Peer Review File

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First Round Peer Review

Reviewer A

Congratulations to the authors for this cleanly conducted, statistically clearly calculated and with a practical statement ending investigation. Overall, these are comprehensible hypotheses that are tested with an adequate method. In a final version, the following minor points should be addressed to anticipate questions that may arise for the reader.

Comment 1: In what way and in how many patients was patient blood management performed preoperatively?

Reply 1: We thank the reviewer for this very important question. We considered the implementation of patient blood management protocols as basic, which is why this was not described in the initial version of the manuscript. Patient blood management standards are routinely applied to all patients undergoing surgery at our institution. This includes perioperative measures for managing anemia, optimizing coagulation and using blood conservation strategies. However, detailed data regarding the adherence to these protocols were not available for this present analysis. For clarification, the following paragraph was added to the METHODS section of the manuscript (highlighted in yellow):

Patient blood management

Institutional patient blood management protocols were applicable to all patients in this study, which included perioperative measures for managing anemia, optimizing coagulation, and using blood conservation strategies. Regarding drug anticoagulation, acetylsalicylic acid (ASC) was continued perioperatively in all elective cases. In cases with double platelet inhibition (ASC plus clopidogrel), clopidogrel was paused in a timely manner prior to surgery when feasible. In patients with therapeutic anticoagulation, the drug was paused prior to surgery according to the respective agent, i.e. 24–48 hours for modern oral anticoagulants (apixaban, rivaroxaban, edoxaban) or according to international normalized ratio (INR) values for coumarin derivatives (where bridging with heparin was performed). Hemoglobin levels, thrombocyte levels and INR were monitored perioperatively in all patients and corrected following institutional protocols and the German cross-sectional guidelines for therapy with blood components and plasma derivatives, amended ed., 2020 (13).

Comment 2: How many surgeons were involved in the operations and why was the significant impact of technical performance on bleeding not considered?

Reply 2: We thank the reviewer for this remark. Our unit employed 3 thoracic surgeons during the study period who either performed or assisted all procedures. We agree with the reviewer that bleeding risk may also depend on individual technical skills. However, the procedures in this study were heterogeneously distributed among the surgeons. Therefore, an evaluation of the individual bleeding risk per surgeon would not add much value. In our view, this would be a more interesting analysis if, for example, outcomes of a large cohort of elective VATS lobectomies were studied. We are confident that the reviewer will agree with us on this point.

Comment 3: How was coagulation management, as a key point to prevent a bleeding cascade, handled?

Reply 3: We thank the reviewer for this very important question. Please see also our response to Comment 1. For clarification, the following paragraph was added to the METHODS section of the manuscript (highlighted in yellow):

Patient blood management

Institutional patient blood management protocols were applicable to all patients in this study, which included perioperative measures for managing anemia, optimizing coagulation, and using blood conservation strategies. Regarding drug anticoagulation, acetylsalicylic acid (ASC) was continued perioperatively in all elective cases. In cases with double platelet inhibition (ASC plus clopidogrel), clopidogrel was paused in a timely manner prior to surgery when feasible. In patients with therapeutic anticoagulation, the drug was paused prior to surgery according to the respective agent, i.e. 24–48 hours for modern oral anticoagulants (apixaban, rivaroxaban, edoxaban) or according to international normalized ratio (INR) values for coumarin derivatives (where bridging with heparin was performed). Hemoglobin levels, thrombocyte levels and INR were monitored perioperatively in all patients and corrected following institutional protocols and the German cross-sectional guidelines for therapy with blood components and plasma derivatives, amended ed., 2020 (13).

Comment 4: How and according to what criteria was the decision to administer blood products made?

Reply 4: We thank the reviewer for this question. The decision to administer blood products was made at the discretion of the treating anesthesiologist / surgeon following institutional and national guidelines. The respective national guideline applicable in Germany is given full citation in the METHODS section of the manuscript.

Comment 5: In what context was machine autotransfusion (MAT) used in which patients (e.g., irradiated in tumor patients)?

Reply 5: We thank the reviewer for this question. At our institution, indication for machine autotransfusion is handled rather restrictively in patients with germ-contaminated surgery or in patients with confirmed or suspected malignancy. No patient in this study received machine autotransfusion.

Reviewer B

I read with great interest the manuscript by Galata et al. on blood transfusion and thoracic surgery. The authors are to be commended on their work at their institution aiming to identify risk factors for transfusions and optimize resource utilization in Germany.

Comment 1: In a recent study, Abdelsattar et. al, studied thousands of thoracic patients and identified 5 variables that are nearly identical to the risk factors provided in this manuscript with the addition of BMI. This paper can be found at: Abdelsattar ZM, Joshi V, Cassivi S, Kor D, Shen KR, Nichols F 3rd, Allen M, Blackmon SH, Wigle D. Preoperative Type and Screen Before General Thoracic Surgery: A Nomogram to Reduce Unnecessary Tests. Ann Thorac Surg. 2022 Jul 6:S0003-4975(22)00936-5. doi: 10.1016/j.athoracsur.2022.06.027. Epub ahead of print. PMID: 35809656.

Reply 1: We thank the reviewer for this remark. We agree with the reviewer that the work of Abdelsattar et al. is indeed excellent research. However, it looks at transfusion practice in thoracic surgery from a different angle. We think our work is a valuable addition here.

Comment 2: The authors should discuss their findings in the context of the above paper. The current manuscript as it is, is very simplistic and needs a little bit more depth. Can the authors apply the nomogram presented in the Abdelsattar paper to their cohort? Can it be validated with their data? That would make the paper way more interesting.

Reply 2: We thank the reviewer for this very exciting comment. A common problem with nomograms in clinical research is that they are often only internally validated (which also seems to be the case in the study by Abdelsattar et al.) but lack validation in external, preferably in multiple, disparate datasets. We might to able to provide an anonymized dataset of our study cohort for external validation of the nomogram in the study by Abdelsattar et al. However, we hope that the reviewer will agree that this is beyond the scope of this current manuscript and would constitute a separate work. As requested by the reviewer, we have added the discussion of our findings in the context of the paper by Abdelsattar et al. to the DISCUSSION section of the manuscript (highlighted in yellow):

A large single-center retrospective analysis by Abdelsattar et al. investigating a cohort of 6280 patients found an overall transfusion rate of 7.1% (17). However, this study reported intraoperative blood transfusion only and included a different spectrum of

surgical procedures and patients (47.7% esophageal operations, the majority of those for benign disease).

Comment 3: In Table 4, the odds ratios seem inaccurate. For example, Open surgery has an Odds ratio <1 this contradicts the conclusion unless there is typographical error, please double check all the values as there are several apparent errors. In addition, reporting p-values alone is meaningless. Please report the percentages in this table and their reps octave p-values. The odds ratio should be reported on the left of its p value.

Reply 3: We gratefully thank the reviewer for this very important hint. We assume that "odds ratio <1" means "odds ratio smaller than one". We double-checked Table 4. The typographic error regarding the odds ratio for "open surgery" was corrected in the revised version of the manuscript (highlighted in yellow). Furthermore, we agree with the reviewer that there are different ways of presenting results of statistical tests. The percentages of all relevant parameters are provided in the RESULTS section of the manuscript. Regarding the statistical tests, we provide p-values for all univariable analyses and p-values with odds ratios together with their 95% confidence intervals for the multiple logistic regression analysis. This is a widespread and accepted approach in many high-ranking analyses and publications. We therefore think this approach is also sufficient for the data and scope of our present manuscript.

Comment 4: the author mention that the time from the blood bank to the OR is prolonged. Can you show us some data about this? How long is it? What would be an acceptable duration of time.

Reply 4: We thank the reviewer for this question. The transport time of blood products from the blood bank to the OR at our institution is monitored for internal quality control by the blood bank / regulatory agencies. However, details on these quality control data were not available for the present scientific analysis. In an emergency, the transport takes place immediately. The aim of the practice of carrying out type and screen / crossmatch generously was to avoid losing time to determine the blood group / perform crossmatch in an urgent case. For clarification, the relevant paragraph has been rephrased in the DISCUSSION section of the manuscript (highlighted in yellow):

At our institution, the blood bank is located outside the building complex with the operating theatres, which theoretically can lead to longer transport times for blood products. This consideration led to a high number of routine crossmatches due to patient safety considerations. Nevertheless, this practice needs to be reviewed, considering the low transfusion rate, the fact that blood products are a limited resource, and the significant costs associated with the supply of blood products.

Comment 5: the multi variable model is unclear to me. The authors mention that if p<0.1 then the variable was included in the model, but then also used a stepwise approach. Are the four variables shown, the only variables in the model? This should be clarified.

Reply 5: We thank the reviewer for this question. As described in the METHODS section of the manuscript, variables were entered into the multivariable model if $p<0.10$ in univariable analysis. That means, ALL variables which were statistically significant in univariable analysis were entered into the multivariable model. In the multiple analysis, the backward stepwise selection based on the probability of the Wald statistic was used and a significance level of $\alpha=0.05$ was chosen to determine final independent predictors. Those were Empyema, open surgery, preoperative hemoglobin and age. For clarification, this information was also added to Table 4 (highlighted in yellow):

All variables with p<0.10 in the univariable analyses were entered into the multivariable analysis. In multivariable analysis, only empyema, open surgery, Hb and age remained in the model as independent prognostic factors.

Comment 6: was mortality different between patients who got transfused vs those who did not?

Reply 6: We thank the reviewer for this excellent question. Mortality was not different between patients with and without transfusion (p=0.36). The following sentence was added to the RESULTS section of the manuscript (highlighted in yellow):

In-hospital mortality was not different between patients with and without RBC transfusion (p=0.36).

Comment 7: what is the current transfusion strategy in effect at their hospital? Is there a certain cutoff? Is it the same intraoperatively vs postoperative. These should be clarified in the manuscript to aid the reader in generalizing their findings. Several studies have demonstrated a restrictive strategy is associated with improved outcomes. A discussion also citing this work would add more depth to the paper: Abdelsattar ZM, Hendren S, Wong SL, Campbell DA Jr, Henke P. Variation in Transfusion Practices and the Effect on Outcomes After Noncardiac Surgery. Ann Surg. 2015 Jul;262(1):1-6. doi: 10.1097/SLA.0000000000001264. PMID: 26020111.

Reply 7: We thank the reviewer for this remark. The transfusion strategy at our institution is based on the German cross-sectional guidelines for therapy with blood components and plasma derivatives, amended ed., 2020, as we report in the METHODS section of the manuscript. There is no absolute threshold as to when the transfusion of blood products is indicated (e.g. below a certain hematocrit / Hb value). Instead, multiple factors have to be taken into account, e.g. cause, duration and severity of anemia, extent and rate of blood loss, pre-existing diseases etc. However, we can confirm that, in accordance with the guideline, we pursue a restrictive transfusion strategy at our department. For clarification, we have modified the respective sentence in the METHODS section of the manuscript and cite the paper mentioned by the reviewer (highlighted in yellow):

Indications for RBC transfusion were severe perioperative bleeding and the prevention of tissue hypoxemia according to national and institutional guidelines for hemotherapy (13). In accordance with the guideline, a restrictive transfusion strategy was pursued, which has been shown to be associated with improved outcomes in surgical patients (14).

Comment 8: how did the authors account for conversion to open. For example if a patient started VATS, bled intraop and needed transfusions and conversion to open, were these patients counted as VATS or open? Important to clarify. Also important to clarify how many of the day zero transfusions were intraop or postop.

Reply 8: We thank the reviewer for this important remark. We accounted for conversion to open in our analysis. VATS procedures were only those that were completed as closed chest surgery. All cases which ended open were counted as open. As requested by the reviewer, this information has been added to Table 4 (highlighted in yellow):

"Open surgery‡" – "‡ including conversion".

Furthermore, of the 21 patients transfused on the day of surgery, n=20 received the first RBC concentrate intraoperatively. As requested by the reviewer, this information was added to the legend of Figure 3 (highlighted in yellow):

Of the 21 patients transfused on the day of surgery, 95.2% received the first RBC concentrate intraoperatively.

Comment 9 (minor): I would suggest dropping the pie chart and changing it into a different figure. Pie charts do not add much in the medical literature and are an inefficient way of displaying data in figure format. Overall, I think the paper can be strengthened with the above requests for major revisions.

Reply 9: We thank the reviewer for this suggestion. Several guidelines for data visualization recommend using pie charts when comparing proportional data with less than seven categories (and in cases where percentages add up to 100%). We therefore would like to keep the pie chart. Please see also: Healy K (2018): Data visualization: a practical introduction. Princeton University Press, Princeton.

Reviewer C

Comment 1: In the abstract (line 41-42), the first sentence of the conclusion is the rate of RBC transfusion in non-cardiac thoracic surgery decreased significantly when compared to previous data, especially in elective lung resections. Actually, the authors have not done any comparative study in their work, but a retrospective study, and they extrapolate this statement by comparing their results with the literature. Although they deepen this aspect in the discussion of the article, I

believe that this conclusion cannot be drawn from the results that appear in the abstract and should perhaps be eliminated.

Reply 1: We thank the reviewer for this comment. The abstract was rephrased accordingly (highlighted in yellow):

The rate of RBC transfusion in current non-cardiac thoracic surgery is low, especially in elective lung resections. In urgent cases and open surgery, transfusion rates remain high, particularly in empyema cases.

Comment 2: In the introduction (line 60-65), a comment is made about publications related to the transfusion of blood products in cardiac surgery and in non-cardiac thoracic surgery procedures. Transfusion percentages are given in certain surgeries and I personally understand that these are percentages based on said bibliography, but I think it would be easier for the reader if the bibliographical reference were moved to the end of the commentary.

Reply 2: We thank the reviewer for this comment. The bibliographic references were moved to the end of the paragraph as suggested by the reviewer.

Comment 3: In the methods (line 89-91), a reference is made to the German guidelines for handling blood components. I think it should be included as a reference in the bibliography and cited in the text.

Reply 3: We thank the reviewer for this important question. The guideline was included as a reference as suggested by the reviewer.

Comment 4: In the methods (line 98-99), a transfused patient is defined as one who receives a blood component in the first three postoperative days. I do not know why the authors have chosen that range of days and not the entire postoperative period of the patient until he is discharged.

Reply 4: We thank the reviewer for this excellent question. Limiting the period to the first 3 days after surgery helps to establish a direct link to the operation. This is particularly important in patients who who may be in hospital for a long time. This approach is widely used in the surgical literature, some authors even analyze only intraoperative blood transfusions. An example for this is the excellent paper mentioned by REVIEWER B, Abdelsattar et al., Ann Thorac Surg. 2022 Jul 6:S0003-4975(22)00936-5. PMID: 35809656.

Comment 5: In the methods (line 104-105), the authors define postoperative mortality as intrahospital mortality. There is literature that affirms that it is more realistic to evaluate mortality at one month and not at patient discharge. I don't know if the authors could make the effort to review this aspect.

Reply 5: We thank the reviewer for this comment. We agree with the reviewer that 30-day or 90-day mortality would be preferable to in-hospital mortality in studies that evaluate long-term outcomes after surgery. Unfortunately, these data were not available for this present analysis. However, as the objective of this study was to identify risk factors for RBC transfusion (and not to evaluate e.g. major complications or mortality itself), we think that in-hospital mortality may be sufficient for the purpose of this study. We hope the reviewer agrees with us.

Comment 6: In the results (line 134-135), the authors say that they reoperated on 2.5% of the patients. Perhaps it would be interesting to know how many of these reinterventions were due to bleeding.

Reply 6: We thank the reviewer for this comment. None of the was due to bleeding was for bleeding. As requested by the reviewer, this information was added to the RESULTS section of the manuscript (highlighted in yellow):

Surgical revision was necessary in 2.5% of cases. None of the revisions were due to hemorrhage.

Comment 7: In the discussion (line 219-220), the authors say that the selectivity of our standard operating procedure regarding the risk transfusion was poor and blood usage was inefficient and therefore also not cost-effective. No cost or economic study has been carried out, so I don't think such a claim can be made.

Reply 7: We thank the reviewer for this important comment. As we state in the DISCUSSION section of our manuscript, the crossmatch to transfusion ratio, the transfusion probability, and the transfusion index showed that the selectivity of our standard operating procedure regarding the risk transfusion was poor and blood usage was inefficient. When blood usage is inefficient, it is most likely also not cost effective, even if we did not perform a detailed economic analysis. For clarification, the respective paragraph in the DISCUSSION section was rephrased (highlighted in yellow):

In our study, the crossmatch to transfusion ratio, the transfusion probability, and the transfusion index showed that the selectivity of our standard operating procedure regarding the risk of transfusion was poor and blood usage was inefficient. Therefore, it was most likely also not cost-effective, even if we did not perform a detailed cost analysis.

Comment 8: In tables 1 and 2, there is a column with the heading n/%/median. I think it is confusing for the reader because it forces you to think about what is being evaluated. Perhaps it would be easier to add the unit or measurement value next to each variable.

Reply 8: We thank the reviewer for this hint. We have tested the changes in the tables as recommended by the reviewer but found the tables more confusing and less readable afterwards. Therefore, we decided to keep the tables in their initial form.

Comment 9: In Table 3, the authors have already explained to us why they have chosen the values of Hb<10.4 and age>77, but they do not tell us why they have chosen the cut-off point of >108 minutes as prolonged surgery.

Reply 9: We thank the reviewer for this excellent hint. We have added the requested information to the results section of the manuscript (highlighted in yellow):

The parameter "length of surgery" was not an independent predictor in multivariable analysis; however, the best value to separate patients with versus those without RBC transfusion was >108 min (sensitivity 64.3%, specificity 66.4%, AUC 0.655 with a 95% CI of 0.557–0.753).

In addition, this information was also added to Table 3 (highlighted in yellow):

† Cut-off values determined by ROC analysis.

Comment 10: In Table 3, the authors talk about metastasectomies. It seems that the procedure does not include any anatomical resection or wedge and perhaps they are talking about laser enucleations, but I think they should define it so that the procedure is clear.

Reply 10: We thank the reviewer for this remark. If metastases required anatomical resection, those patients are listed under lobectomy / segmentectomy / pneumonectomy. As the reviewer assumes correctly, "metastasectomy" refers to precision excision of pulmonary metastases, either by electrocautery or laser assisted. This information has been added to Table 3 (highlighted in yellow):

§ Precision excision (electrocautery or laser assisted)

Comment 11: In Table 3, it is striking that more transfusions have been given to patients with empyema than to patients with hemothorax. I don't know if the authors can comment on this...

Reply 11: We thank the reviewer for this comment. Patients with empyema show a tendency to bleed intraoperatively due to inflammation and the wound area caused by decortication, which most likely explains the need for transfusion. Most patients operated for hemothorax do not (or not any longer) have active bleeding at the time of surgery, which explains a lower perioperative transfusion requirement compared with empyema. In other words, most bleedings causing hemothorax are self-limiting.

Comment 12: In Table 3, there are more procedures under the heading other procedures (210) than under lung resections (169). They appear as mediastinum, chest wall, pleura... I think it would be important to define what we are talking about specifically, since a thymectomy is very different from a mediastinoscopy, for example.

Reply 12: We thank the reviewer for this comment. In Table 3, "other procedures" is a subheading, the details are listed below that subheading. Regarding the category "mediastinum": it mainly included procedures for tumor resection or the management of mediastinitis, which probably explains the higher transfusion rate. Mediastinoscopy has a low risk of bleeding, but is rarely performed at our center due to the increasing use of EBUS / TBNA. In order to keep the table clear, we would refrain from providing a detailed breakdown. However, we added this fact to the DISCUSSION section of the manuscript (highlighted in yellow):

As a note, we observed a relatively high transfusion rate (13.0%) for mediastinal procedures. This is plausible as this category consisted mainly of major procedures for mediastinal tumor resection or surgical management of septic complications of mediastinitis.

Reviewer D

Comment 1: The authors note that transfusion rates have improved compared to older studies (primarily evidence from 1994). However, I would think that it would be more appropriate to use more contemporary historical controls. For example, Towe and colleagues (JTCVS 2019) show that in the STS database, rate of incidence of PRBC transfusion is 26% (35% for a thoracotomy and ~20% for VATS), compared to the 44% rate in the Munich group. Similarly, Latif, Isbell and colleagues detail transfusion requirements for various surgical procedures pertaining to resection of NSCLC (JTCVS 2019). In fact, the transfusion rate for all thoracic surgeries combined is quoted as 8.5% (Byrd, JTD 2022), which is very different than the 16% the authors quote. The authors should acknowledge the more contemporary data regarding transfusion requirements for different types of thoracic procedures that exist.

Reply 1: We thank the reviewer for this very important comment. As requested by the reviewer, we cite the paper of Latif et al. in the DISCUSSION section of the manuscript. However, the observed transfusion rate of 10.2% in this paper seems to be for anatomic lung resections only (2-fold our transfusion rate for lobectomy). As demanded by the reviewer, we also cite the paper by Byrd et al., but please let us mention here that their transfusion rate seems to only apply to patients undergoing surgery for lung cancer (and not for all thoracic surgeries). The work by Towe et al. is also cited; this group observed a lower transfusion rate of 26.3%, but focused on acute empyema only and excluded patients with chronic empyema and malignancy, which may explain this difference. The following lines were added to the DISCUSSION section of the manuscript (highlighted in yellow):

A more recent study by Latif et al. reported a rate of perioperative blood transfusion of 10.2% in patients undergoing anatomic lung resection for non-small cell lung cancer (5). Similarly Byrd et al. observed a transfusion rate of 8.5% in all cases with surgery for lung cancer within the STS database (16).

Comment 2: If the authors are going to make comparisons in transfusion rates between different cohorts/ eras, then there should be a better description of what the institutions practices were during the study inclusion period (2021). Specifically:

1) What was the pre-operative assessment and optimization practices in terms of correcting anemia for non-emergent cases?

2) What was the practice for holding or reversing anticoagulation / antiplatelet therapy?

3) What were intra-operative transfusion thresholds?

American Society of Anesthesiology 2015 guidelines have a number of suggestions for minimizing peri-op transfusions. The authors themselves reference the 2021 STS guidelines (Tibi, et al) a few times, although don't mention which specific practices were incorporated into their institutions work-flow.

Reply 2: We thank the reviewer for this important question. We considered the implementation of patient blood management protocols as basic, which it why we did not mention it in the initial version of the manuscript. We have added the requested information to the METHODS section of the manuscript (please see also response to the other reviewers, changes highlighted in yellow):

Patient blood management

Institutional patient blood management protocols were applicable to all patients in this study, which included perioperative measures for managing anemia, optimizing coagulation and using blood conservation strategies. Regarding drug anticoagulation, acetylsalicylic acid (ASC) was continued perioperatively in all elective cases. In cases with double platelet inhibition (ASC plus clopidogrel), clopidogrel was paused in a timely manner prior to surgery when feasible. In patients with therapeutic anticoagulation, the drug was paused prior to surgery according to the respective agent, i.e. 24–48 hours for modern oral anticoagulants (apixaban, rivaroxaban, edoxaban) or according to international normalized ratio (INR) values for coumarin derivatives (where bridging with heparin was performed). Hemoglobin levels, thrombocyte levels and INR were monitored perioperatively in all patients and corrected following institutional protocols and the German cross-sectional guidelines for therapy with blood components and plasma derivatives, amended ed., 2020 (13).

Comment 3: The crossmatch rate at the institution is emphasized quite a bit. The authors should more explicitly describe their maximal surgery blood order schedule. It seems like a major influence in the MSBOS was logistical concerns regarding distance from the blood bank to the surgical theatre. If that is so, the majority of data points in Table 2 regarding transfusion ratios, probabilities, and

indexes are institution-specific and are not of value to other centers. This should be highlighted in the discussion under study weaknesses.

Reply 3: We thank the reviewer for this comment. We have edited the respective paragraph in the DISCUSSION section of the manuscript (highlighted in yellow):

At our institution, the blood bank is located outside the building complex with the operating theatres, which theoretically can lead to longer transport times for blood products. This consideration led to a high number of crossmatches due to patient safety considerations. Nevertheless, this practice needs to be reviewed, considering the low transfusion rate, the fact that blood products are a limited resource, and the significant costs associated with the supply of blood products.

Furthermore, we added the following sentence to the limitations of this study in the DISCUSSION section (highlighted in yellow):

The high rate of cross-matched patients in this study resulted from institution-specific requirements and cannot be generalized.

Comment 4: Interestingly, 51 (13%) of patients were not cross-matched prior to surgery. Why was there non-adherence to hospital protocols for this sub-set of patients?

Reply 4: We thank the reviewer for this question. The institutional protocol provided the option that the attending surgeon and attending anesthesiologist could deviate from the institutional protocol standard if the bleeding risk of the procedure was judged to be exceptionally high or low.

Comment 5: The authors cite ethical concerns regarding high rates of pre-operative type and cross. At many institutions, blood products that have been issued can be returned within an 8-hour period as long as they are stored under optimal conditions. What is the protocol at this single center? Exactly how much blood was wasted?

Reply 5: We thank the reviewer for this comment. Blood products are stored and transported according to guidelines and legal requirements (transfusion law (Transfusionsesetz)) at our institution. In fact, all RBC units that are not used must be returned to the blood bank, regardless of whether they can be further used or not (which is at the discretion of the blood bank). We do not “waste” blood. However, this does not change the fact that an RBC unit that is cross matched for one specific patient is – from this moment on! – not available for any other patient until it is released again by the blood bank. This alone can be an ethical factor to consider in situations where there is a general shortage of blood or where patients have rare blood types.

Comment 6: A major outcome is that empyema and other surgical procedures are associated with higher rates of transfusion, which is not necessarily surprising. However, there is an inherent bias in your center's practice (as suggested by your maximal surgical blood schedule order) where you classify standard vs. high-risk procedures a priori and cross-match accordingly. This bias needs to be mentioned in the discussion.

Reply 6: We thank the reviewer for this comment. We agree with the reviewer that there is risk for bias in our study, which results mainly from its retrospective nature. This is referred to under limitations in the DISCUSSION section of the manuscript. Furthermore, as per institutional guidelines and the requirements of the transfusion law (Transfusionsgesetz, TFG) in Germany, the fact that RBC units are cross matched for a patient (or the number of RBC units that are cross matched) does not at all impact the indication for RBC transfusion. By institutional guidelines and by law (§13 transfusion law), an RBC transfusion can only be carried out when medically indicated. Everything else would not only be unethical but would also be a violation of the law in Germany.

Comment 7: Each disease process is categorized by itself, while procedure approach (open vs minimially invasive) is also categorized, when in actuality there were subcohorts (i.e.- all empyemas were not treated with open thoracotomies or VATS alone). This should be accounted for.

Reply 7: We thank the reviewer for this comment. We agree with the reviewer that we did not analyze all subcohorts that are conceivable. Splitting the study cohort into further subgroups would result in low patient numbers in each of those subgroups, thus leading to statistical tests with questionable results. To reflect this, we added the following sentence to the limitations of the study in the DISCUSSION section of the manuscript:

The number of patients in this study did not allow the analysis of all conceivable subgroups.

Reviewer E

Comment 1: This study analyzes the risk factors for red blood cell transfusion in non-cardiac thoracic surgery and concludes that empyema, laparotomy, preoperative low hemoglobin, and high patient age are risk factors. However, as the author himself stated, these have been previously described as risks for transfusion and are not novel.

Reply 1: We thank the reviewer for this remark. First, we may emphasize here that we did not evaluate patients undergoing "laparotomy". Apart from that, our study is novel as it shows a contemporary analysis of blood transfusion in a larger single center collective in the times of VATS and ERAS, with an explicit focus on thoracic procedures / lung resections. It offers an update on transfusion practice in modern

thoracic surgery, which is not studied frequently. We are convinced that our work is a useful contribution to the existing literature and therefore merits publication.

Reviewer F

Comment 1: The results of the higher rate of transfusion in empyema surgery is easily expected. There are some procedural types for empyema surgery; the bleeding amount would depend on these procedural types. Therefore, it is recommended to describe detailed procedural types of empyema surgery. Furthermore, I think that the procedure styles of empyema are quite different from that of lung cancer in regards to operative bleeding. Therefore, I think that the authors should evaluate the data by dividing these diseases.

Reply 1: We thank the reviewer for this remark. All patients who underwent surgery for empyema underwent thoracoscopic or open decortication. For clarification, this information has been added to Table 4 (*Empyema (decortication)*) and to the METHODS section of the manuscript:

All patients who underwent surgery for empyema underwent thoracoscopic or open decortication.

Furthermore, in our analysis, patients with surgery for lung cancer (segmentectomy, lobectomy, pneumonectomy) are separated from empyema patients.

Comment 2: In empyema surgery, the amount of bleeding depends on the procedural type or the kind of bacterial species. Therefore, the details of these factors should be described and evaluated to assess red blood cell transfusion in non-cardiac thoracic surgery.

Reply 2: We thank the reviewer for this remark. Our study included n=38 patients with surgery for empyema; splitting this cohort into further subgroups (e.g. according to bacterial species) is unlikely to return reliable statistical results. Moreover, the procedural type was identical in all cases (decortication), as described above.

Comment 3: To avoid red blood cell transfusion, the embolization of the bronchial artery might be required before empyema surgery based on the condition of the empyema patients. Was the supplemental preoperative procedure performed?

Reply 3: We thank the reviewer for this remark. Embolization of the bronchial artery is not routinely performed in empyema patients at our center. Furthermore, no case of empyema in this study had embolization of the bronchial artery. We hope the reviewer can accept that we will not comment on this point to keep the manuscript concise.

Comment 4: It is more valuable to assess the cut-off value for each disease and procedural type in order to safely manage non-cardiac thoracic surgeries.

Reply 4: We thank the reviewer for this remark. We did not analyze risk factors for each disease / procedure separately as the number of patients in each subgroup would be too low to obtain reliable statistical results. Furthermore, our multivariable analysis models shows that some diseases / procedures (e.g. empyema surgery) are risk factors for transfusion while others are not.

Comment 5: I felt that the contents of the introduction were not considerable enough to improve the problems of non-cardiac thoracic surgery or to improve the managements of the surgery. I recommend better describing the background and aim of this study.

Reply 5: We thank the reviewer for this remark. We have once again checked the INTRODUCTION. We admit that it is rather short, but it explains the background and aim of the present analysis. To keep the manuscript clean and concise, we ask the reviewer for his understanding that we refrain from further elaboration of the INTRODUCTION.

Comment 6: In line 35-36, the following sentence was very confusing to understand the meaning; “Patients with lung resections (44.6%) required transfusion in 2.4% of all cases (lobectomy: 5.2%) versus 44.7% in patients undergoing surgery for empyema.”.

Reply 6: We thank the reviewer for this advice. The phrase was modified accordingly (changes highlighted in yellow):

Patients with lung resections required transfusion in 2.4% of the cases versus 44.7% in patients undergoing surgery for empyema.

Comment 7: In line 42, the words “previous data” should not be used in the abstract because I couldn’t understand what the previous data indicated.

Reply 7: We thank the reviewer for this comment. The abstract was modified accordingly (changes highlighted in yellow):

The rate of RBC transfusion in current non-cardiac thoracic surgery is low, especially in elective lung resections.

Comment 8: In line 80-81, minor procedures should be described in details.

Reply 8: We thank the reviewer for this comment. The following sentence was modified in the METHODS section of the manuscript (changes highlighted in yellow):

Patients undergoing minor procedures (chest tube insertion under local anesthesia, minor wound care) or patients with extra-thoracic procedures were excluded.

Second Round Peer Review

Reviewer D

This version reads much more easily- thank you for heeding the reviewer comments.

Comment 1: For the most part you shifted away from the surgical blood ordering schedule and focused on actual blood transfusion, which makes this a better paper. Your blood ordering practices are mostly unique to your institution, which detracts from the

manuscript. I would amend your abstract conclusion to focus less on the blood ordering schedules. I would also minimize paragraph 8 (line248-261).

Reply 1: We thank the reviewer for this comment. The sentences "Maximum surgical blood ordering schedules based on the type of procedure alone seem outdated. Ethically and economically, it is advisable to reduce preoperative blood ordering to a reasonable degree." were removed from the abstract conclusion, as requested by the reviewer. Furthermore, paragraph 8 (lines 248-261) was shortened, as requested by the reviewer.

Comment 2: A large draw-back to your study is that it is a single-center study. Your center does not perform esophageal procedures, lung transplants, etc. Almost 3/4 of your cases are minimally invasive. I think this needs to be mentioned more explicitly, although it doesn't necessarily need to be a negative. Is your practice scope similar to most thoracic surgery departments in the EU, world? Help your reader understand if their patient population matches yours. I think the overall message is still very valuable- open cases, empyemas, etc. are associated with higher risk of bleeding.

Reply 2: We thank the reviewer for this comment. We agree with the reviewer that the single center design of our study is a limitation. This is reflected in the DISCUSSION section of the manuscript. As requested by the reviewer, the following paragraph was added to the DISCUSSION section of the manuscript: Our study shows current transfusion data in the era of minimally invasive surgery in a cohort comprising the typical spectrum of modern thoracic procedures (excluding esophageal resections and lung transplants). Our data thus are most likely representative of many centers in Europe.

Comment 3: A patient was counted as having been transfused if they received PRBCs within the first 3 days. You should mention why this time frame was chosen (as opposed to any prbc transfusion during the hospitalization, or just perioperative transfusion).

Reply 3: We thank the reviewer for this remark. The following sentence was added to the METHODS section of the manuscript: This time interval was chosen to detect transfusion events likely related to the procedure.

Comment 4: Fig 3a is difficult to read.

Reply 4: We thank the reviewer for this hint. For the final version of the manuscript, Fig.3a will be provided as a high quality vector graphic which will facilitate reading.