Peer review file
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Reviewer A

Comment: The impact of significant postoperative 12-hour blood loss on 30-day mortality was excluded from the analysis in the current study. If possible, the authors should try to explore whether there was also a correlation.

Reply – Thank you for this comment. In this study, our aim was to explore long-term impact of bleeding. It is widely recognised in the literature that significant bleeding and need for re-exploration is associated with 30-day mortality, which is why we have not focused on this in our current manuscript. We have shown in a publication from our centre that significant bleeding and the need for re-exploration is associated with a more than double 30-day mortality in a propensity matched study. As such we have decided not to include that in this manuscript, however, we have added mention of these previous findings.

Change – In discussion: In this study, we also performed a propensity matched analysis which demonstrated a more than double 30-day mortality in patients who experience significant port-operative bleeding highlighting the impact of bleeding on early outcomes

Comment: For patients undergoing CABG, more clinical details such as history of myocardial infarction (MI), myocardial viability, the incidence of preoperative existing ischemic mitral regurgitation, postoperative MI as reflected by the elevated cardiac troponin levels, etc. should be reported. Their influence on the long-term survival should also be analysed.

Reply – Thank you for this comment. We agree that this would be very useful to interrogate. Unfortunately,because the patients underwent surgery so long ago (2003 – 2013), we are unable to access this data and perform the suggested analysis. We have expanded our limitations section to include this limitation.

Change – Limitations: Furthermore, we do not have data on myocardial viability, perioperative myocardial infarction or the presence of ischaemic mitral regurgitation – all of which may also impact on early and late outcomes following surgery

Comment: The incidence of preoperative tricuspid regurgitation, liver dysfunction (particularly related to alcoholic cirrhosis), or right heart failure may affect perioperative hemostasis and their impact on long-term clinical outcome in these patients should be reported, respectively

Reply – Again, this is very true. Unfortunately, for the same reasons we do not have access to this data. I should add, that I have previously looked at the impact of cirrhosis on outcomes following cardiac surgery and we identified only 37 patients over a 10 year period and so this group is thankfully quite small. We have added this to the limitations section also.

Change – Limitations - Additionally, factors such as hepatic cirrhosis and tricuspid valve regurgitation may also impact coagulation status, and are variables that we have been unable to account for.

Reviewer B

Comment: There were no comments to address

Reply – Thank you for your review and comments on our manuscript

Change – No changes required.

Reviewer C

Comment: Consider adding a supplementary analysis including patients who died within 30 days. Because you excluded several patient groups, the findings of the study will only be applicable to populations similar to those who were included. The generalizability of the findings should be discussed

Reply - Thank you for your comment. The findings of our study is indeed only applicable patients similar to those we decided to include.
Theis study was focused on assessing the blood loss impact in a homogenous cohort of patients who underwent coronary bypass grafting.
The following patients were not included from analysis: previous cardiac surgery, single coronary artery bypass graft, minimally invasive direct coronary artery bypass grafting, off-pump coronary artery bypass grafting and end-stage renal failure undergoing haemodialysis. These non-inclusion criteria were mainly decided due to small numbers of patients in these sub-groups (for example, only 4.7% underwent off pump coronary bypass, without full dose of heparin, and are not comparable to patients who received heparin for the cardiopulmonary bypass). After these non-inclusion criteria, 6337 of the 7927 patients (79.9%) who underwent CABG were included.
Finally, the aim was to assess the impact of postoperative blood loss on long-term survival, independently of severe postoperative complications. Therefore patients who died within the first 30-days following surgery (considered postoperative mortality) were also excluded from the analysis. We however agree that our findings are therefore only applicable for patients who survived the first 30 days.
Following your comment, we performed additional analysis including those patients. 7927 patients underwent CABG over the period of our study. Of these, 6265 patients met inclusion criteria. The 30-day mortality of this cohort was 1.2% (n=72). Including these patients (n=6337), the main results remain however similar with a significant long-term impact of Blood loss in the first 12 hours if the loss was >500ml (HR 1.14, p=0.015) and >1000ml (HR 1.38, p<0.001).

Change – Included in methods: The following patients were excluded from analysis due to there being small numbers in each group. In results: The same results were seen for the entire cohort including those patients who died within 30 days (Supplementary Figure 1)

We have included the survival curve as a supplementary figure. In the limitations: In this study we have focused on patients with 30-day conditional survival and as such this will limit the generalisability of the findings.

Comment: The study population underwent surgery from 2003-2013 – please discuss the implications regarding the external validity (generalizability) of the study results, specifically regarding contemporary patient populations.

Reply – We absolutely agree. However, in order to have long-term follow-up the patient population needs to have had surgery a long time ago, so it is a difficult problem to overcome unfortunately. However, we have acknowledged this further in the limitations section as suggested

Change – Limitations section: We acknowledge that some practices during this period may not reflect contemporary practice and this must be considered when thinking about the generalisability of the results - however this enables us to consider long term outcomes.

Comment: The possible effect of clopidogrel was not accounted for but acknowledged as a limitation of the study.

Reply – Thank you for the observation – and as you say we have included this in the limitations.

Change – no change required

Comment: How was vital status ascertained? Describe in detail including the validity of the procedure used.

Reply – In the UK because of the national health service it is possible to ascertain the vital status for any patient. We have detailed this further in the methods;

Change – In the methods: Mortality information was obtained from the UK National Health Service patient administration system and was therefore available for all patients included in the study

Comment: When categorizing a continuous variable (blood loss), much information is lost. Please provide additional analyses that support your choice of categorization cut-points.

Reply - For the blood loss continuous variable, the log-linearity assumption was not confirmed (checked by using the quartiles of the variable). Therefore, a transformation of the variable in a categorical variable was performed.

The 500 and 1000 threshold were decided following clinical judgment (from our point of view, blood loss of 450ml rather than 250ml is unlikely to impact the patient status, whereas blood loss >1000ml is very likely to have consequences).

Change – We have included the following in the methods: For the blood loss continuous variable, the log-linearity assumption was not confirmed (checked by using the quartiles of the variable). Therefore, a transformation of the variable in a categorical variable was performed. The 500 and 1000 thresholds were chosen following clinical judgment. Additionally, we have added an additional figure – a histogram showing the distribution of blood loss at 12 hours to highlight this.

Comment: In order to reliably demonstrate an association between exposure and outcome in this study, effective adjustment for confounding factors is necessary. A true confounder is associated with both exposure and outcome without being on the causal pathway. You will need to convince the reader that you have controlled for all major confounding factors, because there is a high risk for residual confounding in this study.

Reply - Thank you for your comment. Since this is a retrospective study, we completely agree that potential confounding factors might not have been taken in account in our model, like the preoperative treatment and their last take date. We however did our best to get as many perioperative variables as possible.
In order to reduce the residual confounding in our study, we first assessed and include variables associated with the blood loss result (table 4). Secondly, for the survival analysis, we assessed available variables that could impact on the patient survival. Finally, we assessed variables that was described as risk factors of bleeding in the literature. A first selection of covariates was performed with the log-rank test ($P<0.20$). Then a Cox model was estimated with a backward procedure performed manually variable by variable. This procedure allows the identification of possible confounding factors (variation of Blood Loss regression coefficient of >20%).
The following perioperative data were considered as possible correlates of death: operative age (years), sex, body mass index, family history, high blood pressure history, diabetes mellitus, smoking history, dyslipidaemia, obesity, chronic obstructive pulmonary disease, preoperative creatinine clearance, Left ventricular function, surgery priority, preoperative haemoglobin, Cardiopulmonary bypass time, Cross clamping time, number of grafts, type of grafts, Final Hb in theatre, re-exploration for bleeding in the first 48 hours, Blood transfusion, and, finally, Blood Loss in the first 12 hours.

Change – The change is linked with the next comment so see below:

Comment: The multivariable analyses are not sufficiently well described and the short presentation in the manuscript leaves me with a strong impression that it is not correctly performed. Please refer to these guidelines that will help in reporting what was done (in particular, I would recommend the authors to direct their attention to the subheading "Excluding covariates that are non-significant in the (final) model" in reference 1 below):

Reply Thank you for your comment. The multivariable analysis was performed as follows:

- Univariable pre-screening have been performed, including covariates associated with the blood loss variable and/or the outcome (death). The main outcome of this study was the time between surgery and patient death, so we used of the Kaplan-Meier estimator and the log-rank test. The threshold for the P-value was 0.20. Median follow-up was 9.4 years and 2139 events (=death) have been reported. Age and Blood loss have been forced into the model.
- Continuous covariates have been transformed if the log-linearity assumption was not confirmed (checked by using the quartiles of the covariate). The rationale for using a particular cut-off was mainly based on clinical judgement or available data in the literature.
- The following perioperative data were considered as possible correlates: operative age (years), sex, body mass index, family history, high blood pressure history, diabetes mellitus, smoking history, dyslipidaemia, obesity, chronic obstructive pulmonary disease, preoperative creatinine clearance, Left ventricular function, surgery priority, preoperative haemoglobin, Cardiopulmonary bypass time, Cross clamping time, number of grafts, type of grafts, Final Hb in theatre, re-exploration for bleeding in the first 48 hours, Blood transfusion, and, finally, Blood Loss in the first 12 hours.
- For the multivariable analysis, a Cox proportional hazards regression model have been performed. Hazards proportionality was checked graphically by plotting log-minus-log survival curves and by testing the scaled Schoenfeld residuals. No violation was observed for the included variables. As advised in the mentioned guidelines, backward elimination was performed, manually variable by variable. This procedure allowed us the identification of possible confounding factors (variation of Blood Loss regression coefficient of >20%). During this backward selection, 6 variables have been eliminated. In the full model with all covariates included, the HRs for the Blood loss covariate were respectively 1.136 [1.016-1.269] and 1.351 [1.125-1.622] in the >500 ml and >1000ml bleeding groups (very close to the HRs from the final model).

Following your comment, we modified the manuscript as follows:

Change – Methods section: The main outcome of this study was the time between surgery and patient death. A first selection of covariates was performed with the use of the, including covariates associated with the blood loss variable ($P<0.20$) and/or the main outcome (Kaplan-Meier estimator and log-rank test, $P<0.20$). Continuous covariates have been transformed if the log-linearity assumption was not confirmed (checked by using the quartiles of the covariate).
The following perioperative data were considered as possible correlates of death: operative age (years), sex, body mass index, family history, high blood pressure history, diabetes mellitus, smoking history, dyslipidaemia, obesity, chronic obstructive pulmonary disease, preoperative creatinine clearance, Left ventricular function, surgery priority, preoperative haemoglobin, Cardiopulmonary bypass time, Cross clamping time, number of grafts, type of grafts, Final Hb in theatre, re-exploration for bleeding in the first 48 hours, Blood transfusion, and, finally, Blood Loss in the first 12 hours.

For the multivariable analysis, a Cox proportional hazards regression model have been performed. Age and Blood loss have been forced into the model. Hazards proportionality was checked graphically by plotting log-minus-log survival curves and by testing the scaled Schoenfeld residuals, and no violation was observed. A backward elimination was performed, manually variable by variable. This procedure allowed us the identification of possible confounding factors (variation of Blood Loss regression coefficient of >20%).

Comment: Line 180-182: You state that more than 1000 ml of bleeding at 12 hours was associated mortality but re-exploration and receiving blood transfusions were not. This does not make sense. Please explain this paradoxical finding.

Reply – Thank you for this observation. Our feeling is that this finding is to do with the fact that patients who require significant transfusion or who undergo re-exploration – if they do badly, suffer in the early perioperative period. In keeping with this – we have previously performed a propensity analysis and saw that patients who were re-explored, had twice the 30-day mortality of matched patients who did not, highlighting the impact of re-exploration on early outcomes. However, this work considers 30-day conditional survival and the assumption we are concluding is that even if a patient is re-explored, if they survive 30-days then the re-exploration in and of itself has no bearing on long-term outcome.

Change – We have included in the discussion: Our data agree that for patients who are re-explored or receive blood transfusion, if they survive to 30-days their long-term outcomes are unaffected by this early insult. This implies that once patients recover there are no long-term impacts of having been re-explored or receiving blood transfusion, and that the negative effects of these are both focused in the early post-operative period. This is not the case for bleeding though, which does appear to have an impact.

Comment: Lastly, the clinical utility of these findings may be limited because there is a general consensus among cardiac surgeons that excess postoperative bleeding should be avoided.

Reply – You are right, however, although it is widely accepted attention to haemostasis does vary between surgeons – as evidenced when we implemented our haemostasis checklist – we saw a significant reduction in bleeding, re-exploration and blood product consumption through a relatively simple change. So a reminder of the importance of bleeding on outcomes will hopefully help to reenforce the message of what surgeons already know.

Reviewer D

Comment: Is there any association between the lowest postoperative Hb value and long-term survival?

Reply – This is an interesting question. Unfortunately, because the patients underwent surgery so long ago (2003 – 2013) this level of data is unavailable for the patients and so we were unable to perform this analysis – however we agree that it would be very intereting.

Change – we have added the following to the discussion: Unfortunately, discharge haemoglobin was not available for these patients, but it would have been interesting to see if this correlated with long-term outcome.

Comment: About half of the patients in the >500ml and >1000ml bleeding groups did not receive a blood transfusion (Table 4). Is there a difference in long-term survival between those patients and those who did receive blood transfusion?

Reply Following your advice, we performed additional analysis in the sub-groups of patients with >500 and >1000 ml of bleeding. We found no significant differences the transfusion effect on the long-term survival, respectively HR = 1.04 [0.87-1.23] and 0.98 [0.72-1.35] in the >500 ml and >1000ml bleeding groups.

Change – In the results: The impact of receiving blood transfusion on long-term survival was also explored. There were no significant differences in the long-term survival comparing those who received or did not receive transfusion, respectively HR = 1.04 [0.87-1.23] and 0.98 [0.72-1.35] in the >500 ml and >1000ml bleeding groups. (Figure 3) And we have included the survival curves as figure 3.

Reviewer E

Comment: Looking into bleeding I would have expected data regarding hemostasis with lab results/bedside tests including specific tests (eg ROTEM - may be nothing was available 10 years ago?) and management (platelet concentrates, factor concentrates, FFP, antifibrinolytic agents). Especially the restrictive policy of reexplorations and potential liberal use of clotting products could have some influence on long term outcome.

Reply – Thank you for this comment – you are correct that it would have been good to have this data. Unfortunately, because of the retrospective nature of this work and that the patients underwent surgery between 2003-2013 this data is not available to us.

Change – We have significantly expanded our limitation section to acknowledge these and other factors that are due to inablility to access data from so long ago.

Comment: Intersting would be the number of patients with bleeding and reexploration (y/n) and RCB transfusion (y/n). Because you stated, that reexploration and RCB transfusion had no influence on long term outcome I wonder, if reexploration and RBC are not rather protecting regarding long term outcome in bleeding cases.

Reply – It is an interesting thought. As per one of the comments above, we have analysed and presented survival curves demonstrating that receiving a blood transfusion does not impact

on long-term survival within the >500ml and >1000ml groups. Similarly we report that those re-explored do not have inferior survival. It must be borne in mind that this cohort are patients with 30-day conditional survival and we anticipate that his masks the impact of significant transfusion and re-exploration – as these are both associated with worse early mortality.

Change – as per the comment 8 reviewer c above and others

Comment: Disappointing are the puzzling numbers. Starting from the overall variable number of cases (6270, 6265, 6265-72deaths or? eg lines 63,156,157,tables) continuing with the tables (n=6265 eg BMI adding up to 6130 patients adding to 100% by percentage of what?) or in the text (eg line 159: 71,9% (n=4112) - of which patient population??, This has to be clarified/corrected.

Reply – Thank you for this important observation. You are correct that there was some discrepancy. There are are 6265 patients in the study and this has now been corrected. In terms of the percentages – these reflect % of those for whom there was data available. Because for some fields there was blank data for a small number of patients, this is why for example, for BMI, there are 100% distributed to 6130 patients – the remaining 135 had no data available.

Change – We have included in the legend of the tables: Percentages quoted are for the patients with data available for that particular variable.

Comment: I appreciated the question in line 247 about the reasons of your findings. In your undertanding a prolonged anaemia could contribute to reduced long term survival. Do you have any data (hemoglobin at discharge) to support this thesis? Furthermore, patients with preop low hemoglobin are in danger as well thus should be one conclusion to be more liberate with transfusions? This however would be an argument against the "trend towards restrictive...transfusion [line237], especially in the sick CABG population.

Reply – Thank you – you are right. We have included an additional section in the discussion highlighting that per-operative haemoglobin is important. Whilst you are right that liberal post-operative transfusion is potentially harmful – here we are talking about preoperative optimisation – which need not necessarily be transfusion but can be things like iron supplementation etc preoperatively to optimise the haemoglobin.

Regarding your other point – unfortunately we do not have access to the discharge haemoglobin which would be very interesting to have looked at.

Change - Furthermore, it is well recognised that peri-operative anaemia is associated with inferior long-term outcomes and it may be that a persistent anaemia, if untreated, may contribute to the inferior long-term survival[21] As such elective patients at our centre with pre-operative anaemia are reviewed by a haematologist for pre-operative optimisation.

Unfortunately, discharge haemoglobin was not available for these patients, but it would have been interesting to see if this correlated with long-term outcome.

Reviewer F

Comment: Authors should clearly specify how follow-up was performed and what was the completeness of follow-up. Those are key information and they are missing

Reply – In the UK because of the national health service it is possible to ascertain the vital status for any patient. We have detailed this further in the methods;

Change – In the methods: Mortality information was obtained from the UK National Health Service patient administration system and was therefore available for all patients included in the study