Factors influencing the therapeutic failure of high-flow nasal cannula oxygen humidification in patients with interstitial pneumonia complicated by respiratory failure

W.-P. ZHAO[1], W. ZHANG[2], J.-P. LI[3], L.-L. QU[3]

[1]Nursing Department, The First People's Hospital of Baiyin City, Gansu Province, Baiyin City, Gansu Province, China
[2]Department of Respiratory Medicine, The First People's Hospital of Baiyin City, Gansu Province, Baiyin City, Gansu Province, China
[3]Respiratory and Critical Care Medical Center Department, The First People's Hospital of Baiyin City, Gansu Province, Baiyin City, Gansu Province, China

Wenping Zhao and Wei Zhang participated equally as co-first authors
Jiping Li and Leilei Qu participated equally as co-corresponding authors

Abstract. – OBJECTIVE: The aim of this study was to explore the factors influencing the treatment failure of high-flow nasal cannula (HFNC) therapy in patients with interstitial pneumonia (IP) complicated by respiratory failure.

PATIENTS AND METHODS: A total of 158 patients with IP and respiratory failure treated with HFNC in our hospital from January 2020 to August 2023 were selected as the study population. Based on treatment efficacy, they were categorized into the HFNC treatment failure group and the HFNC treatment success group. Clinical data were compared between the two groups. Multiple logistic regression analysis was employed to identify independent factors influencing treatment failure, and the predictive value of these factors for HFNC treatment failure was assessed using receiver operating characteristic (ROC) curve analysis.

RESULTS: After 7 days of HFNC treatment, among the 158 patients with IP and respiratory failure, 25 (15.8%) declared treatment failure, while the remaining 133 (84.2%) showed treatment success. Patients in the HFNC treatment failure group had significantly higher age, duration of IP, pre-treatment respiratory rate, C-reactive protein (CRP), and controlling nutritional status (CONUT) scores compared to the HFNC treatment success group. The PaO_2/FiO_2 ratio, left ventricular ejection fraction, and Glasgow Coma Scale (GCS) were significantly lower in the HFNC treatment failure group ($p<0.05$). Multiple logistic regression analysis revealed that pre-treatment PaO_2/FiO_2 ratio, CRP, CONUT, and GCS scores were independent factors influencing HFNC treatment failure in patients with IP and respiratory failure ($p<0.05$). Lower PaO_2/FiO_2 ratio and GCS scores, and higher CRP and CONUT scores were associated with an increased risk of HFNC treatment failure. ROC curve analysis indicated that pre-treatment PaO_2/FiO_2 ratio, CRP, CONUT, and GCS scores in patients with IP and respiratory failure had a high predictive value for HFNC treatment failure ($p<0.05$).

CONCLUSIONS: The HFNC failure rate in patients with IP and respiratory failure is 15.8%. Pre-treatment PaO_2/FiO_2 ratio, CRP, CONUT, and GCS scores are independent factors associated with HFNC treatment failure and warrant clinical attention.

Key Words:
High-flow nasal cannula, Interstitial pneumonia, Respiratory failure.

Introduction

Interstitial pneumonia (IP) refers to a disease caused by various factors, leading to inflammation and fibrosis in the lung interstitium, bronchi, and alveolar sacs. It is characterized by symptoms such as cough, fever, shortness of breath, fatigue, and weight loss. Inflammation often involves alveolar epithelial cells, endothelial cells of capillaries, basal membrane, and tissues around blood vessels and lymphatic vessels. Ultimately, it results in fibrosis of the lung interstitium, affecting gas exchange between alveoli and capillaries, posing a life-threatening risk with a poor

Corresponding Author: Leilei Qu, MD; e-mail: 13893095721@163

prognosis. Oxygen therapy is often required to improve respiratory function, and the diagnosis and treatment of IP have been a focus of clinical research[1-5].

A high-flow nasal cannula (HFNC) is a novel, non-invasive respiratory support method that provides high-flow, warmed, and humidified oxygen to patients through a non-sealed nasal cannula. It aims to maintain blood oxygen concentration, improve respiratory conditions, and has advantages such as easy operation and good patient comfort. Its application has become increasingly widespread, demonstrating better efficacy in improving the overall prognosis of patients with respiratory failure compared to traditional oxygen therapy[6-10]. However, some patients do not respond well to treatment, and symptoms such as low oxygen levels, cough, and respiratory distress do not significantly improve. In such cases, endotracheal intubation and mechanical ventilation may be required, delaying the timing of treatment and affecting the prognosis. Therefore, analyzing the factors influencing HFNC treatment failure is crucial for guiding clinical treatment strategies. This study retrospectively analyzed 158 cases of IP patients with concomitant respiratory failure treated with HFNC in our hospital from January 2020 to August 2023, exploring the factors influencing HFNC treatment failure.

Patients and Methods

Patients

A total of 158 IP patients with concomitant respiratory failure treated with HFNC from January 2020 to August 2023 were selected as the study subjects. Inclusion criteria: (1) thin-section lung CT suggesting IP, pulmonary function tests indicating restrictive ventilatory dysfunction, and patients presenting symptoms such as cough and respiratory distress, suggesting the acute exacerbation of IP; (2) arterial partial pressure of O_2 (PaO_2)<60 mmHg, and arterial partial pressure of CO_2 ($PaCO_2$) normal, indicating type I acute respiratory failure, requiring oxygen therapy to improve ventilation. Exclusion criteria: (1) history of lung surgery or concomitant respiratory system diseases such as pulmonary embolism, malignant lung tumors, and pulmonary tuberculosis; (2) critical condition with an expected survival period of less than 30 days; (3) severe liver or kidney dysfunction, severe infection, or other serious diseases involving other organs.

Methods

All patients received symptomatic supportive treatment, including anti-inflammatory, antitussive, and expectorant therapy, after the diagnosis of IP with concomitant respiratory failure was confirmed. At the same time, HFNC treatment was implemented using the high-flow respiratory humidification apparatus (HUMID-BM) provided by Respircare (Shenzhen, China). The gas temperature was set at 37°C with 100% relative humidity, and the oxygen flow rate was adjusted to around 38 L/min. The inhaled oxygen concentration was controlled at around 40%, and relevant parameters were adjusted promptly based on vital signs, blood gas analysis, and other results. The treatment was planned to last for 7 days for efficacy evaluation. If patients experienced hemodynamic instability, worsening infection, and respiratory distress, or if the ratio of PaO_2 to the fraction of inspired oxygen (FiO_2) fell below 100, indicating worsening condition, mechanical ventilation treatment was considered, and these cases were classified as the HFNC treatment failure group, while the remaining patients were classified as the HFNC treatment success group.

Clinical data, including gender, age, smoking history, duration of IP, heart rate (HR), respiratory rate (RR), $PaCO_2$, PaO_2/FiO_2 ratio, left ventricular ejection fraction (LVEF), C-reactive protein (CRP), Controlling Nutritional Status (CONUT) score, and Glasgow Coma Scale (GCS), were collected and compared between the HFNC treatment failure group and the HFNC treatment success group.

Statistical Analysis

SPSS 28.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Normally distributed measurement data (such as age, duration of IP, HR, RR) were expressed as mean ± standard deviation. Independent sample *t*-tests were used to compare measurement data between the HFNC treatment failure group and the HFNC treatment success group. Enumeration data (such as gender and smoking history) were expressed as the number of cases and percentages, and Chi-square tests were used to compare enumeration data between the two groups. Multifactorial logistics regression analysis was employed to identify independent factors influencing HFNC treatment failure. The receiver operating characteristic (ROC) curve was used to evaluate the predictive value of parameters for HFNC treatment failure, with the area under the curve (AUC) indicating a higher predictive value. Sensitivity, specificity, positive predictive value, and negative predictive value were derived from the AUC. A p-value <0.05 was considered statistically significant.

Results

Comparison of Clinical Data Between HFNC Treatment Failure Group and HFNC Treatment Success Group

Among the 158 IP patients with concomitant respiratory failure, after 7 days of HFNC treatment, 25 patients (15.8%) were declared treatment failure and required mechanical ventilation, while the remaining 133 patients (84.2%) had successful treatment. As shown in Table I, patients in the HFNC treatment failure group had significantly higher age, duration of IP, RR before treatment, CRP, and CONUT score, and significantly lower PaO_2/FiO_2 ratio, LVEF, and GCS score compared to the HFNC treatment success group ($p<0.05$).

Multifactorial Logistics Regression Analysis of HFNC Treatment Failure in IP Patients with Concomitant Respiratory Failure

As shown in Table II, multifactorial logistics regression analysis results indicated that the PaO_2/FiO_2 ratio before treatment, CRP, CONUT, and GCS score were independent factors influencing HFNC treatment failure in IP patients with concomitant respiratory failure ($p<0.05$). The lower the PaO_2/FiO_2 ratio and GCS score, and the higher the CRP and CONUT scores, the higher the risk of HFNC treatment failure.

Predictive Value of PaO_2/FiO_2 Ratio, CRP, CONUT, and GCS Score for HFNC Treatment Failure in IP Patients with Concomitant Respiratory Failure

As shown in Table III, ROC curve analysis results indicated that the PaO_2/FiO_2 ratio, CRP, CONUT, and GCS score before treatment in IP patients with concomitant respiratory failure had a high predictive value for HFNC treatment failure ($p<0.05$).

Discussion

Interstitial pneumonia (IP) is an inflammatory disease primarily affecting the lung interstitium, including parts between alveolar epithelial cells and the basal layer of endothelial cells. IP is a highly heterogeneous disease with unclear etiology and pathogenesis, possibly related to drugs, external environment, granulomatous diseases, connective tissue diseases, viral infections, and other factors. It is characterized by inflammation and fibrosis in the lung interstitium, often

Table I. Comparison of clinical data between the HFNC treatment failure group and HFNC treatment success group.

Group	Male [n (%)]	Age	Smoking history [n (%)]	IP duration	Heart rate (beats/min)	Respiratory rate (breaths/min)
HFNC treatment Failure group (n=25)	15 (60.0)	65.69±8.03	15 (60.0)	42.50±6.23	102.26±10.23	30.83±3.36
HFNC treatment Success group (n=133)	85 (63.9)	62.28±6.98	66 (49.6)	40.09±5.09	98.90±9.39	29.03±3.98
$\chi^2/t/Z$	0.139	2.187	0.907	2.093	1.618	2.122
p	0.710	0.030	0.341	0.038	0.108	0.035
Group	**$PaCO_2$ (mmHg)**	**PaO_2/FiO_2 Ratio**	**LVEF (%)**	**CRP (mg/L)**	**CONUT score**	**GCS score**
HFNC treatment Failure group (n=25)	37.53±2.26	188.63±19.36	49.28±6.69	36.69±8.03	6.38±2.03	12.26±1.69
HFNC treatment Success group (n=133)	37.06±2.08	198.69±17.96	53.32±8.06	30.89±6.98	4.26±1.56	13.09±1.08
$\chi^2/t/Z$	1.022	2.538	2.356	3.720	5.926	3.136
p	0.308	0.012	0.020	<0.001	<0.001	0.002

High-flow nasal cannula (HFNC), C-reactive protein (CRP), Glasgow Coma Scale (GCS), controlling nutritional status (CONUT), left ventricular ejection fraction (LVEF).

Table II. Multifactor logistic regression analysis results.

Factor	Coefficient	Standard error	Odds ratio	95% confidence interval	Wald χ^2 value	*p*-value
PaO_2/FiO_2 ratio	-0.108	0.053	0.898	0.809 to 0.996	4.121	0.042
CRP (mg/L)	0.806	0.335	2.239	1.161 to 4.317	5.789	0.016
CONUT score	1.629	0.589	5.098	1.607 to 16.172	7.648	0.006
GCS score	-0.402	0.156	0.669	0.493 to 0.908	6.640	0.010

C-reactive protein (CRP), Glasgow Coma Scale (GCS), controlling nutritional status (CONUT).

Table III. ROC curve analysis results.

Indicator	AUC	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Youden's index
PaO_2/FiO_2 ratio	0.706	76.0	87.2	61.3	95.1	0.632
CRP (mg/L)	0.769	84.0	84.2	63.6	96.6	0.682
CONUT score	0.856	88.0	92.5	64.7	97.6	0.805
GCS score	0.823	92.0	87.2	65.7	98.3	0.792

C-reactive protein (CRP), Glasgow Coma Scale (GCS), controlling nutritional status (CONUT), area under the curve (AUC).

irreversible, affecting the gas exchange process and causing progressively worsening dyspnea. Patients may experience reduced exercise tolerance, imposing a heavy burden on both patients and their families. Some patients may experience acute exacerbation of the condition due to factors such as respiratory tract infections, leading to hypoxemia and, in severe cases, acute respiratory failure, threatening the patient's life. Timely respiratory support is essential for improving the prognosis[11-13]. For patients with acute respiratory failure, non-invasive ventilation techniques such as nasal cannulas or masks are commonly used in clinical practice for oxygen therapy, aiming to correct respiratory function and improve prognosis. However, it is observed that some patients cannot tolerate or refuse traditional respiratory support techniques such as masks or nasal cannulas due to facial skin damage, eye irritation symptoms, claustrophobia, or inconvenience in daily life, limiting their clinical application. On the other hand, invasive mechanical ventilation is more traumatic and is considered a last resort.

In recent years, High-Flow Nasal Cannula (HFNC) therapy has gained widespread clinical use. HFNC is a novel and simplified respiratory support method, providing high-flow, heated, and humidified oxygen by adjusting relevant parameters. It delivers a constant and appropriate oxygen concentration through nasal prongs, with a soft and comfortable interface, making it highly tolerated. HFNC is applicable to patients with respiratory failure caused by various diseases, reducing respiratory resistance, work of breathing, and frequency while alleviating respiratory distress and improving the oxygenation index. A retrospective study by Omote et al[14] indicated that both HFNC and non-invasive positive pressure ventilation could improve oxygenation in patients with interstitial pneumonia and acute respiratory failure. HFNC, compared to non-invasive positive pressure ventilation, was more effective in increasing mean arterial pressure and decreasing APACHE II scores. However, there was no significant difference in the intubation rate on the 30th day between the two methods. Multifactorial analysis suggested that HFNC independently influenced patient mortality within 30 days. Nevertheless, HFNC is not the ultimate means of non-invasive oxygen therapy. Ineffectiveness may still be observed in some patients, and ultimately, tracheal intubation and mechanical ventilation are required to improve oxygenation. The delayed timing of tracheal intubation in these cases may adversely affect prognosis. Therefore, accurately predicting the efficacy of HFNC before implementation is crucial for devising effective clinical treatment strategies. This study aimed to analyze the factors influencing the failure of HFNC therapy in patients with IP and respiratory failure, providing a reference for the clinical application of HFNC. Univariate analysis showed that HFNC treatment failure was associated with age, duration of IP, respiratory rate before treatment (RR), C-reactive protein (CRP), CONUT score, PaO_2/FiO_2 ratio before treatment, left ventricular ejection fraction (LVEF), and Glasgow Coma Scale (GCS) score. Further multifactorial logistic regression analysis revealed that the PaO_2/FiO_2 ratio, CRP, CONUT score, and GCS score before treatment were independent factors influencing HFNC treatment failure ($p<0.05$). ROC curve analysis demonstrated that the PaO_2/FiO_2 ratio, CRP, CONUT score, and GCS score before treatment in IP patients with respiratory failure had high predictive value for HFNC treatment failure ($p<0.05$).

The PaO_2/FiO_2 ratio, also known as the oxygenation index, is the most commonly used indicator in clinical practice to assess respiratory function and blood oxygen levels in oxygen-receiving populations. It effectively reflects the degree of hypoxia and lung damage. IP induces varying degrees of damage to the alveoli and lung parenchyma, leading to insufficient ventilation and affecting the exchange of oxygen and carbon dioxide. Severe cases may result in hypoxemia and acute respiratory failure. This study found that the lower the PaO_2/FiO_2 ratio before HFNC treatment, the higher the risk of HFNC treatment failure. This suggests that the PaO_2/FiO_2 ratio can serve as an effective predictive indicator of HFNC efficacy. Patients with a lower PaO_2/FiO_2 ratio have poorer oxygenation, worse gas exchange function in the lungs, and relatively more fatigue in the respiratory muscles; a higher risk of correcting hypoxemia is difficult, increasing the risk of HFNC ineffectiveness. CRP is one of the most commonly used inflammatory markers in clinical practice and a crucial indicator reflecting the body's infection status. For IP patients with acute respiratory failure, inflammation and fibrosis in the pulmonary interstitium may lead to respiratory tract infections. Infections increase the secretion of inflammatory substances in the respiratory tract, worsening the condition and promoting the progression of interstitial inflammation and fibrosis. This results in poorer lung function, thereby affecting the efficacy of HFNC oxygen therapy. Therefore, patients with acute respiratory tract infections should receive antibiotic treatment based on susceptibility results, and controlling infections can further improve the respiratory support effect of HFNC, reduce the risk of treatment failure, and improve prognosis. The CONUT score is a novel nutritional assessment tool that relies on three commonly used indicators – serum albumin (Alb), total cholesterol (TC), and total peripheral lymphocyte count – to evaluate the nutritional status of patients. These three indicators represent protein reserves, immune-inflammatory status, and energy consumption. The assessment method is simple and objective, with high clinical applicability, assisting in screening patients for nutritional risk, and being associated with the prognosis of various respiratory system diseases[15-20]. This study demonstrated that the higher the CONUT score, the higher the risk of HFNC treatment failure in IP patients with respiratory failure. This may be due to the association between nutritional status and the strength of respiratory muscles. Malnourished patients are more likely to experience respiratory muscle fatigue, affecting the structure and function of respiratory muscles. Therefore, in clinical practice, attention should be paid not only to respiratory function but also to the presence and degree of malnutrition in patients. Implementing appropriate nutritional support can help reduce the breakdown metabolism rate, alleviate negative nitrogen balance, and assist in improving respiratory function. Additionally, this study found that the consciousness status of IP patients with respiratory failure is also related to the efficacy of HFNC. The lower the GCS score, the higher the risk of HFNC treatment failure. This may be because patients with impaired consciousness have a weaker ability to expectorate autonomously and weaker cough reflexes, making them more prone to risks such as sputum accumulation and obstruction of the airway behind the tongue. Their lung ventilation function is relatively weaker, affecting the efficacy of HFNC.

Conclusions

In summary, the failure rate of HFNC in IP patients with respiratory failure is 15.8%. The PaO_2/FiO_2 ratio, CRP, CONUT score, and GCS score before treatment are independent factors influencing HFNC treatment failure and deserve clinical attention.

Conflict of Interest
The authors have no conflict of interest to declare.

Ethics Approval

This study has been approved by the Ethics Committee of The First People's Hospital of Baiyin City, with the approval number YL-KY-2022-013. All research activities were conducted in accordance with the international ethical standards and Helsinki Declaration.

Informed Consent

Patients were involved in the study after signing the informed consent.

Funding

This research was funded by Baiyin City's Science and Technology Programme, grant number 2023-1-36Y.

ORCID ID

Wenping Zhao: 0009-0009-1054-0872
Wei Zhang: 0009-0008-8674-6132
Jiping Li: 0009-0001-8067-0447
Leilei Qu: 0009-0001-6194-1598

References

1) Manfredi A, Luppi F, Cassone G, Vacchi C, Salvarani C, Sebastiani M. Pathogenesis and treatment of idiopathic and rheumatoid arthritis-related interstitial pneumonia. The possible lesson from COVID-19 pneumonia. Expert Rev Clin Immunol 2020; 16: 751-770.
2) Case AH, Beegle S, Hotchkin DL, Kaelin T, Kim HJ, Podolanczuk AJ, Ramaswamy M, Remolina C, Salvatore MM, Tu C, de Andrade JA. Defining the pathway to timely diagnosis and treatment of interstitial lung disease: a US Delphi survey. BMJ Open Respir Res 2023; 10: e001594.
3) Turgeon D, Balter MS, Pagnoux C. Interstitial lung disease in patients with anti-neutrophil cytoplasm antibody-associated vasculitis: an update on pathogenesis and treatment. Curr Opin Pulm Med 2023; 29: 436-442.
4) De Souza FHC, De Araújo DB, Hoff LS, Baldi BG, Faria MSMS, Da Rocha Junior LF, Da Silva LRS, Behrens Pinto GL, Bezerra MC, Miossi R, Cordeiro RA, Shinjo SK. Diagnosis and treatment of interstitial lung disease related to systemic autoimmune myopathies: a narrative review. Reumatismo 2023; 75.
5) Fisher DA, Murphy MC, Montesi SB, Hariri LP, Hallowell RW, Keane FK, Lanuti M, Mooradian MJ, Fintelmann FJ. Diagnosis and Treatment of Lung Cancer in the Setting of Interstitial Lung Disease. Radiol Clin North Am 2022; 60: 993-1002.
6) Zhou Y, Shi X, Pu Z, Liu A. Clinical effect of high-flow nasal cannula oxygen therapy combined with naloxone on severe respiratory failure in older adult patients: a randomized controlled trial. Am J Transl Res 2023; 15: 6613-6620.
7) Yan L, Lu Y, Deng M, Zhang Q, Bian Y, Zhou X, Hou G. Efficacy of high-flow nasal cannula in patients with acute heart failure: a systematic review and meta-analysis. BMC Pulm Med 2023; 23: 476.
8) Zhao Z, Chang MY, Zhang T, Gow CH. Monitoring the Efficacy of High-Flow Nasal Cannula Oxygen Therapy in Patients with Acute Hypoxemic Respiratory Failure in the General Respiratory Ward: A Prospective Observational Study. Biomedicines 2023; 11: 3067.
9) Le Pape S, Savart S, Arrivé F, Frat JP, Ragot S, Coudroy R, Thille AW. High-flow nasal cannula oxygen versus conventional oxygen therapy for acute respiratory failure due to COVID-19: a systematic review and meta-analysis. Ann Intensive Care 2023; 13: 114.
10) Weinreich UM, Burchardt C, Huremovic J. The effect of domiciliary high flow nasal cannula treatment on dyspnea and walking distance in patients with interstitial lung disease - A pilot study. Chron Respir Dis 2022; 19: 14799731221137085.
11) Clark KP, Degenholtz HB, Lindell KO, Kass DJ. Supplemental Oxygen Therapy in Interstitial Lung Disease: A Narrative Review. Ann Am Thorac Soc 2023; 20: 1541-1549.
12) Viani M, Ventura V, Bianchi F, d'Alessandro M, Bergantini L, Sestini P, Bargagli E. Oxygen Therapy during Exercise in Patients with Interstitial Lung Diseases. Biomolecules 2022; 12: 717.
13) Cuerpo S, Palomo M, Hernández-González F, Francesqui J, Albacar N, Hernández C, Blanco I, Embid C, Sellares J. Improving home oxygen therapy in patients with interstitial lung diseases: application of a noninvasive ventilation device. Ther Adv Respir Dis 2020; 14: 1753466620963027.
14) Omote N, Matsuda N, Hashimoto N, Nishida K, Sakamoto K, Ando A, Nakahara Y, Nishikimi M, Higashi M, Matsui S, Hasegawa Y. High-flow nasal cannula therapy for acute respiratory failure in patients with interstitial pneumonia: a retrospective observational study. Nagoya J Med Sci 2020; 82: 301-313.
15) Lee SC, Lee JG, Lee SH, Kim EY, Chang J, Kim DJ, Paik HC, Chung KY, Jung JY. Prediction of postoperative pulmonary complications using preoperative controlling nutritional status (CONUT) score in patients with resectable non-small cell lung cancer. Sci Rep 2020; 10: 12385.
16) Cai YS, Li XY, Ye X, Li X, Fu YL, Hu B, Li H, Miao JB. Preoperative controlling nutritional status score (CONUT) predicts postoperative complications of patients with bronchiectasis after lung resections. Front Nutr 2023; 10: 1000046.
17) Li L, Wang Y, Yang P, Xu L, Liu S, Zhang S, Weng X. Correlation of the controlling nutritional status score and the prognostic nutritional index with the prognosis of patients treated with radiotherapy for small-cell lung cancer. Ann Palliat Med 2021; 10: 11635-11642.

18) Peng J, Hao Y, Rao B, Cao Y. Prognostic impact of the pre-treatment controlling nutritional status score in patients with non-small cell lung cancer: A meta-analysis. Medicine (Baltimore) 2021; 100: e26488.

19) Ohba T, Takamori S, Toyozawa R, Nosaki K, Umeyama Y, Haratake N, Miura N, Yamaguchi M, Taguchi K, Seto T, Shimokawa M, Takenoyama M. Prognostic impact of the Controlling Nutritional Status score in patients with non-small cell lung cancer treated with pembrolizumab. J Thorac Dis 2019; 11: 3757-3768.

20) Toyokawa G, Kozuma Y, Matsubara T, Haratake N, Takamori S, Akamine T, Takada K, Katsura M, Shimokawa M, Shoji F, Okamoto T, Maehara Y. Prognostic impact of controlling nutritional status score in resected lung squamous cell carcinoma. J Thorac Dis 2017; 9: 2942-2951.