Lung-protective ventilation in intensive care unit and operation room

Tidal volume size, level of positive end-expiratory pressure and driving pressure

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Chapter 4

Incidence of mortality and morbidity related to postoperative lung injury in patients who have undergone abdominal or thoracic surgery: A systematic review and meta-analysis

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Abstract

Background: Lung injury is a serious complication of surgery. We did a systematic review and meta-analysis to assess whether incidence, morbidity, and in-hospital mortality associated with postoperative lung injury are affected by type of surgery and whether outcomes are dependent on type of ventilation.

Methods: We searched MEDLINE, CINAHL, Web of Science, and Cochrane Central Register of Controlled Trials for observational studies and randomised controlled trials published up to April, 2014, comparing lung-protective mechanical ventilation with conventional mechanical ventilation during abdominal or thoracic surgery in adults. Individual patients' data were assessed. Attributable mortality was calculated by subtracting the in-hospital mortality of patients without postoperative lung injury from that of patients with postoperative lung injury.

Findings: We identified 12 investigations involving 3365 patients. The total incidence of postoperative lung injury was similar for abdominal and thoracic surgery (3·4% vs 4·3%, p = 0·198). Patients who developed postoperative lung injury were older, had higher American Society of Anesthesiology scores and prevalence of sepsis or pneumonia, more frequently had received blood transfusions during surgery, and received ventilation with higher tidal volumes, lower positive end-expiratory pressure levels, or both, than patients who did not. Patients with postoperative lung injury spent longer in intensive care (8·0 [SD 12·4] vs 1·1 [3·7] days, p < 0·0001) and hospital (20·9 [18·1] vs 14·7 [14·3] days, p < 0·0001) and had higher in-hospital mortality (20·3% vs 1·4% p < 0·0001) than those without injury. Overall attributable mortality for postoperative lung injury was 19% (95% CI 18–19), and differed significantly between abdominal and thoracic surgery patients (12·2%, 95% CI 12·0–12·6 vs 26·5%, 26·2–27·0, p = 0·0008). The risk of in-hospital mortality was independent of ventilation strategy (adjusted HR 0·71, 95% CI 0·41–1·22).

Interpretation: Postoperative lung injury is associated with increases in in-hospital mortality and durations of stay in intensive care and hospital. Attributable mortality due to postoperative lung injury is higher after thoracic surgery than after abdominal surgery. Lung-

protective mechanical ventilation strategies reduce incidence of postoperative lung injury but does not improve mortality.

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Introduction

More than 230 million major surgical procedures are performed worldwide each year.[1] Complications after major surgery increase use of resources and are important causes of death.[1] Postoperative pulmonary complications, including postoperative lung injury, are associated particularly with morbidity and mortality after major surgery.[2-4] Evidence suggests that intraoperative lung-protective mechanical ventilation strategies, which use low tidal volumes with or without high levels of positive end-expiratory pressure (PEEP), prevent postoperative lung injury compared with conventional ventilation (high tidal volume and low PEEP levels).[2-4] A large retrospective study showed that use of low tidal volumes during general anaesthesia for surgery were associated with increased mortality, and excess mortality was suggested to have been caused by the use of too-low PEEP levels.[5]

The exact effects of postoperative lung injury on morbidity and mortality are uncertain, and the outcome of postoperative lung injury could be different in patients who had abdominal surgery from those who underwent thoracic surgery. Additionally, whether different lung-protective ventilation strategies affect the development of postoperative lung injury and outcomes needs to be better defined.[2-4]

Improved understanding of the incidence, morbidity, and mortality of postoperative lung injury could help in the design of future trials and might improve the approach to prevention and treatment of this condition. We aimed to test the hypotheses that crude and attributable mortality differ between patients after abdominal and thoracic surgery and that outcome of postoperative lung injury is dependent on intraoperative ventilation settings.

Methods

The full statistical analysis plan for this meta-analysis has been published.[6] We did an individual-patient-data meta-analysis of studies and trials of intraoperative ventilation during abdominal and thoracic surgery, which allowed us to quantify crude and attributable mortality of postoperative lung injury and assess its relation to different ventilation strategies. We compared incidence of lung injury and outcomes in patients who underwent abdominal surgery with those in patients who underwent thoracic surgery.

Two authors (ASN and CSVB) searched MEDLINE, CINAHL, Web of Science, and Cochrane Central Register of Controlled Trials for observational studies and randomised controlled trials published up to April, 2014. The search strategy combined the following medical subject headings and keywords "([protective ventilation OR lower tidal volume OR low tidal volume OR positive end–expiratory pressure OR positive end–expiratory pressure OR PEEP])". No restrictions were placed on publication language. The abstracts and, where appropriate, full text of articles and cross-referenced studies identified from retrieved articles were screened for pertinent information. We also searched online for proceedings of annual meetings of critical care and anaesthesiology societies to identify relevant studies published in abstract form only.

Selection of studies

Eligible studies compared different tidal volume and PEEP settings (lung-protective versus conventional ventilation) during intraoperative ventilation for surgical general anaesthesia and reported the outcomes of interest in this study. Other inclusion criteria were that the studies were done in adults (age 18 years or older) undergoing elective abdominal or thoracic surgery. Studies or trials were excluded if they included patients with pre-existing lung injury or those who received ventilation in a nonsurgical setting (eg, ventilation continued in intensive care). We used the Jadad score to assess the quality of the randomised controlled trials, and the GRACE checklist to assess observational studies.

Collection of individual patients' data

We contacted the corresponding authors of eligible published studies by email, with a letter detailing the background and objectives of our meta-analysis and a datasheet for input of individual patients' data. Completed forms were sent to the principal investigator. Any further communications were by email. Corresponding authors were also contacted about unpublished data to obtain the maximum pool of clinical data. The same two investigators who did the literature search handled the individual patient data. Data were accepted in electronic formats (eg, SPSS, STATA, Word document, Excel document, and Access document) and only the collaboration coordinators had direct access to the data. ASN and CSVB validated the data, checking the received dataset for input errors and inconsistencies. Differences were discussed with MJS and resolved by consensus.

Definitions

For postoperative lung injury we used the definitions for acute lung injury and acute respiratory distress syndrome of the American–European Consensus criteria group (ratio of arterial partial pressure of oxygen [PaO_2] to fractional concentration of oxygen in inspired air [FiO_2] lower than 300),[7] since all studies were done before the publication of the Berlin definition. Follow-up was defined as the time from surgery (day 0) to hospital discharge, or in-hospital death. The number of days after discharge from intensive care or hospital between days 1 and 28 and the number of patients alive at day 28 were recorded.

Lung-protective ventilation was defined as that using low tidal volume (8 mL/kg predicted bodyweight or less), with or without high PEEP levels (5 cm H2O or higher) and with or without recruitment manoeuvres. Conventional ventilation was defined as that using high tidal volume (higher than 8 mL/kg predicted bodyweight) with low PEEP levels (less than 5 cm H2O) and without recruitment manoeuvres. These definitions were based on those described in several reports and set a priori in the study protocol.[2-4,6]

Statistical analysis

Attributable mortality was calculated by subtracting the in-hospital mortality of patients without postoperative lung injury from that of patients with postoperative lung injury. The incidence of postoperative lung injury was calculated as number of cases per person-years ([number of cases/person-days] × [365 person-days/1 person-year]). A random effects model was used to pool the overall data.

We constructed survival curves with the Kaplan- Meier method and compared the group findings with the log-rank test. Time to event was defined as the time from the day of surgery to the onset of postoperative lung injury. We used a Cox's proportional hazards regression model to assess simultaneously the effects of multiple covariates on outcome, with censoring of patients' data at the time of death, hospital discharge, or after 30 days. The initial model included age, sex, body-mass index, American Society of Anesthesiology (ASA) score, smoking, and predisposing disorders (shock, pneumonia, blood transfusion, sepsis, or a combination of these). Variables with *p* values lower than 0·2 in the univariate analysis were included in the multivariate regression. The final model was developed by dropping each variable in turn from the model and using a likelihood-ratio test to compare the full and the nested models (stepwise backwards approach). The threshold for exclusion of a variable from the multivariate model was $p = 0{\cdot}05$. In all models, the categorical variables were tested for trend with the absence of postoperative lung injury as the reference, and the proportional-hazards assumption was assessed. We tested pairs of variables in the final model and biologically plausible variables for interaction. The effect of each variable in these models was assessed with the use of the Wald test and described with the hazard ratio (HR) and 95% CI.

Subgroup analyses were done to investigate the effects of intraoperative ventilation (conventional vs lung-protective ventilation), age (younger than 65 years vs 65 years or older), surgery (abdominal vs thoracic), and severity of illness (ASA score less than 3 vs 3 or higher).

All analyses were done with SPSS (version 20) and R (version 2.12.0). For all analyses we deemed two-sided *p* values lower than 0·05 to be significant.

Role of the funding source

There was no funder for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified three observational studies and 21 randomised controlled trials comparing different tidal volume, PEEP settings, or both, in intraoperative ventilation during general anaesthesia for major abdominal or thoracic surgery.[8-31] We were unable to collect data from five randomised controlled trials because the corresponding author could not provide data of interest or no longer had access to the complete database (n = 3)[20–22] or could not be contacted (n = 2).[23,24] Seven papers were excluded because assessed patients underwent cardiac (n = 6)[25–30] or orthopaedic surgery (n = 1).[31] Thus, we assessed data for 3365 patients in 12 studies (Table 1, Figure 1).

Characteristics of patients and predisposing disorders at baseline and during surgery differed between patients who did and did not develop postoperative lung injury. Patients who developed postoperative lung injury were older, presented with higher ASA scores, had higher prevalence of sepsis or pneumonia, more frequently received blood transfusions, and were ventilated with higher tidal volumes, lower PEEP levels, or both, than those who did not develop lung injury (Table 2). When stratified by type of surgery similar patterns were seen in patients who underwent thoracic surgery, but fewer differences were seen between patients who underwent abdominal surgery and did and did not develop postoperative lung injury (Appendix). Values for tidal volume, PEEP level, and respiratory rate differed significantly between patients receiving lung-protective or conventional ventilation but those for other ventilation parameters did not (Appendix).

The incidence of postoperative lung injury in the whole cohort was 3·9% (crude incidence 0·99 cases per person-year). The individual and pooled incidence rates for postoperative lung injury are shown in Figure 2. The incidence of postoperative lung injury was higher in patients older than 65 years (4·7 vs 2·8%, p = 0·008) and in those who received conventional ventilation (6·7 vs 2·0%, p < 0·0001), whereas rates were similar after abdominal and thoracic surgery (3·4 vs 4·3%, p = 0·198; Table 3). When results were stratified by type of surgery, the results remained similar for ventilation and age (Appendix). Postoperative lung injury developed within a mean of 2·9 (SD 2·2) days after surgery (median 2·0, IQR 2·0–3·0), and 52 (42%) of cases developed on postoperative day 2 (Figure 3).

Development of postoperative lung injury was associated with increases in risk of in-hospital mortality and lengthened durations of stay in intensive care and hospital (Table 3). The mean number of days after discharge from intensive care or from hospital to day 28 was lower in patients who developed postoperative lung injury (21 [SD 8] vs 27 [2] days, $p < 0.0001$, and 10 [7] vs 15 [7] days, $p < 0.0001$) than in those who did not. When adjusted for age, severity of illness according to ASA score, smoking, and predisposing disorders, the risk of in-hospital mortality was substantially increased in patients who developed postoperative lung injury (Table 4, Figures 4, 5, Appendix). Patients who developed postoperative lung injury had reduced chance per day for discharge from intensive care (Table 4). The estimated overall attributable mortality due to postoperative lung injury was 19·0% (95% CI 18·0–19·1%).

Among patients who developed postoperative lung injury, the total duration of mechanical ventilation and durations of stay in intensive care and hospital were similar for those who did and did not survive (Appendix). The mean time to death was 35·2 (SD 63·4) days (median 18·0, IQR 10·0–31·0). Patients who received conventional ventilation during surgery died earlier than those who received lung-protective ventilation (mean 17·8 [SD 13·1] vs 51·2 [84·3] days, $p = 0.027$).

The attributable mortality of postoperative lung injury was lower in patients who underwent abdominal surgery than in those who underwent thoracic surgery (12·2%, 95% CI 12·0–12·6 vs 26·5%, 26·2–27·0, $p = 0.0008$). Development of postoperative lung injury was associated with increased durations of stay in intensive care and hospital that did not differ substantially between patients who underwent abdominal or thoracic surgery (Appendix). When adjusted for age, severity of illness according to ASA score, smoking, and predisposing disorders, the risk of postoperative lung injury was lower in those who received lung-protective ventilation during surgery than in those who received conventional ventilation (adjusted HR 0·31, 95% CI 0·19–0·45). The risk of in-hospital mortality, however, was independent of ventilation strategy (0·71, 0·41–1·22). Attributable mortality for postoperative lung injury was similar in those who received lung-protective and conventional ventilation (18·5%, 95% CI 17·8–19·2 vs 19·3%, 19·0–19·7, $p = 0.359$). Notably, patients who received conventional ventilation and developed postoperative lung injury died earlier than patients who received lung-protective ventilation and developed postoperative lung injury (mean time to death 18 [SD 16] vs 35 [53] days, $p = 0{\cdot}018$). Characteristics of patients with postoperative lung injury stratified by type of ventilation used during surgery were similar for those who underwent abdominal and thoracic surgery (Appendix). We found no interaction between mortality and the study type (randomised controlled trial versus non-randomised controlled trial) in the overall cohort ($p_{\text{interaction}} = 0{\cdot}11$) or for abdominal surgery ($p_{\text{interaction}} = 0{\cdot}23$) or thoracic surgery ($p_{\text{interaction}} = 0{\cdot}78$, Appendix).

On the basis of the excluded studies with available data,[22,24,25] the crude incidence of postoperative lung injury was 6·6%, which is similar to the rate we found for the studies we included ($p = 0{\cdot}116$). Lung-protective ventilation was associated with reduced incidence of postoperative lung injury compared with conventional ventilation (5·3% vs 13·1%, $p = 0{\cdot}031$), findings that also concur with the present study results. We found no interaction between mortality and incidence of postoperative lung injury in the excluded studies (Appendix).

Discussion

This meta-analysis of data at the individual patient level shows that postoperative lung injury is associated with high attributable mortality. Additionally, it is associated with important increases in resource use, as reflected by longer stays in intensive care and hospital than for patients without postoperative lung injury. The incidence of postoperative lung injury was similar in patients undergoing abdominal or thoracic surgery, but the attributable mortality was higher in those who underwent thoracic procedures. Use of lung-protective ventilation during surgery was associated with reduced incidence of postoperative lung injury compared with conventional ventilation. If postoperative lung injury developed, intraoperative lung-protective ventilation strategies were not associated with reduced attributable mortality, which suggests that the benefits of lung-protective ventilation are due mainly to the reduction in incidence of postoperative lung injury.

Our analysis had several strengths. First, we analysed data at the individual patient level, including a larger number of patients who had a higher number of variables and better documented risk factors than in previous studies.[1-4] Second, the primary and secondary outcomes were clearly defined in most investigations and postoperative lung injury was defined a priori. Third, we included recent, large, and well-designed randomised controlled trials.[18,19] Fourth, we analysed patients undergoing abdominal and thoracic surgery, who are at high risk of developing postoperative lung injury.[1] Finally, individual-patient-data meta-analyses including higher numbers of randomised controlled trials have some advantages over large observational studies.

Since the number of major surgical procedures performed worldwide each year is high, the finding that postoperative lung injury is associated with such poor outcomes is important. The mechanisms contributing to the development of this complication and preventive measures urgently need to be identified. The use of low tidal volumes during intraoperative ventilation seems to be a clinically relevant and modifiable strategy,[2,18] and ventilation strategies that use high PEEP levels are associated with potentially dangerous side-effects.[19]

Our results are at least partly in line with those from previous investigations.[2,12,22] Earlier studies suggest that incidence of postoperative lung injury is 3% in patients undergoing high-risk elective surgery,[2] which is similar to the 3·9% rate we found. Previous findings have also shown increased durations of hospital stay in patients who developed postoperative lung injury and in-hospital mortality similar to those in our study (up to 17%). Additionally, 60-day and 1-year survival were lower for patients with postoperative lung injury than that for patients without this complication.[2] Of note, though, is that incidence and outcomes of postoperative lung injury might differ with different types of surgery[3] and definitions.

Our findings add to the knowledge of outcomes after postoperative lung injury and potential measures to prevent this complication. Development of postoperative lung injury was dependent on the intraoperative ventilation strategy and, therefore, should be seen as a potentially preventable complication by the use of lung-protective mechanical ventilation strategies during surgery. Our analysis also showed that many patients who develop lung injury do so after the first postoperative day, which suggests that patients should be monitored for more than 1 day after surgery by the health-care workers who apply intraoperative ventilation and that optimum timing for monitoring and clinical management need to be explored further. Finally, the attributable mortality for postoperative lung injury is similar after intraoperative ventilation with conventional settings to that after ventilation with lung-protective strategies, which means that the benefits with the latter are mainly due to reduced incidence of injury. This finding, however, might simply reflect heterogeneous factors associated with death in this population well beyond postoperative lung injury.

We are intrigued that among patients who developed postoperative lung injury, those who received conventional intraoperative ventilation died earlier than those who received lung-protective intraoperative ventilation, despite attributable mortality being the same. A possible explanation is that patients who received conventional intraoperative ventilation received injurious ventilation after surgery, and maybe even after the development of lung injury. Unfortunately, we could not collect data on ventilator settings after surgery and, therefore, the reasons remain speculative.

Our study had some limitations. Our analyses were restricted to studies of intraoperative lung-protective ventilation, and data on postoperative ventilation were not available. Not all investigators could provide data for individual patients and, therefore, data from seven otherwise eligible studies were not included. Our results, however, are supported by those of a classic meta-analysis that included those studies.[4] No information was available on choices of treatment after surgery, such as postoperative ventilation, blood transfusion, fluid regimens, pain control, cardiac protection, and so on. Anaesthetists who applied lung-protective ventilation might have provided other lung-protective strategies after surgery. Therefore, we could not assess how much in-hospital mortality is affected by the adequacy of treatment. Additionally, we do not know the cause of death in each patient. Since there is no gold standard for the diagnosis of postoperative lung injury, misclassification of patients with this complication might have led to underestimation, overestimation, or both of attributable morbidity. We were unable to collect information on history of previous abdominal or thoracic surgery, which might have affected outcomes. Our results should be analysed within the context of the included studies, since we pooled data from studies with heterogeneous research methods and quantitative approaches. The number of studies included is moderate and, therefore, our statistical model might have lacked power to detect associations and ascertain potential sources of confounding. We did not include previous pulmonary alterations as a covariate in the model, although only 4·9% of the population assessed presented with chronic obstructive pulmonary disease or other chronic pulmonary disorders. Minimally invasive techniques for thoracic surgery are being used increasingly and are associated with a shorter duration of surgery and length of stay in hospital. Since the studies we included did not assess these techniques, we do not know whether the outcomes and effects of lung-protective ventilation during minimally invasive procedures would be altered. A study has, however, suggested that lung-protective ventilation strategies are beneficial in patients who undergo minimally invasive oesophagectomy.[32] Finally, although the type of intraoperative ventilation seems to play an important part in development of acute lung injury, other factors related to postoperative management could plausibly be contributory, especially for patients who developed lung injury several days after surgery or cessation of mechanical ventilation.

On the basis of the individual patient data from 12 studies of intraoperative lung-protective ventilation, development of postoperative lung injury is associated with high attributable mortality that is raised more in patients undergoing thoracic surgery than in those undergoing abdominal surgery. Intraoperative lung-protective ventilation is associated with reduced incidence of postoperative lung injury, but does not seem to affect in-hospital mortality.

Funding

Support was provided solely from institutional and/or departmental sources.

Research in context

Systematic review

We searched MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) up to April 2014. The sensitive search strategy combined the following Medical Subject Headings and Keywords ([protective ventilation OR lower tidal volume OR low tidal volume OR positive end–expiratory pressure OR positive end expiratory pressure OR PEEP]). We restricted our analysis to studies in surgery. We assessed the quality of identified studies to ensure minimization of bias.

Interpretation

Development of postoperative lung injury is associated with high attributable mortality. The attributable mortality of postoperative lung injury is higher in patients undergoing thoracic compared to abdominal surgery. Intraoperative protective ventilation is associated with lower incidence of postoperative lung injury, but seems not to affect in–hospital mortality.

Table 1 – Characteristics of included studies

	Country	Design of Study	Jadad Score	Type of Surgery	Number of Patients		Postoperative Lung Injury		Mortality	
					Protective ventilation	Conventional ventilation	Protective ventilation	Conventional ventilation	Protective ventilation	Conventional ventilation
Wrigge 2004[8]	Germany	RCT	2	Abdominal or Thoracic*	29 (47%)	33 (53%)	0 (0%)	3 (9%)	0 (0%)	0 (0%)
Schilling 2005[9]	Germany	RCT	2	Thoracic*	75 (68%)	35 (32%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Wolthui 2008[10]	Dutch	RCT	3	Abdominal	24 (52%)	22 (48%)	0 (0%)	2 (9%)	0 (0%)	0 (0%)
Lin 2008[11]	China	RCT	1	Thoracic*	50 (49%)	52 (51%)	1 (2%)	14 (27%)	0 (0%)	1 (2%)
Licker 2009[12]	Switzerland	Non-RCT	---	Thoracic*	558 (51%)	533 (49%)	15 (3%)	28 (5%)	13 (2%)	15 (3%)
Weingarten 2010[13]	USA	RCT	3	Abdominal	20 (50%)	20 (50%)	0 (0%)	1 (5%)	1 (5%)	0 (0%)
Fernandez-Bustamante 2011[14]	USA	Non-RCT	---	Abdominal	154 (36%)	275 (64%)	7 (4%)	14 (5%)	3 (2%)	3 1(%)
Treschan 2012[15]	Germany	RCT	5	Abdominal	50 (49%)	51 (51%)	1 (2%)	0 (0%)	3 (6%)	5 (10%)
Unzueta 2012[16]	Spain	RCT	2	Thoracic*	40 (100%)	---	0 (0%)	---	1 (2%)	---
Severgnini 2013[17]	Italy	RCT	5	Abdominal	28 (51%)	27 (49%)	9 (32%)	16 (59%)	0 (0%)	0 (0%)
Futier 2013[18]	France	RCT	5	Abdominal	200 (50%)	200 (50%)	1 (0.5%)	8 (4%)	6 (3%)	7 (3%)
PROVE Network Investigators 2014[19]	Europe and USA	RCT	5	Abdominal	889 (100%)	---	7 (0.8%)	---	14 (2%)	---

RCT: randomized controlled trial

*: Thoracic surgery comprised 52% lobectomy, 20% pneumectomy, 20% small resections (eg, partial lobectomy, atypical and wedge resections), 3% esophagectomy, and 5% others (eg, mediastinal resection and explorative thoracotomy)

Table 2 – Characteristics of patients

	Total (n = 3365)	No postoperative lung injury (n = 3150)*	Postoperative lung injury (n = 123)*	p value
Age (years)	62·6 (12·7)	62·5 (12·7)	66·4 (11·6)	0·001
Male	2019 (60·0%)	1941 (61·6%)	78 (63·4%)	0·834
ASA	2·4 (0·6)	2·4 (0·6)	2·6 (0·6)	0·003
BMI (kg/m^2)	25·7 (4·8)	25·7 (4·9)	26·1 (4·8)	0·323
Current smoker	1107 (32·9%)	1058 (33·5%)	49 (39·8%)	0·122
Predisposing disorders				
Shock	54 (1·6%)	52 (1·6%)	2 (1·6%)	0·714
Pneumonia	25 (0·7%)	11 (0·3%)	14 (11·3%)	< 0·0001
Transfusion of blood products	183 (5·4%)	168 (5·3%)	15 (12·1%)	< 0·0001
Sepsis	12 (0·3%)	8 (0·2%)	4 (3·2%)	< 0·0001
Ventilation¶				
Tidal volume (ml/kg PBW)	8·2 (1·9)	8·2 (1·8)	9·3 (2·1)	< 0·0001
PEEP (cmH_2O)	4·4 (3·8)	4·3 (3·7)	2·9 (3·4)	< 0·0001
Respiratory rate (mpm)	11·9 (2·7)	11·9 (2·7)	11·7 (2·2)	0·384
FiO_2 (%)	44·9 (14·2)	41·4 (3·9)	40·5 (4·2)	0·102
Oxygenation¶				
Arterial pH	7·3 (0·1)	7·3 (0·1)	7·4 (0·0)	0·002
PaO_2:FiO_2	320·0 (176·7)	315·0 (180·3)	302·4 (165·8)	0·681
$PaCO_2$ (mmHg)	40·5 (6·5)	40·7 (6·7)	41·3 (3·8)	0·708
ICU length of Stay (days)	1·5 (4·8)	1·1 (3·7)	8·0 (12·4)	< 0·0001
Hospital length of stay (days)	15·1 (14·8)	14·7 (14·3)	20·9 (18·1)	< 0·0001
Mortality (%)	70 (2·1%)	45 (1·4%)	25 (20·3%)	< 0·0001

ASA: American Society of Anesthesiology; BMI: body-mass index; PBW: predicted bodyweight; PEEP: positive end-expiratory pressure; mpm: movements per minute; FiO_2:fractional concentration of oxygen in inspired air; PaO_2: arterial partial pressure of oxygen; $PaCO_2$: arterial partial pressure of carbon dioxide; ICU: intensive-care unit

Data are mean (SD) or number (%)

* The sum of these values is less than 3365 because of missing data

¶ During surgery

Table 3 – Incidence and characteristics of patients who developed postoperative lung injury*

	Number of Patients (%)			Mean (SD) ICU stay (days)		*p*	In-hospital mortality		*p*	Mean (SD) time to onset of PLI (days)
	No PLI	PLI	Incidence**	No PLI	PLI		No PLI	PLI		
All patients	3150 (96·1%)	123 (3·9%)	0·99	1·1 (3·7)	8·0 (12·4)	< 0·0001	45 (1·4%)	25 (20·3%)	< 0·0001	2·9 (2·2)
Ventilation										
Conventional ventilation	1041 (93·3%)	75 (6·7%)	1·71	1·0 (3·0)	9·2 (10·2)	< 0·0001	17 (1·4%)	17 (20·7%)	< 0·0001	2·5 (1·5)
Protective ventilation	1762 (98·0%)	37 (2·0%)	0·46	1·3 (4·3)	6·1 (16·2)	< 0·0001	28 (1·5%)	8 (20·0%)	< 0·0001	3·9 (3·3)
Age										
< 65 years	1504 (97·2%)	44 (2·8%)	0·76	0·8 (2·6)	5·0 (6·0)	< 0·0001	8 (0·5%)	6 (12·8%)	< 0·0001	2·5 (1·2)
≥ 65 years	1390 (95·3%)	68 (4·7%)	1·02	1·5 (4·7)	10·5 (15·4)	< 0·0001	37 (2·5%)	19 (25·3%)	< 0·0001	3·2 (2·6)
ASA score										
< 3	1391 (96·6%)	49 (3·4%)	0·81	1·0 (4·0)	4·2 (5·3)	0·001	10 (0·7%)	9 (17·0%)	< 0·0001	2·5 (1·2)
≥ 3	1106 (95·3%)	55 (4·7%)	1·14	1·8 (4·4)	9·0 (14·4)	0·017	25 (2·3%)	16 (29·1%)	< 0·001	3·4 (2·9)
Surgery										
Abdominal	1798 (96·6%)	64 (3·4%)	0·79	1·0 (4·1)	9·0 (14·5)	< 0·0001	32 (1·8%)	9 (14·1%)	< 0·0001	2·3 (0·9)
Thoracic	1285 (95·7%)	58 (4·3%)	1·32	1·5 (0·9)	5·9 (2·1)	< 0·0001	13 (1·0%)	16 (27·6%)	< 0·0001	3·4 (2·7)

ICU: intensive-care unit; PLI: postoperative lung injury; ASA: American Society of Anesthesiology.

* For some characteristics numbers do not add up to the total number of patients because of missing values

** Expressed as cases per person-year

Table 4 – Outcomes in patients with postoperative lung injury

	HR of in-hospital mortality (95% CI)	HR of ICU discharge (95% CI)
All patients	9·58 (5·32–17·34)	0·45 (0·33–0·66)
Ventilation		
Conventional ventilation	14·22 (5·91–34·26)	0·39 (0·25–0·58)
Protective ventilation	6·07 (2·47–14·55)	0·71 (0·42–1·19)
Age		
< 65 years	33·10 (8·32–131·39)	0·52 (0·32–0·83)
≥ 65 years	7·32 (3·72–14·23)	0·43 (0·26–0·68)
ASA score		
< 3	26·67 (9·44–75·22)	0·55 (0·34–0·92)
≥ 3	6·05 (2·91–12·66)	0·41 (0·26–0·60)
Surgery		
Abdominal	7·12 (2·67–19·08)	0·47 (0·32–0·69)
Thoracic	10·46 (4·72–23·18)	0·19 (0·08–0·40)

HR: hazard ratio; ICU: intensive care unit; CI: confidence interval

Figure Legends

Figure 1 – Selection of studies

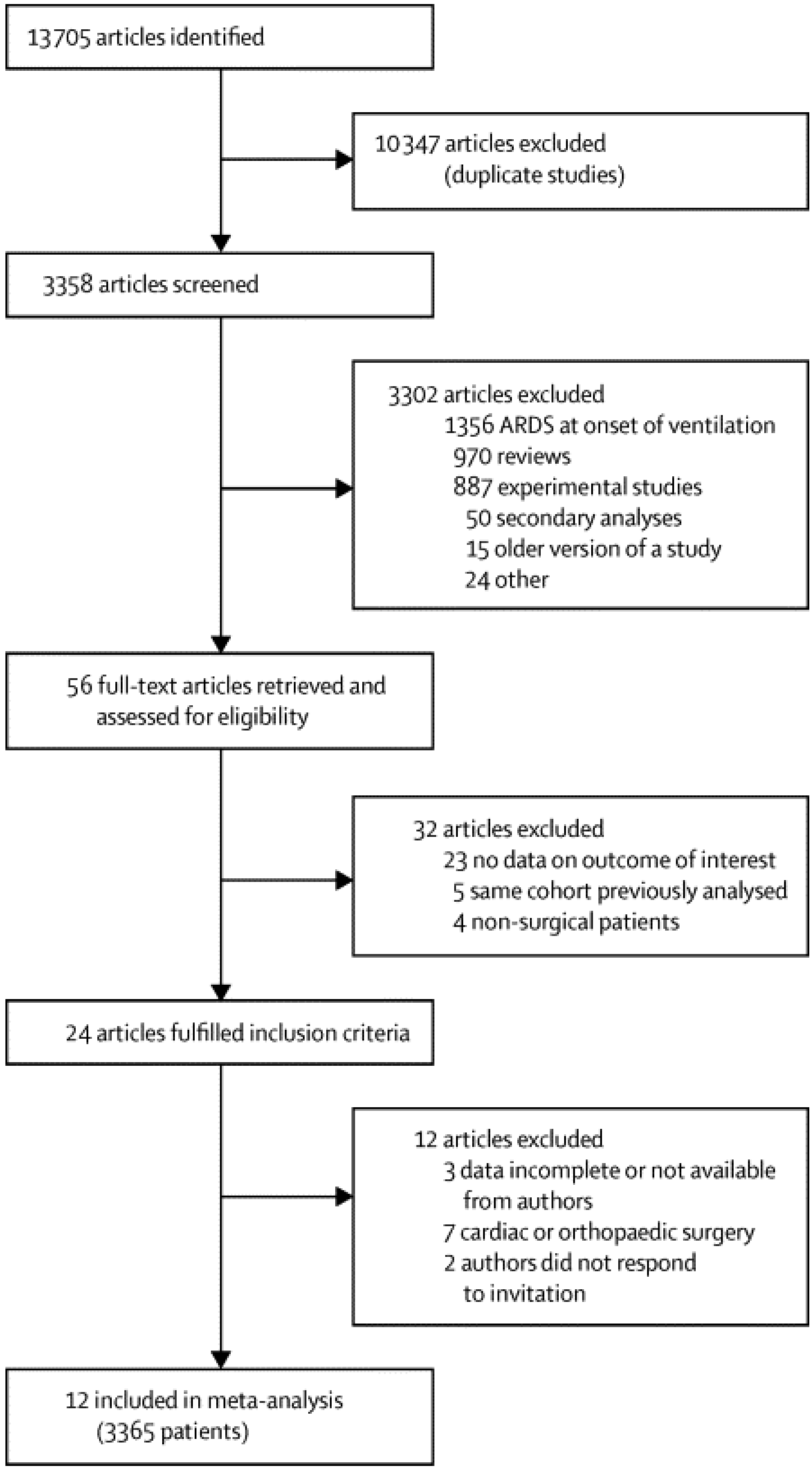
Figure 2 – Individual and pooled incidence of postoperative lung injury

Figure 3 – Timing of postoperative lung injury during hospital stay

Figure 4 – Kaplan-Meier estimates of overall survival in patients with and without postoperative lung injury

Figure 5 – Kaplan-Meier estimates of overall survival by type of surgery and type of intraoperative ventilation

Figure 1 – Selection of studies



ARDS: acute respiratory distress syndrome

Serpa Neto A, et al. Lancet Respir Med 2014; 2:1007-15

Figure 2 – Individual and pooled incidence of postoperative lung injury

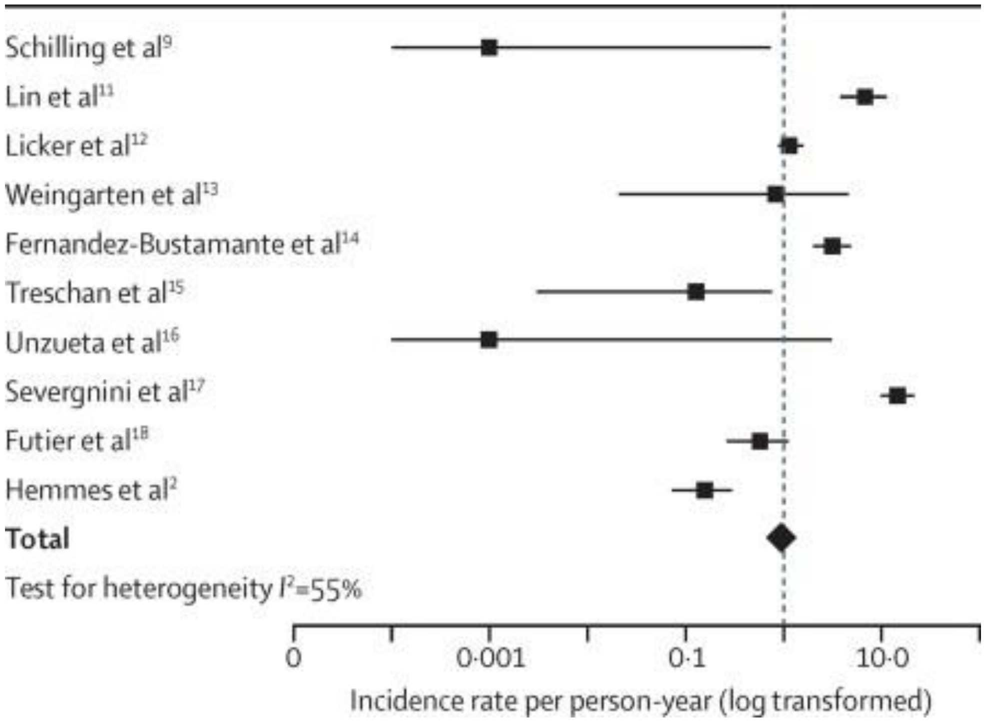
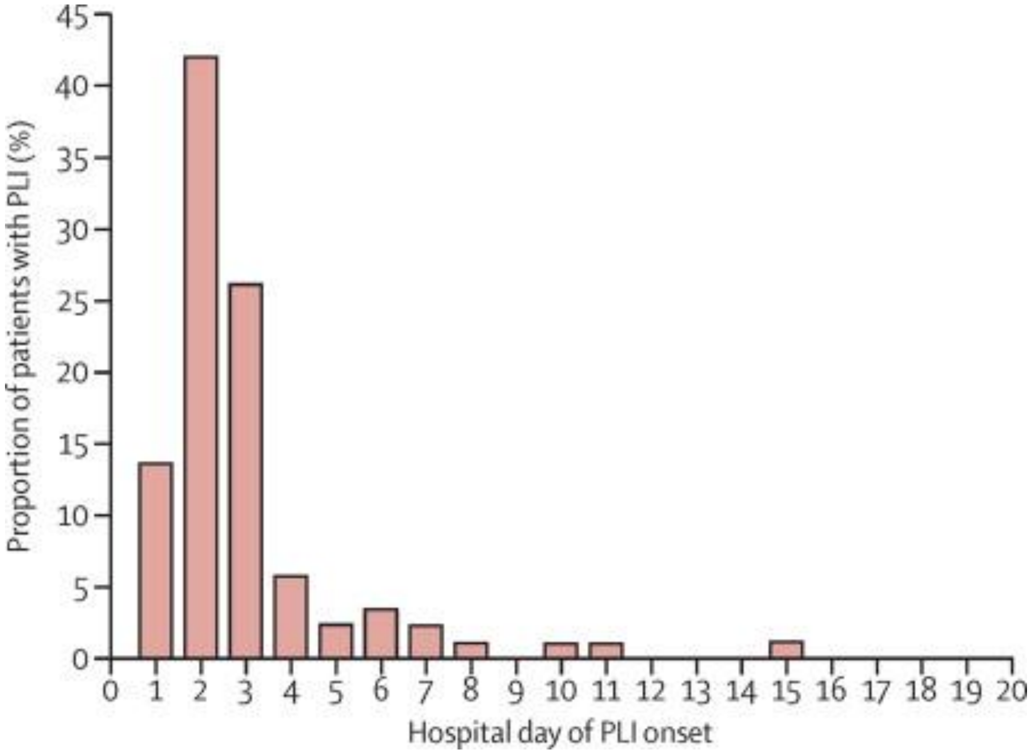
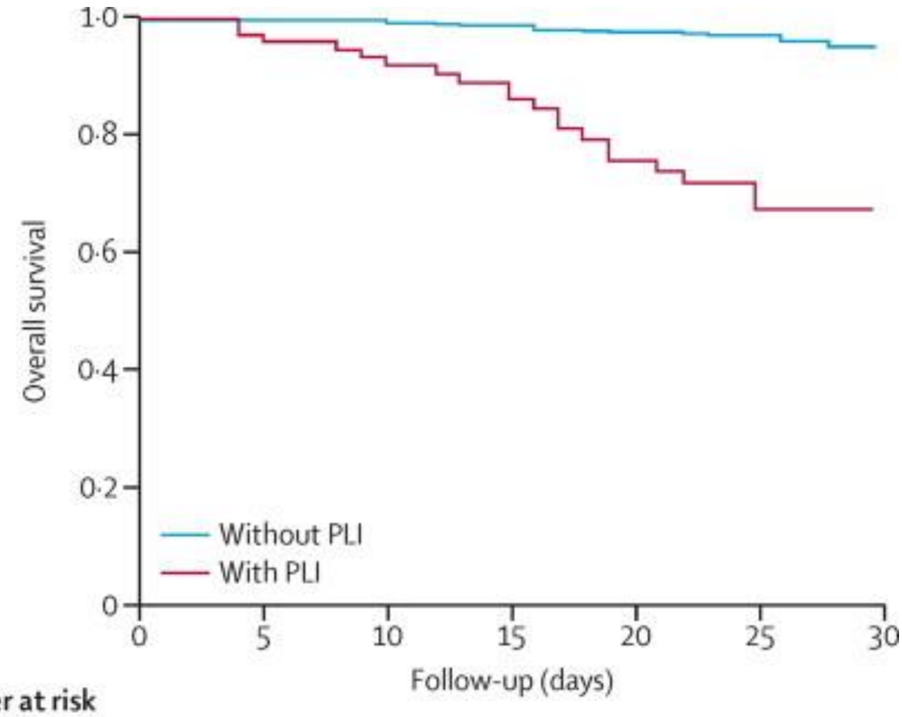


Figure 3 – Timing of postoperative lung injury during hospital stay



Day 0 is the day of surgery. PLI: postoperative lung injury

Figure 4 – Kaplan-Meier estimates of overall survival in patients with and without postoperative lung injury

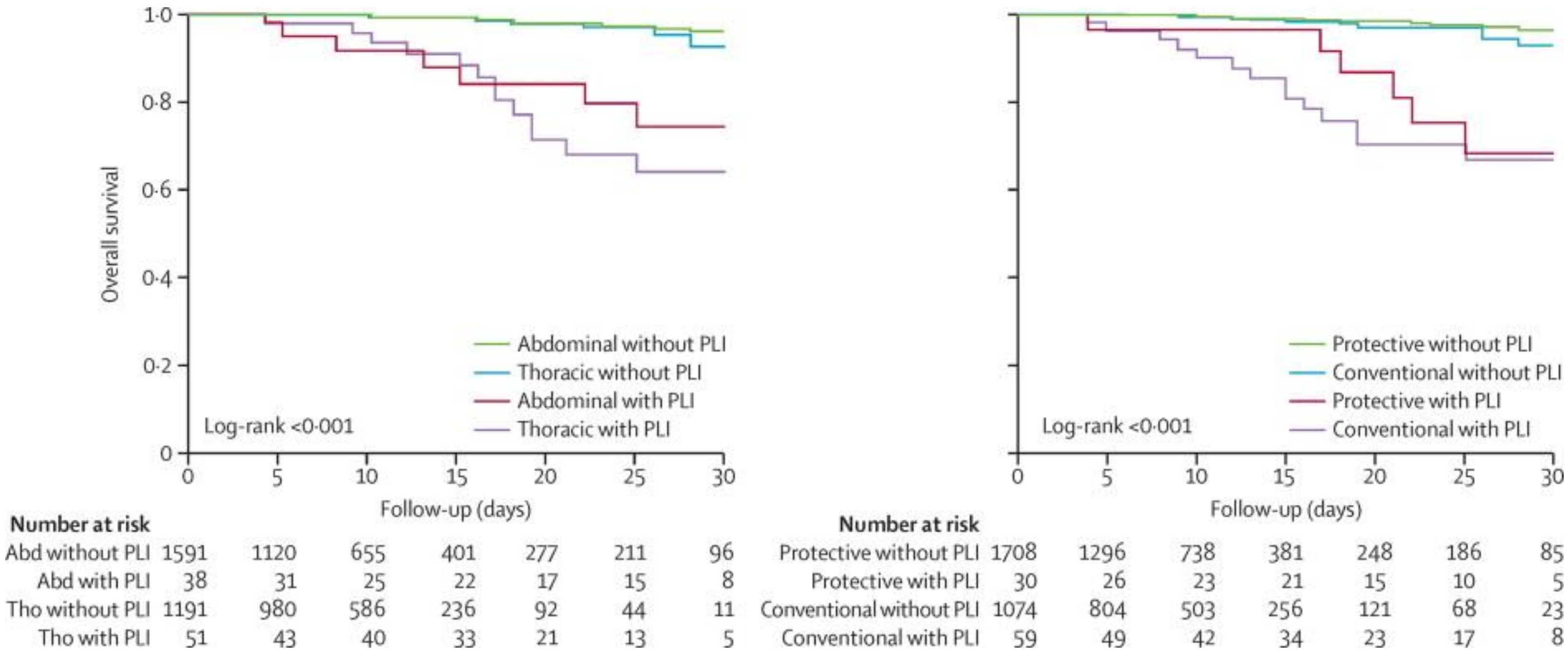


Number at risk

	0	5	10	15	20	25	30
Without PLI	2782	2100	1241	637	369	254	107
With PLI	89	74	65	55	38	27	13

Day 0 is the day of surgery. Data were censored at 30 days after surgery. PLI: postoperative lung injury

Figure 5 – Kaplan-Meier estimates of overall survival by type of surgery and type of intraoperative ventilation



(A) Survival in patients undergoing abdominal or thoracic surgery with or without developing postoperative lung injury. (B) Patients who received protective or conventional ventilation with or without developing postoperative lung injury. Day 0 is the day of surgery. Data were censored at 30 days after surgery. Abd: abdominal; Tho: thoracic; PLI: postoperative lung injury

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Supplementary Appendix to 'Incidence of mortality and morbidity related to postoperative lung injury in patients who have undergone abdominal or thoracic surgery: A systematic review and meta-analysis'

eTable 1 – Characteristics of included studies

	Allocation Concealment	Baseline Similarity	Early Stopping[a]	Lost to Follow-up	Intention-to-Treat Analysis
Wrigge, 2004	Sealed envelopes	Age: similar Illness severity: similar (ASA)	No	4·6%	NS
Schilling, 2005	Random numbers	Age: similar	No	No	NS
Wolthuis, 2008	Sealed envelopes	Age: similar Illness severity: similar (ASA)	No	No	No
Lin, 2008	NS	Age: similar	No	No	NS
Licker, 2009	Not applicable	Age: similar Illness severity: favor higher V_T (ASA)	Not applicable	Not applicable	Not applicable
Fernandez-Bustamante, 2011	Not applicable	Age: similar Illness severity: similar (ASA)	Not applicable	Not applicable	Not applicable
Weingarten, 2010	Schedule	Age: similar Illness severity: similar (ASA)	No	No	NS
Treschan, 2012	Sealed envelopes	Age: similar Illness severity: similar (ASA)	No	No	Yes
Unzueta, 2012	Random table	Age: similar Illness severity: similar (ASA)	No	No	NS
Severgnini, 2013	Sealed envelopes	Age: similar Illness severity: similar (ASA)	No	1·7%	NS
Futier, 2013	Computer-Generated	Age: similar Illness severity: similar (PORI)	No	No	Yes
PROVE Network Investigators, 2014	Computer-Generated	Age: similar Illness severity: similar (ARISCAT)	No	No	Yes

NS: not specified; V_T: tidal volume; STSMS: society of thoracic surgeons mortality score; PORI: preoperative risk index

[a]**:** Early termination for benefit or futility and the presence of an explicit a *priori* stopping rules

eTable 2 – Jadad scale

	Was the study described as randomized?	Was the study described as double blind?	Was there a description of withdrawals and dropouts?	The method of randomization was described in the paper, and that method was appropriate.	The method of blinding was described, and it was appropriate.
Wrigge, 2004	Yes	No	Yes	No	No
Schilling, 2005	Yes	No	Yes	No	No
Wolthuis, 2008	Yes	No	Yes	Yes	No
Lin, 2008	Yes	No	No	No	No
Weingarten, 2010	Yes	No	Yes	Yes	No
Treschan, 2012	Yes	Yes	Yes	Yes	Yes
Unzueta, 2012	Yes	No	Yes	No	No
Severgnini, 2013	Yes	Yes	Yes	Yes	Yes
Futier, 2013	Yes	Yes	Yes	Yes	Yes
PROVE Network Investigators, 2014	Yes	Yes	Yes	Yes	Yes

eTable 3 – GRACE checklist

	Adequate Treatment	Adequate Outcomes	Objective Outcomes	Valid Outcomes	Similar Outcomes	Covariates Recorded	New Initiators	Concurrent Comparators	Covariates Accounted For	Immortal Time Bias	Sensitivity Analysis
	D1	**D2**	**D3**	**D4**	**D5**	**D6**	**M1**	**M2**	**M3**	**M4**	**M5**
Licker, 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Fernandez-Bustamante, 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Dreyer NA, Velentgas P, Westrich K, Dubois R. The GRACE checklist for rating the quality of observational studies of comparative effectiveness: a tale of hope and caution. J Manag Care Pharm 2014;20:301-8.

eTable 4 – Demographics of patients undergoing thoracic surgery

	Total (*n* = 1374)	**No postoperative lung injury* (*n* = 1285)**	**Postoperative lung injury* (*n* = 58)**	***p* value**
Age (years)	61·73 (11·85)	61·57 (11·88)	66·00 (10·35)	0·005
Male	872 (63·4%)	837 (65·1%)	35 (60·3%)	0·482
ASA	2·45 (0·63)	2·44 (0·63)	2·72 (0·64)	0·001
BMI (kg/m^2)	25·10 (4·43)	25·10 (4·45)	25·07 (4·36)	0·956
Predisposing disorders				
Shock	1 (0·0%)	0 (0·0%)	1 (1·7%)	0·714
Pneumonia	9 (0·6%)	4 (0·3%)	5 (8·6%)	< 0·0001
Transfusion of blood products	39 (2·8%)	26 (2·0%)	13 (22·4%)	< 0·0001
Sepsis	5 (0·3%)	1 (0·0%)	4 (6·8%)	< 0·0001
Ventilation¶				
Tidal volume, ml/kg PBW	7·78 (2·05)	7·64 (1·84)	9·54 (2·53)	< 0·0001
Respiratory rate, mpm	12·90 (2·21)	12·94 (2·21)	11·81 (1·89)	0·001
FiO_2, %	45·00 (16·61)	45·17 (16·86)	40·40 (5·07)	0·064
Oxygenation¶				
Arterial pH	7·26 (0·12)	7·28 (0·10)	7·13 (0·15)	< 0·0001
PaO_2:FiO_2	392·64 (118·45)	398·87 (118·69)	294·28 (55·22)	0·001
$PaCO_2$ (mmHg)	41·17 (6·89)	41·13 (7·05)	41·86 (3·31)	0·689
ICU length of stay (days)	1·88 (1·52)	1·57 (0·90)	5·93 (2·15)	< 0·0001
Hospital length of stay (days)	13·05 (6·47)	12·71 (6·10)	20·72 (9·14)	< 0·0001
In-Hospital Mortality (%)	29 (2·1%)	13 (1·0%)	16 (27·5%)	< 0·0001

ASA: American Society of Anesthesiology; BMI: body-mass index; PBW: predicted bodyweight; PEEP: positive end-expiratory pressure; mpm: movements per minute; FiO_2:fractional concentration of oxygen in inspired air; PaO_2: arterial partial pressure of oxygen; $PaCO_2$: arterial partial pressure of carbon dioxide; ICU: intensive-care unit

Data are mean (SD) or number (%)

* The sum of these values is less than 3365 because of missing data

¶ During surgery

eTable 5 – Demographics of patients undergoing abdominal surgery

	Total (*n* = 1991)	No postoperative lung injury* (*n* = 1798)	Postoperative lung injury* (*n* = 64)	*p* value
Age (years)	63·24 (13·25)	63·20 (13·21)	66·75 (12·66)	0·035
Male	1235 (62·0%)	1191 (66·2%)	44 (68·7%)	0·433
ASA	2·32 (0·67)	2·34 (0·67)	2·43 (0·63)	0·347
BMI (kg/m^2)	26·13 (5·02)	26·11 (5·09)	27·12 (5·00)	0·122
Predisposing disorders				
Shock	51 (2·5%)	50 (2·7%)	1 (1·5%)	0·714
Pneumonia	8 (0·4%)	7 (0·3%)	1 (1·5%)	0·231
Transfusion of blood products	157 (7·8%)	144 (8·0%)	13 (20·3%)	< 0·0001
Sepsis	7 (0·3%)	7 (0·3%)	0 (0·0%)	0·871
Ventilation¶				
Tidal volume, ml/kg PBW	8·56 (1·80)	8·53 (1·76)	9·15 (1·72)	0·006
Respiratory rate, mpm	11·00 (2·86)	10·97 (2·83)	11·62 (2·38)	0·093
FiO_2, %	44·87 (9·64)	45·34 (10·07)	40·78 (2·70)	0·011
Oxygenation¶				
Arterial pH	7·35 (0·06)	7·33 (0·05)	7·43 (0·04)	0·462
PaO_2:FiO_2	334·73 (220·76)	365·58 (230·31)	308·14 (214·2)	0·245
$PaCO_2$ (mmHg)	38·62 (5·16)	38·49 (3·79)	32·42 (4·62)	0·493
ICU length of stay (days)	1·41 (5·24)	1·08 (4·10)	9·00 (14·57)	< 0·0001
Hospital length of stay (days)	16·53 (18·45)	16·17 (17·92)	21·09 (23·58)	0·035
In-Hospital Mortality (%)	42 (2·1%)	33 (1·8%)	9 (14·1%)	< 0·0001

ASA: American Society of Anesthesiology; BMI: body-mass index; PBW: predicted bodyweight; PEEP: positive end-expiratory pressure; mpm: movements per minute; FiO_2:fractional concentration of oxygen in inspired air; PaO_2: arterial partial pressure of oxygen; $PaCO_2$: arterial partial pressure of carbon dioxide; ICU: intensive-care unit

Data are mean (SD) or number (%)

* The sum of these values is less than 3365 because of missing data

¶ During surgery

eTable 6 – Ventilatory parameters and duration of ventilation

	Total			Abdominal			Thoracic		
	Protective (*n* = 1799)	**Conventional (*n* = 1116)**	***p* value**	**Protective (*n* = 1155)**	**Conventional (*n* = 707)**	***p* value**	**Protective (*n* = 707)**	**Conventional (*n* = 636)**	***p* value**
Tidal volume (ml/kg PBW)	7·10 (1·15)	9·95 (1·62)	< 0·01	7·54 (0·93)	10·40 (1·52)	< 0·01	6·34 (1·09)	9·46 (1·58)	< 0·01
PEEP (cmH_2O)	5·41 (4·10)	2·79 (2·68)	< 0·01	6·44 (4·57)	2·72 (3·29)	< 0·01	3·61 (2·08)	2·87 (1·77)	< 0·01
Respiratory rate (bpm)	12·91 (2·82)	10·45 (1·77)	< 0·01	11·76 (2·97)	9·60 (1·97)	< 0·01	14·38 (1·73)	11·15 (1·21)	< 0·01
Plateau pressure (cmH_2O)	16·52 (5·87)	16·49 (4·03)	0·912	19·12 (5·81)	17·32 (6·53)	< 0·01	13·63 (4·43)	16·23 (2·75)	< 0·01
Duration of ventilation (minutes)	369·23 (758·59)	408·53 (844·14)	0·857	382·74 (788·87)	487·21 (755·43)	0·101	401·12 (672·21)	498·21 (512·32)	0·222
ICU length of stay (days)	1·49 (5·24)	1·51 (4·33)	0·935	1·42 (5·92)	1·40 (4·59)	0·958	1·71 (0·99)	2·13 (2·04)	0·045
Hospital length of stay (days)	15·77 (16·75)	14·01 (14·97)	0·231	15·99 (17·34)	15·76 (13·76)	0·121	12·01 (5·80)	14·28 (6·98)	< 0·01

PBW: predicted body weight; PEEP: positive end-expiratory pressure; BPM: beats per minute; ICU: intensive care unit

Data are mean (SD) or number (%)

eTable 7 – Incidence of postoperative lung injury and its characteristics in patients undergoing thoracic surgery*

	Postoperative Lung Injury				No-Postoperative Lung Injury		
	Number of Patients	**Onset (days)**	**Mortality**	**ICU LOS (days)**	**Number of Patients**	**Mortality**	**ICU LOS (days)**
All patients	58 (4·3%)	3·4 (2·7)	16 (27·6%)	5·9 (2·1)	1285 (95·7%)	13 (1·0%)	1·5 (0·9)
Ventilation							
Conventional ventilation	42 (6·7%)	2·7 (1·7)	12 (28·6%)	6·0 (2·1)	578 (93·3%)	4 (0·7%)	1·3 (0·7)
Protective ventilation	16 (2·2%)	5·5 (4·2)	4 (25·0%)	4·0 (4·5)	707 (97·8%)	9 (1·3%)	1·6 (0·9)
Age							
< 65 years	25 (3·3%)	2·6 (1·3)	6 (24·0%)	5·1 (1·1)	717 (96·7%)	1 (0·1%)	1·4 (0·8)
≥ 65 years	33 (5·5%)	3·9 (3·3)	10 (30·3%)	6·8 (2·7)	566 (94·5%)	12 (2·1%)	1·7 (0·9)
ASA score							
< 3	22 (3·0%)	2·9 (1·4)	8 (36·4%)	5·5 (2·0)	694 (97·0%)	3 (0·4%)	1·4 (0·8)
≥ 3	36 (5·8%)	3·6 (3·1)	8 (22·2%)	6·4 (2·3)	581 (94·2%)	10 (1·7%)	1·6 (0·9)

ICU: intensive care unit; LOS: length of stay

Data are mean (SD) or number (%)

* For some characteristics numbers do not add up to the total number of patients because of missing values

eTable 8 – Incidence of postoperative lung injury and its characteristics in patients undergoing abdominal surgery*

	Postoperative Lung Injury				No-Postoperative Lung Injury		
	Number of Patients	Onset (days)	Mortality	ICU LOS (days)	Number of Patients	Mortality	ICU LOS (days)
All patients	64 (3·4%)	2·3 (0·9)	9 (14·1%)	9·0 (14·5)	1798 (96·6%)	32 (1·8)	1·0 (4·1)
Ventilation							
Conventional ventilation	40 (6·0%)	2·2 (1·0)	5 (12·5%)	11·1 (12·6)	620 (94·0%)	13 (2·1)	0·9 (3·2)
Protective ventilation	24 (1·9%)	2·4 (0·8)	4 (16·7%)	6·2 (16·7)	1178 (98·1%)	19 (1·6)	1·2 (4·9)
Age							
< 65 years	22 (2·4%)	2·2 (0·9)	0 (0·0%)	4·9 (7·4)	884 (97·6%)	7 (0·8)	0·6 (2·9)
≥ 65 years	42 (4·3%)	2·3 (1·0)	9 (21·4%)	11·6 (17·3)	914 (95·7%)	25 (2·7)	1·5 (5·1)
ASA score							
< 3	31 (3·7%)	2·2 (1·0)	1 (3·2%)	3·5 (6·5)	797 (96·3%)	7 (0·9)	0·9 (4·7)
≥ 3	24 (3·9%)	2·5 (0·5)	5 (20·8%)	10·0 (16·8)	577 (96·1%)	14 (2·4)	1·8 (5·1)

ICU: intensive care unit; LOS: length of stay

Data are mean (SD) or number (%)

* For some characteristics numbers do not add up to the total number of patients because of missing values

eTable 9 – Characteristics of patients with postoperative lung injury

	Total (*n* = 123)	**Survivors (*n* = 98)**	**Non-Survivors (*n* = 25)**	***p* value**
Age (years)	66·39 (11·58)	65·14 (11·96)	71·24 (8·52)	0·018
Male	78 (63·4%)	61 (62·2%)	17 (68·0%)	0·635
ASA	2·58 (0·65)	2·54 (0·63)	2·72 (0·70)	0·252
BMI (kg/m^2)	26·14 (4·79)	26·24 (4·92)	25·74 (4·36)	0·643
Ventilation¶				
Tidal volume (ml/kg PBW)	9·34 (2·14)	9·33 (2·12)	9·36 (2·29)	0·943
PEEP (cmH_2O)	2·86 (3·43)	2·88 (3·60)	2·80 (2·70)	0·911
Respiratory rate (mpm)	11·71 (2·17)	11·40 (2·26)	10·66 (1·63)	0·450
FiO_2 (%)	40·56 (4·21)	55·55 (22·36)	57·11 (25·02)	0·845
Duration of ventilation (hours)	30·35 (75·50)	29·80 (78·95)	34·13 (47·81)	0·867
ICU length of stay (days)	8·17 (12·55)	8·34 (13·23)	7·00 (6·37)	0·793
Hospital length of stay (days)	20·91 (18·08)	20·33 (17·42)	23·16 (20·66)	0·489

ASA: American Society of Anesthesiology; BMI: body-mass index; PBW: predicted bodyweight; PEEP: positive end-expiratory pressure; mpm: movements per minute; FiO_2:fractional concentration of oxygen in inspired air; PaO_2: arterial partial pressure of oxygen; $PaCO_2$: arterial partial pressure of carbon dioxide; ICU: intensive-care unit

Data are mean (SD) or number (%)

¶ During surgery

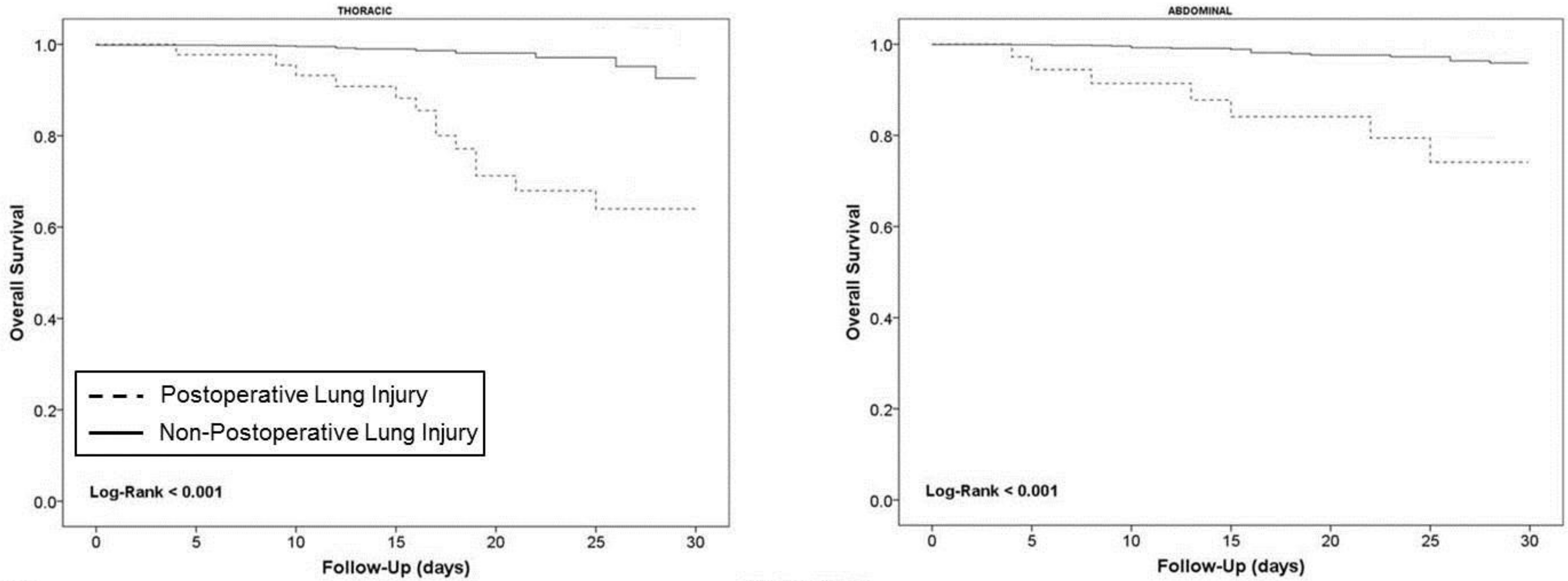
eTable 10 – Characteristics of the patients with postoperative lung injury under protective or conventional ventilation

	General (*n* = 122)			Thoracic (*n* = 58)			Abdominal (*n* = 64)		
	Protective (*n* = 40)	Conventional (*n* = 82)	*p*	Protective (*n* = 16)	Conventional (*n* = 42)	*p*	Protective (*n* = 24)	Conventional (*n* = 40)	*p*
Age (years)	64·3 (14·0)	67·4 (10·2)	0·169	63·2 (14·3)	67·0 (8·4)	0·215	65·0 (14·0)	67·8 (11·9)	0·407
Male	28 (70·0%)	50 (61·0%)	0·330	11 (71·0%)	28 (67·0%)	0.138	16 (66·0%)	29 (72·0%)	0.455
ASA	2·58 (0·7)	2·58 (0·6)	0·947	2·8 (0·5)	2·7 (0·7)	0·523	2·4 (0·7)	2·4 (0·6)	0·988
BMI (kg/m^2)	25·7 (5·3)	26·3 (4·5)	0·496	25·4 (5·5)	25·0 (3·9)	0·752	26·0 (5·3)	27·9 (4·7)	0·144
Ventilation¶									
Tidal volume (ml/kg PBW)	7·4 (1·3)	10·3 (1·8)	< 0·001	7·2 (1·9)	10·4 (2·1)	< 0·001	7·5 (0·6)	10·2 (1·3)	< 0·001
PEEP (cmH$_2$O)	5·7 (3·9)	1·5 (2·1)	< 0·001	2·6 (1·5)	1·3 (1·6)	0·008	7·8 (3·6)	1·6 (2·5)	< 0·001
Respiratory rate (mpm)	13·1 (2·4)	10·8 (1·4)	< 0·001	13·5 (1·6)	10·9 (1·3)	< 0·001	12·9 (2·8)	10·7 (1·5)	< 0·001
FiO$_2$ (%)	40·0 (4·4)	41·0 (4·1)	0·396	38·5 94·6)	41·4 (5·0)	0·068	55·6 (22·1)	55·8 (23·1)	0·968
Oxygenation¶									
Arterial pH	7·32 (0·11)	7·14 (0·16)	0·165	---	---	---	7·38 (0·01)	7·45 (0·03)	0·495
PaO$_2$:FiO$_2$	258·5 (103·7)	317·0 (181·1)	0·367	---	---	---	247·1 (104·6)	345·7 (257·1)	0·318
PaCO$_2$ (mmHg)	35·5 (3·5)	42·1 (3·15)	0·204	---	---	---	37·1 (0·2)	30·5 (4·0)	0·081
Duration of ventilation (hours)	28·8 (70·3)	31·1 (78·4)	0·904	---	---		29·9 (71·6)	40·4 (89·5)	0·626
ICU length of stay (days)	6·1 (16·2)	9·2 (10·3)	0·393	---	---		6·3 (16·7)	11·1 (12·6)	0·296
Hospital length of stay (days)	21·2 (24·1)	20·8 (14·6)	0·905	20·1 (5·4)	21·0 (10·2)	0·737	22·0 (31·3)	20·6 (18·2)	0·820
In-Hospital Mortality (%)	8 (20·0%)	17 (20·7%)	0·925	4 (25·0%)	12 (28·6%)	0·786	4 (16·7%)	5 (12·5%)	0·642

ASA: American Society of Anesthesiology; BMI: body-mass index; PBW: predicted bodyweight; PEEP: positive end-expiratory pressure; mpm: movements per minute; FiO$_2$:fractional concentration of oxygen in inspired air; PaO$_2$: arterial partial pressure of oxygen; PaCO$_2$: arterial partial pressure of carbon dioxide; ICU: intensive-care unit

Data are mean (SD) or number (%)¶ During surgery

eFigure 1 – In-hospital mortality in patients who developed or not postoperative lung injury in thoracic or abdominal surgery



Number at Risk (Thoracic)

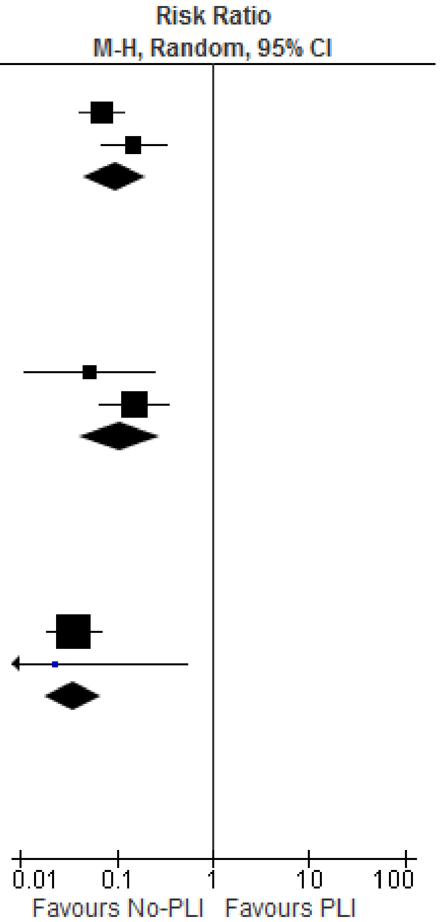
	0	5	10	15	20	25	30
Non-ARDS	1,191	980	586	236	92	44	11
ARDS	51	43	40	33	21	13	05

Number at Risk (Abdominal)

	0	5	10	15	20	25	30
Non-ARDS	1,591	1,120	655	401	277	211	96
ARDS	38	31	25	22	17	15	08

eFigure 2 – Interaction between mortality and design of the study

Study or Subgroup	No-PLI Events	No-PLI Total	PLI Events	PLI Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Overall Mortality						
No-RCT	28	1456	18	64	57.1%	0.07 [0.04, 0.12]
RCT	29	1627	7	58	42.9%	0.15 [0.07, 0.32]
Subtotal (95% CI)		**3083**		**122**	**100.0%**	**0.10 [0.04, 0.20]**
Total events	57		25			
Heterogeneity: Tau² = 0.18; Chi² = 2.56, df = 1 (P = 0.11); I² = 61%						
Test for overall effect: Z = 6.14 (P < 0.00001)						
1.2.2 Mortality in Abdominal Surgery						
No-RCT	3	408	3	21	30.7%	0.05 [0.01, 0.24]
RCT	29	1390	6	43	69.3%	0.15 [0.07, 0.34]
Subtotal (95% CI)		**1798**		**64**	**100.0%**	**0.11 [0.04, 0.28]**
Total events	32		9			
Heterogeneity: Tau² = 0.17; Chi² = 1.43, df = 1 (P = 0.23); I² = 30%						
Test for overall effect: Z = 4.53 (P < 0.00001)						
1.2.3 Mortality in Thoracic Surgery						
No-RCT	13	1048	15	43	95.6%	0.04 [0.02, 0.07]
RCT	0	237	1	15	4.4%	0.02 [0.00, 0.53]
Subtotal (95% CI)		**1285**		**58**	**100.0%**	**0.03 [0.02, 0.07]**
Total events	13		16			
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%						
Test for overall effect: Z = 9.94 (P < 0.00001)						



eFigure 3 – Interaction between outcome and excluded studies

Study or Subgroup	Protective Ventilation Events	Protective Ventilation Total	Conventional Ventilation Events	Conventional Ventilation Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Postoperative Lung Injury						
Excluded Studies	4	76	10	76	10.7%	0.40 [0.13, 1.22]
Our Analysis	37	1799	75	1116	89.3%	0.31 [0.21, 0.45]
Subtotal (95% CI)		**1875**		**1192**	**100.0%**	**0.31 [0.22, 0.45]**
Total events	41		85			
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.66); I² = 0%						
Test for overall effect: Z = 6.20 (P < 0.00001)						
1.1.2 Mortality						
Excluded Studies	2	88	3	89	6.4%	0.67 [0.12, 3.94]
Our Analysis	37	1799	34	1116	93.6%	0.68 [0.43, 1.07]
Subtotal (95% CI)		**1887**		**1205**	**100.0%**	**0.68 [0.43, 1.05]**
Total events	39		37			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%						
Test for overall effect: Z = 1.73 (P = 0.08)