	15 (9–24)	8 (5–15)	< 0.001
Length of ventilation (d)	10 (5–18)	1 (0–3)	< 0.001	11 (7–20)	6 (3–11)	< 0.001

(Continued)

TABLE 1. (Continued).
Baseline Characteristics and Description of ICU Stay

Characteristic	Ventilated			Ventilated \geq 48 hr		
	COVID-19 (n = 479)	Non- COVID-19 (n = 19,744)	p	COVID-19 (n = 426)	Non- COVID-19 (n = 5,907)	p
Ventilated \geq 48 hr	426 (89)	5,907 (30)	< 0.001	–	–	–
Mortality within 48 hr of intubation	13 (3)	1,073 (5)	0.012	–	–	–
ICU mortality	123 (26)	2,176 (11)	< 0.001	110 (26)	1,042 (18)	< 0.001
30-d mortality	114 (24)	3,055 (15)	< 0.001	98 (23)	1,503 (25)	0.289

^aVentilated: 7,521 missing values (COVID-19, n = 1; non-COVID-19, n = 7,520), ventilated \geq 48 hr: 329 missing values (COVID-19, n = 0; non-COVID-19, n = 329).

^bDefined as any antibiotic administered (Anatomical Therapeutic Chemical [ATC] codes of J01) from 7 d before up until ICU admission.

^cDefined as any systemic corticosteroid (ATC codes of H02) administered from 7 d before up until ICU admission.

^dVentilated: 7,521 missing values (COVID-19, n = 1; non-COVID-19, n = 7,520), ventilated \geq 48 hr: 329 missing values (COVID-19, n = 0; non-COVID-19, n = 329).

^eVentilated: 8,040 missing values (COVID-19, n = 7; non-COVID-19, n = 8,033), ventilated \geq 48 hr: 500 missing values (COVID-19, n = 6; non-COVID-19, n = 494).

Data are presented as absolute frequency (% of the included episodes) or as median and interquartile range. χ^2 test was used for categorical variables and Wilcoxon signed-rank test for continuous variables.

Mechanical Ventilation Characteristics

Out of the 20,223 investigated ventilator episodes, 6,333 (31%) were lasting for 48 hours or more, thus being at risk for VA-LRTI (Table 1). Upon comparison of COVID-19 episodes with the 10 most common non-COVID-19 diagnoses as well as influenza, COVID-19 had the longest median ventilator treatment duration, 10 days (IQR, 5–18 d), followed by acute respiratory distress syndrome (ARDS), severe sepsis, and bacterial pneumonia; 5 days (IQR, 2–11 d), 4 days (IQR, 1–7 d), and 4 days (IQR, 2–7 d), respectively (Fig. 1A).

The proportion testing positive for a significant pathogen before intubation as well as during the first 48 hours of intubation did not differ between COVID-19 and non-COVID-19 episodes (Table S3, <http://links.lww.com/CCM/G989>). Among the 426 COVID-19 and 5,907 non-COVID-19 episodes ventilated greater than or equal to 48 hours, 65% (277/426) and 53% (3,108/5,907) had a LRT culture performed from 48 hours of intubation and onwards, respectively. For both COVID-19 and non-COVID-19, LRT cultures were most often sampled from tracheal secretion 52% (223/426) and 38% (2,261/5,907), respectively. Nontraumatic intracranial hemorrhage and aortic aneurysm and dissection were the conditions having

a LRT culture performed most often (Fig. S1, <http://links.lww.com/CCM/G989>).

Incidence of VA-LRTI

In COVID-19, 30% (129/426) had a VA-LRTI (LRT culture positive for a new significant pathogen greater than or equal to 48 hr after start of mechanical ventilation), whereas in non-COVID-19, the corresponding proportion was 18% (1,081/5,907) (Table 2). The VA-LRTI incidence rate per 1,000 ventilator days at risk was 31 (95% CI, 26–37) for COVID-19, compared with 34 (95% CI, 32–36) for non-COVID-19. Among specific non-COVID-19 diagnoses, severe sepsis, ARDS, influenza, and bacterial pneumonia had the lowest incidence rate, whereas nontraumatic intracranial hemorrhage, aortic aneurysm and dissection, and heart failure had the highest incidence rate. When pooling specific infectious non-COVID-19 diagnoses, the incidence rate was 11 (95% CI, 8–15), whereas for noninfectious diagnoses, the incidence rate was 47 (95% CI, 43–50).

The higher incidence proportion but lower incidence rates in the COVID-19 cohort compared with the non-COVID-19 cohort were consistent in sensitivity analyses restricted to episodes from 2017 and

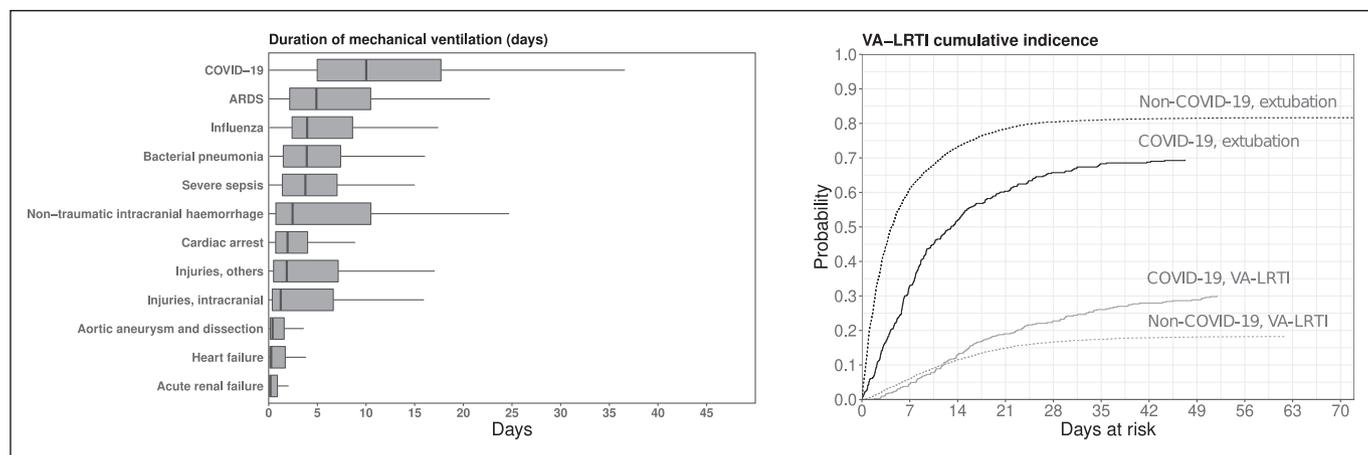


Figure 1. Mechanical ventilation treatment durations and ventilator-associated lower respiratory tract infections (VA-LRTIs) in COVID-19 and non-COVID-19 conditions. **A**, Duration of mechanical ventilation for COVID-19, influenza and the 10 most common specific main diagnoses given by the ICU physician. **B**, Cumulative risk (incidence) of VA-LRTIs in COVID-19 and non-COVID-19 episodes treated with mechanical ventilation for at least 48 hr, considering extubation (dead or alive) as a competing event. ARDS = acute respiratory distress syndrome.

onwards and during the COVID-19 pandemic, respectively, as well as when only including episodes with LRT culture performed and restricting VA-LRTIs to episodes with fever or leukocyte count alterations (Table S4, <http://links.lww.com/CCM/G989>).

The probability of extubation without VA-LRTI was lower in COVID-19 compared with non-COVID-19, including all specific diagnoses (Fig. 1B and Table 3). No significant difference in the cumulative risk of VA-LRTI was observed between the non-COVID-19 and COVID-19 cohort. These findings were consistent across all sensitivity analyses, besides restriction to episodes with Pao_2/FiO_2 less than 13.3 kPa at admission, where the risk of VA-LRTI was decreased in non-COVID-19 (adjusted CSHR [aCSHR], 0.54; 95% CI, 0.40–0.73) (Table S5, <http://links.lww.com/CCM/G989>). Further, the results were consistent when adjusting for the specific comorbidities presented in Table 1 instead of CCI (data not shown). The cumulative risk of VA-LRTI was, compared with COVID-19, decreased for all specific infectious diagnoses (bacterial pneumonia, influenza, and sepsis) as well as ARDS, whereas for aortic aneurysm and dissection, intracranial injuries, and nontraumatic intracranial hemorrhage, the risk was increased.

VA-LRTI During the First and Second Wave of the COVID-19 Pandemic

In the COVID-19 cohort, 381 and 93 episodes were registered during the first (March 9, 2020, to July 31,

2020) and second (October 1, 2020, to December 31, 2020) wave, respectively (Table S6, <http://links.lww.com/CCM/G989>). Patients during the second wave were older, had higher prevalence of diabetes and hypertension, and were more likely to have received systemic corticosteroids before ICU admission and being treated with prone positioning during the ICU stay. The length of mechanical ventilation was shorter during the second wave (8 d; IQR, 5–16 d) compared with the first wave (11 d; IQR, 6–19 d). A higher proportion of mortality within 24 hours of extubation was observed during the second wave (32%, 30/93) compared with the first wave (20%, 76/381). In the non-COVID-19 cohort, 567 and 324 ventilator episodes were registered during the first and second wave, respectively. No major differences were observed for age, sex, ICU LOS, LRT culture performed, and 30-day mortality between the waves.

Among COVID-19 episodes ventilated greater than or equal to 48 hours, the VA-LRTI incidence proportion was 29% (99/345) during the first wave and 38% (30/80) during the second wave (Table 2). For non-COVID-19, the VA-LRTI incidence proportion was 19% (37/194) during the first wave and 21% (28/131) during the second wave. For COVID-19, the VA-LRTI incidence rate per 1,000 ventilator days at risk was 28 (95% CI, 22–34) for the first wave and 52 (95% CI, 35–75) for the second wave. For non-COVID-19, the corresponding VA-LRTI incidence were 37 (95% CI, 26–50) and 52 (95% CI, 34–75), respectively.

TABLE 2.**Incidence of Ventilator-Associated Lower Respiratory Tract Infections in COVID-19 and Non-COVID-19**

Cohort	Ventilated, <i>n</i>	Ventilated ≥ 48 hr, <i>n</i> (%)	No. Ventilator-Associated Lower Respiratory Tract Infection, <i>n</i> (%)	Ventilator Days at Risk	Incidence Rate per 1,000 Days at Risk (95% CI)
COVID-19	479	426 (89)	129 (30)	4,160	31 (26–37)
Non-COVID-19	19,744	5,907 (30)	1,081 (18)	31,895	34 (32–36)
Acute respiratory distress syndrome	381	295 (77)	22 (7)	2,068	11 (7–16)
Infectious diseases ^a	1,103	760 (69)	52 (7)	4,577	11 (8–15)
Bacterial pneumonia	212	147 (69)	13 (9)	771	17 (9–29)
Influenza	134	108 (81)	7 (6)	663	11 (4–22)
Severe sepsis	757	505 (67)	32 (6)	3,143	10 (7–14)
Noninfectious diseases ^b	6,242	2,901 (46)	769 (27)	16,529	47 (43–50)
Acute renal failure	250	39 (16)	6 (15)	115	52 (19–114)
Aortic aneurysm and dissection	563	123 (22)	39 (32)	646	60 (43–83)
Cardiac arrest	1,432	698 (49)	101 (14)	2,279	44 (36–54)
Heart failure	429	99 (23)	23 (23)	402	57 (36–86)
Injuries, intracranial	637	269 (42)	75 (28)	1,561	48 (38–60)
Injuries, others	1,300	628 (48)	147 (23)	3,911	38 (32–44)
Nontraumatic intracranial hemorrhage	1,152	619 (54)	249 (40)	3,457	72 (63–82)
First vs second wave					
COVID-19					
First wave	381	345 (91)	99 (29)	3,586	28 (22–34)
Second wave	93	80 (86)	30 (38)	572	52 (35–75)
Non-COVID-19					
First wave	567	194 (34)	37 (19)	1,013	37 (26–50)
Second wave	324	131 (40)	28 (21)	542	52 (34–75)

^aIncluded bacterial pneumonia, influenza, and severe sepsis. Acute respiratory distress syndrome (ARDS) was excluded as information on infectious or noninfectious etiology was absent.

^bIncluded acute renal failure, aortic aneurysm and dissection, cardiac arrest, heart failure, intracranial injuries, other injuries, and nontraumatic intracranial hemorrhage. ARDS was excluded as information on infectious or noninfectious etiology was absent.

The incidence proportion and incidence rate of ventilator-associated lower respiratory tract infection in COVID-19, all non-COVID-19, influenza as well as the 10 most common specific diagnoses given by the ICU physician is presented. The incidence during the first and second week of the COVID-19 pandemic is compared in the COVID-19 and non-COVID-19 group.

For the COVID-19 cohort, the rate of VA-LRTI in subjects who were still event-free were significantly increased during the second wave (aCSHR, 1.86; 95% CI, 1.15–3.01). The adjusted SHR (aSHR) during the second compared with first wave among COVID-19 patients was 1.85 (95% CI, 1.14–2.99). For the non-COVID-19 cohort, no significant differences were observed for neither extubation nor VA-LRTI.

Distribution of Identified VA-LRTI Pathogens

Staphylococcus aureus was the most identified pathogen in both COVID-19 and non-COVID-19 patients (**Fig. 2**). For the COVID-19 cohort, 34% (44/129) of the VA-LRTIs occurred before 5 days of mechanical ventilation, whereas for non-COVID-19 the proportion was 58% (630/1,081). Among the bacterial pathogens identified during less than 5 days

TABLE 3.
Ventilator-Associated Lower Respiratory Tract Infections Cause-Specific Hazard Ratios and Subdistribution Hazard Ratios

Cohort	Possible Endpoints (Competing Events)					
	VA-LRTI				Extubation (Without VA-LRTI)	
	CSHR (95% CI) Crude	CSHR (95% CI) Adjusted ^a	SHR (95% CI) Crude	SHR (95% CI) Adjusted ^a	CSHR (95% CI) Crude	CSHR (95% CI) Adjusted ^a
COVID-19	Reference	Reference	Reference	Reference	Reference	Reference
Non-COVID-19	0.96 (0.80–1.15)	0.98 (0.82–1.18)	0.96 (0.81–1.14)	0.98 (0.82–1.17)	1.99 (1.77–2.24)	2.02 (1.79–2.27)
Acute respiratory distress syndrome	0.34 (0.22–0.54)	0.33 (0.20–0.53)	0.34 (0.22–0.54)	0.33 (0.20–0.53)	1.88 (1.59–2.21)	1.82 (1.52–2.18)
Infectious diseases ^b	0.36 (0.26–0.50)	0.34 (0.24–0.48)	0.36 (0.26–0.50)	0.34 (0.24–0.48)	2.13 (1.86–2.44)	2.28 (1.97–2.64)
Bacterial pneumonia	0.51 (0.29–0.91)	0.50 (0.28–0.91)	0.51 (0.29–0.90)	0.50 (0.28–0.92)	2.55 (2.07–3.14)	2.63 (2.10–3.30)
Influenza	0.33 (0.16–0.71)	0.32 (0.15–0.70)	0.33 (0.17–0.67)	0.32 (0.16–0.66)	2.15 (1.71–2.70)	2.15 (1.69–2.74)
Severe sepsis	0.33 (0.22–0.48)	0.29 (0.19–0.45)	0.33 (0.22–0.48)	0.29 (0.19–0.43)	2.10 (1.82–2.44)	2.26 (1.92–2.66)
Noninfectious diseases ^c	1.41 (1.16–1.70)	1.38 (1.14–1.67)	1.40 (1.18–1.68)	1.38 (1.15–1.65)	1.98 (1.75–2.24)	2.08 (1.83–2.36)
Acute renal failure	1.55 (0.68–3.55)	1.49 (0.63–3.53)	1.55 (0.70–3.41)	1.49 (0.65–3.46)	4.56 (3.13–6.64)	4.36 (2.93–6.50)
Aortic aneurysm and dissection	1.86 (1.30–2.67)	1.81 (1.21–2.70)	1.86 (1.26–2.74)	1.81 (1.17–2.79)	1.83 (1.43–2.34)	2.12 (1.61–2.80)
Cardiac arrest	1.14 (0.87–1.50)	1.14 (0.86–1.50)	1.14 (0.88–1.48)	1.13 (0.87–1.48)	3.30 (2.86–3.82)	3.36 (2.90–3.90)
Heart failure	1.69 (1.07–2.65)	1.54 (0.95–2.49)	1.68 (1.07–2.65)	1.54 (0.97–2.45)	2.89 (2.23–3.76)	2.79 (2.11–3.70)
Injuries, intracranial	1.45 (1.08–1.93)	1.42 (1.05–1.92)	1.45 (1.08–1.93)	1.42 (1.05–1.92)	1.81 (1.50–2.18)	1.90 (1.57–2.30)
Injuries, others	1.11 (0.87–1.41)	1.20 (0.93–1.55)	1.11 (0.88–1.40)	1.20 (0.93–1.55)	1.74 (1.50–2.01)	1.82 (1.56–2.14)
Nontraumatic intracranial hemorrhage	2.11 (1.70–2.62)	2.05 (1.63–2.58)	2.11 (1.71–2.60)	2.05 (1.65–2.54)	1.54 (1.32–1.80)	1.60 (1.35–1.89)
First vs second wave						
COVID-19 ^d						
First wave	Reference	Reference	Reference	Reference	Reference	Reference
Second wave	1.85 (1.22–2.79)	1.86 (1.15–3.01)	1.85 (1.23–2.77)	1.85 (1.14–2.99)	1.36 (1.00–1.84)	1.70 (1.19–2.43)
Non-COVID-19						
First wave	Reference	Reference	Reference	Reference	Reference	Reference
Second wave	1.34 (0.81–2.19)	1.37 (0.83–2.25)	1.34 (0.82–2.18)	1.37 (0.84–2.24)	1.17 (0.91–1.51)	1.16 (0.90–1.49)

CSHR = cause-specific hazard ratio, SHR = subdistribution hazard ratio, VA-LRTI = ventilator-associated lower respiratory tract infection.

^aAdjusted for age (continuous), sex (categorical), and Charlson Comorbidity Index score (continuous).

^bIncluded bacterial pneumonia, influenza, and severe sepsis. Acute respiratory distress syndrome (ARDS) was excluded as information on infectious or noninfectious etiology was absent.

^cIncluded acute renal failure, aortic aneurysm and dissection, cardiac arrest, heart failure, intracranial injuries, other injuries, and nontraumatic intracranial hemorrhage. ARDS was excluded as information on infectious or noninfectious etiology was absent.

^dAdjusted for age (continuous), sex (categorical), and Charlson Comorbidity Index score (continuous), obesity (categorical), prone positioning (categorical), and steroids before ICU admission (categorical). Two episodes were excluded from the analysis due to missing information about obesity. Competing risk analysis of VA-LRTI and extubation (dead or alive) using Cox proportional hazard models (CSHRs) and Fine and Gray models (SHRs).

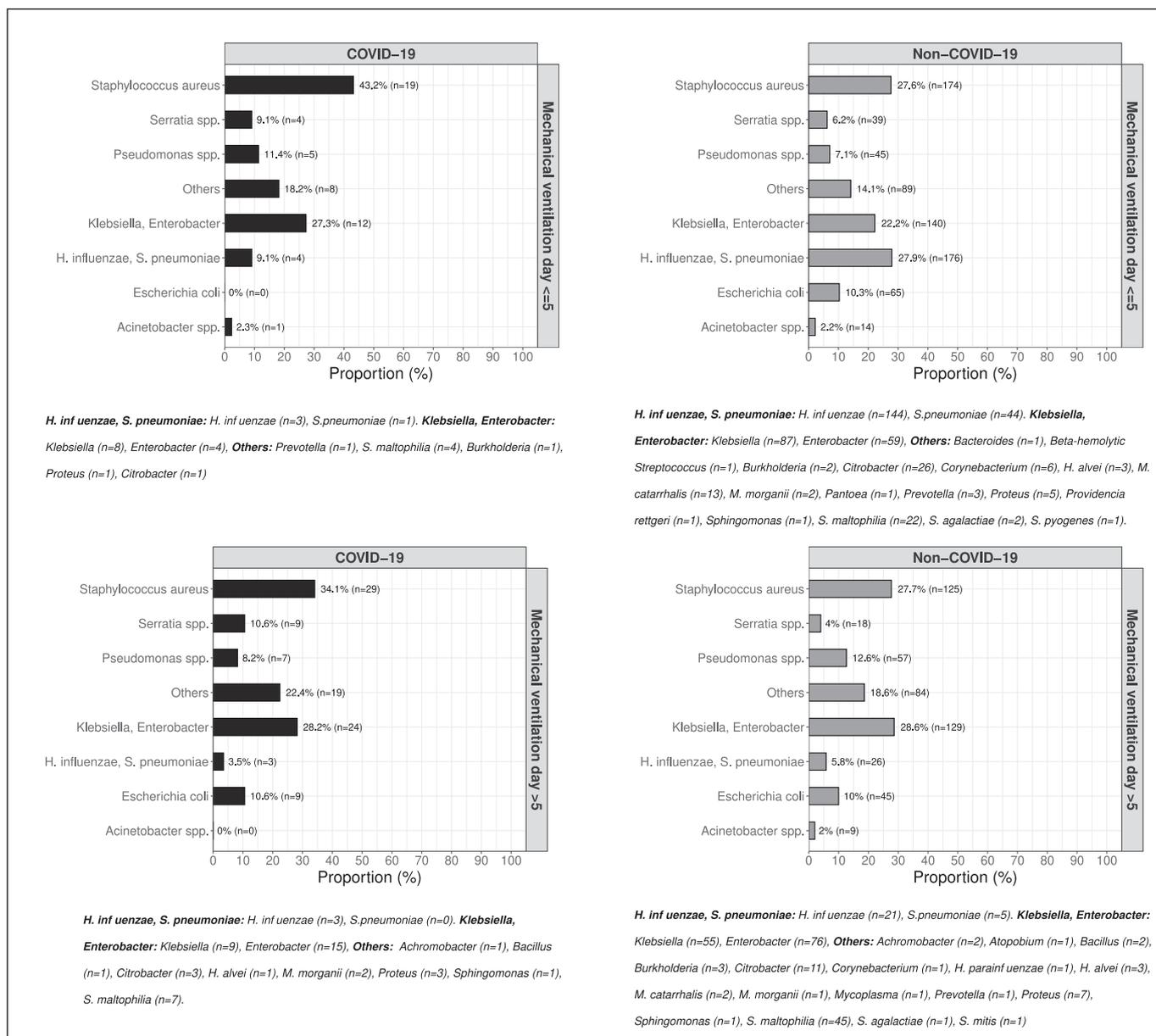


Figure 2. Bacterial pathogens identified in COVID-19 and non-COVID-19. Distribution of significant growth of bacterial pathogens in COVID-19 and non-COVID-19 patients for mechanical ventilation day less than or equal to 5 and day greater than 5, respectively. Proportions represent the proportion of all ventilator-associated lower respiratory tract infection (VA-LRTI) per strata (i.e., COVID-19 vs non-COVID-19 and early vs late). All bacterial findings from the first significant culture is presented; thus, the proportion adds up to more than 100%. *H. alvei* = *Hafnia alvei*, *H. influenzae* = *Haemophilus influenzae*, *H. parainfl uenzae* = *Haemophilus parainfl uenzae*, *M. catarrhalis* = *Moraxella catarrhalis*, *M. morgani* = *Morganella morgani*, *S. agalactiae* = *Streptococcus agalactiae*, *S. maltophilia* = *Stenotrophomonas maltophilia*, *S. mitis* = *Streptococcus mitis*, *S. pneumoniae* = *Streptococcus pneumoniae*, *S. pyogenes* = *Streptococcus pyogenes*, spp. = species.

of mechanical ventilation, the COVID-19 group had a significantly higher proportion of *S. aureus* and lower proportion of *Haemophilus influenzae* and *Streptococcus pneumoniae*, as well as *Escherichia coli* compared with the non-COVID-19 group. Among pathogens identified greater than 5 days after mechanical ventilation, COVID-19 patients had a significantly higher proportion of *Serratia* species

identified compared with non-COVID-19 patients. Overall, the three most common pathogens identified among COVID-19 VA-LRTI patients were *S. aureus* (37%, 48/129), *Enterobacter* species (15%, 19/129), and *Klebsiella* species (13%, 17/129) and for non-COVID-19 *S. aureus* (28%, 299/1,081), *H. influenzae* (15%, 165/1,081), and *Klebsiella* species (13%, 142/1,081).

DISCUSSION

Herein, we investigated the incidence of bacterial VA-LRTI in COVID-19 as compared with non-COVID-19 patients, and the main findings were: 1) COVID-19 was characterized by the longest mechanical ventilation treatment among all ICU cohorts; 2) the incidence of VA-LRTI in COVID-19 patients, 31 (95% CI, 26–38) per 1,000 ventilator days at risk, was not significantly different compared with the pooled non-COVID-19 cohort, 37 (95% CI, 35–39) per 1,000 ventilator days at risk, but higher than for all investigated infectious diagnoses; 3) the second wave was, compared with the first wave, associated with an increased rate of VA-LRTI in COVID-19, and 4) the microbiological findings differed somewhat between the COVID-19 and non-COVID-19 cohort, yet the pathogen distribution is in line with current empirical treatment recommendations for VAP (23).

Previous reports on VA-LRTI and VAP incidence in COVID-19 have observed high incidence proportions, ranging from 29% to 86% (10–16). In studies where incidence rate per 1,000 days of mechanical ventilation have been reported, it has ranged from 18 to 39 per 1,000 ventilator days (11–13, 18). We observed a 30% incidence proportion of VA-LRTI in COVID-19 and an incidence rate of 31 VA-LRTI per 1,000 days of mechanical ventilation at risk. Differences in definitions of VAP and VA-LRTI preclude direct comparison of incident rates from different studies, further impeded by the difficulty in accurately identifying these conditions. A previous prospective, observational study in 114 ICUs before the COVID-19 pandemic reported a 10.2 and 8.8 per 1,000 mechanically ventilated days incidence rate of VAT and VAP, respectively (5). These incidence numbers contrast significantly with the main incidence rates observed in this and other COVID-19–related VAP and VA-LRTI studies, highlighting difficulties in comparison of incidence rates, perhaps in particular during the COVID-19 pandemic. Further, differences in VAP and VA-LRTI incidence differ between different geographical areas and hospitals, with different or no ventilator bundles or decolonization practices in place (19). At Karolinska University Hospital, antimicrobial decolonization is not part of standard procedure. Most clinical phenotypes of COVID-19 in patients admitted to the ICU present with bilateral radiologic infiltrates and severe

hypoxemia, leaving the microbiological findings from LRT the most robust criterion to support VAP diagnosis in COVID-19 (9). Further, structural aspects of the provided healthcare and varying pressure on ICU personnel and capacity cannot be excluded as potential reasons for differences in incidence, as well as different uses of prone positioning, systemic corticosteroids, antivirals, and antibiotics.

Our finding of an increased VA-LRTI aCSHR as well as aSHR for the COVID-19 cohort during the second wave might be due to several reasons. COVID-19 patients admitted to the ICU during the second wave were older and had more comorbidities. However, a previous multicenter cohort study did not find age to be associated with an increased risk of VAP (24). Further, among COVID-19 patients, prone positioning was more adopted during the second wave of the pandemic. In a study of adults intubated for severe ARDS and allocated either to at least 16 hours of consecutive prone position or standard supine care, there was a higher incidence rate for VA-LRTI among prone positioned patients (25). Further, the use of corticosteroids was more common during the second wave, possibly increasing the risk for VA-LRTI. However, dexamethasone treatment in clinical trials on ARDS was not associated with an increased risk for bacterial pneumonia and the incidence of VA-LRTI has been shown to be significantly lower among immunocompromised patients (6, 26, 27). Further, structural aspects of the provided healthcare and varying pressure on ICU personnel and capacity cannot be excluded as potential reasons.

Strengths of our study are the fair sample size with comparison of VA-LRTI between all ventilated ICU patients as well as specific infectious and noninfectious diagnoses with several sensitivity analyses addressing potential confounding factors. Further, we had extensive information about covariates, inclusion of patients from the first and second epidemic waves, detailed information about significant LRT bacterial growth, and consistent results across multiple adjusted analyses. Limitations are the retrospective study design confined to a two-hospital academic center, which might reduce the generalizability of our findings to other hospitals. While we did not use strict criteria of pneumonia, including radiology, symptoms, and laboratory parameters, we only included significant LRT bacterial findings to increase the robustness of our findings (17).

Yet, our results were robust in analyses even when restricted to patients with leukocytosis, leukopenia, or fever. Further, LRT microbiological sampling indications might have differed somewhat before and during the pandemic. Due to limited testing rates, we could not investigate the rates of COVID-19–associated pulmonary aspergillosis (CAPA), which in a previous report was observed in 10% of mechanically ventilated COVID-19 patients had CAPA (28). Finally, due to storage in a separate EHR system, we had limited access to data on vital signs and drugs administered during the entire course of the ICU stay, as well as preventive measures, use of sedation, and neuromuscular blocking agents.

CONCLUSIONS

COVID-19 patients were ventilated for substantially longer durations compared with all other investigated diagnoses. The incidence proportion of VA-LRTI was significantly higher in COVID-19 compared with non-COVID-19 episodes, whereas the incidence rate of VA-LRTI was not increased, although substantial differences between ICU admission diagnoses were observed. Significant differences in the incidence of VA-LRTI occurred between the first and second wave of the COVID-19 pandemic, warranting further investigation with regards to the effect of specific COVID-19 interventions and structural aspects of the provided healthcare.

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Drs. Hedberg and Ternhag shared first authorship.

Dr. Hedberg had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs. Hedberg, Ternhag, Mårtensson, and Nauc ler were involved in study concept and design. Dr. Hedberg was involved in acquisition, analysis, or interpretation of data. Drs. Hedberg, Ternhag, and Nauc ler were involved in drafting of the article. Dr. Nauc ler was involved statistical analysis. All authors involved in critical revision of the article for important intellectual content.

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