

# Peri-operative blood transfusion in elective major surgery: incidence, indications and outcome – an observational multicentre study

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**Background** - Patients’ demographic and epidemiological characteristics, local variations in clinicians’ knowledge and experience and types of surgery can influence peri-operative transfusion practices. Sharing data on transfusion practices and recipients may improve patients’ care and implementation of Patient Blood Management (PBM).

**Materials and methods** - This was a multicentre, prospective, observational, cross-sectional study that included 61 centres. Clinical and transfusion data of patients undergoing major elective surgery were collected; transfusion predictors and patients’ outcomes were analysed.

**Results** - Of 6,121 patients, 1,579 (25.8%) received a peri-operative transfusion. A total of 5,812 blood components were transfused: red blood cells (RBC), fresh-frozen plasma and platelets in 1,425 (23.3%), 762 (12.4%) and 88 (1.4%) cases, respectively). Pre-operative anaemia was identified in 2,019 (33%) patients. Half of the RBC units were used by patients in the age group 45-69 years. Specific procedures with the highest RBC use were coronary artery bypass grafting (16.9% of all units) and hip arthroplasty (14.9%). Low haemoglobin concentration was the most common indication for intra-operative RBC transfusion (57%) and plasma and platelet transfusions were mostly initiated for acute bleeding (61.3% and 61.1%, respectively). The RBC transfusion rate in study centres varied from 2% to 72%. RBC transfusion was inappropriate in 99% (n=150/151) of pre-operative, 23% (n=211/926) of intra-operative and 43% (n=308/716) of post-operative RBC transfusion episodes. Pre-operative haemoglobin, increased blood loss, open surgery and duration of surgery were the main independent predictors of intra-operative RBC transfusion. Low pre-operative haemoglobin concentration was independently associated with post-operative pulmonary complications.

**Conclusions** - These findings identified areas for improvement in peri-operative transfusion practice and PBM implementation in Turkey.

**Keywords:** Blood components, patient blood management, peri-operative, transfusion.

## INTRODUCTION

Transfusion practice for surgical patients has changed from replacing surgically lost blood with allogenic blood transfusions to implementing strategies that reduce transfusion requirements<sup>1,2</sup>. The new concept is Patient Blood Management (PBM), which is “the timely application of evidence-based medical and surgical concepts designed to maintain

haemoglobin concentration, optimize haemostasis and minimize blood loss in an effort to improve patient outcome<sup>3</sup>. In this context, the decision of transfusion has become an important aspect of peri-operative patient care<sup>4</sup>. Despite several but in part contradictory peri-operative transfusion guidelines, it is challenging for an anaesthesiologist to implement transfusion guidelines because of local variations in clinicians' knowledge and experience and characteristics of surgery<sup>5-9</sup>. Analysing such factors in a representative sample of surgical transfusion recipients can elucidate areas for implementing restrictive transfusion guidelines and PBM<sup>4,11</sup>.

The Turkish Society of Anaesthesiology and Reanimation conducted the Turkish National Perioperative Transfusion Study (TULIP-TS) to determine the areas for improvements in transfusion practice, to define practice standards, to collect data on future transfusion requirements and for health care planning, and to form a scientific basis for future research.

The aim of the present study was to evaluate the peri-operative transfusion practices in patients undergoing elective major surgery; the incidence of and indications for peri-operative transfusion and the impact of transfusion on patients' outcomes were analysed.

## **MATERIALS AND METHODS**

The TULIP-TS was a multicentre, prospective, observational study involving patients undergoing major elective surgery. All patients received local standard care and no intervention was applied. The study was conducted in a 1-month period between April 2, 2018 and May 3, 2018. The ethics committee of the University of Health Sciences Diskapi Yildirim Beyazit Teaching Hospital approved the study (12/06/2017-39/12). Each participating centre provided local review board approval and consent was obtained from each patient. The study was registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT03468738).

Hospitals performing major surgery in at least one of the following specialties were invited to participate in the study: general, orthopaedic, urological, cardiovascular, thoracic, paediatric, gynaecological, obstetric, transplant surgery and neurosurgery. After initial evaluation of hospitals that voluntarily indicated their interest in taking part in the study, nine additional hospitals were invited to participate in order to achieve a geographical distribution

across the country as well as to ensure hospital diversity. Centres were selected on the basis of a pre-study survey. This survey included questions regarding the annual numbers of major surgical procedures and blood component utilisation in each study centre. The minimum expected enrolment rate of each centre was calculated accordingly.

Patients undergoing major elective surgical procedures were considered eligible. All age groups and both genders were included. The surgical procedures were predefined according to the Classification of Diagnostic, Therapeutic, and Surgical Procedures of the National Social Insurance Institution, in which every procedure has a unique code (*Online Supplementary Content, Table SI*)<sup>12</sup>. In order to avoid enrolment bias, all patients undergoing a certain surgical procedure were enrolled irrespectively of whether they received a transfusion. Emergency cases requiring surgery in less than 2 hours and patients admitted to the operating area through the emergency department were excluded.

The following data were collected: the patient's characteristics, diagnosis, comorbidities, physiological parameters, surgical parameters, laboratory results (haemoglobin concentration, platelet count, and coagulation profile), anaesthesia management and monitoring, intra-operative PBM strategies (autologous blood donation, cell salvage, acute normovolaemic haemodilution, procoagulant drugs), transfusion-related data (indication [*Online Supplementary Content, Table SII*], blood components, and amount), estimated blood loss, urine output, intravenous fluids, unanticipated intensive care unit admission and prolonged duration of stay according to the local standard of care, post-operative adverse outcomes, and all-cause mortality at day 30 after surgery. Comorbidity, physiological and surgical risk scores were determined for each patient<sup>13-15</sup>. The haemoglobin concentration on admission to hospital was defined as the pre-operative haemoglobin; this value was used to define pre-operative anaemia (<12 g/dL in females; <13 g/dL in males; <11 g/dL in pregnancy)<sup>16</sup>. The last measured haemoglobin concentration before red blood cell (RBC) transfusion was defined as the pre-transfusion haemoglobin. For RBC transfusions, the pre-transfusion haemoglobin values were considered as a measure of transfusion trigger. Post-transfusion haemoglobin values were recorded. Blood components were RBC,

fresh-frozen plasma (FFP), and platelets (1 Unit [U] of aphaeresis platelet equals 5 U of random platelets). Inappropriate RBC transfusion was defined as RBC transfusion in patients with a haemoglobin concentration  $\geq 7$  g/dL without active bleeding and/or the presence of co-morbid disease and/or physiological transfusion trigger<sup>6,7</sup>. Blood loss was estimated using both the blood absorbed in sponges and the blood aspirated into canisters during an operation. The European Perioperative Clinical Outcome definitions were used to define post-operative adverse outcomes including hypotension, new onset arrhythmia, angina, non-fatal cardiac arrest, acute myocardial infarction, congestive heart failure, cardiogenic pulmonary oedema, new onset anticoagulation, myocardial injury in non-cardiac surgery, acute kidney injury, thromboembolic-ischaeamic events, infections, stroke, new neurological deficit, and pulmonary complications<sup>17</sup>. Mortality within 30 days of surgery was documented from the National Death Certification System. All patients were followed up for a 1-month period. The drop-out criterion was withdrawal of a patient's consent.

The primary outcome was the incidence of peri-operative transfusion. Transfusion indications and the impact of transfusion on patients' outcomes were the other outcomes.

### Data collection

OpenClinica© open source software 3.3 (OpenClinica LLC, Waltham, MA, USA) was used for the data collection and management. Data were first collected on paper case report forms (CRF) and thereafter entered into the database. All CRF were completed by the study investigators. The investigators were given training regarding the study protocol, obtaining consent from patients, and using the database. Patient recruitment and data plausibility checks were performed daily. Independent query management, data cleaning, and source data verification provided high quality data. Enrolment bias was investigated by comparing the enrolment rate of each study centre with its minimum expected enrolment rate and by cross-checking the scheduled surgery lists of the study centre for eligible patients.

### Statistical analysis

The Predictive Analytical Software statistics for Windows, version 18 (SPSS Inc., Chicago, IL, USA) was used for

the analyses. Descriptive statistics were expressed as numbers (proportion) for categorical variables and as mean  $\pm$  standard deviation, median (interquartile range) for numerical variables. In binary logistic regression multivariable analysis, potential predictive variables were included according to their clinical relevance and test requirements. The variables were checked for singularity and multicollinearity. Linearity assumption was checked by the Box-Tidwell test. The final model fit was tested using the Hosmer-Lemeshow test. Results were expressed as odds ratio (OR) and 95% confidence intervals (CI). All tests were two-tailed and an alpha significance level less than 0.05 was considered statistically significant.

### Sample size

In 2017, the blood component utilisation throughout the country was 2,453,051 U RBC, 1,263,462 U FFP, and 540,217 U platelets (*unpublished data, Ministry of Health, Turkey*). According to the pre-study survey, 25% of these components were issued to the hospitals included in this study (RBC: 467,321 U, FFP: 457,219 U, and platelet: 96,928 U). Furthermore, based on the annual numbers of major operations performed in the study centres, the expected number of patients to be enrolled was 6,000. The results of our pilot study revealed a transfusion rate of 28%; accordingly, we assumed we would be able to collect data from over 1,500 transfused patients<sup>18</sup>.

Although data were collected from all age groups, as patients aged <18 years have unique features and surgical characteristics as well as anaemia definitions and transfusion indications, only data from adult patients are analysed here.

## RESULTS

Sixty-one centres participated in the study: 32 university hospitals, 23 teaching hospitals, four private hospitals and two state hospitals. The hospital size ranged from 250 to 1,300 beds. During the study period, 6,570 patients were assessed for eligibility, 79 patients did not consent to participate in the study, and 6,491 patients were recorded. The planned operations were not completed in 12 patients and 16 patients were lost during follow-up. Three patients were considered ineligible because their operations were performed within less than 2 hours of hospital admission (diagnosis of epidural haematoma). Eighty patients were not included in the analysis because of protocol

violations; the number of patients recorded was less than the minimum expected enrolment rate and only the patients in whom transfusion occurred were recruited, which was considered an enrolment bias. Thus, the final analyses was based on 6,121 adult patients (Figure 1). The annual number of blood transfusions performed in the study centres accounted for one quarter of the nationwide blood component utilisation in 2017 and it is, therefore, considered that the results of this study can reflect the peri-operative transfusion practice throughout the country. Blood components are prepared in accordance with the European Directorate for the Quality of Medicines and Healthcare<sup>19</sup>. This standardisation enables international comparison of the results.

Features of the study population are summarised in Table I. The median (interquartile range) pre-operative haemoglobin concentration was 12.9 (11.6-14.1) g/dL and pre-operative anaemia was identified in 2,019 (33%) patients; anaemia was more common in males than in females (34.7% vs 32.0 %,  $p=0.02$ ) and the incidence increased with age. During the peri-operative course, 1,579 (25.8%) patients received at least 1 unit of a blood component; a total of 5,812 blood components were transfused (Table II). A transfusion was given to 154 (9.8%) patients pre-operatively, 1,057 (66.9%) patients intra-operatively, and 889 (56.3%) patients post-operatively. There were more female transfusion recipients (52.6% vs 47.3%). The median (interquartile range) age of the transfusion recipients was

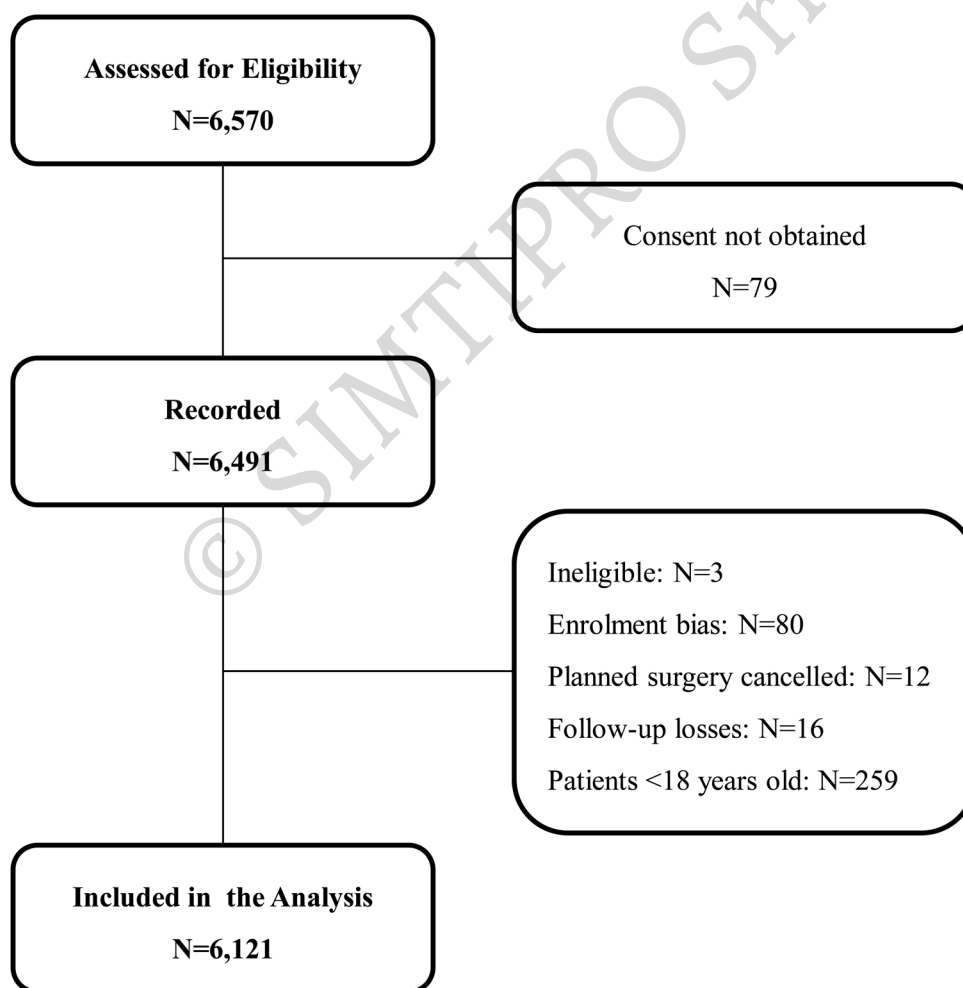


Figure 1 - Flow chart of patients' enrolment

**Table I - Characteristics, anaesthesia and surgical data of the patients transfused or not transfused in the peri-operative period**

| Characteristics of the patients            | Overall<br>n=6,121 | Transfused<br>n=1,579 | Non-transfused<br>n=4,542 |
|--|--------------------|-----------------------|---------------------------|
| <b>Age, years</b>                          | 57 (43-67)         | 62 (52-70)            | 55 (39-66)                |
| <b>Gender</b>                              |                    |                       |                           |
| Male                                       | 2,262 (37%)        | 747 (47.3%)           | 1,515 (33.3%)             |
| Female                                     | 3,859 (63%)        | 832 (52.6%)           | 3,027 (66.6%)             |
| <b>BMI, kg.m<sup>2</sup></b>               | 27.7 (24.9-31.4)   | 27.3 (24.2-30.7)      | 28.1 (25.1-31.9)          |
| <b>ASA</b>                                 |                    |                       |                           |
| I-II                                       | 4,525 (74.2%)      | 862 (54.7%)           | 3,663 (81%)               |
| ≥III                                       | 1,576 (25.8%)      | 714 (45.3%)           | 862 (19%)                 |
| <b>CCI</b>                                 | 0.67 ± 1.11        | 0.95 ± 1.27           | 0.57 ± 1.03               |
| <b>P-POSSUM</b>                            | 2.16 ± 5.9         | 4.87 ± 10.14          | 1.21 ± 2.76               |
| <b>SRS</b>                                 | 2.38 ± 2.71        | 3.92 ± 3.83           | 1.85 ± 1.92               |
| <b>Coagulation disorder</b>                | 37 (0.6%)          | 25 (1.6%)             | 12 (0.3%)                 |
| <b>Antiplatelet/ Anticoagulant drug</b>    |                    |                       |                           |
| Acetyl salicylic acid                      | 934 (15.3%)        | 437 (27.8%)           | 497 (11%)                 |
| Clopidogrel                                | 634 (68.3%)        | 268 (61.6%)           | 366 (74.2%)               |
| Dual therapy                               | 150 (16.2%)        | 78 (17.9%)            | 72 (14.6%)                |
| NOAC                                       | 12 (1.3%)          | 4 (0.9%)              | 8 (1.6%)                  |
| Warfarin                                   | 30 (3.2%)          | 16 (3.7%)             | 14 (2.8%)                 |
| Ticlopidine                                | 56 (6%)            | 37 (8.5%)             | 19 (3.9%)                 |
| Ticlopidine                                | 2 (0.2%)           | 2 (0.5%)              | 0 (0%)                    |
| <b>Abnormal coagulation profile</b>        | 506 (8.4%)         | 222 (14.2%)           | 284 (6.4%)                |
| <b>Pre-operative haemoglobin, g/dL</b>     | 12.9 (11.6-14.1)   | 12 (10.4-13.6)        | 13 (11.9-14.2)            |
| <b>Pre-operative anaemia</b>               |                    |                       |                           |
| Male                                       | 2019 (33%)         | 870 (55.1%)           | 1,152 (25.4%)             |
| Female                                     | 787 (34.7%)        | 388 (51.9%)           | 399 (26.4%)               |
| Pregnancy                                  | 1,232 (32.0%)      | 481 (58.0%)           | 751 (24.9%)               |
| Pregnancy                                  | 146 (21.3%)        | 19 (70.4%)            | 127 (19.3%)               |
| <b>Pre-operative anaemia by age groups</b> |                    |                       |                           |
| 18-44 yrs, n=1,672                         | 459 (27.4%)        | 324 (28.7%)           | 324 (28.7%)               |
| 45-69 yrs, n=1,609                         | 1,009 (31.1%)      | 554 (28%)             | 554 (28%)                 |
| 70-79 yrs, n=942                           | 353 (37.4%)        | 156 (16.5%)           | 156 (16.5%)               |
| ≥80 yrs, n=251                             | 157 (62.5%)        | 76 (52.8%)            | 76 (52.8%)                |
| <b>Anaemia investigations</b>              |                    |                       |                           |
| Ferritin/Transferrin                       | 55 (0.8%)          | 30 (1.8%)             | 25 (0.5%)                 |
| BUN; Creatinin                             | 51 (0.8%)          | 26 (1.6%)             | 25 (0.5%)                 |
| CRP  | 36 (0.5%)          | 19 (1.2%)             | 17 (0.3%)                 |
| <b>Anaemia treatment</b>                   |                    |                       |                           |
| Oral iron                                  | 79 (1.3%)          | 18 (1.1%)             | 61 (1.3%)                 |
| Intravenous iron                           | 8 (0.1%)           | 2 (0.1%)              | 6 (0.1%)                  |
| Vitamin B12, folic acid                    | 7 (0.1%)           | 2 (0.1%)              | 5 (0.1%)                  |
| <b>Haemostatic agents</b>                  |                    |                       |                           |
| Tranexamic acid                            | 584 (9.5%)         | 247 (17.3%)           | 337 (7.4%)                |
| Fibrinogen                                 | 8 (1.3%)           | 7 (2.5%)              | 1 (0.3%)                  |
| <b>Autologous transfusion</b>              |                    |                       |                           |
| None                                       | 5,956 (98.4%)      | 1,479 (94.7%)         | 4,477 (99.7%)             |
| Acute normovolemic haemodilution           | 58 (1%)            | 56 (3.6%)             | 2 (0%)                    |
| Pre-operative autologous donation          | 22 (0.4%)          | 13 (0.8%)             | 9 (0.2%)                  |
| Cell salvage                               | 15 (0.2%)          | 13 (0.8%)             | 2 (0%)                    |
| <b>Controlled hypotension</b>              | 626 (10.3%)        | 241 (15.4%)           | 385 (8.6%)                |

Values are mean ± standard deviation, median (interquartile range) or numbers (proportion). BMI: body mass index; ASA: American Society of Anaesthesiologists physical class; CCI: Carlson co-morbidity index; P-POSSUM: Portsmouth physiological and operative severity score; SRS: Surgical risk scale; NOAC: novel oral anticoagulants; BUN: blood urea nitrogen; CRP: C-reactive protein. \*In non-cardiac surgery.

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**Table I - Characteristics, anaesthesia and surgical data of the patients transfused or not transfused in the peri-operative period (continued from previous page)**

| Characteristics of the patients        | Overall<br>n=6,121 | Transfused<br>n=1,579 | Non-transfused<br>n=4,542 |
|--|--------------------|-----------------------|---------------------------|
| <b>Surgical specialty</b>              |                    |                       |                           |
| Orthopaedics                           | 1,408 (23.0%)      | 401 (25.4%)           | 1,007 (22.2%)             |
| Gynaecology/obstetrics                 | 1,403 (23.0%)      | 125 (7.9%)            | 1,288 (28.4%)             |
| General surgery                        | 973 (15.9%)        | 230 (14.6%)           | 743 (16.4%)               |
| Neurosurgery                           | 935 (15.3%)        | 169 (10.7%)           | 766 (16.9%)               |
| Cardiovascular/thoracic                | 761 (12.4%)        | 502 (31.8%)           | 259 (5.7%)                |
| Urology                                | 547 (8.9%)         | 120 (7.6%)            | 427 (9.4%)                |
| Transplantation                        | 84 (1.4%)          | 32 (2%)               | 52 (1.1%)                 |
| <b>Duration of surgery, min</b>        | 155.5 ± 102.6      | 214.9 (113.4)         | 134.7 ± 89.7              |
| <b>*Intra-operative blood loss, mL</b> | 373.8 ± 485.4      | 704.4 ± 775.3         | 262.9 ± 253.1             |

Values are mean ± standard deviation, median (interquartile range) or numbers (proportion).

BMI: body mass index; ASA: American Society of Anaesthesiologists physical class; CCI: Carlson co-morbidity index; P-POSSUM: Portsmouth physiological and operative severity score; SRS: Surgical risk scale; NOAC: novel oral anticoagulants; BUN: blood urea nitrogen; CRP: C-reactive protein. \*In non-cardiac surgery.

62 (52-70) years and the rate of receiving a transfusion was the highest in patients >80 years old (144/251, 57.3%) (Table II). A median of 2 (1-3) U of RBC, 2 (1-4) U of FFP and 4 (4-8) U of platelets were transfused per patient. Among transfused patients 861/1,579 (54.5%) cases received >1 U of RBC; the numbers of patients receiving each blood component and numbers of transfused RBC units by age groups are displayed in Figure 2. Cardiovascular/thoracic surgery was the surgical specialty with the highest RBC, FFP and platelet transfusion rate, 31.3%, 62.5% and 65.0% respectively. The procedures with the highest RBC transfusion rate were coronary artery bypass grafting (n=313/359, 87.2%) and in non-cardiac surgery vertebrae instrumentation for diagnosis of a malignancy (n=37/81, 45.6%) (Table II).

The most common RBC transfusion indication was a "haemoglobin trigger", which was the case for all pre-operative RBC transfusions and 57.3% of intra-operative and 72.8% of post-operative RBC transfusions (Table II). The mean haemoglobin concentrations prior to a RBC transfusion were 9.2±1.4 g/dL pre-operatively, 8.9±1.9 g/dL, intra-operatively, and 8.8±1.3 g/dL post-operatively. The mean haemoglobin trigger in study centres varied from 6.6±0.9 to 10.7±1.2 g/dL intra-operatively and from 7.0±1.0 to 10.6±1.2 g/dL post-operatively (Figure 3). The mean haemoglobin concentrations after RBC transfusion were 10.3±1.2 g/dL pre-operatively, 9.8±1.8 g/dL intra-operatively, and 9.7±1.3 g/dL post-operatively. Haemoglobin

concentrations were measured after each RBC transfusion for 81.0% of the RBC transfusions. Transfusion indications for FFP were hypotension (36.2%), oozing (32.6%); surgical blood loss (30.4%) and guided by point-of-care coagulation testing (1.4%) intra-operatively, and oozing (49.4%), hypotension (20.5%) and surgical blood loss (11.8%) post-operatively. Transfusion indications for platelets were oozing (39.7%), surgical blood loss (19.0%) and guided by point-of-care testing (1.7%) intra-operatively, and oozing (44.7%) and surgical blood loss (26.3%) post-operatively.

The RBC transfusion rate in study centres varied from 3 to 46% intra-operatively and from 2 to 72% post-operatively. According to our predefined criteria, RBC transfusion was inappropriate in 150 (99%) patients pre-operatively, in 211 (23%) intra-operatively and in 308 (43%) post-operatively (Figure 3). The logistic regression analysis of the total RBC transfusions and inappropriate RBC transfusions in both the intra-operative and post-operative periods did not reveal an association between these ( $r=0.216$ ,  $p=0.104$  and  $r=0.207$ ,  $p=0.125$ , respectively).

Patient-, procedure-, and anaesthesia-related factors associated with intra-operative RBC transfusions are presented in Table III. Independent risk factors for intra-operative RBC transfusion were age (OR: 1.025, 95% CI: 1.019-1.031;  $p<0.001$ ), body mass index (OR: 0.982, 95% CI: 0.965-0.997;  $p=0.018$ ), presence of coronary artery disease (OR 1.279, 95% CI: 1.019-1.606;  $p=0.034$ ), presence of heart failure (OR 1.489, 95% CI: 1.066-2.101;  $p=0.023$ ),

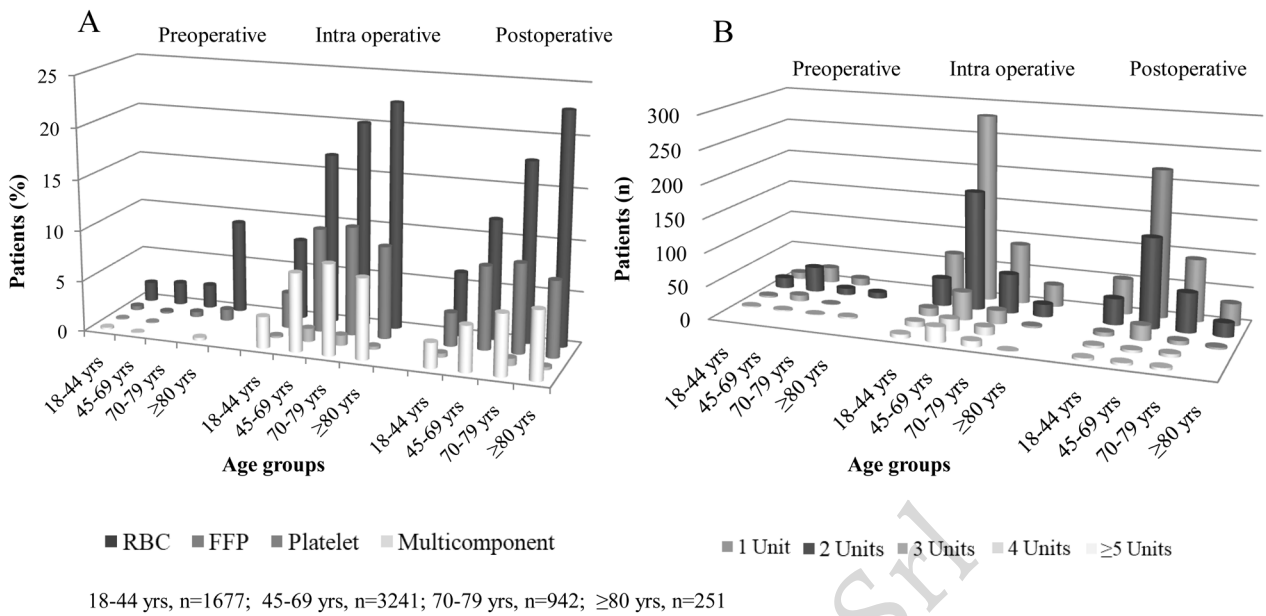
Table II - Peri-operative transfusion data and Red blood cell transfusion indications

| A. Peri-operative transfusion data of the study population         |                     |                 |                |             |
|--|---------------------|-----------------|----------------|-------------|
| N=6,121  | Total               | RBC             | FFP            | Platelets   |
| <b>Transfused patients</b>   |                     |                 |                |             |
| Peri-operative   | 1,579 (25.8%)       | 1,425 (23.3%)   | 762 (12.4%)    | 88 (1.4%)   |
| Pre-operative  | 154/1,579 (9.8%)    | 151 (10.6%)     | 25 (3.3%)      | 5 (5.7%)    |
| Intra-operative  | 1,057/1,579 (66.9%) | 926 (65.0%)     | 517 (67.8%)    | 59 (67.0%)  |
| Post-operative   | 889/1,579 (56.3%)   | 716 (50.2%)     | 425 (55.8%)    | 38 (43.2%)  |
| <b>Patients transfused by gender</b>                               |                     |                 |                |             |
| Male, n=2,262  | 747 (47.3%)         | 639 (28.2%)     | 417 (18.4%)    | 60 (2.6%)   |
| Female, n=3,859  | 832 (52.6%)         | 786 (20.3%)     | 344 (8.9%)     | 28 (0.7%)   |
| <b>Transfused patients by age group</b>                            |                     |                 |                |             |
| 18-44 yrs, n=1,672   | 230 (13.7%)         | 213 (12.7%)     | 101 (6%)       | 11 (1.8%)   |
| 45-69 yrs, n=1,609   | 923 (57.3%)         | 807 (50.1%)     | 475 (29.5%)    | 58 (3.6%)   |
| 70-79 yrs, n=942   | 312 (33.1%)         | 296 (31.4%)     | 147 (15.6%)    | 17 (1.8%)   |
| ≥80 yrs, n=251   | 107 (42.7%)         | 104 (41.4%)     | 37 (14.7%)     | 2 (0.7%)    |
| <b>Blood components</b>  |                     |                 |                |             |
| Units transfused   | 5,812 (100.0%)      | 3,137 (53.9%)   | 2,092 (35.9%)  | 583 (10.0%) |
| Units transfused per patient                                       | 2 (1-4)             | 2 (1-3)         | 2 (1-4)        | 4 (4-8)     |
| <b>Transfused units by surgical specialty (n=5,812)</b>            |                     |                 |                |             |
| Cardiovascular/thoracic  | 2,670 (45.9%)       | 982 (31.3%)     | 1,309 (62.5%)  | 379 (65.0%) |
| Orthopaedics   | 850 (14.6%)         | 719 (22.9%)     | 126 (6.0%)     | 5 (0.8%)    |
| General surgery  | 755 (12.9%)         | 450 (14.3%)     | 261 (12.4%)    | 44 (7.5%)   |
| Neurosurgery   | 450 (7.7%)          | 353 (11.2%)     | 93 (4.4%)      | 4 (0.6%)    |
| Gynaecology/obstetrics   | 425 (7.3%)          | 278 (8.8%)      | 115 (5.4%)     | 32 (5.4%)   |
| Urology  | 334 (5.7%)          | 236 (7.5%)      | 83 (3.9%)      | 15 (2.5%)   |
| Transplantation  | 328 (5.6%)          | 119 (3.7%)      | 105 (5.0%)     | 104 (17.8%) |
| <b>Transfused patients by surgical procedure*</b>                  |                     |                 |                |             |
| CABG, n=359  | 296 (82.4%)         | 313 (87.2%)     | 249(69.5%)     | 43(11.9%)   |
| CABG + valve surgery, n=36   | 36 (100.0%)         | 27 (75.0%)      | 31(86.1%)      | 1(2.7%)     |
| Valve surgery, n=128   | 111 (86.7%)         | 88 (68.7%)      | 97 (52.3%)     | 17(13.2%)   |
| Vertebrae - Instrumentation - Malign, n=81                         | 37(45.6%)           | 37 (45.6%)      | 25(30.8%)      |             |
| Hip arthroplasty - Fracture, n=266                                 | 127 (47.7%)         | 114 (42.8%)     | 12(4.5%)       | 1(0.3%)     |
| Hip arthroplasty - Coxarthrosis, n=265                             | 110 (41.5%)         | 112 (42.2%)     | 26 (9.8%)      |             |
| Vertebrae - Instrumentation - Benign, n=207                        | 59 (28.5)           | 59 (28.5%)      | 22(10.6%)      |             |
| Colectomy - Malign, n=285  | 85 (29.8%)          | 76 (26.6%)      | 39(13.6%)      |             |
| Prostatectomy - Malign, n=136                                      | 31 (22.7%)          | 30 (22.0%)      | 11(8.0%)       |             |
| B. Red blood cell transfusion indications reported by participants |                     |                 |                |             |
|  | Pre-operative       | Intra-operative | Post-operative |             |
| <b>Haemoglobin trigger</b>   | 151 (100%)          | 527 (57.3%)     | 521 (72.8%)    |             |
| Haemoglobin <7 g/dL  | 12 (7.9%)           | 48 (9.5%)       | 12 (2.4%)      |             |
| Haemoglobin 7-10 g/dL  | 98 (64.9%)          | 435 (86.1%)     | 454 (91.2%)    |             |
| Haemoglobin >10 g/dL   | 41 (27.1%)          | 22 (4.4%)       | 32 (6.4%)      |             |
| <b>Surgical blood loss</b>   | -                   | 341 (37.1%)     | 109 (15.2%)    |             |
| <b>Hypotension</b>   | -                   | 295 (32.1%)     | 103 (14.4%)    |             |
| <b>Oozing</b>  | -                   | 189 (20.5%)     | 175 (24.4%)    |             |
| <b>Tachycardia</b>   | -                   | 140 (15.1%)     | 46 (6.4%)      |             |
| <b>Haemoglobin trigger and physiological trigger**</b>             | -                   | 175 (19.0%)     | 88 (12.3%)     |             |
| <b>Haemoglobin trigger and blood loss</b>                          | -                   | 124 (13.5%)     | 49 (6.8%)      |             |
| <b>Haemoglobin trigger, physiological trigger and blood loss</b>   | -                   | 73 (7.8%)       | 6 (0.8%)       |             |
| <b>Blood loss and physiological trigger</b>                        | -                   | 109 (11.8%)     | 20 (2.8%)      |             |
| <b>Presence of a co-morbidity</b>                                  | -                   | 26 (2.8%)       | 13 (1.8%)      |             |
| <b>Decreased tissue oxygenation†</b>                               | -                   | 11 (1.1%)       | -              |             |
| <b>Inappropriate RBC transfusion ‡</b>                             | 150 (99%)           | 211 (23%)       | 308 (43%)      |             |

Values are mean ± standard deviation, median (interquartile range) or numbers (proportion).

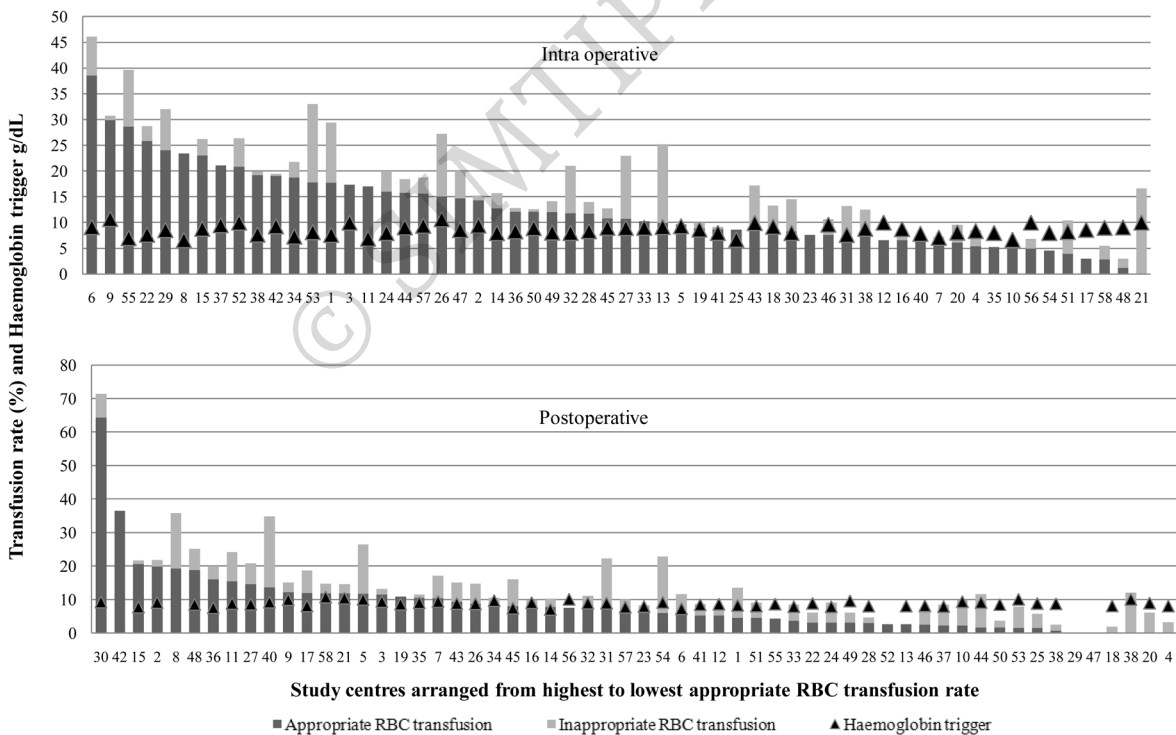
\*The first seven procedures with the highest RBC transfusion rate are presented. There are patients in whom transfusion occurred in >1 period, with >1 component, and with >1 U. \*\* Physiological trigger includes hypotension, tachycardia, acidosis, high lactate levels. † Decreased tissue oxygenation includes jugular venous oximetry and regional oxygen saturation. ‡ Inappropriate transfusion = haemoglobin concentration ≥7 g/dL and without active bleeding and/or without the presence of comorbid disease and/or physiological transfusion trigger.

RBC: red blood cells; FFP: fresh-frozen plasma; CABG: coronary artery bypass grafting; U: unit.



**Figure 2 - Transfusion data by age groups**

A: Number of blood components transfused in each age group; B: Number of red blood cell units transfused in each age group. RBC: red blood cells, FFP: fresh-frozen plasma.



**Figure 3 - Intra-operative and post-operative red blood cell transfusion rates and mean haemoglobin triggers in study centres**

RBC: red blood cells.



Table III - Multivariate analyses

| A. Factors associated with intra-operative red blood cell transfusion |                       |        |                       |        |
|---|-----------------------|--------|-----------------------|--------|
| Factors   | Univariate analysis   |        | Multivariate analysis |        |
|   | OR (95% CI)           | p      | OR (95% CI)           | p      |
| <b>Patient-related factors</b>  |                       |        |                       |        |
| Gender (male vs female)   | 1.747 (1.517-2.011)   | <0.001 | 1.025 (1.019-1.031)   | <0.001 |
| Age change per year increase  | 1.025 (1.020-1.029)   | <0.001 | 0.982 (0.965-0.997)   | 0.018  |
| BMI   | 0.961 (0.948-0.975)   | <0.001 |                       |        |
| ASA change per class increase   | 1.954 (1.783-2.141)   | <0.001 |                       |        |
| CCI change per class increase   | 1.644 (1.373-1.968)   | <0.001 |                       |        |
| SRS   | 1.272 (1.241-1.304)   | <0.001 |                       |        |
| P-POSSUM change per class increase                                    | 4.153 (3.569-4.840)   | <0.001 |                       |        |
| Coronary artery disease   | 2.472 (2.080-2.938)   | <0.001 | 1.279 (1.019-1.606)   | 0.034  |
| Heart failure   | 2.999 (2.305-3.903)   | <0.001 | 1.489 (1.056-2.101)   | 0.023  |
| Stroke  | 1.921 (1.262-2.923)   | 0.002  | -                     | 0.733  |
| Malignancy  | 1.290 (1.020-1.630)   | 0.033  | -                     | 0.121  |
| Pre-operative haemoglobin decrease per 1 g/dL                         | 1.329 (1.280-1.381)   | <0.001 | 1.471 (1.403-1.541)   | <0.001 |
| Pre-operative anaemia   | 2.819 (2.444-3.251)   | <0.001 |                       |        |
| Presence of antiplatelet/anticoagulant drugs                          | 2.290 (1.937-2.707)   | <0.001 |                       |        |
| Presence of an abnormal coagulation profile*                          | 2.404 (1.952-2.960)   | <0.001 | 1.447 (1.101-1.901)   | 0.008  |
| Presence of a coagulation disorder                                    | 4.839 (2.525-9.273)   | <0.001 |                       |        |
| Presence of pre-operative RBC transfusion                             | 2.703 (1.905-3.835)   | <0.001 |                       |        |
| Pre-operative RBC transfusion per 1 unit increase                     | 1.393 (1.184-1.638)   | <0.001 |                       |        |
| <b>Procedure-related factors</b>                                      |                       |        |                       |        |
| Amount of blood loss increase per 100 mL                              | 1.364 (1.333-1.395)   | <0.001 |                       |        |
| Blood loss more than 400 mL   | 10.796 (9.206-12.260) | <0.001 | 8.677 (7.191-10.470)  | <0.001 |
| Duration of surgery increase per 1 min                                | 1.008 (1.007-1.008)   | <0.001 |                       |        |
| Duration of surgery more than 180 min                                 | 5.539 (4.778-6.421)   | <0.001 | 2.985 (2.468-3.610)   | <0.001 |
| Surgical technique (open vs other**)                                  | 5.708 (3.776-8.629)   | <0.001 | 3.266 (2.064-5.167)   | <0.001 |
| <b>Anaesthesia-related factors</b>                                    |                       |        |                       |        |
| Use of haemostatic agents   | 2.098 (1.716-2.098)   | <0.001 |                       |        |
| Anaesthesia method (general vs other†)                                | 2.229 (1.853-2.683)   | <0.001 |                       |        |
| <b>Hospital-related factors</b>                                       |                       |        |                       |        |
| Type of hospital (university-teaching vs other‡)                      | 1.335 (1.106-1.611)   | 0.003  | -                     | 0.160  |
| Size of hospital (>750 beds vs ≤750 beds)                             | 1.324 (1.142-1.534)   | <0.001 | -                     | 0.057  |

Values are odds ratio and 95% confidence intervals. \*Prothrombin time, activated prothrombin time, and international normalized ratio above institutional laboratory references. \*\*Laparoscopic, robotic. †Neuro-axial block, peripheral block. ‡ state, private.

ASA: American Society of Anesthesiologists; CCI: Carlson co-morbidity index; SRS: Surgical risk score; P-POSSUM: Portsmouth physiological and operative severity score for the enumeration of morbidity and mortality; RBC: red blood cells; CI: confidence interval.

continued on next page

Table III - Multivariate analyses (continued from previous page)

| B. Factors associated with post-operative pulmonary complications |                     |        |                       |        |
|---|---------------------|--------|-----------------------|--------|
| Factors   | Univariate analysis |        | Multivariate analysis |        |
|   | OR (95% CI)         | p      | OR (95% CI)           | p      |
| <b>Patient-related factors</b>                                    |                     |        |                       |        |
| Gender (male vs female)   | 2.132 (1.473-3.085) | <0.001 | 1.530 (1.003-2.253)   | 0.048  |
| Age change per year increase                                      | 1.039 (1.025-1.052) | <0.001 | 1.030 (1.016-1.045)   | <0.001 |
| BMI   | 0.997 (0.964-1.032) | 0.879  |                       |        |
| ASA change per class increase                                     | 1.920 (1.578-2.335) | <0.001 |                       |        |
| CCI change per class increase                                     | 2.106 (1.471-3.014) | <0.001 |                       |        |
| SRS   | 1,157 (1,117-1,198) | <0,001 |                       |        |
| P-POSSUM change per class increase                                | 2.727 (2.163-3.437) | <0.001 |                       |        |
| Coronary artery disease   | 2.988 (2.002-4.459) | <0.001 | 1.581 (1.024-2.441)   | 0.039  |
| Heart failure   | 3.082 (1.739-5.464) | <0.001 |                       |        |
| Stroke  | 1.348 (0.422-4.304) | 0.614  | -                     | 0.652  |
| Malignancy  | 1.254 (0.685-2.295) | 0.463  | -                     | 0.937  |
| Pre-operative haemoglobin decrease per 1 g/dL                     | 1.143 (1.040-1.256) | 0.006  | 1.171 (1.064-1.289)   | 0.001  |
| Pre-operative anaemia   | 1.800 (1.246-2.600) | 0.002  |                       |        |
| Use of antiplatelet/anticoagulant drugs                           | 1.868 (1.220-2.860) | 0.004  |                       |        |
| Presence of an abnormal coagulation profile*                      | 1.937 (1.148-3.267) | 0.013  | -                     | 0.250  |
| Presence of pre-operative RBC transfusion                         | 2.614 (1.196-5.713) | 0.016  |                       |        |
| Pre-operative RBC transfusion per 1 unit increase                 | 1.542 (1.157-2.054) | 0.003  |                       |        |
| <b>Procedure-related factors</b>                                  |                     |        |                       |        |
| Amount of blood loss increase per 100 mL                          | 1.042 (1.020-1.064) | <0.001 |                       |        |
| Blood loss more than 400 mL                                       | 2.934 (2.030-4.242) | <0.001 | 2.025 (1.347-3.044)   | 0.001  |
| Duration of surgery increase per 1 min                            | 1.004 (1.003-1.006) | <0.001 |                       |        |
| Duration of surgery more than 180 minutes                         | 3.207 (2.212-4.650) | <0.001 | 2.006 (1.321-3.045)   | 0.001  |
| Surgical technique (open vs other†)                               | 1.396 (0.726-2.682) | 0.317  | -                     | 0.771  |
| <b>Anaesthesia-related factors</b>                                |                     |        |                       |        |
| Presence of haemostatic agents                                    | 0.993 (0.530-1.859) | 0.983  |                       |        |
| Anaesthesia method (general vs other‡)                            | 2.280 (1.359-3.825) | 0.002  |                       |        |
| Intra-operative crystalloid infusion (per liter)                  | 1,400 (1,258-1,558) | <0,001 |                       |        |
| Intra-operative colloid infusion (per liter)                      | 2,519 (1,623-3,910) | <0,001 |                       |        |
| Intra-operative blood transfusion (per unit)                      | 1,334 (1,185-1,501) | <0,001 |                       |        |
| Use of intra-operative blood transfusion                          | 3,686 (2,520-5,392) | <0,001 |                       |        |

Values are odds ratio and 95% confidence intervals. \*Prothrombin time, activated prothrombin time, and international normalized ratio above institutional laboratory references. \*\*Laparoscopic, robotic. †Neuro-axial block, peripheral block. ‡state, private.

ASA: American Society of Anesthesiologists; CCI: Carlson co-morbidity index; SRS: Surgical risk score; P-POSSUM: Portsmouth physiological and operative severity score for the enumeration of morbidity and mortality; RBC: red blood cells; CI: confidence interval.

**Table IV** - Univariate analysis of the post-operative outcomes of the transfused and non-transfused patients

|                              | Overall     | Transfused | Non-transfused | p      |
|------------------------------|-------------|------------|----------------|--------|
| Mortality                    | 85 (1.4%)   | 58 (0.9%)  | 27 (0.4%)      | <0.001 |
| Unanticipated ICU admission  | 34 (0.6%)   | 19 (0.3%)  | 15 (0.2%)      | <0.001 |
| PLOS                         | 155 (2.5%)  | 84 (1.3%)  | 71 (0.1%)      | <0.001 |
| <b>Single organ outcomes</b> |             |            |                |        |
| Pneumonia                    | 39 (0.6%)   | 26 (0.4%)  | 13 (0.2%)      | <0.001 |
| Pulmonary embolism           | 13 (0.2%)   | 5 (0.08%)  | 8 (0.1%)       | <0.001 |
| Acute kidney injury          | 27 (0.4%)   | 15 (0.2%)  | 12 (0.1%)      | <0.001 |
| Myocardial infarction        | 8 (0.1%)    | 6 (0.09%)  | 2 (0.03%)      | <0.001 |
| Stroke                       | 13 (0.2%)   | 8 (0.1%)   | 5 (0.08%)      | <0.001 |
| Infection                    | 130 (2.1%)  | 57 (0.9%)  | 73 (1.1%)      | <0.001 |
| <b>Composite outcomes</b>    |             |            |                |        |
| Major adverse cardiac event  | 33 (0.5%)   | 26 (0.4%)  | 7 (0.1%)       | <0.001 |
| Pulmonary complications      | 116 (1.9 %) | 68 (1.1%)  | 48 (0.7%)      | <0.001 |
| Post-operative morbidity     | 103 (1.7%)  | 58 (0.9%)  | 45 (0.7%)      | <0.001 |

Values are numbers (proportion). ICU: intensive care unit; PLOS: prolonged length of stay according to local standard care;

Infection includes: infection source unknown, surgical site infection (superficial, deep, and organ/space), urinary tract infection, blood stream infection  
Major adverse cardiac event includes: arrhythmia, angina, new requirement for anticoagulation, cardiogenic pulmonary oedema, non-fatal cardiac arrest, cardiac arrest, myocardial infarction, myocardial injury after non-cardiac surgery, congestive failure. Pulmonary complications include: pneumonia, pulmonary embolism, respiratory failure, respiratory infection, acute respiratory distress syndrome.

Post-operative morbidity includes: new requirement for oxygen or respiratory support, hypotension, ischaemia, arrhythmia, urinary catheter, increased creatinine, delirium, stroke, new neurological deficit, coma, thromboembolic event, ischaemic event.

low pre-operative haemoglobin concentration, per 1 g/dL decrease (OR: 1.471, 95% CI: 1.403-1.541;  $p < 0.001$ ), presence of an abnormal coagulation profile (OR 1.447, 95% CI: 1.101-1.901;  $p = 0.008$ ), blood loss >400 mL (OR: 8.677, 95% CI: 7.191-10.470;  $p < 0.001$ ), duration of surgery >180 min (OR: 2.985, 95% CI: 2.468-3.610;  $p < 0.001$ ), and open surgical technique (OR: 3.266, 95% CI: 2.064-5.167;  $p < 0.001$ ).

Adverse outcomes following surgery were observed in 371 (6.1%) patients (Table IV). The unadjusted rates of post-operative adverse outcomes and mortality were higher in patients who received a transfusion. The adverse outcome rate was 3.7% ( $n = 229/6,121$  patients) in transfused patients and 2.3% ( $n = 142/6,121$  patients) in non-transfused patients ( $p < 0.001$ ). The all-cause mortality rate at day 30 was 1.4% ( $n = 58/1,579$  transfused patients and  $n = 27/4,542$

non-transfused patients) ( $p < 0.001$ ). After adjusting for confounders, the regression models did not provide statistically significant explanatory power; a multivariate analysis could only be performed for the composite "post-operative pulmonary complications". Factors associated with an increased risk of post-operative pulmonary complications are presented in Table III; pre-operative low haemoglobin concentration was associated with post-operative pulmonary complications whereas intra-operative RBC transfusion was not.

## DISCUSSION

This study provides detailed clinical data for a large number of surgical patients, comprising both transfusion recipients and non-recipients, and a description of transfusion practices and patients' outcomes.

In the present study transfusion practice is evaluated throughout all three peri-operative periods because the decision to transfuse is made by different clinicians with presumably diverse indications in each stage. In general, anaesthesiologists are primary decision-makers during surgery, whereas surgeons make the decisions regarding transfusion before and after surgery.

We documented a high peri-operative incidence of transfusion. Even though the highest proportion of transfusions occurred intra-operatively; transfusions performed before and after surgery constituted almost an equal proportion of peri-operative transfusion.

One of the important results of the TULIP-TS is that one-third of the study population had pre-operative anaemia. We used the World Health Organisation definition to detect anaemia. This definition is considered deficient because females have lower circulating blood volume and, therefore, the same amount of blood loss during similar surgery leads to a higher proportion of lost circulating blood volume compared to that in men<sup>20</sup>. Using a definition of anaemia of <13 g/dL for both sexes, a higher incidence of pre-operative anaemia could have been documented in females.

The management of pre-operative anaemia is an integral aspect of PBM. Pre-operative anaemia increases the likelihood of RBC transfusion in surgical patients and is associated with adverse outcomes<sup>21</sup>. Iron deficiency is the most common cause of anaemia in surgical patients and can be treated with either oral or intravenous iron replacement depending on the timing of surgery<sup>20</sup>. Intravenous iron therapy is recommended prior to surgery as it both increases haemoglobin concentration and decreases the requirement for RBC transfusion<sup>22</sup>.

Unfortunately, in our study population pre-operative anaemia was either left untreated or RBC transfusions were given, with a low haemoglobin concentration being the reason for all the pre-operative RBC transfusions. The mean pre-operative haemoglobin concentration that we determined suggests that the "historical 10 g haemoglobin rule" is still accepted among surgeons.

According to our results intra-operative RBC transfusions were triggered primarily by a haemoglobin threshold. Current guidelines suggest that RBC transfusion is indicated when haemoglobin concentration is <7 g/dL, can be administered depending on co-morbidities,

intravascular volume and blood loss when haemoglobin concentration is 7-10 g/dL and is unnecessary when haemoglobin concentration is >10 g/dL, and a target haemoglobin concentration of 7-9 g/dL is recommended during active bleeding<sup>5-9</sup>. Adapting low haemoglobin thresholds for transfusion reduces RBC utilization<sup>20,22</sup>. Nevertheless, indications for intra-operative RBC transfusion are not clearly defined and the 7-10 g/dL haemoglobin concentration range, in particular, is left to clinicians' discretion<sup>5-11</sup>.

In the TULIP-TS the intra-operative haemoglobin trigger was mostly between 7-10 g/dL; however, a reason to justify all of these transfusions was not reported by the participants. These findings indicate that a restrictive transfusion strategy is not well adopted among anaesthesiologists.

The appropriateness of RBC transfusion was assessed on the basis of a haemoglobin trigger (<7 g/dL) and the presence of active bleeding and/or a co-morbidity and/or indicators of impaired oxygenation to rationalise higher haemoglobin triggers. Accordingly, over one-fifth of intra-operative RBC transfusion episodes were considered inappropriate.

We examined the potential predictors of intra-operative RBC transfusion. A low pre-operative haemoglobin concentration also appeared as an independent risk factor for intra-operative RBC transfusion; the probability of intra-operative RBC transfusion increased by 1.5-fold for each 1 g/dL decrease in pre-operative haemoglobin concentration. The analyses also included adjustments for the patients' co-morbidity, physiological and surgical risk indices which include vital signs, laboratory values, drugs and the magnitude of surgery as parameters. The results show that not the severity of illness but the presence of coronary arterial disease and heart failure were independently associated with increased transfusion requirement. The study centres were included in this analysis according to their healthcare provision levels and size; we found that neither the type nor the size of the hospital was a predictor of intra-operative RBC transfusion. This result is in accordance with previous studies reporting wide variability between hospitals in blood component transfusion irrespective of hospital type or surgical case volume<sup>23</sup>.

Increased blood loss was the second most reported trigger

of intra-operative RBC transfusion, and a physiological transfusion trigger -hypotension- was the subsequent reason for initiating a RBC transfusion. Physiological triggers based on signs of impaired global or regional oxygenation can be used to guide transfusion, provided that the volume status and anaesthesia is optimised<sup>24</sup>. Physiological triggers should replace arbitrary haemoglobin values to determine individual transfusion requirements<sup>24</sup>.

Post-operative RBC transfusions were also mainly triggered by a haemoglobin threshold. We evaluated inappropriate post-operative RBC transfusions separately and found a higher rate compared to that in the intra-operative period, suggesting that the surgeons are even more reluctant to use restrictive haemoglobin triggers. Of particular interest with regards to inappropriate RBC use, we documented that inappropriate pre-operative RBC transfusions accounted for over 10% of all RBC transfusions; 23% of the intra-operative and 43% of the post-operative RBC transfusion episodes were considered inappropriate. These data show the potential extent of decrease in RBC use after implementation of PBM.

The main indication for FFP and platelet transfusions was "blood loss" and specifically "oozing" both in the intra-operative and post-operative periods. Although this type of blood loss suggests coagulopathy, the FFP and platelet transfusions were not accompanied by coagulation testing. Oozing and post-operative bleeding also suggests that bleeding disorders or drugs that compromise the coagulation pathway may be involved<sup>25</sup>. Our results did not support these assumptions; however, the results showed that the presence of an abnormal coagulation profile increased the risk of intra-operative RBC transfusion. Oozing itself is a subjective definition; blood transfusion because of oozing without coagulation testing actually shows that a clinician's knowledge, experience and personal preferences affect transfusion decisions.

The utilisation of blood conservation strategies during the study period was very low. One exception to this observation was the use of tranexamic acid. Tranexamic acid was used in 9.5% of the overall study population; however, considering that the majority of the study population underwent orthopaedic procedures it could be commented that the usage is still low.

One of the main drivers of the change in transfusion

practices is the relation of transfusion with adverse outcomes, morbidity and mortality<sup>26-29</sup>.

Our results show higher rates of mortality and other adverse outcomes except for infections in transfused patients. Despite these results, since the incidence of adverse outcomes in the study population was low, the explanatory power of multivariate analysis was not sufficient to document a relationship between transfusion and adverse outcomes. We did document an increased risk of post-operative pulmonary complications in patients with a low pre-operative haemoglobin concentration.

Previous studies on transfusion in surgical patients are limited to certain surgical procedures<sup>2,30</sup>. Our study is comparable to the European Transfusion Practice and Outcome Study, although only RBC-transfused patients were included and only intra-operative transfusion was evaluated in that study<sup>31</sup>. The TULIP-TS is more comprehensive since the results indicate that the rate of transfusions outside the operating theatre might approximate the rate of those performed intra-operatively. The prospective design is a strength of this study which enabled transfusion indications to be evaluated in relation to all patients' conditions, in contrast to registries which associate the transfusion indication with only one diagnosis<sup>32</sup>.

Moreover, this study included all patients undergoing major surgery and, therefore, the case mix of this sample can be regarded as representative of the surgical population. We report data from both transfusion recipients and non-recipients. Despite providing data from a large number of surgical patients, the short duration of recruitment is a limitation because certain surgical procedures may have been unequally represented in the study period. Another limitation is that post-operative transfusion was only monitored on the first day following surgery; some patients in the study population may have received transfusions in the following days, which could have affected the outcomes. Finally post-transfusion haemoglobin concentration was not recorded after each transfusion so the intended goal of transfusion could not be determined.

In this comprehensive evaluation of current peri-operative transfusion practices in Turkey we identified blood use that is non-compliant with evidence-based transfusion practice. We also found that PBM strategies are only applied individually, and transfusion decisions are mainly affected by physicians' preferences.

Implementing a nationwide PBM programme may improve our transfusion practice<sup>1</sup>. Specific areas for improvement pointed out by our results are: pre-operative anaemia management, adapting low haemoglobin thresholds, increasing the utilisation of autologous transfusion methods and tranexamic acid when appropriate and increasing the use of coagulation testing<sup>20,33-38</sup>. This study indicated that the priority specialties for implementing PBM strategies are cardiovascular surgery and orthopaedics.

We also detected wide variations between study centres, especially in the haemoglobin triggers, RBC transfusion rates and inappropriate RBC transfusion rates. We consider this variation as a result of transfusion decisions being made by a single and different clinician in each peri-operative period. There is clear need to reduce blood use variability among hospitals and clinicians. Our results indicate that a formal training plan for surgeons and anaesthesiologists should be developed. Also practice standards in accordance with local legislation and infrastructure are needed. Involving surgeons in these efforts may improve success<sup>39</sup>. The performance of hospitals and physicians should be audited according to these standards. Establishing clinical transfusion management committees at hospitals may solve problems regarding transfusions based on clinicians' preferences. Both the transfusion rates and the haemoglobin triggers that we have determined constitute a reference point and can be used to assess the effectiveness of our PBM programmes in future audits.

We plan to present these results to the Ministry of Health and pursue legal enactment of implementation of a national PBM programme, acceptance of PBM strategies for hospital quality assessments, and constitution of clinical transfusion committees.

## **CONCLUSIONS**

In Turkey, 25.8% of the patients presenting for elective major surgery received blood transfusion. The indications for RBC transfusion included haemoglobin threshold, presence of bleeding, and subsequent physiological triggers of transfusion.

Pre-operative anaemia was detected in more than one-third of the patients presenting for surgery. A low pre-operative haemoglobin concentration was not only

an independent risk factor for intra-operative RBC transfusion but was also associated with a higher risk of post-operative pulmonary complications.

## **ACKNOWLEDGEMENTS**

We thank Dr. H. K. Gülkesen, Department of Biostatistics and Medical Informatics, Akdeniz University, School of Medicine, Antalya, Turkey. We also acknowledge the Department of Blood Organ Transplantation Services, Ministry of Health for providing the data on annual blood component utilisation in the country.

## **FUNDING AND RESOURCES**

This study was funded by the Turkish Society of Anaesthesiology and Reanimation.

## **AUTHORSHIP CONTRIBUTIONS**

DU, YS, RP, DRS, FT and NA designed the research study and wrote the paper; DU, YS and NA analysed the data; DU, YS, RP, DRS, FT and NA reviewed the clinical aspects of the analysis. All the Authors approved the final version of the paper.

## **CONFLICT OF INTEREST**

*DU has received travel support for consulting or lecturing from the Turkish Society of Anaesthesiology and Reanimation, Istanbul, Turkey; the Society of Anaesthesiology and Reanimation Specialists, Ankara, Turkey; and Abdi İbrahim İlaç Pazarlama, Istanbul, Turkey; RP has received travel support for consulting or lecturing from the Turkish Society of Anaesthesiology and Reanimation, Istanbul, Turkey; DRS has received honoraria/travel support for consulting or lecturing from Danube University of Krems, Austria; US Department of Defense, Washington, USA; European Society of Anaesthesiology, Brussels, Belgium; Korean Society for Patient Blood Management, Seoul, Korea; Korean Society of Anaesthesiologists, Seoul, Korea; Baxter AG, Volketswil, Switzerland; Baxter S.p.A., Rome, Italy; Bayer AG, Zürich, Switzerland; Bayer Pharma AG, Berlin, Germany; B. Braun Melsungen AG, Melsungen, Germany; Boehringer Ingelheim GmbH, Basel, Switzerland; Bristol-Myers-Squibb, Rueil-Malmaison Cedex, France and Baar, Switzerland; CSL Behring GmbH, Hattersheim am Main, Germany and Berne, Switzerland; Celgene International II Sàrl, Couvet, Switzerland; Curacyte AG, Munich, Germany; Daiichi Sankyo AG, Thalwil, Switzerland; GlaxoSmithKline GmbH & Co. KG, Hamburg, Germany; Haemonetics, Braintree, MA, USA; Instrumentation Laboratory (Werfen), Bedford, MA,*

USA; LFB Biomédicaments, Courtaboeuf Cedex, France; Merck Sharp & Dohme, Kenilworth, NJ, USA; Octapharma AG, Lachen, Switzerland; Organon AG, Pfäffikon/SZ, Switzerland; PAION Deutschland GmbH, Aachen, Germany; Pharmacosmos A/S, Holbaek, Denmark; Photonics Healthcare B.V., Utrecht, the Netherlands; Pierre Fabre Pharma, Alschwil, Switzerland; Roche Diagnostics International Ltd, Reinach, Switzerland; Roche Pharma AG, Reinach, Switzerland; Sarstedt AG & Co., Sevelen, Switzerland and Nümbrecht, Germany; Schering-Plough International, Inc., Kenilworth, NJ, USA; Tem International GmbH, Munich, Germany; Verum Diagnostica GmbH, Munich, Germany; Vifor Pharma, Munich, Germany, Vienna, Austria and Villars-sur-Glâne, Switzerland; Vifor (International) AG, St. Gallen, Switzerland; and Zuellig Pharma Holdings, Singapore, Singapore. Dr. Spahn's academic department has received grant support from the Swiss National Science Foundation, Berne, Switzerland; the Swiss Society of Anaesthesiology and Reanimation (SGAR), Berne, Switzerland; the Swiss Foundation for Anaesthesia Research, Zurich, Switzerland; and Vifor SA, Villars-sur-Glâne, Switzerland. Dr. Spahn is co-chair of the ABC-Trauma Faculty, sponsored by unrestricted educational grants from Novo Nordisk Health Care AG, Zurich, Switzerland; CSL Behring GmbH, Marburg, Germany; LFB Biomédicaments, Courtaboeuf Cedex, France; and Octapharma AG, Lachen, Switzerland; YS has received travel support for consulting or lecturing from the Turkish Society of Anaesthesiology and Reanimation, Istanbul, Turkey; FT has received travel support for consulting or lecturing from the Turkish Society of Anaesthesiology and Reanimation, Istanbul, Turkey; NA has received honoraria from MSD Turkey; Eczacıbaşı İlaç Pazarlama, Abbiye Turkey; and Gen İlaç, Medtronic Medikal Teknoloji, Turkey. Dr. Alkis has received travel support for consulting or lecturing from the Turkish Society of Anaesthesiology and Reanimation; Draeger Medikal Ticaret ve Servis A.Ş.; Medtronic Medikal Teknoloji; CSL Behring GmbH, Hattersheim am Main, Germany and Berne, Switzerland; Vifor (International) AG, St. Gallen, Switzerland; Abdi İbrahim Pharmaceuticals, Istanbul, Turkey; and Masimo Medikal Ürünler Ticaret Limited Sti. Turkey. Dr. Alkis's academic department has received grant support from Gen İlaç, Eczacıbaşı İlaç Pazarlama, Turkey.

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## APPENDIX 1

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