Journal of Clinical Anesthesia 75 (2021) 110461

Contents lists available at ScienceDirect

Journal of Clinical Anesthesia

journal homepage: www.elsevier.com/locate/jclinane

Effects of high versus low inspiratory oxygen fraction on postoperative clinical outcomes in patients undergoing surgery under general anesthesia: A systematic review and meta-analysis of randomized controlled trials

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ARTICLE INFO

Keywords:
Atelectasis
General anesthesia
Inspiratory oxygen fraction
Postoperative outcome
Pneumonia

ABSTRACT

Objectives: To determine whether high perioperative inspired oxygen fraction (FiO_2) compared with low FiO_2 has more deleterious postoperative clinical outcomes in patients undergoing non-thoracic surgery under general anesthesia.
Design: Meta-analysis of randomized controlled trials.
Setting: Operating room, postoperative recovery room and surgical ward.
Patients: Surgical patients under general anesthesia.
Intervention: High perioperative FiO_2 ($\geq$0.8) vs. low FiO_2 ($\leq$0.5).
Measurements: The primary outcome was mortality within 30 days. Secondary outcomes were pulmonary outcomes (atelectasis, pneumonia, respiratory failure, postoperative pulmonary complications [PPCs], and postoperative oxygen parameters), intensive care unit (ICU) admissions, and length of hospital stay. A subgroup analysis was performed to explore the treatment effect by body mass index (BMI).
Main results: Twenty-six trials with a total 4991 patients were studied. The mortality in the high FiO_2 group did not differ from that in the low FiO_2 group (risk ratio [RR] 0.91, 95% confidence interval [CI] 0.42–1.97, $P = 0.810$). Nor were there any significant differences between the groups in such outcomes as pneumonia (RR 1.19, 95% CI 0.74–1.92, $P = 0.470$), respiratory failure (RR 1.29, 95% CI 0.82–2.04, $P = 0.270$), PPCs (RR 1.05, 95% CI 0.69–1.59, $P = 0.830$), ICU admission (RR 0.94, 95% CI 0.55–1.60, $P = 0.810$), and length of hospital stay (mean difference [MD] 0.27 d, 95% CI -0.28–0.81, $P = 0.340$). The high FiO_2 was associated with postoperative atelectasis more often (risk ratio 1.27, 95% CI 1.00–1.62, $P = 0.050$), and lower postoperative arterial partial oxygen pressure (MD −5.03 mmHg, 95% CI -7.90– -2.16, $P < 0.001$). In subgroup analysis of BMI >30 kg/m^2, these parameters were similarly affected between the groups.
Conclusions: The use of high FiO_2 compared to low FiO_2 did not affect the short-term mortality, although it may increase the incidence of atelectasis in adult, non-thoracic patients undergoing surgical procedures. Nor were there any significant differences in other secondary outcomes.

1. Introduction

Guidelines on the use of supplemental oxygen from the World Health Organization and from the US Centers for Disease Control have recommended the use of 0.8 fraction of inspiratory oxygen (FiO_2) during the perioperative period to reduce or to prevent the risk of infection at the surgical site in adult patients undergoing general anesthesia [1,2]. Anesthesiologists indeed routinely administer high concentrations of

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https://doi.org/10.1016/j.jclinane.2021.110461
Received 28 February 2021; Received in revised form 7 July 2021; Accepted 11 July 2021
Available online 11 September 2021

oxygen during anesthetic induction and emergence from general anesthesia to prevent hypoxemia, especially in patients with difficult airway or in critically-ill patients [3,4].

However, there has been a debate on the safety of the perioperative use of high FiO_2. One hundred percent oxygen, even in a short period of time, was associated with the formation of absorption atelectasis in 90% of anesthetized patients [5,6], resulting in reduced lung compliance, impaired oxygenation, and lung injury. It may worsen gas exchange when given before extubation [7]. A recent meta-analysis demonstrated that high FiO_2 during anesthesia was associated with impaired postoperative oxygen parameters and increased severity of atelectasis [8]. The postoperative atelectasis has been noted as a risk factor to develop pulmonary complications, such as pneumonia leading to increased morbidity and mortality, and a prolonged hospital stay [9–11]. High FiO_2 was related with major respiratory complications and increased 30-day mortality in a retrospective study which analyzed 73,922 patients undergoing non-cardiothoracic surgery [12]. A liberal oxygen therapy increased mortality without improving other important clinical outcomes in acutely-ill adult patients [13].

On the contrary, a recent meta-analysis failed to note significant drawbacks such as mortality, intensive care unit (ICU) admission, pneumonia, and atelectasis following the use of high FiO_2 in surgical patients undergoing general anesthesia [14]. An intervention-controlled trial with 5749 patients also found no deleterious effects on 30-day mortality and healing-related complications by the use of high FiO_2 [15].

Most randomized controlled studies (RCTs) and meta-analyses of perioperative oxygen trials have focused on the prevention of surgical site infection or nausea and vomiting [15–22]. Little attention has been paid on diverse clinical events such as mortality, ICU admission, length of hospital stay, or clinically relevant pulmonary side-effects [14,23]. Moreover, most systematic reviews and meta-analyses included studies that used nitrous oxide (N_2O) in the inspiratory gas mixture [16,17,23–25]. N_2O is known to increase the incidence of atelectasis and pneumonia, and to prolong the hospital stay [26,27]. Obesity may also affect the degree of atelectasis [28,29].

The present study was aimed at evaluating the effect of high FiO_2 (80–100%) in patients who underwent non-thoracic surgery under general anesthesia with air as a carrier gas. The mortality was the primary outcome. Secondary outcomes included pulmonary events (atelectasis, pneumonia, respiratory failure, postoperative pulmonary complications [PPCs], postoperative oxygen parameters, and pulmonary function), ICU admissions, and length of hospital stay. A subgroup analysis was performed to explore the treatment effect by body mass index (BMI).

2. Materials and methods

The present study was registered at the International Prospective Registry of Systemic Reviews (CRD42020181140), and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement guidelines (Supplementary Table S1) [30].

2.1. Data sources and searches

An information specialist was informed regarding previous systematic reviews and some RCTs related to postoperative pulmonary complications and clinical outcomes, and a search strategy was developed. The search strategy was applied to MEDLINE, EMBASE, and COCHRANE. A copy of the detailed search strategy is included in Supplementary Table S2. The last search was performed in April 2021. Reference lists in previous systematic reviews and related articles and ongoing studies from clinical trials (clinicalTrials.gov) were examined directly to avoid omissions in the initial search. Language and publication year restrictions were not applied.

2.2. Study selection

Studies were eligible if they (1) were RCTs, (2) were performed in adult patients ($\geq$ 18 yr) undergoing general anesthesia for surgery, (3) had administration of high FiO_2 ($\geq$ 80%) vs. low FiO_2 ($\leq$50%) as defined by Koo et al. [8] during intervention period (i.e., induction, maintenance and emergence of anesthesia) and (4) reported relevant clinical outcomes such as mortality, pulmonary outcomes (atelectasis, pneumonia, respiratory failure, postoperative pulmonary complications [PPCs], postoperative oxygen parameters, and postoperative pulmonary function [i.e., the ratio of forced expiratory volume in one second to forced vital capacity [FEV_1/FVC]), ICU admission, length of hospital stay. Studies were excluded if they (1) comprised thoracic surgery, (2) used N_2O as a carrier gas during general anesthesia, and (3) were subgroup analysis of an original RCT.

Two authors (J. H. and S. C.) independently screened titles and abstracts to look for relevant studies. The full-text of articles was finally evaluated to determine if they met the eligibility criteria. The uncertainties or conflicts in study selection were resolved through consultation with the first author (C.H.L.).

2.3. Data extraction and quality assessment

Two authors (J. H. and S. C.) independently extracted data which were then checked for accuracy by the first author (C.H.L.). The unpublished data were collected through directly contacting the authors via e-mail. Mortality (in-hospital or within 30-days) was evaluated as the primary outcome. Secondary outcomes were pulmonary outcomes (atelectasis, pneumonia, respiratory failure and PPCs that occurred within the first 30 days following surgery [31], postoperative oxygen parameters and FEV_1/FVC within the first postoperative day), ICU admissions, and length of hospital stay.

The incidence of atelectasis was evaluated by using chest X-ray or computed tomography (CT) scan, and the severity was expressed as a percentage of extent of atelectasis surface to total lung surface with attenuation values between −100 and +100 Hounsfield units on CT scan. PPCs, a composite of postoperative pulmonary complications, was defined as the occurrence of three or more of the following signs (atelectasis, pneumonia, respiratory failure, pleural effusion, pneumothorax, bronchospasm, and aspiration pneumonitis) according to the criteria by ESA-ESICM joint taskforce on perioperative outcome measures [31]. Postoperative oxygen parameters were arterial partial oxygen pressure (PaO_2), alveolar-arterial oxygen gradient (A-aDO_2), and arterial oxygen saturation measure by pulse oximetry (SpO_2).

Results reported in median and interquartile ranges were calculated to means and SDs using the methods of Wan et al. [32]. Results represented in forms of graph were extracted to mean and SD using GetData Graph Digitalizer v2.26.0.20 (S.Fedorov, GetData Graph Digitizer, http://getdata-graph-digitizer.com). Risk of bias was analyzed using the Cochrane Risk of Bias tool (ROB v2.0). This has five domains (bias arising from the randomization process, bias due to deviations from intended interventions, bias caused by missing outcome data, bias in measuring outcome, and bias in selecting reported results) and an overall judgment. Each domain and the overall judgment classify the study as low, some concern, and high risk of bias. Two independent authors (J.H. and Y.H.K.) evaluated methodological quality and risk of bias. Any disagreement was discussed and adjusted by the first and corresponding authors (C.H.L. and H.J.K.). Publication bias was assessed using the funnel plot when at least 10 trials were available and the Egger test for continuous outcomes and Harbord test for binary test were used. In addition, quality of evidence for each outcome was assessed with the "Grading of Recommendations Assessment, Development, and Evaluation" (GRADE) [33].

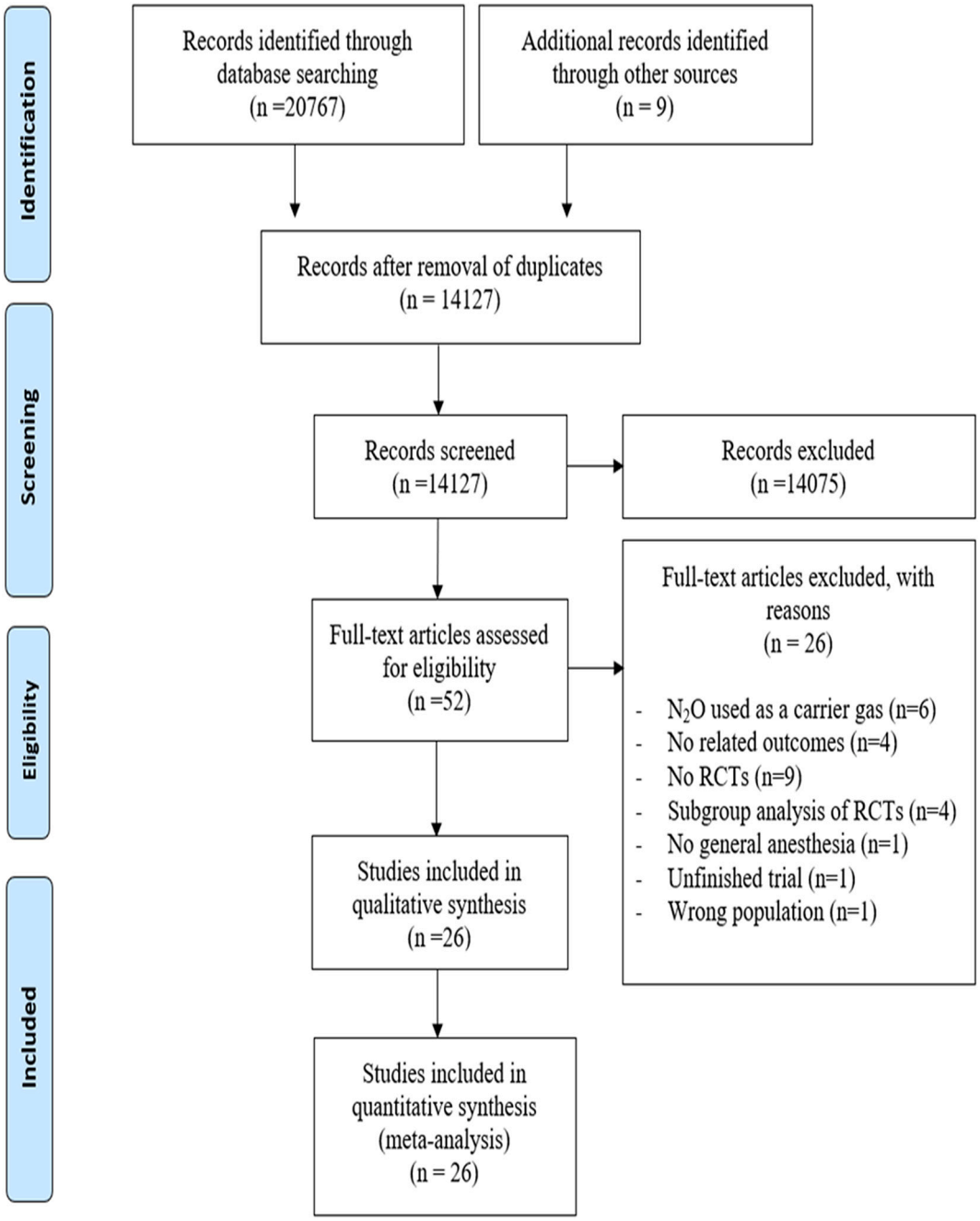

Fig. 1. Flow chart of database search and study selection.

2.4. Data synthesis and analysis

Revman 5.3 software (Cochrane Collaboration, Oxford, UK) and Stata version 15.0 (Stata Statistical Software, release 15; Stata Corp, College Station, TX, USA) were used for data synthesis and analysis. Depending on the reported effect size measures, pooled risk ratios (RR) or mean difference (MD), and 95% confidence intervals (CI) were calculated. A random effects approach (inverse variance or Mantel-Haenszel) was chosen to allow for the expected heterogeneity across the studies: epidemiological and content knowledge suggested that data collected from various surgeries and different study designs would not meet the assumptions of the fixed-effects meta-analysis. The degree of heterogeneity among studies was based on I^2 statistics and the ranges of 0–50%, 50–75%, and 75–100% were regarded as low, moderate and high, respectively. Subgroup analysis was done to examine whether the treatment effect is affected by BMI $> 30\,kg/m^2$. Using sensitivity analyses, we also examined the effect of high FiO_2 by the type of carrier gas (mentioned vs. not mentioned), time period of intervention during anesthesia (emergence vs. maintenance), and risk of bias (high vs. low and some concern) because of concerns related to their validity.

3. Results

Of 14,127 records that were initially screened, 52 full-text articles met the inclusion criteria. Twenty-six articles were then excluded: 6 used N_2O in the inspired gas mixture, 4 had no related outcomes, and 9 were not RCTs. The studies performed under regional anesthesia (n = 1) or performed in patients less than 6 yr (n = 1) and an unfinished trial (n = 1) were also excluded. Four were subgroup analyses of one multicenter trial and thus were excluded due to data duplication (Fig. 1).

Table 1
Characteristics of the studies included in the systemic reviews and meta-analysis.

Author	Year	RCT Design, Participants (n)	Patients characteristics	Respiratory status	Group (FiO2)	ASA state	Intervention Period	Type of surgery	Outcomes (follow-up)
Akca [39]	1999	Multi-center 30	18–65 yrs	No-pulmonary disease	High (0.8) Low (0.3)	I to III	M + E + PO 2 h	Elective colon	Incidence and severity of atelectasis (1 d) PaO2 and A-aDO2 (1 d), FEV1/FVC (1 d)
Belda [48]	2005	Multi-center 291	18–80 yrs	No-respiratory infection	High (0.8) Low (0.3)	I to III	I + M + PO 6 h	Colorectal	Mortality (14 d), ICU admission, LOHS
Benoit [40]	2002	Single-center 20	18–64 yrs. BMI < 30 kg/m^2	No-pulmonary disease	High (1) Low (0.4)	I to II	E	Extremities	Severity of atelectasis (immediate) PaO2 (recovery)
Chen [43]	2013	Single-center 60	≥ 18 yrs	No-impairment of gaseous exchange	High (0.8) Low (0.3)	I to IV	M + PO 24 h	Colorectal	Mortality (30 d), Pneumonia (30 d), LOHS
Edmark [41]	2014	Single-center 59	30–85 yrs. BMI < 35 kg/m^2	No-COPD	High (1) Low (0.3)	I to III	E	Orthopedic	Severity of atelectasis (immediate) SpO2 (emergence)
Eskandr [37]	2019	Single-center 60	20–60 yrs. BMI > 30 kg/m^2	No-pulmonary disease	High (0.9) Low (0.4)	I to II	M + E + PO 2 h	Laparoscopic cholecystectomy	Incidence of atelectasis and FEV1/FVC (1 d) PaO2 (2 h), SpO2 (recovery)
Ferrando [58]	2020	Multi-center 717	≥ 18 yrs BMI < 35 kg/m^2	No-ARDS, −pneumothorax or -giant bullae	High (0.8) Low (0.3)	I to III	M + PO 3 h	Abdominal	Mortality (30 d), PPCs (7 d), LOHS
Greif [35]	1999	Single-center 231	18–80 yrs	No-respiratory infection	High (0.8) Low (0.3)	N/M	M + PO 2 h	Colon resection	SpO2 (1 d)
Greif [51]	2000	Multi-center 500	18–80 yrs	No-respiratory infection	High (0.8) Low (0.3)	I to III	M + PO 2 h	Open colorectal	Mortality (15 d), ICU admission, LOHS
Joyce [55]	1995	Single-center 30	35–74 yrs Weight < 100 kg	No-obstructive lung disease or -respiratory disease	High (1) Low (0.3)	N/M	M + E,	CABG with CPB	PaO_2 (1 d)
Kim [56]	2020	Single-center 90	20–70 yrs. BMI < 35 kg/m^2	No-severe COPD, −emphysema or -pneumothorax No-bullae or -previous resection surgery	High (1) Low (04)	I to II	M,	Laparoscopic or colorectal	Incidence of atelectasis (hospital stay) PPCs (hospital stay), LOHS
Kleinasser [42]	2014	Single-center 53	COPD	COPD	High (1) Low (0.3)	N/M	E	Carotid endarterectomy	PaO2 and A-aDO2 (1 h)
Korkulu [52]	2012	Single-center 50	19–76 yrs	No-pulmonary disease	High (1) Low (0.4)	I to II	M	Laparoscopic cholecystectomy	PaO2 and A-aDO2 (recovery)
Kotani [45]	2000	Single-center 60	BMI < 30 kg/m^2	No-respiratory infection, -COPD or -restrictive pulmonary disease	High (1) Low (0.3)	I to II	M + E	Orthopedic	PaO2 (recovery), Incidence of atelectasis (1 d)
Kurz [44]	2015	Multi-center 555	≤ 80 yrs	No-respiratory infection, −severe COPD	High (0.8) Low (0.3)	I to III	M + PO 1 h	Colorectal	Mortality (30 d), LOHS
Li [59]	2020	Single-center 251	≥ 18 yrs	No-acute lung injury or -ARDS	High (0.8) Low (0.3)	I to III	M	Abdominal	Mortality (30 d), LOHS, ICU admission Incidence of atelectasis, Pneumonia, Respiratory failure and PPCs (7 d)
Lim (p)* [36]	2005	Single-center 38	16–65 yrs	No-pulmonary disease	High (1) Low (0.3)	I to II	E	Extremities	PaO2 and A-aDO2 (30 min)
Lim (s)† [36]	2005	Single-center 40	16–65 yrs	No-pulmonary disease	High (1) Low (0.3)	I to II	E	Extremities	PaO2 and A-aDO2 (30 min)
Mackintosh [50]	2012	Single-center 50	18–70 yrs	Preoperative SpO2 ≥ 90% or No-spontaneous pneumothorax	High (0.9) Low (0.3)	N/M	M	General	SpO2 (recovery)

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Table 1 (*continued*)

Author	Year	RCT Design, Participants (n)	Patients characteristics	Respiratory status	Group (FiO2)	ASA state	Intervention Period	Type of surgery	Outcomes (follow-up)
Meyhoff [54]	2009	Multi-center 1386	≥ 18 yrs	Preoperative SpO2 ≥ 90%,	High (0.8) Low (0.3)	I to III	M + PO 2 h	Laparotomy	Mortality (30 d), ICU admission Incidence of atelectasis, Respiratory failure and pneumonia (14 d)
Park [38]	2020	Single-center 46	18–79 yrs BMI < 30 kg/m^2	No-pulmonary disease or -previous lung resection	High (0.8) Low (0.4)	I to III	E	Laparoscopic colorectal	Incidence of atelectasis (2 d), SpO2 (recovery)
Renner [46]	2004	Single-center 64	18–65 yrs. BMI < 30 kg/m^2	No smoking history	High (1) Low (0.3)	I to II	E	Peripheral musculoskeletal	PaO2 (1 h)
Shaefi [57]	2021	Single-center 100	≥ 65 yrs		High (1) Low (0.35)	N/M	M,	CABG with CPB	Mortality (30 d), Pneumonia (30 d), LOHS
Staher [34]	2011	Single-center 203	≥18 yrs BMI >30 kg/m^2	Preoperative SpO2 ≥ 90%	High (0.8) Low (0.3)	I to III	M + PO 2 h	Laparotomy	Mortality (30 d), LOHS, ICU admission Incidence of atelectasis and pneumonia (14 d)
Stall [49]	2013	Single-center 235	≥ 18 yrs	No-respiratory infection, -COPD or preoperative SpO2 ≥ 90%	High (0.8) Low (0.3)	I to III	M + PO 2 h	Orthopedic	LOHS
Wansnik [53]	2015	Single-center 64		No-pulmonary disease	High (0.8) Low (0.3)	N/M	M + PO 2 h	Appendectomy	LOHS
Zorembra [47]	2010	Single-center 142	BMI 25–35 kg/m^2	No-asthma	High (0.8) Low (0.4)	I to III	M	Minor peripheral	SpO2 (2 h)

* Propofol used as anesthetics; †sevoflurane used as anesthetics. A-aDO_2: alveolar-arterial oxygen gradient; BMI: body mass index; CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary disease; CPB: cardiopulmonary bypass; E: emergence; I: induction of anesthesia; ICU: intensive care unit; FEV_1/FVC: the ratio of the forced expiratory volume in 1 s to forced vital capacity; LOHS: length of hospital stay; M: maintenance of anesthesia; N/M: not mentioned; PaO_2: arterial oxygen partial pressure; PO: postoperative; PPCs: postoperative pulmonary complications; RCT: randomized controlled trial; SpO_2: arterial oxygen saturation by pulse oximetry.

However, a subgroup analysis of a multicenter trial was included in analyzing the patients with BMI greater than 30 kg/m^2 [34]. A single center study in a multicenter trial was included because the results did not overlap [35]. One article had two studies [36]. Taken together, 4991 patients of 26 studies were included in the final analysis [34–59], whereof 2504 were assigned to the high FiO_2 group and 2487 to the low FiO_2 group. They are listed in Table 1.

3.1. Risk of bias

The results of risk of bias from each of the included studies based on the Cochrane Risk of Bias tool (ROB v2.0) are reported in Fig. 2 [60]. There was 92% consent between the raters for all items and there was no disagreements by more than the +/− 1 level. The main contributor to high risk of bias was the randomization process with six trials. Fourteen trials presented a low risk of bias in all categories examined. The quality of evidence for each outcome was assessed with the "Grading of Recommendations Assessment, Development, and Evaluation (GRADE)." Mortality was graded as a low level of evidence. Incidence of atelectasis (by chest radiography), respiratory failure, PaO_2, A-aDO_2, FEV_1/FVC, ICU admission, and length of hospital stay were graded as moderate level of evidence, incidence of atelectasis (by CT), pneumonia, and PPCs as low level of evidence, and severity of atelectasis and SpO_2 as very low level of evidence (Table 2 and supplementary Table S3).

3.2. Primary outcome

3.2.1. Mortality

Two studies were without records on deaths in either treatment arm. Eight studies reported in-hospital or 30-day mortality of 3860 patients: 39/1935 patients died in the high FiO_2 group and 34/1925 patients in the low FiO_2 group, being the mortality not significantly different between the groups (RR, 0.91; 95% CI, 0.42–1.97, $P = 0.810$) (Fig. 3A). Heterogeneity between studies was low ($I^2 = 30\%$).

3.3. Secondary outcomes

3.3.1. Pulmonary outcomes

3.3.1.1. Incidence of atelectasis. Seven studies with a total of 1948 patients used chest radiography and 2 studies with a total of 90 patients used chest CT scan to examine the atelectasis (Fig. 3Ba). High FiO_2 increased the incidence of atelectasis on chest radiography with a borderline significance (127/981 events in the high FiO_2 vs. 96/967 events in the low FiO_2 group; RR 1.27, 95% CI 1.00–1.62, $P = 0.050$). It also significantly increased the incidence of atelectasis on chest CT scans (38/46 events in the high FiO_2 vs. 27/44 events in the low FiO_2 group; RR 1.35, 95% CI 1.03–1.77, $P = 0.030$). Low heterogeneity was observed in both tools ($I^2 = 0\%$, in both).

3.3.1.2. Severity of atelectasis. Three studies reported the severity of atelectasis using CT scans in a total of 109 patients. The area of atelectasis was larger in the high FiO_2 group than in the low FiO_2 group (MD 2.04%, 95% CI 0.14–3.94, $P = 0.040$) (Fig. 3Bb). A moderate level of heterogeneity was shown ($I^2 = 68\%$).

3.3.1.3. Pneumonia. Four studies with a total of 1797 patients reported on pneumonia, whereof 76/890 events were observed in the high FiO_2

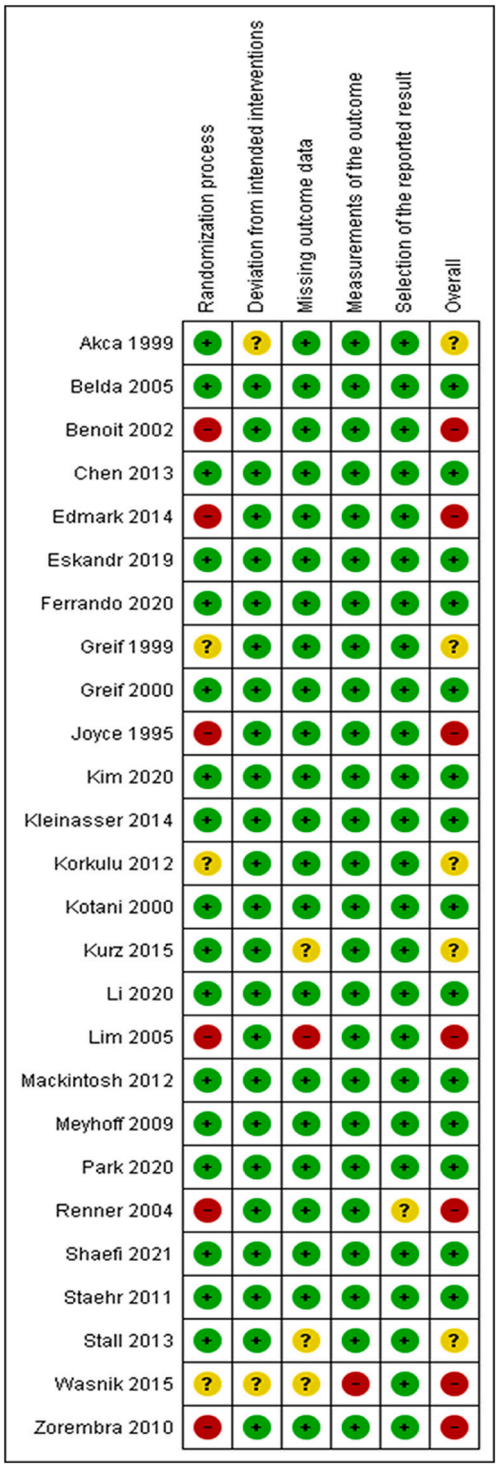

Fig. 2. Assessment of quality by the Cochrane risk of bias tool. Red denotes high risk, yellow unclear risk and green low risk. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

group and 67/907 events in the low FiO_2 group, the incidence being not significantly different between the two groups (RR 1.19, 95% CI 0.74–1.92, $P = 0.470$) (Fig. 3Bc). A low heterogeneity was observed ($I^2 = 33\%$).

3.3.1.4. Respiratory failure. Two studies with a total of 1637 patients reported on respiratory failure, whereof 40/811 events were observed in the high FiO_2 group and 31/826 events in the low FiO_2 group. There was no significant difference in the incidence of respiratory failure between the groups (RR 1.29, 95% CI 0.82–2.04, $P = 0.270$) (Fig. 3 Bd). A low heterogeneity was observed ($I^2 = 0\%$).

3.3.1.5. PPCs. Three studies of a total 1058 patients reported on PPCs with 108/534 events in the high FiO_2 group and 101/524 events in the low FiO_2 group, showing no significant difference in the incidence of PPCs between the groups (RR 1.05, 95% CI 0.69–1.59, $P = 0.830$) (Fig. 3Be). A moderate heterogeneity was observed ($I^2 = 56\%$).

3.3.1.6. Postoperative oxygen parameters

3.3.1.6.1. PaO_2. The combined effect of 10 studies of a total 445 patients comparing the effect of high FiO_2 with low FiO_2 on PaO_2 demonstrated a lower postoperative PaO_2 with high FiO_2 (mean difference [MD] -5.03 mmHg, 95% CI, −7.90 to −2.16, $P < 0.001$)(Fig. 3Bf1). Heterogeneity between studies was low ($I^2 = 44\%$). The Egger test for publication bias was non-significant ($P = 0.595$) and the funnel plot did not demonstrate asymmetry by visual inspection (supplementary Fig. S1B).

3.3.1.6.2. A-aDO_2. Five studies of a total 211 patients reported on A-aDO_2. The high FiO_2 group had larger A-aDO_2 than the low FiO_2 group (MD 3.75 mmHg, 95% CI 1.74–5.76, $P < 0.001$ (Fig. 3Bf2). Low heterogeneity was observed in the analysis ($I^2 = 20\%$).

3.3.1.6.3. SpO_2. Six studies of a total 588 patients reported on SpO_2. There was no significant difference in SpO_2 between the groups (MD -0.20%, 95% CI −0.88–0.47, $P = 0.560$) (Fig. 3Bf3). A moderate level of heterogeneity was shown ($I^2 = 72\%$).

3.3.1.7. Pulmonary function (FEV_1/FVC). Two studies of 90 patients reported on the FEV_1/FVC. There was no significant difference in FEV_1/FVC between the two groups (MD −0.28%, 95% CI −6.23–5.66, $P = 0.930$) (Fig. 3Bg). Low heterogeneity was observed ($I^2 = 0\%$).

3.3.2. ICU admissions

Four studies of a total 2428 patients reported on ICU admissions with 63/1209 events in the high FiO_2 group and 63/1219 events in the low FiO_2 group. No significant difference was noted in ICU admissions between the groups (RR 0.94, 95% CI 0.55–1.60, $P = 0.810$) (Fig. 3C). A low heterogeneity was observed ($I^2 = 27\%$).

3.3.3. Length of hospital stay

Ten studies of total 2863 patients reported on length of hospital stay. The pooled mean length of hospital stay was 9.4 days in the high FiO_2 and 9.3 days in the low FiO_2, not significantly differing between the groups (MD 0.27 d, 95% CI −0.28–0.81, $P = 0.340$) (Fig. 3D). A low heterogeneity was observed ($I^2 = 47\%$). The Egger test for publication bias was non-significant ($P = 0.548$) and the funnel plot did not demonstrate asymmetry by visual inspection (Supplementary Fig. S1A).

3.4. Subgroup and sensitivity analyses

Two studies reported data on patients with high BMI (>30 kg/m^2) [34,37]. Subgroup analysis did not show any significant differences in mortality, atelectasis, pneumonia, SpO_2, FEV_1/FVC, or ICU admission compared with those examined in general population of patients. However, the length of hospital stay was shorter in the high FiO_2 group than in the low FiO_2 group (MD -2.30, 95% CI −4.36 to −0.24, $P = 0.030$) and postoperative PaO_2 was not different between the two groups in this population (Table 3).

A sensitivity analysis of five trials which did not describe carrier gas [37,47,49,53,58] did not show changes in effect direction or statistical significance. A sensitivity analysis by the time period of the intervention revealed that severity of atelectasis and A-aDO_2 were significantly different between the two groups only when intervention was performed

Table 2
Quality of the evidence (Summary of Findings table).*

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect/Mean Difference (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Low O_2	High O_2				
Mortality	**18 per 1000**	**17 per 1000** (8 to 36)	**RR 0.91** (0.42 to 1.97)	3860 (8 studies)	⊕⊕⊖⊖ **low**	
Incidence of atelectasis (chest radiography)	**99 per 1000**	**126 per 1000** (99 to 161)	**RR 1.27** (1 to 1.62)	1948 (7 studies)	⊕⊕⊕⊖ **moderate**	
Incidence of atelectasis (CT)	**600 per 1000**	**810 per 1000** (618 to 1000)	**RR 1.35** (1.03 to 1.77)	76 (2 studies)	⊕⊕⊖⊖ **low**	
Severity of atelectasis		The mean severity of atelectasis in the intervention groups was **2.04 higher** (0.14 to 3.94 higher)	**MD 2.04** (0.14 to 3.94)	109 (3 studies)	⊕⊖⊖⊖ **very low**	
Pneumonia	**74 per 1000**	**88 per 1000** (55 to 142)	**RR 1.19** (0.74 to 1.92)	1797 (4 studies)	⊕⊕⊖⊖ **low**	
Respiratory failure	**38 per 1000**	**48 per 1000** (31 to 77)	**RR 1.29** (0.82 to 2.04)	1637 (2 studies)	⊕⊕⊕⊖ **moderate**	
Postoperative Pulmonary Complications (PPCs)	**193 per 1000**	**202 per 1000** (133 to 306)	**RR 1.05** (0.69 to 1.59)	1058 (3 studies)	⊕⊕⊖⊖ **low**	
PaO_2		The mean PaO_2 in the intervention groups was **5.03 lower** (7.9 to 2.16 lower)	**MD -5.03** (−7.90 to −2.16)	445 (10 studies)	⊕⊕⊕⊖ **moderate**	
A-aDO_2		The mean A-aDO_2 in the intervention groups was **3.75 higher** (1.74 to 5.76 higher)	**MD 3.75** (1.74 to 5.76)	211 (5 studies)	⊕⊕⊕⊖ **moderate**	
SpO_2		The mean SpO_2 in the intervention groups was **0.20 lower** (0.86 lower to 0.46 higher)	**MD -0.20** (−0.86 to 0.46)	588 (6 studies)	⊕⊖⊖⊖ **very low**	
FEV_1/FVC		The mean FEV_1/FVC in the intervention groups was **0.28 lower** (6.23 lower to 5.66 higher)	**MD -0.28** (−6.23 to 5.66)	90 (2 studies)	⊕⊕⊕⊖ **moderate**	
ICU admission	**52 per 1000**	**49 per 1000** (28 to 83)	**RR 0.94** (0.55 to 1.6)	2428 (4 studies)	⊕⊕⊕⊖ **moderate**	
Length of hospital stay		The mean length of hospital stay in the intervention groups was **0.27 higher** (0.28 lower to 0.81 higher)	**MD 0.27** (−0.28 to 0.81)	2863 (10 studies)	⊕⊕⊕⊖ **moderate**	

A-aDO_2: alveolar-arterial oxygen gradient; CI: confidence interval; CT: computed tomography; FEV_1/FVC: the ratio of forced expiratory volume in 1 s to forced vital capacity; ICU: intensive care unit; MD: mean difference; No: number of patients; PaO_2: arterial partial oxygen pressure; **PPCs**: postoperative pulmonary complications; RR: risk ratio; SpO_2: arterial oxygen saturation by pulse oximetry.
GRADE Working Group grades of evidence. **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate.
* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

during emergence. In addition, sensitivity analysis excluding "high" risk of bias studies resulted in a reduced length of hospital stay in the low FiO_2 group (MD 0.42, 95% CI 0.07–0.76, $P = 0.020$).

4. Discussion

A meta-analysis of 26 RCTs involving 4991 patients demonstrated that high and low FiO_2 did not differentially affect the mortality in adult, non-thoracic surgical patients. Nor were differences noted in the incidence of pneumonia, respiratory failure, PPCs, and ICU admission, and length of hospital stay between the groups. The high FiO_2 was, however, associated with a significantly higher incidence and severity of atelectasis.

Whether high perioperative vs. low FiO_2 is related to an increased risk of postoperative mortality has been controversial: favorable [25], harmful [12,61], or no effects [14,15,23,24]. In all eight studies reviewed in our meta-analysis, high FiO_2 was not associated with an increased risk of mortality [43,44,48,51,54,57–59]. These findings are consistent with those documented recently [14,23,24]. However, they had very wide CIs and inconsistent results, indicating that the ability to accurately determine the strength of the association between high FiO_2 and mortality may be limited. Reported risk ratios relating the mortality to high FiO_2 ranged from a RR of 0.17 (95% CI, 0.02–1.37) [51] to one with very wide Cl (RR, 1.57; 95% CI, 0.52–4.75) [58] and pooled RR 0.91 (95% CI 0.42–1.97).

Interestingly, two [54,58] of eight studies showed relatively greater RR (1.54 and 1.57) for the mortality than in other six studies (0.17 to 0.35), suggesting an association between high FiO_2 and increased risk of death. In one study with high RR [54], the long-term mortality among patients receiving high FiO_2 was pronounced especially in those who had cancer surgery [61]. It was postulated that high FiO_2 might have a negative impact on mortality possibly through neovascularization [62], growth factor stimulation, formation of reactive oxygen species [63], and immunosuppression [64] in cancer patients. In the other study showing great RR (1.57), most (~85%) of the patients had oncological surgery [58]. In contrast, Podolyak et al. [65] reported that supplemental perioperative oxygen did not augment postoperative mortality, either in overall or in patients with cancer. Further RCTs are needed to determine whether the high perioperative FiO_2 is associated with an increased risk of mortality, especially in patients with cancer surgery.

Despite the increased incidence and severity of atelectasis in the high FiO_2 group, the incidence of postoperative pneumonia, respiratory failure or PPCs did not differ between the two groups in our meta-analysis. These results are in line with previous ones demonstrating that postoperative pneumonia is not associated with an absorption atelectasis occurred during anesthesia [66,67]. An animal study demonstrated that reduction of atelectasis with exogenous surfactants or open lung ventilation attenuated bacterial growth and translocation and reduced the risk of pneumonia [10]. However, Group B streptococci intentionally injected into the trachea to induce bacterial pneumonia in

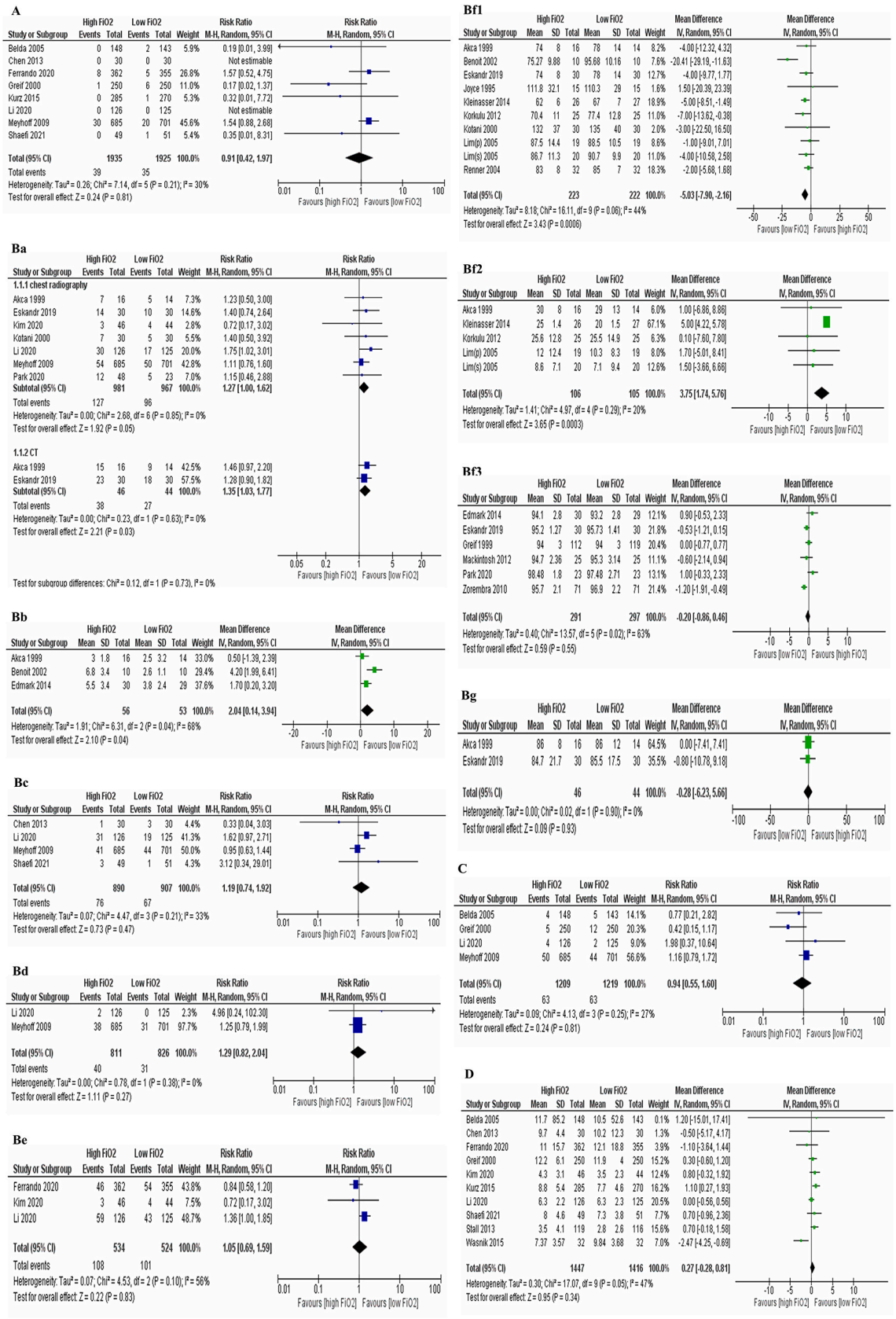

Fig. 3. Forest plot comparing the effect of high and low inspired oxygen fraction (FiO_2) on mortality (A), pulmonary outcomes {B; incidence (Ba) and severity (Bb) of atelectasis, pneumonia (Bc), respiratory failure (Bd), postoperative pulmonary complications (PPCs, Be), postoperative oxygen parameters [arterial partial oxygen pressure (PaO_2, Bf1), alveolar-arterial oxygen gradient (A-aDO_2, Bf2), and arterial oxygen saturation by pulse oximetry (SpO_2, Bf3)], and the ratio of forced expiratory volume in 1 s to forced vital capacity (FEV_1/FVC, Bg)}, intensive care unit (ICU) admission (C) and length of hospital stay (D). CI: confidence interval; M-H: Mantel-Haenszel; IV: inverse variance.

Table 3
Subgroup analysis for patients with BMI >30 kg/m^2.

Outcomes	Studies	N	Events, High FiO_2, n/N	Events, Low FiO_2, n/N	Risk ratio (95% CI)	I^2	*P* value
Mortality	All	8	39/1935	35/1925	0.91 [0.42, 1.97]	30	0.810
	BMI > 30	1	1/102	3/111	0.36 [0.04, 3.43]		0.380
Atelectasis	All	7	127/981	96/967	1.27 [1.00, 1.62]	0	0.050
	BMI > 30	2	23/132	17/141	1.40 [0.83, 2.37]	0	0.210
Pneumonia	All	4	76/890	67/907	1.19 [0.74, 1.92]	33	0.470
	BMI > 30	1	6/102	5/111	1.31 [0.41, 4.15]		0.650
ICU admission	All	4	63/1209	63/1219	0.94 [0.55, 1.60]	27	0.810
	BMI > 30	1	11/102	9/111	1.33 [0.57, 3.08]		0.510

Outcomes	Studies	Studies (N)	High FiO_2, N	Low FiO_2, N	Mean difference (95% CI)	I^2	*P* value
PaO_2	All	10	223	222	-5.03 [−7.90, −2.16]	44	<0.001
	BMI > 30	1	30	30	−4.00 [−9.77, 1.77]		0.170
SpO_2	All	6	291	297	−0.20 [−0.86, 0.46]	63	0.550
	BMI > 30	1	30	30	−0.53 [−1.21, 0.15]		0.130
FEV_1/FVC	All	2	46	44	−0.28 [−6.23, 5.66]	0	0.930
	BMI > 30	1	30	30	−0.80 [−10.78, 9.18]		0.880
Hospital stay	All	10	1447	1416	0.27 [−0.28, 0.81]	47	0.340
	BMI > 30	1	102	111	−2.30 [−4.36, −0.24]		0.030

BMI: body mass index; CI: confidence interval; FEV_1/FVC: the ratio of the forced expiratory volume in one second to forced vital capacity; ICU: intensive care unit; N: number of studies or patients; n: number of events; PaO_2: arterial partial oxygen pressure; SpO_2: arterial oxygen saturation by pulse oximetry.

the collapsed lung region in this study. It is likely that, although atelectasis itself does not complicate pneumonia, it may contribute to the development of PPCs in the presence of various pre-existing factors, e.g., chronic bronchitis, smoking history, dehydration, malnutrition, placement of a nasogastric tube, or poor oral hygiene [6,68,69].

On the contrary, several previous meta-analyses reported no differences in the incidence of atelectasis between the high and low FiO_2 groups [14,17]. Discrepancy among the studies could be, at least in part, explained by type of inspired gas mixture. N_2O promotes absorption atelectasis in the lung as effectively as breathing 100% oxygen [26] and thus its presence in the inhaled gas mixture might have increased the incidence of atelectasis in the low FiO_2 group, resulting in a comparable incidence of atelectasis between the groups. In fact, in the preliminary sensitivity analysis, we did not find a significant difference in the incidence of atelectasis between the high and low FiO_2 groups when the studies using N_2O in the inhaled gas mixture were included (RR, 0.09; 95% CI, 0.76–1.56, $P = 0.630$).

Atelectasis has been reported to increase along with BMI during general anesthesia in normal and overweight patients in forms of compression as well as absorption atelectasis [28,29]. However, our subgroup analysis on patients with BMI >30 kg/m^2 did not show any significant differences of clinical outcomes, including mortality, atelectasis, pneumonia, and ICU admission compared with the general population. This finding is in line with that of Hedenstierna et al. [70], in which atelectasis was not further increased in the obese with BMI ≥30 kg/m^2 undergoing general anesthesia.

Postoperative PaO_2 was decreased and thus A-aDO_2 was increased in patients given high FiO_2 while SpO_2 was comparable between the groups, being consistent with a previous meta-analysis [8]. The discrepancy between PaO_2 and SpO_2 may be explained by the oxyhemoglobin saturation curve, showing a plateau at high PaO_2. The postoperative oxygen saturation does not appear to be a surrogate marker of clinical outcomes in this circumstance in healthy patients.

4.1. Strengths and limitations

Our meta-analysis is the comprehensive and most up-to-date search of the worldwide literature without restriction to English-written articles only. It also comprises a large number of RCTs ($n = 26$) and clinically-important clinical outcomes (e.g., mortality, pneumonia, respiratory failure, PPCs, ICU admissions, and the length of hospital stay), excluding the studies that used N_2O as a carrier gas to rule out its possible effect on atelectasis or pneumonia.

There are several limitations in our meta-analysis. First, the study conditions and the time period of intervention were not identical. We divided the patients into high FiO_2 and low FiO_2 groups according to the dosage of inspired oxygen during the intervention period, as did most of the previous studies. However, a high concentration of oxygen is generally used in a similar manner at induction of anesthesia or at emergence from anesthesia in the both groups. The influence of high oxygen concentration also in the low FiO_2 group may not be completely ruled out. Ideally, the high FiO_2 group should include any patients who were exposed to high oxygen concentration for even a short period of time during surgery, and patients of low FiO_2 group should not be exposed to high inspired oxygen concentration at any time during the anesthesia.

Second, the duration and time period of intervention exposed to high or low FiO_2 differed markedly among the studies from only at emergence of general anesthesia to during (i.e., maintenance period) and for 2-to-24 postoperative hrs. Different duration and time period of designated FiO_2 may differentially affect clinical outcomes. Indeed, sensitivity analysis by the time period of intervention (maintenance vs. emergence) revealed that all outcomes except PaO_2 were comparable between high and low FiO_2 groups when intervention was attempted during the maintenance period, whereas atelectasis was more severe and A-aDO_2 larger at high FiO_2 when intervention was attempted during the emergence period. Third, the results of mortality (i.e., low-quality evidence) due to low incidence and limited number of studies should be interpreted carefully. Given the low incidence, the size of required information to demonstrate a relative risk reduction at an estimate with a type I error of 5% and a type II error of 20% is 5262 patients, which is approximately 1400 larger than the current sample size. Nevertheless, mathematical predictions do not appear to change the results with additional data (data not shown). Lastly, outcome measures such as pneumonia or PPCs were defined differently and their follow-up periods varied among the pooled trials, and the criteria for ICU admission or hospital discharge were diverse and not well described. Future RCTs or meta-analyses may require consensus definitions for standardized endpoints, as suggested by Abbott et al. [71].

5. Conclusions

There is a lack of evidence that the high FiO_2 compared to low FiO_2 has a deleterious impact on the mortality in adult patients undergoing non-thoracic surgery under general anesthesia. The incidence of pneumonia, respiratory failure, PPCs, ICU admissions, and length of hospital

stay were comparable between the groups; while the incidence and the severity of atelectasis were increased and postoperative PaO_2 was lowered by high FiO_2. It is suggested that clinicians should not be reluctant to administer a high FiO_2 in an effort to reduce adverse events during general anesthesia.

Authors' contributions

Planning the study design and methodology: CHL, HJK.
Devising search strategies: CHL, HJK.
Conducting searches: JH, SC, YHK.
Determining eligibility of search results: JH, SC, YHK, CHL.
Extracting and assessing data validity: JH, SC, YHK, CHL.
Data analyses: CHL, YHK,
Data interpretation: CHL, YHK, KYY,
Statistical analysis: CHL, HJK.
Writing manuscript: CHL, HJK, KYY.
Reviewing of final version: all authors.

Declarations of interests

All authors report no conflict of interests.

Funding

This study was supported by Korea University grants.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinane.2021.110461.

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