**Reviewer A**

This manuscript describes the incidence of TRALI after red blood cell (RBC) transfusion as a consequence of severe PPH. To my surprise there is no gynaecologist among the authors. The manuscript could benefit from such an input.

1. I doubt very much whether all 16 cases of TRALI are real cases since according to the definition there is ‘A clear temporal relationship to an alternative risk factor for ALI’ since most of these patients had preeclampsia. Perhaps it would be better to classify these cases as possible TRALI.

*Among 71 patient, we identified 13 patients with TRALI and 1 patients (with pre-existing pneumonia) with possible TRALI. Among the 13 patients with TRALI, 3 suffered from preeclampsia. According to the 2004 consensus definition, alternative risk factors for ALI include pneumonia, toxic inhalation, lung contusion, near drowning, aspiration, shock, multiple trauma, burn injury, acute pancreatitis, drug overdose and cardiopulmonary bypass but not preeclampsia. Indeed, we cannot define these cases as possible TRALI. Nevertheless, we add a new paragraph addressing the possibility that patients with preeclampsia develop pulmonary edema and how this condition was excluded in our cases* *(Discussion, pag. 9 ).*

1. Explain this very high number of TRALI cases and compare it with other diseases that need RBC transfusion.

*The high incidence of TRALI observed has been discussed and compared to that observed in critically ill patients in the current literature(Discussion, first paragraph)*

1. The number of patients in the study is very small.

*We underlined that one limit of this study resides in the small number of included patients (Discussion, first paragraph)*

1. The English has to be improved. There are several spelling errors.

*The manuscript has been carefully revised for English and spelling errors .*

1. Title: The title is not correct since TRALI is a complication of RBC transfusion. Mention the abbreviation TRALI in the title.

*The title of the manuscript has been changed as follows:* *Acute lung injury complicating blood transfusion in severe post-partum hemorrhage: incidence and risk factors.*

1. Abstract: Mention in a diagram the consensus definition of TRALI as in the article of Kleinman.

*The consensus definition has been added in extenso to the abstract.*

1. Introduction: Could be shortened a little bit.

*The Introduction has been slightly shortened, as suggested.*

1. Patients and methods: Were the patients consecutively collected? Did all patients have abnormal X-rays? In many preeclampsia cases there must have been atrial hypertension or not? How was preeclampsia defined?

*We clearly stated that patients were consecutively collected; according to the criteria adopted to identify TRALI, X-rays were abnormal in all identified cases. Clinical criteria were utilized to define preeclampsia (gestational hypertension and proteinuria > 0.3 g/24 hours); we add a new reference to indicate utilized criteria (reference 18)*

1. Could you retrive more data on the donors, were the women all nulliparous?

*Unfortunately, no data on the parity of donors were available in our databases.*

1. Results: Why were cases not notified to the hemovigilance officer?

*In all these cases the diagnosis was retrospectively achieved and one of the aim of this study is just to emphasize how the diagnosis of TRALI is largely underestimated in our country.*

1. I like to see more in detail the data on the preeclamptic patients, did they have severe preeclampsia or not ?

*In two patients preeclampsia complicated into HELLP syndrome: in one of them TRALI was diagnosed. No patients had severe hypertension.*

1. Discussion: The sentences on aspirin use to prevent preeclampsia are not at the right place here and should be omitted.

*The sentence on aspirin use has been cancelled, as suggested.*

1. I think that the main limitation of this study is that preeclamptic patients often develop pulmonary oedema especially in the postpartum period. Discuss this.

*As suggested, we discussed this issue (Discussion pag.9 ).*

1. What is multiparametric monitoring?

*The term “multiparametric monitoring” has been expanded in the wider definition of “continuous monitoring of ECG, p02, blood pressure and breath rate“(Discussion pag. 10 ).*

1. References: Use abbreviations.

*Whenever possible, abbreviations have been used.*

1. Tables: Put more explanations and definitions of the abbreviations in the legenda.

*As suggested, more explanations to the legend have been added (Table I).*

**Reviewer C**

This manuscript describes a retrospective analysis of data from 71 women with postpartum hemorrhage who received at least 3 units of erythrocytes to identify risk factors for Transfusion Related Acute Lung Injury (TRALI).“Hypertensive disorders of pregnancy” was the only clinical variable that was significantly associated with TRALI in multivariate analysis, with a point estimate of the odds ratio of 27.7.

1. My primary concern has to do with the clinical overlap between pulmonary edema related to preeclampsia, and TRALI. Pulmonary edema is listed as a diagnostic criterion, severe feature, and indication for delivery for preeclampsia (Hypertension in Pregnancy, ACOG 2014; Guidelines for the management of hypertensive disorders of pregnancy 2008, SOMANZ 2008). Hypoxemia also predicts progression of preeclampsia (Millman AL, J Obstet Gynaecol Can 2011;33:705). Preeclampsia has been associated with postpartum hemorrhage (Koopmans CM Acta Obstet Gynecol Scand 2014;93:399-407), and massive postpartum blood transfusion (Mhyre JM Obstet Gynecol 2013;122:1288-94.What is to differentiate pulmonary edema due to preeclampsia, from TRALI?

*In our series of patients 4 cases of pre-eclampsia were recorded and three of them were suspected fro TRALI. These patients had no uncontrolled hypertension at the time of delivery. During delivery and post-partum all patients were connected to a monitor registering vital parameters and fluid balance; these data were available in clinical records of patients. Considering the blood pressure value registrations, the temporal relationship between transfusions and onset of hypoxemia, the lack of response to therapy administered and in particular to diuretics, the anesthesiologists independently revising the clinical records considered hypoxemia secondary to ALI and not to pulmonary edema. Nonetheless, in the revised manuscript, we addressed in a new paragraph that differential diagnosis of TRALI in pre-eclamptic patients should include beside inflammatory lung involvement also pulmonary edema (Discussion, page 9).*

**Specific suggestions follow:**

1. Page 3, rather than define postpartum hemorrhage, consider citing the definition of persistent postpartum hemorrhage (Abdul-Kadir R, Transfusion 2014;54:1756-68). How does this link to the authors definition of severe PPH requiring at least 3 units of erythrocytes? Callaghan W recently defined severe maternal morbidity as a requirement for 4 or more units of erythrocytes (Callaghan Obstet Gynecol 2014;123:978-81).

*The definition of persistent postpartum hemorrhage according to Abdul-Kadir et al. has been cited and new reference has been added (Introduction, first paragraph and new ref. 4).Throughout the manuscript the adjective “severe” before PPH has been omitted; since we included only patients receiving at least 3 units of RBC, we underlined that our observations are restricted to a limited subgroup of patients with PPH (first paragraph of the Introduction).*

1. P4, paragraph 2, midway: change: “diagnosed in case of…” to “diagnosed in the event of…”

*The sentence has been changed as suggested.*

1. How was cardiogenic pulmonary edema excluded?

*As previously stated, the pulmonary edema was excluded considering that patients did not show hypertension at the time of hypoxemia and that hypoxemia was not responsive to diuretics.*

1. To help the reader more easily navigate, list the clinical variables at the bottom of page 4 in the same order as listed in Table II.

*Clinical variables in Table II have been put in the correct order, as suggested*

1. At what time point were fibrinogen and hemoglobin levels measured? At what time point was DIC diagnosed?

*Fibrinogen and hemoglobin values were measured at delivery; DIC was diagnosed in the post-partum, after PPH.*

1. P5, second line: revise total length of stay to the postpartum length of stay (# of days from delivery to discharge) in order to eliminate confounding for prolonged antepartum observation in an effort to maximize fetal maturity prior to delivery.

*These data have been revised and values of post-partum hospitalization duration have been given in the revised manuscript.*

1. Define SAGM.

*As suggested, SAGM solution has been defined (Saline, adenine, glucose, mannitol solution).*

1. **Statistics.** Was there any effort to test for normality of continuous variables? Any formal test? Visual inspection?

*The Shapiro-Wilk normality test was utilized (we added a sentence to the Statistics paragraph).*

1. Cite a reference for the “Enter method.” Were any control variables entered? Was this a full model fit without variable elimination? Was there any testing for collinearity?

*A reference for the Enter method has been cited (new ref. 16). There was no test for collinearity and no control variables were entered.*

1. P7: “Interestingly, TRALI did not occur in the two patients with [cardiac] disease…” This is not very interesting because the authors defined TRALI as hypoxemia in the absence of a competing diagnosis such as cardiac disease.

*“Interestingly” has been omitted.*

1. P7: “had a longer hospitalization…” change to postpartum length of stay as recommended above.

*See response to comment n.7*

1. P8: Change “currently no more eligible..” to “currently no longer eligible…”

*The sentence has been changed as suggested.*

1. P8: change “we found a clear implication…” to “we found a univariate association…” Note that the statistical significance of this association is marginal (P=0.047).

*The sentence has been modified as follows : “we found a we found a possible implication” (Discussion, page 9).*

1. P9: This paragraph should review the distinct pathophysiology between pulmonary edema caused by preeclampsia from that caused by TRALI, and describe how the authors are able to distinguish these two conditions with the data available.

*As suggested a new paragraph addressing these issues has been added (Discussion, page 9 ).*

1. Table II: EBL is missing.

*As suggested, we added in Table II the estimated blood losses.*

1. Table III: change “pre-existing co-morbidities” to “any co-morbidity”

*As suggested, we changed pre-existing co-morbidities to any co-morbidity*