Peer Review File
Article information: https://dx.doi.org/10.21037/aob-23-39

Reviewer A

This is an excellent review paper that add our knowledge about TRALI from historical perspective. The pathogenesis part could be improved by including the new papers from recent years.
Thank you, we have included more recent references as suggested by reviewers.

Reviewer B

The manuscript "The History of Transfusion Related Acute Lung Injury: How We Got to Where We Are Today" submitted by Van Denakker and Friedman is a well-written and comprehensive review on TRALI and will be of interest for AOB readers.
Please see the following for a few suggested revisions:
1. Please define all abbreviations when they first appear in the article.
2. Suggest replacing FFP with plasma?
We left as FFP since the reference was specifically comparing FFP with S/D plasma.

3. Page 7, 3rd paragraph, "The threshold model sought to explain the heterogeneity in TRALI severity, where neutrophils in mild a TRALI reaction (i.e., requiring only non-invasive supplemental oxygen supportive care) may undergo a lower level of activation compared to those of a severe reaction (i.e., requiring mechanical ventilation)."
? "in a mild TRALI reaction"
Typo "…in mild a TRALI reaction" corrected.

Reviewer C

The authors provide a comprehensive review of the evolution of the definition of TRALI. This is followed by detailed discussion of the pathogenesis and mitigation. This is an excellent review.

Suggestion - there is mention of murine models but large animal ovine TRALI models which have been informative are missing.

Tung JP et al. Age of blood and recipient factors determine the severity of transfusion-related acute lung injury (TRALI). Critical Care. 2012;16(1):R19.

Tung JP A novel in vivo ovine model of transfusion-related acute lung injury (TRALI). Vox sanguinis. 2011;100(2):219-30.

Thank you, we have incorporated these ovine studies into the manuscript.

As the authors state non-antibody mediated TRALI needs further investigation.

This would link with the following article published in AoB

Fung YL, Tung J. Non-antibody mediated TRALI an enigma. Annals of Blood. 2019;4(7).

Thank you, we have added reference to Fung and Tung.

Reviewer D

Van Denakker and Friedman present a review manuscript on the history of TRALI, in which they reflect on clinical criteria, pathophysiology, mitigation strategies, and promising new therapeutic modalities.

TRALI remains an important clinical problem, with a complex pathophysiology and without available therapies. The taken approach is interesting, however, the pathophysiology is poorly addressed and the cited literature needs to be significantly updated. The authors are suggested to address to following points:

1) The abstract should make clear that, despite the success of the mitigation strategy, TRALI still remains a leading cause of transfusion-related deaths, and that it is still underreported and challenging to distinguish from TACO.

Thank you, we added this into the abstract for clarity.

2) While I understand that the authors are not experts on the pathophysiology of TRALI, and that this is not a major focus of this review, certain statements should be modified and updated with more recent insights. For instance, when discussing the first and second hit in TRALI, it is stated that both hits affect neutrophils (priming of neutrophils in the first hit, followed by activation of neutrophils in the second hit). It has become clear over the years that this view is too simplistic, as many other cell types also have an important role in induction of TRALI (Semple et al, Blood 2019). Apart from neutrophils, macrophages are also critical in induction of TRALI (Zeeuw van der Laan et al, Curr Opin Hematol. 2020). Importantly, Osteopontin secreted by macrophages is critical to attract neutrophils to the lungs in TRALI (Kapur et al, Blood 2019). And very recently complement-driven trafficking of the macrophages from the lungs to the blood was described in antibody-mediated TRALI (Van der Velden et al, Blood 2023). In addition, the pulmonary endothelium is important in induction of TRALI (Morsing et al, Blood Rev. 2018, Morsing et al, Transfusion 2022), and the pulmonary endothelium also undergoes priming in the first hit. Also, in Table 2 the

mechanism of action in TRALI is presented incompletely and too simplistically, as several cells and factors contribute to endothelial damage in TRALI. Please use the mentioned references to update the literature in the manuscript.

Thank you, we have added these important research contributions into the manuscript and updated Table 2.

3) In relation to the previous point, it is also stated that Transfused HNA and HLA class I antibodies bind to their cognate antigens on primed neutrophils which results in the classic TRALI reaction. It is important to realize that binding to endothelium may be even more important (e.g. Bayat et al, Arterioscler Thromb Vasc Biol. 2013, Cleary et al, J Clin Invest 2020, van der Velden et al, Blood 2023).

Thank you, we have noted this important point.

4) It is mentioned that mouse models have demonstrated the significant role activated platelets play in TRALI. This statement should be corrected to this has indeed been described is some studies, but that the literature reveals conflicting data regarding the importance and critical relevance of recipient platelets in TRALI (Zeeuw van der Laan et al, Transfus Med Rev. 2020, Semple et al, Transfusion 2020).

Thank you, we added this point.

5) Regarding NETs in TRALI, it should be mentioned that complement-driven NET-formation may be important in TRALI and NETs were also found to be present in a large cohort of TRALI patient plasma samples (van der Velden et al, Blood 2023).

Thank you, point added.

6) Recent reports have highlighted the importance of reverse TRALI and this should be better mentioned (e.g. Bayat et al, Blood Adv 2022).

Thank you, this point was added.

7) When discussing TRALI in comparison to TACO, please also cite a recent review on this topic (discussing both clinical and pathophysiological comparison) by Semple et al, Blood 2019.

Thank you, we included this citation when comparing TRALI to TACO

8) Elevated BNP an pro-BNP is incorrectly stated as a relevant biomarker for TACO. NT-proBNP was recently found to be not associated with TACO in a critically ill patient population. (Bulle et al, Transfusion 2023). Importantly, critically ill patients are at increased risk for development of TRALI. More research is needed to identify biomarkers for TACO (and TRALI).

Thank you, this point was added.

9) Several statements are unreferenced: * low IL-10 levels in TRALI patients (Kapur et al, Ann Transl Med. 2017, van der Velden et al, Blood 2023). * C-reactive protein (CRP), an acute phase reactant elevated in inflammation, is a known “first-hit” risk factor for TRALI (Kapur et al, Blood 2015, Kapur et al, Oncotarget 2016, van der Velden et al, Blood 2023). Please adjust.
Thank you, references were provided

10) For targeting complement as a potential strategy for TRALI, a very recent paper on this topic should also be cited in this respect (van der Velden et al, Blood 2023).
Thank you, this point was added.

11) Table 2 should also make clear that TRALI can also occur upon transfusion of platelets or red blood cells (besides plasma).
Thank you, agreed, this was included

Reviewer E

Transfusion-related acute lung injury (TRAL) is defined clinically by the acute onset of hypoxemia and non-cardiogenic pulmonary edema. Cases suggestive of TRALI were described in the literature as early as 1951; however, the term TRALI was only coined in 1983 by Mark Popovsky. Similar clinical definitions of TRALI were developed by the European Haemovigilance Network, the Canadian Consensus Conference, the National Heart, Lung, and Blood Institute, and the National Healthcare Safety Network. More recently a re-definition has been suggested to align with the updated clinical definition of acute respiratory distress syndrome. TRALI is potentially fatal, and prior to the introduction of risk-mitigation strategies it was one of the most frequent causes of transfusion-related morbidity and mortality. Even with the success of these risk-mitigation strategies, TRALI cases continue to occur, highlighting our incomplete understanding of how it develops. TRALI is caused by the transfusion of blood products containing either anti-leukocyte antibodies or biological response modifiers. However, the precise cellular mechanisms underlying how TRALI develops remain uncertain. There are no specific treatments for TRALI, with supplemental oxygen and mechanical ventilation being the principal strategies. Laboratory and animal models have provided many insights into how TRALI develops and potential treatments for TRALI. The review paper submitted here, explores how our understanding of TRALI has developed over time. It describes the development of the clinical definitions and differential diagnoses, TRALI incidence rates, TRALI pathogenesis, TRALI prevention and mitigation, TRALI management and prognosis, the current limitations, and steps for the future.

Thank you, we incorporated this introduction in place of our original.

Specific comments:

1. Introduction:

a. When discussing the TRALI definition, please also mention the recent re-definition (Vlaar et al, Transfusion, 2019).

Thank you, we have included Vlaar et al.

b. When discussing TRALI pathogenesis, please also refer to Tung et al (Blood Reviews, 2022).

Thank you, this reference was added.

c. When discussing risk-reduction strategies, please also mention strategies to reduce the plasma content of blood products (e.g. re-suspending platelets in platelet additive solution rather than plasma).

Thank you, PAS platelets have been included.

d. The sentence spanning lines 96-99 is confusing to read. Please rewrite. Please also refer to reference 3, as well as the most recent SHOT report and Vossoughi et al (Transfusion, 2019).

e. Line 103: "phenomenon" seems like an odd word choice.

This introduction has been rewritten.

2. Evolution of TRALI Case Definition section:

a. Lines 118-120 refer to a consistency with previous reports; however, this was one of the earliest reports. Should this be "subsequent" rather than "previous"?

We agree, this was reworded to "subsequent".

3. Incidence section:

a. Should also mention the higher incidence of TRALI observed in prospective studies (e.g. Gajic et al, Am J Respir Crit Care Med, 2007)

Thank you, this point was added.

b. A table would be good to summarize the different incidence rates of TRALI

Thank you, for the suggestion, however because of the variation in incidence rates, this is quite difficult.

c. Could also include Australian regional data (Sivakaanthan et al, Blood Transfusion, 2022)

Thank you, the paper was referenced and included in the discussion.

4. Pathogenesis section: This section fails to acknowledge the complexity regarding our understanding of TRALI pathogenesis. I would point the authors towards the review paper by Tung et al (Blood Reviews, 2012) for a detailed explanation of various pathogenetic mechanisms for

TRALI. Specifically:

a. The authors describe the initial development of the antibody-mediated and the two-hit models of TRALI pathogenesis, as well as the later description of the threshold model. They correctly describe neutrophils as a key cell type involved in TRALI pathogenesis; however, TRALI has been described in neutropenic patients (Finlayson et al, Internal Medicine Journal, 2011; Jain et al, Indian Journal of Hematology and Blood Transfusion), and depletion of neutrophils in some animal models has not protected the animals from TRALI development (e.g. Strait et al, Journal of Experimental Medicine, 2011; Bayat et al, Arteriosclerosis, Thrombosis, and Vascular Biology, 2013). This points towards the possibility of pathogenetic mechanisms for TRALI development that do not require neutrophils. Please amend this section to acknowledge this.

Thank you, these points were added.

b. Furthermore, mouse models of major histocompatibility complex (MHC) class I monoclonal antibody (mAb) mediated TRALI and anti-HNA-3a mediated TRALI have suggested pathogenetic mechanisms in which it is mAb binding to cognate antigen expressed on pulmonary endothelial cells rather than neutrophils that is the trigger for TRALI development (Looney et al, Journal of Clinical Investigation, 2006; Strait et al, Journal of Experimental Medicine, 2011; Bayat et al, Arteriosclerosis, Thrombosis, and Vascular Biology, 2013). Please amend this section to acknowledge this.

Thank you, this point was added.

c. In describing the two-hit TRALI mechanism, the authors fail to identify that the neutrophil priming that precipitates pulmonary neutrophil sequestration involves more than just the cytoskeletal changes that lead to neutrophil rigidity and a “mechanical sequestration”. It also involves the up-regulation of adhesion molecules (e.g. CD11b/CD18) that interact with the pulmonary endothelium such that there is also “firm adhesion”. Also, primed neutrophils have delayed apoptosis, and are hyper-responsive to a subsequent activating stimulus. Please amend this section appropriately.

Thank you, these points were included and the section was amended.

d. The authors incorrectly state that HNAs are solely expressed on neutrophils (lines 268-269). For example, as well as being expressed on neutrophils, HNA-3 is also expressed on other cells and tissues including lymphocytes, platelets, endothelial cells, liver, colon (Storch et al, Blood, 2014; Flesch et al, Transfusion, 2013; Kommareddi et al, 2010, Protein J). HNA-4 and HNA-5 are both also expressed on other cells including monocytes/macrophages and lymphocytes. Please amend this section to correct this.

Thank you, we corrected this statement.

e. The authors correctly state that HLA Class II is not constitutively expressed on neutrophils.

However, they neglect to mention that it can be induced by some agonists such as MCSF, GMCSG, LPS, IFN-gamma or TNF-alpha (for primary references please see Tung et al, Blood Reviews, 2022). A rat model was developed that showed that priming with agonists such as above, induced neutrophil expression of the OX6 MHC class II antigen, and that these mice were susceptible to neutrophil-dependent anti-OX6 mAb-mediated TRALI (Kelher et al, Transfusion, 2016). Please amend this section to acknowledge this research.
Thank you, we included this point

f. The authors incorrectly state that BRMs are also referred to as bioactive lipids or aging blood products. The term "BRM" is a collective term for the myriad of mediators that are present in blood components and have been implicated in non-antibody mediated TRALI. These typically are thought to accumulate during storage such that their concentrations are higher in "aging blood products". Examples of BRMs include bioactive lipids such as lysophosphatidylcholines, arachidonic acid, and hydroxyeicosatetraenoic acids. They also include proteins such as sCD40L, IL-8, and extracellular vesicles. Please amend this section to acknowledge this.
This section has been amended as suggested.

g. The discussion of the role of platelets and NETs in TRALI pathogenesis (lines 290-296) regards both antibody-mediated and BRM-mediated TRALI. Therefore, this should be its own paragraph rather than being part of the BRM-mediated TRALI paragraph. Furthermore, the authors fail to acknowledge the conflicting results regarding the role of platelets in TRALI pathogenesis. I direct the authors towards some recent review papers (Ling et al, Respiratory Physiology & Neurobiology, 2023; Zeeuw van der Laan et al, 2020, Transfusion Medicine Reviews; Semple and Kapur, Transfusion, 2020) to help them improve this section. Could also reference additional evidence for NETs from Thomas et al (Blood, 2012) and van der Velden et al (Blood, 2023).
Thank you, paragraph separated as recommended and conflicting evidence of role of platelets noted. References added.

h. The authors describe reverse or inverse TRALI as involving patient antibodies reacting with neutrophils in the transfused blood product. They should also acknowledge that this risk has been addressed in many countries by the introduction of routine pre-storage leukodepletion of blood products. Nonetheless, there is still a potential for reverse TRALI even with leukodepleted blood products, as soluble antigens may be transfused and provoke TRALI development (Bayat et al, Blood Advances, 2021). Please amend this section to acknowledge this.
Thank you, this was addressed

5. TACO section:
a. I direct the authors towards the review by Semple and Kapur (Blood, 2019) which should be referenced in this section.

b. This section should also mention biomarkers (BNP and N-terminal pro-BNP)

c. This section should also mention the recent updated definition of TACO (Available from: https://www.isbtweb.org/resource/tacodefinition.html).

Thank you, these suggestions were included

6. Prevention and mitigation section:

a. I am unsure why the words "with effect" are included in the section title.

b. A figure and/or table would be helpful for this section.

c. The international section could be improved with reference to Reeskink et al (Vox Sangunis, 2012).

Thank you, these suggestions were included

7. Management and prognosis section:

a. I would suggest splitting these into separate sections.

b. Depending on the configuration, ECMO can also provide respiratory support, and is only offered in specialised hospitals. So that sentence (lines 463-466) requires editing.

c. The lack of protective effect of targeting platelets should also refer to the conflicting results from animal models (see earlier comment on platelets and TRALI)

Thank you, these comments were addressed

General Comments:

1. Please check that all abbreviations are defined on first use, and within the table legends (even if already defined within the manuscript text). Some examples (there might be others):

a. Line 129: CCC

b. Line 145: LAH

c. Table 1

d. Table 2

Thank you, abbreviations were defined throughout

2. Neutrophils and PMNs are both used when it would be better to choose one term and use that consistently.

Thank you, we edited to "PMN" for consistency.

3. Typographical errors, some examples are listed below:

a. Lines 143, 153, etc: the "2" in "O2" should be in subscript.

b. Line 226: "describe" should be "described"

c. Line 247: "doesn't" should be "didn't"

d. Line 281: "BAL's" should be "BALs" and "CD40L" should be "soluble CD40L"

e. Line 308: “inverted” should be “inverse”

4. Where a single reference is referred to in a series of sentences it would provide greater clarity for the reader if each sentence was referenced.

5. Additional references needed:
a. Lines 159-166
b. Line 181 and line 198: Berlin ARDS definition should be referenced
c. Lines 494-495

Reviewer F

General Comments:

I appreciate the opportunity to review your work. I read with interest the manuscript "The History of Transfusion Related Acute Lung Injury: How We Got to Where We Are Today". I believe this article may offer readers significant information regarding TRALI. Hereby, my comments:

Major comments:

1. Line 225: Please discuss why the incidence of TRALI in the German hemovigilance data is significantly lower than in other countries.
Thank you, they do not fully know why, but we included their speculating factors.

2. Line 337: Please state the incidence and mortality of TAD. Is it typically perceived as milder in its clinical expression compared to TRALI?
Thank you, this has been included.

3. Line 510: I believe the evolution in ARDS management has also contributed to reducing TRALI-related fatalities. How about a brief description regarding lung protective ventilation, appropriate use of neuromuscular blocking agents, prone position, conservative fluid management, etc.?
Thank you, this has been included.

Minor comments:

1. Line 198: If possible, please provide background on the exclusion of cardiopulmonary bypass

from the indirect ARDS risk factors.
Thank you, this has been included.

2. Line 316: Please state the usefulness of ejection fraction on echocardiography and pulmonary capillary wedge pressure (PCWP) value when differentiating TRALI from TACO.
Thank you, this has been included.

3. Line 465: If needed, please mention regarding inhaled nitric oxide (iNO) for improving oxygenation in the respiratory management of TARLI. As TRALI is a transient condition, would iNO as a bridging therapy be useful?
Thank you, this has been included.

Reviewer G

This is a narrative review on TRALI that includes sections on history, pathogenesis, diagnosis, epidemiology, prevention, and management/prognosis. While generally well written, it is unclear what this effort adds to the current literature. This reviewer has the following comments to offer:

This is a narrative review on TRALI. A recently published scoping review on TRALI demonstrated that, among the TRALI literature, there are more narrative reviews than original studies. There are several hundred narrative reviews on TRALI and it is not clear to this reviewer that another adds to the existing body of literature.

Narrative reviews, unlike systematic reviews, may miss key studies due to a lack of a systematic approach to identification, screening, and inclusion of studies. The section on TRALI incidence, for example, does not cover numerous studies and it is difficult to summarize the epidemiology of TRALI in a short section that includes a narrative review.
Thank you, while we agree that there are many reviews covering TRALI, this particular review is the most up to date and cover the historical aspect. Additional studies on incidence have been included.

In summarizing risk reduction of TRALI donor eligibility interventions, the authors did not mention existing meta-analysis on this topic.
Thank you, this has been address in various sections of the manuscript

The statement that we are reliant on passive surveillance is not entirely accurate. There are multiple published studies that have used active surveillance.
Thank you, this has been amended.

Minor comments:

Introduction: note that CCC is not the current consensus definition. Vlaar et al is mentioned later, but should be mentioned in the introduction.
Thank you, this has been included.

Page 6, line 271: minor typo, “implemented” should read “implicated”.
This typo has been corrected.

Page 8, line 321: Note that BNP is often elevated in TRALI as well.
Thank you, we have added in a line regarding the limited use of BNP.

Page 10, line 456: The Dutch study mentioned here (Klanderman et al) was not a review but was an original study. It reported much higher rates of TRALI than other studies in part due to active surveillance, but likely also other factors.
Thank you, this has been corrected.

Reviewer H

The authors have summarized the history of TRALI definition and its evolution and discussing different aspect including the differences between TRALI and TACO diagnosis. The review is well written.

1. Line 52: The statement “TRALI typically occurs following the transfusion” should be corrected to “TRALI typically occurs during or after a transfusion".
Thank you, this has been corrected.

2. Line 77: the definition of TRALI should include “occurring during or after a transfusion of” as per definition in line 86.
Thank you, this has been corrected.

3. Line 222: reference #2 is superscript, please check references format. Remove the single bracket after “European and United Kingdom”.
Thank you, this has been corrected.

4. Line 226: please remove the second “0,”
Thank you, this has been corrected.

5. Line 253: reference #11 is superscript, please check references format.
Thank you, this has been corrected.

6. Line 262: the authors could refer to more recent publications discussing the mechanism of antibody-mediated and non-antibody mediated TRALI. For example, ref #86 would be more appropriate.
Thank you, this has been updated.

7. Line 265: anti-HLAs and anti-HNAs antibodies are acquired during pregnancy, previous transfusion, or transplantation. Please add this information
Thank you, this has been updated.

8. Line 268: the authors say "HNAs are expressed solely on neutrophils while HLA class I antigens are also expressed on endothelial cells". This statement is incorrect. It should be expanded and better explained as HNA-1 and HNA-2 antigens are exclusive to neutrophils (i.e., Bayat et al, ISBT Science Series 2020) but other HNAs, particularly HNA-3, are expressed on neutrophils, endothelial cells as shown in recent studies, and other cell types (i.e., Browne Int J Immunogenet 2021).
Thank you, this has been updated.

9. Line 295: reference #55 is superscript, please check references format.
Thank you, this has been updated.

10. In the BRM section, authors might consider mentioning the role in TRALI of platelet-derived Extracellular vesicles due to the accumulation of ceramide on their surface (McVey et al, Blood 2021; Am J Physiol Lung Cell Mol Physiol 2017).
Thank you, this has been updated.

11. Line 290-296: the authors state the role of platelet in the pathogenesis of TRALI. However, it should be mentioned that this has been a debate. Some studies show the involvement of platelet in TRALI, while others show partial or no involvement (Semple and Kapur, Transfusion 2020; Zeeuw van der Laan et al, Transfus Med Rev 2020).
Thank you, this has been updated.

12. Line 299: the authors mention the threshold model that was described in Bux and Sachs Br J Haematol. 2007, not in ref #11, please correct reference
Thank you, this has been updated.

13. Line 306-311: The authors may consider expanding on the mechanism of reverse TRALI as it has been discussed very briefly.

Thank you, this has been updated.

14. When discussing the differences between TACO and TRALI, the authors might consider referring to other comprehensive reviews such as Semple et al, Blood 2019; Roubinian Hematology Am Soc Hematol Educ Program. 2018; Roubinian and Triulzi, Hematol Oncol Clin North Am, 2019.
Thank you, this has been updated.

15. Line 319: double space between "origin. TACO" please correct.
Thank you, this has been corrected.

16. Line 323: double space between "feature. Transudative" Please correct.
Thank you, this has been updated.

17. I found interesting the differences in the diagnosis between TRALI, TACO and TAD. The authors might consider adding some more information on TAD in table 2.
Thank you, this has been included.

18. The pathogenesis of TRALI is discussed, however, the authors don't mention the neutrophil-independent mechanisms of TRALI development. This should be at least briefly addressed.
Thank you, this has been updated.

Reviewer I

The review by Vandenakker and Friedman is focusing on a very interesting topic. It is well structured and covers many aspects of this transfusion related pathological consequence or adverse event.

There are some points of concern, or observations, which I will enumerate as follows:

- In many parts of the manuscript, TRALI is explained as an event that is mediated by high-plasma containing transfusion products.

I think that this definition is somehow incomplete, and while when reading further, it is explained better (including the two-hit mechanism, vs the antibody-mediated mechanism), it can lead to confusion. Furthermore, red blood cell concentrates do not contain plasma... My suggestion would be to explain the association of TRALI events to each transfusion product, and maybe explain that while its incidence is higher in plasma-containing products, it can also occur when transfusing RBCs concentrates (which are plasma free). The safety of transfusions by chosing male-donor products or

non-pregnant female donors, is also something to consider, but that has made transfusions in general safer (not only focusing on TRALI, but any other immune-related event).
Thank you, this suggestion has been incorporated throughout the manuscript.

It would be nice to have also insight on the studies in human, which ones were done in patients with underlying condition or not.
Thank you, we included more human study references into the manuscript.

Furthermore, all references cited are a bit old. There have been a lot of publications, more updated, which the authors could explore in depth. For example, studies in human (i.e. DOI: 10.1111/trf.17157, PMID: 35748490 - where they compare old and fresh platelet concentrates, or those with or without antipathogen treatment), or additional studies in mouse models (PMID: 36640155); implications of platelet alterations in sepsis (PMID: 35288057), TRALI in hepatic transplantation..., due to platelet microparticles (PMID: 33232973) etc etc etc. The review could be a little bit more updated.
Thank you, we included more up to date references throughout the manuscript.

Minor points:

- Revise English again, there are some sentences or sections that could be improved in style (i.e. line 344 "to reduce of"... should be "to reduce...", as an example. Check all the document for minor mistakes as this).
This typo has been corrected.

- Revise Editing, positioning of stop-dots, before or after referring to Tables, IL nomenclature (see line 250), repetitions (line 277) or Bibliographic References.

- line 236: ... parity ad the formation of HLA antibodies... sounds odd; would it be better the "presence" of HLA antibodies, or the "induction" of HLA antibodies?
This has been changed to “induction”.

- The following reference could be added to the section in lines 298-304: DOI: 10.1038/s41586-021-04263-y. It describes neutrophils with different phenotype, different levels of activation, and that could be something that could be specifically
Thank you, reference added.