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# Interaction between peri-operative blood transfusion, tidal volume, airway pressure and postoperative ARDS: an individual patient data meta-analysis

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**Background:** Transfusion of blood products and mechanical ventilation with injurious settings are considered risk factors for postoperative lung injury in surgical Patients.

**Methods:** A systematic review and individual patient data meta-analysis was done to determine the independent effects of peri-operative transfusion of blood products, intra-operative tidal volume and airway pressure in adult patients undergoing mechanical ventilation for general surgery, as well as their interactions



on the occurrence of postoperative acute respiratory distress syndrome (ARDS). Observational studies and randomized trials were identified by a systematic search of MEDLINE, CINAHL, Web of Science, and CENTRAL and screened for inclusion into a meta-analysis. Individual patient data were obtained from the corresponding authors. Patients were stratified according to whether they received transfusion in the peri-operative period [red blood cell concentrates (RBC) and/or fresh frozen plasma (FFP)], tidal volume size [ $\leq 7$  mL/kg predicted body weight (PBW), 7–10 and  $>10$  mL/kg PBW] and airway pressure level used during surgery ( $\leq 15$ , 15–20 and  $>20$  cmH<sub>2</sub>O). The primary outcome was development of postoperative ARDS.

**Results:** Seventeen investigations were included (3,659 patients). Postoperative ARDS occurred in 40 (7.2%) patients who received at least one blood product compared to 40 patients (2.5%) who did not [adjusted hazard ratio (HR), 2.32; 95% confidence interval (CI), 1.25–4.33;  $P=0.008$ ]. Incidence of postoperative ARDS was highest in patients ventilated with tidal volumes of  $>10$  mL/kg PBW and having airway pressures of  $>20$  cmH<sub>2</sub>O receiving both RBC and FFP, and lowest in patients ventilated with tidal volume of  $\leq 7$  mL/kg PBW and having airway pressures of  $\leq 15$  cmH<sub>2</sub>O with no transfusion. There was a significant interaction between transfusion and airway pressure level ( $P=0.002$ ) on the risk of postoperative ARDS.

**Conclusions:** Peri-operative transfusion of blood products is associated with an increased risk of postoperative ARDS, which seems more dependent on airway pressure than tidal volume size.

**Keywords:** Acute respiratory distress syndrome (ARDS); surgery; transfusion; tidal volume, ventilator-associated lung injury

## Introduction

Transfusion of blood products is a well-known risk factor for acute respiratory distress syndrome (ARDS) in both critically and non-critically ill patients (1-6). Peri-operative transfusion of blood products is also recognized as a risk factor for pulmonary complications after surgery (7-9). Remarkably, while half of all issued blood products are transfused peri-operatively (7-9), the number of studies investigating the association with postoperative pulmonary complications is low.

Mechanical ventilation using high tidal volumes and/or high airway pressures is associated with worse outcomes in patients with ARDS and probably also in patients who do not meet ARDS criteria at the onset of ventilation (10,11). Numerous studies in surgical patients suggest that even short-term intra-operative ventilation with higher tidal volumes and/or higher airway pressures increased the risk for postoperative pulmonary complications and prolonged duration of ventilation and hospital stay (11,12).

It is conceivable that an interaction between the effects of peri-operative transfusion and higher tidal volumes and/or higher airway pressures during surgery on the development of postoperative ARDS exists. Lung

injury following transfusion may occur via a ‘double hit mechanism’, in which the first hit primes pulmonary neutrophils and endothelium (3). Mediators in transfused blood products then could serve as a second hit by a further activation of neutrophils and the endothelial cells, finally resulting in lung capillary permeability and subsequent pulmonary edema (3). Observational studies have shown that mechanical ventilation and high peak airway pressure are risk factors for the development of lung injury following transfusion in critically ill patients (13,14). The interaction between transfusion and ventilation parameters in patients with healthy lungs under anesthesia for surgery has never been assessed.

We hypothesized that peri-operative transfusion is associated with the development of postoperative ARDS, and that this association is dependent on the tidal volume size and/or airway pressure level during intra-operative ventilation of patients under anesthesia for surgery.

## Methods

The full methodology of the present meta-analysis is available in the Supplement I. The statistical analysis plan has been published previously (15).

### ***Search strategy***

A search strategy followed Medical Subject Headings and Keywords (*protective ventilation OR lower tidal volume OR low tidal volume OR positive end-expiratory pressure OR PEEP*).

### ***Selection of studies***

Observational studies or randomized controlled trials of ‘protective’ intra-operative ventilation using lower tidal volumes identified by the search and reporting outcomes of interest were screened for inclusion. Inclusion criteria were: use of lower versus higher tidal volume and/or use of higher versus lower PEEP in each arm; adults (i.e., age >18 years); and patients receiving ventilation in the setting of general anesthesia for surgery. Investigations were excluded from this meta-analysis if they: (I) included patients with pre-existing ARDS; or (II) reported on patients receiving ventilation in a non-surgical setting (i.e., in the intensive care unit).

### ***Transfusion and ventilation parameters***

After approval, corresponding authors of retrieved studies or trials were asked to send information on ventilation parameters obtained hourly during the surgical procedure. In addition to ventilatory parameters, authors were asked to provide the number and types of transfusions during the surgical procedure. A blood transfusion was defined as the infusion of red blood cell (RBC) and/or fresh frozen plasma (FFP) in the perioperative period. The blood products were counted as units since we could not collect data regarding volumes of units.

### ***Primary outcome***

The primary outcome was development of postoperative ARDS during follow-up.

### ***Secondary outcomes***

Secondary outcomes included: in-hospital mortality; duration of postoperative ventilation; development of pulmonary infection; postoperative intensive care unit (ICU) length of stay; and hospital length of stay.

### ***Statistical analysis***

All analyses were conducted according to the presence

or not of any transfusion during the perioperative period (RBC and/or FFP). In addition, patients were stratified according to the transfusion or not of RBC or FFP, to the transfusion of  $\geq 3$  units RBC or  $< 3$  units of RBC, and to transfusion both products (i.e., RBC and FFP), according to the tidal volume size used during intra-operative ventilation [ $\leq 7$  mL/kg predicted body weight (PBW), 7–10 and  $> 10$  mL/kg PBW], and the resulting airway pressures ( $\leq 15$ , 15–20 and  $> 20$  cmH<sub>2</sub>O).

Time-to-event was defined as time from day of surgery to the event, reported in days. Cox proportional-hazards regression models were used to examine simultaneous effects of multiple covariates on outcomes. Patient’s data at the time of death, hospital discharge, or after 30 days were censored. Categorical outcome variables were tested for trend with the no-transfusion group as reference. The proportional-hazards assumption was assessed. Pairs of variables in the final model were tested for interaction. The effect of each variable in these models was assessed with the Wald test and reported using hazard ratio (HR) with 95% confidence interval (CI). Kaplan-Meier curves and log-rank tests were used to determine the univariate significance of the study variables.

*A priori* subgroup analyses were: (I) type of study (observational study *vs.* randomized controlled trial); (II) ASA score ( $< 3$  *vs.*  $\geq 3$  and for each level); (III) presence of risk factors for ARDS (yes or no and defined as pneumonia, shock, and sepsis); (IV) type of surgery (cardiac, abdominal, thoracic, and orthopedic); (V) age ( $< 65$  *vs.*  $\geq 65$  years); and (VI) sex (male *vs.* female).

Analyses were done with SPSS v.20 or R v.2.12.0. A two-sided P value  $< 0.05$  was considered significant.

## **Results**

### ***Search result and collection of individual patient data***

Three observational studies and 21 randomized controlled trials of ‘protective’ intra-operative ventilation were identified (12,16–38). We were not able to collect data from one observational study and six randomized controlled trials due to the following reasons: the corresponding author could not provide data (n=4) (32–35) or no contact could be made with the corresponding author (n=3) (36–38). The total enrollment based on the observational studies and randomized controlled trials for which individual patient data could be collected was 3,659 patients (*Figure S1, Tables S1,S2*) (9–25).

**Table 1** Baseline characteristics of patients according to transfusion or not<sup>1</sup>

Variables	No transfusion (n=1,786)	Any transfusion* (n=644)	P**	≥01 unit of RBC (n=628)	≥01 unit of FFP (n=167)
Age, years	63.0±13.2	63.4±12.5	0.447	63.5±12.5	61.2±12.7
Gender, female	656 (36.7)	245 (38.0)	0.554	239 (38.1)	62 (37.1)
BMI, kg/m <sup>2</sup>	26.3±5.1	26.0±5.0	0.108	26.0±5.0	25.8±4.2
Design of the study, RCT	1,465 (82.0)	536 (83.2)	0.492	520 (82.8)	151 (90.4)
ASA					
Mean	2.3±0.7	2.4±0.7	0.101	2.4±0.7	2.3±0.7
1	124 (9.3)	56 (10.9)	0.341	55 (10.9)	20 (14.4)
2	633 (47.4)	204 (39.8)	0.003	202 (40.2)	64 (46.0)
3	520 (39.0)	225 (43.9)	0.061	218 (43.3)	53 (38.1)
4	57 (4.3)	28 (5.5)	0.31	28 (5.6)	2 (1.40)
5	1 (0.1)	0 (0.0)	0.802	0 (0.0)	0 (0.0)
Type of surgery					
Cardiac	129 (7.2)	106 (16.5)	0.001	94 (15.0)	27 (16.2)
Thoracic	84 (4.7)	128 (19.9)	0.001	128 (20.4)	48 (28.7)
Abdominal	1,557 (87.2)	402 (62.4)	0.001	398 (63.4)	91 (54.5)
Orthopedic	16 (0.9)	8 (1.2)	0.667	8 (1.3)	1 (0.6)
Risk factor for ARDS, yes	157 (8.8)	69 (10.7)	0.431	69 (11.0)	16 (9.60)
Tidal volume, mL/kg PBW	8.5±1.8	8.5±2.2	0.712	8.5±2.2	8.3±1.6
Units of					
RBC	–	4.0±4.1	0.001	4.1±4.1	5.6±5.2
FFP	–	1.7±3.4	0.001	1.6±3.5	4.2±4.4

<sup>1</sup>, plus-minus values are mean ± SD and other values are n (%); \*, at least one unit of red blood cell and/or fresh frozen plasma; \*\*, no transfusion vs. any transfusion (Student's *t*-test). RBC, red blood cell; FFP, fresh-frozen plasma; RCT, randomized controlled trial; ARDS, acute respiratory distress syndrome; PBW, predicted body weight.

*Table 1* details the distribution of demographic characteristics according to the presence or absence of transfusion and the number of units transfused. One thousand seventy-hundred eight-six patients did not receive any transfusion, and 644 patients received at least one transfusion. The distribution of the prevalence of risk factors for ARDS, the mean ASA, and the tidal volume was similar in the all groups.

Six hundred twenty-eight patients received at least one unit of RBC and one hundred sixty-seven patients received at least one unit of FFP. The number of units of RBC and FFP according to type of surgery are shown in *Figure S2* and the percentage of patients transfused with RBC or FFP according to the type of surgery are shown in *Figure S3*.

### **Predictors of transfusion**

The probability of any transfusion was predicted by higher ASA, presence of shock, sepsis and/or pneumonia (risk factors for ARDS) and by the type of surgery (cardiac and thoracic). The probability of transfusion of at least one unit of RBC was also predicted by higher ASA, presence of risk factor for ARDS and by the type of surgery (cardiac and thoracic). The probability of transfusion of at least one unit of FFP was predicted solely by the type of surgery (cardiac and thoracic) (*Table 2*).

### **Primary outcome**

Postoperative ARDS occurred in 40 (7.2%) patients



**Table 2** Predictors of transfusion in all patients undergoing surgery<sup>†</sup>

Risk factors	Any transfusion*	≥01 unit of RBC	≥01 unit of FFP
Age, years	0.99 (0.99–1.00)	0.99 (0.99–1.00)	0.99 (0.98–1.01)
Gender, male	0.89 (0.70–1.13)	0.90 (0.71–1.14)	0.82 (0.52–1.28)
BMI, kg/m <sup>2</sup>	1.00 (0.98–1.02)	1.00 (0.98–1.03)	1.01 (0.97–1.05)
ASA	1.21 (1.04–1.42)	1.19 (1.01–1.40)	1.21 (0.84–1.73)
Risk factor for ARDS, no	0.02 (0.01–0.05)	0.02 (0.01–0.05)	0.79 (0.56–1.57)
Surgery			
Abdominal (reference)	1.00	1.00	1.00
Thoracic	5.81 (4.21–8.01)	5.94 (4.30–8.20)	5.31 (3.87–7.81)
Orthopedic	1.74 (0.71–4.28)	1.79 (0.73–4.40)	1.54 (0.65–3.48)
Cardiac	8.16 (5.02–13.27)	6.13 (3.81–9.86)	7.22 (5.75–10.93)

<sup>†</sup>, values are hazard ratio (95% confidence interval); \*, at least one unit of red blood cell and/or fresh frozen plasma. RBC, red blood cell; FFP, fresh-frozen plasma.

**Table 3** Risk for the development of ARDS with transfusion of blood products

Blood products	ARDS		In-hospital mortality		Pulmonary infection	
	Unadjusted	Adjusted*	Unadjusted	Adjusted*	Unadjusted	Adjusted*
Any transfusion	2.41 (1.40–4.15)	2.32 (1.25–4.33)	2.15 (1.20–3.86)	0.72 (0.23–2.26)	2.47 (1.77–3.45)	1.53 (0.96–2.43)
Transfusion of RBC	2.47 (1.43–4.26)	2.36 (1.27–4.41)	2.22 (1.24–3.99)	0.73 (0.23–2.31)	2.39 (1.71–3.35)	1.56 (0.98–2.49)
Transfusion of FFP	3.78 (2.56–5.43)	3.52 (2.88–5.01)	3.45 (1.45–8.19)	0.75 (0.30–2.19)	1.09 (0.78–2.21)	1.13 (0.51–2.52)
Transfusion of ≥03 units of RBC	3.61 (2.04–6.39)	4.28 (2.23–8.21)	3.73 (1.96–7.09)	0.65 (0.15–2.92)	2.81 (1.92–4.10)	1.63 (0.95–2.77)
Transfusion of RBC and FFP	14.94 (9.82–22.33)	8.63 (6.09–14.65)	3.53 (1.47–8.50)	1.08 (0.12–9.55)	3.61 (2.22–5.88)	1.21 (0.54–2.71)

\*, adjusted by: type of study, age, ASA, presence of risk factor, tidal volume, highest PEEP, highest plateau pressure, and highest compliance. ARDS, acute respiratory distress syndrome; RBC, red blood cell; FFP, fresh frozen plasma.

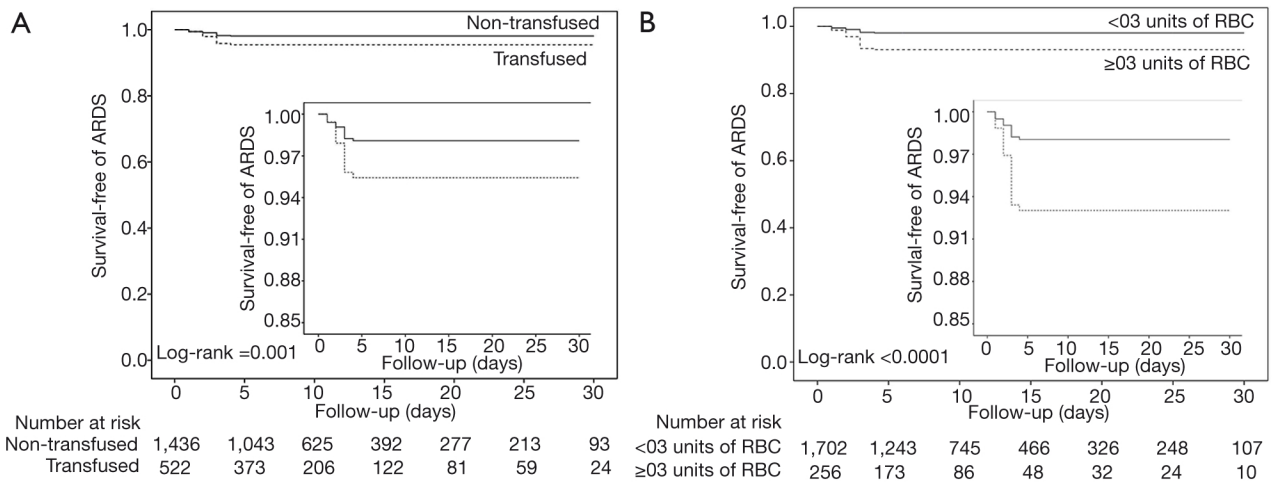
who received at least one blood product compared to 40 patients (2.5%) not transfused (adjusted HR, 2.32; 95% CI, 1.25–4.32; P=0.008) (Table 3, Figure 1A). Postoperative ARDS occurred in 29 (10.7%) patients who received more than 3 units RBC compared to 51 patients (2.7%) who received less than three units RBC (adjusted HR, 4.28; 95% CI, 2.23–8.21; P<0.0001) (Table 3, Figure 1B). The risk of ARDS was higher in patients who received at least one unit of FFP (adjusted HR, 3.52; 95% CI, 2.88–5.01; P=0.003), in patients who received at least one unit of RBC (adjusted HR, 2.36; 95% CI, 1.27–4.41; P=0.007) and in patients who received transfusion of both RBC and FFP (adjusted HR, 8.63; 95% CI, 6.09–14.65; P<0.001) (Table 3, Figure S4).

Incidence of ARDS was higher in patients ventilated with tidal volumes >10 mL/kg PBW and receiving RBC and FFP compared to patients ventilated with tidal volume ≤7 mL/kg PBW receiving no transfusion (42.9% vs. 1.0%; P<0.001) (Figure 2A), and higher in patients with airway pressures >20 cmH<sub>2</sub>O and receiving RBC and FFP compared to patients with airway pressures ≤15 cmH<sub>2</sub>O receiving no transfusion (25% vs. 1.4%; P<0.001) (Figure 2B).

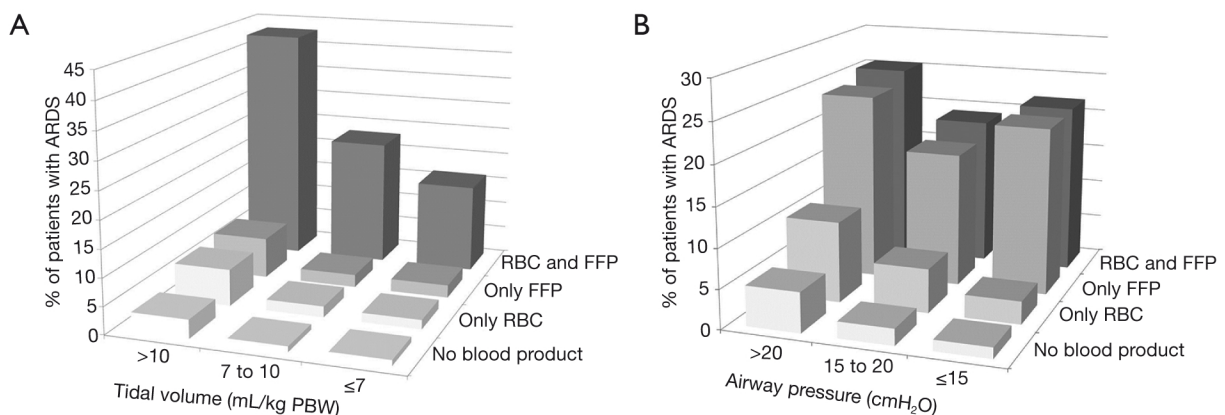
### Secondary outcomes

The crude mortality was lower in patients who were not transfused. However, after adjustment for baseline





**Figure 1** Kaplan-Meier estimates of the probability of the primary outcome. Data for the Kaplan-Meier estimates of the probability of the primary outcome of postoperative ARDS in (A) patients not transfused (black solid line), and patients who received at least one unit of blood product (black dotted line), and (B) patients who received less than three units of RBC (black solid line), and patients who received more than three units of RBC (black dotted line). Data were censored at 30 days after surgery. ARDS, acute respiratory distress syndrome; RBC, red blood cell.

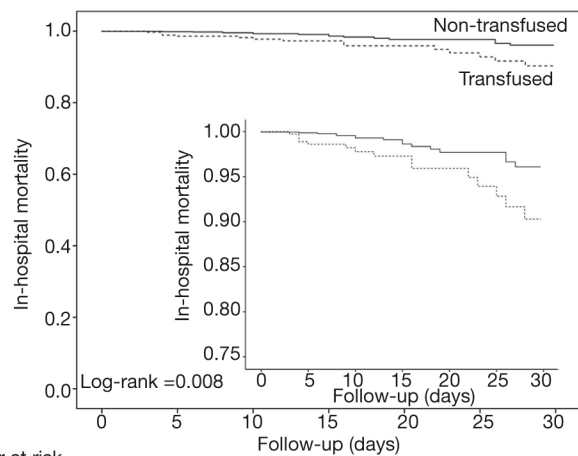


**Figure 2** Incidence of postoperative ARDS according to (A) tidal volume size used during general anesthesia, transfusion and type of blood products; and (B) plateau pressure used during general anesthesia and transfusion and type of blood products. ARDS, acute respiratory distress syndrome; RBC, red blood cell; FFP, fresh frozen plasma; PBW, predicted body weight.

covariates, there was no difference in in-hospital mortality in patients who received or not any transfusion (Table 3, Figure 3), received any RBC, at least 3 units of RBC or any FFP (Table 3, Figure S5). There was no correlation between having received any transfusion and development of pulmonary infection (Table 3). Duration of postoperative mechanical ventilation and ICU length of stay was higher in patients who were transfused compared to those who were not transfused ( $828.6 \pm 2,094.3$  vs.  $382.9 \pm 809.3$  minutes;  $P < 0.001$ ; and  $2.5 \pm 5.5$  vs.  $1.1 \pm 3.9$  days;

$P < 0.001$ , respectively) (Figure S6). Hospital length of stay was similar in the two groups ( $14.6 \pm 15.8$  vs.  $15.5 \pm 17.5$  days;  $P = 0.265$ ).

Patients who developed postoperative ARDS had received more units of RBC ( $3.0 \pm 4.3$  vs.  $1.0 \pm 2.8$  units;  $P < 0.001$ ) and FFP ( $3.1 \pm 3.0$  vs.  $0.4 \pm 1.9$  units;  $P < 0.001$ ) compared to those who did not developed postoperative ARDS (Figure S7). The percentage of patients who developed ARDS according to the number of units of RBC and FFP transfused are shown in Figure S8.



**Figure 3** Kaplan-Meier estimates of the probability of in-hospital mortality. Data for the Kaplan-Meier estimates of the probability of the secondary outcome of in-hospital mortality in patients not transfused (black solid line), and patients who received at least one unit of blood product (black dotted line). Data were censored at 30 days after surgery.

### Pre-specified subgroup analyses

While there was trend for interaction on the effects of transfusion on primary outcome according to tidal volume size ( $P=0.070$  for interaction), there was a significant interaction on primary outcome between transfusion and airway pressure used during surgery ( $P=0.002$ ). There was no significant interaction according to the other prespecified subgroup analyses, like of ASA score ( $P=0.340$ ), type of surgery ( $P=0.320$ ), and sex ( $P=0.310$ ) (Figure 4).

## Discussion

This individual patient meta-analysis of 3,659 patients who received ventilation during general anesthesia for surgery from 17 clinical studies found evidence for a strong association between peri-operative transfusion of blood products and the incidence of postoperative ARDS independently from the severity of the disease. There was a trend for interaction between blood transfusion and the intra-operative tidal volume, and a significant interaction between blood transfusion and the airway pressure on the development of postoperative ARDS.

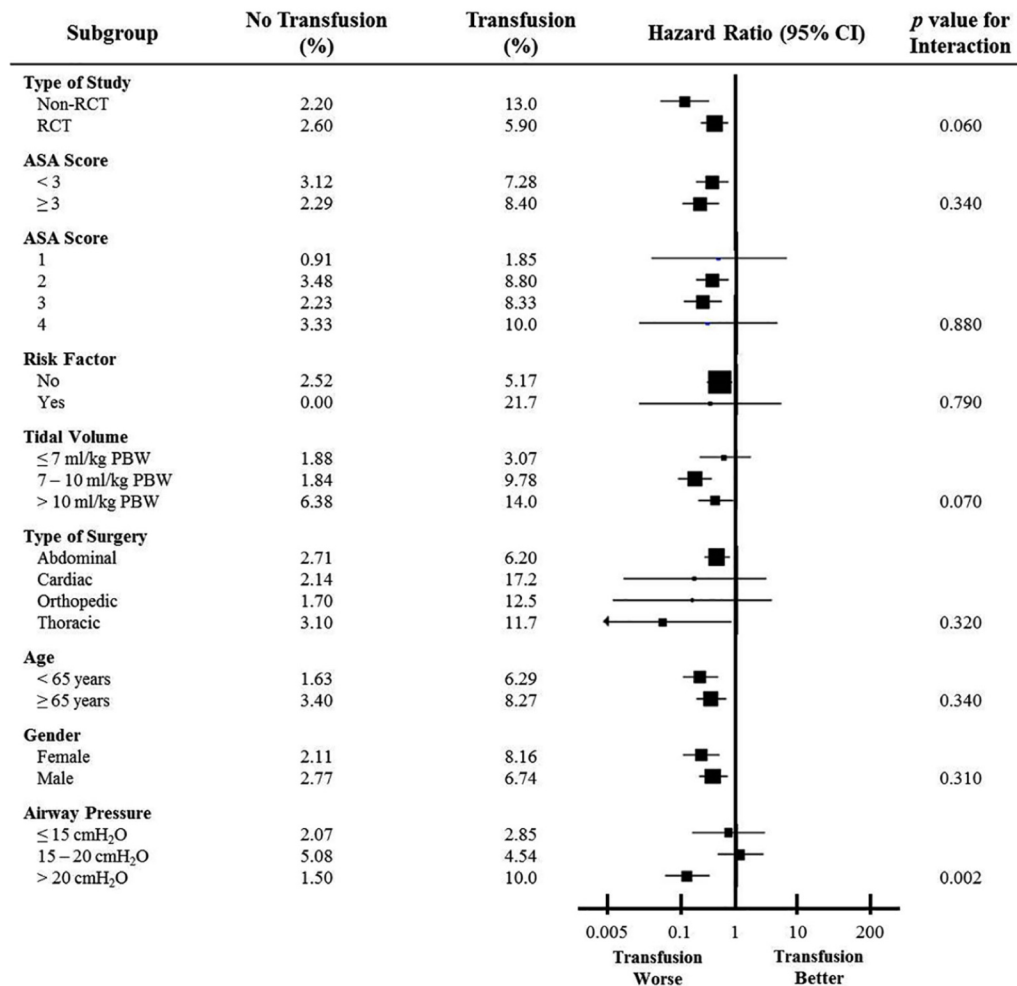
The results of this meta-analysis expand our knowledge on the association between transfusion and ARDS. A significantly higher odds of ARDS was found in critically

ill medical patients who received blood transfusion (1). Higher risk of ARDS was also found in critically ill patients who received ventilation for more than 48 hours (5,39) and in trauma patients (4,40). Moreover, two randomized controlled trials, one in critically ill patients (41) and one in trauma patients (42) showed that a restrictive transfusion compared to liberal transfusion was associated with a lower incidence of ARDS. Thus, blood transfusion is associated with ARDS development in almost all subgroup of non-surgical patients.

Studies of transfusion and postoperative ARDS in surgical patients are scarce, and most studies were in cardiac surgery patients (9,43-45). In cardiac surgery, a restrictive transfusion strategy compared to a more liberal strategy resulted in similar rates of mortality and severe morbidity while use of blood products was less (43-45). Also, RBC transfusion is an independent risk factor for increased hospital length of stay in those patients undergoing cardiac surgery (46). The present meta-analysis of studies in general surgery patients, at least in part confirms the findings in cardiac surgery patients by showing a strong association between transfusion of blood products and postoperative ARDS, which holds for all types of surgery.

A two-hit hypothesis has been proposed for lung injury after transfusion (47). The first hit results in priming of granulocytes and adherence to the pulmonary endothelium. Then, the second hit is caused by mediators in the blood transfusion, which activate the endothelial cells and pulmonary granulocytes, resulting in pulmonary permeability and lung edema (3,47). Studies suggest that mechanical ventilation with higher tidal volume and higher airway pressures stretch the lung and results in priming of pulmonary granulocytes or endothelium making the lung susceptible to the second hit of blood transfusion (13,14,48).

Lung injury following transfusion can occur after any type of blood product (49). Plasma-rich products including platelets and FFP have been the most commonly implicated blood products (13,50,51) and FFP is usually associated with the most severe pulmonary reactions. We were not able to study effects of platelet transfusions due to problems in the report from corresponding authors. We did find in this study that the risk of lung injury was somewhat higher following FFP compared to RBC, but risk of RBC was also considerable. In line with this, several studies found a significant relationship between transfusion of RBC and pulmonary complications in general patients (41-46,52,53). Of note, we found that this relationship was dependent on the amount of transfusion, which has also been reported



**Figure 4** Hazard ratios for study outcomes according to subgroup. The size of the squares is proportional to the number of patients in the subgroup.

before (14,45,46). These data suggest that restrictive use of FFP and RBCs should be advocated whenever possible.

Since high tidal volume can be a first hit to the lung, it has been proposed that the use of ventilation with lower tidal volumes could be protective against lung injury induced by blood transfusion (3). Here we present for the first time the effect of blood transfusion on postoperative ARDS in patients ventilated with a variety of tidal volumes during general surgery. While there was only a trend for interaction between tidal volume and transfusion on ARDS development, a significant interaction between transfusion and airway pressure was found as a risk factor for ARDS. Thus, limiting tidal volume size, but especially airway pressure with intra-operative ventilation may mitigate the risk of lung injury induced by blood transfusion.

The stronger association between blood transfusion

and airway pressure, as compared to transfusion and tidal volume, is remarkable. Recent studies suggest that increases in pulmonary vascular pressure as induced by mechanical ventilation are injurious. Cyclic changes in pressure in the tissue surrounding extra-alveolar vessels may be important in the pathogenesis of ventilator-induced lung injury (54). Also, increases in alveolar pressure are associated with increased damage in the vascular bed, promoting damage of endothelial cells and contributing to lung hemorrhage and permeability alterations induced by mechanical ventilation (55).

The present study has some limitations. First, from seven studies, not all original data could be retrieved (32-38). Second, we do not have information on some other factors that could have contributed to lung injury, including fluid balance and recruitment maneuvers. Third,



we were not able to assess the reasons for blood transfusion. Fourth, different types of surgery were included. However, no interaction was found between type of surgery and primary outcome according to the prespecified subgroup analyses. Finally, blood transfusion may be collinear with other unmeasured aspects of severity of illness or treatment management.

## Conclusions

In conclusion, this individual patient data meta-analysis suggests that transfusion of blood products (RBC and/or FFP) is strongly associated with postoperative ARDS in surgical patients. Non-protective ventilation settings, mainly high airway pressures, were found as a risk factor for postoperative ARDS together with blood transfusion.

## Acknowledgements

None.

## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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### ***Search strategy***

Published studies were retrieved by directly contact with all corresponding authors from published studies on protective ventilation in surgery. This was achieved by the inclusion of the primary studies of a recent regular systematic review and meta-analysis by our group. In addition, the list of studies was updated to identify more recent studies. For this, two authors performed a computerized blinded search of MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) up to April 2013. 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*). All reviewed articles and cross-referenced studies from retrieved articles were screened for pertinent information.

### ***Selection of studies***

All observational studies and randomized controlled trials (RCT) that reported outcomes in patients ventilated with lower  $V_T$  in one arm and in those ventilated with higher  $V_T$  in another were screened for inclusion. Key inclusion criteria are: (I) lower versus higher  $V_T$  in each arm; (II) age >18 years; (III) patients undergoing any surgical procedures under general anesthesia and MV; and (IV) patients without ARDS at the onset of MV. Studies overlapping with other studies as indicated by the corresponding author were excluded. There was no restriction of study design or language.

### ***Methodological quality assessment***

Two investigators carried out the data extraction and quality assessment from all the retrieved published studies based on the full text articles. Discrepancies were resolved by consensus. In RCTs, we assessed allocation concealment, baseline similarity of groups (with regard to age, and severity of illness), early stopping of treatment, and lost to follow-up. Also, Jadad score was used to assess the quality of the RCTs.

### ***Collection of individual patient data***

Corresponding authors of the identified eligible published studies were contacted via email with a cover letter detailing the objectives of the collaborative meta-analysis, background information, and a datasheet for input of individual patient results for the project. The cover letter and the datasheet are shown below. The filled-out data templates was sent back to the principal investigator and further communication was mainly by email. Corresponding authors were also contacted about unpublished data to enlarge the clinical data pool.

### ***Data management, security and validation***

The same two investigators who performed the electronic database search also collected and assembled the individual patient data provided by the investigators. Data was accepted in any kind of electronic format (SPSS, STATA, Word document, Excel document, and Access document) and only the coordinators of the collaboration have direct access to the data. Both investigators performed data validation, checking the received data set for data entry mistakes and inconsistency. Differences was discussed and settled in consensus.

### ***Mechanical ventilator and transfusion parameters***

The corresponding author of each study was asked to fill the datasheet with MV parameters [plateau pressure (P<sub>plateau</sub>), peak pressure (P<sub>peak</sub>), positive end-expiratory pressure (PEEP), respiratory rate (RR), inspired fraction of oxygen (FiO<sub>2</sub>), and minute-ventilation (MV)] and oxygenation parameters [partial pressure of oxygen (PaO<sub>2</sub>), partial pressure of carbon dioxide (PaCO<sub>2</sub>), pH, and PaO<sub>2</sub>/FiO<sub>2</sub> ratio] obtained hourly during the procedure. Since some authors did not record the parameters hourly, we divided the measurements in three periods: (I) beginning of the surgery, defined as the parameters measured in the first hour of the procedure; (II) middle of the surgery, beginning of the surgery, defined as the parameters measured in the middle of the procedure (total time of procedure divided by two); and (III) end of the surgery, defined as the parameters measured in the last hour of the procedure. Since parameters in the end of the study can suffer influence of any lung injury developed during surgery and parameters the beginning of surgery doesn't have sufficient time to



induce changes in the lung, we chose to use the parameters in the middle of the surgery in the outcome analyses. A blood transfusion was defined as the infusion of red blood cells (RBCs) and/or fresh frozen plasma (FFP) in the perioperative period. The blood products were counted as units.

### ***Primary and secondary outcomes***

The primary outcome was ARDS development (according to the definition used by each author), where these data are available. The secondary clinical outcomes include: (I) in-hospital mortality, defined as any death during hospital stay; (II) barotrauma, according to the definition used by the author; (III) time of mechanical ventilation, defined as the time since initiation of mechanical ventilation and successful discontinuation; (IV) pulmonary infection, according to the definition used by the author; (V) ICU length of stay, defined as the time since admission in ICU and discharge of it; (VI) hospital length of stay, defined as the time since admission in hospital and discharge of it; (VII) RBC transfusion, defined as the amount of RBC in ml used during the follow-up; and (VIII) FFP transfusion, defined as the amount of FFP in ml used during the follow-up. Secondary laboratorial outcomes include: (I) levels of plasma interleukin (IL)-6, IL-8, IL-10, and TNF- $\alpha$  in pg/mL; and (II) levels of bronchoalveolar (BAL) IL-6, IL-8, and TNF- $\alpha$  in pg/mL.

Safety outcomes include: (I) PaO<sub>2</sub> in mmHg; (II) PaCO<sub>2</sub> in mmHg; (III) PaO<sub>2</sub>/FiO<sub>2</sub> ratio; (IV) pH; and (V) incidence of acidosis, defined as pH <7.35.

### ***Statistical analysis***

Careful evaluation was performed to ensure completeness of data and to check consistency. Baseline characteristics of patients were presented separately for each trial and overall. Continuous variables were presented as mean and standard deviation (mean  $\pm$  SD) or median and interquartile range [median(IQR)] if not normally distributed. Binary and categorical variables were presented as frequencies and percentages [n (%)].

The formal statistical power depended on the number of patients ultimately included and was thus not fixed in advance. Post hoc calculations based strictly on the number of ARDS observed in each V<sub>T</sub> group indicated that the sample size we obtained provided 100% power to detect an interaction represented by a hazard ratio of 2.1 with a two-sided  $\alpha$  of 0.05.

All analyses were conducted according to the presence or not of any transfusion during the perioperative period (RBC and/or FFP). In addition, patients were also stratified according to the transfusion or not of RBC or FFP, to the transfusion of more than 3 units RBC or less than three and to transfusion of RBC and FFP.

Time-to-event was defined as time from the day of surgery to the event. We used a Cox proportional-hazards regression model to examine simultaneously effects of multiple covariates on outcomes, censoring a patient's data at the time of death, hospital discharge, or after 30 days (11). In all models, the categorical variables were tested for trend with the transfusion group as reference and the proportional-hazards assumption was assessed. A test for interaction between pairs of variables in the final model was performed. The effect of each variable in these models was assessed with the use of the Wald test and described by the HR with 95% CI.

The initial model included age, gender, type of study, BMI, type of surgery, ASA, tidal volume, highest PEEP, highest plateau pressure, highest compliance, and risk factors for ARDS. Variables with a P<0.2 in the univariate analysis are included in the multivariate regression. The final model was developed by dropping each variable in turn from the model and conducting a likelihood-ratio test to compare the full and the nested models. We used a significance level of 0.05 as the cutoff to exclude a variable from the model. Finally, the variable of transfusion was added to the model in order to test the resultant model against that without the variable. We constructed Kaplan-Meier curves and used log-rank test to determine the univariate significance of the study variables.

Time-course variables (e.g., repeated measures of ventilatory parameters, vital signs, oxygenation parameters and others) are also analyzed by a linear mixed model. Repeated-measures generalized linear model (GLM) was used to assess the time-interaction for ventilatory and oxygenation parameters during surgery. The model includes two factors: (I) study group (fixed factor), each level of the study group factor can have a different linear effect on the value of the dependent variable; (II) time as covariate, time is considered to be a random sample from a larger population of values, the effect is not limited to the chosen times.

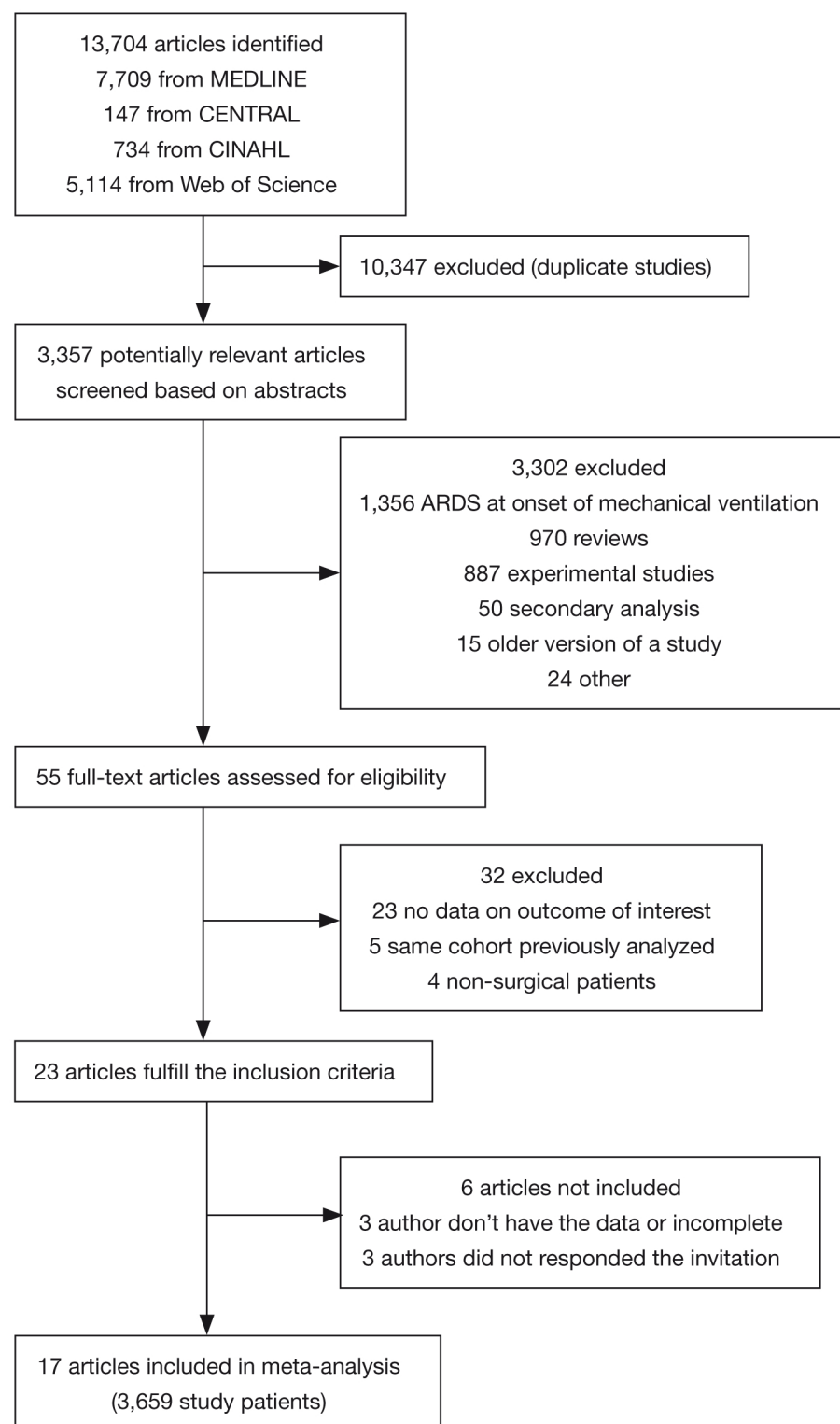
Subgroup analyses were used to assess the effect of V<sub>T</sub> in the following pre-specified subgroups: (I) type of study (observational study *vs.* RCT); (II) ASA score (<3 *vs.*  $\geq$ 3 and for each level); (III) presence of risk factors for ARDS (yes or no and defined as pneumonia, shock, and sepsis); (IV)



tidal volume [ $\leq 7$  mL/kg predicted body weight (PBW), 7–10 mL/kg PBW, and  $>10$  mL/kg PBW]; (V) type of surgery (cardiac, abdominal, thoracic, and orthopedic); (VI) age ( $<65$  *vs.*  $\geq 65$  years); (VII) gender (male *vs.* female); and plateau pressure ( $\leq 15$  *vs.* 15–20 *vs.*  $>20$  cmH<sub>2</sub>O). In data not normally distributed, analyses were performed after  $\log_{10}$  transformation to permit the use of parametric statistics. If

the data still differed significantly from normal even after  $\log_{10}$  transformation, these data were analyzed by non-parametric tests.

All analyses were conducted with Review Manager v.5.1.1, SPSS v.20 and R v.2.12.0. For all analyses two-sided P values  $<0.05$  were considered significant.



**Figure S1** Literature search strategy.

**Table S1** Characteristics of the included studies

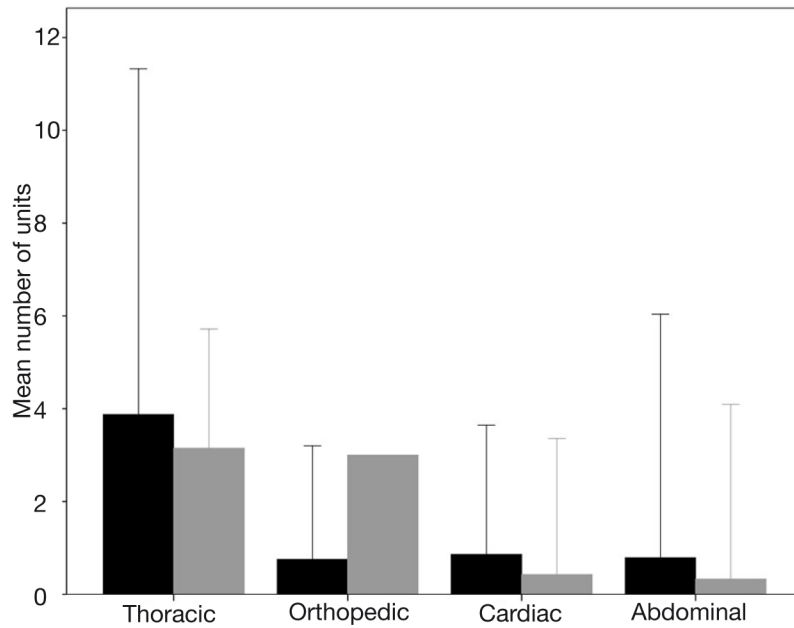
Study, year	N	Protective		Conservative		Type of surgery	Design	Outcomes assessed	Jadad score
		V <sub>T</sub>	N	V <sub>T</sub>	N				
Wrigge, 2004	62	6	29	12	33	ABD/THO	RCT	TMV + PCYT + BCYT	3
Wrigge, 2005	44	6	21	12	23	Cardiac	RCT	MOR + BAR + INF + TMV + LOS + TRA + PCYT + BCYT	2
Zupancich, 2005	33	8	21	10	12	Cardiac	RCT	TMV + LOS + PCYT + BCYT	3
Reis Miranda, 2005	44	6	23	8	21	Cardiac	RCT	MOR + BAR + ARDS + INF + TMV + LOS + TRA + PCYT	4
Schilling, 2005	110	5	75	10	35	Thoracic	RCT	MOR + BAR + INF + TMV + LOS + TRA + PCYT + BCYT	3
Wolthuis, 2008	46	6	24	12	22	General	RCT	TMV + TRA + PCYT + BCYT	3
Lin, 2008	102	5	50	9	52	Thoracic	RCT	MOR + BAR + ARDS + INF + TMV + LOS + TRA + PCYT	2
Licker, 2009	1,091	6	558	9	533	Thoracic	OBS	ARDS + INF + LOS	0
Weingarten, 2010	40	6	20	10	20	Abdominal	RCT	MOR + BAR + ARDS + INF + TMV + LOS + TRA + PCYT	3
Fernandez-Bustamante, 2011	429	8	154	10	275	Abdominal	OBS	ARDS + INF + TMV + LOS + TRA	0
Sundar, 2011	149	6	75	10	74	Cardiac	RCT	MOR + TMV + TRA + LOS	4
Treschan, 2012	101	6	52	12	49	Abdominal	RCT	MOR + BAR + ARDS + INF + TMV + LOS + TRA	4
Memtsoudis, 2012	24	6	10	12	14	Spine	RCT	MOR + BAR + ARDS + INF + TMV + LOS + TRA + PCYT	4
Unzueta, 2012	40	6	40	–	–	Thoracic	RCT	MOR + ARDS + INF + TMV + LOS	3
Severgnini, 2013	55	7	28	9	27	Abdominal	RCT	MOR + BAR + INF + TMV + LOS + TRA + ARDS	4
Futier, 2013	400	6	200	12	200	Abdominal	RCT	MOR + ARDS + INF + TMV + LOS + TRA	4
Hemmes, 2014	889	6	889	–	–	Abdominal	RCT	MOR + ARDS + INF + TMV + LOS + TRA	4

V<sub>T</sub>, tidal volume (mL/kg PBW); RCT, randomized controlled trial; OBS, observational; TMV, time of mechanical ventilation; ICULS, ICU length of stay; ABD, abdominal; THO, thoracic; MOR, mortality; BAR, barotrauma; ARDS, acute respiratory distress syndrome; INF, infection; TMV, time of mechanical ventilation; LOS, length of stay; TRA, transfusion; PCYT, plasma cytokine; BCYT, bronchoalveolar lavage cytokine.

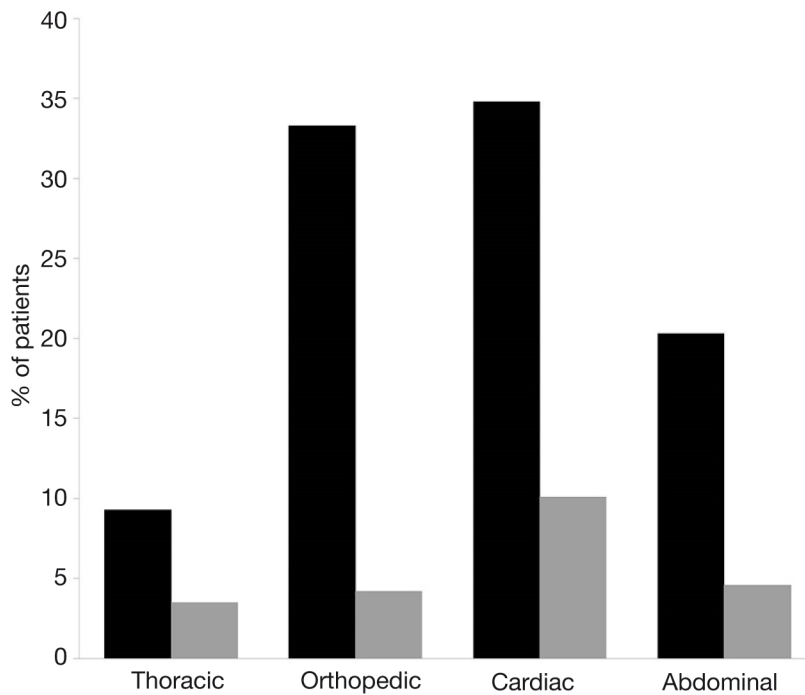
**Table S2** Scientific quality of included studies

Study, year	Allocation concealment	Baseline similarity	Early stopping <sup>a</sup>	Lost to follow-up	Intention-to-treat analysis
Wrigge, 2004	Sealed envelopes	Age: similar; illness severity: similar (ASA)	No	4.6%	NS
Wrigge, 2005	NS	Age: similar	No	No	NS
Zupancich, 2005	NS	Age: similar	No	No	NS
Reis Miranda, 2005	Sealed envelopes	Age: similar	No	No	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
Sundar, 2011	Block randomization	Age: similar; illness severity: similar (STSMS)	No	1.3%	Yes
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
Memtsoudis, 2012	Sealed envelopes	Age: lower in higher $V_T$ ; illness severity: favor lower $V_T$ (ASA)	No	No	NS
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
Hemmes, 2014	Computer-Generated	Age: similar; illness severity: similar (ARISCAT)	No	No	Yes

<sup>a</sup>, early termination for benefit or futility and the presence of an explicit *a priori* stopping rules. NS, not specified;  $V_T$ , tidal volume; STSMS, society of thoracic surgeons mortality score; PORI, preoperative risk index.

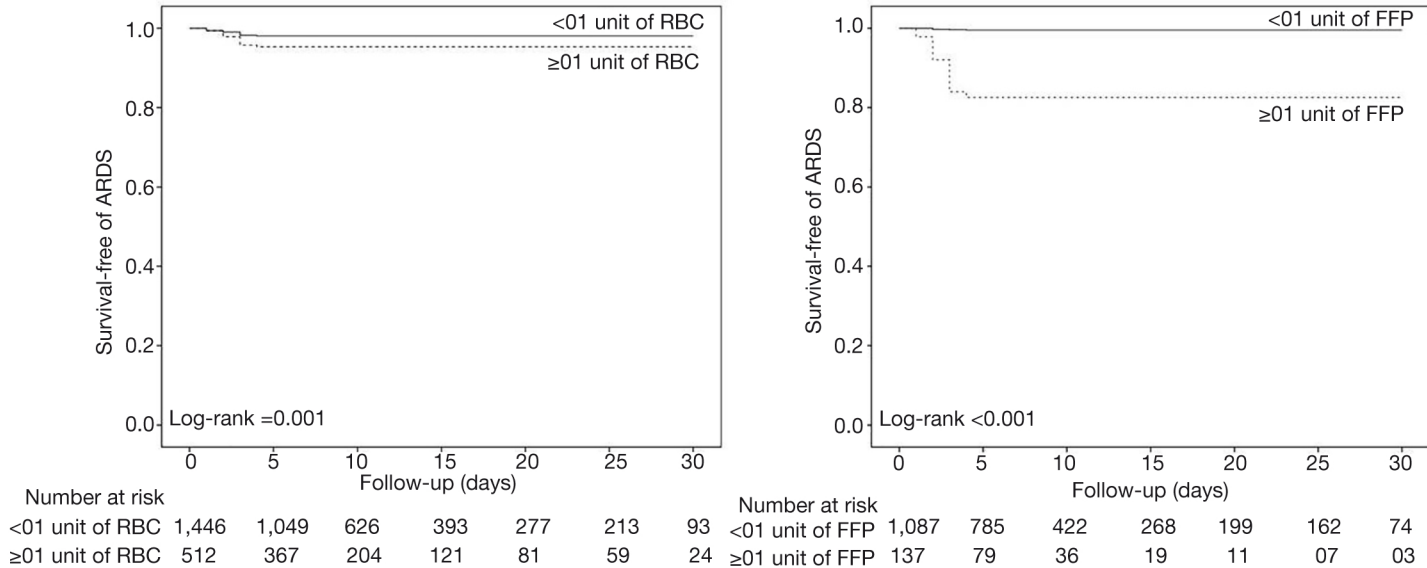


**Figure S2** Units of RBC (black bars) and FFP (gray bars) transfused according to the type of surgery (mean  $\pm$  SD). RBC, red blood cell; FFP, fresh-frozen plasma.

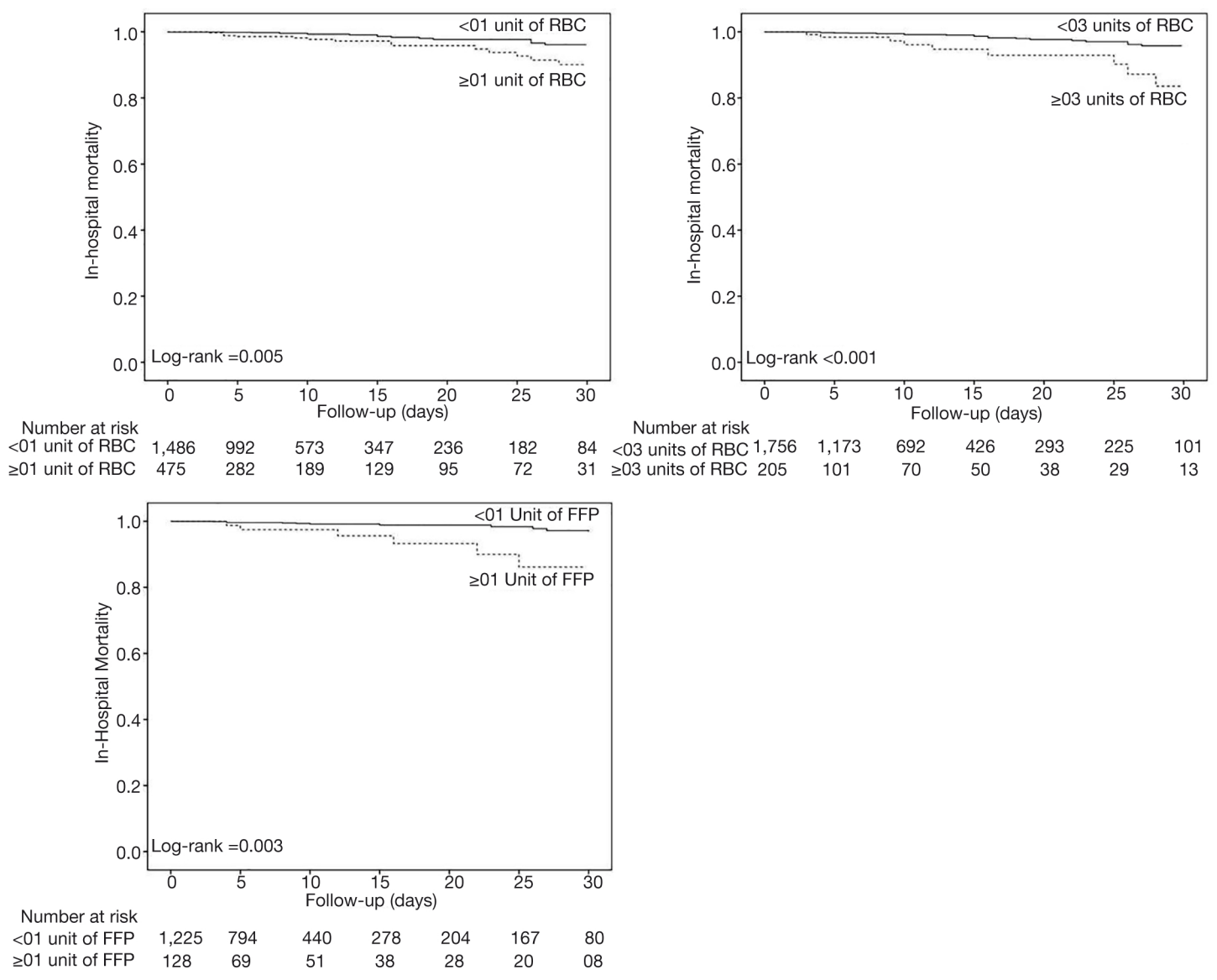


**Figure S3** Percentage of patients who received at least one unit of RBC (black bars) or FFP (gray bars) according to the type of surgery. RBC, red blood cell; FFP, fresh-frozen plasma.

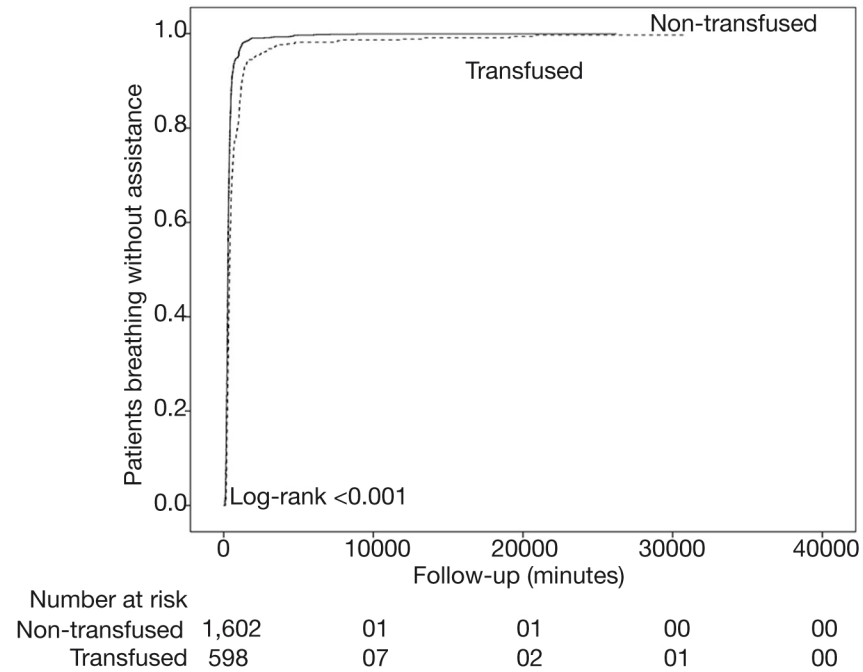




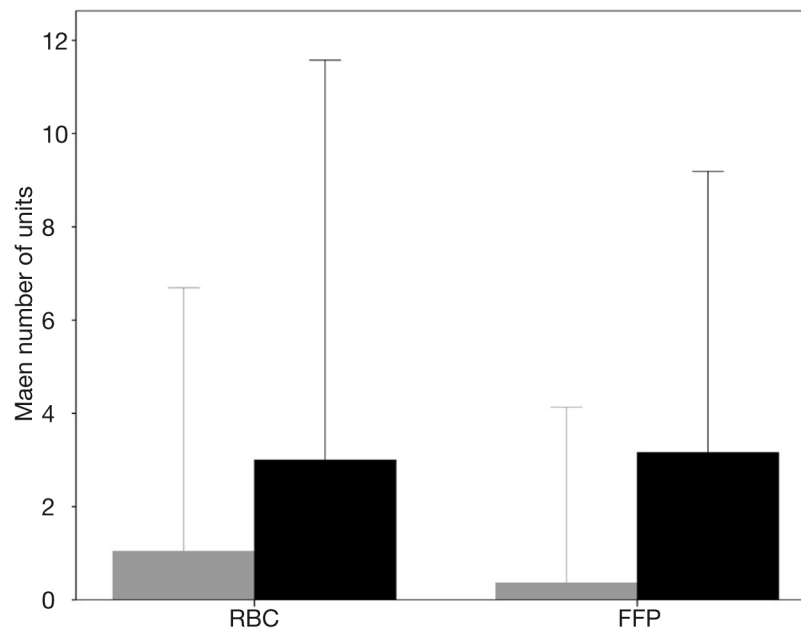
**Figure S4** Survival-free of ARDS according to the transfusion of RBC or FFP. ARDS, acute respiratory distress syndrome; RBC, red blood cell; FFP, fresh-frozen plasma.



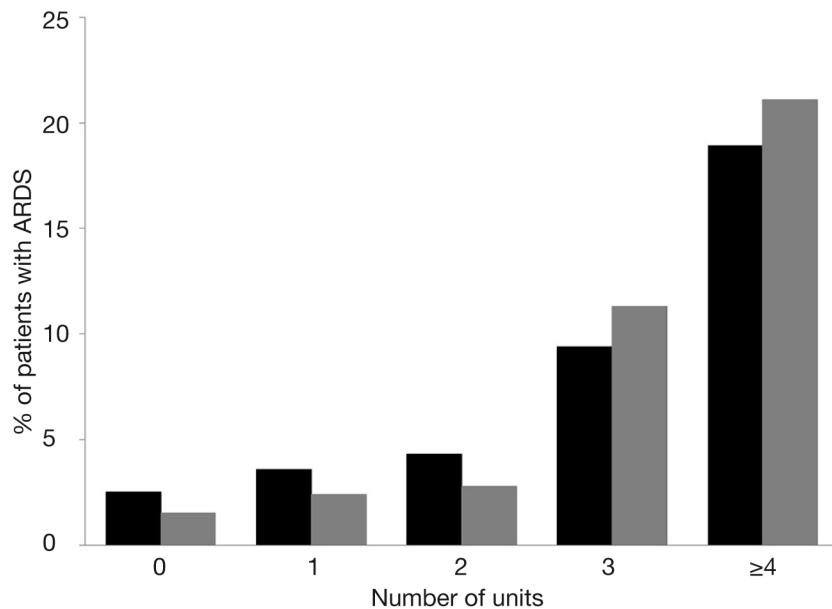
**Figure S5** In-hospital mortality according to the transfusion of RBC, ≥03 units of RBC or FFP. RBC, red blood cell; FFP, fresh-frozen plasma.



**Figure S6** Patients breathing without assistance according to transfusion or not of blood products.



**Figure S7** Units of RBC and FFP transfused in patients who developed (black bars) and do not developed (gray bars) postoperative ARDS (mean  $\pm$  SD). ARDS, acute respiratory distress syndrome; RBC, red blood cell; FFP, fresh-frozen plasma.



**Figure S8** Percentage of patients who developed ARDS according to the number of units of RBC (black bars) and FFP (gray bars) transfused. ARDS, acute respiratory distress syndrome; RBC, red blood cell; FFP, fresh-frozen plasma.