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# Transfusion-related acute lung injury in cardiac surgery

*Kalp cerrahisinde transfüzyon ilişkili akut akciğer hasarı*

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Transfusion of blood and blood products is an important issue which may be cause of increased morbidity and mortality due to reduced pulmonary function. Although blood transfusion-related acute lung injury is uncommon, it may lead to serious pulmonary morbidity. As a special subgroup of patients, cardiac surgery constitutes a complex medical condition due to three etiological factors of acute lung injury: cardiopulmonary bypass, mechanical ventilation and blood transfusion. In this article, we reviewed transfusion-related acute lung injury in cardiac surgery taking the Berlin definition into consideration.

*Keywords:* Acute lung injury; cardiac surgery; transfusion.

Kan ve kan ürünlerinin transfüzyonu, akciğer fonksiyonlarında azalmaya bağlı olarak morbidite ve mortalitede artışın nedeni olabilen önemli bir sorundur. Kan transfüzyonu ile ilişkili akut akciğer hasarı nadir olmakla birlikte, ciddi akciğer morbiditesine yol açabilmektedir. Özel bir hasta altgrubu olarak, kardiyak cerrahi, akut akciğer hasarının üç etyolojik etkeninden dolayı kompleks bir medikal durumu oluşturur: kardiyopulmoner baypas, mekanik ventilasyon ve kan transfüzyonu. Bu makalede, Berlin tanımı göz önüne alınarak, kalp cerrahisinde transfüzyona bağlı akut akciğer hasarı incelendi.

*Anahtar sözcükler:* Akut akciğer hasarı; kalp cerrahisi; transfüzyon.

Acute respiratory distress syndrome (ARDS) is a serious pulmonary disease. Many factors may cause this clinical setting which can be divided into two groups as pulmonary (aspiration pneumonia, infectious pneumonia, toxic inhalation, blood transfusion) and extra-pulmonary factors (sepsis, septic shock, burn, multiple trauma, reperfusion injury).

Cardiac surgery patients form a distinct subgroup including many risks for ARDS. Cardiac surgery is one of the risks for ARDS due to three main factors: cardiopulmonary bypass (CPB), mechanical ventilation and blood transfusion. Firstly, CPB rarely causes ARDS (0.5-1.7%), however, the mortality rate increases from 50% to 91.6%.[1] Secondly, mechanical ventilation may promote or develop lung injury, although it is a main step of treatment of ARDS.[2,3] Thirdly, transfusion of blood product in the perioperative period may induce ARDS, as different blood products may be required intraoperatively due to various indications.

## Acute respiratory distress syndrome

Ashbaugh et al.[4] defined the first case of ARDS in the literature. Signs and symptoms were severe dyspnea, tachypnea, cyanosis refractory to oxygen therapy, diffuse alveolar infilrates on chest radiograph and pulmonary edema. In 1994, ARDS was defined by the American-European Consensus Conference (AECC) as 'acute onset of hypoxemia with bilateral infiltrates on frontal chest radiograph and with no evidence of left atrial hypertension'.[5] In this consensus report, ARDS was defined as a severe clinical form of acute lung injury based on the degree of oxygenation.

In 2012, ARDS was re-defined by the Berlin study group[6] It is also known as 'The Berlin definition' which was based on four criteria: *(i)* timing of onset, *(ii)* chest imaging, *(iii)* origin of edema, and *(iv)* oxygenation. The first criterion, acute onset, was explained as one week after a known clinical insult or new or worsening respiratory symptoms. The second

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criterion was bilateral opacities on chest imaging which could not fully explained by effusions, lobar/lung collapse, or nodules. The third criterion was respiratory failure which could not fully explained by cardiac failure or fluid overload. In the absence of any risk factors, an objective evaluation would be necessary to exclude hydrostatic edema. Finally, the degree of hypoxemia was divided into three groups as mild [200 mmHg< $PaO_2/FiO_2$ ≤300 mmHg with positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) ≥5 $cmH_2O$], moderate (100 mmHg <$PaO_2/FiO_2$ ≤200 mmHg with PEEP ≥5 $cmH_2O$) and severe ($PaO_2/FiO_2$ ≤100 mmHg with PEEP ≥5 $cmH_2O$). The last criterion identified all of the stages of disease as ARDS, eliminating the term of 'acute lung injury'. However, we used the term as 'Transfusion-related acute lung injury-TRALI' based on of the publications in the literature. The comparison of definitions of ARDS is summarized in Table 1.

**Transfusion-related acute lung injury**

Previously, cases which are likely to be TRALI were reported with different terms. Some of these terms were 'pulmonary hypersensitivity'[7] and 'pulmonary edema'[8] due to blood transfusions. The term 'transfusion-related acute lung injury' was firstly used by Popovsky et al.[9] in 1983 Physical examination may reveal dyspnea, tachypnea, cyanosis, fever, tachycardia hypotension, and the presence of froth in endotracheal tube.[10] In addition, transient acute leukopenia, leukocyte antigen-antibody match between donor and recipient, and increased neutrophil priming activity in the plasma of blood products may be observed in the laboratory test results.[10]

Since 1994, TRALI was defined several times.[5,6,10,11] Two of these reports[5,6] referred to a general definition of ARDS, while the others[10,11] were specific for TRALI (Table 2). In contrast to these definitions, TRALI may be classified as ARDS in changing severity (mild, moderate or severe) according to the Berlin definition.[6]

Other causes of ARDS must be eliminated in the diagnosis of TRALI. Except the main causes of ARDS, transfusion-associated circulatory overload sepsis, anaphylactic transfusion reactions must be also considered in the differential diagnosis.[12] Circulatory overload is the most important clinical setting to distinguish from TRALI, which refers to hydrostatic pulmonary edema, and may be diagnosed with new electrocardiographic ischemic changes or new troponin T levels.[13]

The treatment for TRALI is similar with the treatment of ARDS. It is supportive treatment and requires mechanical ventilation to improve oxygenation. In case of transfusion-related lung injury, transfusion must be discontinuted and blood samples for white blood cell count must be drawn as well as chest radiography. In addition, the other units from the same donation(s) must be quarantined and other units must be transfused, if indicated.[14]

In particular, cardiac surgery patients usually require blood product transfusions for different

**Table 1. Differences between American-European Consensus Conference and Berlin definition for acute respiratory distress syndrome**

| | AECC definition | Berlin definition |
|---|---|---|
| Timing | Acute (?) | Acute (within 1 week of a known clinical insult or worsening symptoms) |
| Category | ALI with $PaO_2/FiO_2$ <300 mmHg | Mild: 200 mmHg <$PaO_2/FiO_2$ ≤300 mmHg**<br>Moderate: 100 mmHg <$PaO_2/FiO_2$ ≤200 mmHg**<br>Severe: $PaO_2/FiO_2$ ≤100 mmHg** |
| Oxygenation | $PaO_2/FiO_2$ ≤300 mmHg* | Minimal PEEP levels added to $PaO_2/FiO_2$ |
| Chest radiograph | Bilateral infiltrates | Bilateral opacities (not fully explained by effusions, lobar/lung collapse or nodules) |
| PAWP | PAWP ≤18 mmHg<br>(When measured or no clinical evidence of left atrial hypertension) | None (removed)<br>Objective assessment needs (eg. echocardiography) to exclude hydrostatic edema |
| Risk factor | None | When none identified, need to rule out hydrostatic edema |

AECC: The American-European Consensus Conference; ALI: Acute lung injury; PEEP: Positive end-expiratory pressure; PAWP: Pulmonary artery wedge pressure; $PaO_2/FiO_2$: Partial arterial pressure/fraction of inspired oxigen; * Regardless of PEEP; ** With positive end-expiratory pressure or continuous positive airway pressure ≥5 $cmH_2O$.

indications. Therefore, blood transfusion is a possible etiological factor of ARDS in those patients. The differential diagnosis of lung injury is of utmost importance for the best treatment of the patients. In this systematic review, we aimed to investigate the incidence and possible causes of TRALI in cardiac surgery patients and to evaluate the results according to the Berlin definition.

## MATERIALS AND METHODS

For the investigation of TRALI in perioperative period of cardiac surgery, an electronic literature review which covered the years of 1983 and 2013 was conducted as of the date of March 01, 2013 by two authors.

In this study, we only conducted electronic literature. As research terms, the word combinations [acute lung injury, ARDS, transfusion related acute lung injury, cardiac surgery, valve surgery, cardiopulmonary artery bypass grafting, CPB, platelet, red blood cell (RBC), fresh frozen plasma (FFP), cryoprecipitate], and as database Pubmed, Ovid, Science Direct were used. Screening was limited to cardiac surgical procedures.

The literature research was started from 1983 when TRALI was firstly reported. The research was limited to English (full texts and abstracts) and its articles containing detailed data (age, sex, number of patients, blood product and units transfused, surgical procedures, onset time of TRALI, concomitant diseases, survival rates of cases reported, and total number of patients along with TRALI patients, conclusion of studies and survival rates) were included.

The methodology was organized according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and checked by the PRISMA checklist.[15]

**Table 2. Definitions of transfusion-related acute lung injury**

*Canadian blood services TRALI consensus panel statement*

1- TRALI criteria
ALI
Acute onset
Hypoxemia: $PaO_2/FiO_2 \leq 300$ or $SpO_2 < 90\%$
Bilateral infiltrates on chest radiograph
No evidence of left atrial hypertension
No ALI before transfusion, during or within six hours of transfusion, No temporal relationship to an alternative risk factor for ALI

2- Possible TRALI
ALI
No ALI before transfusion
During or within six hours of transfusion
A clear temporal relationship to an alternative risk factor for ALI

*The National Heart, Lung, and Blood Institute working group on TRALI*

1- Patients without ALI risk factors
New ALI and onset of symptoms or signs is during or within six hours after end of transfusion of plasma containing blood products

2- Patients with ALI risk factors
New ALI and onset of symptoms or signs is during or within six hours after end of transfusion of plasma containing blood products. (TRALI; new ALI is inferred to be related to transfusion or both transfusion and other risk factor,
Not TRALI; new ALI is related to other factor, while transfusion is coincidental)

TRALI: Transfusion-related acute lung injury; ALI: Acute lung injury.

## RESULTS

The flow diagram of database research is shown in Figure 1. Through a database search, we obtained a total of 159 records. After duplicates were removed (n=54), 105 records were evaluated

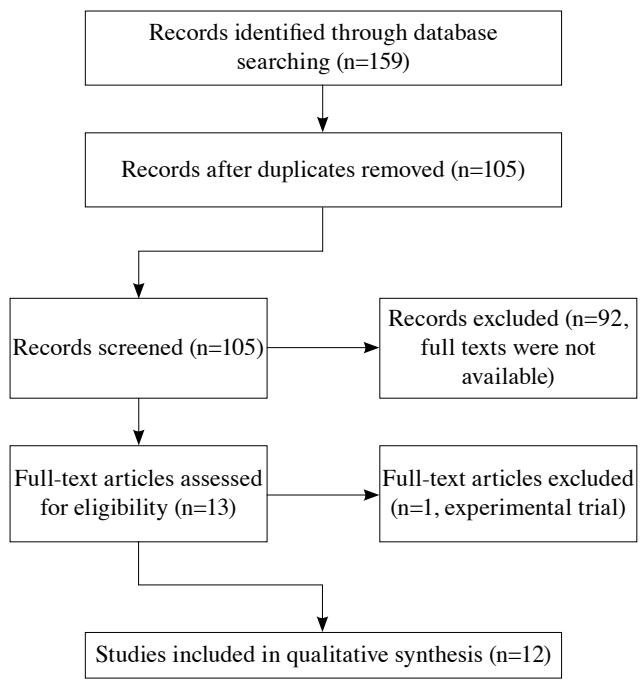


**Figure 1.** Flow diagram of database search. Figure was drawn according to recommendations of Moher et al.[15]

**Table 3. Cases about transfusion-related acute lung injury in cardiac surgery**

| Reference | Age/gender | Blood product/unit | CPB | Operation | Onset time | Concomitant disease | Survival |
|---|---|---|---|---|---|---|---|
| Lin et al.[16] | 62/M | PLT/5 | Yes | CABG | Postoperative fiftieth minute | Hypertension, sleep apnea | Discharged |
| Kalkat et al.[17] | 62/M | FFP/1 | Yes | CABG | Postoperative | NA | Discharged |
| Brander et al.[18] | 46/M | FFP/1 | Yes | Aort surgery | Postoperative third hour | NA | Discharged |
| Nouraei et al.[19] | 4/F | FFP/2 RBC/1 | Yes | Ross procedure | Postoperative | NA | Discharged |
| Bawany and Sharif[20] | 68/M | PLT/6 | Yes | CABG | Postoperative second hour | No | Exitus |
| Kojima et al.[21] | 66/M | FFP/1 | Yes | CABG | Postoperative first hour | Asthma | Discharged |
| Lecamwasam et al.[22] | 66/M | FFP/2 | Yes | CABG and MVR | Postoperative | AF | Discharged |
| Singh and Zeltsman[23] | 22/M | RBC/? | Yes | Congenital heart surgery | Intraoperative | Aspergilloma | Exitus |

CPB: Cardiopulmonary bypass; PLT: Platelet; CABG: Coronary artery bypass grafting; FFP: Fresh frozen plasma; NA: Not available; RBC: Red blood cell; MVR: Mitral valve replacement; AF: Atrial fibrillation.

for screening. Ninety-two of these records were excluded, as they were not found to be related to TRALI in the cardiac surgery setting. Thirteen records were assessed for eligibility and one of them was excluded either, as it was an experimental trial.

Twelve studies were included in the qualitative synthesis. Eight of them[16-23] were case reports, while the others were case-control[24] prospective cohort[25] and randomized-controlled trials.[26,27] Trials were at a level of IIb according to the definition of 'levels of evidence'.[28] Case reports and trials are summarized in Tables 3, 4.

**Table 4. Trials about transfusion-related acute lung injury in cardiac surgery**

| Reference | Total patients/ cases | Gender/ number | Blood product | Comorbid diseases | Operation | Comment | Survival |
|---|---|---|---|---|---|---|---|
| Vlaar et al.[26] | 668/16 | M/12 F/4 | RBC FFP PLT | Alcohol abuse, smoking, MI, hypertension, diabetes, vascular disease, malignancy, CVA, | CABG, Valve, Bentall | Risk factors were: Age, pump time, amount of transfusions, RBC, FFP, PLT, storage time of RBC, total transfused plasma | Exitus (2) |
| Koch et al.[25] | 16847/0 | NA | RBC FFP PLT | Heart failure, smoking, prior MI, diabetes mellitus, COPD | CABG, Valve, CABG+valve | ARDS cases were not related to transfusions of blood products | NA |
| Nakazawa et al.[27] | 82/5 | NA | RBC FFP PLT | Liver dysfunction, renal dysfunction, | CABG, TAA, Non-cardiac (30) | Cardiopulmonary bypass and preoperative liver dysfunction were significantly associated with $PaO_2/FiO_2$ <300 | NA |
| Tuinman et al.[24] | 45/2 | NA | RBC | Unknown | CABG, Valve | Transfusion may be mediator of acute lung injury | NA |

RBC: Red blood cell; CABG: Coronary artery bypass grafting; FFP: Fresh frozen plasma; PLT: Platelet; MI: Myocardial infarction; CVA: Cerebrovascular accident; ARDS: Acute respiratory distress syndrome; NA: Not available; COPD: Chronic obstructive pulmonary disease; TAA: Thoracic aorta aneurysm.

## DISCUSSION

The patients undergoing cardiac surgery are more prone to necessitate transfusion than other surgical populations. Particularly, the non-physiological conditions of CPB may affect coagulation system adversely and increase the need for transfusion for different indications. Therefore, blood or blood product transfusion-related morbidity and mortality have been an interesting research area of research for clinicians.

In the literature, adverse outcomes of transfusions were well-documented in cardiac surgery patients. Blood transfusion was determined as one of the main risk factors for new-onset of atrial fibrillation,[29] development of infections,[30] prolonged mechanical ventilation,[31,32] acute renal injury,[31] decreased quality of life,[33] mortality,[33-36] and ARDS.[16-23]

The records of ARDS mainly encompass the case reports.[16-23] Although 56.4% of patients needed blood transfusion in the first 72 hours of postoperative period[34] and transfusion increased the pulmonary morbidity[25] in cardiac surgery patients as well, it is obvious that TRALI has not been adequately investigated in prospective trials.

The cases of TRALI usually occurred in the early postoperative period.[16-23] The leading cause of TRALI was described as FFP.[17-19,21,22] In addition to FFP, cases due to transfusion of platelet and RBC alone were also reported.[16,23] Singh and Zeltsman[23] performed blood transfusion intraoperatively, while the others used blood products postoperatively.[16-22] Two of eight patients died.[20,23] Cardiopulmonary bypass was used in all cases and the differential diagnosis was done by echocardiography.

Our electronic search of database matched four clinical trial investigating TRALI in cardiac surgery patients.[24-27] Vlaar et al.[26] and Koch et al.[25] discussed lung injury. Additionally, the incidence of TRALI was found to be 2.3% by Vlaar et al.,[26] 4.4% by Tuinman et al.[24] and 6% by Nakazawa et al.[27] Of note, Nakazawa et al.[27] reported the incidence of TRALI in a mixed surgical patient population. The number of patients undergoing cardiac surgery and developed TRALI was not precisely reported in the latter study. However, the authors identified CPB, but not transfusion, as one of the risk factors of lung injury based on the multivariate regression analysis.

While the other authors found the incidence of TRALI to be 2.3-4.4%, Koch et al.[25] observed lung injury approximately >64% by criteria of hypoxemia ($PaO_2/FiO_2$ <300). However, they did not evaluate these cases as TRALI, since there was no correlation between the lung injury and transfusion. Based on these results, Koch et al.[25] suggested that the definition of TRALI was problematic for cardiac surgery patients, as transfusion was not correlated with the ratio of $PaO_2/FiO_2$ <300, while it was correlated with other pulmonary morbidities.

Furthermore, risk factors were evaluated in cardiac surgery,[26] intensive care unit[37] and mixed population.[38] Vlaar et al.[26] defined age, duration of CPB, total amount of blood products, number of RBCs stored more than 14 days, total amount of plasma, presence of antibodies in donor plasma, and total amount of transfused bioactive lipids as the risk factors for TRALI in cardiac surgery.

On the other hand, the sex of the patients was not determined as a risk factor in the studies.[26,37,38] However, most of the case reports[16-18,20-23] and patients in a case-control study[26] were male, while no relevant information was obtained from the other studies.[24,27] On the contrary to the sex of the patients (recipients), sex of donors predispose to TRALI.[27,38] Anti-HLA and anti-HNA antibodies were highly prevalent in multi-parous female donors.[39] Vlaar and Juffermans[39] stated that the exclusion of female donors for plasma and thrombocyte products led to a 33-66% reduction in the incidence of TRALI.

Although the age was established as a patient-related risk factor, the cut-off value was not reported.[26] Six of the case reports were older than 40 years.[16-18,20-22] Also, it must be noted that most of the patients (83%) were older than 40 years and the incidence of TRALI was low in patients aged 20 to 39 years in Toy et al.'s[38] trial.

The total amount of blood products transfused was accepted as a predisposing factor by Vlaar et al.[26] but not by Toy et al.[38] In another trial of Vlaar et al.[37] the volume of platelets and plasma transfused was associated with transfusion-related acute lung injury in the univariate analysis, however the association disappeared in the multivariate analysis. Kalkat et al.,[17] Brander et al.[18] and Lecamwasam et al.[22] reported TRALI with one unit of FFP. The presence[26] or volume[40] of antibodies in donor plasma were also critical as well as the total amount of blood products. However, it is still unclear which one is more important: the total amount of blood or volume of antibodies? In a recent case report, recurrent ARDS developed due to repeated blood transfusions and the second and later episodes occurred in a shorter time than the first episode.[40]

Middelburg et al.[41] demonstrated that storage time of plasma (up to 2 years) and RBCs (up to 35 days) was not associated with TRALI, while storage time of platelet was associated with TRALI. On the other hand, Toy et al.[38] found little or no risk associated with older RBC units. Vlaar et al.[26] also found similar result about storage time of platelet, however, they noted the storage time of RBC as a risk factor. The cut-off value of storage time was >14 days for RBC. In the case reports, storage time of blood products was not mentioned.[16-23]

The degree of additive effect of CPB and mechanical ventilation to development of TRALI was not clearly established. However, it is clear that these factors (CPB and mechanical ventilation) may be very important for the development of TRALI in the perioperative period of cardiac surgery alone or with blood transfusion. In addition, an experimental study showed that mechanical ventilation with higher tidal volume (15 $mL.kg^{-1}$ vs. 7.5 $mL.kg^{-1}$) contributed to the occurrence of TRALI.[42] On the contrary to this knowledge, applied tidal volumes were not noted.[16-23]

Nakazawa et al.[27] observed a $PaO_2/FiO_2$ ratio lower than 300 in 19 patients after transfusion and TRALI developed in five patients. Cardiopulmonary bypass was associated with the decline in $PaO_2/FiO_2$ ratio. Vlaar et al.[26] showed the duration of CPB as a risk factor of TRALI, however, they did not report a cut-off value. Case reports of TRALI[16-23] in cardiac surgery were applied under CPB and no case was reported with off-pump technique.

Transfusion-related acute lung injury occurred within six hours after transfusion.[10] However, it was not defined specifically in the current definition, the Berlin definition.[6] Although the timing criterion of acute onset disease as proposed by the Berlin definition for ARDS is one week, the differential diagnosis of etiological factors for non-surgical patients may be simplier. However, one-week timing criterion may pose many difficulties and complicate the diagnosis in cardiac surgery patients.

### Conclusion

In conclusion, the limited number of clinical trials investigating TRALI in cardiac surgery patients is a contradiction. In our opinion, we concluded on several implications as follows:

- The first definition of TRALI must be revised only as ARDS and removed the term of 'TRALI' due to the Berlin definition;
- Objective research techniques (e.g. echocardiography) are mandatory to rule out other possible factors;
- Although transfusion-related ARDS is rare, transfusion of blood or blood products must be minimalized in accordance with the published guidelines to decrease both ARDS and other pulmonary morbidities, and
- Transfusion-related ARDS in cardiac surgery patients needs a larger trial which will help us to establish the correct incidence (lower or higher than known) according to last definition of ARDS.

However, we believe that further researches which focus on the possible biochemical markers of ARDS and its etiological factors would clearly identify the real incidence of ARDS and the degree of effect of transfusion on ARDS.

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