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Original Article

Application value and safety of NIPPV combined with routine clearance in the treatment of stroke-associated pneumonia in elderly patients

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Abstract: Objective: To investigate the application value and safety of NIPPV (noninvasive positive pressure ventilation) combined with routine clearance in elderly patients with stroke-associated pneumonia (SAP). Methods: Altogether 88 elderly SAP patients treated in our hospital from January 2021 to January 2022 were retrospectively evaluated. Among them, 48 cases treated with NIPPV and routine clearance were regarded as an experimental group (EG), and 40 with routine clearance alone were enrolled to a control group (CG). The sputum clearance rate and CPIS score were compared. The safety of NIPPV was evaluated. The clearance treatment cost, hospitalization time and expenses, and the changes of inflammatory factors (IL-6, TNF-α, C-reactive protein (CRP)) were compared before and after treatment. The efficacy of airway clearance after treatment and the risk factors affecting the severity of infection was assessed. Results: The sputum clearance rate in the EG was higher than that in the CG ($P < 0.05$). After treatment, the CPIS score of EG was lower ($P < 0.05$). The hospitalization time and expenses of CG were higher. After treatment, the serum inflammatory factors in CG were higher ($P < 0.05$), while the clinical efficacy of EG was higher ($P < 0.05$). Treatment plan, course of disease and diabetes are risk factors for postoperative infection. Conclusion: NIPPV combined with routine clearance is effective for elderly SAP patients, which can shorten the hospitalization time and reduce the expenses.

Keywords: Noninvasive positive pressure ventilation, routine clearance, senile stroke-associated pneumonia, infection

Introduction

Stroke is a serious manifestation of various cerebrovascular diseases. Statistics show that the standard prevalence rate of stroke among people aged 40 and over in China has been increasing, from 1.89% in 2012 to 2.32% in 2018 [1]. The number of patients aged 40 and over in China is 13.18 million, of which about 1.94 million people died of stroke in 2018 [2]. Pulmonary infection is the most common complication of stroke patients, ranking first among all related complications [3]. Stroke-associated pneumonia (SAP) can prolong the hospitalization time, increase the economic burden and increase the mortality of patients [4]. There are many pathogenic factors of SAP, such as cough dysfunction [5]. Cough is a defense mode of the body. Effective cough is vital to protect airway and prevent pneumonia. There is a remarkable correlation between spontaneous cough and impaired cough reflex and subsequent pneumonia [6]. A large number of studies have shown that stroke will not only affect the limb function of hemiplegic side, but also change the respiratory function [7]. Therefore, finding an effective solution is the key to solve this problem.

If the sputum can't be removed by effective cough from stroke patients, its retention may provide an environment for the reproduction of pathogenic microorganisms, aggravate the inflammatory reaction, and even lead to death [8]. Airway clearance technology is quite marked for SAP patients [9]. Compared with conventional treatment, this technology can improve oxygenation, shorten the use time of ventilator,

reduce the hospitalization time in ICU, solve atelectasis/pulmonary consolidation and/or improve breathing [10]. However, for some older SAP patients, the respiratory muscle strength is poor due to multiple factors such as bed rest, nutrition, neuromuscular dysfunction, and increased respiratory power consumption caused by lung infection. In addition, stroke leads to decreased central function of cough, chest and lung illness, or hypofunction, which finally reveals as ineffective cough [11]. Noninvasive positive pressure ventilation (NIPPV) can help patients open their airways and alveoli, which is beneficial to bronchial drainage and alveolar drainage [12]. Some scholars used NIPPV to treat patients with pulmonary cystic fibrosis and achieved good results [13].

In this research, we explored the application value and safety of NIPPV combined with routine clearance in elderly SAP patients and provided a choice for clinical treatment.

Methods and data

Clinical data of patients

Altogether 88 SAP patients admitted to the Department of Neurology and Respiratory and Critical Care Medicine of our hospital from January 1, 2020 to January 1, 2022 were retrospectively included in this study. Among them, 48 cases treated with NIPPV and routine clearance were seen as the experimental group (EG), and 40 treated with routine clearance alone were enrolled to the control group (CG). This research was approved by the Medical Ethics Committee of our hospital (2020 (Review) A84 (approval)). With the retrospective nature, the informed consent from patients was waived.

Exclusion and exclusion criteria

Inclusion criteria: ① Patients who meet the diagnostic criteria of SAP without established artificial airway (the criteria are based on the Chinese Expert Consensus on the Diagnosis and Treatment of Stroke-related Pneumonia [14] 2019 Update); ② Patients with clear consciousness and stable vital signs; ③ Patients with vital capacity of patients less than 10 mL/kg or the inspiratory volume < 1/3 of the expected value, the peak expiratory flow rate < 160 L/min, and peak cough flow rate < 180 L/min as indicated by pulmonary function examination; ④ Patients with an aged of 18-80 years old.

Exclusion criteria: ① Patients with contraindications of airway clearance: intracranial pressure > 20 mmHg, head and neck injury, active bleeding with hemodynamic instability, aspiration, recent spinal trauma or surgery, rib fracture, esophageal surgery, bronchopleural fistula, pneumothorax and pleural effusion, pulmonary edema, pulmonary embolism, dysphoria, anxiety, old age and infirmity who can't tolerate body position change, severe arrhythmia or acute coronary syndrome, pacemaker implantation and abnormal coagulation mechanism; ② Patients with contraindications of NPPV: disturbance of consciousness, weak breathing or severe organ dysfunction (upper gastrointestinal hemorrhage, hemodynamic instability, etc.), undrained pneumothorax or mediastinal emphysema, severe abdominal distension, upper airway or maxillofacial injury/postoperative/deformity, inability to cooperate with NPPV or mask discomfort, etc.

Therapeutic regimens

Patients in the CG were treated with airway clearance scheme: 1. Airway clearance techniques mainly include active recirculation breathing technique, tapping, postural drainage and cough training. The patients were instructed to perform active repeated breathing during atomization. Active circulatory breathing is an alternating process of breathing control, chest expansion exercise and forced exhalation technique. The therapist instructed the patients to take a bedside sitting posture, relax his/her upper chest and shoulders, and keep calm breathing. After the operation, the patients were trained to do chest expansion exercises, take a deep breath, give full play to the diaphragm, exhale forcibly for 2-3 times, keep the glottis open after taking a deep breath, tighten the abdomen, do 2-3 quick breathing movements quickly, and complete a whole set of movements. It can be cycled 5-10 times. 2. Postural drainage: In view of the location of sputum accumulation during auscultation, different lung segments can be drained at different positions. The sputum in the middle and inner segments and the basal segment of the left upper lobe can be drained in right position. Drainage in supine position requires head

down and feet up, and right lung drainage inverted. 3. Beating: lateral chest beating was performed in the order of outside to inside and bottom to top, 3-5 times/d, 5-6 minutes/time, 100-180 minutes/d. 4. Exercise: The therapist should instruct the patient to take a deep breath, close the glottis (hold his breath) for 3-5 s after inhaling, then lean forward, contract the abdominal muscles, press the upper abdomen, increase the internal pressure of chest and abdomen, cough hard, expectorate, and repeat for 3-5 times.

EG was treated with NIPPV on the basis of the CG. In spontaneous breathing-time control (ST) mode, expiratory positive airway pressure (EPAP) was set to 4-6 cm H_2O, and the pressure parameter of inspiratory positive airway pressure (IPAP) was titrated to adjust the tidal volume gradually from 6-8 ml/kg to the therapeutic dose. The treatment time was 3 times a day with 10-15 minutes each time. It is necessary to strengthen monitoring during treatment, guide patients to breathe deeply and slowly, and guide or assist patients to cough effectively after treatment. If the patient had cough and expectoration during NIPPV treatment, stop it immediately, and continue treatment after he cleared the sputum.

Elisa test

Before treatment, 3 mL of vein blood was taken from all patients on an empty stomach in the morning, centrifuged (3000 r/min) for 10 minutes after standing 2 h at room temperature. The supernatant was collected and stored at -20°C to avoid repeated freezing and thawing. Afterwards, 100 μL/well of serum was added into the corresponding well, the plate was incubated 2 h at indoor temperature, then washed 5 times, and 100 μL/well of biotinylated antibody was added. Next, the plate was sealed and cultured 1 h indoor. The plate was cleaned 5 times, horseradish peroxidase labeled Streptavidin 100 μL/well was added, then sealed, and incubated 20 minutes in the dark. The plate was cleaned 5 times, 100 μL/well of developer TMB solution was added, then sealed, and incubated 15 minutes under dark conditions. Afterwards, 50 μL/well of stop solution was added, and the A450 value of microplate reader was tested immediately after mixing. The kits were purchased from Shanghai Enzyme-linked Biotechnology Co., Ltd., China. (IL-6, ml058097; TNF-α, ml077385; C-reactive protein (CRP), ml057570).

Clinical pulmonary infection score (CPIS)

CPIS is a combination of clinical, imaging and microbiological criteria to assess the severity of infection. There are 7 indices, including body temperature, white blood cell count, tracheal secretion, oxygenation, chest radiography, lung infiltration shadow and tracheal aspiration culture. The highest score is 12, and antibiotics can be discontinued when the score is less than 6.

Modified medical research council (mMRC) score

mMRC is a vital score to evaluate the respiratory conditions of patients clinically. The score is divided into 4 grades: 0: dyspnea only during strenuous exercise; 1: shortness of breath when walking briskly on flat ground or climbing small slopes; 2: walking more slowly than their peers on flat ground because of difficulty in breathing; or having to stop to catch a breath when walking at their own pace; 3: stop to take a breath after walking about 100 yards or a few minutes on flat ground. 4: out of breath, unable to leave home, or get tired to get dressed.

Outcome measures

Main outcome measures: The expectoration of patients in both groups before and after treatment (Day 14) was compared. The 4-point expectoration scoring method was used (totally 4 points): 1 point: normal functional - sputum can be cleared; 2 points: moderate disability - sputum can be cleared after numerous attempts; 3 points: severe disability - difficult to cough up sputum with great effort; 4 points: no function - unable to cough. Clinical pulmonary infection score (CPIS) was employed to compare the changes of infection before and after treatment (Day 14). The dyspnea scale (mMRC) was conducted to assess the severity of dyspnea before and after treatment (Day 14). The changes of inflammatory factors (IL-6, TNF-α, CRP) were compared before and after treatment.

Secondary outcome measures: For both groups, the hospitalization time and expenses

Table 1. Clinical data of patients

Factor	CG (n = 40)	EG (n = 48)	*P* value
Age			0.963
≥ 65 years old	31	37	
< 65 years old	9	11	
Gender			0.334
Man	30	40	
Woman	10	8	
Type of stroke			0.496
Cerebral infarction	20	28	
Hematencephalon	18	16	
Subarachnoid hemorrhage	2	4	
Past medical history			
Diabetes	25	27	0.553
Hypertension	22	28	0.753
Smoking history			0.918
Yes	33	40	
No	7	8	
Alcoholism history			0.642
Yes	10	10	
No	30	38	
Hospital stays (days)	19.48 ± 4.43	12.91 ± 3.19	< 0.001

were calculated. The incidence of adverse reactions after treatment was counted. The survival of patients one month after treatment were made, and Cox regression was employed to assess the risk factors affecting their short-term prognosis. The differences of clinical baseline data were compared.

Statistical analysis

SPSS 20.0 software was used to process data. Shapiro-Wilk method was used for normality test first, and the measurement data conforming to normal distribution was expressed by mean ± standard deviation (mean ± sd). The inter-group comparison was done by using independent-samples T test and the intra-group comparison was done using paired t-test. The counting data were compared by χ^2 test. Cox regression analysis was conducted to determine the relationship between each potential variable and patient mortality, and multivariate Cox regression analysis was conducted to screen the independent variables affecting patient mortality. Kaplan-Meier survival curve was conducted to assess the survival rate. ROC curve was employed to assess the clinical value of independent variables in predicting short-term survival. $P < 0.05$ was regarded as statistically remarkable.

Results

Comparison of clinical data of patients

It was found that there was no statistical difference in age, gender, stroke type, past medical history, smoking and alcoholism history between two groups; however, the hospitalization time of CG was significantly longer than that of EG ($P > 0.05$, **Table 1**).

Expectoration between both groups

We found that there was no statistical difference in expectoration score between two groups before treatment ($P > 0.05$). After treatment, the expectoration scores of patients in both groups were decreased while the scores in EG was significantly lower than that in CG ($P < 0.05$, **Table 2**).

Changes of CPIS and mMRC scores in patients

We found that there was no statistical difference in the CPIS and mMRC scores between two groups before treatment ($P > 0.05$). After treatment, the two scores decreased in both groups, but the scores of the EG were lower than those of the CG, with statistical differences (all $P < 0.05$, **Table 3**).

Changes of serum inflammatory factors in patients

We compared the serum inflammatory factors before and after treatment and found that there was no statistical difference in the concentrations of IL-6, TNF-α and CRP before treatment ($P > 0.05$). While after treatment, the three levels decreased, but those in the EG were lower, with statistical differences (all $P < 0.05$, **Figure 1**).

Comparison of medical bills

We counted the clearance treatment cost and total hospitalization expenses of two groups of

Table 2. Comparison of expectoration scores of patients

Group	Sputum score	
	Before treatment	After treatment
CG (n = 40)	3.50 ± 0.51	2.75 ± 0.81*
EG (n = 48)	3.58 ± 0.50	1.94 ± 0.78*
t value	0.696	4.778
p value	0.488	< 0.001

Note: *means P < 0.05 compared with before treatment.

Table 3. Changes of CPIS and mMRC scores

Group	CPIS score		mMRC score	
	Before treatment	After treatment	Before treatment	After treatment
CG (n = 40)	8.45 ± 1.51	7.20 ± 1.01*	3.33 ± 0.47	2.53 ± 0.51*
EG (n = 48)	8.54 ± 1.50	6.31 ± 1.09*	3.64 ± 0.48	1.91 ± 0.84*
t value	0.773	3.909	3.127	3.989
p value	0.284	< 0.001	0.002	< 0.001

Note: *means P < 0.05 compared with before treatment; EG, experimental group; CG, control group; CPIS, clinical pulmonary infection score; mMRC, dyspnea scale.

patients. It was found that the two in the CG were higher than those in the EG, with a statistical difference (all P < 0.05, **Figure 2**).

Incidence of adverse reactions in patients

The incidence of adverse reactions after treatment was statistically analyzed. The total incidence of adverse reactions revealed no statistical difference (P > 0.05, **Table 4**).

Analysis of risk factors for mortality of patients

The survival of patients one month after treatment were counted. Of the 88 patients, 11 died within one month, with a mortality of 12.5%. The clinical data were collected and assigned (**Table 5**) for analysis. Univariate Cox regression analysis manifested that treatment regimen (HR: 0.169, 95% CI: 0.037-0.782), age (HR: 7.045, 95% CI: 2.059-24.109) and diabetes (HR: 4.390, 95% CI: 1.164-16.561) were the risk factors of death (P < 0.05). Multivariate Cox regression analysis demonstrated that therapeutic regimens (HR: 0.139, 95% CI: 0.030-0.649) and age (HR: 5.554, 95% CI: 1.561-19.759) were independent risk factors for death (P < 0.05, **Tables 6**, **7**). In view of the analysis of Kmurm survival curve, the short-term survival of patients < 65 years old was improved by NIPPV combined with routine clearance therapy (**Figure 3**, P < 0.05). To verify the effectiveness of the two indicators in the short-term prognosis of patients, we also drew the ROC curve.

It revealed that the therapeutic regimens and the area under the age curve were more than 0.7, which could be used as an observational index to predict the short-term prognosis of patients (P < 0.05, **Figure 4**; **Table 8**).

Discussion

SAP is a common but severe complication in stroke patients. Research has revealed that sudden pneumonia has a high mortality [15]. Continuous sympathetic nerve excitement after stroke pneumonia easily reduces the immunity and clearance ability of local respiratory tract, leading to pulmonary edema, hypoxia, etc, [16]. Moreover, stroke patients are prone to the drop of protective reflex mechanism of swallowing dysfunction, the decrease of functional sensitivity of lower esophageal sphincter, cough reflex and swallowing damage, and the decline of coordination between respiratory and swallowing movements, all of which are the causes of pneumonia [17].

Clearance therapy is an essential clinical treatment for stroke pneumonia. It helps to discharge airway secretions and reduce and control related complications under drug and non-drug therapies [18]. Physical or mechanical means were adopted on the airflow to help the trachea and bronchus to expectorate, or induce cough to expectorate. For some elderly SAP patients, their own body function and immune function are reduced, and long-term bed rest leads to lung infection, which leads to an increase in respiratory power consumption, and finally shows as ineffective cough [19]. For those with ineffective cough, even if the sputum is drained to the central airway, patients are often unable to clear the sputum.

NIPPV can achieve an effective airway secretion drainage effect through reasonable setting of model and parameters [13]. We analyzed the

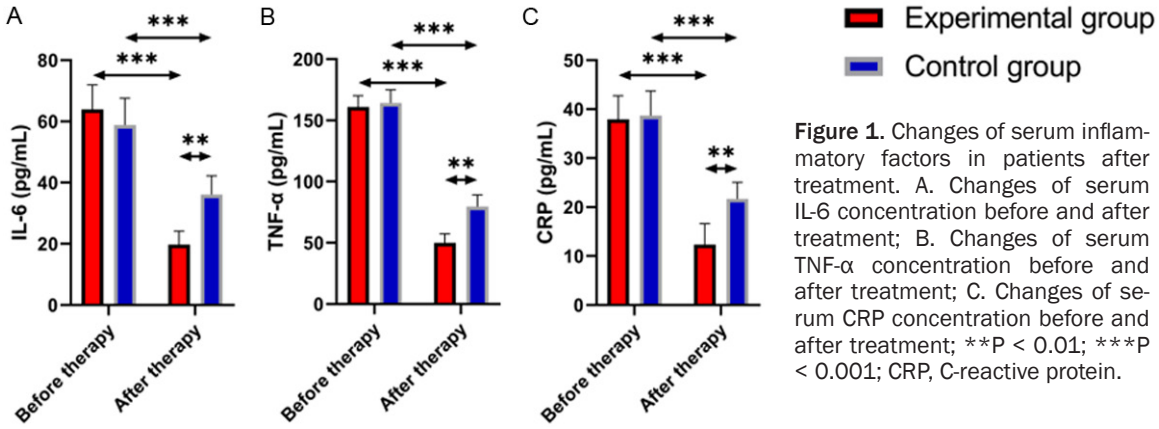

Figure 1. Changes of serum inflammatory factors in patients after treatment. A. Changes of serum IL-6 concentration before and after treatment; B. Changes of serum TNF-α concentration before and after treatment; C. Changes of serum CRP concentration before and after treatment; **P < 0.01; ***P < 0.001; CRP, C-reactive protein.

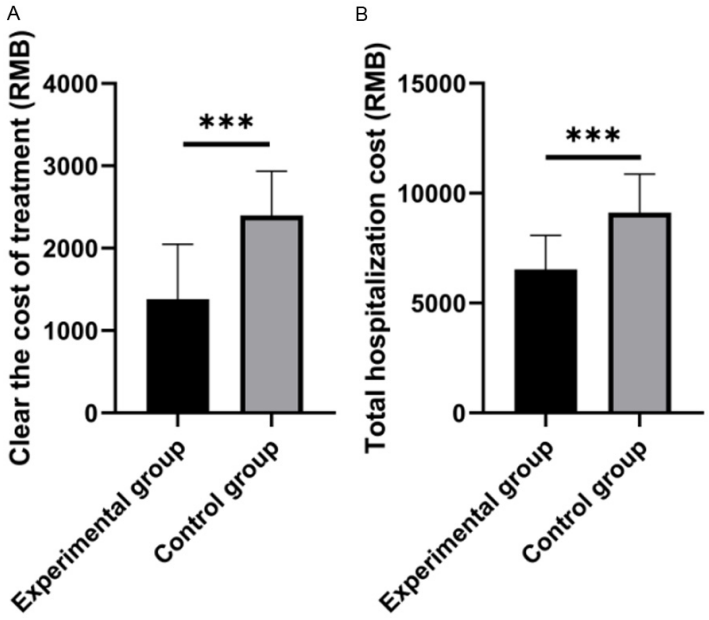

Figure 2. Clearance treatment and total hospitalization costs. A. Comparison of clearance treatment costs; B. Comparison of total hospitalization expenses; ***P < 0.001.

Table 4. Comparison of adverse reactions in patients

Group	Nausea and vomiting	Itchy skin	Headache and fatigue	Total incidence rate
CG (n = 40)	3 (7.50%)	2 (5.00%)	2 (5.00%)	17.50
EG (n = 48)	3 (6.25%)	1 (2.08%)	1 (2.08%)	10.42
χ^2 value				0.930
p value				0.335

Note: EG, experimental group; CG, control group.

application value and safety of NIPPV combined with clearance therapy in elderly SAP patients and found that the expectoration score of the EG was lower than that of the CG after treatment, which indicated that NIPPV could improve the effective expectoration of patients. Moreover, we also compared the CPIS and mMRC scores of two groups. CPIS, a scoring system combining clinical imaging and microbiology standards, was employed to assess the severity of infection and predict whether the patients could adjust or stop using antibiotics [20]. mMRC is a scoring scale used to evaluate patients' breathing condition, which can directly reflect their breathing capacity [21]. We found that the CPIS and mMRC scores in the CG were higher than those of EG after treatment, which indicated that NIPPV could improve respiratory function and reduce pulmonary infection. Besides, we also discovered that the IL-6, TNF-α and CRP concentrations in the EG were lower than those in the CG after treatment. The main reason is that combined therapy can improve the abnormal state of alveolar pressure and thoracic negative pressure, thus improving gas exchange. Furthermore, the absorption of inflammatory metabolites can be reduced by effectively removing airway secretions, reducing airway secretions and eliminating infection sources. What's more, we compared the treatment costs and adverse reactions between two groups of patients and discovered that the medical bills of patients in the EG were lower than those of CG, and there was no sta-

Table 5. Assignment table

Factor	Assignment
Age	≥ 65 years old = 0, < 65 years old = 1
Gender	Male = 0, Female = 1
Type of stroke	Cerebral infarction = 0, cerebral hemorrhage = 1, subarachnoid hemorrhage = 2
Diabetes	Yes = 1, No = 0
Hypertension	Yes = 1, No = 0
Smoking history	Yes = 1, No = 0
Alcoholism history	Yes = 1, No = 0
Hospital stays	It belongs to continuous variables, and the original data are used to replace the analysis
Therapeutic regimens	NIPPV and Routine clearance treatment = 1, routine clearance treatment = 0

Table 6. Univariate Cox regression analysis

Factor	Univariate analysis					
	β	SE	Wald	*p* value	HR value	95% CI
Age	1.952	0.628	9.676	0.002	7.045	2.059-24.109
Gender	0.845	0.627	1.819	0.177	2.329	0.682-7.956
Type of stroke	0.53	0.447	1.403	0.236	1.699	0.707-4.083
Diabetes	1.479	0.677	4.77	0.029	4.390	1.164-16.561
Hypertension	-0.266	0.627	0.18	0.671	0.766	0.224-2.618
Smoking history	0.622	0.677	0.845	0.358	1.863	0.494-7.024
Alcoholism history	0.135	0.782	0.03	0.863	1.144	0.247-5.295
Hospital stays	0.099	0.058	2.879	0.09	1.104	0.985-1.238
Therapeutic regimens	-1.778	0.782	5.171	0.023	0.169	0.037-0.782

Table 7. Multivariate Cox regression analysis

Factor	Multivariate analysis					
	β	SE	Wald	*p* value	HR value	95% CI
Age	1.715	0.647	7.012	0.008	5.554	1.561-19.759
Diabetes	1.324	0.701	3.563	0.059	3.759	0.950-14.863
Therapeutic regimens	-1.971	0.785	6.308	0.012	0.139	0.030-0.649

tistical difference in adverse reactions between them. This is mainly due to the long hospitalization time of patients in the CG, thus increasing medical bills. There is no difference in the incidence of adverse reactions between both groups, which shows that NIPPV combined with clearance therapy can not affect the increase of adverse reactions of patients, and it is safe.

In the end, we counted the deaths of patients one month after treatment and found that 11 of 88 patients died within one month, with a mortality of 12.5%, which is consistent with the research results of Gao and others [22, 23]. Cox regression analysis found that age was an independent factor affecting the death of patients. ROC curve further verified that the two indicators had high clinical value in predicting short-term survival of patients. Cox regression analysis manifested that the treatment plan and age were independently relevant to death. For the elderly patients, the decline of organ function and the weakening of immune ability bring about the decline of resistance and the increase of susceptibility to pathogens, thus increasing the risk of infection. We first found that NIPPV combined with clearance therapy could improve the prognosis of elderly SAP patients, which is worthy of clinical promotion.

NIPPV combined with clearance therapy can relieve SAP in the elderly. Nevertheless, there

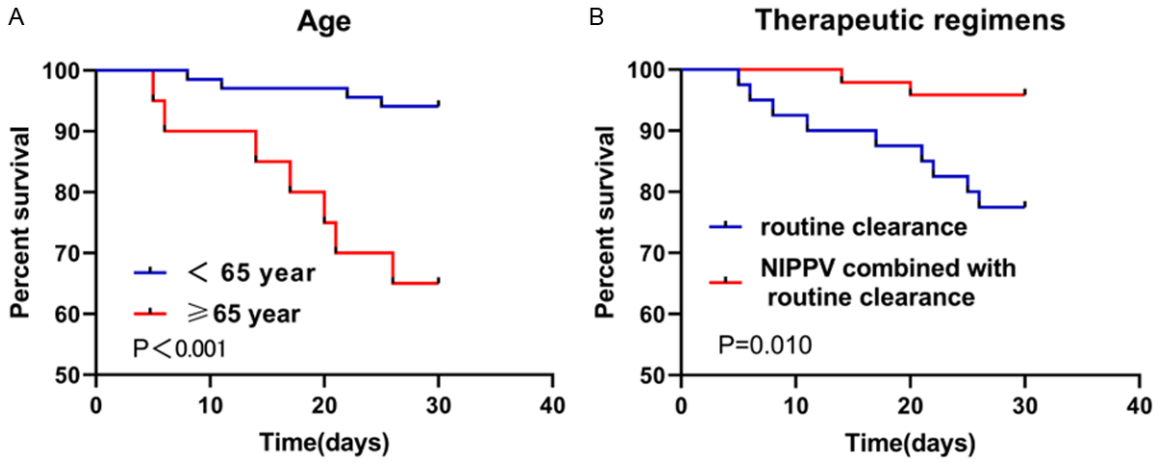

Figure 3. Relationship between age, therapeutic regimens and short-term survival of patients. A. Analysis of relationship between age and short-term survival time of patients by K-M test; B. Analysis of relationship between treatment regimen and short-term survival time of patients by Kmurm test.

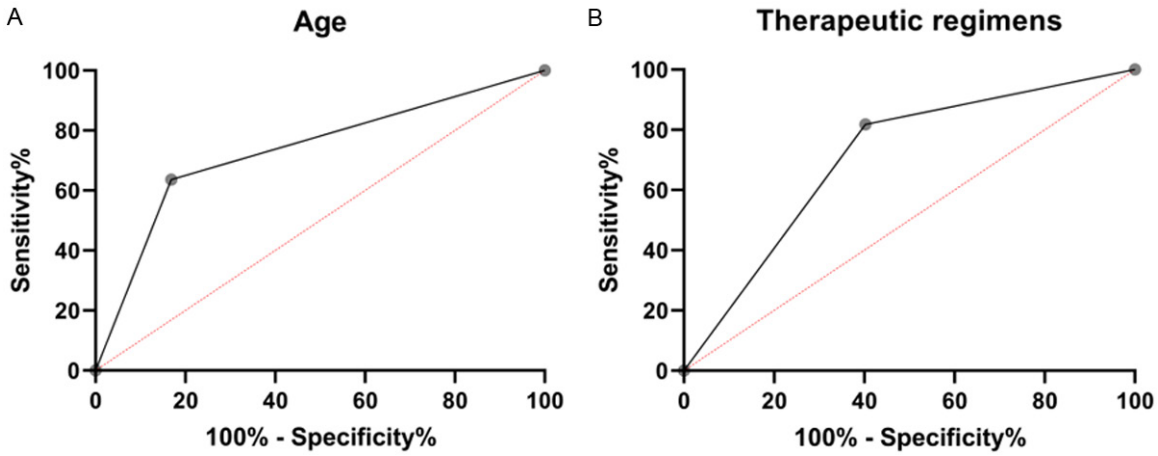

Figure 4. Clinical value of age and treatment regimens in predicting short-term survival of patients. A. Clinical value of age in predicting short-term survival of patients; B. Clinical value of treatment regimen in predicting short-term survival of patients.

Table 8. ROC curve index parameters

Factor	AUC	95% CI	*p* value	Specificity	Sensitivity	Youden index
Age	0.734	0.558-0.909	0.013	83.12%	63.64%	46.75%
Therapeutic regimens	0.708	0.555-0.860	0.026	59.74%	81.82%	41.56%

are still some limitations. First of all, in this retrospective study, the sample size is small which may affect the reliability of research results. Secondly, we have not followed up patients for a long time, and it is still vague whether the treatment plan will affect their long-term survival. Thus, we hope to collect more samples in the follow-up research to improve our research conclusions.

To sum up, NIPPV combined with routine clearance is effective for elderly SAP patients, which can shorten the treatment time and reduce the expenses. Hence, it is worthy of promotion.

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Disclosure of conflict of interest

None.

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