The effect of inverse ratio ventilation on cardiopulmonary function in obese laparoscopic surgery patients: A systematic review and meta-analysis

ABSTRACT

This study aimed to evaluate the effect of inverse ratio ventilation (IRV) strategy on cardiopulmonary function in obese patients under general anesthesia. Databases such as China National Knowledge Infrastructure (CNKI), Wangfang, WeiP, Web of Science, the Cochrane Library, and PubMed were systematically searched. All randomized controlled trials' literature on IRV during laparoscopic surgery in obese patients under general anesthesia was collected. After data were extracted and cross-checked, Rev Man 5.3 software was used for meta-analysis. Finally, five randomized controlled clinical trials (RCTs) were included in the meta-analysis, with a total of 312 patients. Compared with the conventional ventilation group, the inspiratory peak pressure was lower at pneumoperitoneum 30 min and pneumoperitoneum 60 min; the PaO_2 and oxygenation index were higher at pneumoperitoneum 60 min, and mean airway pressure was higher at pneumoperitoneum 30 min and pneumoperitoneum 60 min; the dynamic lung compliance was superior at pneumoperitoneum 30 min and pneumoperitoneum 60 min. IRV applied to laparoscopic surgery in obese patients under general anesthesia not only reduces peak airway pressure and improves intraoperative oxygenation index and PaO2 but also enhances mean airway pressure and dynamic lung compliance, which has a specific lung protective effect. It can be used as an option for the mechanical ventilation model in obese patients in clinical practice.

Key words: General anesthesia, laparoscopy, mechanical ventilation, meta-analysis, obesity

Introduction

With the development of the social economy and the continuous change in diet structure, the improvement of people's standard of living has brought the problem of obesity to the forefront, and obese patients can develop many complications and are increasingly likely to undergo surgical procedures.[1] However, the incidence of perioperative complications and mortality in obese patients are significantly higher than in normal-weight patients, which brings special features and new challenges to our anesthesia.[2] Obese patients accumulate a lot of fat in the chest and abdomen, and the compliance of both lung and chest walls is reduced. In the supine position and during laparoscopic surgery, the abdominal contents and CO_2 will also compress the diaphragm, which will restrict the movement of the diaphragm, causing a decrease in functional residual air

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Wu Jinghua, Niu Xiong, Li Min

Department of Anesthesia, Yongchuan Hospital of Chongqing Medical University, Chongqing, China

Address for correspondence: Dr. Wu Jinghua, Yongchuan Hospital of Chongqing Medical University, Xuanhua Road 439, Chongqing, China. E-mail: 1250457833@qq.com

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volume and dysregulation of ventilation and blood flow in the lungs, resulting in low PaO_2 or even hypoxia. It is proven that post-general anesthesia pulmonary dysplasia lasts at least 24 hours or even longer in obese patients and disappears within a short time after surgery in normal-weight patients.[3] Therefore, it is important to choose the appropriate model of ventilation in obese patients under general anesthesia. Inverse ratio ventilation (IRV) is a ventilator ventilation model that has recently been proven to promote gas exchange, arterial oxygenation, and respiratory mechanics in patients with acute respiratory distress syndrome or acute lung damage while under general anesthesia. The inverse inspiratory-to-expiratory ratio maintains increased alveolar pressure, reduces the formation of dead space, produces endogenous positive end-expiratory pressure (PEEP), and thus improves arterial oxygenation and respiratory function.[4,5]

IRV not only improves the distribution of gas in poorly ventilated alveoli, while opening small airways and atrophied alveoli, but the endogenous PEEP it produces also increases the pressure of gas and fluid infiltration into surrounding tissues, which facilitates alveolar stabilization, so IRV improves patient oxygenation without affecting hemodynamics.[6] In addition, the IRV strategy improves oxygenation while also reducing peak inspiratory pressure and inspiratory plateau pressure, which can reduce volumetric and barotropic injuries caused by mechanical ventilation, which have been confirmed in many studies,[7,8] and these have a positive impact on obese patients. However, the results of Adabala *et al*.[9] showed that despite the improvement of respiratory mechanics indices by IRV, these did not prevent the deterioration of postoperative pulmonary function. In the study by Hur *et al*.,[10] it was concluded that prolonged inspiratory time did not have a significant effect on respiratory mechanics, so there is a lack of certainty as to whether IRV has positive implications.

Therefore, the author intends to evaluate the safety and feasibility of IRV in obese patients using meta-analysis, as well as the effects on cardiopulmonary function and postoperative complications, to provide a new choice of ventilation strategy for clinical anesthesia of obese patients.

Inclusion and Exclusion Criteria

Inclusion criteria

(1) Study subjects: obese patients undergoing laparoscopic surgery under general anesthesia with body mass index (BMI) >28 kg/m^2; (2) interventions: The control group was given conventional volume-controlled protective pulmonary mechanical ventilation (inspiratory-to-expiratory ratio of 1:2), while the experimental group was given IRV (inspiratory-to-expiratory ratio of 1-4:1), and the rest of the indexes were the same as the control group; (3) outcome indexes: ① inspiratory peak pressure, ② mean airway pressure, ③ dynamic lung compliance, ④ oxygenation index, ⑤ mean arterial pressure, ⑥ $PaCO_{2,}$ ⑦ $PETCO_{2,}$ ⑧ PaO_2 and $SaO_{2,}$ ⑨ heart rate, and ⑩ pulmonary complications; and (4) type of study: all randomized controlled trials on intraoperative use of IRV strategy in obese patients.

Exclusion criteria

(1) The model adopted was not a volume control model, such as a pressure control model; (2) the data were unclear, and the literature could not be extracted; (3) existing relevant meta-analyses, literature reviews, and case reports were excluded; (4) the full text was still not available after searching the literature by various means; (5) the study results were not published, and the study was ongoing; (6) Chinese and English belonged to the same; and (7) if the Chinese and English are the same literature, one of them is excluded.

Search strategy

The literature of all randomized controlled trial studies of obese patients under general anesthesia in laparoscopic surgery using the IRV strategy was collected by searching China National Knowledge Infrastructure (CNKI), Wangfang, VIP, Web of Science, EMBASE, the Cochrane of the Library, PubMed, and other databases by the computer system, and the search time was from the establishment to May 21, 2022. The literature was searched while tracking the references included in the literature, and all obtained literature was screened. English search terms included the following: obesity; overweight; obese; fat; inverse ratio ventilation; prolong the inspiratory time; extended inspiratory time; laparoscope laparoscopic; and take PubMed for example: " （obesity OR overweight OR obese OR fat) AND ("inverse ratio ventilation" OR "prolong inspiratory time" OR "extended inspiratory time")."

Literature quality evaluation and data extraction

Two researchers independently screened the relevant literature, continuously cross-checked while extracting information and data, and resolved any disagreements through discussion or by asking for third-party assistance. The methodological quality of the included controlled experiments was evaluated by two independent investigators using the Cochrane Risk Assessment Scale: (1) Was the study randomized and was the randomized method described? (2) Was the study allocation concealed, double-blinded, and did it describe the double-blind method? (3) Is there a specific treatment for withdrawal or loss of access? (4) Are the outcome data complete? (5) Does it produce selective reporting bias?

Statistical methods

For the meta-analysis, RevMan 5.3 software was used. Data from the included studies were tested for heterogeneity using the statistic I^2. If $I^2 < 50\%$, the heterogeneity was considered low and a fixed-effects model was used for data analysis; if $I^2 > 50\%$, the heterogeneity was considered too strong, and the sources of heterogeneity were initially identified and excluded, after excluding obvious heterogeneity. If $I^2 < 50\%$, a fixed-effects model was used, and if still $I^2 > 50\%$, a random-effects model was used for analysis. To analyze the results, we used relative risk (RR) as the effect indicator for count data and mean difference (MD) as the effect indicator for peak inspiratory pressure, mean airway pressure, compatibility of lung dynamics, oxygenation index, mean arterial pressure, $PaCO_2$, $PETCO_2$, PaO_2, SaO_2, and heart rate. We provided the 95% confidence interval (CI).

Results

Literature search results

Following the first review of 105 relevant papers, the title, abstract, and full text of the resulting literature were examined, excluding existing meta-analyses and reviews, and the remaining five papers are included in the study. After screening according to the inclusion and exclusion criteria, with a total of 312 patients, a brief flowchart of the included literature is shown in Figure 1.

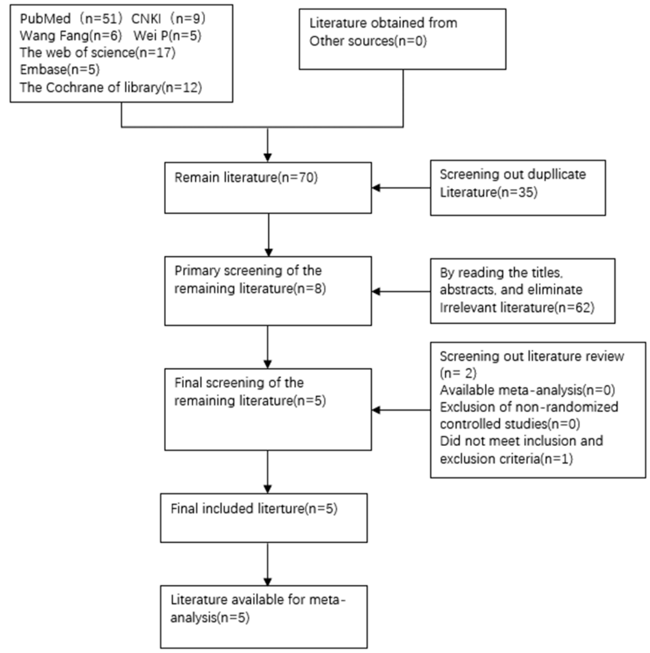

Figure 1: Flowchart of literature search

Basic characteristics and quality evaluation of included studies

There were one English literature and four Chinese literature studies in the final screening, and the basic characteristics of the literature are shown in Table 1. All included literature used the random number method of grouping, but none of the literature specified whether the allocation was hidden or not, because it was a clinical open trial, and because of the ethical restrictions and the patient's right to know, so the blinding and allocation concealment were difficult to achieve in a sense [Figure 2].

Meta-analysis results

Peak inspiratory pressure

A total of five[11-15] studies (n = 312) in the literature reported data on peak inspiratory pressure at 60 min after pneumoperitoneum, and three[11,13,15] papers (n = 172) reported data on peak inspiratory pressure at 30 min after pneumoperitoneum. Further subgroup analysis by time and meta-analysis with the random-effects model showed that the IRV group after general anesthesia in obese patients was more effective than the results of the random-effects model. Meta-analysis showed that the peak inspiratory pressure was lower in the conventional ventilation group than in the conventional ventilation group at 30 min after pneumoperitoneum [MD = -3.48, 95% CI (-4.12, -2.85), $I^2 = 45\%$, $P < 0.00001$] and 60 min after pneumoperitoneum [MD = -3.26, 95% CI (-3.94, -2.59) $I^2 = 43\%$, $P < 0.00001$], and both were statistically significance; after sensitivity analysis due to high heterogeneity and exclusion of one study, meta-analysis using fixed-effects model showed that the IRV group after general anesthesia in obese patients was lower than the conventional ventilation group at 30 min after pneumoperitoneum [MD = -3.06, 95% CI (-3.77, -2.34), $I^2 = 0\%$, $P < 0.00001$] and 60 min after pneumoperitoneum [MD = -3.58, 95% CI (-4.08, -3.07), $I^2 = 0\%$, $P < 0.00001$], which remained statistically significant [Figure 3a and b].

Mean airway pressure

A total of five[11-15] studies (n = 312) in the literature reported data on mean airway pressure at 60 min post-pneumoperitoneum after general anesthesia, and three[11,13,15] papers (n = 172) reported data on mean airway pressure at 30 min post-pneumoperitoneum, and meta-analysis of the random-effects model showed that obese patients had higher mean airway pressure after general anesthesia in the IRV group compared with the control group. Airway pressure was significantly and statistically higher in both 30 min [MD = 2.56, 95% CI (1.26, 3.86), $I^2 = 94\%$, $P = 0.0001$] and 60 min [MD = 1.38, 95% CI (0.09, 2.67), $I^2 = 94\%$, $P = 0.04$] after pneumoperitoneum; considering the high heterogeneity, in a sensitivity analysis, after excluding one study at 30 min of pneumoperitoneum and three studies at 60 min of pneumoperitoneum, the results of meta-analysis using fixed-effects model showed that the

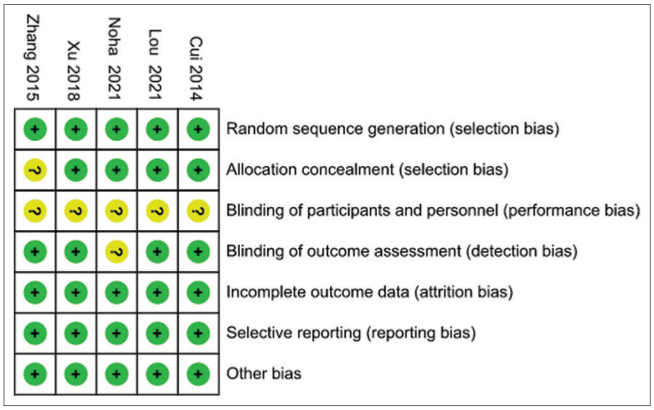

Figure 2: Risk of bias of randomized controlled trials. Green circle, low risk; yellow circle, some concerns; red circle, high risk

IRV group after general anesthesia in obese patients was significantly higher than the conventional ventilation group at 30 min after pneumoperitoneum [MD = 1.95, 95% CI (1.51, 2.39), $I^2 = 0\%$, $P < 0.00001$] and at 60 min [MD = 1.87, 95% CI (1.40, 2.35), $I^2 = 0\%$, $P < 0.00001$], which remained statistically significant [Figure 3c, d].

Pulmonary dynamic compliance

A total of five[11-15] studies (n = 312) in the literature reported data on pulmonary dynamic compliance 60 min after general anesthesia, and three[11,13,15] papers (n = 172) reported data on pulmonary dynamic compliance 30 min after pneumoperitoneum, and meta-analysis with random-effects model showed that the IRV group after general anesthesia in obese patients had a higher pulmonary dynamic compliance than the control group Pulmonary dynamic compliance was significantly higher and statistically significant in both 30 min [MD = 2.78, 95% CI (2.05, 3.52), $I^2 = 0\%$, $P < 0.00001$] and 60 min [MD = 3.24, 95% CI (1.69, 4.78), $I^2 = 86\%$, $P < 0.00001$] after pneumoperitoneum compared with the control group; due to the higher pneumoperitoneum of 60 min, heterogeneity was high, and sensitivity analysis was performed, and after excluding one study, meta-analysis with fixed-effects model showed that the IRV group was higher than the conventional ventilation group at 60 min of pneumoperitoneum [MD = 1.87, 95% CI (1.40, 2.33), $I^2 = 0\%$, $P < 0.00001$], which was still statistically significant [Figure 3e, f].

Oxygenation index

Among them, three[12-14] papers (n = 200) reported data on oxygenation index at 60 min after pneumoperitoneum, and the results of a meta-analysis with a random-effects model showed that the oxygenation index in the IRV group after general anesthesia in obese patients was significantly higher than in the control group at 60 min after pneumoperitoneum [MD = 56.06, 95% CI (32.87, 79.25), $I^2 = 70\%$, $P < 0.00001$], which significantly increased and

Table 1: Characteristics of included articles in the meta-analysis

Author	Year	Study design	Type of surgery	Age	Number of patients	Body mass index (kg/m^2)	American Society of Anesthesiologists	Inverse ratio of ventilation (inhalation time to expiration time)	Primary and secondary objectives
Yanling *et al*.[11]	2014	RCT	Radical rectal cancer surgery	30–64	Total=60 (inverse ratio ventilation=30 vs conventional ventilation=30)	30-40	I or II	1:1	①②③⑤⑥⑦⑧⑨⑩
Wangping *et al*.[12]	2015	RCT	Gynecologic surgery	34-61	Total=80 (inverse ratio ventilation=40 vs conventional ventilation=40)	26-35	I or II	2:1	①②③④⑤⑥⑦⑧⑨⑩
Xu *et al*.[13]	2014	RCT	Gynecologic surgery	30-60	Total=60 (inverse ratio ventilation=30 vs conventional ventilation=30)	≥30	I or II	2:1	①②③④⑥⑦⑧
Lou *et al*.[14]	2021	RCT	Gynecologic surgery	18-65	Total=60 (inverse ratio ventilation=30 vs conventional ventilation=30)	>28	I or II or III	1:1	①②③④⑤⑦⑧⑨⑩
Sayed *et al*.[15]	2016	RCT	Laparoscopic Sleeve Gastrectomy	21-45	Total=52 (inverse ratio ventilation=26 vs conventional ventilation=26)	35-50	II or III	2:1	①②③⑤⑧⑨

① Peak inspiratory pressure, ② mean airway pressure, ③ pulmonary dynamic compliance, ④ oxygenation index, ⑤ mean arterial pressure, ⑥ $PaCO_2$, ⑦ $PETCO_2$, ⑧ PaO_2 and SaO_2, ⑨ heart rate, and ⑩ pulmonary complications was statistically significant; due to high heterogeneity, sensitivity analysis was performed, and after excluding one study, meta-analysis using a fixed-effects model showed that the IRV group had an increase compared with the conventional ventilation group at 60 min after pneumoperitoneum [MD = 66.83, 95% CI (51.11, 82.54), I^2 = 0%, P < 0.00001], which increased and remained statistically significant [Figure 3g, h].

PO_2

A total of three[11,13,15] studies (n = 172) in the literature reported data on pneumoperitoneum 30 min PaO_2 after general anesthesia, and four[11-13,15] papers (n = 252) reported data on pneumoperitoneum 60 min PaO_2 after pneumoperitoneum. Meta-analysis of the random-effects model showed that the IRV group of obese patients after general anesthesia had a higher PO_2 than the control group at 30 min after pneumoperitoneum [MD = 11.40, 95% CI (-0.65, 23.45), I^2 = 79%, P = 0.06] and 60 min after pneumoperitoneum [MD = 39.60, 95% CI (29.57, 49.62), I^2 = 91%, P < 0.001], but the effect of increase at 30 min after pneumoperitoneum was not statistically significant and that at 60 min was statistically significant; due to high heterogeneity, sensitivity analysis was performed for

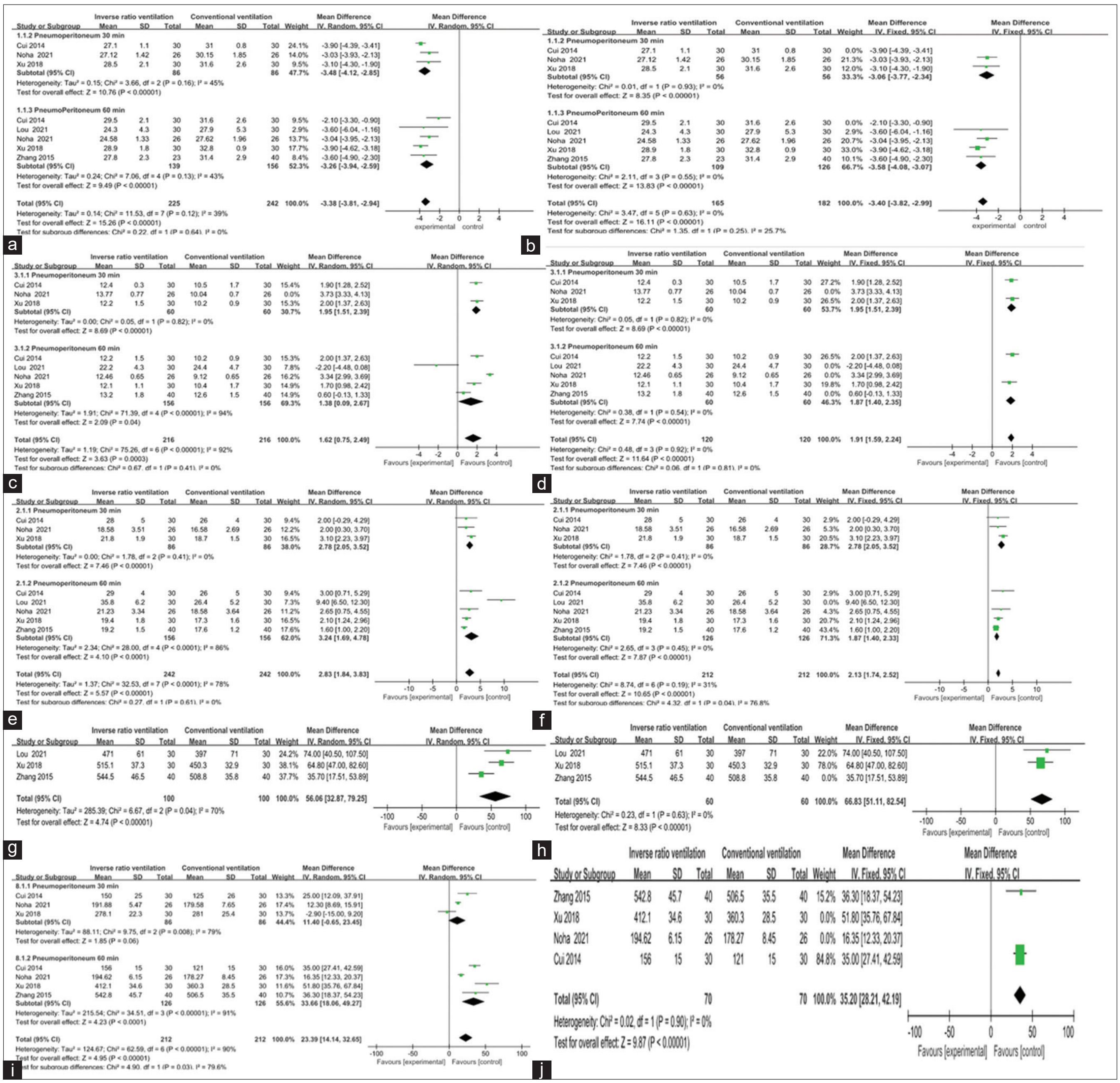

Figure 3: Positive results

pneumoperitoneum 60 min, and after excluding one study, meta-analysis using fixed-effects model showed that the IRV group increased compared with the conventional ventilation group at pneumoperitoneum 60 min [MD = 35.20, 95% CI (28.21, 42.19), $I^2 = 0\%$, $P < 0.00001$] when increased, which was still statistically significant [Figure 3i, j].

This paper also analyzed the heart rate, mean arterial pressure, arterial oxygen saturation (SaO2), arterial blood carbon dioxide partial pressure (PaCO2), and partial pressure of end-breath carbon dioxide(PETCO2). Among them, PETCO2 was reported in two[11,14] papers ($n = 60$) for 60 min after pneumoperitoneum and the results showed no statistical significance using a fixed-effects model. Moreover, meta-analysis showed that the remaining outcomes still have no statistical significance between the data of the IRV group after general anesthesia in obese patients compared with the control group [Figure 4a-e].

Postoperative complications

Only two[12,14] of them (n = 140) reported complications, and the only common outcome indicators were shoulder pain and subcutaneous emphysema. A comparative analysis

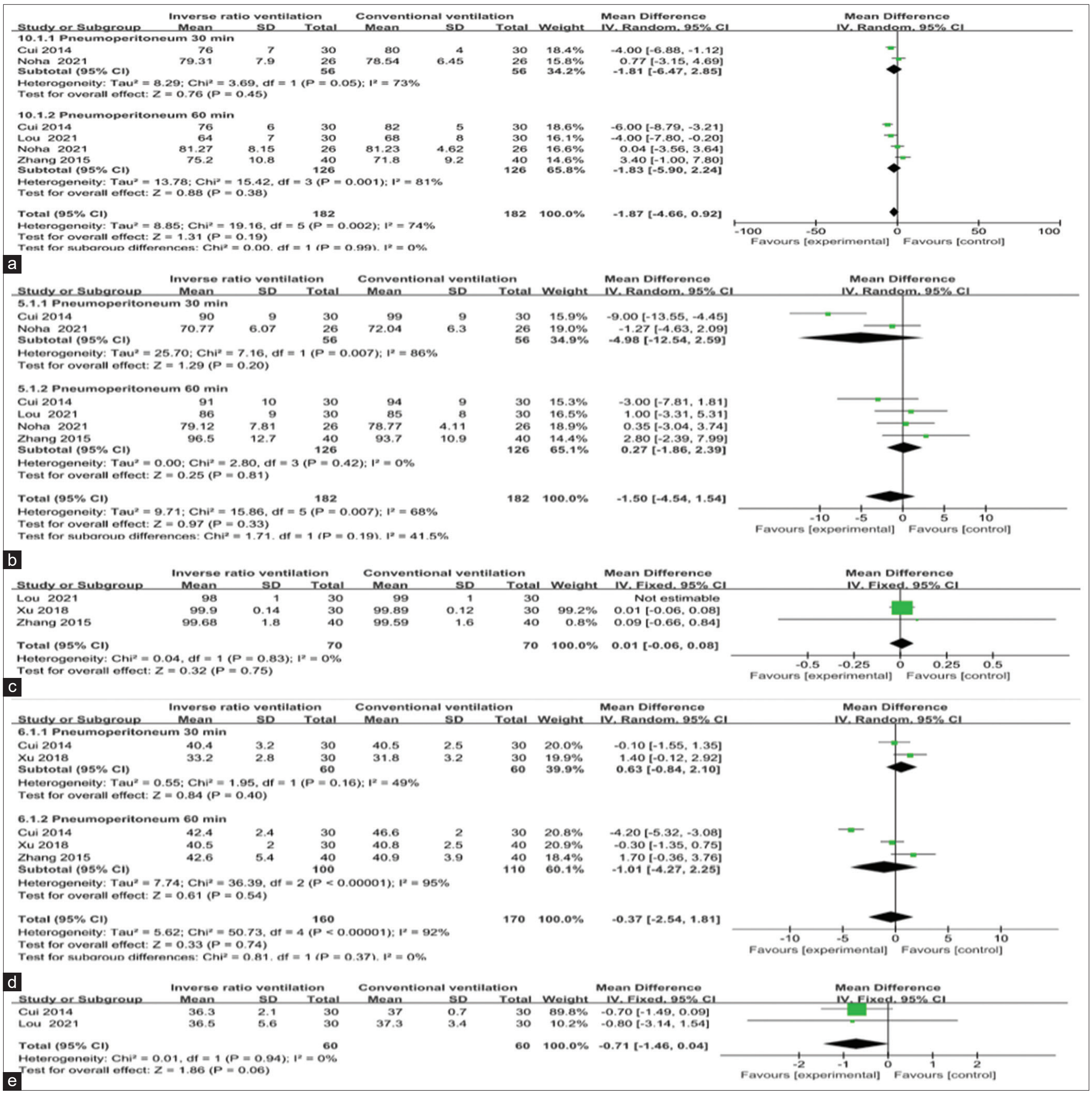

Figure 4: Negative results

of the two groups was performed, and the results of the random-effects model meta-analysis showed that the incidence of postoperative shoulder pain was not statistically significant between the two data groups in the IRV group compared with the control group after general anesthesia in obese patients [OR = 0.57. 95% CI (0.04, 9.15), I^2 = 52%, P = 0.69]; the results of the meta-analysis of the fixed-effects model showed that in the incidence of subcutaneous emphysema in the IRV group compared with the conventional ventilation group, the difference between the data of the two groups was not statistically significant [OR = 0.43, 95% CI (0.09, 2.02), I^2 = 0%, P = 0.28] [Figure 5a and b].

Discussion

In recent years, obesity has become a global epidemic problem affecting every system and is associated with many consequences, including coronary artery disease, hypertension, diabetes, dyslipidemia, obstructive sleep apnea, and socioeconomic and psychosocial impairment.[16] Today, obese patients are increasingly likely to undergo surgical procedures, which poses several challenges for anesthesiologists throughout perioperative management.[17] where the choice of mechanical ventilation mode after general anesthesia has also become a research hotspot.

Respiratory complications are the most common adverse outcome after surgery, especially when it comes to obese patients due to altered respiratory physiology, the probability of postoperative pulmonary complications is significantly increased.[18-20] Moreover, laparoscopic, thoracic, and upper abdominal procedures increase the risk of pulmonary atrophy even more,[21] so obese patients have a higher chance of developing pulmonary atelectasis and pulmonary atrophy during laparoscopic surgery; the results of a study by Kendale *et al*.[22] also showed a positive correlation between BMI and the chance of hypoxemia in obese patients. With the continuous development and application of protective lung ventilation strategies, many advantages such as the incidence of postoperative respiratory complications and postoperative lung function have been significantly transformed, and the study has proven[23] that protective lung ventilation strategies are also applicable to obese patients. All five studies in the literature included in this meta-analysis adopted a strategy of protective lung ventilation with low tidal volumes in combination with inverse proportional ventilation. IRV is an unconventional mode of mechanical ventilation by prolonging the inspiratory time so that the inspiratory time to expiratory time (I: E) is ≥1. IRV can generate endogenous PEEP and develop a lower alveolar partial pressure to maintain a higher mean airway pressure, thereby reducing alveolar and airway nulliparity and improving patient oxygenation.[24]

The results of this meta-analysis showed that in laparoscopic surgery in obese patients under general anesthesia, the choice of mechanical ventilation mode was inverse to that of conventional mechanical ventilation, with a lower peak inspiratory pressure during general anesthesia and a higher airway pressure that would be more likely to cause lung volume injury and air pressure injury, which would reduce the chance of mechanical ventilation-related lung injury and thus achieve some lung protection. In addition, the analysis also showed that PaO_2 and oxygenation index and mean airway pressure were higher compared with the control group, which could prevent hypoxia and also reduce the formation of dead space, produce endogenous PEEP, reduce the risk of atelectasis, and improve the prognosis of patients. This study also showed that dynamic lung compliance was better in the IRV group, which would help to avoid the deterioration of postoperative lung function and have a positive impact on the patient's outcome, mean arterial pressure, heart rate, and end-expiratory CO_2 and $PaCO_2$; there was no significant effect in the IRV group compared with the control group, and the data differences were not statistically significant. The heterogeneity of peak inspiratory pressure, mean airway pressure, dynamic lung

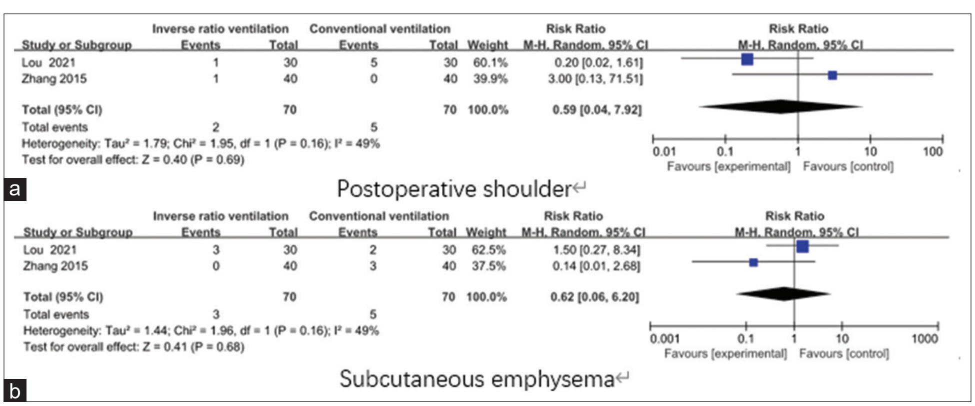

Figure 5: Postoperative shoulder and Subcutaneous emphysema

compliance, oxygenation index, and PaO_2 that appeared during the study was high, and after exploring the source of heterogeneity, it may be due to the inconsistency of tidal volume, which three[11,12,15] papers took 8 ml/kg, 1 7[13] ml/kg, and 1 6[14] ml/kg, although all were small. Although both are small tidal volume ventilation, the difference in values still leads to some heterogeneity. In addition, for the calculation of body weight, only one[15] article chose ideal body weight, while the rest did not mention ideal body weight or whole body weight, which may lead to heterogeneity in the analysis of peak inspiratory pressure. Also, there were differences in inhalation oxygen concentrations in five papers, and two[11,14] chose a ratio of inspiratory time to expiratory time of 1:1 for inverse ventilation, while the remaining three chose 2:1. Although they were all inverse ventilation, the differences in inhalation time caused differences in calculated data such as mean airway pressure, lung dynamic compliance, oxygenation index, and PaO_2, thus leading to a high level of heterogeneity during this meta-analysis. However, after sensitivity analysis and exclusion of relevant literature, the meta-analysis results showed that the data were still statistically significant. Therefore, the IRV strategy applied to laparoscopic surgery in obese patients under general anesthesia can improve oxygenation index, reduce peak inspiratory pressure, and increase mean airway pressure and PaO_2 while also improving dynamic lung compliance. Finally, in terms of the results of postoperative pulmonary complications, this meta-analysis lacks additional data, and the odds of complications in both groups are small and not statistically significant in terms of data. The preliminary consideration is that the five included papers all adopted a protective lung ventilation strategy with lower tidal volumes (6–8 ml/kg), which itself reduces the occurrence of postoperative pulmonary complications, coupled with the sample size being relatively small, so the effect of the difference in data produced after IRV was not significant, and this also indicates that the protective lung ventilation strategy of IRV combined with low tidal volume is relatively safe and can be used as an option for mechanical ventilation mode in obese patients in clinical practice.

There are some limitations of this meta-analysis: (1) The sample sizes of the five included studies were small and none of them described the relevant calculations of sample size, which may affect the analysis results. (2) All studies did not describe the random assignment, or hidden method situation, which may cause selective bias. (3) The results of this meta-analysis were based on small, low-quality trials, and the conclusions need to be confirmed by larger samples and higher-quality trials. (4) The results of postoperative complications were not analyzed sufficiently, probably due to the low tidal volume (6–8 ml/kg) protective lung ventilation strategy adopted in all five included papers, so the effect of IRV was not obvious, and it is hoped that more and higher-quality, multicenter trials will be conducted in this area.

In conclusion, the IRV strategy applied to laparoscopic surgery in obese patients under general anesthesia can improve oxygenation index, reduce peak inspiratory pressure, increase mean airway pressure and PaO_2 while also improving lung dynamic compliance, provide better indices of respiratory mechanics, and have certain lung protective effects, and no significant effects on cardiac function are seen, which has certain safety and feasibility during anesthesia. It can be used as an option of mechanical ventilation strategy for laparoscopic surgery in obese patients under general anesthesia. However, whether inverse ventilation can reduce the related pulmonary complications in clinical practice still needs to be confirmed by more multicenter, high-quality, large sample, and well-designed clinical trials.

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Conflicts of interest
There are no conflicts of interest.

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