Peer Review File

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Reviewer

General Comment: *If I am well understood, the main objective of the paper is to estimate the causal effect of race on cancer-specific survival. Besides the fact that causal inference is a difficult task, estimating the causal effect of race on any outcomes is much more complicated. Racial disparities in the US is a systemic problem that cannot be summarized by a bunch of tumour characteristics and/or sociodemographic variables. I don't see how the study may help in any way to better understand the issue and how the present study adds value compared to that of Ellis et al. cited in ref 5. Estimating the causal effect of race on survival using SEER data, is really difficult as SEER datasets do not include data on many confounding factors.*

General Reply: Thank you for your helpful suggestions. We greatly value this feedback, which significantly improves our research.

We completely agree with the reviewer that the causal inference is a difficult task and we should be very cautious to make a causal conclusion. Actually, our objectives are to identify differences in cancer-specific survival of lung cancer patients by race. We were not meant to conclude any causal effect in this work.

We have been through the manuscript and toned down our implication of a direct link, including the sentence mentioned, which now reads:
"The novel evidence obtained from this study enrich our knowledge of racial differences among lung cancer patients and suggest that race may be associated with lung cancer-specific survival." (see Page 2, line 43-44).

We have also added a section to the subsection "limitations of the study" making it explicit that this type of study only reveals associations, not causal relationships.
" Regarding the complexity of the relationships between variables, causal relationships could not be inferred." (see Page 11, line 251-252)

We fully agree that the association between race and lung cancer-specific survival does have many influencing factors. To adjust for the potential confounders, we used SEER database because this database has a sufficient number of patients and standardized clinicopathological information, including age, gender, tumor characteristics and therapy. And for our opinion, we conducted performed univariate and multifactorial Cox regression analyses, PS score adjustment, and stratified KM analysis. We believe that the current study with SEER database is the only one that can estimate the association between race and cancer-specific survival, and it is the largest analysis to achieve the goal. However, we admit that there may still be many

missing variables, such as smoking status and detailed information on the treatment method. We've added this as a limitation in the limitation section. Further studies are required to confirm our results.
"This suggests that the race may become a limiting factor for LCSS although further studies are required to confirm our results." (see Page 11, line 260-261)

There are six points we would like to address with respect to our reviewer's comments:

Comment 1: *First, authors included treatment information in their multivariate models while they are interested in cancer-specific survival from diagnosis. Including such information is likely to introduce immortal time bias. There are several methods to handle immortal time bias. I invite the authors to read the following papers:*
1. Anderson JR, Cain KC, Gelber RD. Analysis of survival by tumor response. J Clin Oncol Off J Am Soc Clin Oncol. 1983;1(11):710-719. doi:10.1200/JCO.1983.1.11.710
2. Giobbie-Hurder A, Gelber RD, Regan MM. Challenges of guarantee-time bias. J Clin Oncol Off J Am Soc Clin Oncol. 2013;31(23):2963-2969. doi:10.1200/JCO.2013.49.5283
3. Hanley JA, Foster BJ. Avoiding blunders involving "immortal time." Int J Epidemiol. 2014;43(3):949-961. doi:10.1093/ije/dyu105
4. Clark DA, Stinson EB, Griepp RB, Schroeder JS, Shumway NE, Harrison DC. Cardiac transplantation in man. VI. Prognosis of patients selected for cardiac transplantation. Ann Intern Med. 1971;75(1):15-21. doi:10.7326/0003-4819-75-1-15
5. Messmer BJ, Nora JJ, Leachman RD, Cooley DA. Survival-times after cardiac allografts. Lancet Lond Engl. 1969;1(7602):954-956. doi:10.1016/s0140-6736(69)91857-1
6. Hernán MA, Sauer BC, Hernández-Díaz S, Platt R, Shrier I. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. J Clin Epidemiol. 2016;79:70-75. doi:10.1016/j.jclinepi.2016.04.014
7. Shariff SZ, Cuerden MS, Jain AK, Garg AX. The secret of immortal time bias in epidemiologic studies. J Am Soc Nephrol JASN. 2008;19(5):841-843. doi:10.1681/ASN.2007121354
8. Agarwal P, Moshier E, Ru M, et al. Immortal Time Bias in Observational Studies of Time-to-Event Outcomes: Assessing Effects of Postmastectomy Radiation Therapy Using the National Cancer Database. Cancer Control J Moffitt Cancer Cent. 2018;25(1):1073274818789355. doi:10.1177/1073274818789355
9. Ho AMH, Dion PW, Ng CSH, Karmakar MK. Understanding immortal time bias in observational cohort studies. Anaesthesia. 2013;68(2):126-130. doi:10.1111/anae.12120

Reply 1: We agree with the reviewer that the immortal time bias needs further clarification in the manuscript. Indeed, in order to receive treatment for lung cancer, patients need to live from the time they are diagnosed with lung cancer until the day they receive treatment. Our analysis was missing patients who were able to receive

treatment but did not survive to the day they could receive it. Therefore, we did the time-dependent multivariable Cox regression analysis to help address the limitation. We have modified our text as advised (see Page 6, line 126-127; Page 14, line 340; Table 2; Table S1).

Changes in the text:

Page 6, line 126-127: Furthermore, time-dependent analysis was carried out to bivariate the possible effect of immortal time bias due to the external time period between diagnosis and the time of treatment for these patients. (30)

Page 14, line 340: 30. Giobbie-Hurder A, Gelber RD, Regan MM. Challenges of guarantee-time bias. J Clin Oncol 2013;31:2963-9.

Table 2: Time-dependent Cox regression analyses for LCSS with PS covariate adjustment [a], 2004-2015.

Variable	Before PS adjusted		After PS adjusted	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Race				
White	Reference		Reference	
Black	0.94 (0.92, 0.97)	< 0.01	0.97 (0.94, 1.00)	0.06
API	0.85 (0.83, 0.88)	< 0.01	0.90 (0.88, 0.93)	< 0.01
AIAN	1.08 (0.88, 1.31)	0.46	0.99 (0.81, 1.20)	0.91

[a] adjusted for age, sex, race, year of diagnosis, site, histology, AJCC, marital status, grading and therapy; API = Asian or Pacific Islander; AIAN = American Indian/Alaska Native; LCSS = Lung cancer specific survival; CI = Confidential interval; HR = Hazard ratio; PS: propensity score

Table S2: Univariate and time-dependent multivariate [a] analyses of OS and LCSS for lung cancer patients variables included in the study.

Variable	Univariate				Multivariate			
	OS		LCSS		OS		LCSS	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Race		< 0.01						
White	Reference		Reference		Reference		Reference	
Black	1.08 (1.05, 1.11)	< 0.01	1.07 (1.04, 1.10)	< 0.01	0.97 (0.94, 0.99)	0.01	0.94 (0.92, 0.97)	< 0.01
API	0.91 (0.89, 0.94)	< 0.01	0.93 (0.91, 0.96)	< 0.01	0.84 (0.82, 0.87)	< 0.01	0.85 (0.83, 0.88)	< 0.01

AIAN	1.07 (0.89, 1.28)	0.47	1.02 (0.84, 1.24)	0.86	1.13 (0.94, 1.35)	0.18	1.08 (0.88, 1.31)	0.46
Age at diagnosis (year)		< 0.01						
00-49	Reference		Reference		Reference		Reference	
50-59	1.05 (1.00, 1.10)	0.038	1.01 (0.97, 1.06)	0.67	1.06 (1.02, 1.11)	< 0.01	1.03 (0.98, 1.08)	0.19
60-69	1.09 (1.04, 1.14)	< 0.01	1.00 (0.96, 1.04)	0.99	1.20 (1.15, 1.25)	< 0.01	1.12 (1.08, 1.18)	< 0.01
70-79	1.26 (1.21, 1.31)	< 0.01	1.10 (1.05, 1.15)	< 0.01	1.36 (1.30, 1.42)	< 0.01	1.22 (1.17, 1.28)	< 0.01
80+	1.67 (1.60, 1.75)	< 0.01	1.42 (1.36, 1.49)	< 0.01	1.48 (1.41, 1.55)	< 0.01	1.31 (1.25, 1.38)	< 0.01
Gender		< 0.01						
Female	Reference		Reference		Reference		Reference	
Male	1.24 (1.21, 1.26)	< 0.01	1.21 (1.19, 1.24)	< 0.01	1.25 (1.23, 1.28)	< 0.01	1.22 (1.20, 1.24)	< 0.01
Marital status (at diagnosis)								
Married (including common law)	Reference		Reference		Reference		Reference	
Separated	1.23 (1.20, 1.25)	< 0.01	1.20 (1.17, 1.22)	< 0.01	1.13 (1.11, 1.16)	< 0.01	1.11 (1.09, 1.14)	< 0.01
Single (never married)	1.16 (1.13, 1.19)	< 0.01	1.16 (1.13, 1.19)	< 0.01	1.09 (1.06, 1.13)	< 0.01	1.08 (1.04, 1.11)	< 0.01
Unknown	1.04 (1.00, 1.09)	0.07	1.02 (0.97, 1.07)	0.41	0.96 (0.91, 1.00)	0.07	0.94 (0.90, 0.99)	0.02
Site								
Right	Reference		Reference		Reference		Reference	
Left	1.01 (0.99,	0.43	1.01 (0.99,	0.42	1.00 (0.98,	0.76	1.01 (0.99,	0.59

	1.03)		1.03)		1.02)		1.03)	
Unknown	2.15 (2.06, 2.23)	< 0.01	2.22 (2.13, 2.32)	< 0.01	1.04 (1.00, 1.09)	0.05	1.04 (0.99, 1.08)	0.10
Year of diagnosis								
2012–2015	Reference		Reference		Reference		Reference	
2008–2011	1.08 (1.05, 1.10)	< 0.01	1.08 (1.05, 1.11)	< 0.01	1.06 (1.04, 1.09)	< 0.01	1.06 (1.04, 1.09)	< 0.01
2004–2007	1.13 (1.11, 1.16)	< 0.01	1.15 (1.12, 1.18)	< 0.01	1.12 (1.09, 1.14)	< 0.01	1.13 (1.10, 1.15)	< 0.01
Tumor grading								
Grade I	Reference		Reference		Reference		Reference	
Grade II	1.50 (1.43, 1.58)	< 0.01	1.62 (1.53, 1.72)	< 0.01	1.30 (1.24, 1.37)	< 0.01	1.36 (1.28, 1.45)	< 0.01
Grade III	2.45 (2.33, 2.57)	< 0.01	2.85 (2.69, 3.02)	< 0.01	1.54 (1.46, 1.62)	< 0.01	1.64 (1.55, 1.74)	< 0.01
Grade IV	3.38 (3.18, 3.59)	< 0.01	4.08 (3.82, 4.36)	< 0.01	1.64 (1.54, 1.75)	< 0.01	1.75 (1.63, 1.88)	< 0.01
Unknown	3.70 (3.53, 3.89)	< 0.01	4.41 (4.17, 4.66)	< 0.01	1.49 (1.42, 1.57)	< 0.01	1.58 (1.49, 1.67)	< 0.01
Histologic type								
Adenocarcinomas	Reference		Reference		Reference		Reference	
Squamous	1.19 (1.16, 1.22)	< 0.01	1.11 (1.09, 1.14)	< 0.01	1.14 (1.11, 1.17)	< 0.01	1.10 (1.07, 1.13)	< 0.01
Epithelial neoplasms	1.87 (1.83, 1.91)	< 0.01	1.91 (1.87, 1.95)	< 0.01	1.24 (1.22, 1.27)	< 0.01	1.24 (1.21, 1.27)	< 0.01
Others	0.85 (0.81, 0.90)	< 0.01	0.83 (0.78, 0.87)	< 0.01	1.12 (1.07, 1.18)	< 0.01	1.13 (1.07, 1.19)	< 0.01
AJCC stage								
0-I	Reference		Refere		Refere		Referen	

			nce		nce		ce	
II	1.54 (1.47, 1.62)	< 0.01	1.88 (0.78, 1.99)	< 0.01	1.73 (1.64, 1.82)	< 0.01	2.04 (1.93, 2.17)	< 0.01
III	2.73 (2.65, 2.81)	< 0.01	3.65 (3.52, 3.78)	< 0.01	2.17 (2.09, 2.24)	< 0.01	2.71 (2.60, 2.82)	< 0.01
IV	5.60 (5.45, 5.75)	< 0.01	7.85 (7.60, 8.11)	< 0.01	3.93 (3.81, 4.06)	< 0.01	5.15 (4.95, 5.35)	< 0.01
Surgery								
Yes	Reference		Reference		Reference		Reference	
No	4.74 (4.63, 4.86)	< 0.01	5.70 (5.54, 5.87)	< 0.01	26.59 (23.99, 29.48)	< 0.01	46.62 (41.27, 52.66)	< 0.01
Chemotherapy								
Yes	Reference		Reference		Reference		Reference	
No	1.01 (1.00, 1.03)	0.128	0.93 (0.91, 0.94)	< 0.01	17.45 (15.82, 19.25)	< 0.01	28.72 (25.59, 32.22)	< 0.01
Radiation								
Yes	Reference		Reference		Reference		Reference	
No	0.78 (0.77, 0.80)	< 0.01	0.75 (0.74, 0.94)	< 0.01	10.30 (9.33, 11.36)	< 0.01	16.96 (15.11, 19.04)	< 0.01

[a] adjusted for age, sex, race, year of diagnosis, site, histology, AJCC, marital status, grading and therapy; API = Asian or Pacific Islander; AIAN = American Indian/Alaska Native; OS = Overall survival; LCSS = Lung cancer specific survival; CI = Confidential interval; HR = Hazard ratio.

Comment 2: *Second, as the authors are meant to estimate a causal effect, I highly recommend making clear the choice of the variables they included in their models as confounders. One way to make the selection clear is to draw a Directed Acyclic Graph. I can recommend reading the paper from Tennant et al: Tennant PWG, Murray EJ, Arnold KF, et al. Use of directed acyclic graphs (DAGs) to identify confounders in applied health research: review and recommendations. Int J Epidemiol. 2021;50(2):620-632. doi:10.1093/ije/dyaa213*

By drawing the DAGs, authors would probably understand the complexity of race as a causal effect. They may also identify which confounders are missing from their dataset.

Reply 2: Thank you for your nice comments on our article. As mentioned above, we were not aimed to demonstrate a causal effect. In fact, we mainly want to show that race is associated with lung cancer-specific survival. There may be some unclear expressions in the text, so we have made corrections based on your comments.

Changes in the text: (see the general reply for more details)

Comment 3: *Third, the use of propensity-score matching is indeed a method to handle confounding but this method is not recommended because propensity-score matching (1) requires a subjective decision on the way to identify matches; (2) often requires discarding a substantial part of the sample; and (3) likely to lead to selection bias. The authors may consider using propensity score covariate adjustment instead.*

Reply 3: We appreciate the referee's comment on the method of propensity-score matching. Indeed, propensity-score matching can only equalize the observed indicator variables and can come at the cost of losing a large amount of patient data. After rigorous consideration, we used propensity scores as covariates to adjust the Cox regression analysis. Therefore, we have revised the entire text for this purpose. (mainly in Page 1, line 2-3, Page 6, line 122-125, Page 7-9, line 161-196 and Table 2).

Changes in the text:

Page 1, line 2-3: Racial disparities in histological subtype distribution, stage at presentation and cancer-specific survival in lung cancer

Page 6, line 122-125: The propensity score (PS) was used as a continuous covariate in the multivariable Cox proportional-hazards regression model, with racial groups as the dependent variable and confounders including age at diagnosis, gender, marital status, tumor site, year of diagnosis, tumor grading, histological subtype, AJCC stage, surgery status, chemotherapy status and radiation status.

Page 7-9, line 161-196:

3.2. Survival analysis

Baseline clinical features and treatment were evaluated in Cox proportional hazards models of OS and LCSS. A univariable analysis indicated that Black, older age, male, separated and single (never married), earlier year of diagnosis, higher histology grades, squamous and epithelial neoplasms, more advanced TNM stage, patients without surgery and an absence of chemotherapy or radiation were significantly associated with a worse OS ($p < 0.01$, respectively) and LCSS ($p < 0.01$, respectively). (Supplementary Table S1) In crude survival analysis, the API group was associated with significantly better OS ($p < 0.01$) and LCSS ($p < 0.01$). (Figure 2) Furthermore, we included all variables mentioned earlier in the multivariable analysis. After adjustment for potential confounders, API and Black were identified as independent protective factor for both OS (HR: 0.84, 95% CI:

0.82-0.87, p < 0.01; HR: 0.97, 95% CI: 0.94-0.99, p = 0.01, respectively) and LCSS (HR: 0.85, 95% CI: 0.83-0.88, p < 0.01; HR: 0.94, 95% CI: 0.92-0.97, p < 0.01, respectively). (Supplementary Table S1) We used time-dependent Cox proportional hazards model for OS and LCSS in all racial patients who received treatments in different time. (Table 2; Supplementary Table S1) Interestingly, the significance of the married status for survival was analyzed by univariate and multivariate Cox regression analyses. We found the married group was associated with a significantly better LCSS (p < 0.01). (Supplementary Table S1) The results of multivariate analysis were similar with those of univariate analysis.

Among different racial groups, we identified statistically significant differences in LCSS with different conditions. (Supplementary Table S1) The multivariable Cox regression results were presented in Table 2. The adjusted HRs had the PS included in the model. The results showed a better LCSS for API (HR: 0.85, 95% CI: 0.83-0.88; adjusted HR: 0.90, 95% CI: 0.88-0.93; Table 2). When stratifying the data by histological sub-type-specific we see that, lung adenocarcinoma patients who were API had best LCSS. (Supplementary Figure S2a) In stage I and IV, patients who were API had best LCSS. (Table 3; Supplementary Figure S2b) And in grade II, API patients had best LCSS. (Table 3; Supplementary Figure S2c) Meanwhile, in lung cancer patients treated with chemotherapy and radiation, LCSS was longer in API group. (Table 3; Supplementary Figure S2d)

Among adenocarcinoma patients treated with chemotherapy and chemotherapy combined radiation, API group exhibited best LCSS. (Supplementary Figure S3a) In stage IV patients treated with chemotherapy, radiation, and chemotherapy combined radiation, API group demonstrated a significantly best LCSS, respectively. (Supplementary Figure S3b-c) And API group may have best LCSS in grade II with chemotherapy. (Supplementary Figure S3d) The Kaplan–Meier survival curves revealed LCSS advantage for adenocarcinoma in API group (Supplementary Figure S2a), but stratifying adenocarcinoma patients by AJCC stage and grade respectively, we found only in stage I, IV and grade II, LCSS in four racial groups had statistical dif-ferences. (Supplementary Figure S4) Further analysis, in stage IV adenocarcinoma patients who underwent chemotherapy, radiation and chemotherapy combined radiation, LCSS was longer in API patients, respectively. (Supplementary Figure S5b-c) Interestingly, we found that married status was associated with best LCSS (Table S1), and API group had best LCSS in married patients (Supplementary Figure S6).

Table 2: Time-dependent Cox regression analyses for LCSS with PS covariate adjustment [a], 2004-2015.

Variable	Before PS adjusted		After PS adjusted	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Race				
White	Reference		Reference	
Black	0.94 (0.92, 0.97)	< 0.01	0.97 (0.94, 1.00)	0.06
API	0.85 (0.83, 0.88)	< 0.01	0.90 (0.88, 0.93)	< 0.01

AIAN	1.08 (0.88, 1.31)	0.46	0.99 (0.81, 1.20)	0.91

[a] adjusted for age, sex, race, year of diagnosis, site, histology, AJCC, marital status, grading and therapy; API = Asian or Pacific Islander; AIAN = American Indian/Alaska Native; LCSS = Lung cancer specific survival; CI = Confidential interval; HR = Hazard ratio; PS: propensity score

Comment 4: *Fourth, authors interpreted the association between some characteristics (sex, age, tumour characteristics, married status) - included in their multivariate analysis build to estimate the causal effect of race on lung cancer survival - and survival. Interpreting these associations are not recommended. This is known as the Table 2 fallacy. I invite authors to read: Westreich D, Greenland S. The table 2 fallacy: presenting and interpreting confounder and modifier coefficients. Am J Epidemiol. 2013 Feb 15;177(4):292-8. doi: 10.1093/aje/kws412. Epub 2013 Jan 30. PMID: 23371353; PMCID: PMC3626058.*

Reply 4: Thank you for your comment. Indeed, the previously presented Table 2 has a Table 2 fallacy. Based on your third point, we have revised the article. We have modified our text as advised (see Table 2).

Changes in the text:
(see point 3 above for more details)

Comment 5: *There is no need to present p-values in the description part of the paper as no hypothesis is tested.*

Reply 5: Thank you for your valuable comment. We are sorry for the irregularity regarding the presentation of *p*-values that were not placed in the tables or figures. After reviewing the full text, we revised the *p*-values that did not appear and were unnecessary. We have modified our text as advised (see Page 8-9, line 186-196).

Changes in the text:
Page 8-9, line 186-196: Among adenocarcinoma patients treated with chemotherapy and chemotherapy combined radiation, API group exhibited best LCSS. (Supplementary Figure S3a) In stage IV patients treated with chemotherapy, ra-diation, and chemotherapy combined radiation, API group demonstrated a significantly best LCSS, respec-tively. (Supplementary Figure S3b-c) And API group may have best LCSS in grade II with chemotherapy. (Supplementary Figure S3d) The Kaplan–Meier survival curves revealed LCSS advantage for adenocarci-noma in API group (Supplementary Figure S2a), but stratifying adenocarcinoma patients by AJCC stage and grade respectively, we found only in stage I, IV and grade II, LCSS in four racial groups had statistical dif-ferences. (Supplementary Figure S4) Further analysis, in stage IV adenocarcinoma patients who underwent chemotherapy, radiation and chemotherapy combined radiation, LCSS was longer in API patients, respectively. (Supplementary Figure S5b-c) Interestingly, we found that married status was

associated with best LCSS (Table S1), and API group had best LCSS in married patients (Supplementary Figure S6).

Comment 6: *The nomogram was not presented as an objective. Why did authors include it?*

Reply 6: Thank you. We highly appreciate your opinion. After making full-text revisions, we agree with you that the nomogram was indeed not very valuable aids to the findings of this paper. Therefore, after critical consideration we have removed this section.

Changes in the text: Removed all sentences and figures about nomogram.