



# Risk factors of stroke complicated with hospital-acquired pneumonia: a systematic review and meta-analysis of cohort studies

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**Background:** Hospital-acquired pneumonia (HAP) is a common type of nosocomial infection and a common complication experienced by stroke patients during hospitalization. HAP can aggravate patients' primary disease condition and lead to death. Clinically, a variety of factors may affect the occurrence of HAP in patients. In this study, we conducted a meta-analysis of the literature to investigate the risk factors of stroke with HAP for clinical reference.

**Methods:** The PubMed, Medline, Embase and Cochrane Library databases were selected as the sources for the literature search. English-language publications were included. The articles related to stroke with HAP were published from January 2000 to January 2021. The articles were screened and their quality was evaluated using the Newcastle-Ottawa Scale. A meta-analysis was performed of the factors affecting the incidence of HAP using Revman 5.4 software.

**Results:** Ultimately, 7 articles with a total of 1,172 patients were included in the meta-analysis. Of the 1,172 patients, 352 (30.03%) had an HAP infection. The results of the meta-analysis showed that patient age [mean difference (MD) =4.91, 95% confidence interval (CI): 3.90 to 5.93; P<0.00001], National Institutes of Health Stroke Scale (NIHSS) score (MD =3.84, 95% CI: 3.01 to 4.67; P<0.00001), and patient malnutrition [odds ratio (OR) =1.85, 95% CI: 1.13 to 3.04; P=0.02] were risk factors for the development of HAP, while gender, stroke history, smoking history, and comorbidities (diabetes, hypertension, coronary heart disease, and hyperlipidemia) were not risk factors for the development of HAP.

**Discussion:** A total of 7 articles were included in this meta-analysis examining the influencing factors of HAP in stroke patients. The results showed that age, NIHSS score, and malnutrition were risk factors of HAP in stroke patients, while gender, stroke history, smoking history, and complications (diabetes, hypertension, coronary heart disease, and hyperlipidemia) were not influencing factors of HAP.

**Keywords:** Stroke; hospital-acquired pneumonia (HAP); risk factors; meta-analysis

Submitted Oct 12, 2021. Accepted for publication Nov 29, 2021.

doi: 10.21037/apm-21-3278

View this article at: <https://dx.doi.org/10.21037/apm-21-3278>

## Introduction

Hospital-acquired pneumonia (HAP) generally refers to the infection that occurs in patients 2 days after being admitted to hospital, it is usually caused by bacteria, fungi, mycoplasma, viruses, and other microorganisms, and patients with HAP develop substantial pulmonary inflammation, which can affect the clinical treatment of the disease, aggravate the primary disease condition, and lead to patient death (1). The clinical symptoms are not typical, in any case of depression, fever, unexplained dyspnea and increased purulent secretion of respiratory tract, the possibility of HAP should be considered and chest X-ray examination should be performed as early as possible to identify HAP (2). HAP is a common type of nosocomial infection and a common complication during hospitalization, the incidence of HAP in stroke patients is as high as 30% (3). Due to the various pathogens and germs in hospitals, patients with poor resistance to bacteria could easily be infected if exposed to such an environment; In addition, with the patients' swallowing and coughing reactions weakened during bed time, the indwelling of gastric tube is easy to cause reflux and result in aspiration pneumonia; Exogenous invasive operations such as ventilator and endotracheal intubation destroy the integrity of skin and mucosa and increase the chance of infection (4). Some risk factors, such as patient age, gender, underlying diseases (diabetes, hypertension, and heart failure), malnutrition, and dysphagia, are also associated with the occurrence of HAP (5). Studying the risk factors of HAP is very important for the development of preventive measures, a meta-analysis conducted by Wästfelt *et al.* (6) had dived into this topic but it included all the infections including HAP and urinary tract infection (UTI). In this study, a meta-analysis of evidence-based studies was conducted to quantitatively analyze the possible influencing factors of only HAP to provide a basis for targeted preventive measures. We present the following article in accordance with the MOOSE reporting checklist (available at <https://dx.doi.org/10.21037/apm-21-3278>).

## Methods

### *Data source and search strategy*

The PubMed, Medline, Embase, and Cochrane Library databases were selected as data sources for this study. The databases were searched for articles published in the English language between January 2000 and January

2021. We conducted the electronic search through the websites of the databases, and tried to hand searching studies in the paper media. The search method included a quick search of keywords and a combination of keywords. The following search was conducted: *[Predictors/factors] AND [stroke] AND [Ventilator-associated pneumonia/hospital-acquired pneumonia HAP]*. If the original text could not be obtained, we contacted the author for the full text. We only included English articles, studies in other languages would be excluded. We also contacted the authors for unpublished studies.

### *Inclusion criteria*

To be eligible for inclusion in the meta-analysis, articles had to meet the following inclusion criteria: (I) describe an observational study (a cohort study or case-control study) conducted at single or multiple study sites; (II) include patients diagnosed with stroke, without an initial diagnosis or recurrence, ischemic stroke, or hemorrhagic stroke as confirmed by computed tomography (CT) or magnetic resonance imaging, and with at least 2 of the following 3 pneumonia symptoms: (i) a body temperature  $>38^{\circ}\text{C}$ ; (ii) serum white blood cell abnormalities; and/or (iii) secretion production, and (iv) comprise two groups of patients (i.e., pneumonia-infected patients and non-pneumonia infected patients), and compare their data.

### *Exclusion criteria*

Articles were excluded from the meta-analysis if they met any of the following exclusion criteria: (I) described a randomized controlled trial, quasi-randomized trial, or concurrent control, or a non-observational study; epidemiological investigation, cross-sectional observational studies, reviews, case reports or qualitative study (which were excluded, as they did not provide any quantitative data); (II) the patients had been transported to the hospital directly after onset, rather than after treatment at other hospitals; and/or (III) described repeated content, or the original text or data could not be obtained.

### *Selection of articles*

Two researchers independently screened the articles. First, the researchers read the title and abstract of the articles, excluded articles that obviously did not meet the requirements, and then obtained the full text of articles and

read the full text for further screening. The two researchers cross-checked the articles, and if there were doubts about the inclusion of an article that could not be resolved by discussion, a 3rd person was asked to resolve the issue.

### *Data extraction*

Two researchers read the articles, and independently extracted basic information about the article, study characteristics, and observation indicators, which were recorded using Excel sheets. The two researchers cross-checked the extracted data. If the data were incomplete, the original author was contacted, and all the data were requested. If the data could not be obtained, the article was excluded.

### *Outcome indicators*

Data was collected including information about gender, age, National Institutes of Health Stroke Scale (NIHSS) score, stroke history, smoking habits, comorbidities such as diabetes, hypertension, hyperlipidemia, nutritional status, coronary heart disease, stroke type for each study.

### *Literature quality assessment*

The quality of the included articles was evaluated using the Newcastle-Ottawa Scale (NOS) (7). The scale was used to evaluate the subject selection, comparability, and outcome indicators of the articles. A maximum score of 9 points was possible, and a score of >5 points indicated good quality. The higher the score, the better the quality of the article and the less the bias.

### *Statistical analysis*

Revman 5.4 software was used for the statistical analysis. The mean difference (MD) was used to report continuous variables. The odd ratio (OR) and 95% confidence interval (CI) were used to report binary variables. Forest plots were used to present the results. The Q statistic test was used to examine the heterogeneity among the articles. A P value >0.05 indicated no heterogeneity and good consistency. The fixed-effects model analysis was conducted to calculate the OR using the Mantel-Haenszel method. If heterogeneity was found, the random-effects model was conducted to calculate the OR using the Der Simonian and Laird method. If the fixed-effects analysis was consistent with the random-effects analysis, the sensitivity analysis results

were considered stable. A P value <0.05 was considered statistically significant for the effect analyses.

## **Results**

### *Literature search*

In this study, 567 relevant articles were initially retrieved, 155 articles were removed due to duplication. The remaining 412 articles were included in the primary screening, and 7 articles were ultimately included in the met-analysis. The screening process is shown in *Figure 1*.

### *Basic characteristics of included articles*

This study included 7 articles comprising a total of 1,172 patients. Of the 1,172 patients, 352 (30.03%) had an HAP infection. The basic data and factors of the articles are set out in *Table 1*.

### *Excluded articles and reason for exclusion*

Six articles were excluded for different reasons (see *Table 2*); not all the reasons for exclusion were listed.

### *Meta-analysis results*

#### **Age**

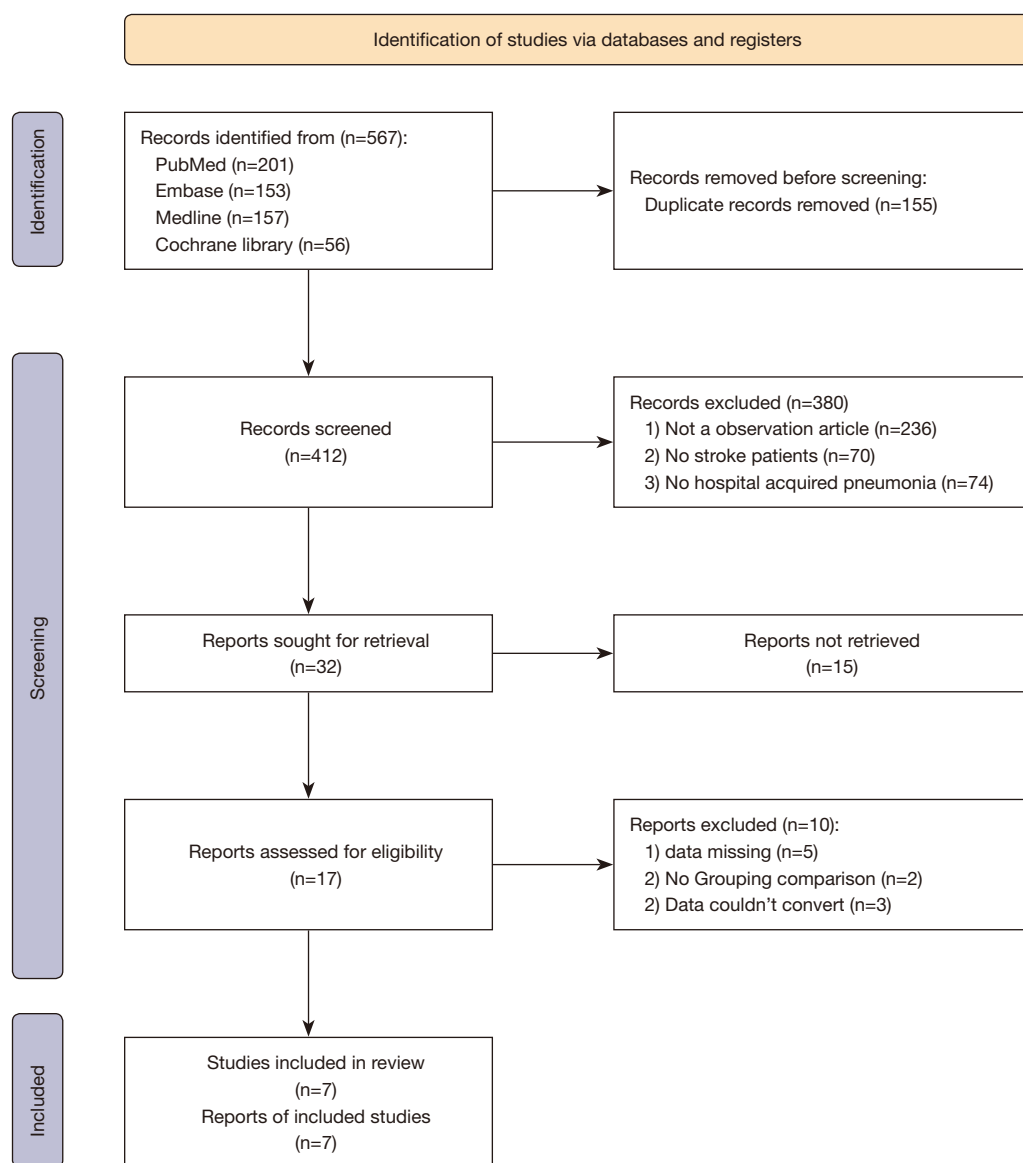
Six articles (8-12,14) examined whether patient age had an effect on HAP infection. There were 301 HAP cases and 809 non-HAP cases. There was no heterogeneity between the articles ( $I^2=0\%$ ,  $P=0.44$ ). The fixed-effects model analysis showed that the patients with HAP infection were significantly older than those without infection (MD =4.91, 95% CI: 3.90 to 5.93;  $P<0.00001$ ; see *Figure 2*).

#### **Gender**

All articles examined the effect of gender on the occurrence of HAP infection in patients. There were 352 HAP cases and 820 non-HAP cases. There was heterogeneity between the articles ( $I^2=77\%$ ,  $P=0.0002$ ). The random-effects model analysis showed that the proportion of male HAP patients was not statistically significant compared to that of non-HAP male patients (OR =0.74, 95% CI: 0.42 to 1.30;  $P=0.29$ ; see *Figure 3*).

#### **NIHSS score**

Six articles (8-12,14) examined the effect of NIHSS score at



**Figure 1** Search and selection flow chart.

admission on the occurrence of HAP. There were 301 HAP cases and 809 non-HAP cases. There was heterogeneity between the articles ( $I^2=86\%$ ,  $P<0.00001$ ). The random-effects model analysis showed that the NIHSS score of HAP patients was significantly higher than that of non-HAP patients (MD =3.84, 95% CI: 3.01 to 4.67;  $P<0.00001$ ; see *Figure 4*), and the difference was statistically significant.

### Others

Software was used to calculate the pooled-effect value of each factor. Ultimately, only the malnutrition factor

(malnutrition) was determined to have an effect on HAP ( $P<0.05$ ). The effect of the other factors remained uncertain ( $P>0.05$ ; see *Table 3*).

### Heterogeneity investigation and sensitivity analysis

There was significant heterogeneity among the 6 studies for the effect of NIHSS score, we excluded studies one by one to explore the heterogeneity source but all the left studies still have heterogeneity, the heterogeneity source may come from different characteristics of the patients, as course,

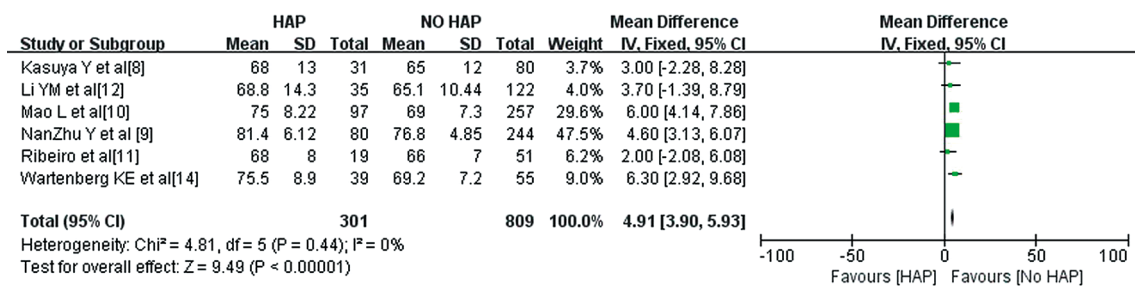
**Table 1** Summary of basic characteristics and risk factors of included articles

Serial number	Author	Study location	Date of publication	Total cases	Number of pneumonia infections in the hospital (%)	Factors	Quality score (points)
1	Kasuya <i>et al.</i> (8)	Louisville, KY 40202, USA	2011	111	31 (27.9)	(a), (b), (c), (d), (e), (f), (h), (l)	6
2	NanZhu <i>et al.</i> (9)	Tianjin, China	2019	324	80 (24.7)	(a), (b), (c), (d), (e), (f), (g), (i)	5
3	Mao <i>et al.</i> (10)	Changzhou, China	2019	257	97 (37.7)	(a), (b), (c), (f), (g), (h), (i), (j)	5
4	Ribeiro <i>et al.</i> (11)	Sao Paulo, Brazil	2015	70	19 (27.1)	(a), (b), (c)	5
5	Li <i>et al.</i> (12)	Shanghai, China	2020	157	35 (22.3)	(a), (b), (c), (e), (f), (g)	6
6	Almeida <i>et al.</i> (13)	Campinas SP, Brazil	2015	159	51 (32.1)	(b), (e), (f), (g), (h), (k), (l)	5
7	Wartenberg <i>et al.</i> (14)	Germany	2011	94	39 (41.5)	(a), (b), (c), (d), (f), (g), (i), (l)	5

(a) Age; (b) Gender; (c) National Institute of Health Stroke Scale (NIHSS) score at admission; (d) Stroke history; (e) Smoking; (f) Diabetes mellitus; (g) Hypertension; (h) Hyperlipidemia; (i) Malnutrition; (j) Dysphagia; (k) Type of stroke; (l) Coronary artery disease.

**Table 2** Excluded articles and reason for exclusion (not all)

Serial number	Author	Date of publication	Reason for exclusion
1	Sui <i>et al.</i> (15)	2011	No group compared
2	Patel <i>et al.</i> (16)	2020	No data available
3	Kopp <i>et al.</i> (17)	2017	Non-stroke patients
4	Folbert <i>et al.</i> (18)	2017	Non-stroke patients
5	Pieralli <i>et al.</i> (19)	2021	Non-hospital acquired pneumonia
6	Mandal <i>et al.</i> (20)	2011	Non-hospital acquired pneumonia

**Figure 2** Effect of patient age on hospital-acquired pneumonia in stroke patients.

severity of the disease.

We conducted a random-effect model for analysis of age factor, the result was very similar to the result of fix-effect model, which indicating the results were stable.

### Analysis of publication bias

A publication bias analysis was not performed due to the small number of articles included in the study.

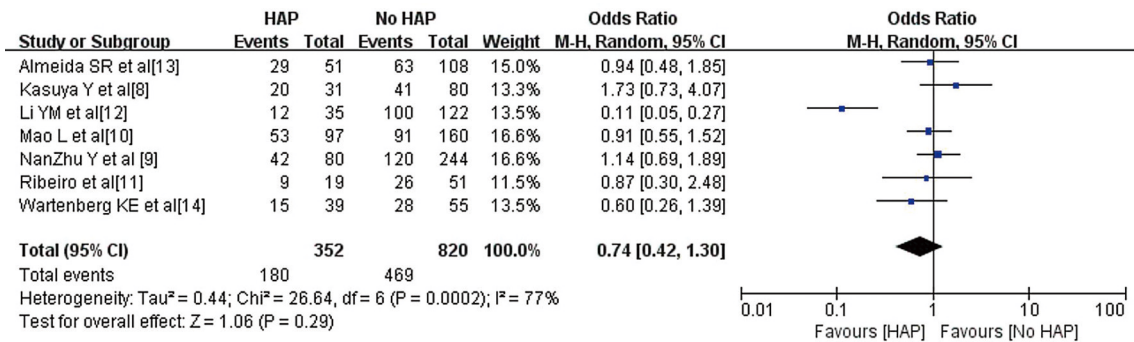


Figure 3 Effect of gender ratio (male) on stroke patients with hospital-acquired pneumonia.

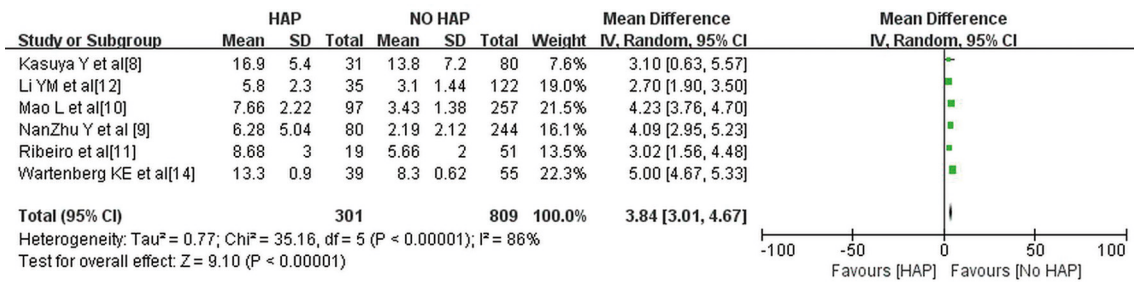


Figure 4 Effect of National Institute of Health Stroke Scale (NIHSS) score on stroke patients with hospital-acquired pneumonia.

Table 3 Meta-analysis results of other factors

Factors	Reported articles	Number of articles	Analysis mode	I <sup>2</sup> with P value	Overall combined OR	P value
Stroke history	(8,9,14)	3	Fixed-Effects Model	0% with 0.61	1.26 (0.82, 1.94)	0.29
Smoking	(8,9,12, 13)	4	Fixed-Effects Model	6% with 0.36	0.73 (0.52, 1.02)	0.06
Diabetes mellitus	(8-10,12-14)	6	Fixed-Effects Model	0% with 0.45	0.87 (0.66, 1.14)	0.31
Hypertension	(9,10,12-14)	5	Random-Effects Model	74% with 0.004	1.19 (0.58, 2.44)	0.63
Malnutrition	(9,10,14)	3	Fixed-Effects Model	0% with 0.83	1.85 (1.13, 3.04)	0.02
Coronary artery disease	(8,13,14)	3	Fixed-Effects Model	20% with 0.29	1.10 (0.70, 1.71)	0.68
Hyperlipidemia	(8,10,13)	3	Fixed-Effects Model	0% with 0.75	0.74 (0.46, 1.18)	0.20

OR, odd ratio.

### Discussion

Infection after stroke, especially pulmonary infection and urinary tract infection, is very common (21). The occurrence of HAP after stroke not only aggravates the economic burden of patients (22), but also greatly affects the prognosis of patients and increases mortality (23). In this meta-analysis, the incidence of HAP was statistically

analyzed. The 7 articles included a total of 1,172 patients. Of the 1,172 patients, 352 (30.03%) had an HAP infection; the incidence floating range of 22.3–41.5% is consistent with that reported in similar studies (24).

The pathogenic bacteria reported to cause HAP were statistically analyzed (10). Gram-negative bacteria accounted for about 74.8% of the pathogenic bacteria,

gram-positive bacteria accounted for about 24.3%, and the rest were fungi, viruses, and other microorganisms. The top 3 pathogenic bacteria were *Klebsiella pneumoniae*, *Mobility baumannii*, and *Staphylococcus aureus*. The occurrence of nosocomial infections may be related to a variety of causes. One study (25) has pointed out that the use of statins in early stage stroke patients may increase the risk of infection. Another study (26) has noted that poor oral care may increase the chance of infection in patients. In addition, a variety of risk factors may increase the incidence of HAP, such as patient age and underlying diseases. To solve the inconsistencies between multiple studies, a comprehensive analysis was conducted of several common factors. The results showed that patient age, NIHSS score at admission, and malnutrition were risk factors of HAP in stroke patients, while patient gender, stroke history, smoking history, and comorbidities (diabetes, hypertension, coronary heart disease, and hyperlipidemia) were not influencing factors of HAP.

#### *Age factor*

The results of this study showed that patients with HAP were significantly older than those without HAP (there were 352 HAP patients and 820 non-HAP patients), which suggests that age is a predictor of HAP. In addition to the well-known decline in immunity that patients may develop with age, Wen *et al.* (27) found that the characteristics of the gut microbiota in elderly adults are very different compared to those of healthy adults, and the gut microbiota in the elderly is characterized by reduced bacterial diversity, which is associated with increased frailty, which in turn aggravates the possibility of infection in the elderly.

#### *Gender factor*

In this study, there was no statistically significant difference between the proportion of male HAP-infected and non-infected patients, which suggests that sex is not a factor that influences whether patients develop HAP. Colbert *et al.* (28) analysed 91,643 stroke patients and found that female patients had a lower incidence of pulmonary infection than male patients, which may be related to different sex hormones and norepinephrine levels between genders. Thus, attention should be paid to the difference in gender of patients when performing prophylactic antibiotic therapy.

#### *NIHSS score factors on admission*

The NIHSS score is a neurological deficit score that predicts the severity of stroke disease in patients. Patients with a higher score, combined with a disturbance of consciousness and dysphagia, may have increased bacterial colonization in the oral cavity due to changes in the composition of oral secretions after stroke. If aspiration occurs, it can easily cause pulmonary infection and pneumonia.

#### *Malnutrition*

Deficits in consciousness and neurological function in stroke patients affect the endocrine function and digestive function of patients, leading to an imbalance in the secretion of hormones, and the weakened regulation of glucose, protein, and fat metabolism, which affects the nutritional status of patients and may cause a lack of the amino acids and fatty acids necessary for immune cell synthesis, resulting in immune dysfunction, which in turn results in the occurrence of infection (29).

In this study, stroke history, smoking history, and comorbidities (diabetes, hypertension, coronary heart disease, and hyperlipidemia) were not found to have an effect on the occurrence of HAP, but this may be related to the fact that the included articles and the number of patients were small. In addition, this meta-analysis only studied the common factors that may affect the occurrence of HAP, and did not cover all the factors. For example, some studies (30) have pointed out that the incidence of cerebral infarction in the left hemisphere was higher than that in the right hemisphere. Further, research (13) has shown that the infection rate of HAP differs significantly between ischemic stroke and hemorrhagic stroke patients. However, as more articles could not be retrieved, these factors could not be analyzed. In relation to the investigation of the occurrence of HAP in stroke patients, the literature needs to be search further to gather stronger evidence.

There is still no consensus on the treatment of stroke with HAP and the choice of antibiotics (31). Vermeij *et al.* (32) pointed out that while prophylactic antibiotics do not improve the therapeutic effect or reduce the mortality rate, they are still very effective in treating some specific types of stroke. In the study of Friedant *et al.* (33), several risk factors of HAP after stroke including age, NIHSS score at admission and malnutrition of patients were used to make a

simple score table of hospital acquired pneumonia, so as to help doctors predict acquired pneumonia in stroke patients and take preventive measures as soon as possible.

We suggest that in order to reduce the occurrence of HAP, we should maintain the air circulation in the ward, disinfect in time, pay attention to the hand hygiene of doctors, timely assist patients to discharge respiratory secretions, clean patients' oral cavity, strengthen patients' nutrition and use antibiotics reasonably.

## Conclusions

In this meta-analysis of the influencing factors of HAP in stroke patients, a total of 7 articles were included. The results showed that patient age, NIHSS score, and malnutrition were risk factors of HAP in stroke patients, while gender, stroke history, smoking history, and complications (diabetes, hypertension, coronary heart disease, and hyperlipidemia) were not influencing factors of HAP.

## Acknowledgments

*Funding:* None.

## Footnote

*Reporting Checklist:* The authors have completed the MOOSE reporting checklist. Available at <https://dx.doi.org/10.21037/apm-21-3278>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://dx.doi.org/10.21037/apm-21-3278>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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- (English Language Editor: L. Huleatt)

**Cite this article as:** Guo T, Dou L, Zhou X. Risk factors of stroke complicated with hospital-acquired pneumonia: a systematic review and meta-analysis of cohort studies. *Ann Palliat Med* 2021;10(12):12381-12389. doi: 10.21037/apm-21-3278