# Real-world data on severe lung cancer: a multicenter retrospective study

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**Background:** Severe lung cancer is a novel concept that describes a patient with poor performance status (PS; 2–4) but with a high probability of receiving survival benefit and improvement in the PS score. However, there is currently no relevant research or real-world data on those with severe lung cancer, such as incidence, cause, clinical features, and risk factors.

**Methods:** The data from patients with advanced lung cancer attending multiple centers from January 1, 2022, to June 30, 2022, were collected for a cross-sectional study. In addition, data from fatal cases from January 1, 2019, to June 30, 2022, were retrospectively collected as another cohort. And we developed a questionnaire to assess clinicians' mastery of severe lung cancer.

**Results:** Three participating institutes enrolled the data set of 1,725 patients, and the dataset of 269 fatal cases were included in another cohort; the incidence of severe lung cancer was 13.10% and 37.55%, respectively. Severe lung cancer patients were mainly stage IV elderly male patients without gene mutation and a history of resection. And the proportion of smoking and comorbidities in severe lung cancer patients is more than in non-severe lung cancer patients (50.4% *vs.* 40.8%, P=0.006; 46.9% *vs.* 36.4%, P=0.002). Treatment-related adverse events (AEs) (46.0%) accounted for the largest proportion of the primary causes of severe lung cancer in the cross-sectional study, while cancer-related symptoms (54.5%) accounted for the largest proportion of the primary causes of sever lung cancer in the 101 fatal cases. For the fatal cases, the overall survival of severe lung cancer patients caused by cancer-related symptoms was longer than that caused by treatment-related AEs (8 *vs.* 3 months; P=0.019). A total of 616 clinicians completed the questionnaire; 90.26% of clinicians agreed with the concept of severe lung cancer.

**Conclusions:** The incidence of severe lung cancer cannot be ignored based on real-world data. Treatment-

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related AEs are gradually account for more of the causes of severe lung cancer, surpassing cancer-related symptoms and comorbidities. Furthermore, the prognosis of patients with advanced lung cancer who develop severe lung cancer due to treatment-related AEs is worse than cancer-related symptoms.

## Introduction

According to Global Cancer Incidence, Mortality and Prevalence (GLOBOCAN) 2020, lung cancer is currently the second most common cancer and the leading cause of death worldwide (1). Two-thirds of patients with lung cancer are diagnosed with stage IIIB, IIIC, and IV, and the prognosis of these patients is clinically poor (2). Eastern Cooperative Oncology Group (ECOG) performance status (PS) scores are evaluated on the basis of the patient's ability of self-care, level of daily activity, and physical ability in terms of walking and working or percentage of time waking hours confined to a bed or chair (3). The assessment of PS scores in patients with cancer provides prognostic information and guides treatment intervention (4,5). As PS

scores are highly heterogeneous and depend on subjective categorization, the evaluation results of different doctors for the same patient can be different. Besides, the results of the doctor's evaluation and the patient's self-evaluation will also differ (6). Nevertheless, the evaluation is still a reliable and relevant prognostic variable, being one of the most important independent prognostic factors in lung cancer (7,8). The recommendation against chemotherapy in patients with poor PS scores dates to the early 1980s, when poor PS score (PS 2–4) was a predictor of poor survival (9). For a long time, patients with poor PS score were typically ineligible for clinical trials, and existing evidence of limited benefits among patients with poor PS has been derived from only a handful of small trials (10,11).

The incidence of poor PS is high among patients in all stages of lung cancer. For example, in extensive epidemiological studies, Buccheri and Radzikowska found that 42–50% of patients with lung cancer had a PS score of 2–4 as assessed by their doctors at diagnosis (12-14). Furthermore, in recent years, the availability of targeted therapies, antiangiogenic agents, and immune checkpoint inhibitors (ICIs) has dramatically prolonged the survival of patients and made poor PS score in these patients less of a concern than that in patients treated with traditional chemotherapy (15,16). Moreover, an increasing number of clinical studies are enrolling patients with a PS score of 2, and some real-world studies have enrolled patients with PS scores of 3 and 4. In addition to advances in oncology, improved survival in patients with a poor PS score has also been attributed to advances in managing sepsis and associated organ failure (17,18). Therefore, we found it was necessary to distinguish a certain portion of patients with poor PS scores and end stage lung cancer who could benefit from modern treatment. Based on previous research, our team pioneered the concept of "advanced severe lung cancer" in 2017 (19,20). Moreover, we drafted the first edition of the international consensus on severe lung cancer in 2021 (21).

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**Highlight box**

**Key findings**
- The incidence rate of severe lung cancer among lung cancer patients in the cross-sectional study was 13.10% and treatment-related AEs are gradually accounting for more of the causes of severe lung cancer, surpassing cancer-related symptoms and comorbidities.
- We summarized the clinical characteristics of severe lung cancer patients and found that the prognosis of severe lung cancer due to adverse reactions was the worst.

**What is known and what is new?**
- Our team pioneered the concept of "advanced severe lung cancer" in 2017 and drafted the "International consensus on severe lung cancer-first edition" in 2021.
- We analyzed the epidemiological data of patients with severe lung cancer through a multicenter retrospective study. Additionally, we assessed clinicians' acceptance of the severe lung cancer concept via a questionnaire.

**What is the implication, and what should change now?**
- We cannot ignore patients with severe lung cancer, especially due to treatment-related adverse effects.

462

Wang et al. Severe lung cancer in the real world

Severe lung cancer is a novel concept, and there is currently no relevant research or real-world data on those with severe lung cancer, such as incidence, cause, clinical features, and risk factors. Therefore, based on the first edition of the international consensus, we (I) conducted a real-world, multicenter study on patients with severe lung cancer and (II) used questionnaires to assess clinicians' acceptance of the severe lung cancer concept. We present the following article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-4/rc).

## Methods

### Patients

This multicenter, retrospective, observational study was conducted in 3 participating institutes through electronic medical records and consisted of 2 cohorts. One cohort was a cross-sectional study that collected data from patients with lung cancer who received antitumor treatment at different centers from January 1, 2022, to June 30, 2022. The other cohort included fatal cases from January 1, 2019, to June 2022. The participating institutes included the First Affiliated Hospital of Guangzhou Medical University (Hospital A), the First Affiliated Hospital of Anhui Medical University (Hospital B), and Shenzhen People's Hospital (Hospital C). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of the First Affiliated Hospital of Guangzhou Medical University (No. 2021-38). Each participating center was informed and agreed with this study. Individual consent for this retrospective analysis was waived.

### Data collection

A total of 10 clinicians familiar with the international consensus on severe lung cancer collected the data from each center. Data entry is carried out after disputes are eliminated and a consensus is reached. First, we recorded the incidence, causes and baseline data of severe lung cancer in patients in the 2 study cohorts (3 primary causes are classified according to the consensus on severe lung cancer: cancer-related symptoms, treatment-related AEs, and comorbidities). We then collected the demographic and survival data for fatal cases (gender, age, preexisting comorbidities, pathological classification, neoplasm staging,

genetic mutations, operation history, comorbidities, history of other tumors). The survival data recorded included the overall survival (OS) time from the first diagnosis of severe lung cancer to death.

The inclusion criteria for patients were the following: (I) age older than 18 years; (II) definite pathologic diagnosis of lung cancer and clinical lung cancer staging (IIIB, IIIC, and IV); (III) undergone at least 1 course of antitumor treatment; (IV) relatively complete baseline data; and (V) in fatal cases, recording of the cause of death in electronic medical records.

The exclusion criteria for patients were the following: (I) age younger than 18 years and (II) lack of antitumor therapy.

The inclusion criteria for severe lung cancer: We formulated the following three criteria based on the concept of severe lung cancer: (I) lung cancer patients with poor PS score [2–4] and thus led to discontinuation of current anticancer therapy; (II) the above patients have achieved improvement in the PS score [0–1] after supportive care and antitumor treatment based on dynamic and precise testing; (III) patients received at least two anti-tumor treatments after their PS scores improved.

### Questionnaire for clinicians

We developed an electronic questionnaire regarding severe lung cancer and sent the electronic questionnaire to clinicians from mainland China who had treated patients with lung cancer (website address of online questionnaires: https://www.wjx.cn ID: 173715842; Appendix 1). The electronic questionnaire was implemented from August 1, 2022, to August 31, 2022. The answers from clinicians were collected and analyzed.

The inclusion criteria for clinicians were the following: (I) a specialist in treating lung cancer; (II) registration as a clinician; and (III) familiarity with the PS score criteria (Appendix 2).

### Pathologic diagnosis and clinical TNM classification

The diagnostic criteria were those outlined in the "2015 Chinese guidelines for the diagnosis and treatment of primary lung cancer". And the tumor classification of patients was performed according to the "World Health Organization Classification of Lung Tumor Tissue" (22,23). The staging criteria followed the eighth edition of the TNM staging method formulated by the International Union against Cancer in 2009 (24).

*The concept of severe lung cancer*

Severe lung cancer is a disease in which the patient has a poor PS score [2–4] in certain stages due to various acute or chronic comorbidities, cancer-related symptoms, and/or treatment-related adverse events (AEs) but also has a high probability of achieving survival benefit and/or improvement in the PS score after supportive care and antitumor treatment based on dynamic and precise testing (21).

*Statistical analysis*

An unpaired *t* test was used to compare continuous variables between the groups. The chi-squared or Fisher exact tests were used to compare categorical variables between the two groups. OS was calculated from the diagnosis of severe lung cancer until death. Cox proportional hazard regression models were used to estimate hazard ratios (HRs) with 95 % confidence intervals (CIs) for OS for multivariate models. Risk factors with P≤0.1 in the univariate analysis were included in the multivariate analysis. The hazard ratios (HR) the 95% confidence intervals (95% CIs) are reported. Kaplan-Meier survival curves were used to evaluate the OS of patients, and the log-rank test was used to assess differences between groups. A P value of <0.05 indicated statistical significance for all tests. The statistical significance levels were all 2-sided. SPSS version 22.0 (IBM Corp., Armonk, NY, USA) was used for analysis, and the graphs were generated using GraphPad Prism 8.0.2 (GraphPad Software, San Diego, CA, USA)

## Results

*Cross-sectional study of patients with severe lung cancer*

Clinical data of patients with lung cancer were collected and analyzed by 12 clinicians from 3 hospitals according to the inclusion criteria and the screening procedure for eligible cases (Figure S1). We collected data from 1,725 patients with advanced lung cancer who received antitumor therapy. Of them, 226 patients (13.10%) developed severe lung cancer (Figure S2). The demographic characteristics of the 1,725 advanced lung cancer patients were shown in *Table 1*. Severe lung cancer patients were mainly stage IV non-squamous NSCLC elderly male patients without gene mutation, and few patients had a history of lung cancer resection. We compared the differences in clinical characteristics between patients with severe lung cancer and non-severe lung cancer and found that the proportion

of patients with smoking history (50.4%) in the severe lung cancer group was significantly more than that in the non-severe lung cancer group (40.8%; $\chi^2$=7.449; P=0.006; *Table 1*), and the proportion of patients with comorbidities in the severe lung cancer group (46.9%) was significantly more than that in the non-severe lung cancer group (36.4%; $\chi^2$=9.171; P=0.002; *Table 1*). We then analyzed the 3 primary causes of severe lung cancer in 226 patients (*Figure 1A*). Among them, treatment-related AEs were the most common primary cause (46.02%), followed by cancer-related symptoms (45.58%), and then pre-existing comorbidities (8.41%). Further analyzing the specific causes, we found that immunotherapy-related adverse events (irAEs) (25.66%) occurred the most frequently among the treatment-related AEs. For cancer-related symptoms, pleural effusion (18.18%) appeared the most often, and chronic obstructive pulmonary disease (COPD; 4.42%) was the most common comorbidity leading to severe lung cancer (*Figure 1B-1D*).

*Statistical analysis of fatal case data*

We included the data of 269 deceased patients with advanced lung cancer according to the inclusion criteria (Figure S3). Among them, 101 cases (37.55%) developed severe lung cancer from diagnosis to death (Figure S4). Furthermore, we analyzed the 3 primary causes of severe lung cancer development in these 101 patients, with the most common being cancer-related symptoms (54.46%), followed by treatment-related AEs (39.60%) (*Figure 2A*). Pre-existing comorbidities accounted more only a minor proportion of primary causes (5.94%). For the specific causes of severe lung cancer, pleural effusion (21.78%) was the most common cause of cancer-related symptoms. The most common cause of treatment-related AEs was chemotherapy-induced neutropenia accompanied by infection (24.75%). COPD, heart failure, and interstitial lung disease had equal proportions among the comorbidities (1.98%) (*Figure 2B-2D*).

We further explored the risk factors for OS in deceased patients who developed severe lung cancer (n=101). The results showed that patients with genetic mutations (adjusted HR 0.619; 95% CI: 0.406–0.944) and severe lung cancer caused by treatment-related AEs (adjusted HR 1.282; 95% CI: 1.042–1.578) were significant risk factors associated with OS (*Table 2*, *Figure 3*). The OS of deceased patients with the genetic mutation was better than that of the control group (8 *vs.* 5 months; P=0.026; Figure S5). In

464

Wang et al. Severe lung cancer in the real world

**Table 1** Differences in clinical characteristics between the severe lung cancer and non-severe lung cancer patients in cross-sectional study

| Category and subcategory | Severe lung cancer (n=226) | Non-severe lung cancer (n=1,499) | Total | P value |
|---|---|---|---|---|
| Age (years), mean ± SD | 64.27±11.16 | 62.85±11.11 | 63.04±11.12 | 0.07 |
| Age, n (%) | | | | 0.19 |
| ≥65 | 124 (54.9) | 752 (50.2) | 876 (50.8) | |
| <65 | 102 (45.1) | 747 (49.8) | 849 (49.2) | |
| Gender, n (%) | | | | 0.50 |
| Male | 164 (72.6) | 1,055 (70.4) | 1,219 (70.7) | |
| Female | 62 (27.4) | 444 (29.6) | 506 (29.3) | |
| Smoking history, n (%) | | | | 0.006 |
| No | 112 (49.6) | 887 (59.2) | 999 (57.9) | |
| Yes | 114 (50.4) | 612 (40.8) | 726 (42.1) | |
| Pathological classification, n (%) | | | | 0.06 |
| Nonsquamous NSCLC | 146 (64.6) | 1,067 (71.2) | 1,213 (70.3) | |
| Squamous cell carcinomas | 57 (25.2) | 279 (18.6) | 336 (19.5) | |
| Small cell lung cancer | 23 (10.2) | 153 (10.2) | 176 (10.2) | |
| Location, n (%) | | | | 0.08 |
| Central | 107 (47.3) | 618 (41.2) | 725 (42.0) | |
| Peripheral | 119 (52.7) | 881 (58.8) | 1,000 (58.0) | |
| Neoplasm staging, n (%) | | | | 0.80 |
| IIIB and IIIC | 35 (15.5) | 242 (16.1) | 277 (16.1) | |
| IV | 191 (84.5) | 1,257 (83.9) | 1,448 (83.8) | |
| Genetic mutations, n (%) | | | | 0.68 |
| No | 167 (73.9) | 1,127 (75.2) | 1,294 (75.0) | |
| Yes | 59 (26.1) | 372 (24.8) | 431 (25.0) | |
| Operation history, n (%) | | | | 0.757 |
| No | 196 (86.7) | 1,311 (87.5) | 1,507 (87.4) | |
| Yes | 30 (13.3) | 188 (12.5) | 218 (12.6) | |
| Comorbidities, n (%) | | | | 0.002 |
| No | 120 (53.1) | 953 (63.6) | 1,073 (62.2) | |
| Yes | 106 (46.9) | 546 (36.4) | 652 (37.8) | |
| History of other tumors, n (%) | | | | 0.326 |
| No | 211 (93.4) | 1,423 (94.9) | 1,634 (94.7) | |
| Yes | 15 (6.6) | 76 (5.1) | 91 (5.3) | |
| Family history of cancer, n (%) | | | | 0.973 |
| No | 219 (96.9) | 1,465 (97.7) | 1,684 (97.6) | |
| Yes | 7 (3.1) | 34 (2.3) | 41 (2.4) | |

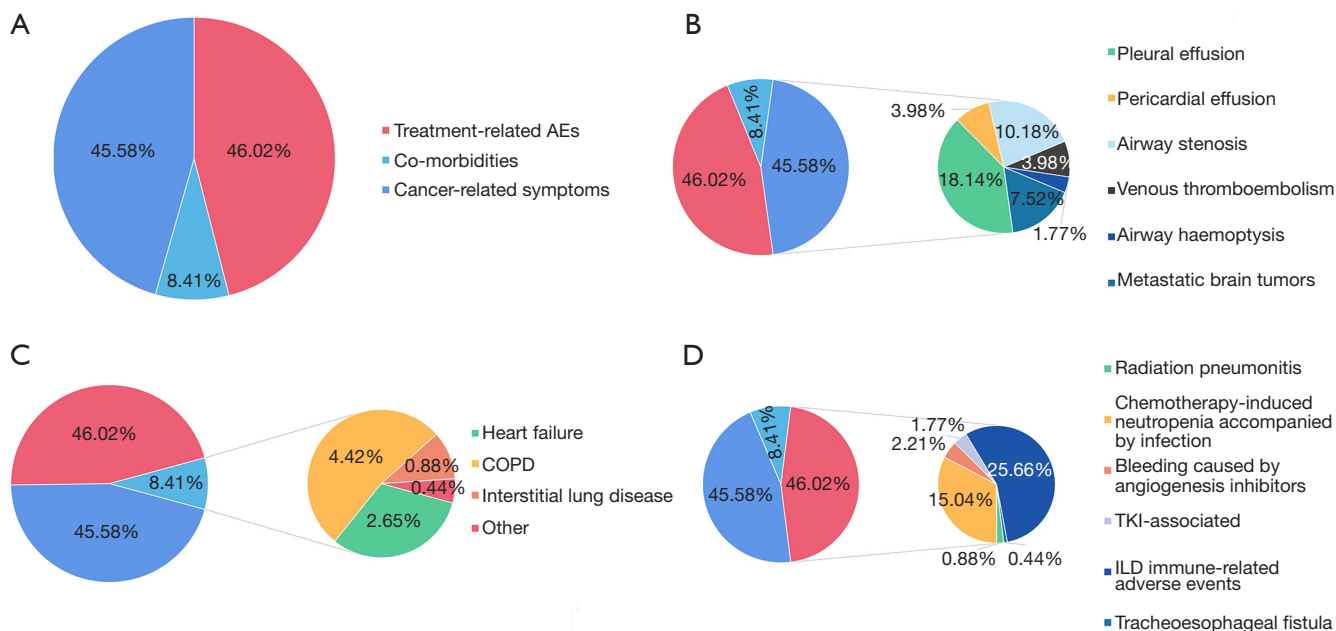SD, standard deviation; NSCLC, non-small cell lung cancer.

**Figure 1** Primary and specific causes of severe lung cancer in the cross-sectional study. (A) The 3 primary causes of severe lung cancer; (B-D) specific causes of severe lung cancer in the cross-sectional study. AEs, adverse events; COPD, chronic obstructive pulmonary disease; TKI, tyrosine kinase inhibitor; ILD, interstitial lung disease.
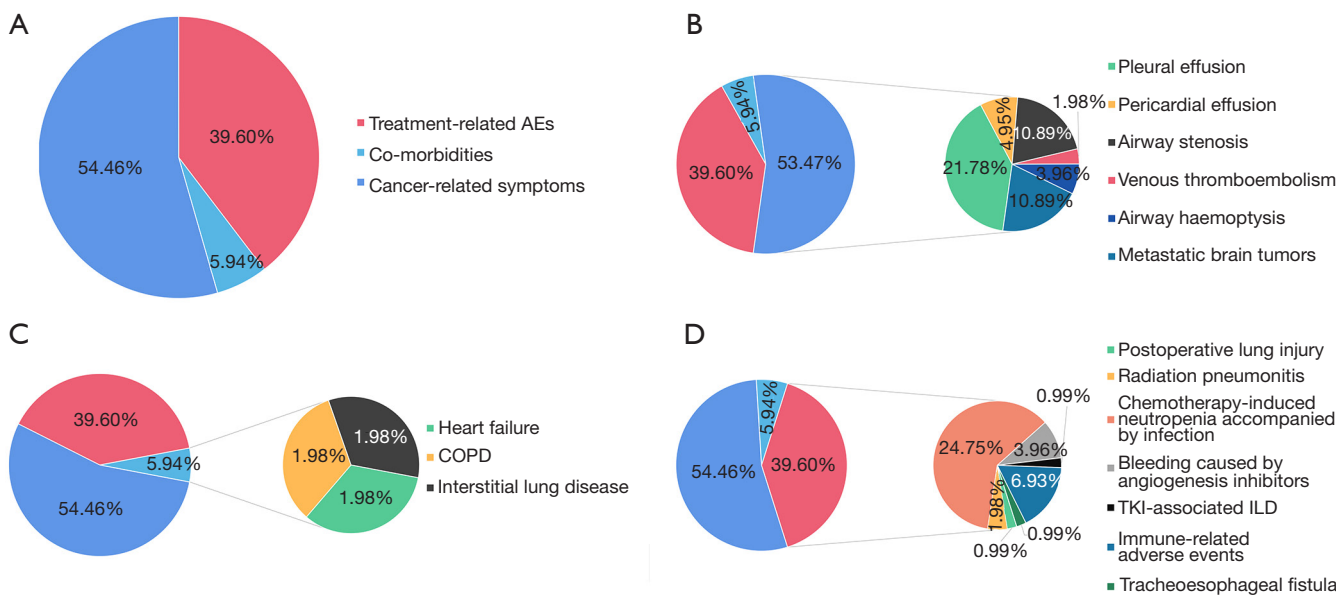


**Figure 2** Primary and specific causes of patients who developed severe lung cancer in 101 fatal cases. (A) The 3 primary causes of severe lung cancer; (B-D) specific causes of severe lung cancer in fatal cases. AEs, adverse events; COPD, chronic obstructive pulmonary disease; TKI, tyrosine kinase inhibitor; ILD, interstitial lung disease.

**Table 2** Cox regression analysis of the association between risk factors and death in deceased serve lung cancer patients (n=101)

| Category and subcategory | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | HR (95% CI) | P value | HR (95% CI) | P value |
| Age (≥65 *vs.* <65 years) | 0.90 (0.61, 1.33) | 0.60 | – | – |
| Gender (male *vs.* female) | 0.91 (0.57, 1.46) | 0.70 | – | – |
| Pathological classification | | | | |
|   Nonsquamous NSCLC | 1 (ref) | – | 1 (ref) | – |
|   Squamous cell carcinomas | 0.55 (0.28, 1.10) | 0.09 | 0.52 (0.26, 1.05) | 0.07 |
|   Small cell lung cancer | 0.62 (0.35, 1.10) | 0.10 | 0.89 (0.68, 1.66) | 0.72 |
| Neoplasm staging (IIIB and IIIC *vs.* IV) | 1.10 (0.62, 1.94) | 0.74 | – | – |
| Genetic mutations (no *vs.* yes) | 0.62 (0.41, 0.94) | 0.03 | 0.58 (0.36, 0.95) | 0.03 |
| Operation history (no *vs.* yes) | 0.77 (0.44, 1.33) | 0.35 | – | – |
| Comorbidities (no *vs.* yes) | 1.09 (0.68, 1.74) | 0.74 | – | – |
| History of other tumors (no *vs.* yes) | 0.80 (0.25, 2.59) | 0.71 | – | – |
| Primary causes | | | | |
|   Cancer-related symptoms | 1 (ref) | – | 1 (ref) | – |
|   Comorbidities | 2.03 (0.85, 4.83) | 0.11 | 0.64 (0.42, 0.98) | 0.78 |
|   Treatment-related AEs | 1.28 (1.04, 1.58) | 0.02 | 1.13 (0.47, 2.74) | 0.04 |

HR, hazard ratio; CI, confidence interval; AEs, adverse events; NSCLC, non-small cell lung cancer.
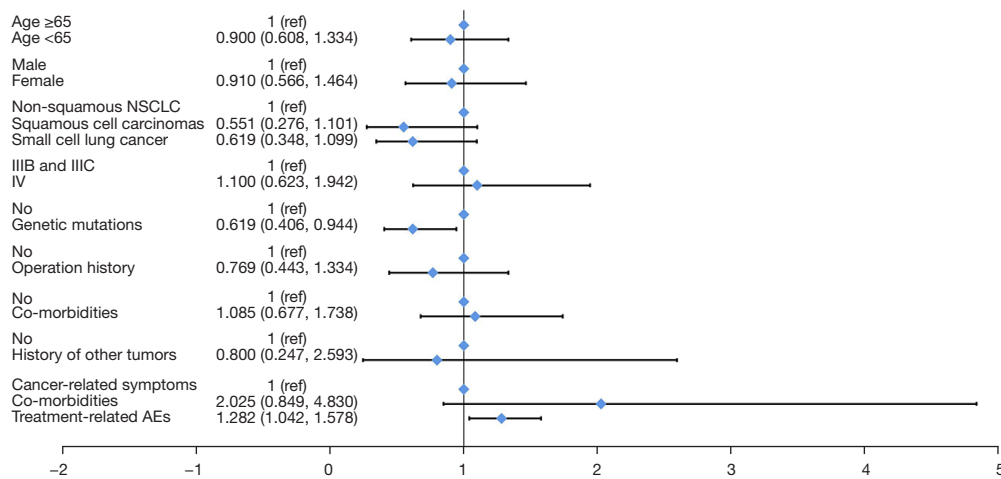


**Figure 3** Forest plot depicting the multivariate analysis of risk factors for 101 fatal cases of severe lung cancer. NSCLC, non-small cell lung cancer; AEs, adverse events.

addition, the OS of patients who developed severe lung cancer due to cancer-related symptoms was better than that of those who developed it from treatment-related AEs (8 *vs.* 3 months; P=0.019). The median OS for patients with comorbidities was 5 months, but due to the small number of patients in this subset (n=6), we did not statistically compare it with the other two causes (*Figure 4*). After excluding the 6 patients with severe lung cancer caused by comorbidities,
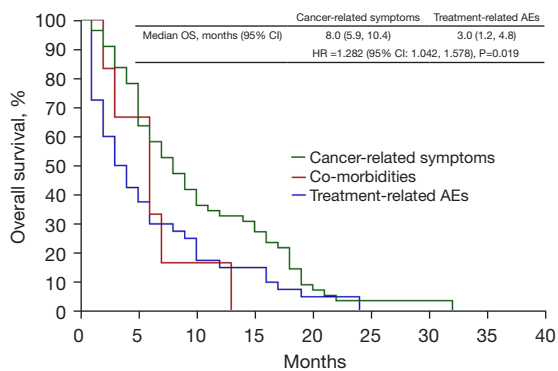
**Figure 4** Survival curves among deceased patients who developed severe lung cancer caused by different causes. Due to the small number of patients (n=6), we omitted patients with severe lung cancer caused by comorbidities. AEs, adverse events; HR, hazard ratio; CI, confidence interval; OS, overall survival.

we compared the baseline data of patients with severe lung cancer caused by cancer-related symptoms (n=55) with those from patients with treatment-related AE causes (n=40) (Table S1). After analyzing the data, we found that there are more patients aged 65 years and above in the treatment-related AE group (65.00%) than cancer-related symptoms group (35.50%), and the difference was statistically significant ($\chi^2$=8.615; P=0.003).

*Questionnaire for clinicians*

In total, 617 clinicians from 27 provinces in mainland China completed the questionnaire, including 316 respiratory physicians, 232 oncologists, 22 thoracic surgeons, 19 radiotherapy physicians, and 5 interventional physicians (Figure S6). Furthermore, 97.01% of clinicians had experience diagnosing and treating newly diagnosed lung cancer patients with poor PS scores, and 41.03% of physicians frequently experienced the above. When asked to identify what caused a poor PS scores, 81.90% of clinicians indicated pre-existing comorbid conditions, and 89.37% indicated cancer-related symptoms (Figure S7A,S7B). When asked about treating using antitumor therapy in patients with lung with cancer, 99.26% of clinicians indicated they experienced treating patients with poor PS scores, and 40.49% of physicians indicated they frequently experienced the above. Moreover, 77.24% of clinicians believed that comorbidities can cause poor PS scores, 91.60% thought that cancer-related symptoms were one of the primary causes, and 78.73% believed that treatment-

related AEs were one of the primary causes (Figure S7C,S7D). As for the severe lung cancer concept, 90.26% of clinicians agreed with this concept, 91.56% believed that the severe lung cancer concept has more therapeutic value than does that of end-stage lung cancer, and 98.21% thought that it is necessary to distinguish groups of patients with severe lung cancer (Figure S8A-S8C). For lung cancer patients with comorbidities, 92.54% of clinicians thought it necessary to treat both lung cancer and comorbidities (Figure S8D). In the questionnaire, we set up a 10-point scale assessment to allow clinicians to evaluate their ability to manage patients with severe lung cancer, with the majority of clinicians scoring between 5 and 8 points (Figure S9A). After comparing the scores of the two major groups of clinicians, we found that most respiratory clinicians scored 7 points (19.69%) while oncologists scored 6 points (28.95%) (Figure S9B). Concerning the treatment strategy recommended in the international consensus on severe lung cancer, each recommendation was supported by more than 75% of clinicians, and the highest rate of support was for multidisciplinary participation and individualized and comprehensive treatment (94.22%), while the lowest was for the escalation/de-escalation of chemotherapy drugs (75.75%) (Figure S10).

## Discussion

Patients with lung cancer with poor PS [2–4] at diagnosis have poor survival rates and a high incidence in clinic (25,26). According to the questionnaire results, 97.01% of clinicians have treated patients with newly diagnosed lung cancer and poor PS scores, and 99.25% encountered poor PS scores in patients undergoing antitumor treatment. Based on this background, we defined a subset of patients with the potential for remission of severe lung cancer, as supported by 90.66% of clinicians. In the study, 12 clinicians from 3 hospitals conducted cross-sectional statistical analysis and found that 10.70–25.35% of patients with advanced lung cancer developed severe lung cancer. Moreover, further analyzing the data of fatal cases revealed that 18.29–56.30% had severe lung cancer at least once from tumor diagnosis to death. The results show that severe lung cancer is prevalent in patients with advanced lung cancer based on real-world evidence.

Distinguishing the causes of severe lung cancer is essential for the subsequent management of patients. Previous research points to cancer-related symptoms or pre-existing comorbid conditions that can affect PS scores of

those with newly diagnosed lung cancer (12,27). According to the questionnaire, more than 81.89% of clinicians agreed that there are two main causes of the poor PS score of newly diagnosed patients. For patients with lung cancer and antitumor therapy, the occurrence of treatment-related AEs is also a fundamental cause of the deterioration of PS score. Targeted drugs and ICIs have dramatically benefited the survival of patients with lung cancer; however, even if ICIs are generally better tolerated than are chemotherapy, they are not free from toxicities (28-30). From analyzing the causes of severe lung cancer in 3 participating institutes, we found that the primary cause for severe lung cancer in the cross-sectional study was treatment-related AEs, with irAEs accounting for the majority. However, in the 101 fatal cases of severe lung cancer, pleural and pericardial effusion as cancer-related symptoms ranked first as causes of severe lung cancer, ahead of treatment-related AEs. We analyzed the factors underlying this contrast and found that the start date for enrollment in the cross-sectional study was January 1, 2022, and thus more patients had the opportunity to receive immunotherapy, resulting in more irAEs. On the other hand, the primary treatment for patients in fatal cases was chemotherapy, so the most common treatment-related adverse reaction was chemotherapy-induced neutropenia accompanied by infection (24.75%). Moreover, pleural and pericardial effusion are common symptoms of patients lung with cancer and can easily lead to poor PS scores and quickly be relieved by treatment in clinical practice. Hence, the survival time of the 101 fatal cases with advanced lung cancer who developed severe lung cancer caused by treatment-related AEs was shorter than that of those caused by cancer-related symptoms (8 and 3 months; P<0.05). Moreover, we believe that with the advances of antitumor treatment, treatment-related AEs will become the main contributor to severe lung cancer.

In our data, the patients with severe lung cancer caused by comorbidities were 8.41% and 5.94% in the 2 study cohorts. We considered that there might be several reasons for the small proportion of patients with comorbidities being the cause of severe lung cancer: (I) as this was a retrospective observational study based on electronic medical records, clinicians might have been unable to distinguish the symptoms of comorbidities and tumors; (II) some clinicians could have ignored the diagnosis and treatment of comorbidities in the patients with lung cancer. For example, previous study has pointed out that oncologists may be neglectful in diagnosing and treating COPD in patients with lung cancer and COPD (31). However, comorbidity

is not only a critical cause of severe lung cancer but also affects the patient's prognosis. Previous studies by our own and Hyunji's group found that standardized management of comorbidities can prolong the survival of those with lung cancer (32,33). Moreover, 92.54% of clinicians in the questionnaire thought that the treatment of both lung cancer and comorbidities was necessary.

The previous reports of poor outcomes of patients with cancer and poor PS scores in the literature might have led clinicians to forego early life-sustaining therapy; however, clinicians must be up to date with the literature to improve their clinical skills and willingness to care for patients (18,34). This was also the main impetus for developing our concept of severe lung cancer. The self-assessment results of clinician' confidence in the questionnaire showed that most clinicians had the confidence and willingness to manage patients with severe lung cancer.

To our best knowledge, this is the first epidemiological study based on real-world data to examine a population of patients with severe lung cancer. Nonetheless, some limitations of the current study should be noted. First, the diagnostic criteria for severe lung cancer were based on the change in the PS score of the patient, and the PS score is a subjective standard. However, we did require at least two clinicians in each participating center to evaluate the PS score independently and negotiate a consensus on the score, but discrepancies were inevitable, especially between different centers. Second, we used a retrospective observational study design that relied on the electronic medical record system. Therefore, the reliability of the data concerning the statistical and analytical results of severe lung cancer causes should be scrutinized. Finally, the level of evidence of questionnaire studies is considered controversial, so the results of the clinician questionnaire should be verified further.

## Conclusions

The incidence of severe lung cancer in advanced lung cancer patients is 13.10% in real-world clinical practice, and the concept of severe lung cancer is supported by the vast majority of clinicians in the field. Severe lung cancer patients were mainly stage IV non-squamous NSCLC elderly male patients without gene mutation, and few patients had a history of lung cancer resection. And compared with common lung cancer patients, the proportion of smoking in severe lung cancer patients is less but more comorbidities. With the development of

antitumor treatment, treatment-related AEs have gradually become the most common cause of severe lung cancer, more so than cancer-related symptoms and co-morbidities. Furthermore, the prognosis of patients with advanced lung cancer who develop severe lung cancer due to treatment-related AEs is worse than that of patients who do so from cancer-related symptoms.

## Acknowledgments

## Footnote

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*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 of the First Affiliated Hospital of Guangzhou Medical University (No. 2021-38). Each participating center was informed and agreed with this study. Individual consent for this retrospective analysis was waived.

*Open Access Statement:* This is an Open Access article

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(English Language Editor: J. Gray)

### Appendix 1 The questionnaire for clinicians on severe lung cancer

*Investigation of severe lung cancer*

Our team proposed the concept of advanced and severe lung cancer in 2012. After continuous improvement, it was officially published in the *Chinese Journal of Oncology* in 2017. In 2019, the team proposed the "Diagnosis and Treatment Strategies for Advanced Severe Lung Cancer" in the *Chinese Journal of Practical Internal Medicine*. Furthermore, it published the "International Consensus on Severe Lung Cancer (First Edition) in the *Journal of Translational Research in Lung Cancer* in 2021. To understand your colleagues' understanding of the concept of severe lung cancer, we conducted this survey. To fully protect your privacy, the survey will be completed anonymously. We also declare that the data collected in this survey will only be used for academic research and will only be handled by professional researchers related to this topic. Furthermore, the statistical analysis will not involve any specific individual or unit; your answers will be confidential. Thank you again for your support and cooperation!

**National Clinical Research Center for Respiratory Disease**
**China Respiratory Oncology Collaboration**

1. Your work unit level is [multiple choice]

☐ Grade-one hospital

☐ Grade-two hospital

☐ Tertiary hospital

2. What is the level of your work unit? [Multiple choice]

☐ Class a

☐ Class b

☐ Class c

3. What department do you work in? [Multiple choice]

☐ Respiratory

☐ Thoracic surgery

☐ Oncology

☐ Radiotherapy department

☐ Intervention division

☐ Others _____ *

4. What is your professional title? [Multiple choice] *

☐ No Title

☐ Junior professional title

☐ Intermediate title

☐ Senior title

5. Your work unit is located in: [fill in the blanks] *

6. Do you see or treat lung cancer at work? [Multiple choice] *

☐ Consultation but no treatment

☐ Consultation and treatment

☐ No consultation but treatment

☐ No consultation or treatment

7. What stage of lung cancer patients have you encountered or treated? [Multiple Choice Questions] *

☐ Early

☐ Locally advanced

☐ Advanced

8. In your newly diagnosed lung cancer patients, are there often patients with PS 2–4? [Multiple choice] *

○ Seldom (30%)

○ Sometimes (50%)

○ Frequently (80%)

9. What are the main factors that cause newly diagnosed lung cancer patients to have PS 2–4? [Multiple Choice Questions] *

☐ Comorbidities (COPD, ILD, hypertension, diabetes, heart failure, stroke, etc.)

☐ Cancer-related symptoms (pulmonary embolism, brain metastasis, bone metastasis, etc.)

☐ Other: _____*

10. Are treated lung cancer patients prone to PS 2–4? [Multiple choice] *

○ Seldom (30%)

○ Sometimes (50%)

○ Frequently (80%)

11. What are the main factors leading to PS 2–4 for lung cancer patients undergoing treatment? [Multiple Choice Questions] *

☐ Comorbidities (COPD, ILD, hypertension, diabetes, heart failure, stroke, etc.)

☐ Tumor complications (pulmonary embolism, brain metastasis, bone metastasis, etc.)

☐ Treatment-related adverse reactions (such as hepatitis, pneumonia, surgical complications, radiotherapy-related complications, etc.)

☐Other: _____*

12. Among the lung cancer patients you have treated, how many are prone to recurring PS of 2–4 (more than twice)? [Multiple choice] *

○ Seldom (30%)

○ Sometimes (50%)

○ Frequently (80%)

13. End stage lung cancer refers to patients whose PS is 2–4, for whom only palliative care relieve symptoms. Do you agree with this view? [Multiple choice] *

○ Agree

○ Somewhat agree

○ Not sure

14. What is your understanding of end stage and advanced lung cancer? [Multiple choice] *

○ End stage lung cancer is advanced lung cancer

○ End stage lung cancer is the critical stage of advanced lung cancer

○ End stage lung cancer is the critical stage of lung cancer and is not entirely related to the stage of lung cancer

○ Not sure

15. Severe lung cancer is a disease in which the patient has a PS (performance status) score between 2 and 4 in certain stages due to various acute or chronic comorbidities, the tumor itself, and treatment-related AEs but also has a high probability of achieving survival benefit and/or improvement in the PS score after supportive care and antitumor treatment based on dynamic and precise testing (PMID: 34295668). Do you agree with the above point of view? [Multiple choice] *

○ Agree

○  Somewhat agree

○  Not sure

16. What is your understanding of severe lung cancer and end stage lung cancer? [Multiple choice] *

○ Severe lung cancer is end stage lung cancer

○ Severe lung cancer is not necessarily end stage lung cancer

○ Severe lung cancer and end stage lung cancer are two completely different concepts

○  Not sure

17. The most significant difference between severe lung cancer and end stage lung cancer is that severe lung cancer has clinical therapeutic value (survival benefit and/or PS score improvement from various treatments). Do you agree with this point of view? [Multiple choice] *

○ Agree

○  Somewhat agree

○  Not sure

18. In clinical work, do you think it is necessary to distinguish patients with end stage lung cancer from those with severe lung cancer? [Multiple choice] *

○  Very necessary

○  Necessary

○ Not necessary

○ It does not matter

19. What is your treatment strategy for patients with severe lung cancer caused by pulmonary complications (such as COPD, interstitial lung, tuberculosis)? [Multiple choice] *

○ Tumor treatment only

○ Treatment of comorbidities only

○ Same treatment for the cancer and lung

○ Palliative care

20. What is your confidence in dealing with severe lung cancer? [Multiple choice] *

○ Not at all sure ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○ Master

21. Which of following treatment strategies for severe lung cancer do you recognize?: [Multiple Choice Questions] *

☐ Same treatment for the cancer and lung

☐ Select the treatment method according to the PS score

☐ Upgrade and downgrade of antitumor drugs

☐ Dynamic and accurate detection (identify treatment targets or avoid high-risk treatment groups)

☐ Combination of antitumor therapy, synergistic effect, and detoxification

## Appendix 2 ECOG Performance Status Scale

| Grade | ECOG Performance Status |
|-------|-------------------------|
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours |
| 3 | Capable of only limited self-care; confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled; cannot carry an any self-care; totally confined to bed or chair |
| 5 | Dead |

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982 Dec;5(6):649-55. PMID: 7165009.

**Table S1** Clinical characteristics of fatal cases with sever lung cancer from different causes (n=95)

| Category and subcategory | Cancer-related symptoms (n=55) | Treatment-related AEs (n=40) | Total | P value |
|---|---|---|---|---|
| Age (y), n (%) | | | | <0.001 |
| ≥65 | 19 (35.6) | 26 (65.0) | 45 (47.4) | |
| <65 | 36 (65.4) | 14 (36.0) | 50 (52.6) | |
| Gender, n (%) | | | | 0.90 |
| Male | 42 (76.4) | 31 (77.5) | 73 (76.8) | |
| Female | 13 (23.6) | 9 (22.5) | 22 (23.2) | |
| Pathological classification, n (%) | | | | 0.30 |
| Nonsquamous NSCLC | 40 (72.7) | 25 (62.5) | 65 (68.4) | |
| Squamous cell carcinomas | 10 (18.2) | 7 (17.5) | 17 (17.9) | |
| Small cell lung cancer | 5 (9.1) | 8 (20.0) | 13 (13.7) | |
| Neoplasm staging, n (%) | | | | 0.58 |
| IIIB and IIIC | 9 (16.4) | 5 (12.5) | 14 (14.7) | |
| IV | 46 (83.6) | 35 (87.5) | 81 (85.3) | |
| Genetic mutations, n (%) | | | | 0.13 |
| No | 30 (54.5) | 30 (72.0) | 60 (63.2) | |
| Yes | 25 (45.5) | 10 (25.0) | 35 (36.8) | |
| Operation history, n (%) | | | | 0.99 |
| No | 47 (85.5) | 34 (85.0) | 81 (85.3) | |
| Yes | 8 (15.5) | 6 (15.0) | 14 (14.7) | |
| Comorbidities, n (%) | | | | 0.48 |
| No | 46 (83.6) | 30 (75.0) | 76 (80.0) | |
| Yes | 9 (16.4) | 10 (25.0) | 19 (20.0) | |
| History of other tumors, n (%) | | | | 0.95 |
| No | 54 (98.2) | 38 (95.0) | 92 (96.8) | |
| Yes | 1 (1.8) | 2 (5.0) | 3 (3.2) | |

NSCLC, non-small cell lung cancer.

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┌─────────────────────────────────────┐
│   Hospitalized patients from Jan 1 to June  │
│          30,2022(n=2191)            │
└─────────────────────────────────────┘
              │           ────────────────►
              │           Patients aged<18 years(n=16)
              ▼
┌─────────────────────────────────────┐
│   Patients aged at least 18 years    │
│           old (n=2175)              │
└─────────────────────────────────────┘
              │           ────────────────►
              │           Non-advanced lung cancer(n=278)
              ▼
┌─────────────────────────────────────┐
│  Patients aged at least 18 years old │
│  with advanced lung cancer (n=1897) │
└─────────────────────────────────────┘
              │           ────────────────►
              │           No anti-tumor treatment (n=143)
              ▼
┌─────────────────────────────────────┐
│    Advanced lung cancer patients with │
│     anti-tumor treatment(n=1754)    │
└─────────────────────────────────────┘
              │           ────────────────►
              │           Incomplete data(n=29)
              ▼
┌─────────────────────────────────────┐
│    Advanced lung cancer patients     │
│            (n=1725)                 │
└─────────────────────────────────────┘
              │
              ▼
        ┌──────────┐
        │  PS(2-4) │──────────────────────────┐
        └──────────┘        No                │
              │ Yes                            │
              ▼                                │
┌─────────────────────────────┐               │
│   PS(0-1) during the follow-up │──────────►  │
│      by June 30,2020        │     No        │
└─────────────────────────────┘               │
              │ Yes                            │
              ▼                                ▼
┌─────────────────────┐         ┌─────────────────────┐
│  Severe lung cancer │         │  Nonsevere lung cancer │
│      (n=226)        │         │      (n=1499)        │
└─────────────────────┘         └─────────────────────┘
```
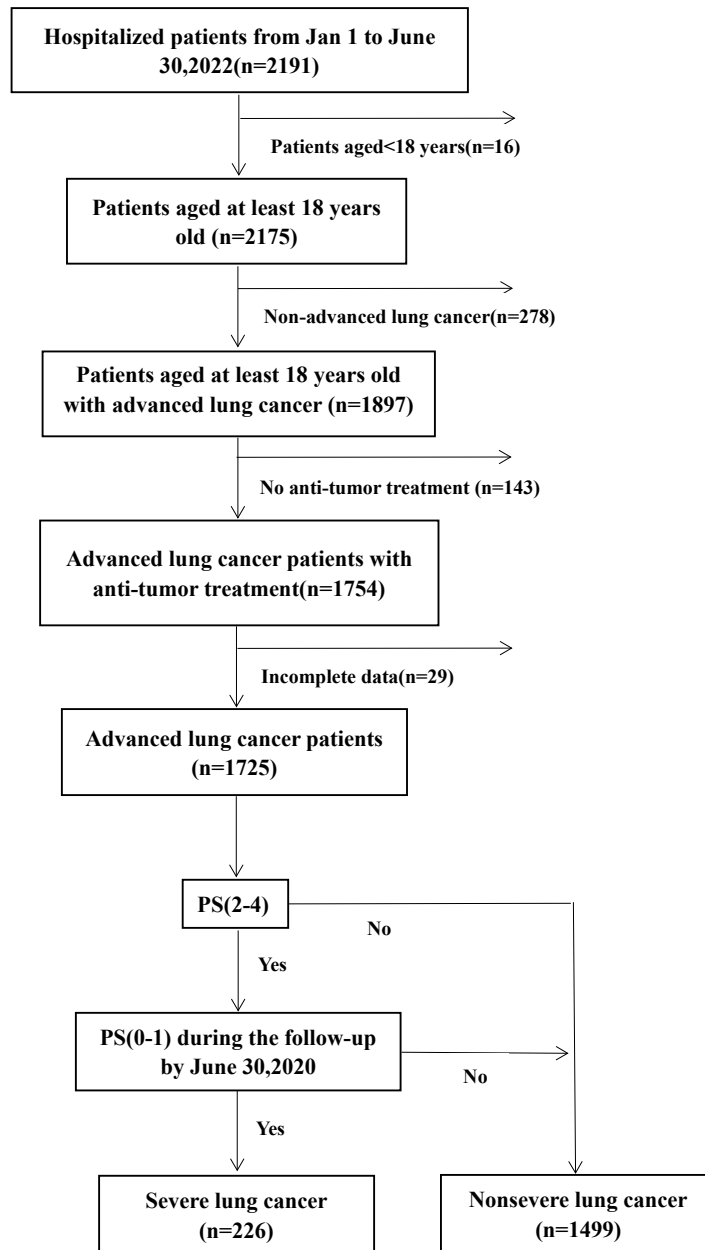
**Figure S1** Flowchart of the enrolled patients with advanced lung cancer in the cross-sectional study. PS, performance status.
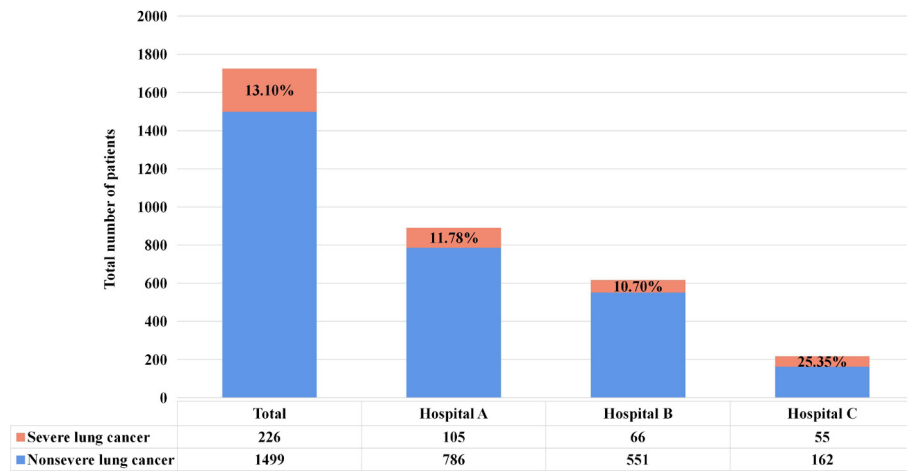
**Figure S2** The incident of severe lung cancer from 3 participating institutes in the cross-sectional study.
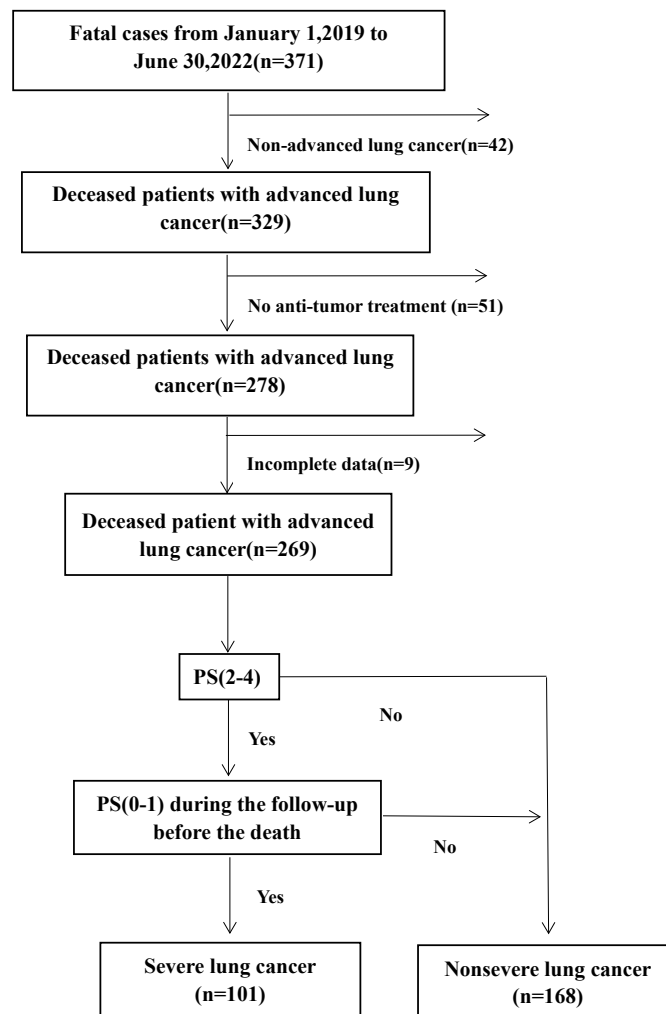


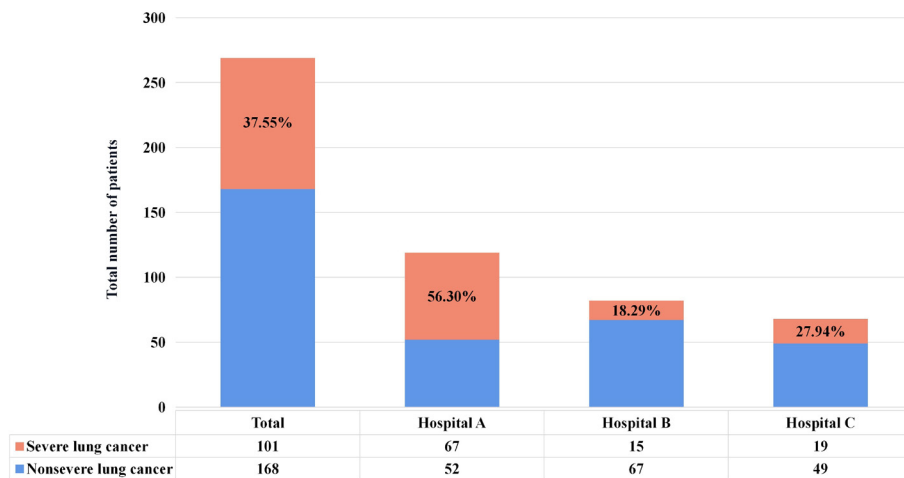**Figure S3** Enrollment flowchart of the fatal cases of advanced lung cancer. PS, performance status.

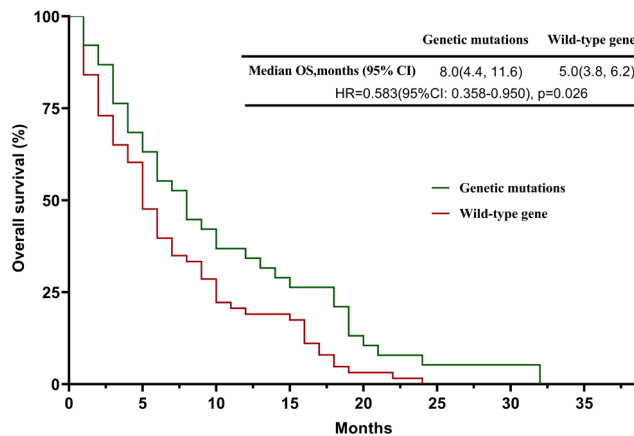**Figure S4** The incident of severe lung cancer from 3 participating institutes in fatal cases.



**Figure S5** Survival curves between patients with genetic mutations and those with wild-type genes in fatal cases of severe lung cancer. OS, overall survival; CI, confidence interval.
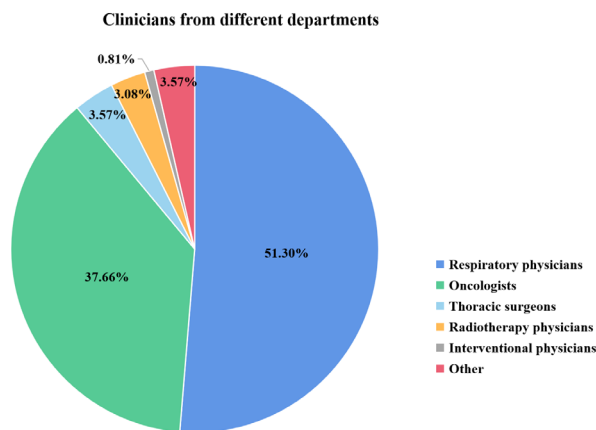


**Figure S6** Department distribution of the 616 clinicians who participated in the questionnaire.
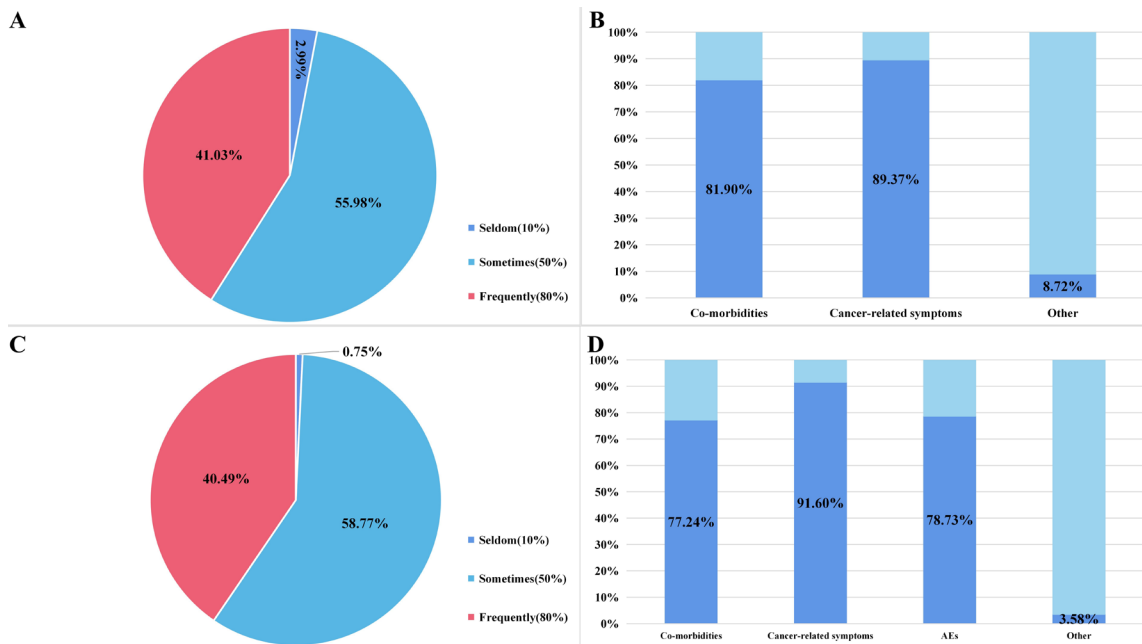
**Figure S7** Panel A shows the frequency at which 616 clinicians diagnosed and treated newly diagnosed lung cancer patients with poor PS scores in clinic. Panel B shows the opinion of 616 clinicians on the causes of poor PS scores in newly diagnosed lung cancer patients. Panel C shows the frequency at which 616 clinicians diagnosed and treated patients with lung cancer and poor PS scores who underwent antitumor therapy in clinic. Panel D shows the opinion of 616 clinicians on the causes of poor PS scores in lung cancer patients who had antitumor treatment in clinic. PS, performance status.
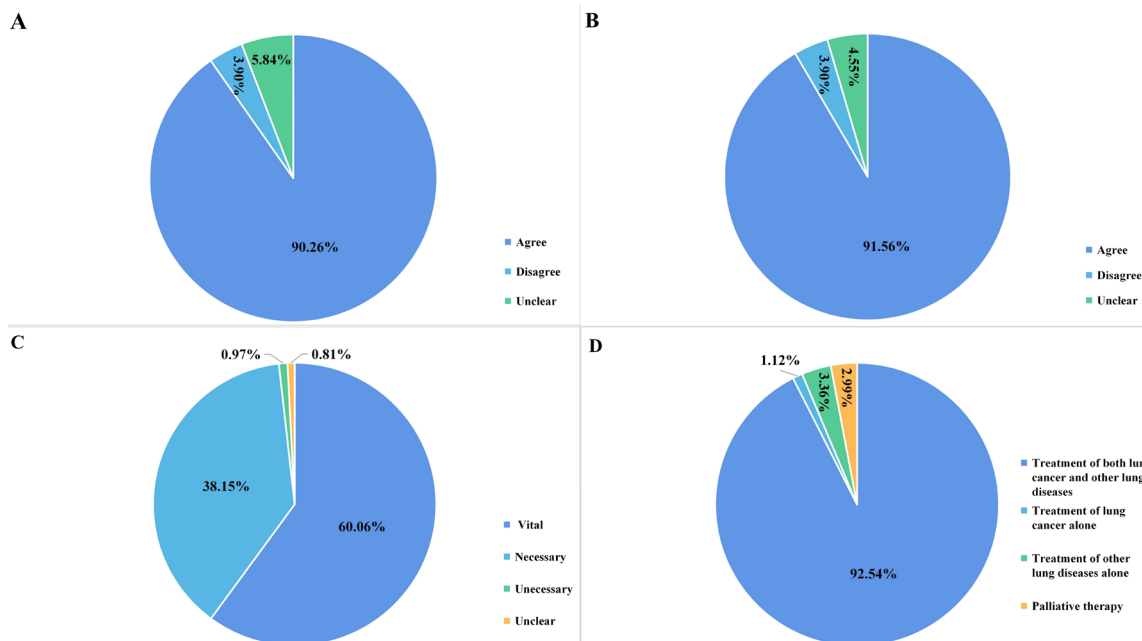


**Figure S8** Panel A shows clinicians' acceptance of the concept of severe lung cancer. Panel B shows clinicians' approval of the therapeutic value of the severe lung cancer concept. Panel C shows clinicians' support of the necessity of distinguishing severe lung cancer from end stage lung cancer. Panel D shows clinicians' support of the necessity to treat both lung cancer and comorbidities.
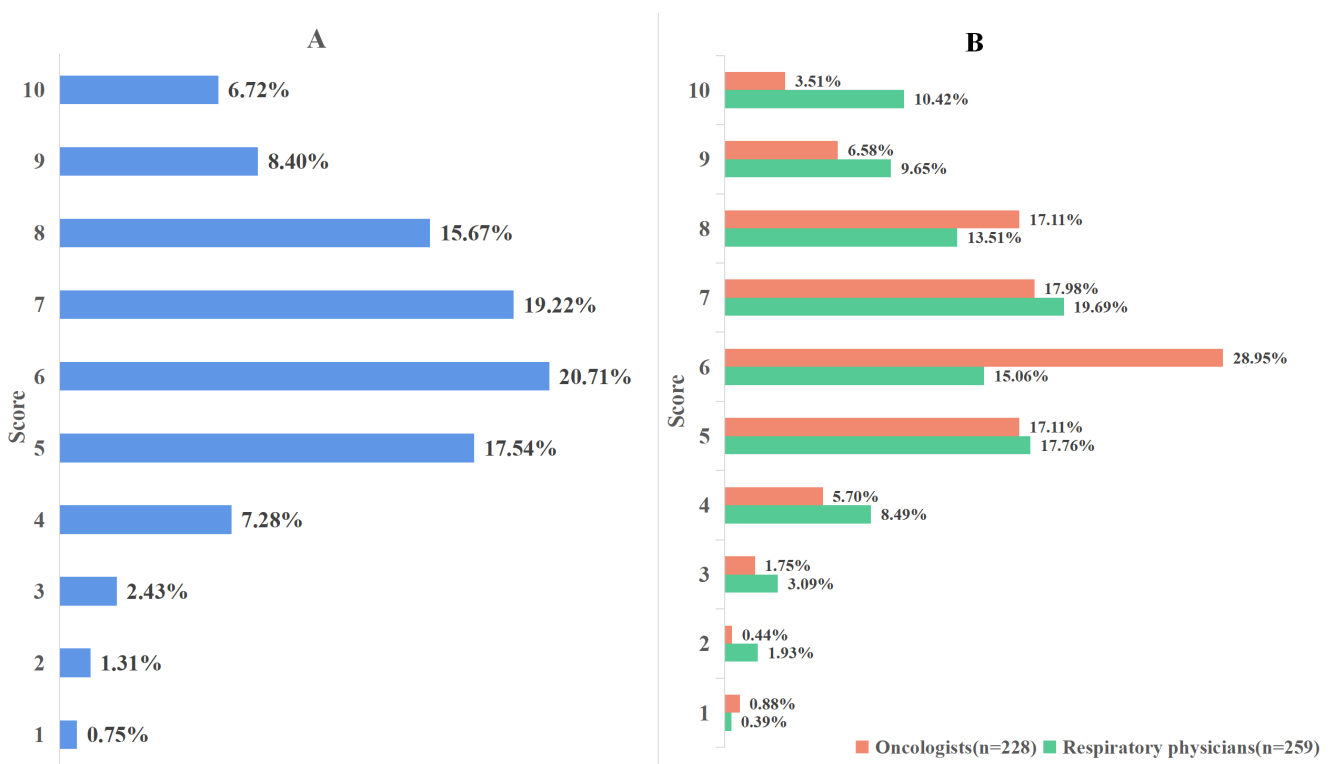
**Figure S9** Panel A shows clinicians' self-assessment of their ability to manage patients with severe lung cancer. Panel B shows the self-assessment of respiratory clinicians' and oncologists' ability to manage patients with severe lung cancer.
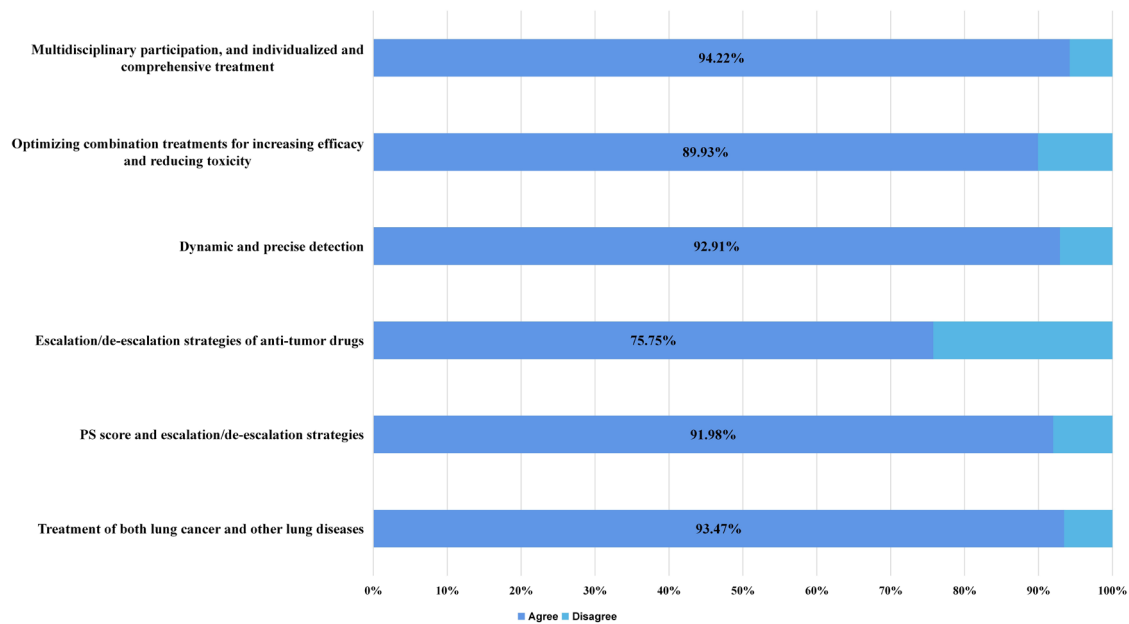


**Figure S10** Clinician support rate for each treatment strategy recommended in the international consensus for severe lung cancer.