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Reviewer A

Comment 1: Squamous cell carcinoma and small cell lung cancer are known to be strongly associated with smoking, but Table S1 shows a high proportion of nonsmokers in those histologic types. On the other hand, the proportion of nonsmokers is much lower for adenocarcinoma. Please discuss the reasons for this. Furthermore, the proportion of males is extremely high in adenocarcinoma. Is there a higher rate of smoking among women in China?

Reply 1: Thank you for the valuable comment. We are so sorry that we placed the column names in the wrong order. Corresponding to the results presented in Table S1, the third, fourth, and fifth column should show the baseline characteristics of included patients with a diagnosis of Small cell carcinoma, Squamous cell carcinoma, and Adenocarcinoma, respectively.

After the corrections on Table S1, we further analyzed the distribution of each histological classification by both sex and smoking status. As is shown in the following table, the proportion of nonsmokers was 34.22% and 18.87% for Small cell carcinoma and Squamous cell carcinoma, respectively, which was much lower than that for Adenocarcinoma (59.88%).

The rate of smoking among female patients in this study was 102/2399 (4.25%), a bit higher than the reported rate of Chinese adult women in the national survey conducted in 2018.

Moreover, most cases of Small cell carcinoma (52.03%) and Squamous cell carcinoma (62.38%) were founded among male current smokers, while most cases of Adenocarcinoma (44.95%) were among female nonsmokers, which was consistent with findings in other studies.

| Sex | Smoking status | Sample sizes (%) | Small cell carcinoma (%) | Squamous cell carcinoma (%) | Adenocarcinoma (%) | Others (%) | Unknown (%) |
|-------------|----------------|------------------|--------------------------|-----------------------------|--------------------|-------------|-------------|
| Male | Never | 1046 (14.31) | 126 (13.43) | 174 (11.02) | 498 (14.93) | 74 (14.29) | 174 (18.49) |
| Male | Current | 3046 (41.66) | 488 (52.03) | 985 (62.38) | 980 (29.39) | 230 (44.40) | 363 (38.58) |
| Male | Former | 786 (10.75) | 105 (11.19) | 263 (16.66) | 271 (8.13) | 55 (10.62) | 92 (9.78) |

| | | | | | | | |
|--------------------|--------------|-----------------|----------------|---------------|-------------------------|----------------|----------------|
| Male | Unkno wn | 34 (0.47) | 6 (0.64) | 9 (0.57) | 10 (0.30) | 3 (0.58) | 6 (0.64) |
| Fema le | Never | 2237 (30.60) | 195 (20.79) | 124 (7.85) | 1499 (44.95) | 142 (27.41) | 277 (29.44) |
| Femal e | Curren t | 102 (1.40) | 14 (1.49) | 17 (1.08) | 45 (1.35) | 9 (1.74) | 17 (1.81) |
| Femal e | Former | 26 (0.36) | 1 (0.11) | 5 (0.32) | 9 (0.27) | 4 (0.77) | 7 (0.74) |
| Femal e | Unkno wn | 34 (0.47) | 3 (0.32) | 2 (0.13) | 23 (0.69) | 1 (0.19) | 5 (0.53) |
| Total | | 7311 | 938 | 1579 | 3335 | 518 | 941 |

Changes in the text: The column names in Table S1 were placed in the correct order.

References:

[1] Chinese Center for Disease Control and Prevention. Results Release of the 2018 China Adult Tobacco Survey. Available online: http://www.chinacdc.cn/yw_9324/201905/t20190530_202932.html.

[2] Pesch B, Kendzia B, Gustavsson P, et al. Cigarette smoking and lung cancer--relative risk estimates for the major histological types from a pooled analysis of case-control studies. *Int J Cancer*. 2012;131(5):1210-1219. doi:10.1002/ijc.27339

[3] Gridelli C, Rossi A, Carbone DP, et al. Non-small-cell lung cancer. *Nat Rev Dis Primers*. 2015;1:15009. Published 2015 May 21. doi:10.1038/nrdp.2015.9

Comment 2: OS and LCSS for advanced stage lung cancer are exactly the same. Did they all die of lung cancer? And why are the P values different despite the same values?

Reply 2: We are so sorry for the mistake. Thanks for your kindly reminder, we have revised Table 2 with the actual results. Please see the revision highlighted in blue in the section of 5-year OS rates (95%CI, %) for the advanced stages, which could now explain the differences among the P values.

We also added some information about the number of death cases, indicating that lung cancer was a major cause of death but could not account for all the death among the included patients with lung cancer.

Table 2 Subgroup survival analysis for lung cancer patients with early- and advanced stages

| | Sample sizes | All death cases | 5-year OS rates (95%CI, %) † | <i>p</i> value ‡ | Lung cancer death cases | 5-year LCSS rates (95%CI, %) †, § | <i>p</i> value ‡ |
|--------------------------|--------------|-----------------|------------------------------|------------------|-------------------------|-----------------------------------|------------------|
| Early Stages¶ | 1392 | 444 | | <0.01** | 348 | | <0.01** |
| Small cell carcinoma | 71 | 39 | 47.9 (37.6-61.0) | | 33 | 51.9 (41.2-65.5) | |
| Squamous cell carcinoma | 331 | 151 | 60.4 (55.4-65.9) | | 116 | 66.6 (61.5-72.0) | |
| Adenocarcinoma | 887 | 217 | 79.0 (76.4-81.8) | | 166 | 83.5 (81.1-86.0) | |
| Others †† | 103 | 37 | 69.9 (61.6-79.3) | | 33 | 73.1 (64.9-82.3) | |
| Advanced Stages‡‡ | 3535 | 2725 | | 0.09 | 2306 | | <0.05* |
| Small cell carcinoma | 522 | 404 | 24.3 (20.9 - 28.3) | | 350 | 28.7 (24.8-33.1) | |
| Squamous cell carcinoma | 818 | 604 | 28.0 (25.1 - 31.2) | | 515 | 33.1 (29.8-36.6) | |
| Adenocarcinoma | 1902 | 1496 | 25.6 (23.7 - 27.6) | | 1249 | 30.7 (28.6-33.0) | |
| Others | 293 | 221 | 25.6 (21.1 - 31.1) | | 192 | 29.6 (24.6-35.7) | |
| Overall | 4927 §§ | 3169 | 37.0 (35.9-38.1) | - | 2654 | 41.6 (40.5-42.8) | - |

† Survival rates were calculated by Kaplan-Meier method and were shown as Rate (%) and its 95% CIs.

‡ *p* values were calculated by Log Rank test.

§ LCSS: lung cancer specific survival.

¶ Including stage I and stage II.

†† Including large cell carcinoma, carcinoid, sarcomatoid carcinoma, and adenosquamous carcinoma.

‡‡ Including stage III and stage IV.

§§ Patient with specific information on both pathological stage and histological classification.

Changes in the text: Data in the Table 2 were updated since we wrongly pasted same values for the 5-year OS rates and 5-year SS rates of the advanced stages. In addition, two variables, all death cases and lung cancer specific death cases, were added in Table 2, in order to show the causes of death among the participants in each group.

Comment 3: In Table 3, OS and LCSS of patients under 60 years of age are worse than those of patients over 60 years of age. In general, younger patients seem to have a better prognosis because they can receive more aggressive treatment. were patients younger than 60 years old more likely to have advanced lung cancer?

Reply 3: Thank you for your comments. As is shown in Tables 3, OS and LCSS of patients under 60 years of age were actually better than those of patients over 60 years of age, which were 40.2 (38.6-41.9) and 44.5 (42.8-46.3) for the younger group, and were 34.1 (32.7-35.7) and 39.0 (37.5-40.7) for the elder group, respectively.

Just as the reviewer suggested, there was a higher proportion of receiving treatment among patients under 60 years of age (90.03%) in this study, compared with patients over 60 years (84.29%). Besides, females (36.02%) and nonsmokers (48.79%) accounted more in the former group, which were 39.86% and 42.40% in the elder group, respectively, although advanced lung cancer accounted for 76.42% among the patients under 60 years, which was slightly higher than that of patients over 60 years (71.81%). The above might explained the better prognosis for the younger group.

Changes in the text: There was no change in the text.

Reviewer B

Comment 1: Although there are no new findings, the authors have analyzed a very large number of cases and the paper should be accepted.

Reply 1: Thank you for pointing this out. We admitted that the analysis methods applied in this work was not innovative, however, as far as we know, this is the first large-scale multicenter hospital-based study reporting survival of primary lung cancer among Chinese patients with different pathological evaluations, aiming to provide references for the evaluation and promotion of prognosis of Chinese patients with lung cancer.

Changes in the text: There was no change in the text.

Comment 2: There is nothing in particular that needs to be corrected, but the paper should be compared with reports from other countries in the discussion section, as there is no comparison with international data such as those reported by the WCLC.

Reply 2: Thank you very much for your important suggestions. We have added the comparison on the 5-year survival rates with international data in the discussion section, including cancer statistics reported by the third cycle of Global surveillance of trends in cancer survival program (CONCORD-3), Surveillance, Epidemiology, and End Results Program (SEER), and the International Association for the Study of Lung Cancer (IASLC). However, direct comparisons on survival of lung cancer

patients among countries should be treated with caution considering the differences of the applied indexes and data sources. (Page 14, Lines 290-303)

As for the effects of pathological stage on prognosis of lung cancer patients, there were sentences presenting international comparison, “*Similar results were also reported by national surveys in developed countries*”. (Page 15, Lines 309)

Changes in the text: The following sentences has been added as the third paragraph in the discussion section. (Page 14, Lines 290-303)

“According to cancer statistics from the third cycle of Global surveillance of trends in cancer survival program (CONCORD-3), 5-year age-standardized net survival among most countries was in the range of 10-19%, while it peaked in Japanese patients diagnosed with lung cancer during 2010-2014 (32.9%). The corresponding rate was 28.1% for the Chinese-American, based on 18 registries of Surveillance, Epidemiology, and End Results Program (SEER) between 2011 and 2017. Nevertheless, direct comparisons on survival of lung cancer patients among countries should be treated with caution considering the differences of the applied indexes. Five-year OS rates by pathologic stage, reported by the International Association for the Study of Lung Cancer (IASLC) based on 94708 cases from 16 countries, were close to the results in this study. The former rates were adjusted to simulate database from registries, indicating that there was still a gap between China and the developed regions since the proportion of receiving treatment was much higher than the general population.”

References:

- [1] Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2018, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2018/, based on November 2020 SEER data submission, posted to the SEER web site, April 2021.
- [2] Allemani C, Matsuda T, Di Carlo V, et al. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet*. 2018;391(10125):1023-1075. doi:10.1016/S0140-6736(17)33326-3
- [3] Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. *J Thorac Oncol*. 2016;11(1):39-51. doi:10.1016/j.jtho.2015.09.009