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Comment on the article titled "Impact of KRAS mutation subtype and concurrent pathogenic mutations on non-small cell lung cancer outcomes"

Dear editor,

I'd like to comment on an article published in the journal "Lung Cancer" titled "Impact of KRAS Mutation Subtype and Concurrent Pathogenic Mutations on Non-Small Cell Lung Cancer Outcomes". In this study conducted by Aredo et.al [1], the author aimed to characterize the effects of KRAS mutation subtypes and concurrent pathogenic mutations on overall survival (OS) and one of their main findings was that one KRAS mutation subtype, the KRAS G12D confer a worse prognosis for patients with KRAS-mutant NSCLC. The author described in the result that on multivariable analysis, KRAS G12D mutations were significantly associated with poor OS (hazard ratio [HR] 2.43, 95% confidence interval [CI] 1.15–5.16; P = 0.021). However, several points should be noted regarding with this. On the univariate Cox analysis, seven clinic-pathological variables were included, and the authors identified distant disease stage, STK11 co-mutations and localized therapies as associated with poor OS. We noted that KRAS G12D mutations were not identified as an independent factor associated with shorter OS (p = 0.107). However, in the multivariate analysis, the author selected all the seven variables mentioned above into the Cox regression model regardless of the significances of these variables in the univariable analysis and found that the KRAS G12D mutations were associated with inferior prognosis ((HR 2.43, 95% CI:1.15–5.16; p = 0.021). Moreover, in the Kaplan-Meier analysis, KRAS G12D mutation subtype was not associated with significant difference in OS (Fig. 1, p = 0.1). In the discussion part, the author credited this discrepancy to the impact of potential confounders, and believed that only after adjusting for potential confounders, such as disease stage and the presence of concurrent pathogenic mutations, are they able to capture the signal from KRAS G12D mutations. However, the methodology the author used should be discussed. As a method proposed for modeling survival analysis data, the Cox proportional hazards model is the most commonly used multivariate approach for analysing survival time data in medical research [2]. It is a survival analysis regression model, which describes the relation between the event incidence, as expressed by the hazard function and a set of covariates. Commonly, the researches selected the variables that achieved significance (usually $p < 0.05$) in the univariate analysis into the multivariable analyses via the Cox regression model [3,4]. Sometimes, considering the limited sample size, some researchers would select the p value of 0.5 as the cutoff point [5]. In this present study, however, neither the log-rank test nor the univariate analysis suggested the potential prognostic value of KRAS G12D mutations. Moreover, several "potential confounders", including gender and smoking status, were not associated with OS in the univariable analysis and the final multivariable analysis. Thus, we doubt the statistical methodology conducted by the author when they draw their conclusion that this is the first study to reveal a negative prognostic effect with KRAS G12D mutations in NSCLC.

To our knowledge, the KRAS G12D mutation subtype has been reported to be an independent prognostic marker for other malignancies, including pancreatic ductal carcinoma and ampullary cancer [6,7]. However, in this study, taking all the above mentioned factors into consideration, it was hard for the author to come to the conclusion that KRAS G12D mutations were associated with poor prognoses for patients with KRAS-mutant NSCLC.

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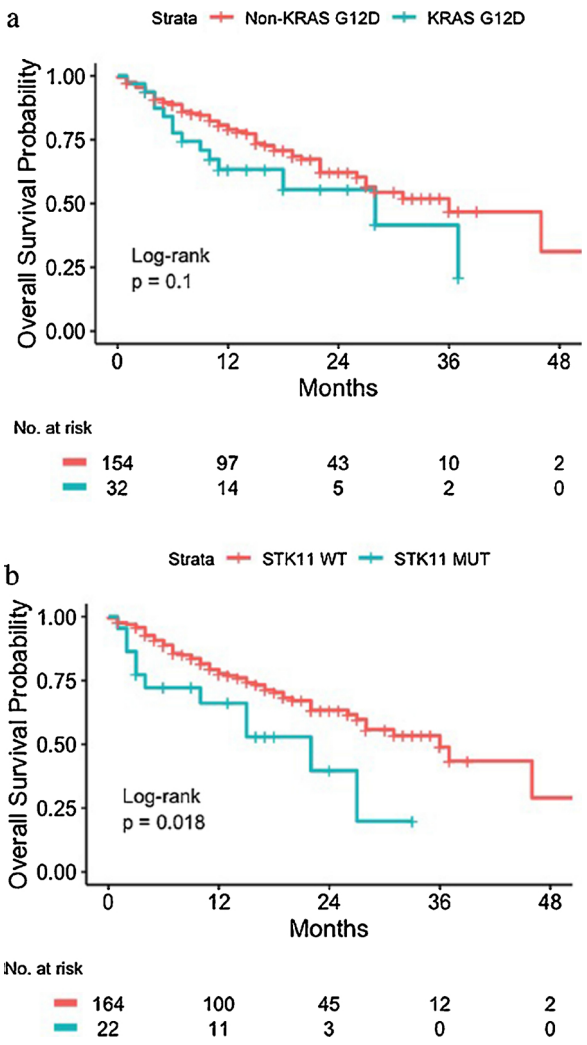

Fig. 1. Kaplan-Meier survival analysis stratified by KRAS G12D mutation status (a) and STK11 co-mutation status (b). Abbreviations: No. number, WT wild- type, MUT mutant.

Declaration of Competing Interest

No conflict of interest exists in the submission of this manuscript, and manuscript was approved by all authors for publication. I would like to declare on behalf of my co-authors that the work described was original research that has not been published previously, and not under consideration for publication elsewhere, in whole or in part. All the authors listed have approved the manuscript that is enclosed.

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Junmiao Wen[a,b,*], Jiayan Chen[a,b], Min Fan[a,b]

[a] *Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, 200032, China*

[b] *Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, 200032, China*

E-mail address: drjimmiewen@126.com (J. Wen).

* Corresponding author.