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Pneumonia in acute ischemic stroke patients requiring invasive ventilation: Impact on short and long-term outcomes

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SUMMARY

Objectives: To describe the epidemiology and prognostic impact of pneumonia in acute ischemic stroke patients requiring invasive mechanical ventilation.
Methods: Retrospective analysis from a prospective multicenter cohort study of critically ill patients with acute ischemic stroke requiring invasive mechanical ventilation at admission. Impact of pneumonia was investigated using Cox regression for 1-year mortality, and competing risk survival models for ICU mortality censored at 30-days.
Results: We included 195 patients. Stroke was supratentorial in 62% and 64% of patients had a Glasgow coma scale score <8 on admission. Mortality at day-30 and 1 year were 56%, and 70%, respectively. Post-stroke pneumonia was identified in 78 (40%) patients, of which 46/78 (59%) episodes were present at ICU admission. Post-stroke pneumonia was associated with an increase in 1-year mortality (adjusted HR 1.49, 95%CI [1.01–2.20]). Post-stroke pneumonia was not associated with ICU mortality but was associated with a 1.6-fold increase in ICU length of stay (CSHR 0.62 [0.39–0.99], $p = 0.06$).
Conclusions: In ischemic stroke patients requiring invasive ventilation, pneumonia occurred in 40% of cases and was associated with a 49% increase in 1-year mortality. Post-stroke pneumonia did not impact day-30 mortality but increased ICU length of stay.

Introduction

Infection is a frequent medical complication after stroke[1] with an observed pooled frequency from a recent meta-analysis of 21%, most frequently involving the lungs (12%) and urinary tract (8%).[2] The mechanisms leading to post-stroke infections are complex and include a combination of brain injury-induced immunosuppression, neurological impairment that fosters lung aspiration, immobilization, and use of urinary catheters.[3,4] Post-stroke infections, in general, are associated with lower survival and less favorable neurologic outcomes.[5] When analyzing by infection type, post-stroke pneumonia but not urinary tract infections seem to be the main driver of this negative impact.[5]

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Studies focusing on critically ill stroke patients report the highest infection rates,[4] ranging from 9 to 57%. Single-center studies suggest that occurrence of post-stroke pneumonia in the intensive care unit (ICU) is associated with an increase of ICU length of stay[6–8] and hospital mortality,[6,9] and poorer functional outcomes in survivors.[9] However, studies conducted on post-stroke infection in critically ill patients have many biases, including retrospective design, non-standardized definition of pneumonia, small number of patients, pooled analysis of ischemic/hemorrhagic strokes, and variable rates of invasive mechanical ventilation (ranging from 2 to 100%), indicating variable severity of studied populations. Moreover, most of these studies only focused on short-term outcomes, namely hospital mortality. Finally, decisions of withholding and withdrawal of life-sustaining treatments during ICU stay that may impact survival analyses were never reported or considered in most of studies, despite being a major confounder.[10] Finally, there are very few data regarding the impact of ICU post-stroke pneumonia on long term survival and functional outcomes.

Therefore, we aimed to describe the epidemiology and impact on short and long-term prognosis of post-stroke pneumonia in critically ill ischemic stroke patients requiring invasive mechanical ventilation and taking withholding/withdrawal of life-sustaining treatments into account. Some of the results of this study have been previously reported in the form of an abstract (French Intensive Care Society annual congress, Paris, January 2019).

Materials and methods

Patient data source

This study was conducted using data from the French prospective multicenter ($n = 30$ ICUs) OUTCOMEREA database, from patients included between 1997 and 2016. The OUTCOMEREA database has been described in previous publications, and has been approved by the French Advisory Committee for Data Processing in Health Research (CCTIRS) and the French Informatics and Liberty Commission (CNIL, registration no. 8999262).[11,12] The database protocol was submitted to the Institutional Review Board of the Clermont-Ferrand University hospital (Clermont-Ferrand, France), who waived the need for informed consent (IRB no. 5891).

Study population and definitions

We included adult patients with acute ischemic stroke, admitted to the Intensive Care Unit (ICU) and requiring invasive mechanical ventilation. All ICU stays in the database were screened for a diagnosis of stroke, using the International Classification of Diseases 10th Revision (ICD-10) codes I63 (“Cerebral infarction”) and I64 (“Stroke, not specified as hemorrhage or infarction”). ICU stays were considered as related to acute stroke in cases of (1) direct ICU admission following stroke onset, or (2) ICU admission during the initial acute care hospital stay following stroke onset. We excluded patients without hospitalization reports, and if stroke was related to traumatic brain injury.

Severity of illness was graded at ICU admission with use of the Simplified Acute Physiology Score (SAPS II).[13] Organ failure was assessed with each component of the sepsis-related organ failure assessment (SOFA) score, and a modified SOFA score was calculated, excluding the neurological component.[14,15] Neurologic status was assessed using the modified Rankin Scale (mRS).[16] Pneumonia was defined as new or persistent pulmonary infiltrates on chest X-ray combined with purulent tracheal secretions and/or fever or hypothermia (body temperature greater ≥38.5 or ≤36.5 °C, respectively) and/or leukocytosis or leukopenia (white blood cells count ≥10 × 10.9 or ≤4 × 10.9/L, respectively). Community-acquired pneumonia (CAP) was defined as pneumonia occurring after stroke onset and before or within 48 h of hospital admission. Hospital-acquired pneumonia (HAP) was defined as pneumonia occurring after 48 h of hospital length of stay in patients without mechanical ventilation or with a duration of mechanical ventilation less than 48 h. Ventilator-acquired pneumonia was defined as pneumonia occurring after 48 h of mechanical ventilation.[17] ICU admission pneumonia was defined as pneumonia occurring within 1 day of ICU admission (irrespective of the type of admission (direct admission from home/Emergency department or indirect from a hospitalization ward). Early-onset pneumonia (EOP) was defined as pneumonia occurring between day 2 and 7 of ICU admission, and late-onset pneumonia (LOP) as pneumonia occurring from day 8 of ICU admission.[18] Sepsis was defined as infection associated with organ dysfunction (SOFA score ≥ 2).[19] Septic shock was defined as sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥ 65 mmHg and a serum lactate level > 2 mmol/L despite adequate volume resuscitation.

Data collection

Data were prospectively collected at admission (demographics, chronic diseases, admission features, baseline severity indexes, admission diagnosis, and admission type), and on a daily basis throughout the ICU stay (clinical and biological parameters, assessment of organ functions, requirement for MV, fluid challenges, ICU-acquired infections, length of stay (LOS), decision to withhold or withdraw life-sustaining therapies, and vital status at ICU and hospital discharge), through an anonymized electronic case report form using the Vigirea, Rhea and e-Rhea softwares (OutcomeRea, Aulnay-sous-Bois, France). Long term survival after hospital discharge was collected by each local investigator. For each stay, we retrospectively collected the following data in the medical charts: (1) stroke history, including date of stroke, localization, specific treatment (i.e. thrombolysis, hemicraniectomy, etc.), (2) chronic diseases potentially related to stroke, including arterial hypertension, atrial fibrillation, history of ischemic or hemorrhagic stroke, (3) modified Rankin scale (mRS) at ICU discharge.

Statistical analysis

Quantitative variables are presented as median, 1st and 3rd quartiles, and compared between groups with the Wilcoxon test. Qualitative variables are presented as frequency and corresponding percentage and compared with the Chi-square test or Fisher exact test as appropriate. Association between the occurrence of post-stroke pneumonia and 30-day ICU mortality and length of stay was assessed using a cause specific hazard model. It provided a cause-specific hazard ratio (CSHR) which estimates the direct effect of the time-dependent exposure of interest (i.e., post-stroke pneumonia) on various outcomes (i.e., ICU mortality and ICU discharge).[20,21] We considered that determinants of 1-year survival were not affected by competing risks, and used a multivariable Cox regression model. Competing risk models were adjusted with non-collinear and clinically pertinent factors associated ($p < 0.05$) with the outcome of interest in univariate analysis and no selection procedure. Cox model for 1-year mortality was adjusted for potentially confounding factors (non-collinear and clinically pertinent factors associated ($p < 0.1$) with the outcome of interest in univariate analysis) with a backward selection procedure. The occurrence of pneumonia and decisions to withhold/withdraw life-sustaining treatments were handled as time-dependent variables. Only the first episode of pneumonia was considered for analysis, and subsequent episodes were disregarded. For missing data, simple imputation with median/most frequent method was used when missing was completely at random with less than 10% missing value per variable.[22] All statistical analyses were carried out

Table 1
Baseline characteristics.

Variable N (%) or median [Q1–Q3]	All N = 195	No pneumonia N = 117	Pneumonia N = 78	p
Age, years	69.4 [61.2–76.5]	71.1 [62.1–78.3]	68 [60.9–75.3]	0.08
Male sex	132 (67.7)	71 (60.7)	61 (78.2)	0.01
History				
Atrial fibrillation/flutter	29 (14.9)	17 (14.5)	12 (15.4)	0.87
Previous ischemic stroke	47 (24.1)	28 (23.9)	19 (24.4)	0.95
Hypercholesterolemia	46 (23.6)	28 (23.9)	18 (23.1)	0.89
Hypertension	123 (63.1)	81 (69.2)	42 (53.8)	0.03
Coronary artery disease	32 (16.4)	19 (16.2)	13 (16.7)	0.94
Peripheral vascular disease	25 (12.8)	19 (16.2)	6 (7.7)	0.08
Obstructive pulmonary disease	16 (8.2)	10 (8.5)	6 (7.7)	0.83
Diabetes mellitus	48 (24.6)	30 (25.6)	18 (23.1)	0.68
BMI $\geq$ 30 kg/m^2	33 (16.9)	21 (17.9)	12 (15.4)	0.64
Pre-admission mRS score $\leq$ 2	175 (89.7)	106 (90.6)	69 (88.5)	0.63
Stroke characteristics				
Supratentorial stroke	121 (62.4)	74 (63.2)	47 (61)	0.76
Specialized neurologic referral	190 (97.4)	113 (96.6)	77 (98.7)	0.65
Specific treatment				0.02
Intravenous thrombolysis	17 (8.7)	5 (4.3)	12 (15.4)	.
In situ thrombolysis	10 (5.1)	6 (5.1)	4 (5.1)	.
Thrombus aspiration	8 (4.1)	7 (6)	1 (1.3)	.
Hemorrhagic transformation	18 (9.3)	14 (12.1)	4 (5.2)	0.11
Time from stroke to ICU admission, days	2 [1–4]	2 [1–3]	2 [1–8]	<0.01
Time from hospital to ICU admission, days	1 [1–4]	1 [1–3]	1 [1–7]	0.08
ICU admission				
Type of ICU admission				0.77
Direct (from ED or home)	90 (46.2)	55 (47)	35 (44.9)	.
Transfer from ward	105 (53.8)	62 (53)	43 (55.1)	.
Main symptom at admission				<0.01
Coma	110 (56.4)	74 (63.2)	36 (46.2)	.
Respiratory failure	40 (20.5)	13 (11.1)	27 (34.6)	.
Seizure	19 (9.7)	14 (12)	5 (6.4)	.
Other	26 (13.3)	16 (13.7)	10 (12.8)	.
Glasgow Coma Scale score	6 [3-–10]	5 [3–9]	6.5 [3–11]	0.03
SAPS 2	56 [45–66]	57 [46–67]	54.5 [44-–63]	0.33
SOFA score	7 [5 – 9]	7 [5–9]	7 [5–10]	0.60

Abbreviations: BMI, Body Mass Index; mRS, modified Rankin Scale; ICU, Intensive Care Unit; ED, Emergency Department; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.

with SAS 9.4 (SAS Institute Inc., Cary, NC, USA). A *p*-value of 0.05 and lower was considered statistically significant.

Results

Patients

Among 22106 ICU admissions from 30 ICUs over the study period, we identified 229 stays involving acute ischemic stroke. We excluded 34 patients without invasive ventilation at admission and included 195 patients from 10 ICUs in the analysis (Supplemental digital content, **SDC 1**). Two ICUs represented 150/195 (77%) of included patients (**SDC 2**). Patients admitted during the second half of the study period (2007–2016) accounted for 71% of the cohort. Baseline characteristics of patients are presented in Table 1. Patients were predominantly males (68%), aged 69.4 [61.2–76.5] years. Ischemic stroke was supratentorial in 121 (62%) cases, and the median time from stroke onset to ICU admission was 2 [1–4] days. Patients received specialized referral for acute stroke therapy (i.e. thrombolysis or endovascular treatment) or neurosurgery in 190 (97%) cases, and acute stroke therapy was carried out in 35 (18%) cases. Patients were admitted mainly for coma (56%) and respiratory failure (20%), with a SAPS2 of 56 [45–66] and a SOFA score of 7 [5–9]. Glasgow Coma Scale score at admission was 6 [3–10]. During ICU stay, 92 (47%) patients required vasopressor support, and 17 (9%) renal replacement therapy (Table 2). Duration of invasive mechanical ventilation was 5 [3–12] days. A decision to withhold/withdraw life-sustaining treatments was made in 65 (33%) cases, with a delay of 5 [2–8] days.

Epidemiology of post-stroke pneumonia

During ICU stay, 78 (40%) patients presented at least one pneumonia episode, among which 12 presented 2 or more episodes (Table 3). Among those 78 episodes, pneumonia was diagnosed at ICU admission in 46/78 (59%) cases. Of the 32/78 pneumonias acquired during ICU stay, 11/32 (34%) were early-onset and 21/32 (66%) were late-onset. The supplemental digital content 3 (**SDC 3**) shows the distribution of pneumonia (ICU admission pneumonia/EOP/LOP) according to the type of ICU admission (direct or from hospitalization ward). Cases of post-stroke pneumonia were classified as CAP, HAP and VAP in 22 (28%), 28 (36%) and 28 (36%) cases, respectively. Pneumonia was associated with sepsis or septic shock in 62 (79%) cases. Diagnostic incidence of pneumonia during ICU stay was highest at ICU admission, as shown by the cumulative incidence curve presented in the Supplemental digital content **(SDC 4)**. Among pneumonia episodes ($n = 78$), 56 had a microbiological identification, and 67 pathogens were identified, 25 (37%) being gram-positive cocci and 42 (63%) gram-negative bacilli (Supplemental digital content, **SDC 5**). When analyzing bacterial identification according to the date of pneumonia onset, we show that cases of pneumonia diagnosed at ICU admission appeared to be more frequently undocumented than EOP and LOP (20/53 (38%) vs 2/24 (8%) vs 0/12 (0%), $p = 0.14$). Conversely, EOP and even more LOP appeared to be more frequently due to

Table 2
ICU management and outcomes.

Variable N (%) or median [Q1–Q3]	All N = 195	No pneumonia N = 117	Pneumonia N = 78	p
Organ support				
Duration of invasive ventilation, days	5 [3–12]	4 [3–7]	9 [5–20]	<0.01
Use of renal replacement therapy	17 (8.7)	6 (5.1)	11 (14.1)	0.03
Use of vasopressors	92 (47.2)	53 (45.3)	39 (50)	0.52
Duration of vasopressor therapy, days	0 [0–2]	0 [0–2]	0.5 [0–4]	0.11
Decisions to withhold and withdraw life-sustaining treatments				
Any decision	65 (33.3)	37 (31.6)	28 (35.9)	0.54
Time to first decision, days	5 [2–8]	4 [2–7]	5 [3–9]	0.33
Withholding	39 (20)	21 (17.9)	18 (23.1)	0.38
Time to withholding decision, days	5 [2–8]	4 [2–7]	6 [2–18]	0.32
Withdrawal	34 (17.4)	21 (17.9)	13 (16.7)	0.82
Time to withdrawal decision, days	5.5 [4–9]	5 [3-–9]	6 [4–9]	0.38
First decision before pneumonia onset (n = 78)	4 (5.1)	–	–	.
Outcomes				
ICU length of stay, days	7 [4–15]	5 [3–9]	12 [7–23]	<0.01
Hospital length of stay, days	15 [6–36]	12 [4.5–28]	28 [10–62]	<0.01
mRS at ICU discharge				<0.01
≤3	22 (11.3)	17 (34.7)	5 (11.6)	.
≥4	70 (35.9)	32 (65.3)	38 (88.4)	.
30-day mortality (N = 193)	108 (55.9)	72 (62.1)	36 (46.8)	0.03
ICU mortality	103 (52.8)	68 (58.1)	35 (44.9)	0.07
Cause of ICU death				0.11
Brain death/cerebral herniation	44 (22.6)	34 (50)	10 (28.6)	.
Systemic causes	13 (6.7)	7 (10.3)	6 (17.1)	.
Following limitation or withdrawal of care	46 (23.6)	27 (39.7)	19 (54.3)	.
Hospital mortality	123 (63.1)	77 (65.8)	46 (59)	0.33
1-year mortality (N = 182)	128 (70.3)	79 (70.5)	49 (70)	0.94

Abbreviations: ICU, Intensive Care Unit; mRS, modified Rankin Scale.

Table 3
Characteristics of post-stroke pneumonia.

Variable	All
N (%) or median [Q1–Q3]	N = 195
At least one pneumonia during ICU stay	78 (40)
Number of pneumonia cases per ICU stay	
1	66 (84.6)
2	10 (12.8)
3 or more	2 (2.6)
Type of pneumonia, according to modality of acquisition (n = 78)	
Community acquired	22 (28.2)
Hospital-acquired	28 (35.9)
Ventilator-acquired	28 (35.9)
Type of pneumonia, according to timing [a] (n = 78)	
At ICU admission	46 (59)
Early-onset	20 (25.6)
Late-onset	12 (15.4)
Pneumonia severity	
Infection	16 (20.5)
Sepsis	28 (35.9)
Septic shock	34 (43.6)

Abbreviations: ICU, Intensive Care Unit.
[a] Early-onset pneumonia: pneumonia occurring between day 2 and 7 of ICU admission. Late-onset pneumonia: pneumonia occurring from day 8 of ICU stay.

Enterobacteriaceae than ICU admission pneumonia (11/53 (21%) vs 7/24 (29%) vs 5/12 (42%), $p = 0.24$). The same pattern was found with non-fermenting gram-negative bacilli (2/53 (4%) vs 2/24 (8%) vs 5/12 (42%), $p = 0.23$) (Fig. 1). Having had pneumonia at day 1 or 2 was not associated in univariate analysis with an increased risk of pneumonia between day 3 and 30 (20% vs 19%, $p = 0.92$). In univariate analysis, intravenous thrombolysis was associated with an increased frequency of post-stroke pneumonia (Table 1, 15% vs 4%, $p = 0.02$). Characteristics of patients who received intravenous thrombolysis are presented in the supplemental digital content (**SDC 6**) and show that patients with intravenous thrombolysis were younger and more frequently admitted from the hospitalization ward before ICU admission. ICU admission for respiratory failure was also associated with an increased frequency of post-stroke pneumonia (Table 1, 35% vs 11%, $p < 0.01$). Patients admitted for respiratory failure were more frequently admitted from hospitalization ward (75% vs 48%, $p < 0.01$), with a longer delay between hospital and ICU admission (2 [1– 8] days vs 1 [1–3] days, $p = 0.03$) (**SDC 7**). Patients admitted for respiratory failure had lower neurological failure (neurologic SOFA 2 [0.5–3] vs 3 [2–4], $p = 0.03$), and higher respiratory (respiratory SOFA 3 [2–4] vs 2 [0–3], $p < 0.01$) and cardiovascular (cardiovascular SOFA 3 [0–4] vs 1 [0–3], $p = 0.01$) failures. Among the 78 patients with a pneumonia episode, only 4 (5%) had a prior decision to withhold/withdraw life-sustaining treatments. Occurrence of pneumonia was associated with neither an increase in the risk of decisions to withhold or withdraw life-sustaining treatments (36% vs 32%, $p = 0.54$), nor the delay of such decision (5 [3–9] days vs 4 [2–7], $p = 0.33$).

Prognostic impact of the occurrence of post-stroke pneumonia

ICU, 30-day, hospital and 1-year mortality rates were respectively 53%, 56%, 63%, and 70%. Kaplan–Meier curves of 30-day and 1-year survival are presented as supplemental digital content (**SDC 8**). ICU length of stay of the total population was 7 [4–15] days, and 12 [6–23] days in ICU survivors only. Good neurologic outcome at ICU discharge, defined as a mRS score ≤3, was present in 22/195 (11%) patients. In ICU survivors, good neurologic outcome at ICU discharge was more frequent in patients without post-stroke pneumonia (17/49 (35%) vs 5/43 (12%), $p < 0.01$). Median follow-up for the vital status of ICU survivors was 747 [58–2112] days. At 1-year, vital status was available for 182 (93%) patients.

Univariate analysis of factors associated with 30-day mortality is presented in the Supplemental digital content (**SDC 9**). Of note, neither age nor stroke characteristics were associated with 30-day mortality. We show that the period of inclusion was associated

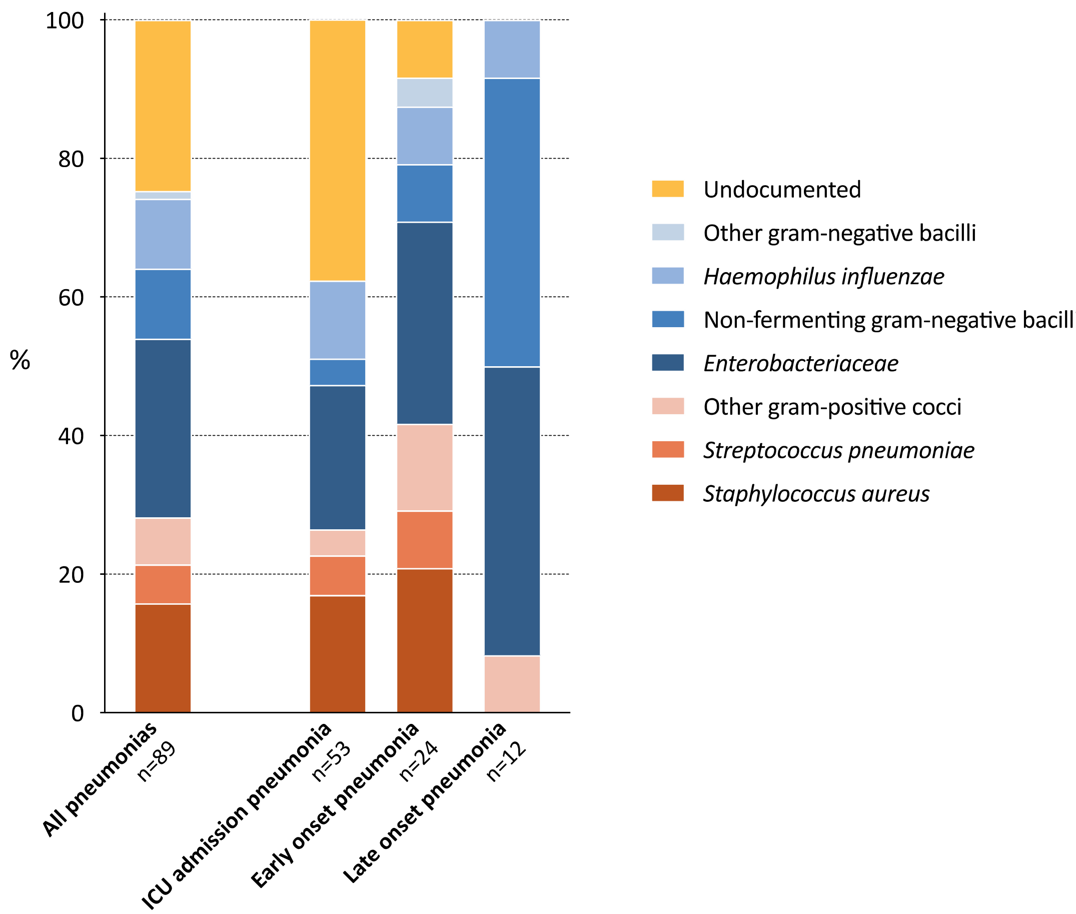

Fig. 1. Microbiological documentation according to date of pneumonia onset.
ICU admission pneumonia: pneumonia occurring within 1 day of ICU admission. Early-onset pneumonia: pneumonia occurring between day 2 and 7 of ICU admission. Late-onset pneumonia: pneumonia occurring from day 8 of ICU admission.

with both 30-day and 1-year mortality. We explored this association (Supplemental digital content, **SDC 10**) and showed that compared to the first period (1997–2006), patients admitted during the second period (2007–2016) had higher admission SOFA scores (8 [6–10] vs 6 [1–8], $p < 0.1$). There was no difference between the 2 inclusion periods with regard to age (69.1 [61–77.3] vs 70.4 [61.6–75.5], $p = 0.71$), GCS score (6.5 [3–10] vs 5 [3–10], $p = 0.13$) and pneumonia rate (40% vs 39%, $p = 0.9$).

In the multivariable competing risk survival analysis, the occurrence of pneumonia was associated with an adjusted ICU discharge cause specific hazard ratio (CSHR) of 0.62 [0.39–0.99], corresponding to a 1.6-fold increase in the duration of ICU stay (Table 4). The occurrence of pneumonia was associated with an adjusted mortality CHSR of 0.96 [0.59–1.57] indicating the absence of effect of post-stroke pneumonia on ICU mortality (Table 4). In ICU survivors, pneumonia during ICU stay was significantly associated with a lower rate of good neurological functional outcome at ICU discharge (12% vs 35%, $p < 0.01$) (Table 2). Long term impact of post-stroke pneumonia was assessed at 1 year. In a Cox proportional hazard model adjusted on decisions to withhold/withdraw life-sustaining treatments, GCS score at admission and period of inclusion, post-stroke pneumonia was significantly associated with 1-year mortality (adjusted HR 1.49, 95%CI [1.01–2.20], $p = 0.046$) (Supplemental digital content, **SDC 11**).

Discussion

In this retrospective analysis of a prospective database of critically ill ischemic stroke patients requiring invasive mechanical ventilation, we show that post-stroke pneumonia occurs in 40% of cases, and was associated with an increase in 1-year mortality. On the short term, post stroke-pneumonia was associated with an increased ICU length of stay but not 30-day mortality. Post-stroke pneumonia seemed to be associated with a reduced functional outcome at ICU discharge.

We show that the prognosis of ischemic stroke patients requiring invasive mechanical ventilation is poor, with a hospital mortality of 63%. The 1-year mortality of 70% suggests that the vast majority of death occur during the initial hospital stay. We report a higher hospital mortality rate than the 47% from a recent United States population-based study[23] of mechanically ventilated stroke patients. Hospital mortality rates in previous studies focusing on post-stroke pneumonia and with high mechanical ventilation rates appear to be much lower, ranging from 14 to 35%.[6,8,24,25] This is explained by the fact that these studies excluded patients that died in the first 48 h. Because our multivariable models were adjusted on decision to withhold/withdraw life-sustaining treatments and because the incidence of post-stroke pneumonia is maximum at ICU admission, we chose to keep in the analysis all patients admitted to the ICU.

Post-stroke pneumonia rates reported in the literature are highly variable, ranging from 9.5 to 75%.[4] This is due to the variability of mechanical ventilation rate in the studied populations and to the non-standardized definition of post-stroke pneumonia. We report here a pneumonia rate of 40% in a population of mechanically ventilated patients from 10 non-neurologic ICUs, using a standardized methodology for pneumonia diagnosis using prospectively collected data. We show that incidence of pneumonia is the

Table 4
Multivariable competing risk analysis for ICU mortality and ICU discharge at day-30.[a]

Variable	ICU mortality			ICU discharge		
	CSHR	95% CI	p	CSHR	95% CI	p
Pneumonia	0.96	[0.59–1.57]	0.88	0.62	[0.39–0.99]	0.047
Decision to withhold and withdraw life-sustaining treatments	4.43	[2.80–7.02]	<0.01	0.65	[0.28–1.53]	0.32
Participating ICUs [b]			0.24			0.04
ICU 1	Ref.	.	.	Ref.	.	.
ICU 2	1.50	[0.93–2.42]	.	1.87	[1.12–3.11]	.
Other ICUs	1.24	[0.72–2.12]	.	1.05	[0.57−–1.93]	.
Study period			0.04			0.13
1997–2006	Ref.	.	.	Ref.	.	.
2007–2016	1.79	[1.02–3.15]	.	1.49	[0.89–2.51]	.
Chronic obstructive pulmonary disease	1.56	[0.85–2.89]	0.15	0.43	[0.13–1.39]	0.16
GCS at admission			0.01			0.11
8–15	Ref.	.	.	Ref.	.	.
3–7	1.90	[1.16–3.10]	.	0.69	[0.43–1.09]	.
Renal SOFA score at admission	1.03	[0.86–1.23]	0.75	0.87	[0.71–1.06]	0.12
Respiratory SOFA score at admission	1.02	[0.86–1.21]	0.78	0.99	[0.81–1.22]	0.96
Hyperglycemia[c] within 24 h of ICU admission	0.98	[0.60–1.58]	0.92	0.27	[0.14–0.51]	<0.01

Abbreviations: CSHR, Cause-Specific Hazard Ratio; CI, Confidence Interval; GCS, Glasgow Coma Scale; SOFA, Sequential Organ Failure Assessment.
Models were adjusted with non-collinear and clinically pertinent factors associated ($p < 0.05$) with the outcome of interest in univariate analysis and no selection procedure.
[a] Multivariable competing risk analysis provides the cause-specific hazard ratio, which estimates the direct effect of an event on both ICU discharge and ICU mortality.
[b] ICU 1 and 2 represent the 2 ICUs (out of 10) with the highest number of patients included, representing 77% of the cohort.
[c] Hyperglycemia was defined as glycemia > 11 mmol/L.

highest at ICU admission. The EOP rate of 26% we report is in accordance with published rates (20–60%) in traumatic brain injury and subarachnoid hemorrhage patients.[26,27] When considering only VAP (Table 3), we report a rate of 14% which is similar to VAP rate reported in general ICU populations.[28,29] Our univariate analysis shows that intravenous thrombolysis appears to be associated with an increased frequency of post-stroke pneumonia. This association has not been noted before, and is likely due to the fact that patients who undergo intravenous thrombolysis are a subset of less severe patients (intravenous thrombolysis is contraindicated for older and comatose patients) at hospital admission, and are more frequently admitted to the ICU for respiratory failure.

Contrarily to the majority of studies performed in stroke units and acute hospital wards where post-stroke pneumonia was an independent risk factor for hospital mortality,[4] MICU/NICU studies[6,8,9,24,30,31] have not shown such an association except for one with only 13% of mechanically ventilated patients and an inadequate methodology (univariate analysis only).[9] In accordance with previously published ICU studies, we show that post-stroke pneumonia has no impact on short-term mortality, but increases ICU length of stay. One of the reasons could be the higher frequency of post-stroke pneumonia in patients admitted for respiratory failure compared to patients admitted for coma. Indeed, we hypothesize that the negative impact of post-stroke pneumonia could be balanced by the better prognosis of patients admitted for respiratory failure compared to patients admitted for coma.[32] It has also been shown previously in general ICU populations that EOP were not associated with ICU or hospital mortality, but increased ICU length of stay.[18,33,34]

As for long-term impact, the majority of MICU/NICU studies have used only in-hospital mortality,[8,24,30,31] which is not the preferred endpoint. We chose to use 1-year mortality as the endpoint, and show that post-stroke pneumonia is associated with an increase in mortality. This is, to the best of our knowledge, the first report of an impact of ICU post-stroke pneumonia on long term mortality of stroke patients.[4] It is interesting to note the discrepancy between the fact that a majority of deaths occur before day-30 and the difference in the effect of pneumonia on short-term and long-term mortality. We believe that these early deaths are directly related to the acute neurologic injury of the ischemic stroke, while post-stroke pneumonia impacts survival of patients that have survived these initial critical days. This hypothesis is comforted by the fact that ICU survivors exposed to a pneumonia had a worse mRS score at ICU discharge.

The strengths of our study include a large multicenter population from a high-quality database, a focus on a well-defined population of ischemic stroke patients requiring invasive mechanical ventilation, adjustment for decisions to withhold/withdraw life-sustaining treatments, and use of an adequate statistical methodology. Our study has also limitations. First, the OUTCOMEREA database has not been built specifically for stroke studies, and all data regarding stroke characteristics has been retrospectively recorded from hospitalization records. Therefore, data on potentially useful scores for prognostication in this setting, such as the NIHSS scores, are lacking.[35] Furthermore, only long-term vital status was available, and evaluation of long-term functional outcome with an appropriate tool (i.e. the modified Rankin scale) would have been more relevant. Second, the inclusion period of 20 years is very wide, and management of stroke patients has greatly improved over the past decades (e.g., development of stroke units, thrombolysis, mechanical thrombectomy…). However, 77% of our cohort has been included between 2007 and 2016, and analyses have been adjusted on the inclusion period when necessary. Third, diagnostic adequacy of pneumonia in ICU is difficult, and despite the use of prospective standard screening criteria for the diagnosis of pneumonia, we cannot exclude that some pneumonia cases were misdiagnosed. In the same line, discrimination between aspiration pneumonia and chemical pneumonitis is complex and it cannot be excluded that pneumonitis cases were wrongfully classified as pneumonia. Fourth, we were not able to adjust our results for left informative censoring (that is, critically ill acute stroke patients not referred to the ICU for reasons such as decisions to withhold/withdraw life-sustaining treatments).

Conclusions

In this retrospective analysis of a prospective database of critically ill ischemic stroke patients requiring invasive mechanical ventilation, we show that post-stroke pneumonia occurs in 40% of cases, and is associated with an increase in 1-year mortality. Post-stroke pneumonia was not associated with 30-day ICU mortality, but increased ICU length of stay. These results suggest that early deaths are directly related to the acute neurologic injury while the detrimental effect of post-stroke pneumonia impacts survival of patients that have survived these initial critical days. Further studies are needed to properly assess the effect of post-stroke pneumonia on long-term functional outcome in ICU survivors.

Conflict of interest

None.

Acknowledgments

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Supplementary materials

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References

1. Chamorro Á, Urra X, Planas Anna M. Infection after acute ischemic Stroke: a manifestation of brain-induced immunodepression. *Stroke* 2007;**38**(3):1097–103. doi:10.1161/01.STR.0000258346.68966.9d.
2. Badve Monica S, Zhou Z, van de Beek D, Anderson Craig S, Hackett Maree L. Frequency of post-stroke pneumonia: systematic review and meta-analysis of observational studies. *Int J Stroke* 2019;**14**(2):125–36. doi:10.1177/1747493018806196.
3. Emsley Hedley CA, Hopkins Stephen J. Acute ischaemic stroke and infection: recent and emerging concepts. *Lancet Neurol* 2008;**7**(4):341–53. doi:10.1016/S1474-4422(08)70061-9.
4. Hannawi Y, Hannawi B, Rao Chethan P, Venkatasubba, Suarez Jose I, Bershad Eric M. Stroke-associated pneumonia: major advances and obstacles. *Cerebrovasc Dis* 2013;**35**(5):430–43. doi:10.1159/000350199.
5. Vermeij Frederique H, Scholte op Reimer Wilma JM, de Man P, van Oostenbrugge Robert J, Franke Cees L, de Jong G, et al. Stroke-associated infection is an independent risk factor for poor outcome after acute ischemic stroke: data from the netherlands stroke survey. *Cerebrovasc Dis* 2009;**27**(5):465–71. doi:10.1159/000210093.
6. Berger B, Gumbinger C, Steiner T, Sykora M. Epidemiologic features, risk factors, and outcome of sepsis in stroke patients treated on a neurologic intensive care unit. *J Crit Care* 2014;**29**(2):241–8. doi:10.1016/j.jcrc.2013.11.001.
7. Yang C-C, Shih N-C, Chang W-C, Huang S-K, Chien C-W. Long-term medical utilization following ventilator-associated pneumonia in acute stroke and traumatic brain injury patients: a case-control study. *BMC Health Serv Res* 2011;**11**(1):289. doi:10.1186/1472-6963-11-289.
8. Upadya A, Thorevska N, Sena Kanaga N, Manthous C, Amoateng-Adjepong Y. Predictors and consequences of pneumonia in critically ill patients with stroke. *J Crit Care* 2004;**19**(1):16–22.
9. Hilker R, Poetter C, Findeisen N, Sobesky J, Jacobs A, Neveling M, et al. Nosocomial pneumonia after acute stroke: implications for neurological intensive care medicine. *Stroke* 2003;**34**(4):975–81. doi:10.1161/01.STR.0000063373.70993.CD.
10. Kelly AG, Hoskins KD, Holloway RG. Early stroke mortality, patient preferences, and the withdrawal of care bias. *Neurology* 2012;**79**(9):941–4. doi:10.1212/WNL.0b013e318266fc40.
11. Lautrette A, Garrouste-Orgeas M, Bertrand P-M, Goldgran-Toledano D, Jamali S, Laurent V, et al. Respective impact of no escalation of treatment, withholding and withdrawal of life-sustaining treatment on ICU patients' prognosis: a multicenter study of the outcomerea research group. *Intensive Care Med* 2015;**41**(10):1763–72. doi:10.1007/s00134-015-3944-5.
12. Truche A-S, Darmon M, Bailly S, Clec'h C, Dupuis C, Misset B, et al. Continuous renal replacement therapy versus intermittent hemodialysis in intensive care patients: impact on mortality and renal recovery. *Intensive Care Med* 2016;**42**(9):1408–17. doi:10.1007/s00134-016-4404-6.
13. Le Gall JR, Lemeshow S, Saulnier F. A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993;**270**(24):2957–63.
14. Timsit J-F, Fosse J-P, Troché G, De Lassence A, Alberti C, Garrouste-Orgeas M, et al. Calibration and discrimination by daily logistic organ dysfunction scoring comparatively with daily sequential organ failure assessment scoring for predicting hospital mortality in critically ill patients. *Crit Care Med* 2002;**30**(9):2003–13. doi:10.1097/01.CCM.0000025210.75241.3E.
15. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European Society of intensive care medicine. *Intensive Care Med* 1996;**22**(7):707–10.
16. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke J Cereb Circ* 1988;**19**(5):604–7.
17. Torres A, Niederman Michael S, Chastre Jean, Ewig S, Fernandez-Vandellos P, Hanberger H, et al. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia: guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociación Latinoamericana del Tórax (ALAT). *Eur Respir J* 2017;**50**(3):1700582. doi:10.1183/13993003.00582-2017.
18. Bornstain C, Azoulay E, De Lassence A, Cohen Y, Costa MA, Mourvillier B, et al. Sedation, Sucralfate, and antibiotic use are potential means for protection against early-onset ventilator-associated pneumonia. *Clin Infect Dis* 2004;**38**(10):1401–8. doi:10.1086/386321.
19. Singer M, Deutschman Clifford S, Seymour Christopher W, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016;**315**(8):801. doi:10.1001/jama.2016.0287.
20. Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. *Am J Epidemiol* 2009;**170**(2):244–56. doi:10.1093/aje/kwp107.
21. Wolkewitz M, Cooper BS, Bonten MJM, Barnett AG, Schumacher M. Interpreting and comparing risks in the presence of competing events. *BMJ* 2014;**349**(aug21 5) g5060–g5060. doi:10.1136/bmj.g5060.
22. Vesin A, Azoulay E, Ruckly S, Vignoud L, Rusinovà K, Benoit D, et al. Reporting and handling missing values in clinical studies in intensive care units. *Intensive Care Med* 2013;**39**(8):1396–404. doi:10.1007/s00134-013-2949-1.
23. Lahiri S, Mayer Stephan A, Fink Matthew E, Lord Aaron S, Rosengart A, Mangat Halinder S, et al. Mechanical ventilation for acute Stroke: a multi-state population-based study. *Neurocrit Care* 2015;**23**(1):28–32. doi:10.1007/s12028-014-0082-9.
24. Kasuya Y, Hargett James L, Lenhardt R, Heine Michael F, Doufas Anthony G, Remmel Kerri S, et al. Ventilator-associated pneumonia in critically ill stroke patients: frequency, risk factors, and outcomes. *J Crit Care* 2011;**26**(3):273–9. doi:10.1016/j.jcrc.2010.09.006.
25. Kostadima E, Kaditis AG, Alexopoulos EI, Zakynthinos E, Sfyras D. Early gastrostomy reduces the rate of ventilator-associated pneumonia in stroke or head injury patients. *Eur Respir J* 2005;**26**(1):106–11. doi:10.1183/09031936.05.00096104.
26. Bronchard R, Albaladejo P, Brezac G, Geffroy A, Seince P-F, Morris W, et al. Early onset pneumonia: risk factors and consequences in head trauma patients. *Anesthesiology* 2004;**100**(2):234–9.
27. Lepelletier D, Roquilly A, Demeure dit latte D, Mahe Pierre J, Loutrel O, Champin P, et al. Retrospective analysis of the risk factors and pathogens associated with early-onset ventilator-associated pneumonia in surgical-ICU head-trauma patients. *J Neurosurg Anesthesiol* 2010;**22**(1):32–7. doi:10.1097/ANA.0b013e3181bdf52f.
28. Bekaert M, Timsit J-F, Vansteelandt S, Depuydt P, Vésin A, Garrouste-Orgeas M, et al. Attributable mortality of ventilator-associated Pneumonia: a reappraisal using causal analysis. *Am J Respir Crit Care Med* 2011;**184**(10):1133–9. doi:10.1164/rccm.201105-0867OC.
29. Dananché C, Vanhems P, Machut A, Aupée M, Bervas C, L'Hériteau F, et al. Trends of incidence and risk factors of ventilator-associated pneumonia in elderly patients admitted to french ICUs between 2007 and 2014. *Crit Care Med* 2018;**46**(6):869–77. doi:10.1097/CCM.0000000000003019.
30. Yeh S-J, Huang K-Y, Wang T-G, Chen Y-C, Chen C-H, Tang S-C, et al. Dysphagia screening decreases pneumonia in acute stroke patients admitted to the stroke intensive care unit. *J Neurol Sci* 2011;**306**(1–2):38–41. doi:10.1016/j.jns.2011.04.001.
31. Josephson SA, Moheet Asma M, Gropper Michael A, Nichols Amy D, Smith Wade S. Ventilator-Associated pneumonia in a neurologic intensive care unit does not lead to increased mortality. *Neurocrit Care* 2010;**12**(2):155–8. doi:10.1007/s12028-009-9285-x.
32. Meyfroidt G, Bollaert P-E, Marik Paul E. Acute ischemic stroke in the ICU: to admit or not to admit? *Intensive Care Med* 2014;**40**(5):749–51. doi:10.1007/s00134-014-3289-5.
33. Moine P, Timsit J-F, De Lassence A, Troché G, Fosse J-P, Alberti C, et al. Mortality associated with late-onset pneumonia in the intensive care unit: results of a multi-center cohort study. *Intensive Care Med* 2002;**28**(2):154–63. doi:10.1007/s00134-001-1172-7.
34. Ibn Saied W, Souweine B, Garrouste-Orgeas M, Ruckly S, Darmon M, Bailly S, et al. Respective impact of implementation of prevention strategies, colonization with multiresistant bacteria and antimicrobial use on the risk of early-and late-onset VAP: an analysis of the OUTCOMEREA network. *PLoS ONE* 2017;**12**(11):e0187791. doi:10.1371/journal.pone.0187791.
35. Sonneville R, Gimenez L, Labreuche J, Smonig R, Magalhaes E, Bouadma L, et al. What is the prognosis of acute stroke patients requiring ICU admission? *Intensive Care Med* 2017;**43**(2):271–2. doi:10.1007/s00134-016-4553-7.