

## **ABO blood group is related to bleeding in cardiac surgery**

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Søren Mose Hansen, conceived of the presented idea and study design. Claus Andersen, feedback, and supervision throughout the study.

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## **Abstract**

**Background:** Increased bleeding and blood product transfusions during cardiac surgery are associated with poor outcomes. The patient's ABO blood group is related to hemostatic balance, although it is unclear whether this influences bleeding during cardiac surgery. This study aimed to evaluate whether ABO blood group is related to bleeding during cardiac surgery.

**Methods:** This retrospective study evaluated data from 17,058 cardiac surgical procedures that were performed in four Danish cardiosurgical centers. Data regarding chest tube drainage and transfusion volumes were retrieved from a clinical database and combined with information regarding ABO group. The primary outcome was chest tube drainage volume and the secondary outcomes were transfused volumes of various blood products.

**Results:** Blood group O had the largest chest tube drainage volume (mean: 745 mL, 95% CI: 720–771 mL) and blood group AB had the smallest volume (mean: 664 mL, 95% CI: 598–731mL). The inter-group difference in the mean drainage volume was 81 mL (95% CI: 8–154 mL,  $p < 0.05$ ). Patients with

blood group A or blood group B had mean drainage volumes that were between the volumes for groups AB and O. Relative to group O, group AB received smaller mean volumes of all blood products. The most pronounced difference was in platelet concentrates, with mean values of 170 mL for group O (95% CI: 157–184 mL) and 63 mL for group AB (95% CI: 34–92 mL).

**Conclusion:** The patient's ABO group appears to be related to volumes of chest tube drainage and transfused blood products during cardiac surgery.

**Keywords:** hemorrhage, ABO blood group system, thoracic surgery, blood loss, surgery, erythrocyte transfusion.

**Editorial Comment:** The association between blood group and both bleeding and blood product administration was assessed in this retrospective analysis of a multi-centre cohort of cardiac surgery patients. Findings include that cases with blood group AB was associated with slightly less chest tube output in 24 hours postoperatively and received less blood products compared with other blood groups. One possible explanation was increased amount of von Willebrand factor and factor VIII, although the lack of additional patient characteristics and management data limited the assessment.

## Introduction

Bleeding and blood product transfusions are important determinants of cardiac surgery resource use and outcomes [1, 2]. For example, a multivariate analysis revealed that bleeding and transfusion of red blood cells were associated with an approximately 3-fold increased risk of operative mortality [3]. Furthermore, bleeding complications are associated with longer stays in the intensive care unit (ICU) and hospital [4].

There is broad variability in bleeding among patients who are undergoing open cardiac surgery, which may be related to patient-level variations in hemostatic balance. For example, patient-level differences exist in terms of the risk of venous thromboembolism (VTE). A large retrospective study of more than one million Scandinavian blood donors revealed that non-O blood groups were associated with an increased risk of VTE (odds ratio [OR]: 1.80, 95% confidence interval [CI]: 1.71–1.88), relative to blood group O [5]. However, the relationship between ABO group and bleeding is less clear. One systematic review, which included 22 studies, suggested that patients with blood group O had a small but significantly increased risk of bleeding events (OR: 1.33; 95% CI: 1.25–1.42),

reported events included gastrointestinal bleeding, bleeding complications during anticoagulation treatment, intracranial bleeding, and mucosal bleeding (epistaxis) [6].

The relationship between ABO blood group and bleeding may be related to correlations between ABO blood group and plasma concentrations of von Willebrand factor (vWF) and factor VIII. One study of 1,117 blood donors revealed that blood group O had the lowest average concentration of circulating von Willebrand antigen (vWF:Ag, 75%), blood group AB had the highest concentration (123%), and intermediate concentrations were observed in group A (106%) and group B (117%) [7]. The higher vWF:Ag concentrations in individuals with blood group AB are likely related to individuals with blood group A or blood group B being homozygous or heterozygous for the alleles encoding the A- and B-transferases. In this context, individuals with the *AO* or *BO* genotype have higher vWF:Ag concentrations than individuals with the *OO* genotype, but lower concentrations than individuals with the *AA*, *BB*, or *AB* genotype, which all confer similar high concentrations of vWF:Ag [8, 9]. Nevertheless, the exact mechanism underlying the correlation between circulating vWF concentrations and ABO blood group is unclear.

Some studies have considered whether ABO group is related to bleeding during cardiac surgery, with one study evaluating chest drainage in patients undergoing coronary artery bypass grafting [10] and another study examining perioperative transfusion of red blood cells (PRBCs) [11]. However, those studies failed to support firm conclusions regarding the possible association. Therefore, the present study aimed to evaluate whether ABO blood group was correlated with bleeding and blood product transfusion volumes during cardiac surgery.

## Methods

This retrospective study evaluated perioperative data retrieved from the West Danish Heart Database. Data were retrieved for 18,471 consecutive patients who underwent cardiac surgery at four Danish centers between 2008 and 2018. Patients were considered eligible if they had undergone any type of open-heart surgery and had available information regarding their ABO blood group. Data were extracted regarding the postoperative chest tube drainage (CTD) volume, basic demographic characteristics, type of surgery, extracorporeal circulation, cross-clamp time, and preoperative use of anticoagulants. The CTD volume in the database is the total volume that was collected before the drains were removed. Information regarding ABO group was retrieved from regional transfusion services, as this information is not recorded in the database. This study's protocol, including the merging of ABO group data and registry data, was approved by the Danish Patient Safety Authority.

### **Outcome measures**

The primary outcome was the total CTD volume. The secondary outcomes were total volumes (in mL) of blood products transfused in the operating room and in the postoperative intensive care unit (ICU). Volumes were calculated for red blood cells (RBCs), thawed fresh frozen plasma (FFP), and platelet concentrate (PC).

### **Statistical analysis**

The distributions of volumes for CTD and transfused blood products were severely skewed to the right, as expected. This could have been addressed via logarithmic data transformation (Figure 1), although this would require comparing mean values for log CTD and log transfused volumes, and estimates based on the log scale are not easily interpretable by clinicians. Therefore, we decided to report the estimates based on untransformed data by applying bootstrapping with 1,000 repetitions to account for deviations from the distribution assumptions. The mean volumes for CTD and transfused blood products were compared between the different blood groups (A, B, AB, and O) using linear regression. As a secondary analysis we performed logarithmic transformation of CTD volumes and reported the results from this as geometric means and relative difference in CTD volume relative to blood group O. Covariation between the ABO group, baseline patient characteristics, and perioperative data was tested using the chi-squared test for categorical variables and the median test for continuous variables. Because there were some differences in the baseline variables between the ABO groups, we also analyzed the differences in CTD via multiple linear regression again applying bootstrapping with 1,000 repetitions to adjust for the baseline characteristics. Statistical analysis was performed using STATA (StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC). Results were considered statistically significant at P-values of <0.05.

### **Results**

During the 10-year study period, 18,471 patients had undergone cardiac surgery at the 4 participating centers. A total of 17,058 patients (92%) fulfilled the study's inclusion criteria (Figure 2). These patients included 7,139 patients (42%) with blood group O, 7,426 patients (44%) with blood group A, 1,798 patients (11%) with blood group B, and 695 patients (4.1%) with blood group AB. Important perioperative and patient characteristics according to ABO group are listed in Table 1. The logistic Euro-score (euroSCORE1-log) was marginally lower in the AB group, and there were small inter-group differences in the pre-operative use of platelet inhibitors (group AB: 39%, group O: 42%, group A: 40%, group B: 40%). There was a marginally smaller proportion of aortic surgery cases for

blood group AB than for blood group O (5.8% vs. 7.7%). However, these differences were not statistically significant. There were small but statistically significant differences in the preoperative creatinine concentrations between the groups.

The median total CTD volume was 490 mL, although there was substantial variability in the volumes (range: 0–34,500 mL, interquartile range: 300–800 mL). As expected, the distribution was considerably skewed to the right. The mean CTD volumes (calculated using bootstrapping) for blood groups A, B, AB, and O as well as the difference in CTD relative to group O are reported in Table 2. The mean CTD volume for blood group O was 745 mL, which was larger than in the other groups, although the only significant difference was observed between groups O and AB.

Results from comparing the same volumes using logistic transformation of CTD volumes are reported in table 3.

A similar, albeit not significant ( $p=0.12$ ), result was observed using a multiple linear regression model (with bootstrapping) that incorporated the logistic Euro-score (euroSCORE1-log), pre-operative creatinine concentration, preoperative use of platelet inhibitors, and frequency of aortic surgery.

Table 4 shows the total perioperative use of blood products, including the total volumes of RBCs, FFP, and PC transfused in the operating room and the ICU. The results revealed that patients with blood group O received the largest transfusion volumes, and that patients with blood group AB received the smallest transfusion volumes. The observed differences were small and non-significant in volumes of RBCs and FFP used for groups O, A, and B. However, patients with blood group AB had significantly smaller volumes of transfused RBCs, FFP and PCs relative to patients with blood group O. On average, patients with blood group AB received 34% smaller volumes of RBCs and 37% smaller volumes of PC, relative to patients with blood group O.

Using the same multiple linear regression model as mentioned above revealed a smaller but still significant difference in the volume of transfused RBCs (group AB vs. group O:  $-42$  mL, 95% CI:  $-69$  mL to  $-16$  mL,  $p=0.002$ ) and platelets (group AB vs. group O:  $-84$  mL, 95% CI:  $-150$  mL to  $-18$  mL,  $p=0.01$ ). Differences relative to group A and B were non-significant in this model.

## Discussion

This study identified small differences in postoperative CTD drainage, with the lowest volume observed for patients with blood group AB and the highest volume observed for patients with blood group O. However, the differences across the ABO groups were small and explained only a small part of the total variation in postoperative drainage volume. In addition, the only significant difference was between blood groups O and AB. The differences in CTD volumes were also reflected in the

volumes of transfused blood products, with significant smaller volumes transfused in patients with blood group AB compared to patients with blood group O.

Our findings regarding the relationships between ABO group and the volumes of bleeding and transfusions agree with previously reported findings. However, to the best of our knowledge, only 2 studies have evaluated the relationship between ABO group and bleeding during cardiac surgery.

One single-center prospective study evaluated 780 patients who were undergoing coronary artery bypass grafting and measured the CTD volume during the first 12 postoperative hours. Patients with blood group O had a slightly larger mean drainage volume ( $616 \pm 362$  mL), relative to patients with non-O groups ( $585 \pm 346$  mL), although the difference was not statistically significant ( $p=0.18$ ) [10]. The second study retrospectively evaluated 13,627 cases and measured the number of perioperative blood product transfusions (on the day of surgery and the first 2 postoperative days.) The results revealed that patients with blood group AB received a median number of 2 transfusions of packed red blood cells (PRBCs), which was not significantly lower than the median number of 3 PRBC transfusions in the other groups, although Kaplan-Meier curve analysis revealed that patients with blood group AB had better long-term survival [11].

Our findings regarding postoperative bleeding are also consistent with the reported correlation between ABO blood group and concentrations of factor VIII and vWF. For example, lower concentrations of these factors are found in individuals with blood group O, intermediate concentrations are found in individuals with blood group A, and high concentrations are found in individuals with blood groups B and AB [12]. Thus, differences in hemostatic balance that are associated with the ABO group may affect bleeding during cardiac surgery. However, we observed small differences in baseline patient characteristics and surgical complexity, which might have contributed to the observed differences in the CTD volumes. Nevertheless, including these baseline characteristics in a multiple regression model seemed to explain at least some of the observed inter-group differences in CTD volumes. Therefore, the relationships between ABO group and concentrations of vWF/factor VIII do not appear to completely explain the correlations between ABO blood group and the volumes of bleeding and transfused blood products. Other mechanisms might include differences between the different ABO groups in terms of the type and frequency of cardiac diseases and comorbidities at the time of cardiac surgery. These factors would likely affect surgical complexity and the preoperative use of platelet inhibitors.

Interestingly, the differences in transfusion volumes were larger than the difference in CTD volumes. We are unable to provide a clear explanation for this phenomenon. However, it is possible that the difference were related to increased diffuse bleeding, which might have prompted transfusions of larger volumes of FFP and PC.



Our study considered all types of open cardiac surgery. Previous studies only considered coronary artery bypass grafting and combined bypass grafting and valve procedures [10, 11]. Considering all types of open cardiac surgery includes more patients with a high risk of bleeding, although it also makes our study population more heterogeneous. This could have introduced additional confounders and mechanisms, other than hemostatic balance, that might explain the correlation between blood group and CTD volume. Furthermore, we were unable to collect 12-h data regarding CTD volume and had to consider the total CTD volume. This might be a limitation, as interstitial fluid leakage due to inflammation or decompensation can contribute to the total CTD volume in prolonged chest tube placement.

The present study's retrospective design and reliance on data from an existing database are also potential limitations, as we did not have complete data regarding the patients' characteristics and managements. For example, the relationship between ABO blood group and CTD volume might be influenced by anticoagulation activity, pre-operative hemoglobin concentration, the indication for surgery (e.g., valve surgery for degenerative disease or endocarditis, and aortic root surgery for dilatation or dissection), repeat surgery, the indication(s) for transfusion, and hemostatic interventions. However, none of these parameters are known to be associated with ABO blood group. Another potential limitation is the lack of data regarding vWF and factor VIII concentrations, as well as the ABO genotype, which precludes a definitive conclusion regarding hemostatic balance as the explanation for the correlation between ABO blood group and bleeding. Moreover, although the ABO blood group appears to be correlated with CTD volumes, the actual differences in volumes were fairly small. Thus, based on the existing evidence, ABO blood group may not be relevant in the clinical decision-making process regarding hemostatic management during cardiac surgery.

Nevertheless, our findings indicate that patient-level differences in hemostatic balance, even when they are within the normal range, might be important and should be considered when designing studies and protocols addressing hemostatic optimization during cardiac surgery. For example, patients with low but normal vWF concentrations might experience greater benefit from treatments that increase circulating vWF concentrations (i.e., desmopressin), although well-designed studies are needed to generate more robust evidence regarding this strategy.

## **Conclusion**

The present study revealed that the ABO blood group was correlated with the volumes of bleeding and transfusion products used during cardiac surgery. Relative to patients with blood group O, patients with blood group AB had a significantly lower mean CTD volume and received significantly smaller volumes of perioperative FFP and PC transfusions. These correlations may be explained by

variations in hemostatic balance that are related to low but normal vWF and factor VIII concentrations in patients with blood group O, and high but normal concentrations in patients with blood group AB. However, it is also important to note that the ABO blood group could be correlated with other determinants of bleeding, such as underlying diseases, type of cardiac surgery, surgical complexity, use of platelet inhibitors, and other factors. Moreover, the ABO blood group only explained a small part of the broad variation in postoperative bleeding. Therefore, the current evidence does not support the use of ABO blood group to guide hemostatic practice during cardiac surgery. Further studies are needed to examine the clinical relevance of patient-level differences in hemostatic balance, even when they are considered within the normal ranges.

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Table1. Baseline characteristics of the study population (demographics and clinical covariates)

		Blood group						P
		N	O	A	B	AB	P	
Age (y)	median [IQR]	17,058	68.8 [61.1 - 75.1]	68.5 [60.8 - 74.7]	68.6 [60.9 - 74.7]	68.2 [60.4 - 74.5]	0.24	
Female Gender	n, %	17,053	1,781 (25%)	1,812 (24.4%)	430 (23.9%)	172 (24.8%)	0.78	
Height (cm)	median [IQR]	17,011	173 [167 - 169]	174 [167 - 180]	173 [167 - 179]	173 [166 - 180]	0.42	
Weight (Kg)	median [IQR]	17.011	81 [71 - 91]	81 [71 - 91]	80 [71 - 90]	80 [72 - 90]	0.74	
Euro-score1 -Sum	median [IQR]	17,053	5 [3 - 7]	5 [3 - 7]	5 [3 - 7]	5 [3 - 7]	0.17	
Euro-score1 – log	median [IQR]	17,052	3.95 [2.07 - 7.96]	3.88 [2.07 - 7.89]	3.82 [2.07 - 7.48]	3.7 [1.82 - 7.17]	0.30	
Pre Creat (µmol/l)	median [IQR]	16,254	84 [73 - 99]	83 [72 - 98]	85 [72 - 99]	84 [73 - 97]	0.01*	
Pre LVEF (%)	median [IQR]	16,217	60 [50 - 60]	60 [50 - 60]	60 [50 - 60]	60 [50 - 60]	0.09	
CPB time (minutes)	median [IQR]	15,110	95 [73 - 126]	95 [73 - 170]	96 [73 - 127]	91 [69 - 124]	0.12	
cross-clamp time (minutes)	median [IQR]	15,085	61 [43 - 83]	61 [42 - 83]	61 [42 - 83]	58 [40 - 82]	0.10	
Platelet inhibitor	n, %	16,842	2,939 (41.7%)	2,919 (39.8%)	702 (39.6%)	267 (38.9%)	0.07	
ASA 5 d.	n, %	16,842	2,450 (34.8%)	2,411 (32.9%)	586 (33.1%)	216 (31.4%)	0.06	
Clopidogrel 5 d.	n, %	16,842	289 (4.1%)	278 (3.8%)	69 (3.9%)	21 (3.1%)	0.52	
Ticagrelor 5 d.	n, %	13,782	68 (1.2%)	64 (1.1%)	11 (0.8%)	5 (0.9%)	0.51	
Anti Coagulant	n, %	16,862	580 (8.2%)	637 (8.7%)	162 (9.2%)	55 (8%)	0.54	
VKA 2d	n, %	16,862	99 (1.4%)	114 (1.6%)	21 (1.2%)	12 (1.8%)	0.59	
NOAC 2d	n, %	2,054	3 (0.3%)	2 (0.2%)	0 (0%)	1 (1.2%)	0.38	
Fondaparinux	n, %	5,428	144 (6.2%)	165 (7.1%)	34 (6.4%)	14 (6.4%)	0.57	
TXA	n, %	15,213	6,103 (96.3%)	6,394 (96.3%)	1,568 (96.6%)	591 (96.9%)	0.80	
Aprotinin	n, %	15,213	148 (2.3%)	158 (2.4%)	43 (2.7%)	9 (1.5%)	0.44	
CABG	n, %	17,058	4,664 (65.3%)	4,944 (66.6%)	1,204 (67%)	457 (65.8%)	0.35	
Aorta Valve	n, %	17,058	2,471 (34.6%)	2,501 (33.7%)	587 (32.7%)	253 (36.4%)	0.19	
Mitral Valve	n, %	17,058	552 (7.7%)	589 (7.9%)	163 (9.1%)	51 (7.3%)	0.28	
Aortic surgery	n, %	17,058	549 (7.7%)	527 (7.1%)	132 (7.4%)	40 (5.8%)	0.21	
Combined procedure	n, %	17,058	1,059 (14.8%)	1,091 (14.7%)	275 (15.3%)	102 (14.7%)	0.93	

Table 2 . Patient distribution by blood group, mean drainage by blood group and difference in mean drainage compared to blood group O

Blood Group	N	Mean CTD, ml [95% CI]	Regression, Δ CTD, ml, [95% CI]	p-value, regression
O	7,139	745 [719; 772]	-	-
A	7,426	737 [713; 762]	-8 [-43; 27]	0.65
B	1,798	715 [663; 766]	-31 [-89; 28]	0.30
AB	695	664 [598; 731]	-81 [-154; -8]	0.03*
All	17,058			

Mean values of chest tube drainage in the postoperative intensive care unit in ml. 95% confidence interval in brackets. Difference in CTD compared to blood group O calculated by linear regression. P-values for difference between blood group O and the three other groups. \* indicates  $p < 0.05$

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Table 3. Patient distribution by blood group, geometric mean of CTD for each bloodgroup calculated relative difference in CTD compared to blood group O and p-values for difference in log (CTD+1ml) compared to blood group O.

Blood Group	N	Geometric Mean CTD, ml [95% CI]	Relative CTD compared to group O [95% CI]	p-value, regression
O	7,139	507 [497; 517]	-	-
A	7,426	504 [494; 514]	99% [97%;102% ]	0.67
B	1,798	493 [473; 513]	97% [92%;;102%]	0.20
AB	695	464 [435; 495]	92% [86%; 98%]	0.009*
All	17,058			

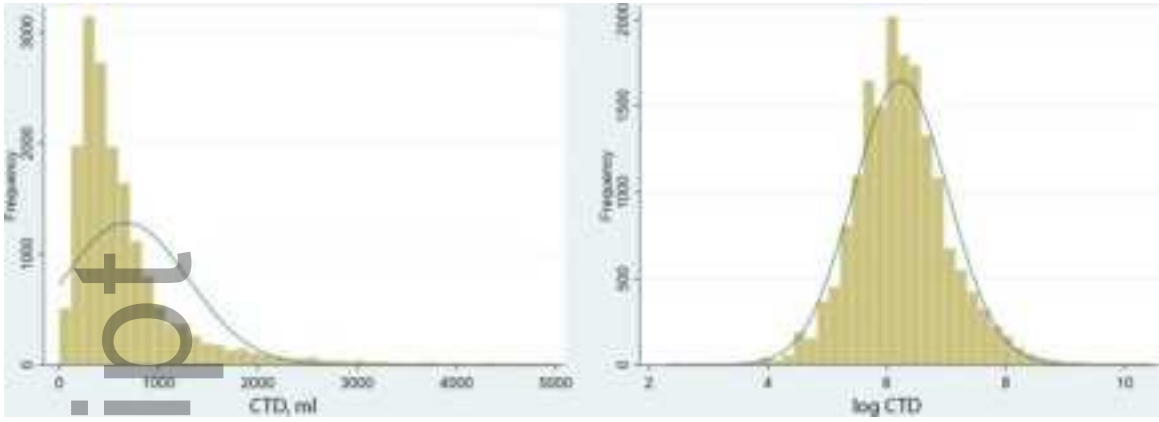
Geometric means of chest tube drainage in the postoperative intensive care unit in ml according to ABO blood group. 95% confidence interval in brackets. Relative difference in ln CTD compared to blood group O calculated by linear regression of logarithmic transformed data 1 ml added to all drain volumes before logarithmic transformation to avoid dropout of CTD=0ml. P-values for difference between blood group O and each of the three other groups. \* indicates  $p < 0.05$

Table 4. Mean volume of transfused blood products by ABO blood group, analyzed as difference from blood group O.

Blood group		N	Packed red cells		FFP		Platelet concentrate	
			ml [95% CI]	p-value	ml [95% CI]	p-value	ml [95% CI]	p-value
O	mean	7,139	369 [340, 397]	--	269 [247, 290]	--	170 [157, 184]	--
A	difference from group O	7,426	-22 [-64, 20]	0.302	-22 [-52, 9]	0.164	-7 [-26, 13]	0.50
B	difference from group O	1,798	10 [-95, 115]	0.849	-24 [-76, 0]	0.355	-28 [-55, 0]	0.04*
AB	difference from group O	695	-126 [-191, -60]	<0.001*	-83 [-136, -30]	0.002*	-63 [-92, -34]	<0.001*
All		17,058						

Total volumes of blood products transfused in the OR and ICU combined in blood group O – for blood group A,B and AB the difference in transfused mean volumes compared to blood group O is shown.\* indicates p<0,05

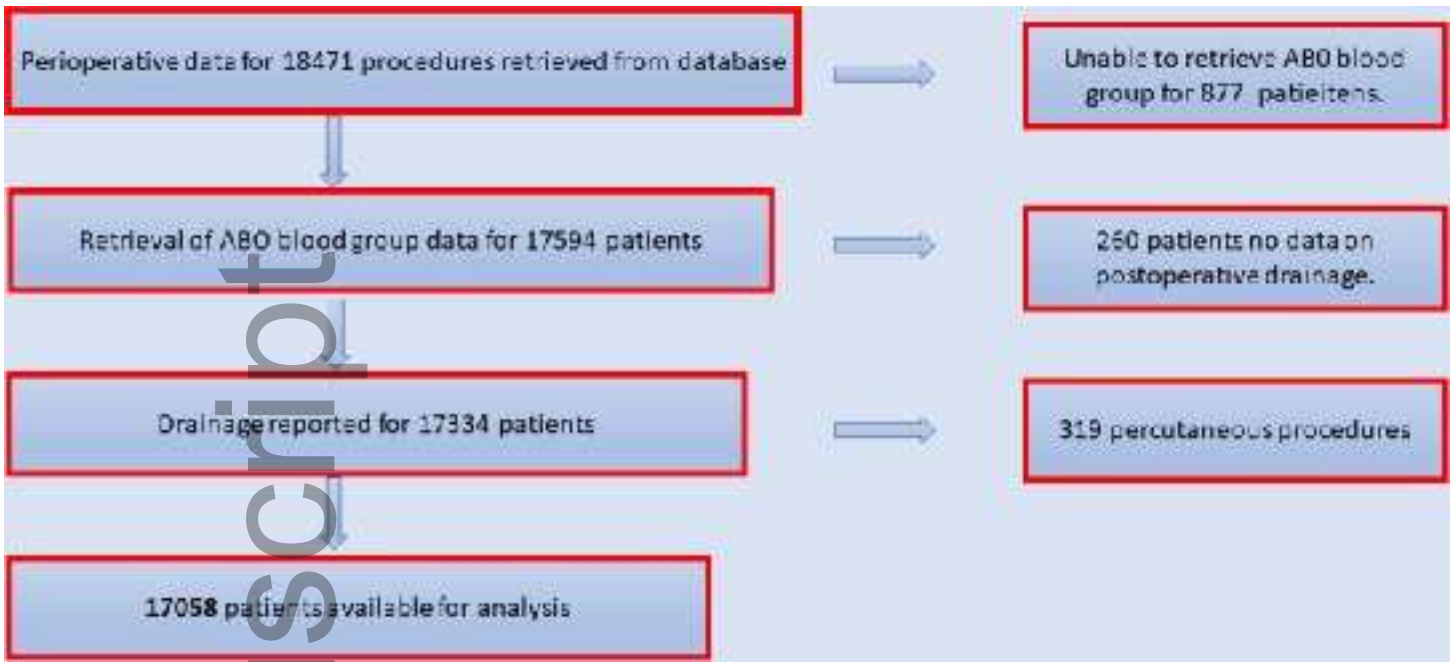
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