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High-flow nasal cannula oxygen therapy versus conventional oxygen therapy in patients after planned extubation

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We read with great interest the recent systematic review and meta-analysis of high-flow nasal cannula (HFNC) oxygen therapy versus conventional oxygen therapy (COT) in patients after planned extubation [1]. We greatly appreciate Zhu Y and colleagues' efforts, but some important issues may better be discussed.

First, randomized controlled trials (RCTs) and non-RCTs may be inappropriately combined together in the meta-analysis, which goes against the principle of pooling studies with the similar design [2, 3]. Thus, results from RCTs and non-RCTs may better be separately pooled (Fig. 1a, b). Our Fig. 1 a and b show that the pooled results of RCTs and non-RCTs were not entirely consistent and subgroup analyses significantly decreased the heterogeneity, which suggested that the heterogeneity may originate from pooling studies with the different design. While we found that the pooled results of RCTs were even more biased in favor of HFNC than non-RCTs.

Second, using the standardized mean difference as the summary statistic for the meta-analyses of PaO_2 and respiratory rates may be improper. The standardized mean difference is utilized as the summary statistic in the meta-analysis when the trials all assess the same outcome, but measure it in various ways [3]. Moreover, the standardized mean difference is unitless, which only shows the difference in a relatively measurement scale rather than a real difference in variability [3]. Therefore, the mean difference may better be used as the summary statistic to pool data (Fig. 1a, b).

Third, trial sequential analysis for comparison of post-extubation respiratory failure between two groups may better be drawn based on the accurate relative risk reduction (RRR) of 37.17% ($\frac{\frac{118}{534}-\frac{74}{533}}{\frac{118}{534}}$). Then, Fig. 1c is drawn to show that the line of cumulative *Z*-curve neither crossed the line of the trial sequential monitoring boundary for benefit nor the required information size boundary, which established inconclusive evidence [4]. But in the authors' Figure S7, the line of cumulative *Z*-curve obviously crossed the line of the trial sequential monitoring boundary for benefit, which may mislead the interpretation because of the inaccurate trial sequential analysis. Therefore, the figure of trial sequential analysis may better be not drawn based on a rough estimated RRR.

Authors' response

Youfeng Zhu, Haiyan Yin and Jianrui Wei

To the Editor,

Thank you very much for giving us the opportunity to respond to the valuable comments pointed out by Meng-Si Luo and colleagues with regard to our study [1].

First, randomized controlled trials (RCTs) and cross-over studies were not pooled together for primary outcome and main secondary outcomes in our article, only pooled together for secondary outcomes of respiratory rate, PaO_2, and comfort score. According to the guidelines described in the *Cochrane Handbook for Systematic Reviews of Interventions*, quasi-RCTs and cross-over studies can be included for analysis, particularly when few RCTs addressing the topic of the review are identified [3]. Furthermore, for resolving the potential bias

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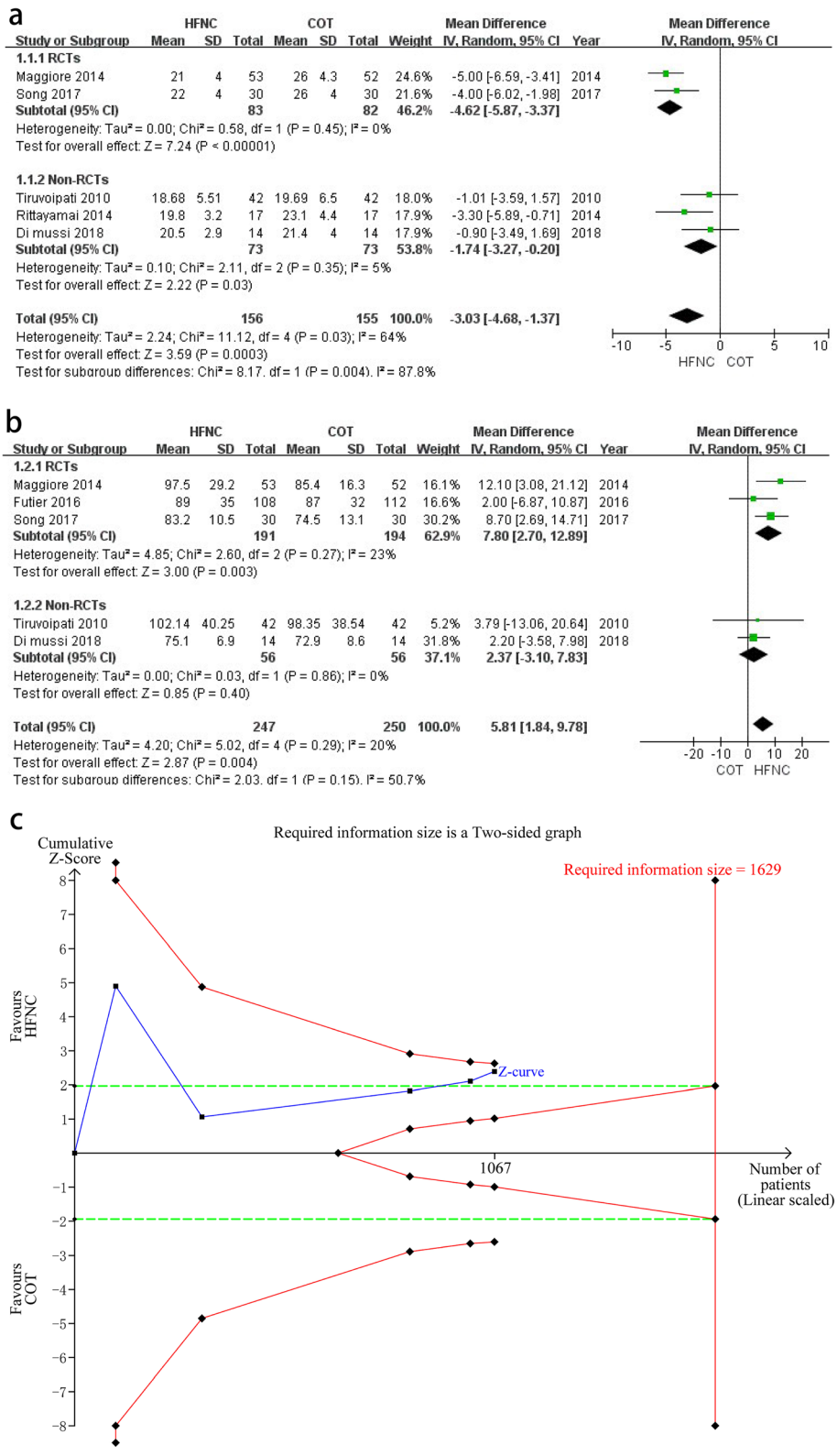

Fig. 1 **a** Comparison of respiratory rates between the HFNC group and COT group. **b** Comparison of PaO_2 between the HFNC group and COT group. **c** Trial sequential analysis for comparison of postextubation respiratory failure between the two groups

of pooling these studies together, subgroup studies with regard to study type (RCTs vs cross-over studies) were also performed in our study (Table 3 of our article).

Second, we thank Dr. Luo and agree that the weighted mean difference (WMD) should be used when outcome measurements in all trials are made on the same scale. WMD would be better for analyzing respiratory rate and PaO_2. However, as the comfort score was measured with different scales among the included studies, the standardized mean difference (SMD) should be used.

Third, according to the user manual for trial sequential analysis (TSA), the estimation of the control group event proportion and an anticipated intervention effect are important determinants of the calculated required information size when doing TSA [5]. The anticipated intervention effect is usually expressed as a relative risk reduction (RRR). The estimation of RRR can be performed by using clinical experience and evidence from related studies [5, 6]. Furthermore, information size estimation must incorporate all sources of variation in a meta-analysis, including heterogeneity. As there was moderate heterogeneity ($\chi^2 = 7.82$, $df = 4$, $P = 0.10$, $I^2 = 49\%$) among the included studies, which might have been due to the heterogeneous population of patients and various treatment measures after extubation, the accurate RRR of 37.17% could not reflect the realistic RRR. Hence, basing on the RRR of 37.17% to draw the trial sequential analysis for comparison of postextubation respiratory failure between two groups is improper and may also mislead the results. Furthermore, we are cautious to our conclusion and underlined in our article that "a decisive conclusion should be made cautiously. Further large-scale, multicenter studies are needed to confirm our results."

Abbreviations

HFNC: High-flow nasal cannula; COT: Conventional oxygen therapy; RCT: Randomized clinical trial; RRR: The relative risk reduction

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Authors' contributions

M-SL was responsible for conception of the letter and wrote the manuscript. G-JH and LW conceived and revised this manuscript. All authors had read and approved this final manuscript.

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Competing interests

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