



Predicting Poststroke Pneumonia in Patients With Anterior Large Vessel Occlusion: A Prospective, Population-Based Stroke Registry Analysis

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Objective: To assess predictive factors for poststroke pneumonia (PSP) in patients with acute ischemic stroke (AIS) due to large vessel occlusion (LVO) of the anterior circulation, with special regard to the impact of intravenous thrombolysis (IVT) and endovascular treatment (EVT) on the risk of PSP. As a secondary goal, the validity of the A²DS², PNEUMONIA, and ISAN scores in LVO will be determined.

Methods: Analysis was based on consecutive data for the years 2017 to 2019 from the prospective inpatient stroke registry covering the entire federal state of Hesse, Germany, using the Kruskal-Wallis test and binary logistic regression.

Results: Data from 4,281 patients with LVO were included in the analysis (54.8% female, median age = 78 years, range = 18–102), of whom 66.4% ($n = 2,843$) received recanalization therapy (RCT). In total, 19.4% ($n = 832$) of all LVO patients developed PSP. Development of PSP was associated with an increase in overall in-hospital mortality of 32.1% compared with LVO patients without PSP (16.4%; $p < 0.001$). Incidence of PSP was increased in 2132 patients with either EVT ($n = 928$; 25.9% PSP incidence) or combined EVT plus IVT ($n = 1,204$; 24.1%), compared with 2,149 patients with IVT alone ($n = 711$; 15.2%) or conservative treatment only ($n = 1,438$; 13.5%; $p < 0.001$). Multivariate analysis identified EVT (OR 1.5) and combined EVT plus IVT (OR 1.5) as significant independent risk factors for PSP. Furthermore, male sex (OR 1.9), age ≥ 65 years (OR 1.7), dysphagia (OR 3.2) as well as impaired consciousness at arrival (OR 1.7) and the comorbidities diabetes (OR 1.4) and atrial fibrillation (OR 1.3) were significantly associated risk factors (each $p < 0.001$). Minor stroke (NIHSS ≤ 4) was associated with a significant lower risk of PSP (OR 0.5). Performance of risk stratification scores varied between A²DS² (96.1% sensitivity, 20.7% specificity), PNEUMONIA (78.2% sensitivity and 45.1% specificity) and ISAN score (98.0% sensitivity, 20.0% specificity).

Conclusion: Nearly one in five stroke patients with LVO develops PSP during acute care. This risk of PSP is further increased if an EVT is performed. Other predictive factors are consistent with those previously described for all AIS patients. Available risk stratification scores proved to be sensitive tools in LVO patients but lack specificity.

Keywords: infection, mechanical recanalization, endovascular thrombectomy, thrombolysis, neurocritical care, alteplase, complication

INTRODUCTION

Poststroke pneumonia (PSP) or stroke-associated pneumonia is a frequent and often preventable medical complication of acute ischemic stroke (AIS) that occurs in ~1 in 10 stroke patients and is among the major modifiable risk factors of in-hospital deaths related to stroke (1, 2). In addition to overall mortality, PSP considerably increases length of stay (LOS) and hospitalization costs, which underscores the need to screen for and prevent infections after stroke (3–5). Therefore, knowledge of predictive factors for PSP is a crucial prerequisite to identify high-risk patients and initiate prophylactic measures (6). As shown in the literature, risk factors commonly associated with PSP in AIS patients include advanced age, male sex, stroke severity as assessed by NIHSS, and clinical features such as atrial fibrillation, diabetes, and dysphagia (7, 8).

A subgroup with particular risk of PSP comprises AIS patients with an anterior large vessel occlusion (LVO); these patients commonly suffer more severe stroke syndromes and have higher overall mortality (9). Since 2015, in addition to intravenous thrombolysis (IVT), an increasing number of patients have benefitted greatly from endovascular treatment (EVT), which is primarily performed at high-volume stroke centers (10–12). However, EVT also bears potential health risks for patients due to the general anesthesia (GA) required for treatment and the possible need for prolonged invasive ventilation and intensive care, which was shown to predict unfavorable outcomes and increase pneumonia rates (13, 14). Hence, it is worthwhile to investigate which predictive factors for PSP apply to LVO patients and to what extent, and how application of recanalizing therapies (RCT) affects the overall risk for PSP in the individual patient. A previous retrospective analysis of 112 consecutive Chinese LVO patients who received EVT indicated that an unfavorable recanalization outcome is an independent risk factor for PSP (15). Analysis of a larger sample of LVO patients with and without RCT could provide more robust information regarding the predictive clinical factors of PSP.

Several risk stratification scores for PSP based on readily available clinical baseline data have been developed and repeatedly tested for AIS patients (7, 8). Well-validated tools include the A²DS², PNEUMONIA, and ISAN scores, which are routinely used in the clinic to guide the monitoring of high-risk patients and inform decisions on prophylactic pneumonia management (16, 17). However, these tools were developed prior to the establishment of EVT in clinical practice and were not validated for the subgroup of stroke patients with LVO.

The primary goal of this study was to evaluate the predictive factors of PSP in stroke patients with LVO of the anterior circulation and to investigate the impact that RCT has on that risk. The secondary goal was to assess the validity of risk stratification scores in this subgroup of stroke patients.

METHODS

Patient Cohort

This analysis was based on the 2017, 2018, and 2019 datasets from the mandatory prospective stroke inpatient quality assurance registry that included data for all patients with AIS with LVO of the anterior circulation treated at any of the 119 hospitals within the entire federal state of Hesse, Germany (6,285,000 inhabitants). Data entry into the registry is obligatory based on a federal contract on quality assurance in acute stroke care. Due to the anonymized data collection in the context of quality assurance measures, individual consent is not required. The data analysis was approved by the local ethics committee (313/16). All patients who met the following criteria were considered for the current evaluation: (1) discharge diagnosis of ischemic stroke (ICD-10: I63), (2) age \geq 18 years, and (3) LVO in the anterior circulation [M1- or M2-occlusion of the middle cerebral artery (MCA) and carotid-T occlusion] confirmed by computed tomographic angiography (CTA), MR-angiography (MRA), or digital subtraction angiography (DSA). Information on presence of extracranial or intracranial carotid stenosis or occlusion was not available in the stroke registry, hence not considered in this study. The data included information regarding whether patients were transferred to another hospital for treatment. To avoid duplicate cases, all cases with notice of a transfer between hospitals were excluded. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS, defined as mild \leq 4, moderate 5–15, severe 16–20, very severe $>$ 20) (18), and the level of disability was assessed using modified Rankin Scale (mRS). All patients that met inclusion criteria were analyzed in this study. Patients were not excluded in case of unfavorable outcome (e.g., palliative care) or event of death during hospital care (e.g., mRS = 6).

Diagnosis of PSP was entered manually into the database by stroke-unit physicians if criteria were met (see Section Poststroke Pneumonia Definition). Within the study centers, interventionalists were free to perform EVT under conscious sedation (CS) or GA and to individually choose the preferred method for EVT. Since neither type of anesthesia nor

method of EVT were recorded in the registry, no further statement or analysis in this regard was feasible in the current study.

Poststroke Pneumonia Definition

The presence of PSP is an obligatory data entry point in the quality assurance stroke registry Hesse. Clinical pneumonia was defined in the quality assurance registry Hesse documentation manual by using a combination of imaging, clinical, and laboratory criteria in accordance with guidelines from the Centers for Disease Control and Prevention (19), guidelines on hospital-acquired pneumonia from the German Society for Infectious Diseases (20), and guidelines from the American Thoracic Society (21). Poststroke pneumonia could only be coded if patients developed pneumonia during the hospital stay and did not fulfill the criteria for community-acquired pneumonia beforehand.

Clinically defined (poststroke) pneumonia could be coded if:

- Chest X-ray revealed either a new or progressive and persistent infiltrate, consolidation, cavitation, or pleural effusion

and at least one of the following signs/symptoms occurred:

- Fever ($\geq 38.3^{\circ}\text{C}$ or 100.94°F) without another explanation
- Leukopenia ($< 4,000$ leukocytes/ mm^3) or leukocytosis ($> 12,000$ leukocytes/ mm^3)
- For adults > 70 years of age: altered mental status not due to another cause (pneumonia-induced disorientation)

with at least two of the following criteria:

- New onset of purulent sputum or change in character of sputum
- New onset or worsening cough, dyspnea, or tachypnea
- Rales or bronchial breath sounds
- Worsening gas exchange [for example, O_2 desaturations (e.g., $\text{PaO}_2/\text{FiO}_2 \leq 240$), increased oxygen requirements, or increased ventilator demand]

In summary, documentation of pneumonia required a corresponding radiographic finding and a total of three of the additional criteria from the above list.

Predictive Scores

A^2DS^2 Score

The A^2DS^2 score for the prediction of PSP was determined as presented in the literature (16), with a 10-point score including the items age ≥ 75 years (1 point), atrial fibrillation (1), dysphagia (2), and stroke severity as assessed by NIHSS (0–4 = 0, 5–15 = 3, ≥ 16 = 5 points). The cutoff point ($\text{A}^2\text{DS}^2 \geq 4$) was chosen based on the original validation study of the score (16).

PNEUMONIA Score

The PNEUMONIA score was developed by Kwon et al. in 2006 and consists of five items, each of which is evaluated with a 0- or 1-point score, resulting in a minimum score of 0 points and a maximum score of 5 points. One point each is assigned for an NIHSS ≥ 11 , age ≥ 65 years, male sex, need for mechanical ventilation, and dysphagia. In the initial study (17), all patients

with a score of 5 developed pneumonia within the first 30 days after AIS; scores of 4, 3, 2, and 1 were associated with PSP in 74.2, 38.2, 5.3, and 0.9% of cases, respectively.

ISAN

The ISAN score was developed by Smith et al. in 2015 and uses four differently weighted items to calculate a sum score ranging from 0 to 21. Components of the score include age (< 60 years = 0 points, 60–69 years = 3 points, 70–79 years = 4 points, 80–98 years = 6 points, > 90 years = 8 points), sex (female 0 points, male 1 point), NIHSS at admission (0–4 = 0 points, 5–15 = 4 points, 16–20 = 8 points, > 20 = 10 points), and mRS at admission [independent (mRS 0–1) = 0 points, not independent (mRS > 1) = 2 points] (22). The sum score allows classification of four different PSP risk groups, defined as low (ISAN = 0–5), medium (ISAN = 6–10), high (ISAN = 11–14), and very high (ISAN ≥ 15).

Statistical and Graphical Analysis

Statistical analysis was performed with SPSS Statistics version 27 by the IBM Corporation (Armonk, NY, US) using the adequate non-parametric Kruskal-Wallis test for univariate analysis and binary logistic regression for multivariate analysis. Univariate analysis was used to identify predictive parameters at a p -value < 0.05 that were included in the multivariate regression model. Since the multivariate analysis was based on values not corrected for multiple testing to address a possible suppressor effect, we refrained from additional *post-hoc* correction of the results of the univariate analysis that were used only descriptively (23). Regression coefficient (B) and odds ratio ($\text{Exp}\beta$) were used to interpret the significance of each factor with an OR of ≥ 1.25 and ≤ 0.75 , respectively, that was considered clinically relevant (16). In addition, p -values < 0.05 were considered statistically significant. The risk stratification scores were analyzed for their power to predict PSP in the study cohort, and receiver operating characteristic (ROC) curves were calculated. Sankey diagrams were created using SankeyMATIC by Steve Bogart (<https://sankeymatic.com>) and ROC curves were created using SPSS. Both figures were edited using Pixelmator Pro (Pixelmator Team, Vilnius, LTU).

RESULTS

Patient Characteristics and Descriptive Statistics

A total of 4,281 patients with AIS and LVO of the anterior circulation were included in the study analysis. Gender distribution showed 54.8% female and 45.2% male patients, with a mean age of 74.9 years (± 13.3 years, median = 78 years, range = 18–102 years). Overall, 19.4% ($n = 832$) of patients developed PSP. Treatment with any RCT (IVT, EVT, or both) was reported in 66.4% of the patients ($n = 2,843$). In detail, 32.6% of patients received EVT ($n = 928$), 42.3% of patients received EVT plus IVT ($n = 1,204$), and 25.0% of patients received IVT ($n = 711$). Of the 1,438 patients treated conservatively, 13.5% developed PSP during their in-hospital stay. In comparison,

22.4% of patients with any RCT developed PSP during their in-hospital stay. PSP rates for patients receiving RCT were 25.9% for EVT, 24.1% for EVT plus IVT, and 15.2% for IVT. Comparison of $n = 2132$ patients undergoing EVT (either alone or with prior IVT) and patients without EVT ($n = 2149$) revealed significant differences regarding age, stroke severity, and need for intensive care treatment. A detailed overview of the two groups is provided in **Supplementary Table 1**. The distribution of patients regarding RCT and subsequent development of PSP is shown as a Sankey diagram in **Figure 1**.

Univariate Analysis

Univariate analysis revealed sex, age category, and premorbid overall health condition as associated sociodemographic factors for PSP. Moreover, stroke severity (NIHSS) and presence of aphasia, dysphagia, dysarthria, motor impairment or impaired consciousness at admission were disease-specific factors associated with PSP. Regarding the LVO, the presence of MCA M1-occlusion was associated with a higher risk for PSP, whereas MCA M2-occlusion was accompanied by a lower risk for PSP. Atrial fibrillation, diabetes mellitus, and arterial hypertension were identified as comorbidities associated with PSP. Performance of RCT during the current admission, as well as EVT and EVT plus IVT, were associated with a higher incidence of PSP, whereas IVT alone was associated with a lower PSP prevalence. The results of the univariate analysis are displayed in **Table 1**.

Multivariate Analysis

Multivariate analysis resulted in a model that was statistically superior to the univariate analysis ($p < 0.001$, Cox & Snell $R^2 = 0.130$, Nagelkerke's $R^2 = 0.195$) and showed a small effect size

(Cohen's $D = 0.24$). Within the model, male sex, age ≥ 65 years, presence of dysphagia at admission, impaired consciousness at admission, the comorbidities of atrial fibrillation and diabetes mellitus, and performance of RCT and EVT during the current admission contributed significantly to an increased risk for PSP, while a moderate stroke with NIHSS 5–15 was associated with a decreased risk for PSP. Notably, an EVT success rate worse than TICI 2b did not result in an increased risk for PSP. The results of the multivariate analysis are provided in **Table 2**.

Mortality and Need for Intensive Care Treatment

The overall mortality of the cohort was 20.3% and was associated with prevalence of PSP ($p < 0.001$). In patients with PSP, mortality was increased at 32.1% when compared with a 16.4% mortality in patients without PSP during acute care. In addition, the need for intensive care was reported overall in 42.6% of LVO patients ($n = 1761$) and was significantly associated with an increased frequency (29.2%) of PSP ($p < 0.001$, **Supplementary Table 1**). After EVT, 65.7% of patients needed temporal intensive care treatment, compared with 67.3% after combined EVT plus IVT, 20.1% after IVT alone, and 17.5% with only conservative treatment (no RCT).

Validation of Predictive Scores

A²DS² Score

For A²DS² score, ROC analysis revealed an overall model quality of 0.68 with an AUC of 0.704 (95% CI 0.864–0.724). Based on the A²DS² sum score of ≥ 4 as the cutoff value defined in the original study, a sensitivity of 96.1% and a specificity of 20.7% were calculated. See **Figure 2A** for an illustration of ROC curves.

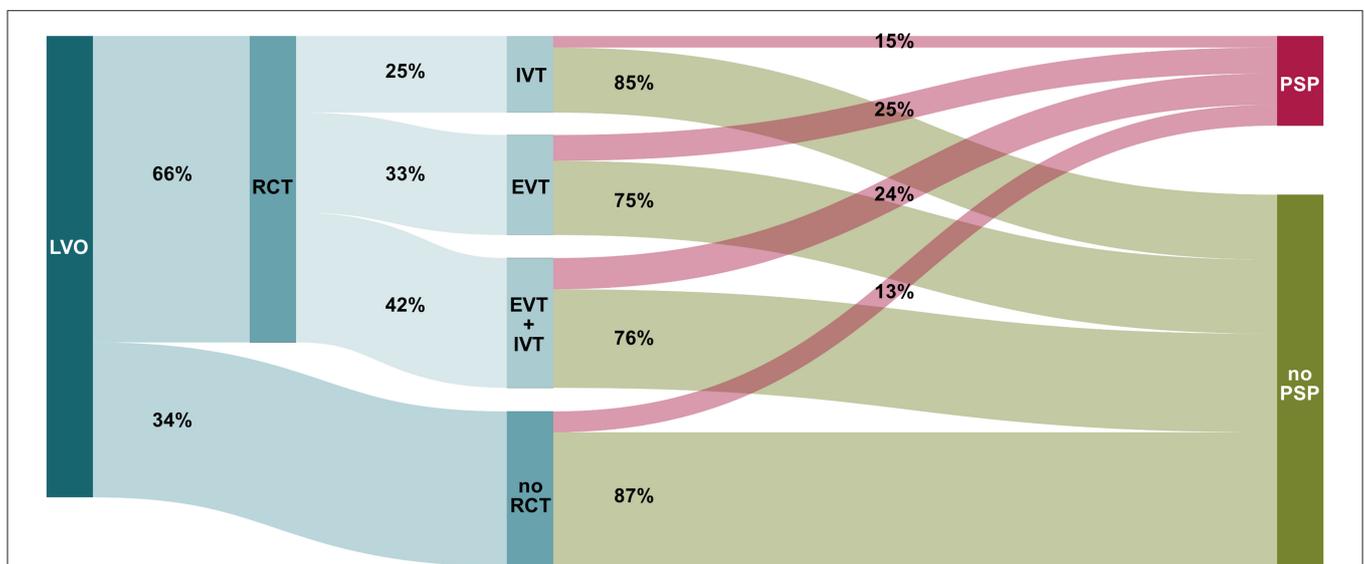


FIGURE 1 | Sankey diagram illustrating the share of patients who do or do not develop poststroke pneumonia (PSP) in acute ischemic stroke (AIS) due to large vessel occlusion (LVO) of the anterior circulation, depending on the respective recanalizing therapy (RCT, recanalization therapy; IVT, intra-venous thrombolysis; EVT, endovascular treatment).

TABLE 1 | Univariate analysis of predictive factors for developing poststroke pneumonia after large vessel occlusion.

Risk factor		Predictive of PSP		Not predictive of PSP		p-value ^a
		%	n	%	n	
Sociodemographic factors						
Sex	Female	17.2	404	82.8	1,941	<0.001
	Male	22.1	428	77.9	1,508	
Age, years	<65	12.6	110	87.4	764	<0.001
	≥65	21.2	722	78.8	2,685	
mRS at admission	≤3	8.1	84	91.9	953	<0.001
	≥4	23.1	748	76.9	2,496	
Symptoms at admission						
Initial NIHSS	≤4	6.2	39	93.8	587	<0.001
	5–15	16.2	320	83.8	1,659	
	16–20	28.2	313	71.8	795	
	≥21	28.3	160	71.7	406	
Aphasia	Yes	21.5	530	78.5	1,931	<0.001
	No	15.1	248	84.9	1,391	
Dysphagia	Yes	20.4	502	79.6	1,956	<0.001
	No	16.2	241	83.8	1,245	
Dysarthria	Yes	20.4	502	79.6	1,956	0.001
	No	16.2	241	83.8	1,245	
Motor impairment/paresis	Yes	20.5	772	79.5	2,988	<0.001
	No	7.8	34	92.2	400	
Impaired consciousness	Yes	29.9	328	70.1	769	<0.001
	No	15.8	504	84.2	2,680	
Large vessel occlusion						
ICA, carotid triangle	Yes	17.6	136	82.4	635	0.164
	No	19.8	696	80.2	2,814	
MCA, M1 segment	Yes	21.4	461	78.6	1,693	0.001
	No	17.4	371	82.6	1,756	
MCA, M2 segment	Yes	17.3	235	82.7	1,121	0.018
	No	20.4	597	79.6	2,328	
Comorbidities						
Atrial fibrillation	Yes	24.4	457	75.6	1,417	<0.001
	No	16.6	375	83.4	1,882	
Hypertension	Yes	20.7	716	79.3	2,739	0.035
	No	17.2	116	82.8	560	
Diabetes mellitus	Yes	24.8	232	75.2	704	<0.001
	No	18.8	600	81.2	2,595	
Recanalization therapy						
Recanalization therapy	Yes	22.4	638	77.6	2,205	<0.001
	No	13.5	194	86.5	1,244	
Only i.v. thrombolysis (IVT)	Yes	15.2	108	84.8	603	0.002
	No	20.3	724	79.7	2,846	
Only endovascular recanalization (EVT)	Yes	25.9	240	74.1	688	<0.001
	No	17.7	592	82.3	2,761	
Failure of EVT (<TICI 2b)	Yes	35.8	57	64.2	102	<0.001
	No	18.8	775	81.2	3,347	
IVT and EVT	Yes	22.4	638	77.6	2,205	<0.001
	No	13.5	194	86.5	1,244	

PSP, poststroke pneumonia; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; ICA, internal carotid artery; MCA, middle cerebral artery; IVT, intravenous thrombolysis; EVT, endovascular treatment; TICI, Thrombolysis in Cerebral Infarction scale. ^aCalculated between both PSP categories using Kruskal-Wallis Test. The level of significance of ($P < 0.05$) are shown in bold.

TABLE 2 | Multivariate analysis of possible predictive factors for developing poststroke pneumonia after large vessel occlusion.

Parameter	B	p-value ^a	OR	95% CI of Exp (B)	
Sociodemographic					
Male sex	0.66	<0.000	1.94	1.60	2.34
mRS at admission ≥ 4	-0.23	0.169	0.79	0.57	1.10
Age ≥ 65 years	0.53	0.002	1.69	1.22	2.45
Symptoms at admission					
NIHSS ≤ 4 (minor)	-0.24	0.683	0.78	0.24	2.53
NIHSS 5–15 (moderate)	-0.63	0.029	0.53	0.30	0.94
NIHSS 16–20 (severe)	-0.27	0.069	0.76	0.57	1.02
NIHSS ≥ 21 (very severe)	0.07	0.638	1.07	0.81	1.42
Aphasia	-0.03	0.773	0.97	0.78	1.20
Dysarthria	-0.10	0.380	0.91	0.74	1.12
Dysphagia	1.17	<0.000	3.24	2.49	4.21
Paresis	0.05	0.859	1.05	0.62	1.78
Impaired consciousness	1.33	0.003	1.72	1.58	1.90
Large vessel occlusion					
MCA, M1	-0.15	0.275	0.87	0.67	1.12
MCA, M2	-0.01	0.970	1.00	0.75	1.32
Comorbidities					
Atrial fibrillation	0.27	0.007	1.31	1.07	1.59
Hypertension	-0.14	0.300	0.87	0.66	1.14
Diabetes mellitus	0.33	0.002	1.39	1.12	1.71
Recanalization therapy					
IVT or EVT	10.75	0.000	1.48	1.37	1.61
EVT	0.40	0.009	1.49	1.10	2.01
IVT	0.03	0.817	1.03	0.80	1.32
Failure of EVT	0.43	0.050	1.54	1.00	2.36

PSP, poststroke pneumonia; mRS, modified Rankin Scale; OR, odds ratio; NIHSS, National Institutes of Health Stroke Scale; MCA, middle cerebral artery; IVT, intravenous thrombolysis; EVT, endovascular treatment; failure of EVT, outcome worse than TICI 2b.

^aCalculated using a categorical binary logistic regression model.

The level of significance of ($P < 0.05$) are shown in bold.

PNEUMONIA Score

For PNEUMONIA score, ROC analysis showed an AUC of 0.734 (95% CI 0.715–0.753). Based on the analysis, a cutoff value of ≥ 2 showed a sensitivity of 78.2% and a specificity of 45.1%. See **Figure 2B** for an illustration of ROC curves.

ISAN Score

For ISAN score, ROC analysis showed an overall model quality of 0.63 with an AUC of 0.650 (95% CI 0.631–0.670). Based on the analysis, a cutoff value of ≥ 11 showed a sensitivity of 98.0% and a specificity of 20.0%. See **Figure 2C** for an illustration of ROC curves. Based on the ISAN risk categories, prevalence of PSP was 4.2% in the low-risk group, 13.0% in the medium-risk group, 22.3% in the high-risk group, and 29.0% in the very high-risk group.

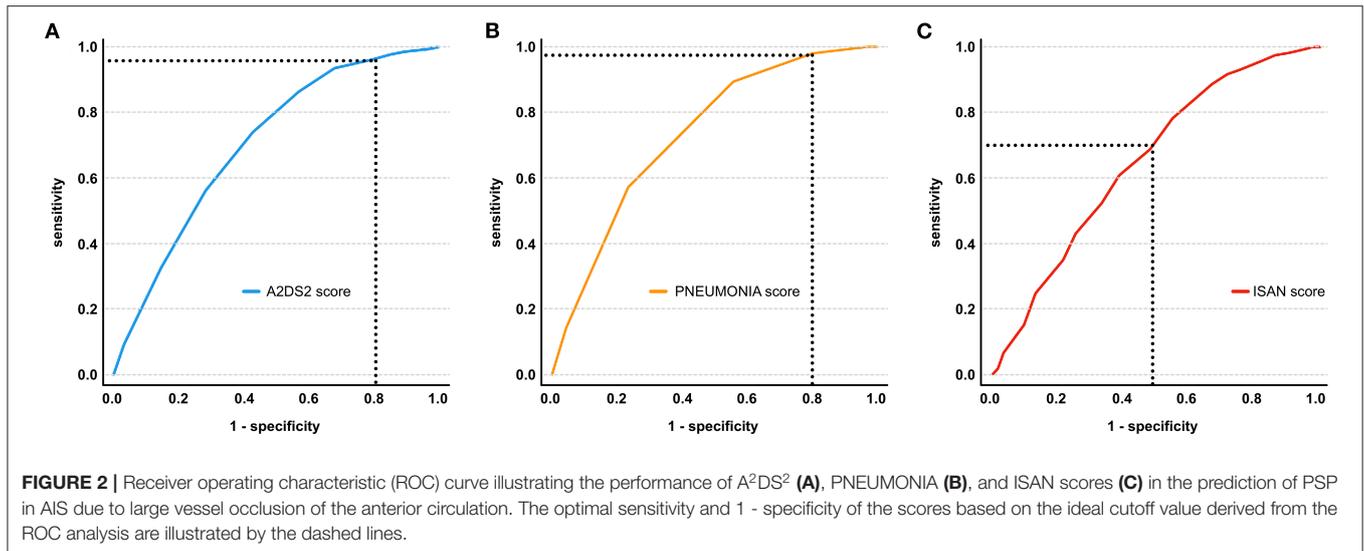
DISCUSSION

PSP is a frequently reported complication in patients with AIS that has been associated with morbidity, mortality, increased

LOS, and increased disease specific costs (3, 24, 25). In the literature, the reported incidence of PSP after AIS varies from 5.4 to 44% depending on the definition and clinical setting and is associated with various sociodemographic and disease-related aspects (1, 16, 24, 26, 27). In this study, 19.4% of LVO stroke patients developed PSP, which was significantly more frequent than the approximated 10% incidence of PSP following AIS of any etiology (1). Moreover, the data show a strong correlation between PSP occurrence and poor patient outcome. Presence of PSP was significantly associated with the increased necessity of ICU treatment and a two-fold increase in overall in-hospital mortality compared with AIS patients without PSP (32.1% mortality compared with 16.4% mortality), underlining the importance of identifying and quantifying risk factors for PSP development and implementing early detection mechanisms and preventive measures in clinical practice.

The multivariate analysis of LVO patients demonstrated that the baseline parameters of male sex, age above 65 years, dysphagia, and impaired consciousness at admission, as well as the comorbidities atrial fibrillation and diabetes, were significantly associated with PSP. These findings are largely consistent with previously reported predictive factors for PSP in all stroke patients (16, 17, 28). This indicates that LVO patients suffer more severe stroke syndromes and are at an overall higher risk of developing PSP, although the predictive risk factors remain mostly identical. In addition, multivariate analysis demonstrated that in LVO patients, the performance of EVT (OR 1.5) as well as the combination of EVT plus IVT (OR 1.5) were strong independent risk factors for PSP occurrence. While LVO patients who received conservative treatment only developed PSP in 13.5% of cases, application of EVT nearly doubled that risk to 25.9%. Notably, the group of patients that was selected for EVT differed in sociodemographic and clinical aspects (NIHSS, comorbidities), as well as in the affected vascular territories, from patients that did not receive EVT (**Supplementary Table 1**). However, these factors were part of the logistic regression that showed EVT as a strong independent risk factor. Though the design of this registry study does not allow us to prove causality, relevant factors that make EVT patients in particular more prone to developing PSP may be identified based on the literature.

In the presented cohort, an especially high percentage of patients (29.2%) developed PSP after receiving EVT and undergoing a consecutive ICU stay with artificial ventilation, which is in line with previous publications (24). A predominant factor for the necessity of ICU treatment—and development of PSP—is possibly the performance of general anesthesia (GA) with endotracheal intubation during EVT and the prolonged need for assisted ventilation. In comparison with EVT under conscious sedation (CS), GA was associated with lower rates of functional independence, higher incidence of PSP, and periprocedural hypotension (14). Especially prolonged weaning from the respirator may be a risk factor for PSP (13). In contrast, a comparative study stressed that the increased overall mortality of patients under GA relies on multiple factors and cannot be directly attributed to the higher rate of associated PSP, highlighting a need for further clinical studies (29).



In the univariate analysis (Table 1), failure of EVT—defined as a recanalization result worse than TICI 2b—was significantly associated with an increased risk of PSP. In the multivariate analysis of this study, however, failure of EVT was not associated with a significant additional risk of PSP. Though the item was indicative of an increased pneumonia risk in the multivariate regression model (OR 1.54; B 0.43), the effect did not reach a level of significance ($p = 0.05$). Thus, the recanalization result itself did not describe the risk of pneumonia as well as other items, such as male sex, age ≥ 65 years, dysphagia, impaired consciousness, or the fact that EVT and/or IVT was performed at all (Table 2). It can be assumed that the performance of EVT alone—especially in elderly patients with comorbidities—may contribute considerably to the risk of developing PSP, e.g., due to a decreased resilience and compensability of swallowing disorders (30, 31), and that these factors may outweigh the additional detrimental (or beneficial) effects of a good or poor recanalization result. In consequence, stroke physicians should be aware in their clinical routine that a patient undergoing EVT is always at an increased risk of developing PSP, even if the intervention is successful (32).

To prevent PSP, the administration of periprocedural antibiotics during EVT under GA has been discussed to some controversy. After three large phase 3 trials, a 2018 Cochrane meta-analysis showed no effect of preventive antibiotics against pneumonia in 4,488 acute stroke patients (33). However, the authors later stressed that a beneficial effect might still be applicable for certain subgroups of stroke patients and/or certain antibiotic regimens that have not yet been explored (34). In this regard, a *post-hoc* analysis of the PASS trial data revealed a beneficial effect of prophylactic intravenous ceftriaxone for patients after IVT (35). It is yet undetermined whether a subgroup of LVO patients with specific predictive risk factors undergoing EVT might also benefit from prophylactic intravenous antibiotics. A retrospective review of 549 cases of endovascular interventions (not exclusively stroke patients) with

and without prophylactic antibiotics failed to show a significant beneficial effect (36). Therefore, a challenge for future studies is the identification of stroke patients that are most likely to benefit from prophylactic antibiotic treatment (34). For now, under consideration of the findings from the current study, stroke physicians should remain vigilant when treating at-risk patients with LVO and consider treatment with antibiotics at a low threshold upon signs of infection, if predictive risk factors for PSP apply.

Stroke patients show interconnected attributes that contribute to neurogenic dysphagia with (micro) aspiration and the likelihood of developing pneumonia, such as impaired consciousness, diminished airway reflexes, pharyngeal muscle relaxation, delayed swallowing reflexes, and volume depletion (29, 37). It is therefore important to determine which stroke patients are at an increased risk of developing PSP compared to others. Several risk stratification scores have been derived for the prediction of PSP in AIS patients and have been introduced into clinical practice. Their performance, however, was validated for all AIS patients and not tested for LVO stroke patients specifically. In this study, we aimed to assess the diagnostic utility of existing scores for LVO patients. Based on available data from 4,281 patients, the A²DS², PNEUMONIA, and ISAN scores could be assessed, while other scores had to be dismissed due to insufficient information in our registry. The ROC analyses revealed considerable sensitivities of 96.1 and 98.2 for A²DS² and ISAN scores, respectively, which were paired with low specificities of 20.7 and 20.0%, and in both cases were only close to acceptable model quality (0.68 and 0.63). In contrast, PNEUMONIA score showed an acceptable model quality (0.71) with a sensitivity of 78.2% and a specificity of 45.1%. In conclusion, all three score systems can be applied in clinical practice as screening tools for LVO stroke patients at risk of PSP, but their statistical limitations leading to false-positive (A²DS² and ISAN) as well as false-negative (PNEUMONIA) results require careful interpretation.

Limitations of this study include the lack of information regarding the individual causality of PSP, as only frequencies could be correlated. The quality health care data was assessed state-wide in smaller hospitals and large stroke centers with possibly varying treatment options. Because of non-recorded clinical variables in the quality assurance stroke registry for Hesse, such as Glasgow Coma Scale at admission, systolic blood pressure in the first 24 h after admission, white blood cell count, blood glucose levels, stroke subtype, and history of pneumonia, the use of some PSP prediction scores, such as PANTHERIS, AIS-APS, or Chumbler's score, was not feasible in this study (26, 28, 38). Furthermore, no data was available on whether patients received GA or CS during EVT in the hospitals. It can only be assumed that a vast majority of patients receiving EVT were treated under GA because it is considered the standard procedure in Hesse, but no data on the modality was recorded. Noteworthy, presence of intracranial carotid occlusion could not be considered in this study, consequently no conclusion can be drawn for this subgroup of patients from this study.

A clear strength of this study lies in the predefined consensus on operational diagnostic criteria of pneumonia in the documentation manual. This contributes to a more homogeneous collective of PSP patients, which addresses a matter of criticism in prior registry studies on this topic (8, 27).

CONCLUSION

Nearly one in five stroke patients with LVO developed PSP during acute care in this study. This risk of PSP was further increased if an EVT was performed, and if patients underwent ICU treatment. Other predictive factors were consistent with those previously described for all AIS patients, and the risk of developing PSP largely relied on the patients' predisposition and the severity of the stroke syndrome at admission. The

risk stratification scores A²DS², PNEUMONIA, and ISAN score proved to be sensitive tools in LVO patients but lacked specificity.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: data will be made available after reasonable request due to German regulations on data protection. Requests to access these datasets should be directed to Martin A. Schaller-Paule, martin.schaller@kgu.de.

ETHICS STATEMENT

The analysis was approved by the Institutional Review Board of the Ethical Committee at the University Hospital Frankfurt (313/16). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MS-P and LW conceived the study, performed the statistical analysis, and wrote the first draft of the manuscript. BM manages the state-wide prospective quality assurance database. AS gained ethical approval. FB and CF were involved in data preparation. MS-P, CF, FB, KK, BM, SL, FR, AS, and LW reviewed, revised, and edited the manuscript and approved the final version of the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fneur.2022.824450/full#supplementary-material>

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