Title: Single nucleotide polymorphisms associated with postoperative inadequate analgesia after single-port VATS in Chinese population

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Author’s response to reviews:

Dear reviewers and editors,
Thank you very much for your letter and advice on our manuscript. The comments have been carefully taken into account and a new revised manuscript has been uploaded. We have highlighted all the altered paragraphs in light gray. The responses are as follows,

Response to reviewer #1:
Question 1: It seems that some English sentences are poor. For example, "This result was consistent with previous reported" should be changed to "This result was consistent with previous reports". The authors should check and edit the entire manuscript again.
To question 1: Thanks for your advice. We have checked the entire manuscript again and revised the poor expression at Discussion section, line 277, page 13.

Question 2: The latter "S" letter in the "SNPS" should be lowercase. [Line 38]
To question 2: Thanks for your advice. We have revised it at Abstract section, line 38, page 2.

Question 3: The authors explained how genes, known to be involved in systems related to pain perception and modulation based on evidence in the literature, were selected in the present study. However, it seems that the rs2952768 SNP, which was selected in the present study (Table S1), is not related to the 13 genes described and is not related to the UGT2B7 gene. The authors should explain more about this SNP.
To question 3: Thanks for your carefully review. The rs2952768 SNP, which was selected in the present study (Table S1), is related to the CREB1 (cAMP responsive element binding protein 1) gene, not to the UGT2B7 gene. We have revised it at Table 1, Table S1, and at Abstract section, line 29, page 2. More details about this SNP have been explained at Background section, line 102, page 5.

Question 4: It is recommended that the authors describe the total number of patients recruited in the Methods section (Patient characteristics).
To question 4: Thanks for your advice. We have added the total number of patients in the Methods section, line 117, page 6.
Question 5: The authors describe that "Significant associations between genetic mutations and postoperative inadequate analgesia were detected in nine SNPs among six genes (ESR1, P2RY12, SCN11A, SCN10A, SCN9A, and TAOK3) by the logistic regression (see Table 4)." However, only six SNPs seem to show significant associations (P-Value unadjusted < 0.05) according to Table 4. The authors should correct it. [Line 249-251]
To question 5: Thanks for your advice. We have corrected it at Results section, line 250-251, page 12.

Question 6: The authors describe that "After adjusting for potential confounders, four SNPs remained significant: rs33985936 (SCN11A), rs11709492 (SCN11A), rs6795970 (SCN10A), and 3312G>T (SCN9A)." However, five SNPs seem to show significant associations (P-Value adjusted < 0.05) including rs9340799 (ESR1) according to Table 4. The authors should correct it. [Line 251-253]
To question 6: Thanks for your comments. For ESR1 (rs9340799), after adjusting for potential confounders, although the P-value of the correlation was statistically significant (p < 0.05), the odds ratio didn’t have clinical significance (OR = 0.13, 95% CI: 0.02-1.08). We couldn’t identify from the 95% CI whether the GG genotype decrease or increase the risk of postoperative inadequate analgesia. The contradiction between P-value and 95% CI may be caused by the unstable correlation between rs9340799 and postoperative inadequate analgesia. This instability may be caused by the small sample size. So we didn’t include the rs9340799 (ESR1) to the final results. We have discussed the effect of rs9340799 (ESR1) at Discussion section, line 323-330, page 15.

Question 7: If rs9340799 (ESR1) SNP actually shows significant association (P-Value adjusted < 0.05) as well as other four SNPs (rs11709492, rs33985936, rs6795970, and 3312G>T), the authors should discuss the rs9340799 (ESR1) SNP in addition to the other four SNPs.
To question 7: Thanks for your advice. We have discussed the effect of rs9340799 (ESR1) at Discussion section, line 323-330, page 15.

Question 2: Table 1, Table 4, Table S1. The name of the genes should be italicized.
To question 2: Thanks for your advice. We have revised it at Table 1, Table 4, Table S1.

Response to reviewer #2:
Thanks for your positive comments and advice.

Question 1: The authors exclude from analysis other important genes involved in pain perception and opioid response (eg OPRM1, COMT). Theoretically, genetic variation in these genes may account for different pain perception and opioid response, thus influencing the ratio of patients experiencing incomplete analgesia. I guess it is not possible to study these genes now, and control for possible confounding effect, but I guess this aspect may at least be stated and discussed in the discussion session.
To question 1: Thanks for your advice. We have added the explanation of the effect of other important genes involved in pain perception and opioid response on postoperative inadequate analgesia at Discussion session, line 316-330, page 15.