Endobronchial Therapy With Gentamicin and Dexamethasone After Airway Clearance by Bronchoscopy in Exacerbation of Non-cystic Fibrosis Bronchiectasis: a Real-world Observational Study

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Abstract

Purpose To retrospectively analyze the clinical efficacy and safety of endobronchial therapy with gentamicin and dexamethasone after airway clearance (AC) by bronchoscopy in exacerbation of non-cystic fibrosis bronchiectasis.

Methods We retrospectively reviewed 2156 patients with bronchiectasis between January 2015 and June 2016, and 367 consecutive patients with exacerbation of bronchiectasis who had complete data and underwent AC by bronchoscopy. The final cohort included 181 cases of intratracheal instillation with gentamicin and dexamethasone after AC (a group with airway drugs, named Drug group) and 186 cases of AC only (a group without airway drugs, named Control group). The last follow-up was on June 30, 2017.

Results The total cough score and the total symptom score in the Drug group were improved compared to the Control group during exacerbation and three months after discharge ($P < 0.001$). Re-examination of chest HRCT within 4–6 months after discharge revealed that the extent of mucous plugging, collapse/consolidation, and the Bhalla score were all significantly improved in the Drug group. Moreover, the re-exacerbations in the Drug group were significantly decreased within one year after discharge. Univariate analysis showed a highly significant prolongation of the time to first re-exacerbation in bronchiectasis due to treatment with airway drugs compared without. Multivariate Cox regression analysis showed that the risk of first re-exacerbation in the Drug group decreased by 29.7% compared with the Control group.

Conclusions Endobronchial therapy with gentamicin and dexamethasone after AC by bronchoscopy is a safe and effective method for non-cystic fibrosis bronchiectasis.

Trial registration <http://www.chictr.org.cn>. No.: ChiCTR1900022247.

Introduction

Non-cystic fibrosis bronchiectasis is a chronic suppurative and inflammatory lung disease of diverse etiology characterized by pathological and irreversible dilatation of the bronchial tree [1]. The impairment of the mucociliary clearance, which results from the chronic airway inflammation, may cause long-term colonization or recurrent infection of bacteria, especially *Pseudomonas Aeruginosa* (PA), while bacterial colonization and recurrent infection can aggravate airway inflammation [2]. Sputum retention caused by impairment of mucociliary clearance can result in mucous plugs, which in turn contribute to airflow obstruction and dyspnea [3]. Clinically, the major manifestations of bronchiectasis are chronic cough with purulent sputum, dyspnea, and fatigue that may diminish the patients' quality of life [4, 5]. The frequency of exacerbation and the decline in lung function may lead to poor prognosis in bronchiectasis [6]. The number of exacerbations in patients with bronchiectasis is 1.8 per year (SD, 1.4), with a hospitalization rate from 26.6–40.4% [7]. Therefore, the expected mortality rate in patients with bronchiectasis is more than twice as high as that in healthy people [6].

The purpose of bronchiectasis management is to reduce exacerbation, prevent complications, and improve quality of life [1]. Long-term nebulized gentamicin can reduce the bacterial burden in the airways, decrease sputum production, attenuate lung function decline, and reduce acute pulmonary exacerbations without nephrotoxicity or ototoxicity [8]. Yet, some patients may have bronchospasm, dyspnea, and chest pain, and may not tolerate long-term nebulized antibiotics [9, 10]. Dexamethasone is one of the most common glucocorticoids, which can inhibit expression levels of inflammatory factors in the airway and reduce the secretion of airway mucus [11]. Nimmo *et al* investigated the pulmonary deposition of dexamethasone after intratracheal instillation by using radiolabelled dexamethasone in the Survanta mixture [12]. They found that the instilled dexamethasone was well distributed throughout all four lobes of the lungs. A similar distribution of dexamethasone was observed when using saline as the vehicle. Topical administration could also reduce the systemic side effects. Based on these researches, we have found that endobronchial therapy with gentamicin and dexamethasone after airway clearance (AC) by bronchoscopy in exacerbation of non-cystic fibrosis bronchiectasis could alleviate the severity of bronchiectasis, and reduce the occurrence of exacerbations without any obvious side events after many years of exploration in clinical practice. In the current study, we retrospectively reviewed the diagnosis and treatment of 367 patients with exacerbation of bronchiectasis in order to preliminarily evaluate the efficacy and safety of this method.

Materials And Methods

Patients

Data from patients with exacerbation of bronchiectasis who underwent AC by bronchoscopy were retrospectively collected from inpatients at the Shanghai Pulmonary Hospital (Shanghai, China) between January 1, 2015 and June 30, 2016. The last follow-up was performed on June 30, 2017.

The inclusion criteria were as follows: patients with bronchiectasis confirmed by chest high resolution CT (HRCT); patients needing antibiotic treatment at hospital due to exacerbation [13]; patients who underwent AC by bronchoscopy at the hospital. Exclusion criteria were: the presence of cystic pulmonary fibrosis; patients with active pulmonary tuberculosis; those awaiting surgery; patients who underwent interventional therapy

for hemoptysis; those with allergic bronchopulmonary aspergillosis (ABPA); patients who did not have bronchoscopy for different reasons or combined with lung cancer.

In the Drug group (a group with airway drugs), pre-heating of 0.9% physiological saline to 37°C (2ml, Otsuka Pharmaceutical Co. Ltd) with gentamicin sulfate (80000U/2ml, Yichang renfu pharmaceutical Co. LTD) and dexamethasone sodium phosphate injection was performed (5mg/1ml, Guangzhou Baiyunshan Tianxin Pharmaceutical Co. Ltd). Topical intrabronchial therapy was administered by using the above saline, gentamicin, and dexamethasone after AC by bronchoscopy. The patients from the Control group (the group without airway drugs)-just underwent AC by bronchoscopy.

Interventions

All patients received routine treatment, such as anti-inflammation and symptomatic treatment at the hospital, and they all signed informed consent before bronchoscopy. After the airway mucus was removed, the local intra-bronchia was irrigated by 10-20ml 37°C 0.9% physiological saline, after which the bronchoalveolar lavage fluid was retrieved for testing. According to the amount of mucus in the airway, appropriate irrigation can be carried out repeatedly. There were no other drugs in the bronchus of the Control group. The mixture of gentamicin, dexamethasone, and saline was infused according to the region of the lesion in the Drug group, e.g., in the bifurcation region of bronchus of localized bronchiectasis, in the bifurcation region of upper (include lingular segment) or lower lobe (include right middle lobe) of bronchus on one side or both side depending on unilateral or bilateral diffuse bronchiectasis. An electrocardiogram monitor instrument was used during and after the operation and to observe the presence of adverse events.

Assessments

We collected the hospitalization data (as baseline data) of patients during exacerbation of bronchiectasis, including age, gender, smoking history, body mass index (BMI), duration of bronchiectasis, past medical history and complications, clinical symptoms, blood routine test, arterial blood gas, microbial culture results of sputum and alveolar lavage fluid, pulmonary function, and chest HRCT. The follow-up data included the clinical symptoms at 3 months after discharge, the chest HRCT within 4 to 6 months after discharge, the numbers of exacerbation within 12 months after discharge, and the time to first re-exacerbation and the use of antibiotics after discharge. The clinical symptom score scale of bronchiectasis were developed according to the domestic and foreign literatures [14-16] (**Supplementary Table 1**). The chest HRCT was independently reviewed by two experienced radiologists, and the severity of the bronchiectasis was graded by the Bhalla scoring system [17,18] (**Supplementary Table 2**). The cumulative months of oral and intravenous antibiotics were recorded within 1 year after discharge.

Statistical analysis

The measurement data were all expressed by mean±SD (standard deviation), and the counting data were expressed by the rate (%) or composition rate (%). The student t-test was used for comparison of the normally distributed continuous data and Mann-Whitney U test for non-normally distributed data. Differences of categorical variables were assessed by the Chi-square or Fisher exact test. A two-tailed p-value of less than 0.05 was considered statistically significant. Kaplan-Meier curves were used to evaluate differences between patients in the Drug and Control group for the time period to first re-exacerbation. The log-rank test was utilized to determine statistical significance when comparing curves. Multivariable Cox's proportional hazards regression analyses were used to calculate the hazard ratio (HR) and 95% confidence intervals (CIs) for the first re-exacerbation associated with or without airway drugs. All data were processed and analyzed using Statistical Package for the Social Sciences, version 20.0, and Graphpad Prism 7.0.

Result

A total of 2,156 hospitalized patients who were diagnosed with bronchiectasis were enrolled in the study. 367 patients were finally included in this study, including 181 cases in the Drug group and 186 cases in the Control group (**Fig 1**).

The baseline data of the patients in the two groups during exacerbation

The baseline data of the patients in the two groups during exacerbation are shown in **Table 1**. Although PaO₂ in the Drug group was significantly lower than that in the Control group (p<0.05), the mean values of the two groups were both greater than 80mmHg and there was no difference between the two groups in blood oxygen saturation (p>0.05), which suggested that the baseline levels of PaO₂ in the two groups were comparable. There was no significant difference between the two groups in the past medical history and the comorbidities (**Supplementary Table 3**; all p>0.05). A large amount of purulent or foamy secretions under the bronchoscope (**Fig 2**) was mainly found in 240 patients (65.40%) with exacerbation of bronchiectasis. At the same time, there was no significant difference between 123 cases (67.96%) in the Drug group and 117 cases (62.90%) in the Control group ($\chi^2=1.035$, P=0.309). Mucous plugging was found under the bronchoscope in 11 patients (3.00%), and no significant difference was found between the Drug group (7 cases (3.87%)) and the Control group (4 cases (2.15%)) ($\chi^2=0.930$, P=0.335). There was a small amount of hemorrhage with one case under the bronchoscope in each group.

There were no significant differences in the clinical symptoms in the two groups during exacerbation (**Table 2**; $p>0.05$).

The chest HRCT during exacerbation was compared between the two groups. There were no significant differences in all the items of the Bhalla score (**Supplementary Table 4**; all $p>0.05$).

The detection of pathogenic bacteria during exacerbation was analyzed. The isolation rates of *PA* in the two groups (including sputum and/BALF) were 28.18% (51/181) and 19.89% (37/186), respectively ($P=0.063$). The detection rates of non-tuberculous mycobacteria were 9.94% (18/181) and 6.45% (12/186), respectively ($P=0.222$), and the isolation rates of other pathogenic bacteria were 6.63% (12/181) and 8.06% (15/186), respectively ($P=0.599$). There were no significant differences in pathogenic microorganisms between the two groups during exacerbation.

Changes of clinical symptoms, chest HRCT and pulmonary function

The clinical symptoms of all the patients were reassessed 3 months after discharge (all $P<0.05$; **Table 2** and **Fig 3**). And some patients took chest CT (105 patients) and pulmonary function (24 patients) again within 12 months after discharge (**Table 3**, **Fig 4** and **Supplementary Table 5**).

The re-exacerbation and antibiotics usage

Within 12 months after discharge, 119 re-exacerbation events occurred in the Drug group, which was significantly less than (171) in the Control group (**Table 4** and **Fig 5**). The time to first re-exacerbation was highly significant prolonged in the Drug group compared with the Control group (6.35 ± 3.13 months vs. 5.33 ± 3.00 months, $P=0.017$) and the frequency of re-exacerbation was significantly lower in the Drug group ($\chi^2=7.162$, $P=0.007$) (**Fig 6a**). After adjusting for age, gender, smoking history, BMI, duration of bronchiectasis and the PaO_2 , oxygen saturation, hemoglobin, the total clinical symptom score, the Bhalla score, and the detection rate of *PA* during an exacerbation, the multiple Cox regression model result showed that the risk of the first re-exacerbation in the Drug group was 70.3% that of the Control group ($\text{HR}=0.703$, 95% CI 0.516 - 0.956, $P=0.025$). The risk was reduced by 29.7% because of the airway drugs (**Fig 6b**).

The number of cumulative months of the antibiotics used in the Drug group was significantly lower than that in the Control group within one year after discharge ($P<0.05$). Moreover, 93 (51.38%) patients did not use oral antibiotics, and 127 patients (70.17%) in the Drug group did not use antibiotics intravenously, which were both significantly less than those in the Control group (**Table 4**).

Adverse events

During the bronchoscopy procedure, six patients (1.63%) altogether experienced bronchoscopy-related bleeding, including 4 patients in the Drug group and 2 patients in the Control group ($P=0.692$). The bleeding stopped after local instillation of hemagglutinin or epinephrine, and there was no persistent bleeding. No other adverse event occurred during the operation procedures.

Discussion

During the exacerbation of bronchiectasis, the main clinical manifestations include cough, abundant and viscous sputum, and similar, all of which may affect the patients' respiratory function and quality of life. In this study, the total cough score in patients with bronchiectasis during exacerbation was significantly higher, the expectoration volume was increased, and the sputum was stiff. A large amount of intratracheal purulent secretions was observed under bronchoscopy in 65.40% of the patients.

Bronchoscopy has been widely used as a routine method for diagnosing and treating airway diseases [19–21]. According to the European Respiratory Society guidelines [1], patients with bronchiectasis should be regularly subjected to airway clearance techniques (ACT) to facilitate secretion removal and reduce cough symptom [22]. Bronchoscopy can effectively remove vast intratracheal viscous sputum and mucus plugs under direct vision, stimulate cough reflex, and facilitate expectoration of sputum. It can also effectively promote the recruitment of airway collapse and help to remove pathogenic bacteria rapidly [23]. In this study, we found that after removing mucus and bronchoalveolar lavage under bronchoscopy, the cough and expectoration volume of the patients in both groups during the follow-up showed significant improvement (**Table 2**). Which suggest that the mucus removal by bronchoscopy (including aspiration and lavage) is an effective method for AC in bronchiectasis patients.

Previous studies have shown that long-term nebulized gentamicin is effective in non-cystic fibrosis bronchiectasis [8]. No patient had a gentamicin resistant *PA* strain at the end of the 12 months follow-up. In this study, the local instillation of gentamicin in the bronchiectasis lesion increased the local drug concentration and changed the living condition of the bacteria, thus directly acting as a bactericidal and bacteriostatic agent, which could avoid the inhalation related adverse reactions.

Dexamethasone is a long-acting glucocorticoid with strong anti-inflammatory effects and can also be used as a topical medication for other diseases. For example, intratympanic dexamethasone injection can be used to treat sudden sensorineural hearing loss with no serious adverse

events [24]. These findings support the advantages of dexamethasone as a topical medication. Our results revealed that, based on bronchoscopy AC therapy, topical instillation of gentamicin and dexamethasone significantly improved the symptoms of cough and sputum compared to simple clearance (**Table 2**). The incidence of re-exacerbation was also significantly lower than in the Control group (**Table 4, Figs. 5 and 6**).

In addition to the improvement of clinical symptoms and exacerbation, the changes of chest HRCT showed that the local instillation of gentamicin and dexamethasone after the removal of airway mucus could alleviate the inflammation of the bronchial walls, reduce the formation of sputum plugs and relieve the lung injury and damage through the anti-infection and anti-inflammatory mechanisms (**Table 3, Fig. 4**).

Exacerbation implies the need for antibiotics because of the deterioration in local symptoms and/or systemic upset due to infection. In the present study, the data of re-exacerbation and antibiotics usage (**Table 4**) showed that endobronchial therapy with gentamicin and dexamethasone after AC by bronchoscopy could reduce exacerbation, as well as avoid the occurrence of drug resistance and other adverse reactions caused by frequent systemic antibiotics. Furthermore, it could lessen the financial and social burden.

In this study, only six patients suffered from bronchoscopy related bleeding. Remaining patients experienced no adverse events. The measurement of local instillation with gentamicin and dexamethasone did not bring extra adverse events. Therefore, endobronchial therapy with gentamicin and dexamethasone after AC by bronchoscopy is safe.

Limitations

This research is a retrospective real world study, and some of the data are incomplete. Notably, more data about the effects of endobronchial therapy with gentamicin and dexamethasone after AC by bronchoscopy on lung function are needed to support our findings further.

Conclusion

Endobronchial therapy after AC by bronchoscopy is a safe and effective treatment measure for exacerbation of bronchiectasis that can quickly and efficiently remove airway secretions under direct vision. Local application of gentamicin and dexamethasone has a direct effect on sterilization and bacteriostasis and can enhance local anti-inflammatory effects. It can also enhance the treatment outcomes, reduce and delay exacerbation, minimize the use of antibiotics, and improve the quality of life.

Declarations

Author Contributions QL, BH, HJ,YZ, XS, SM, MQ and HL: study conception and design. QL, BH, HJ,YZ, XS, SM, MQ, JS, YC and HL: acquisition, analysis and interpretation of data. QL, BH, HJ,YZ, XS, SM, MQ and HL: drafting and final approval of the manuscript.

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Conflict of interest statement The authors declare that there is no conflict of interest.

Ethical Approval The study was approved by the ethics committee of Shanghai Pulmonary Hospital (No. K19-108). The requirement for written informed consent was waived because all patient information was anonymized and deidentified during data recording.

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Tables

Table 1 Baseline data and clinical characteristics of subjects with non-CF bronchiectasis during exacerbation

Patient characteristics	Drug group (n=181)	Control group (n=186)	P-value
Sex (female/male)	117/64	109/77	0.234
Age (years)	54.93±12.30	54.03±12.68	0.490
Smoking (n, yes %)	31(17.13%)	30(16.13%)	0.797
BMI (kg/m ²)	22.32±3.16	21.72±3.22	0.072
Duration of bronchiectasis (years)	14.09±14.80	12.91±13.37	0.921
Hb g/L	126.37±13.87	129.34±15.38	0.055
Leukocyte ×10 ⁹ /L	6.48±2.19	6.53±2.23	0.866
Neutrophilic granulocyte, ×10 ⁹ /L	3.97±2.05	4.09±1.94	0.268
PaO ₂ , mmHg	82.98±14.61	86.15±13.96	0.014
PaCO ₂ , mmHg	40.02±3.91	39.38±4.78	0.169
Arterial oxygen saturation %	95.73±2.06	96.00±2.64	0.064
Pulmonary function	n=135	n=140	-
FEV ₁ , L	1.81±0.80	1.86±0.81	0.595
FEV ₁ predicted, %	65.15±21.67	67.96±23.61	0.305
FVC, L	2.54±0.88	2.58±0.89	0.738
FEV ₁ /FVC %	69.78±12.81	70.62±12.44	0.586

Data are presented as n (%) or mean±SD except as otherwise noted. Hb, haematoglobin. PaO₂, partial pressure of oxygen. PaCO₂, arterial blood partial pressure of carbon dioxide. BMI, body mass index. FEV₁, forced expiratory volume in 1s. FVC, forced vital capacity.

Table 2 Comparison of clinical symptom scores

	Drug group (n=181)				Control group (n=186)				P value
	*Baseline	3 months later	P value	& D-value	Baseline	3 months later	P value	& D-value	
Cough	6.18±2.00	#3.03±1.64	0.001	3.15±1.88	6.06±1.84	3.76±1.70	0.001	2.31±1.70	<0.001
Expectoration	7.36±2.35	#4.57±2.89	0.001	2.78±2.53	7.21±2.28	6.05±2.85	0.001	1.16±2.23	<0.001
Expectoration volume	5.20±2.40	#2.62±2.17	0.001	2.59±2.04	5.44±2.46	3.10±2.18	0.001	2.33±1.95	0.251
Total cough score	18.75±5.67	#10.23±5.77	0.001	8.52±4.71	18.71±5.35	12.90±5.44	0.001	5.81±4.09	<0.001
Dyspnea	2.32±2.34	1.03±1.56	0.001	1.29±2.08	2.19±2.19	1.26±1.70	0.001	0.94±1.71	0.180
Hemoptysis	1.11±2.00	0.36±1.17	0.001	0.75±2.10	1.39±1.98	0.47±1.22	0.001	0.92±1.87	0.191
Chest pain	0.60±1.43	0.23±0.92	0.003	0.36±1.17	0.77±1.52	0.26±0.95	0.001	0.52±1.47	0.131
Total symptom score	22.77±7.06	#11.85±7.05	0.001	10.92±5.89	23.06±6.11	14.89±6.35	0.001	8.18±4.77	<0.001

Data are presented as mean±SD except as otherwise noted. *There were no statistical differences of all the clinical symptom scores between two groups during exacerbation ($P \geq 0.05$). #There were statistical differences between two groups 3 months later ($P \geq 0.05$). &D-value, difference value, the difference between baseline and 3 months later. [¶]The P -value of the D-value between two groups.

Table 3 Comparison of HRCT within 4-6 months

	Drug group (n=47)				Control group (n=58)				[¶] P Value
	Baseline	4-6months later	P Value	&D-value	Baseline	4-6months later	P Value	&D-value	
Severity of bronchiectasis	1.91±0.75	1.81±0.80	0.467	0.11±0.37	2.05±0.74	2.03±0.75	0.903	0.02±0.13	0.087
Peribronchial thickening	2.11±0.67	1.64±0.67	0.001	0.47±0.80	2.10±0.67	1.90±0.69	0.104	0.21±0.52	0.006
Extent of bronchiectasis (No. of BP segments)	*1.60±0.71	#1.60±0.71	1	0±0.21	1.97±0.88	1.97±0.88	1	0±0	1
Extent of mucous plugging (No. of BP segments)	*0.98±0.79	0.47±0.62	0.001	0.51±0.59	0.52±0.57	0.40±0.53	0.246	0.12±0.38	<0.001
Sacculations or abscesses (No. of BP segments)	0.53±0.72	#0.28±0.58	0.047	0.26±0.44	0.60±0.53	0.45±0.54	0.105	0.16±0.37	0.204
Generations of bronchial divisions involved (bronchiectasis/plugging)	2.57±0.68	2.55±0.75	0.982	0.02±0.15	2.69±0.57	2.69±0.57	1	0±0	0.267
No. of bullae	0.11±0.52	0.11±0.52	1	0±0	0.21±0.49	0.21±0.49	1	0±0	1
Emphysema (No. of BP segments)	0.34±0.73	0.32±0.69	0.960	0.02±0.15	0.16±0.41	0.16±0.41	1	0±0	0.267
Collapse/consolidation	1.11±0.67	0.66±0.73	0.002	0.45±0.77	1.02±0.69	0.72±0.74	0.025	0.29±0.59	0.133
Bhalla score	13.74±3.72	15.57±3.60	0.017	-1.83±1.62	13.69±2.89	14.48±2.85	0.139	-0.79±1.37	<0.001

Data are presented as mean±SD except as otherwise noted. HRCT, High Resolution Computed Tomography. No., number. BP, bronchopulmonary. *There were statistical differences between two groups during exacerbation ($P \geq 0.05$), the P values of others were more than 0.05. #There were statistical differences between two groups 4-6 months later ($P \geq 0.05$), the P values of others were more than 0.05. &D-value, difference value, the difference between Baseline and 4-6 months later. [¶]The P -value of the D-value between two groups.

Table 4 Comparisons of the no. of re-exacerbation and the cumulative months of the antibiotics usage within 12 months

	Drug group (n=181)	Control group (n=186)	P -value
No. of exacerbation	0.66±0.91	0.92±1.00	0.005
Months of oral antibiotics	1.29±2.09	1.90±2.33	0.001
Months of intravenous antibiotics	0.43±0.79	0.65±0.91	0.012

Data are presented as mean±SD except as otherwise noted. No., number.

Figures

Figure 1

Flow chart of the study. CF, cystic fibrosis; TB, tuberculosis; ABPA, allergic bronchopulmonary aspergillosis.

Figure 2

Characteristic under bronchoscope. (a, b) Female, 64 years old, cough, and expectoration repeatedly occurring for more than 20 years. a, purulent secretion in the left principal bronchus; b, after airway mucus clearance by bronchoscopy. (c, d) Male, 42 years old, cough, and expectoration repeatedly for 15 years. a, mucus plug in the posterior segment of the upper lobe of the left lung (black arrow); b, after airway mucus clearance by bronchoscopy (black arrow).

Figure 3

Tendency charts of total cough score and total symptom score in the two groups. 3m, three months after discharge. * $p < 0.05$

Figure 4

HRCT features before and after endobronchial therapy with non-CF bronchiectasis. (a, b) A female 42 years old patient with airway drugs. Cough and expectoration repeatedly for 4 years. a, HRCT during exacerbation; b, HRCT 5 months later. (c, d) A female 63 years old patient in the Drug group. Cough and expectoration repeatedly for 40 years. c, HRCT during exacerbation. d, HRCT 4 months later.

Figure 5

The number of re-exacerbation within 12 months in the two groups.

Figure 6

Proportion of patients free from re-exacerbations. (a) The result of univariate analysis. (b) The result of multivariate Cox regression analysis.

Supplementary Files

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- [SupplementaryTables.docx](#)