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Unique profiles of targetable genomic alterations and prognosis in young Chinese patients with lung adenocarcinoma

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ABSTRACT

Objective: Lung adenocarcinoma in young patients is a rare entity, and the targetable genomic alterations (GAs) are poorly studied. In other cancers, it has been demonstrated that young age defines unique disease biology. Here, the association of young age with GAs and prognosis is studied in a large cohort of Chinese patients.

Methods: We retrospectively screened 1000 consecutive patients, and identified 181 patients aged 40 years or younger. GAs were identified by next-generation sequencing (NGS) assay. The clinical and genetic characteristics were analyzed.

Results: Among younger group, 167(92.3%) patients were diagnosed with advanced-stage adenocarcinoma, 98(54.1%) were female, 27(14.9%) were smokers, and the median age was 35 years. Targetable GAs which were significantly more common in the younger population ($P < 0.001$), were associated with young age ($P < 0.05$). The frequency of ALK translocations, EGFR and KRAS mutations was 37.6%, 34.3% and 6.1%, respectively. Younger patients had a higher prevalence of rare GAs including HER2, ROS1 and MET ($P < 0.05$). Prognosis for younger patients was similar (median OS of patients with GAs, 23.91 vs 23.67 months, $P > 0.05$) or better than that for older population (median OS of patients without GAs, 44.28 vs 41.88 months, $P < 0.05$) according to GAs. Therapy modality was an independent prognostic factor ($P < 0.05$), and 83% of death rate decreased if given preferred therapy.

Conclusion: Younger patients with lung adenocarcinoma had unique prevalence of targetable GAs. Comprehensive genotyping including NGS is recommended for personalized therapy and prognosis evaluation in this population.

1. Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related death globally and in China, with adenocarcinoma being the most common subtype [1,2].

Recently, molecularly targeted therapies have revolutionized the treatment for patients who harbor targetable genomic alterations (GAs) such as epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) translocations [3,4]. The test of EGFR mutations and ALK translocations is now routine for patients with lung adenocarcinoma, however, patients with ROS proto-oncogene 1 (ROS1), human epidermal growth factor 2 (HER2), and MET translocations have experienced significant survival benefit from matched targeted therapies in clinical trials [5,6]. Thus, lung adenocarcinoma is increasingly recognized as a highly heterogeneous disease with genotypic diversity in each subgroup [7], and genotyping is becoming increasingly detailed.

Lung adenocarcinoma is more common in patients older than 65 years [8]. Only 1.1%–5% of the disease occurs in young patients under 40 years [9–11], However, the incidence rate has increased notably in recent years [12]. Younger patients have unknown risk factors and controversy persists regarding age-related alterations at molecular levels [7]. Recently, it has been demonstrated that young age defines unique disease biology in other cancers. Younger patients with breast cancer have been identified to have a higher proportion of BRCA1/BRCA2 mutation and HER2 over-expression than the older [13–15]. High frequency of microsatellite instability has been found in younger patients with colon cancer [16,17]. In addition, EGFR mutations were found in approximately 40% of East Asian NSCLC patients, while only in about 15% Caucasian [3]. As a result, lung adenocarcinoma arising in younger groups with different ethnicities probably possess unique targetable GAs. However, the details of these remain unclear.

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Lung cancer among the younger patients is predominately diagnosed at advanced disease stage [9–11,18–20]. Previous studies showed that younger patients had a better, similar, or even unexpectedly worse prognosis compared to older population [7,10,19–21].

On the basis of these studies, we hypothesized that young age at diagnosis could define a population enriched with targetable GAs. The aim of our study was to examine the correlation between young age, targetable genotypes and prognosis, so as to provide greater characterization of young population with lung adenocarcinoma.

2. Materials and methods

2.1. Patients and samples

We retrospectively screened 1000 consecutive patients who were diagnosed with lung adenocarcinoma at Affiliated Cancer Hospital of Zhengzhou University between 2012 and 2017. EGFR tested by amplification refractory system (ARMS), and ALK tested by Ventana immunohistochemistry (Ventana IHC) or fluorescence in situ hybridization (FISH) were diagnostic routine for every individual in this hospital, and the results were collected. Positive family of malignancies was defined as family members of three immediate generations having malignancies. The following data was collected: sex, age, performance status, TNM stage, smoking history, history of family malignancies, former hepatitis B/C or auto-immune diseases, progression-free survival (PFS) and overall survival (OS). Patients with secondary malignancies were excluded. An approval of ethics committee was obtained, and the study was conducted according to the guidelines of the Helsinki Declaration.

2.2. NGS-based assay

In this study, tissue samples were analyzed by next-generation sequencing (NGS) assay using a capture-based sequencing panel [22]. QIAamp DNA FFPE kit (Qiagen, US) was used to extract DNA. DNA shearing was performed with Covaris M220, followed by end repair, phosphorylation and adaptor ligation. Fragments of 200 − 400bp were selected via Agencourt AMPure beads (Beckman Coulter, US) followed by hybridization with capture probes baits, hybrid selection with magnetic beads and PCR amplification. Target enrichment was performed with Lung-Tissue panel covering with eight common targetable GAs including EGFR, KRAS, BRAF, HER2, ALK, ROS1, RET and MET (Burning Rock Biotech Ltd, China). A bioanalyzer high-sensitivity DNA assay was performed to assess the quality and size of fragments and indexed samples were sequenced on Nextseq500 sequencer (Illumina, Inc, US) with pair-end reads.

Sequencing data were mapped to the human genome 19 using BWA aligner 0.7.10. Local alignment optimization, variant calling and annotation were performed using GATK 3.2, MuTect, and VarScan. Tissue samples were compared against their own white blood cells to identify somatic variants. Variants were filtered by VarScan fpfilter pipeline.

2.3. Statistical analysis

All statistical analysis was conducted using Statistical Analysis Software SPSS 19.0 at a nominal significance level of 0.05. Pearson chi-square tests or Fisher exact tests were used to assess the correlation between targetable GAs and clinical variables. Survival was estimated by Kaplan-Meier method, and the differences between groups were estimated by Log-rank tests. Cox regression model was used to analyze the prognostic factors.

Table 1
Clinical characteristics of lung adenocarcinoma.

Characteristic	Total N (%)	Aged ≤ 40years N (%)	Aged>40years N (%)	*P*
No. of patients	1000	181	819	
Age, yr, mean ± SD	54.77 ± 12.06	35.16 ± 4.80	59.10 ± 8.29	
Gender				0.029
Female	613(61.3%)	98(54.1%)	515(62.9%)	
Male	387(38.7%)	83(45.9%)	304(37.1%)	
Brain metastasis				0.18
No	720(72%)	123(68%)	597(72.9%)	
Yes	280(28%)	58(32%)	222(27.1%)	
Stage				< 0.001
I	64(6.4%)	5(2.8%)	59(7.2%)	
II	217(21.7%)	9(5.0%)	208(25.4%)	
III	136(13.6%)	11(6.1%)	125(15.3%)	
IV	583(58.3%)	156(86.2%)	427(52.1%)	
Smoking history				< 0.001
Never	605(60.5%)	154(85.1%)	451(55.1%)	
Former/current	395(39.5%)	27(14.9%)	368(44.9%)	
History of hepatitis B/C or AI diseases				< 0.001
Former/current	163(16.3%)	73(40.3%)	90(11%)	
Never	877(83.7)	108(59.7%)	729(89.0%)	
Family malignancies				< 0.001
Positive	169(16.9%)	59(32.6%)	110(13.4%)	
Negative	831(83.1%)	122(67.4%)	709(86.6%)	
Modality of therapy				
NO	1(0.1%)	0	1(0.1%)	< 0.001
R ± C/T	287(28.7%)	28(15.5%)	259(31.6%)	
C + T	482(48.2%)	79(43.6%)	403(49.2%)	
C	227(22.7%)	72(39.8%)	155(18.9%)	
T	3(0.3%)	2(1.1%)	1(0.1%)	

NO: no anti-tumor therapy; R: radical resection; C: chemotherapy; T: targeted therapy; AI: auto-immune; yr: year.

3. Results

3.1. Patient characteristics

Among the total patients, 613(61.3%) patients were female, 395(39.5%) were former/current smokers, and the median age was 55 years (range, 43–67 years). 719(71.9%) patients were diagnosed at advanced stage (III/IV). Surprisingly, we found 163(16.3%) of the patients were currently/formerly infected by hepatitis B/C virus or suffering from auto-immune diseases. 169(16.9%) patients had positive family of malignancies.

Of these patients, 181 patients (18.1%) were aged ≤40 years at diagnosis. The clinical characteristics are shown in Table 1. The median age was 35 years (range, 30–40 years), of whom, 98(54.1%) patients were female, and 167(92.3%) were at advanced stage. Compared to the older, the prevalence of advanced-stage disease was significantly higher in younger patients (92.3% vs 67.4%, $P < 0.001$), but the frequency of brain metastasis was not significantly different ($P = 0.18$). Accordingly, the frequency of radical resection was significantly lower ($P < 0.001$). Smoking was less common (14.9% vs 44.9%, $P < 0.001$), whereas the incidence of hepatitis B/C infection and/or auto-immune diseases (40.3% vs 11%, $P < 0.001$) and proportion of patients with positive family malignancies (32.6% vs 13.4%, $P < 0.001$) were significantly higher in younger patients.

3.2. Targetable genomic alterations in lung adenocarcinoma

The results of EGFR and ALK tested by NGS were largely consistent with the former results. As shown in Table 2, the frequency of EGFR, ALK, KRAS, HER2, ROS1 and MET alterations among the total patients

Table 2
Distribution of genomic alterations according to age.

Genotype	Total N (%)	Age ≤ 40yr N (%)	Aged > 40yr N (%)	*P*
Wild	301(30.1%)	29(16%)	272(33.2%)	< 0.001
EGFR	472(47.2%)	62(34.3%)	410(50.1%)	< 0.001
Exon 19 deletion		47(75.5%)	165(40.2%)	< 0.001
L858R		10(16.1%)	62(43.9%)	< 0.001
G719X		0	19(4.6%)	< 0.001
L861Q		0	10(2.4%)	< 0.001
Exon 20 insertion		5(8.1%)	5(1.2%)	< 0.001
T790M		0	21(5.1%)	< 0.001
Others		0	10(2.4%)	< 0.001
ALK	101(10.1%)	68(37.6%)	33(4.0%)	< 0.001
KRAS	96(9.6%)	11(6.1%)	85(10.4%)	0.075
HER2	13(1.3%)	4(2.2%)	9(1.1%)	0.232
ROS1	11(1.1%)	3(1.7%)	8(1.0%)	0.25
MET	6(0.6%)	4(2.2%)	2(0.2%)	< 0.001

Others means other subtypes of EGFR mutations, including exon 20 point-mutation, C797 mutation, and EGFR double-point mutations except T790 M.

was 47.2%, 10.1%, 9.6%, 1.3%, 1.1% and 0.6% respectively. However, none of the studied patients harbored BRAF mutations or RET translocations. Patients without the above GAs were defined as wild group (8-Wild), and the number of patients in this group was 301(30.1%).

3.3. Association between targetable genomic alterations and age

Fig. 1A, B and Table 2 show that the incidence of targetable GAs in younger population was significantly higher than the older (84% Vs 66.8%, $P < 0.001$).

Among younger group, EGFR mutations and ALK translocations were identified in 62(34.3%) and 68(37.6%) patients respectively, the frequency of ALK translocations was significantly much higher than the older (37.6% vs 4.0%, $P < 0.001$), whereas EGFR mutations were less common (34.3% vs 50.1%, $P < 0.001$). The frequency of KRAS mutations was not significantly different from that of the older (6.1% Vs 10.4%, $P>0.05$).

Table 2 indicates that the distribution of EGFR mutation status was associated with age at diagnosis. Among younger patients, Exon 19 deletion was significantly more common (75.5% vs 40.2%, $P < 0.001$), whereas L858R mutations in exon 21 was less frequent (16.1% vs 43.9%, $P < 0.001$). Among the rare subtypes of EGFR mutation, the frequency of exon 20 insertion was significantly higher (8.1% vs 1.2%, $P < 0.001$), whereas frequency of G719X, L861Q, and EGFR mutations with T790M was much lower than older patients ($P < 0.001$).

According to the median age (nearly 60 years), we divided the total patients into three groups: younger age group (≤ 40 year), middle age group (40–60 year) and older age group (> 60 year). Fig. 1C indicates that the frequency of targetable GAs was associated with age. The frequency of EGFR mutations increases gradually with age (young 34.3%, middle 47.9%, older 53.4%, $P < 0.05$), whereas ALK translocations decline rapidly with age (younger 37.6%, middle 5.3%, older 2.2%, $P < 0.05$). Rare GAs such as ROS1, HER2 and MET were more common in younger patients, compared with others (HER2: younger 2.2%, middle 1.8%, older 0, $P < 0.05$; ROS1: younger 1.7%, middle 1.2%, older 0.6%, $P < 0.05$; MET: younger 2.2%, middle 0.4%, older 0, $P < 0.05$). The frequency of KRAS mutations in middle age group was a little higher (ROS1: young 6.1%, median 10.9%, older 9.6%), but the difference was not significant ($P>0.05$).

Targetable GAs among younger smokers was significantly less frequent compared to that in non-smokers (14.5% vs 85.5%, $P < 0.05$).

3.4. Association between targetable genomic alterations and stage in younger patients

Among younger group, targetable GAs including EGFR, ALK, KRAS, HER2, ROS1 and MET were all identified in patients with advanced-stage lung adenocarcinoma.

3.5. PFS according to age and targetable genomic alterations

The median PFS of younger and older groups was 11.83 (95%CI, 9.74–13.93 months) and 15.02 months (95%CI, 14.15–15.90 months), respectively. Fig. 2A illustrates the significantly shorter PFS of younger group compared to older patients ($P = 0.001$).

According to age and targetable GAs, we divided the total patients into four subgroups, and compared PFS between them. Fig. 2B shows that patients with GAs had significantly shorter PFS than those without GAs ($P < 0.05$). The PFS for younger patients with GAs was compatible with that for older population (8.26 Vs 9.24 months, $P = 0.10$). Among the patients without GAs, the subgroup of younger population had a significantly longer PFS compared to the older (30.28 vs 26.68 months, $P < 0.05$).

3.6. OS according to age and targetable genomic alterations

Among the total patients, the median OS of the younger and older groups was 27.17 (95%CI, 24.68–29.66 months) and 29.70 months (95%CI, 14.15–15.90 months), respectively. Fig. 2C shows that there was no significant difference in OS according to age ($P = 0.34$). Among the 583 patients with stage-IV disease, there was also no difference in OS between younger and the older cohorts (median OS, 23.60 vs 21.19 months, $P > 0.05$).

According to the GAs, we divided total patient group into four

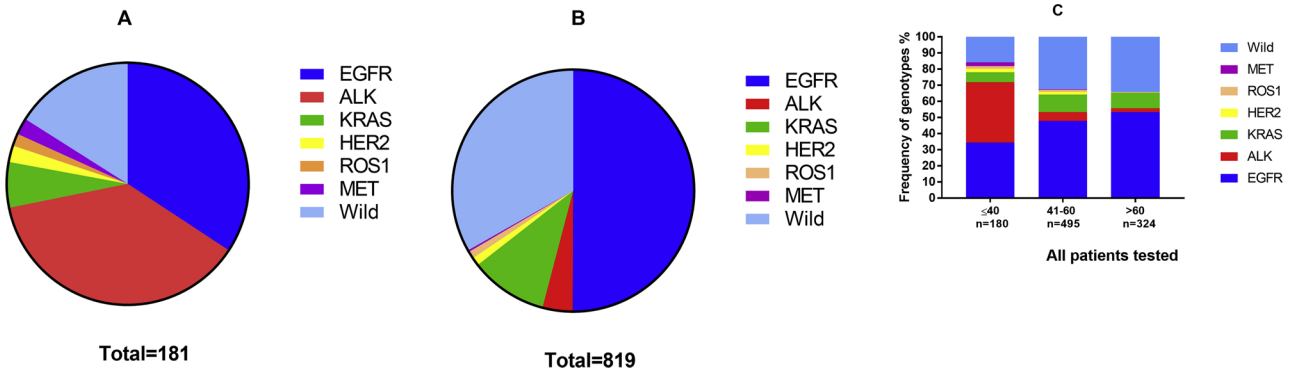

Fig. 1. The frequency of targetable genomic alterations varies according to age. (A) and (B) are the profiles of genomic alterations in young and older patients with lung adenocarcinoma, respectively. ALK translocation was much more common in young patients, whereas the frequency of EGFR mutation was significantly higher in the older population. (C) indicates that the frequency of EGFR, ALK, ROS1, MET, HER2 was associated with young age. In concert with the diminishing age, the frequency of ALK translocations increases dramatically, whereas EGFR mutations decline gradually.

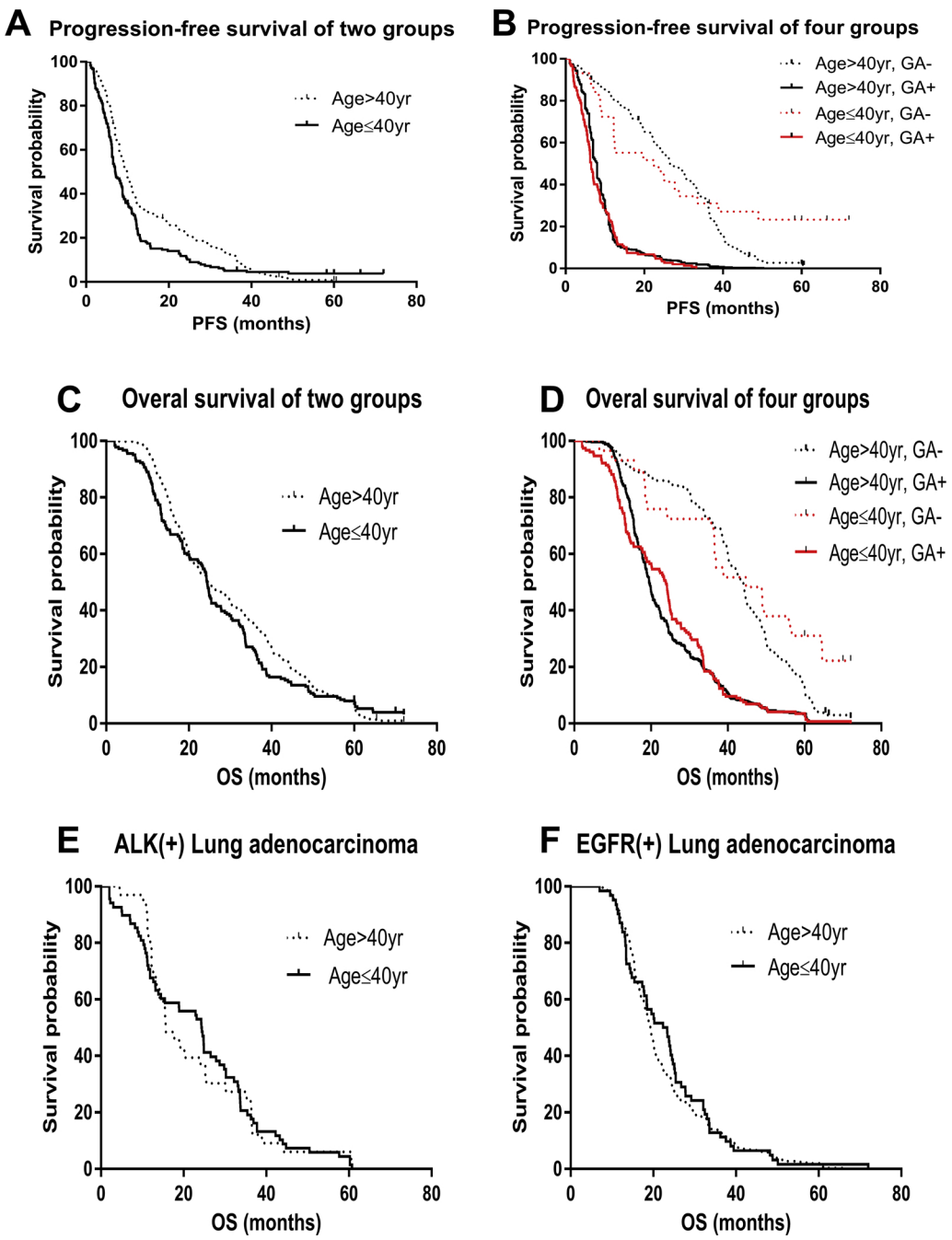

Fig. 2. The prognosis is illustrated for patients with lung adenocarcinoma according to age and genomic alterations (GAs). (A) Younger patients had a significantly shorter progression-free survival (PFS) compared to the older population, but the difference in overall survival (OS) is not significant (C). (B) shows that both the younger and the older subsets with GAs had significantly shorter PFS than those without GAs. Among those patients with GAs, younger patients had a compatible PFS, whereas younger patients without GAs had a significantly longer PFS, compared to the older group. Among the patients who harbored GAs such as ALK translocations and EGFR mutations, there was no significant difference in the prognosis between the younger and the older groups (D, E, F), whereas the OS for younger patients without GAs is significantly better (D).

Table 3
Multivariate analysis of PFS and OS in younger patients with lung adenocarcinoma.

Factor	PFS		OS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Gender	1.33(0.83-2.14)	0.24	1.18(0.75-1.88)	0.48
Stage	1.96(1.16-3.31)	0.01	1.61(0.96-2.69)	0.07
Family malignancies	0.93(0.61-1.42)	0.73	0.77(0.51-1.17)	0.22
HB/CV or AI	0.87(0.59-1.27)	0.47	0.84(0.57-1.23)	0.37
Smoking history	0.94(0.57-1.56)	0.81	0.88(0.53-1.45)	0.61
Genetic alterations	1.45(0.10-22.83)	0.77	0.78(0.05-11.66)	0.85
Therapy modalities	0.40(0.27-0.58)	0.001	0.17(0.11-0.26)	0.001

subgroups and compared OS between them. Fig. 2D indicates that patients with GAs had a significantly shorter OS than those without GAs ($P < 0.001$). Among the patients with GAs, there was no difference in OS between the younger and older groups (median OS, 23.91 vs 23.67 months, $P = 0.62$). However, among the patients without GAs, younger patients had a significantly longer OS than the older (median OS, 44.28 vs 41.88 months, $P = 0.01$).

Among the patients who harbored ALK translocations (ALK+), there was no difference in OS according to age (median OS, young 23.88 vs older 23.10 months, $P = 0.65$, Fig. 2E). Fig. 2F shows that OS for patients with EGFR mutations (EGFR+) was also not significantly different from that for patients without EGFR mutations (median OS, young 23.52 vs older 22.63 months, $P = 0.13$).

3.7. Prognostic factors in younger patients with lung adenocarcinoma

Multivariate Cox proportional hazard model was used to detect the prognostic factors of the younger cohort, as is shown in Table 3. In the multivariate PFS analysis, stage (95% CI 1.16–3.31, HR = 1.96, $P < 0.05$) and therapy modality (95% CI 0.27 − 0.58, HR = 0.40, $P < 0.05$) were significant factors affecting the prognosis ($P < 0.05$). However, in OS analysis, therapy modality was an independent prognostic factor ($P < 0.05$).

According to therapy modalities, we divided younger patients into 6 subgroups: no therapy, Radical resection, Radical resection + chemotherapy/targeted therapy, Chemotherapy/targeted therapy, Targeted therapy and Chemotherapy. Younger patients with GAs but without therapy had the worst prognosis compared with others ($P < 0.05$). Combination therapy including radical resection and chemotherapy/targeted therapy was better than others at improving the prognosis ($P < 0.05$).

4. Discussion

Lung adenocarcinoma in young patients is attracting increasing attention, however, the clinical and genetic characteristics have not been well described [9]. The majority of published data is not from Chinese population, and there are many conflicting results [9,23–26]. In this study, younger patients accounted for 18.1% of all patients. We confirmed that lung adenocarcinoma in younger patients was characterized by a high proportion of women and advanced-stage disease [27]. Interestingly, there was no significant difference in the incidence of brain metastasis between younger and older patients.

The proportion of lung adenocarcinoma is on the rise in young population. Young patients have unknown risk factors [9,28,29]. The proportion of smokers in younger patients was much lower than the older in this study. As a result, exposure to tobacco didn't support a higher susceptibility among young patients. However, our study and previous studies reported that smoking was associated with the profile of GAs [30], such as EGFR and KRAS mutations [31,32]. Interestingly, a significant higher proportion of hepatitis or auto-immune diseases and positive family of malignancy was observed in younger patients in this study. High exposure to immune system disorders and positive family of malignancy might be high-risk factors of lung adenocarcinoma at early age.

We demonstrate that lung adenocarcinoma, usually was considered to be a disease of the elderly, has a median age at diagnosis of 55 years, and the age of onset is falling compared to previous studies [7,8]. The median age of younger patients was 35 years. Therefore, young age at diagnosis is an under-appreciated factor.

Young age has been demonstrated to define unique disease biology in other cancers [13–17]. Recently, Drilon found that targeted NGS could detect potentially targetable GAs missed by non-NGS assay in 65% of patients [33]. Hence, we used NGS to test eight common genotypes, confirming that young age was associated with an increased likelihood of harboring a unique targetable genotype.

EGFR mutation and ALK translocation were identified as the most common genotypes among the total patients. Surprisingly, ALK translocation was the most common genotype in younger population. To the best of our knowledge, our study is the first report that ALK translocations are very common in young Chinese patients with lung adenocarcinoma. Recent studies have demonstrated that ALK translocations are associated with the onset of lung cancer in young patients [34–37]. There are amazing similarities between our findings and 3 previous studies about young patients (< 40 year) with lung adenocarcinoma [35,35,36,37]. Nagashima reported that the frequency of ALK translocations and EGFR mutations among 12 young patients was 42% and 33%, respectively [36]. Gitlitz showed that among young patients with stage IV adenocarcinoma, ALK translocation and EGFR mutation was identified in 44% (22/50) and 26% (13/50) respectively [37]. Tanaka reported that among 81 young patients, 33(41%) patients harbored ALK translocations, and 24 (30%) had EGFR mutations [35]. Our study demonstrated that the frequency of ALK translocation and EGFR mutation was 37.6% (68/181) and 34.3% (62/181), respectively. These results suggested that 71.9% young patients had the chance to experience a better survival from use of EGFR or ALK tyrosine inhibitors. Moreover, ALK translocations and EGFR mutations all occurred in young patients at advanced stage, hence, ALK translocations and EGFR mutations might indicated higher malignant potential of those cancers.

The incidence of KRAS mutations was not significantly different between younger and older population. Young patients had a higher incidence of rare genotypes. The frequency of targetable GAs varied according to age. As a result, young patients had a distinct prevalence of targetable GAs, and age was a predictor for genotypes.

In this study, EGFR mutation was the second most common genotype in the young. Exon 19 deletion and Exon 20 insertion were significantly more common in young patients, whereas L858R mutation, G719X, L861Q, T790 M and other mutation subtypes were less frequent. The result was similar to a study in Japanese patients [35], however, the incidence of EGFR mutation with T790 M before therapy was much higher in Chinese patients. Accordingly, young patients have a distinct prevalence of EGFR-mutated subtypes, and traditional methods such as ARMS are not stringent enough for testing EGFR subtypes, NGS might be the preferred method in the future.

The realization that lung adenocarcinoma in young patients is a genetically unique disease lends itself to the question of whether the prognosis is different from the older. Jemal reported that age-specific lung cancer death rates declined continuously in white women in California, but the prognosis was worse in Southern and Midwest states [38]. Some studies demonstrated that the young patients with NSCLC had unexpectedly poor prognosis compared to other age group [7,21], others reported that the prognosis was not significantly different between young and the older patients [10,19,20,34], and a small number of studies showed the prognosis of young patients was better than that of older patients [9,39]. Our present study showed that younger patients had a much shorter PFS ($P < 0.05$), whereas the difference in OS was not significant ($P > 0.05$). Patients with GAs had significantly shorter PFS and OS, compared to those without GAs. As a result, GA was significantly associated with the prognosis. Among the patients who harbored GAs such as EGFR mutations and ALK translocations, there was no significant difference in the prognosis between the younger and the older groups ($P > 0.05$). However, among the patients without GA, younger patients had a significantly better prognosis, compared to the older ($P < 0.05$). These indicated that the prognosis of younger patients was affected by other factors besides GAs and age.

The results of Cox Regression suggested that therapy modality was an independent prognostic factor for younger patients ($P < 0.05$), and 83% of death rate reduction was seen when the preferred therapy was given. The prognosis of young patients harboring GAs would be improved by anti-cancer therapy. Combination therapy was better at improving the prognosis.

5. Conclusion

Younger patients with lung adenocarcinoma had a unique prevalence of targetable GAs. Comprehensive genotyping including NGS is recommended for personalized therapy. The prognosis of younger patients was similar or better than the older according to GAs, and therapy modality was an independent prognostic factor. Young patients who have a higher incidence of targetable GAs might be prime candidates for precision therapies.

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Conflict of interest

The authors declare no conflict of interest.

Availability of data and material

The datasets used during this study are available from the corresponding author upon reasonable request.

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