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Original Article

Changing profile of lung cancer clinical characteristics in China: Over 8-year population-based study

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ABSTRACT

Background: Although examinations and therapies for bronchial lung cancer, also called lung cancer (LC), have become more effective and precise, the morbidity and mortality of LC remain high worldwide. Describing the changing profile of LC characteristics over time is indispensable. This study aimed to understand the changes in real-world settings of LC and its characteristics in China.

Methods: In this study, 119,785 patients were enrolled from 2012 to 2020 in the Shanghai Pulmonary Hospital. The patients' medical records were extracted from the hospital's database. Demographic characteristics, general clinicopathological information, and blood coagulation indices at the initial diagnoses were analyzed using the Kruskal–Wallis, Nemenyi, chi-squared, and Bonferroni tests. Changes in demographic characteristics during the 8-year study period, namely dynamic changes among different stages and different pathological types, were evaluated.

Results: The percentages of female (from 38.50% [323/839] in 2012 to 48.29% [5112/10,585] in 2020) and non-smoking LC (from 69.34% [475/685] to 80.48% [8055/10,009]) patients increased significantly during the study period, with a trend toward a younger age at diagnosis (from 3.58% [30/839] to 8.99% [952/10,585]). Over the study period, the proportion and absolute number of lung adenocarcinoma cases increased (from 67.97% [433/637] to 76.31% [6606/8657]) while the proportion of lung squamous cell carcinoma decreased (from 21.19% [135/637] to 12.08% [1046/8657]). Comprehensive driver gene mutation examination became more common, and epidermal growth factor receptor (*EGFR*) mutation occurred more frequently in female *vs.* male (62.03% [12793/20625] *vs.* 29.90% [8207/27,447]) and non-smoking *vs.* smoking (53.54% [17,203/32,134] *vs.* 23.73% [3322/13,997]) patients (both $P < 0.001$). The distribution of the common driver genes differed among different stages of LC. *EGFR* mutation was detected most frequently at each stage, and other driver gene alterations were more common in advanced stages ($P < 0.001$). The combination of chemotherapy, targeted therapy, and immunotherapy, as a comprehensive management regimen, gradually became predominant over the study period ($P < 0.001$). A hypercoagulable state was shown in advanced-stage LC patients and patients with the anaplastic lymphoma kinase fusion, indicated by significantly elevated levels of D-dimer, fibrinogen, and fibrinogen degradation products.

Conclusions: This study comprehensively depicted the changing characteristics of Chinese LC patients over an 8-year period to provide preliminary insights into LC treatment.

Trial registration: ClinicalTrials.gov, NCT05423236.

Introduction

As a multi-factorial malignant disease, bronchial lung cancer (LC) remains one of the most common cancers, with high mortality and morbidity worldwide.[1] This suggests that the LC burden has become much heavier in recent years, and the increased use of low-dose spiral computed tomography (LDCT) for early LC screening might have promoted the detection of LC.[2] The etiology of LC is not fully understood. Smoking, genetic susceptibility, and occupational exposure are risk factors for LC.[3] LC has a variety of histological subtypes, in which non-small cell

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lung cancer (NSCLC) and small cell lung cancer (SCLC) constitute 85% and 15% of all LC cases, respectively. Lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) are the two main subtypes of NSCLC. With changes in exposure factors and the development of screening methods, LUAD has replaced LUSC in overall incidence, and the spectrum of LC has changed recently in diagnosed patients.

For early-stage LC, surgery with curative intent is the main treatment.[4] However, many LC patients are diagnosed at advanced stages, and radical surgery is unsuitable for these patients. Therefore, chemotherapy has been the main therapy for advanced LC patients.[5] Chemotherapy provides a survival benefit in some patients and improves their life quality; however, the efficacy is not high.[6] Radiotherapy is another important modality for LC treatment.[7] Since driver mutations were detected in NSCLC, targeted therapy has gradually developed for treating NSCLC with sensitive driver mutations.[8–12] This treatment has also made the detection of driver gene alterations as a routine clinical examination.[13] Targeted therapy effectively prolongs patient survival, but drug resistance is inevitable.[14] Recently, immunotherapy has become widely used in treating LC. Immune checkpoint inhibitors, such as anti-programed death 1 (anti-PD-1) and anti-programed death ligand 1 monoclonal antibodies, have shown promising treatment effect.[15–19]

The composition and treatment of LC have changed; therefore, these changes should be quantified and visually presented. Additionally, it is necessary to understand the changes in real-world settings of LC and its characteristics in China. For this purpose, we collected our patients' records from 2012 to 2020 and analyzed the characteristics of LC in Chinese patients.

Methods

Ethical approval

This long-term, single-center, real-world study was approved by the institutional review board at Shanghai Pulmonary Hospital (No. K22-272). Shanghai Pulmonary Hospital is a leading pulmonary disease specialty hospital in China, with patients presenting from all regions of the country. The personal information for all enrolled LC patients was de-identified; therefore, the requirement to obtain informed consent was exempted.

Database establishment and patient enrollment

An LC database derived from the electronic medical records system was established by Shanghai Pulmonary Hospital, and data leakage prevention was implemented. Data for 119,785 patients with primary LC were extracted from this database. The patients were all diagnosed at Shanghai Pulmonary Hospital from January 1, 2012 to October 31, 2020. Age was specifically extracted and classified into five groups (0–20 years, 21–40 years, 41–60 years, 61–80 years, and 81–100 years) to control for confounding bias associated with age. Patients were staged according to the Eighth Edition of the Tumor-Node-Metastasis (TNM) Classification for Lung Cancer. The results of the first examination after admission were selected for analysis.

Statistical analyses

Demographic information (including age, sex and smoking history), clinicopathological information (including pathological type, stage, driver gene mutation status and treatment regimens) and blood coagulation indices of the included LC patients were collected and analyzed. All these results were collected from database derived from the electronic medical records. Laboratory tests were completed by the clinical laboratory department of Shanghai Pulmonary Hospital. The data analysis was all done by Yidu Cloud Technology Inc. (Beijing, China). Continuous variables were expressed as median (Q_1, Q_3) and compared by the Kruskal–Wallis test. The Nemenyi test was used for further pairwise multiple comparisons. Categorical variables were expressed as number (%) and compared by the chi-squared test. The Bonferroni *P*-value correction was used for further pairwise multiple comparisons. Box plots were drawn to describe the value of each indicator. A two-sided *P*-value of <0.05 was considered statistically significant. Python v3.8.8 and v3.9.0 (https://www.python.org/downloads/, scipy and statsmodels packages) and excel (Microsoft Inc., Washington, USA) were used for data processing and statistical analysis unless otherwise indicated.

Results

General demographic characteristics of LC over time

According to our clinical records for 119,785 LC patients, we found a dramatic increase in newly diagnosed LC patients, shown by an increase from 8504 in 2013 to 23,647 in 2019. Although we used single-center data, this result suggested that the LC burden became much heavier over the 8 years. The increased use of LDCT for early LC screening might have promoted the detection of LC. Notably, the proportion of patients aged 21–40 years increased gradually from 3.58% (30/839) in 2012 to 8.99% (952/10,585) in 2020 ($P < 0.001$; Fig. 1A). The proportions of female patients (from 38.50% [323/839] to 48.29% [5112/10,585]; $P < 0.001$; Fig. 1B) and non-smokers (from 69.34% [475/685] to 80.48% [8055/10,009]; $P < 0.001$; Fig. 1C) also increased from 2012 to 2020. Epidermal growth factor receptor (*EGFR*) mutation occurred more frequently in female *vs.* male (62.03% [12,793/20,625] *vs.* 29.90% [8207/27,447]) and non-smoking *vs.* smoking (53.54% [17,203/32,134] *vs.* 23.73% [3322/13,997]) patients (both $P < 0.001$). Over time, the disease stage at initial admission in LC patients became earlier markedly ($P < 0.001$; Fig. 1D). Regarding the numbers of patients with all pathological types at the initial visit over the study period, the percentage of LUAD cases increased from 67.97% [433/637] to 76.31% [6606/8657], while that of LUSC decreased from 21.19% [135/637] to 12.08% [1046/8657], $P < 0.001$; Fig. 1E). Among patients with positive driver gene alterations, *EGFR*-positive patients were consistently the most common, and we found a slight increase in percentage (from 77.34% [99/128] to 87.59% [1341/1531]; $P < 0.001$; Table 1) over the study period. The combination of chemotherapy, targeted therapy, and immunotherapy, as a comprehensive management regimen, gradually became predominant in Shanghai Pulmonary Hospital over time ($P < 0.001$; Fig. 1F).

Clinicopathological features of LC based on different LC stages

A younger trend is particularly evident in LC. Compared with other stages, higher percentages of young (0–40 years; 11.73%, 3466/29,542) and middle-aged patients (41–60 years; 48.17%, 14,231/29,542) were diagnosed with stage I LC at initial admission ($P < 0.001$; Fig. 2A). Interestingly, there were more women (61.23%, 18,090/29,542) among stage I patients but more men among those with stage II (70.12%, 4157/5928), stage III (79.70%, 12,589/15,795), and stage IV (64.22%, 17,509/27,265) disease ($P < 0.001$; Fig. 2B). Among all the driver gene alterations, *EGFR* mutation was detected most frequently at each stage, especially stage I, and other driver gene alterations were more common in advanced stages ($P < 0.001$, Table 2).

Regarding blood coagulation function, patients with stage IV LC had markedly higher values for activated partial thromboplastin time (APTT; 30.2 [28.1–32.4] s *vs.* 29.7 [27.8–31.8] s), D-dimer (280.00 [147.00–578.25] ng/mL *vs.* 183.00 [108.00–361.00] ng/mL), fibrinogen (Fbg; 3.62 [2.96–4.35] g/L *vs.* 2.94 [2.56–3.38] g/L), prothrombin time (PT; 11.3 [10.8–12.0] s *vs.* 11.3 [10.8–11.9] s), and fibrinogen degradation products (FDP; 1.99 [0.98–4.10] μg/mL *vs.* 1.04 [0.45–2.23] μg/mL) (all $P < 0.001$) compared with those with stage I. However, the comparisons for prothrombin time-international normalized ratio (PT-INR,

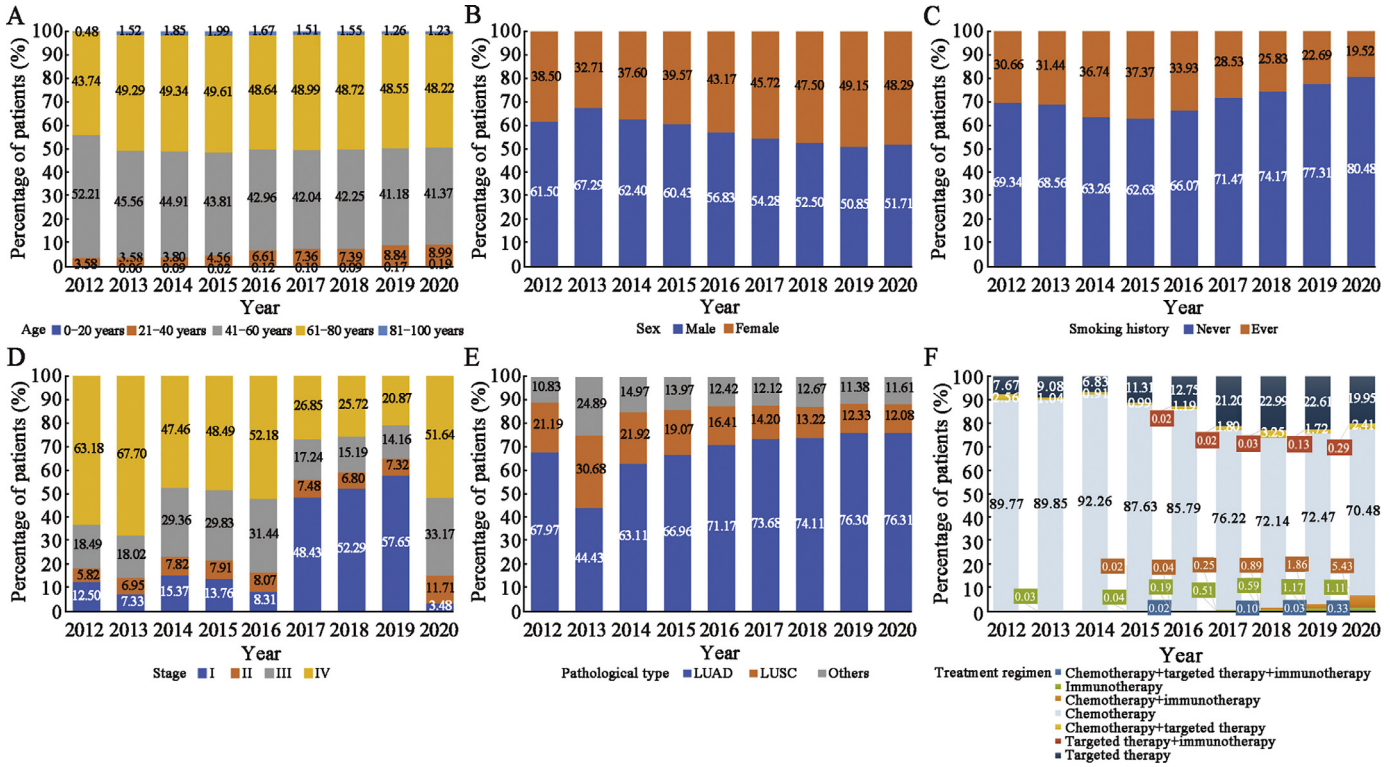

Fig. 1. General demographic characteristics of LC over time. (A) Percentage of patients in each age group across different years. (B) Percentage of patients with each sex across different years. (C) Percentage of patients with or without a history of smoking across different years. (D) Percentage of patients with each stage at initial admission across different years. (E) Percentage of patients with each pathological type of LC across different years. (F) Percentage of patients with each treatment regimen across different years. LC: Lung cancer; LUAD: Lung adenocarcinoma; LUSC: Lung squamous cell carcinoma.

Table 1
Percentage of patients with each driver gene alteration in all LC patients with driver gene alterations across different years (% [*n*/*N*]).

Year	Driver genes					
	EGFR	*ALK*	*BRAF*	*HER-2*	*K-RAS*	*ROS1*
2012	77.34 (99/128)	5.47 (7/128)	0 (0/128)	1.56 (2/128)	15.63 (20/128)	3.13 (4/128)
2013	82.51 (250/303)	7.92 (24/303)	0.33 (1/303)	0.66 (2/303)	10.56 (32/303)	1.32 (4/303)
2014	85.02 (1033/1215)	3.62 (44/1215)	0.91 (11/1215)	0.25 (3/1215)	11.69 (142/1215)	0.82 (10/1215)
2015	79.23 (2133/2692)	3.83 (103/2692)	1.49 (40/2692)	0.45 (12/2692)	15.04 (405/2692)	2.01 (54/2692)
2016	83.24 (2901/3485)	2.73 (95/3485)	1.43 (50/3485)	0.49 (17/3485)	12.11 (422/3485)	1.81 (63/3485)
2017	82.37 (4187/5083)	1.95 (99/5083)	1.16 (59/5083)	0.41 (21/5083)	13.48 (685/5083)	1.61 (82/5083)
2018	87.25 (4442/5091)	2.28 (116/5091)	0.71 (36/5091)	0.67 (34/5091)	8.21 (418/5091)	1.57 (80/5091)
2019	89.25 (4473/5012)	2.13 (107/5012)	1.14 (57/5012)	0.56 (28/5012)	6.30 (316/5012)	1.98 (99/5012)
2020	87.59 (1341/1531)	2.48 (38/1531)	1.57 (24/1531)	0.98 (15/1531)	6.99 (107/1531)	2.42 (37/1531)

ALK: Anaplastic lymphoma kinase; *BRAF*: Serine/threonine-protein kinase braf; *EGFR*: Epidermal growth factor receptor; *HER-2*: Human epidermal growth factor receptor 2; *K-RAS*: v-ki-ras2 Kirsten rat sarcoma 2 viral oncogene homolog; LC: Lung cancer; *ROS1*: ROS proto-oncogene 1 receptor tyrosine kinase.

1.07 [1.01–1.13] *vs.* 1.07 [1.02–1.13]), thrombin time (TT, 14.3 [13.3–15.6] s *vs.* 15.0 [14.1–16.0] s), and antithrombin III activity (ATIII:A, 105.0% [94.0–115.0%] *vs.* 107.0% [97.0–117.0%]) were the opposite (stage IV *vs.* stage I, respectively; all $P < 0.001$; Fig. 2C). Notably, LC-related coagulation dysregulation was present in LC patients in all age groups [Supplementary Fig. 1].

Clinicopathological features of LC based on different driver genes

In all types of LC, LUAD represented the largest proportion in LC patients with driver gene alterations (P <0.001; Fig. 3A). Furthermore, the positive rates of *EGFR* (56.05%, 19,498/34,786), ROS proto-oncogene 1 receptor tyrosine kinase (*ROS1*) (1.27%, 377/29,693), serine/threonine-protein kinase braf (*BRAF*) (1.05%, 229/21,850) and anaplastic lymphoma kinase (*ALK*) (4.47%, 522/11,684) gene mutations were highest in LUAD among the LC types ($P < 0.001$; Table 3). Human epidermal growth factor receptor 2 (*HER-2*) was not included in the routine genetic testing panel, so the positive rate of *HER-2* was not counted.

Regarding blood coagulation indices, patients with *EGFR* mutation had longer TT (14.6 [13.7–15.7] s) and shorter APTT (29.7 [27.7–31.8] s) values, and lower Fbg (3.08 [2.65–3.60] g/L) and FDP (1.39 [0.63–2.86] μg/mL) levels compared with patients with any other driver genes. *ROS1*-positive patients had high PT-INR (1.10 [1.04–1.15]) and PT (11.5 [10.9–12.1] s) values. V-ki-ras2 Kirsten rat sarcoma 2 viral oncogene homolog (*K-RAS*)-positive patients had long APTT (30.6 [28.5–32.8] s) and low ATIII:A (104.0% [94.0–114.0%]) values. Patients with positive *BRAF* had low D-dimer (189.50 [100.75–410.25] ng/mL) and short TT (14.1 [13.4–15.2] s) values. Patients with positive *ALK* had short TT (14.1 [13.2–15.1] s) time and high D-dimer (282.50 [145.75–550.00] ng/mL), Fbg (3.67 [2.91–4.37] g/L), and FDP (1.92 [0.87–3.97] μg/mL) values. Patients with positive *HER-2* had short PT (11.0 [10.7–11.4] s), low PT-INR (1.05 [1.02–1.08]) and high ATIII:A (109.0% [99.5–120.3%]) values (Fig. 3B). The comparison results be-

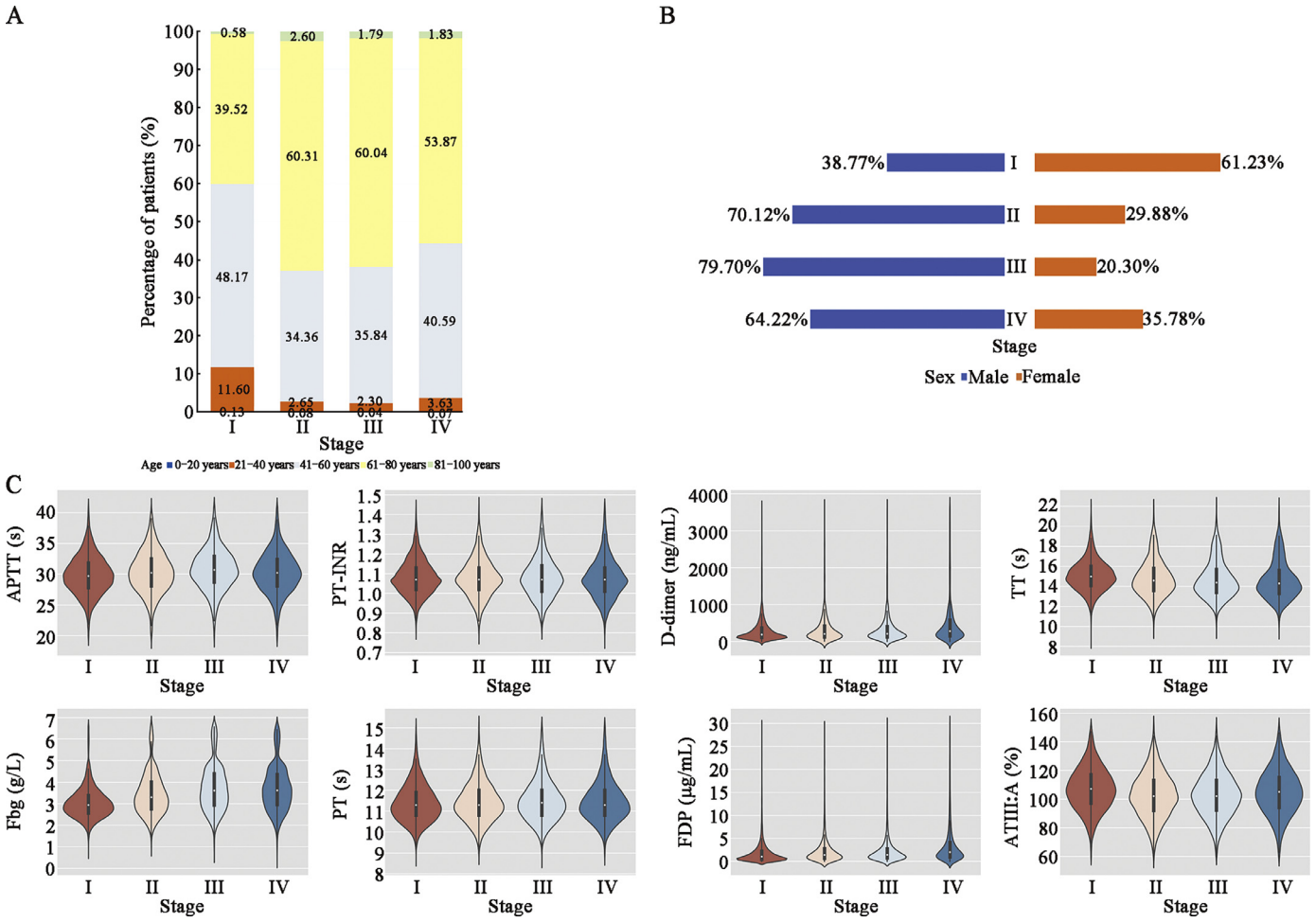

Fig. 2. Clinicopathological features of LC by different stages of lung cancer. (A) Percentage of patients in each age group among different LC stages. (B) Percentage of patients with each sex among different LC stages. (C) Blood coagulation function of patients at different stages. APTT: Activated partial thromboplastin time; ATIII:A: Antithrombin III activity; Fbg: Fibrinogen; FDP: Fibrinogen degradation products; LC: Lung cancer; PT: Prothrombin time; PT-INR: Prothrombin time-international normalized ratio; TT: Thrombin time.

Table 2
Percentage of patints with each driver gene alteration in all LC patients with driver gene alterations among different stages (% [*n*/*N*]).

	Driver genes					
Stages	*EGFR*	*ALK*	*BRAF*	*HER-2*	*K-RAS*	*ROS1*
I	93.99 (7198/7658)	0.18 (14/7658)	0.38 (29/7658)	0.01 (1/7658)	4.48 (343/7658)	1.32 (101/7658)
II	81.90 (964/1177)	1.44 (17/1177)	1.02 (12/1177)	0.08 (1/1177)	14.19 (167/1177)	1.78 (21/1177)
III	68.81 (1425/2071)	5.21 (108/2071)	2.22 (46/2071)	1.06 (22/2071)	22.94 (475/2071)	2.70 (56/2071)
IV	76.82 (5802/7553)	5.93 (448/7553)	1.87 (141/7553)	1.32 (100/7553)	14.52 (1097/7553)	2.16 (163/7553)

ALK: Anaplastic lymphoma kinase; *BRAF*: Serine/threonine-protein kinase braf; *EGFR*: Epidermal growth factor receptor; *HER-2*: Human epidermal growth factor receptor 2; *K-RAS*: v-ki-ras2 Kirsten rat sarcoma 2 viral oncogene homolog; LC: Lung cancer; *ROS1*: ROS proto-oncogene 1 receptor tyrosine kinase.

Table 3
Positive rate of driver gene alterations among all tested LC patients with different pathological types (% [*n*/*N*]).

	Driver genes				
Pathological types	*EGFR*	*ALK*	*BRAF*	*K-RAS*	*ROS1*
LUSC	3.99 (218/5469)	1.11 (17/1531)	0.23 (8/3458)	2.98 (103/3462)	0.36 (16/4480)
LUAD	56.05 (19,498/34,786)	4.47 (522/11,684)	1.05 (229/21,850)	8.63 (1892/21,923)	1.27 (377/29,693)
Others	16.86 (732/4341)	2.19 (65/2962)	0.67 (21/3157)	11.50 (364/3166)	0.71 (26/3664)
P-value	<0.001	<0.001	<0.001	<0.001	<0.001

ALK: Anaplastic lymphoma kinase; *BRAF*: Serine/threonine-protein kinase braf; *EGFR*: Epidermal growth factor receptor; *K-RAS*: v-ki-ras2 Kirsten rat sarcoma 2 viral oncogene homolog; LC: Lung cancer; LUAD: Lung adenocarcinoma; LUSC: Lung squamous cell carcinoma; *ROS1*: ROS proto-oncogene 1 receptor tyrosine kinase.

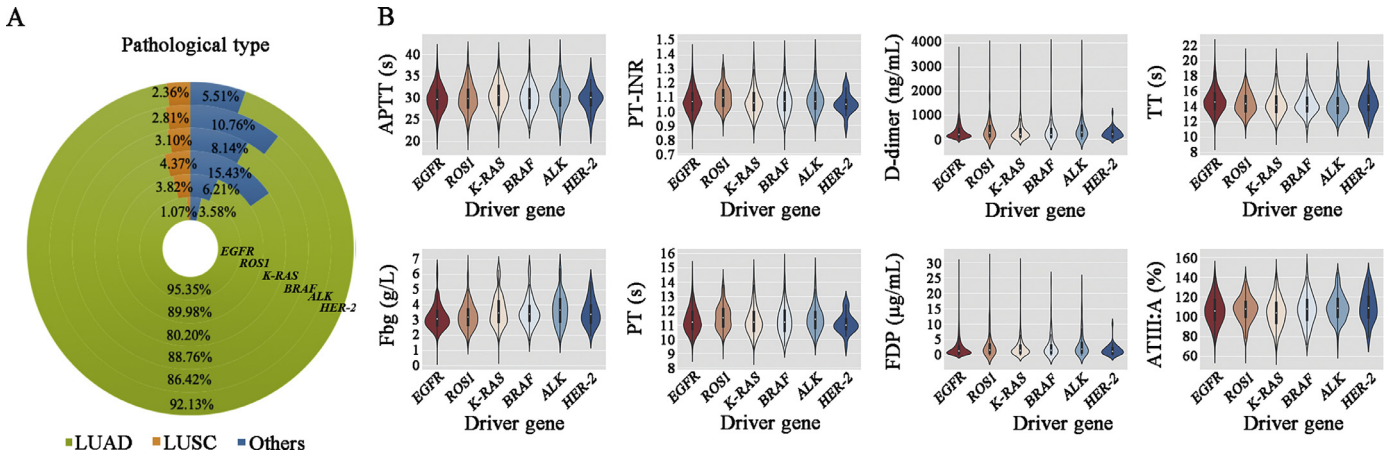

Fig. 3. Clinicopathological features of LC based on different driver genes. (A) Percentage of patients with different driver genes in each pathological type. (B) Blood coagulation function of patients with different driver genes. *ALK*: Anaplastic lymphoma kinase; APTT: Activated partial thromboplastin time; ATIII:A: Antithrombin III activity; *BRAF*: Serine/threonine-protein kinase braf; *EGFR*: Epidermal growth factor receptor; Fbg: Fibrinogen; FDP: Fibrinogen degradation products; *HER-2*: Human epidermal growth factor receptor 2; *K-RAS*: v-ki-ras2 Kirsten rat sarcoma 2 viral oncogene homolog; LC: Lung cancer; LUAD: Lung adenocarcinoma; LUSC: Lung squamous cell carcinoma; PT: Prothrombin time; PT-INR: Prothrombin time-international normalized ratio; *ROS1*: ROS proto-oncogene 1 receptor tyrosine kinase; TT: Thrombin time.

tween groups with different driver genes are shown in Supplementary Table 1.

After stratification for age, we found that these significant differences in blood coagulation indices persisted across 21−80 age groups [Supplementary Fig. 2].

Discussion

Shanghai Pulmonary Hospital, which receives LC patients from all regions of China, is renowned as one of the largest pulmonary disease specialty hospitals nationwide. The epidemiological and clinicopathological characteristics of LC have recently changed dramatically. Relying on the massive medical data of Shanghai Pulmonary Hospital, we were able to update the profile of LC in China. After analyzing the data for LC patients from Shanghai Pulmonary Hospital in this study, who were representative of all patients with LC in China, the temporal trends and patterns of LC with different stages and driver genes were determined.

Tobacco and air pollution remain the leading causes of LC worldwide.[20] Given effective tobacco control by governments,[21] the sex disparity, which was obvious in our data from 2008 to 2012,[22] was generally counterbalanced, and the proportions of smoking patients and LUSC decreased over the study period. However, ensuring air quality in sustainable development should be a top priority.[23] Notably, LC with no history of smoking is more prevalent in women than in men[24]; therefore, never-smoking female patients with LC are receiving attention.[25] Using data from 2012 to 2020, this study showed an increase in the incidence of LC, a trend toward younger age at diagnosis, an increased proportion of early-stage and LUAD patients, extended gene profiling detection, and more comprehensive treatment over the study period. These findings indicate that the hierarchical medical system and precision treatment programs implemented by the China's State Council have indeed been effective. LC has been increasingly important in the differential diagnoses of lung diseases. Moreover, the increased proportion of early-stage LC patients might be a consequence of the generalized use of LDCT for people with a high risk of LC in routine health screening. LDCT-based screening programs effectively enable the identification of patients with early-stage LC and at least partly reduce the mortality associated with LC.[26]

Although a recent study suggested that the incidence of NSCLC in young patients in the USA appeared to decrease from 1975 to 2010,[27] our data revealed an increase in the proportion of young people with NSCLC. This difference in the age trend might be associated with different lifestyles in the two countries. As most young LC patients were diagnosed at an early stage in our data, the popularization of LC screening and strengthening of public health awareness could not be fully excluded as the reasons for the increased incidence of LC in young people. Additionally, the incidence of LC in young people might have been previously underestimated.

We also reported a gender disparity regarding the stage at initial diagnosis, with women accounting for a large proportion of stage I LC cases, consistent with a previous study.[28] Regarding driver genes, early-stage, female, or non-smoking LC patients were closely associated with the *EGFR* mutation, mainly because of the demographically distinct attributes and hallmarks of related molecules.[29] Due to the presence of significant tumor heterogeneity, other oncogenic mutations are more common in advanced- *vs.* early-stage LC, particularly in LUAD.[30,31] The positivity rates of driver genes, except that of *K-RAS*, were higher in LUAD *vs.* other types of LC, in our study. Our results represent the most comprehensive statistics on the mutation spectrum of LC to date. However, due to the small tissue sample sizes in our sample collection, some NSCLC tissues failed to be subclassified and were categorized as other types of LC, which resulted in a high *K-RAS*-positivity rate compared with other types of LC.

In this study, we systematically studied the clinical features of LC with different stages and driver genes via frequently used blood coagulation indices. Our results help prepare clinicians for expected increases in the rates of LC. The coagulation-fibrinolysis system, which is associated with the progression of malignant tumors, is often activated in LC.[32,33] A previous study confirmed an impact on coagulation during the clinical course of LC, despite the small sample size in the study (343 subjects).[34] In the current study, after adjusting for older age, the significantly elevated D-dimer, Fbg, and FDP levels indicated that advanced LC presents with hypercoagulation and secondary hyperfibrinolysis. Regarding the underlying mechanism, thrombin plays a direct role during blood coagulation and can also promote vascular mimicry and spontaneous metastasis in LC.[35] However, LC progression is unrelated to either endogenous or exogenous coagulation mechanisms, as shown by the slight changes in APTT and PT, in our study. Interestingly, this abnormal state was more likely to occur among patients with the *ALK* fusion, instead of *BRAF* or *EGFR* mutations. Some studies have also suggested a significantly high incidence of thromboembolism in patients with *ALK* fusion,

similar to the findings in our population-based study.[36–39] This suggests that LC patients with *ALK* fusion might benefit from thromboprophylaxis; however, prospective studies are needed. The exact mechanisms underlying hypercoagulation in patients with *ALK* fusion have not been fully studied. However, the production of mucin and tissue factors has been suggested as potential reasons for thromboembolic events in advanced *ALK*-positive LC.[40,41] Previous studies also indicated a high risk of thromboembolism in patients with *ROS1* rearrangement.[38,42] However, in our study, aberrations of coagulation indices did not support a thrombophilic status in patients with *ROS1* rearrangement. As there was a low incidence of *ROS1* rearrangement in the Chinese patients in our study, and the patients included in previous studies were mainly White, these inconsistent results might be due to the relatively small sample size of *ROS1* rearrangement in our data and different ethnic backgrounds between our and previous studies.

There are limitations in our study. First, because this is a big-data study, clinical and laboratory test results of some patients were missing, which might affect the overall picture of trends. There was no full-year data for 2012 and 2020, so the presentation of annual trends might be inaccurate. Second, since genetic testing is relatively expensive, not all the patients underwent genetic testing. Furthermore, we are continuing to collect the relevant data beyond 2020 and follow-up information for intensive study of the efficacy of targeted and immune therapies.

Conclusion

In this population-based study, we completely depicted the overall changes and new development trends in recent generations of patients with LC in China. With the advantages of the large sample size and long study period, we explored the characteristics of several rare mutations in depth. Several clinical hypotheses and perspectives were verified, and the directions of future LC research were provided.

Conflicts of interest

None.

Acknowledgment

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pccm.2023.08.006.

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