TRANSLATIONAL CANCER RESEARCH

# Peer Review File

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**Comment 1:** A more suitable justification for the use of random effects model is needed.

**Reply 1:** In our study, the selection of appropriate estimated model between fixed-effect and random-effect model is based on different risk level in heterogeneity. Low risk in heterogeneity ($I^2$<25%) indicated little statistical uncertainty in the combined effect across the studies that we considered the included studies share a common effect size and fit in a fixed-effect model. Moderate to high risk in heterogeneity ($I^2$≥25%) and reject the $I^2$ hypothesis indicated existing statistical uncertainty in the combined effect across the studies that we considered the effect size of included studies is in distribution and we used a random-effect model to estimate the mean of the effect size.

**Changes in the text:** We have modified our text as advised (see Page 7-8, line 129-142)

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**Comment 2:** Is there any equation for the considered model?

**Reply 2:** The selection of appropriate model is mainly affected with the impact of heterogeneity. Among balanced included studies, it refers to uncertainty in the combined effect across studies and mainly comes from two sources, the sampling error (within-study variability) and the true heterogeneity (between-studies variability). The fixed-effect model assumes that all studies in the analysis share a common effect size and results only differ by the sampling error. And on the contrast, when the results is affected with both within-study and between-studies variability, we assume that there is a distribution of true effect sizes and random-effect model is applied to estimate the mean of it.

Thus, we apply a $I^2$ test to quantify the degree of heterogeneity among the studies. The null hypothesis of $I^2$ test assumes that the included studies are homogenous. $I^2$ values reflect the extend of between-studies variability in the total statistical

heterogeneity, which $I^2$=0% means that all variability in effect size estimates is due to sampling error and $I^2$=50% means that half of the total variability is caused by between-studies heterogeneity.

The equation of $I^2$ values is shown as below.

$$I^2 = \frac{\frac{Q}{k-1} - 1}{\frac{Q}{k-1}} \times 100\%$$

The equation defined $I^2$ value in terms of $Q$ values. The $Q$ is computed by summing the squared deviations of each study's effect estimate from the overall effect estimate, weighting the contribution of each study by its inverse. The $k$ is the number of studies and $k$-$1$ is its degrees of freedom.

**Changes in the text:** we have modified our text as advised (see Page 8, line 134-141)

**Comment 3:** The statistical analysis need more explanation for the reader that want reproduce your research.

**Reply 3:** We have modified our statistical analysis section in our manuscript by 1. the pool statistical method is based on "Mantel-Haenszel methods", a strengthen chi-square test involving a weighted mean difference across the set of (2 * 2) tables; 2. clarify the statement on risk classification on heterogeneity with $I^2$ test; 3. justify for the selection scheme between fixed- and random-effects model

**Changes in the text:** We have modified our text as advised (see Page 7-8, line 121-144)

**Comment 4:** Please, increase the quality of figures. There are too many figures with poor explanation.

**Reply 4:** We have modified our description and improved picture quality in our manuscript.

**Changes in the text:** We have modified our text as advised (see Page 23, line 424-459)