Original Article

Risk factors for bronchopleural fistula after lobectomy for lung cancer

Junji Ichinose, Kohei Hashimoto, Yosuke Matsuura, Masayuki Nakao, Sakae Okumura, Mingyon Mun

Department of Thoracic Surgical Oncology, Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Koto-ku, Tokyo, Japan

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Correspondence to: Junji Ichinose, MD, PhD. Department of Thoracic Surgical Oncology, Cancer Institute Hospital of JFCR, 3-8-31 Ariake, Koto-ku, Tokyo 135-8550, Japan. Email: jichinose-tky@umin.ac.jp.

Background: Bronchopleural fistula (BPF) after lobectomy for lung cancer is a rare but serious complication. This study aimed to stratify the risk factors of BPF.

Methods: Patients who underwent lobectomy without bronchoplasty and preoperative treatment for lung cancer between 2005 and 2020 were retrospectively reviewed. We examined the association between the incidence of BPF and background factors, including comorbidities, preoperative blood test results, respiratory function, surgical procedure, and extent of lymphadenectomy.

Results: Among the 3,180 patients who underwent lobectomy, 14 (0.44%) developed BPF. The median interval from surgery to BPF onset was 21 days (range, 10–287). Two of the 14 patients died of BPF (mortality rate, 14%). All 14 patients who developed BPF were men and had undergone right lower lobectomy. Other factors significantly associated with the development of BPF were older age, heavy smoking, obstructive ventilatory failure, interstitial pneumonia, history of malignancy, history of gastric cancer surgery, low serum albumin levels, and histology. Multivariable analysis in the subgroup of men who underwent right lower lobectomy revealed that high level of serum C-reactive protein and a history of gastric cancer surgery were significantly associated with BPF, whereas bronchial stump coverage was inversely associated with BPF.

Conclusions: Men who underwent right lower lobectomy were at increased risk of BPF. The risk was higher when the patient had high serum C-reactive protein or a history of gastric cancer surgery. Bronchial stump coverage might be effective in patients at high risk of BPF.

Keywords: Bronchopleural fistula (BPF); lung cancer; lobectomy; bronchial stump coverage; risk factor

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Introduction

Surgical treatment for lung cancer has become remarkably safe in recent years due to the increase in the number of early-stage lung cancers, the widespread use of minimally invasive surgery, and advances in surgical instruments (1-4). Although the incidence of bronchopleural fistula (BPF) has decreased with the reduction in the number of central-type lung cancers and advances of endoscopic staplers, it still remains a serious complication that can lead to severe pneumonia, empyema, and surgical mortality.

Numerous studies have shown high incidence rates of BPF after pneumonectomy and surgery following neoadjuvant therapy (5-14). However, few reports have thoroughly examined BPF following standard lobectomy without preoperative treatment or bronchoplasty. Predicting the risk of BPF after regular lobectomy is useful in determining indications for preventive measures, such as bronchial stump coverage. The present study examined

the incidence and the risk factors of BPF after lobectomy for lung cancer. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1809/rc).

Methods

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board for Clinical Research of the Cancer Institute Hospital of the Japanese Foundation for Cancer Research on March 22, 2022 (referral No. 2021-GB-117) and individual consent for this retrospective analysis was waived.

Study design

This retrospective, observational study reviewed patients with primary lung cancer who underwent surgical resection between January 2005 and December 2020. The following exclusion criteria were established: patients who underwent preoperative treatment, pneumonectomy, bilobectomy, segmentectomy, bronchoplasty, wedge resection, and segmentectomy.

The primary outcome was the development of BPF within 1 year after surgery confirmed via bronchoscopy, computed tomography, or reoperation. We investigated the association between the development of BPF and the following background factors: age, sex, performance status, smoking history, respiratory function, comorbidities (diabetes mellitus, interstitial pneumonia, ischemic heart disease, cerebrovascular disease, history of malignancy, and past gastric cancer surgery), preoperative blood tests results (serum albumin, C-reactive protein, and carcinoembryonic antigen), affected lobe, surgical approach, method of bronchial closure, extent of lymphadenectomy, histology, pathological nodal metastasis, pathological residual disease at the bronchial stump, and bronchial stump coverage. Furthermore, the subgroup analysis of men who underwent right lower lobectomy was performed to achieve more accurate selection of high-risk patients of BPF.

Surgical procedure

The standard procedure for lung cancer in the study period was lobectomy with lobe-specific selective lymph node dissection (3,15,16), and subcarinal lymphadenectomy was omitted for lung cancer in right upper lobe and left upper division segment. In right lower lobe lung cancer, upper mediastinal lymph node dissection was omitted unless metastasis was found in the hilar and subcarinal lymph nodes. The lobar bronchus was closed using staplers or interrupted suture. Thoracoscopic lobectomy for lung cancer was started in 2008 (17), and almost all lobectomies were performed via thoracoscopic surgery in recent years. However, the extent of lymph node dissection remains similar to that during open thoracotomy. To cover the bronchial stump, a pedicled intercostal muscle flap was used during open thoracotomy, whereas a free pericardial fat pad was used during thoracoscopic surgery.

Statistical analysis

Continuous variables were expressed as the mean ± standard deviation. Variables were compared and analyzed using Student's *t*-test, Welch's method, or χ^2-test. The factors associated with the development of BPF were analyzed by performing multivariable logistic regression and least absolute shrinkage and selection operator (LASSO) regression analyses (18) using covariates with P<0.1 in univariable analysis. LASSO regression is one of the

Highlight box

Key findings

- The incidence rate of bronchopleural fistula (BPF) after undergoing lobectomy for lung cancer was 0.44%.
- All 14 patients who developed BPF were men who had undergone right lower lobectomy.
- A multivariable analysis in the subgroup of men who underwent right lower lobectomy revealed that high serum C-reactive protein levels and a history of gastric cancer surgery were associated with BPF, whereas bronchial stump coverage was inversely associated with BPF.

What is known and what is new?

- Several studies have identified pneumonectomy, presence of residual carcinomatous tissue at the bronchial stump, preoperative irradiation, and diabetes as risk factors for BPF.
- This study revealed male sex, right lower lobectomy, high serum C-reactive protein levels, and history of gastrectomy as factors associated with the development of BPF after lobectomy for lung cancer.

What is the implication, and what should change now?

- Preventive measures, such as bronchial stump coverage, might be more suitable for patients at high risk of BPF.

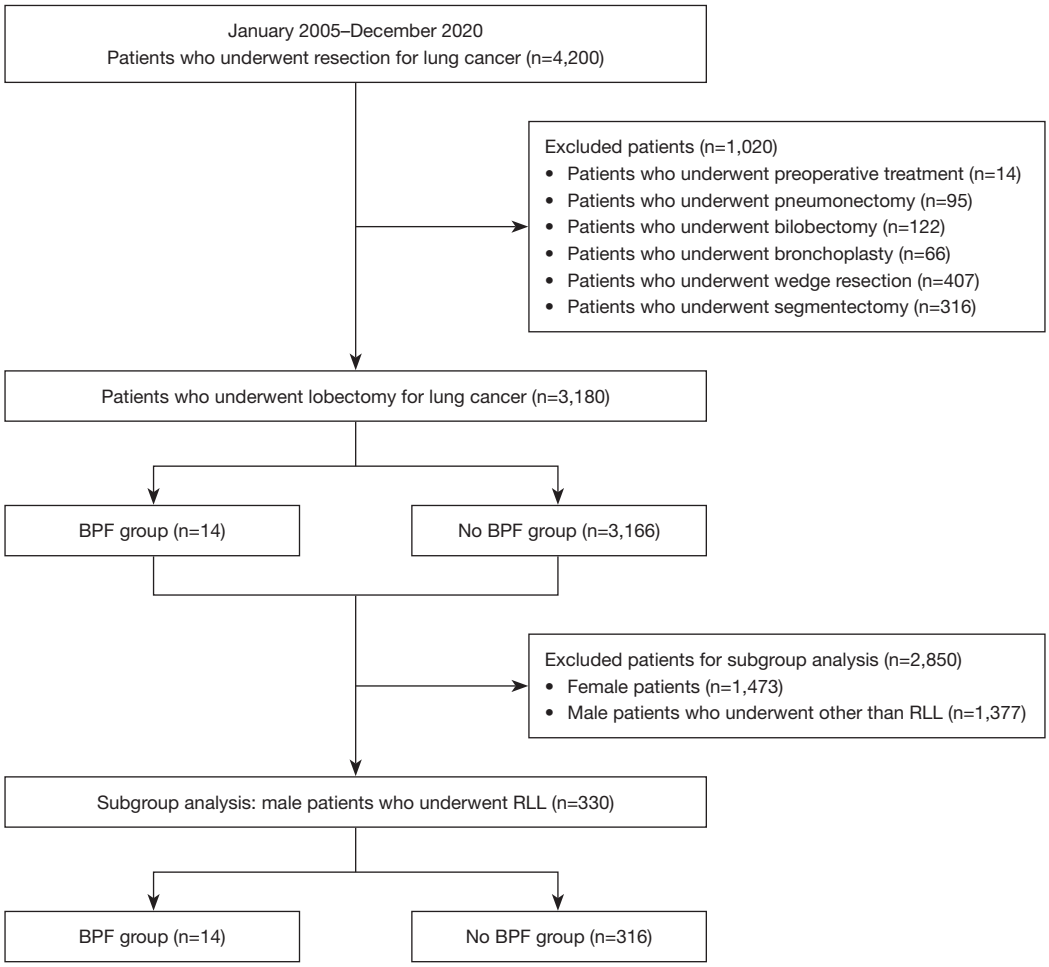

Figure 1 Patient flow diagram. BPF, bronchopleural fistula; RLL, right lower lobectomy.

regularized regression models and minimizes the residual sum of squares subject to the sum of the absolute value of the coefficients being less than a constant. LASSO regression is a method that allows the selection of only those explanatory variables that influence the objective variable. The statistical analyses were performed in the R software environment (version 4.0.3; the R Foundation for Statistical Computing, Vienna, Austria). LASSO regression was performed using the "glmnet" package. $P<0.05$ indicated statistical significance.

Results

A flowchart of the patient selection process is provided in *Figure 1*. Among the 4,200 patients who underwent resection for lung cancer, 1,020 patients were excluded based on the exclusion criteria, and the remaining 3,180 patients were included in the study. There were no patients with incomplete data. Of 195 (6.1%) patients who underwent bronchial stump coverage, intercostal muscle flaps and pericardial fat pads were used in 137 and 58 patients, respectively. The incidence of BPF was 14 (0.44%) in 3,180 patients who underwent lobectomy without bronchoplasty nor preoperative treatment. The median interval from surgery to BPF onset was 21 days (range, 10–287 days). Eight patients (57%) underwent open window thoracostomy. Two of the 14 patients died of BPF within 6 months after its development (mortality rate, 14%). The characteristics of patients with BPF and without BPF are shown in *Table 1*. All 14 patients who developed BPF were men and had undergone right lower lobectomy. Other factors significantly associated with the development of BPF were older age, heavy smoking, obstructive ventilatory failure, interstitial pneumonia, history of malignancy, history of gastric cancer surgery, low serum albumin levels, and

Table 1 Characteristics of patients with and without bronchopleural fistula

Variables	BPF (n=14)	No BPF (n=3,166)	P
Age (years)	72±11	67±10	0.042
Sex			<0.001
Male	14 [100]	1,693 [53]	
Female	0 [0]	1,473 [47]	
Performance status			0.347
0	13 [93]	3,070 [97]	
1–3	1 [7]	96 [3]	
Smoking history, pack-years	54±32	24±31	<0.001
%VC	112±21	114±16	0.632
FEV1.0%	68±11	74±9	0.019
Comorbidities			
Diabetes mellitus	3 [21]	426 [13]	0.421
Interstitial pneumonia	3 [21]	116 [4]	0.014
Ischemic heart disease	1 [7]	137 [4]	0.463
Cerebrovascular disease	0 [0]	115 [4]	1.000
History of malignancy	8 [57]	851 [27]	0.029
Gastric cancer surgery	4 [29]	93 [3]	0.001
Preoperative blood tests			
Albumin (g/dL)	4.0±0.6	4.2±0.3	0.036
C-reactive protein (mg/dL)	0.9±1.4	0.3±1.2	0.062
Carcinoembryonic antigen (ng/mL)	4.4±4.6	9.2±192.0	0.924
Affected lobe			<0.001
Right upper	0 [0]	1,146 [36]	
Right middle	0 [0]	248 [8]	
Right lower	14 [100]	588 [19]	
Left upper	0 [0]	688 [22]	
Left lower	0 [0]	496 [16]	
Thoracoscopic surgery	11 [79]	2,008 [63]	0.281
Stapler closure	14 [100]	3,123 [99]	0.471
Mediastinal lymphadenectomy	11 [79]	2,500 [79]	1.000
Histology			0.001
Adenocarcinoma	6 [43]	2,539 [80]	
Squamous cell carcinoma	7 [50]	342 [11]	
Others	1 [7]	285 [9]	
Nodal metastasis	4 [29]	514 [16]	0.265
Residual disease at the bronchial stump	0 [0]	4 [0.1]	1.000
Bronchial stump coverage	1 [7]	194 [6]	0.588

Data are presented as mean ± standard deviation or number [frequency]. BPF, bronchopleural fistula; %VC, percent vital capacity; FEV1.0%, forced expiratory volume in one second percent.

Table 2 Factors associated with the development of bronchopleural fistula

Variables	Odds ratio	95% CI	P
Male sex	∞	–	–
Right lower lobectomy	∞	–	–
Gastric cancer surgery	7.02	1.25–39.6	0.027
C-reactive protein	1.61	1.02–2.55	0.040
History of malignancy	2.09	0.53–8.29	0.294
Age	1.01	0.93–1.10	0.830
Smoking history	1.00	0.99–1.00	0.530
FEV1.0%	0.96	0.90–1.02	0.203
Interstitial pneumonia	1.81	0.43–7.55	0.417
Albumin	2.03	0.26–15.7	0.497
Not adenocarcinoma	1.19	0.32–4.35	0.794

The symbol ∞ represents infinity. CI, confidence interval; FEV1.0%, forced expiratory volume in one second percent.

histology. The bronchi were closed using staplers in 99% of the cases. Mediastinal lymphadenectomy was omitted in 21% of the cases due to old age, comorbidities, noninvasive cancer, and so on. Multivariable logistic regression analysis using eleven variables revealed that having a history of gastric cancer surgery [odds ratio =7.02, 95% confidence interval (CI): 1.25–39.6, P=0.027] and high serum C-reactive protein levels (odds ratio =1.61, 95% CI: 1.02–2.55, P=0.040) were significantly associated with the development of BPF (*Table 2*). The odds ratios for male sex and right lower lobectomy were infinite.

Table 3 shows the characteristics of patients with BPF and without BPF in a subgroup limited to men who underwent right lower lobectomy. The following three factors were significantly associated with the development of BPF in univariable analysis: history of malignancy, history of gastric cancer surgery, and high serum C-reactive protein. The risk for BPF was not significantly different between patients with and without subcarinal lymphadenectomy (4.5% *vs.* 3.6%, P=0.72). The incidence of BPF was lower in patients who underwent bronchial stump coverage than in those who did not, but the difference was not significant (1.0% *vs.* 5.7%, P=0.072). The multivariable logistic regression analysis revealed that high serum C-reactive protein levels (odds ratio =1.83, 95% CI: 1.17–2.87, P=0.009) and a history of gastric cancer surgery (odds ratio =5.52, 95% CI: 1.06–28.8, P=0.042) were significantly associated with the development of BPF in men who underwent right lower lobectomy (*Table 4*). Conversely, bronchial stump coverage was inversely associated with the development of BPF (odds ratio =0.06, 95% CI: 0.00–0.77, P=0.031). *Table 5* presents the estimates obtained by logistic regression analysis and LASSO regression analysis. Three variables were selected using LASSO regression with $\lambda = 0.02$ that were significantly associated with BPF in the logistic regression analysis.

Discussion

The results of the current study revealed that the incidence of BPF after lobectomy for lung cancer was 0.44% and was limited to men who underwent right lower lobectomy. Multivariable analysis in the subgroup limited to men who underwent right lower lobectomy revealed that high serum C-reactive protein levels and past gastric cancer surgery were significantly associated with BPF, whereas bronchial stump coverage was inversely associated with BPF.

BPF, which occurs in 0.6–4.4% of patients undergoing pulmonary resection and has a high mortality rate of 18–71%, has long been a serious threat (5-8,12,14). Algar *et al.* (19) and Jichen *et al.* (20) reported particularly high mortality rates in early BPF occurring within 1 month after surgery. In 1992, Asamura *et al.* (14) reported a 2.1% and 4.7% incidence rate of BPF after lung cancer surgery and pneumonectomy, respectively. The Japanese Joint Committee of Lung Cancer Registry reported that among the 18,973 patients who underwent lung cancer surgery including sublobar resection in 2010, 77 (0.4%) developed BPF within 30 days after surgery (21). In the current study, 0.44% of the patients who underwent lobectomy developed BPF within 1 year after surgery, with two patients dying of BPF within 6 months after BPF onset (mortality rate, 14%). Our study included cases after the year 2005, and both incidence and mortality rates seemed to have decreased compared to reports over the previous century.

Several studies have identified pneumonectomy, residual carcinomatous tissue at the bronchial stump, preoperative irradiation, and diabetes as risk factors for BPF (6,7,12,14). However, to determine the indication for preventive measures against BPF, evaluating the risk of BPF in patients who underwent standard lobectomy without preoperative therapy is important. In the current study, the incidence of BPF was limited to men who underwent right lower lobectomy, suggesting that men and patients who underwent right lower lobectomy were at increased risk

Table 3 Characteristics of male patients with and without bronchopleural fistula after right lower lobectomy

Variables	BPF (n=14)	No BPF (n=316)	P
Age (years)	72±11	68±10	0.135
Performance status			0.384
0	13 [93]	306 [97]	
1–3	1 [7]	10 [3]	
Smoking history, pack-years	54±32	41±33	0.152
%VC	112±21	112±16	0.928
FEV1.0%	68±11	72±10	0.162
Comorbidities			
Diabetes mellitus	3 [21]	68 [22]	1.000
Interstitial pneumonia	3 [21]	38 [12]	0.396
Ischemic heart disease	1 [7]	18 [6]	0.572
Cerebrovascular disease	0 [0]	12 [4]	1.000
History of malignancy	8 [57]	84 [27]	0.029
Gastric cancer surgery	4 [29]	16 [5]	0.007
Preoperative blood tests			
Albumin (g/dL)	4.0±0.6	4.2±0.3	0.143
C-reactive protein (mg/dL)	0.9±1.4	0.3±0.8	0.005
Carcinoembryonic antigen (ng/mL)	4.4±4.6	6.2±20	0.744
Thoracoscopic surgery	11 [79]	209 [66]	0.400
Mediastinal lymphadenectomy	11 [79]	235 [74]	0.830
Stapler closure	14 [100]	311 [98]	0.520
Histology			0.076
Adenocarcinoma	6 [43]	210 [67]	
Squamous cell carcinoma	7 [50]	73 [23]	
Others	1 [7]	33 [10]	
Nodal metastasis	4 [29]	49 [16]	0.253
Residual disease at the bronchial stump	0 [0]	0 [0]	1.000
Bronchial stump coverage	1 [7]	102 [32]	0.072

Data are presented as mean ± standard deviation or number (frequency). BPF, bronchopleural fistula; %VC, percent vital capacity; FEV1.0%, forced expiratory volume in one second percent.

of BPF. The multivariable analysis in the subgroup of men who underwent right lower lobectomy revealed that high level of serum C-reactive protein and a history of gastric cancer surgery were significantly associated with BPF, whereas bronchial stump coverage was inversely associated with BPF. Therefore, the bronchial stump coverage should be considered for patients with risk factors such as male sex, right lower lobectomy, high serum C-reactive protein levels, and history of gastrectomy.

Various factors may contribute to the development of BPF, including technical problems with suturing, staple malformation, ischemia, infection, and nutritional

Table 4 Factors associated with the development of bronchopleural fistula in male patients after right lower lobectomy

Variables	Odds ratio	95% CI	P
C-reactive protein	1.83	1.17–2.87	0.009
Gastric cancer surgery	5.52	1.06–28.8	0.042
History of malignancy	2.14	0.55–8.38	0.274
Not adenocarcinoma	1.74	0.50–6.12	0.387
Bronchial stump coverage	0.06	0.00–0.77	0.031

CI, confidence interval.

Table 5 Comparison of the estimates obtained by logistic regression analysis and LASSO regression analysis

Variables	Logistic regression		LASSO regression (λ=0.02)
	Estimates	P	Estimates
C-reactive protein	0.60	0.009	0.24
Gastric cancer surgery	1.71	0.042	1.32
History of malignancy	0.76	0.274	–
Not adenocarcinoma	0.55	0.387	–
Bronchial stump coverage	–2.81	0.031	–0.26

LASSO, least absolute shrinkage and selection operator.

deficiencies. A stapler was used for bronchial closure in 99% of the cases, with no correlation observed between the bronchial closure method and the development of BPF. Satoh *et al.* (22) reported that male, smoking, diabetes mellitus, subcarinal lymphadenectomy, and pulmonary complications were risk factors for postoperative ischemic bronchitis. Considering the risk of ischemic bronchitis and distribution of lymph node metastasis (15,16,23), lobe-specific selective lymphadenectomy has been our standard procedure for primary lung cancer, which could have possibly preserved blood flow at the bronchial stump, thereby reducing the incidence of BPF. In this study, history of gastric cancer surgery was significantly associated with the development of BPF. Our previous study had revealed that upper gastrointestinal surgery was an independent factor associated with postoperative pulmonary complications after lung cancer surgery (24). Generally, surgery for upper gastrointestinal cancer can have a profound effect on postoperative nutritional status (25). Nutritional status may have some influence on the risk of BPF. Moreover, regurgitation of gastrointestinal contents following upper gastrointestinal surgery may have caused aspiration pneumonia and increased the risk of developing BPF.

The present study has some limitations worth noting. This was a retrospective, observational, and single-institution study. Moreover, the results of this study may not be applicable to institutions with different methods of bronchial closure or extent of lymphadenectomy. As this study reviewed surgeries performed over the span of 16 years, minor changes in the surgical techniques and perioperative management used during the study period may have affected the results. The proportion of patients with a history of gastric cancer surgery (3%) was higher than globally expected. The regional and institutional specificities might have contributed to the high prevalence of gastric cancer in this study cohort. If the study was conducted in a population with low prevalence of gastric cancer, no statistically significant difference might have been found. Furthermore, considering that only 14 relevant cases were recorded, the predictive performance of the multivariable logistic regression analysis might have been hampered. A larger, multi-institutional study should be conducted in the future. Although events per variables of >10 is a common criterion, some studies have shown that events per variables have a weak correlation with predictive accuracy (26,27). In this study, the reliability of the results was ensured by conducting subgroup analyses and comparing the results obtained by LASSO regression analysis with the results of logistic regression analysis.

Conclusions

The current study showed that men and patients who underwent right lower lobectomy were at increased risk of BPF. The risk was even higher when the patient had high serum C-reactive protein or a history of gastric cancer surgery. Bronchial stump coverage might be effective in patients at high risk of BPF.

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Footnote

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Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1809/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1809/coif). 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board for Clinical Research of the Cancer Institute Hospital of the Japanese Foundation for Cancer Research on March 22, 2022 (referral No. 2021-GB-117) and individual consent for this retrospective analysis was waived.

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