**Supplemental Digital Content (online-only)- Patient Blood Management**

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# Role of Participating Investigators

***Design of the Study***

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***Writing Committee***

Patrick Meybohm (principal investigator), Eva Herrmann, Andrea U. Steinbicker, Suma Choorapoikayil, Kai Zacharowski (principal investigator). No medical writer was involved. All Co-authors have approved submission.

***Gathering of Data***

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***Sponsor***

University Hospital Frankfurt, Germany. There was no agreement concerning confidentiality of the data between the sponsor and the authors or the institutions.

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# Additional methods for study design

*Study design*

As registration of the study was conceived in advance of most participants having surgery, we defined the design of the study as ‘prospective’. As final ethical approval was not received until 17th of December 2012, data of 9,956 control patients discharged in 2012 were collected retrospectively.

*Center characteristics*

The four centers provide active level one trauma, transplant, and cardiac surgery programs, and have the following characteristics regarding beds and inpatients per year (data assessed in 2014): Center 1 (1,307; 49,217), Center 2 (1,224; 46,611), Center 3 (1,195; 49,035), Center 4 (1,457; 58,000).

*Standardization of other blood products*

The decision to transfuse platelets, plasma, or cryoprecipitate was based on clinical assessment and standard laboratory results (e.g., prothrombin time, partial thromboplastin time, and fibrinogen), but also on an increased use of point-of-care diagnostics (e.g., thromboelastometry, multiple electrode aggregometry), but was not further standardized within our PBM project.

Data on platelets, fresh frozen plasma and coagulations factors are provided in Table S6.

# Additional methods for Independent Data Monitoring and Safety Committee

An ‘Independent Data Monitoring and Safety Committee (IDMC)’ checked data obtained. The implementation of the PBM program did not result in a 5% rise of the primary endpoint compared to the Pre-PBM cohort at any quarter. Therefore, the IDMC recommended continuation of the study.

# Additional methods for Outcome measures

The electronic-based diagnoses according to the ICD-10 GM codes were collected. Data were therefore limited to the content of the electronic medical record system of the four hospitals (ORBIS, Agfa HealthCare GmbH, Bonn, Germany). An individual long-term follow-up was not feasible.

Coding of ICD-10 GM codes was performed routinely by well-trained and specialized experts (coders) during the respective hospital stay of the patient. Individual coders were not aware of the study, thus differential coding by pre/post implementation of PBM is highly unlikely.

The primary, composite endpoint was positive in patients with one or more of the following ICD-10 GM codes during hospital stay:

* in-hospital mortality,
* myocardial infarction (acute I21.0, I21.1, I21.2, I21.3, I21.4, I21.9; recurrent I22.0, I22.1, I22.8, I22.9),
* ischemic stroke (cerebral infarction I63.0-I63.6, I63.8, I63.9, non-bleeding, non-infarct stroke I64),
* acute renal failure (acute N17.0, N17.1, N17.2, N17.8, N17.9; unknown N19, following medical care N99.0),
* pneumonia (viral J12.0-J12.3, J12.8, J12.9; Streptococcus pneumoniae J13; Hemophilus influenza J14; bacterial J15.0-J15.9; others J16.0, J16.8; unknown origin J18.0-J18.2, J18.8, J18.9),
* sepsis (Streptococcus A40.0-A40.3, A40.8, A40.9; others A41.0-A41.4, A.41.51, A41.52, A41.58, A41.8, A41.9; Candida B37.7; Herpes virus B00.7; Actinomycotic A42.7), or any of these diagnoses.

In Germany, the ICD-10 GM code does not allow a detailed distinction between pre-existing comorbid conditions (the event occurred within 30 days prior to admission) and new hospital-acquired morbidities (the event occurred in the time frame between hospital admission and discharge).

As pre-existing diagnoses were limited to 30 days prior to admission, we considered all discharge diagnoses as ‘new’/‘hospital-acquired’ with the exception for myocardial infarction in patients with coronary artery surgery (OPS 5-36) and cerebral infarction in patients with surgery of skull, brain or meninges (OPS 5-01 and 5-02), respectively. All other diagnoses were considered for primary endpoint analysis, and patients were not excluded.

In patients with coronary artery surgery (OPS 5-36), n=672 ‘myocardial infarction’ events were pre-existing diagnoses before hospital admission and therefore, were not considered as myocardial infarction for primary endpoint analysis.

In patients with surgery of skull, brain or meninges (OPS 5-01 and 5-02), n=455 ‘ischemic stroke’ events were pre-existing diagnoses before hospital admission, and were not considered as stroke for primary endpoint analysis.

# Additional methods for preoperative optimization of hemoglobin levels

Preoperative screening, diagnosis and therapy of anemia was performed in patients undergoing elective surgery with a probability for red blood cell transfusion > 10%. Procedures were identified by an analysis of hospital data during prior years for each center. Thereby, the following procedures were identified:

* Visceral surgery (esophagus resection, gastrectomy, rectum resection, hemihepatectomy, pancreatectomy)
* Vascular surgery (major peripheral vascular surgery, open aortic surgery)
* Trauma/ orthopedic surgery (open endoprothetic surgery at shoulder, hip, and knee, open spine surgery)
* Cardiac surgery
* Urology (radical cystectomy, kidney resection)

Patients who were anemic had an expanded evaluation including complete blood count, coagulation, iron studies, serum B12 and folate levels, and renal and liver function to identify anemia and other comorbidities. If anemic patients presented with iron deficiency (ferritin < 100ng/ml, transferrin saturation < 20%), patients without contraindications did receive intravenous iron considering any contraindication.

Anemic patients were scheduled for further postoperative diagnostics and/or treatment of anemia, referred back to their general practitioner when surgery could be postponed, and/or referred to a relevant specialty, generally the medical department or hematology/oncology.

Patients who are anemic should have had an expanded evaluation including complete blood count, coagulation, iron studies, serum B12 and folate levels, and renal and liver function to identify anemia and other comorbidities including suboptimal iron stores. If there was evidence of iron deficiency (ferritin < 100ng/ml, transferrin saturation < 20%), patients would receive intravenous iron.

# Additional methods for transfusion trigger

According to the Cross-sectional Guidelines for Therapy with Blood Components and Plasma Derivatives,11 an individual consideration of criteria like current hemoglobin concentration (Hb), the physiologic capacity to compensate the decreased oxygen content of the blood and the presence of cardiovascular risk factors (risk factors) and clinical symptoms of an apparent anemic hypoxia (physiologic transfusion trigger) is recommended in the decision for or against a transfusion of RBC.

The following figure S1 displays the transfusion trigger checklist summarizing the German Cross-sectional Guidelines.

# Figure S1. Transfusion trigger checklist



# Additional methods for Statistical analysis

Recall that the primary composite endpoint was analyzed with a one-sided Cochrane Mantel-Haenszel test with significance level of α = 2.5% for the odds ratio resulting in H0: OR ≥ OR\* vs. H1 OR < OR\*. Thereby, OR\* was derived from the incidence in the Pre-PBM cohort which was increased by the non-inferiority margin of 0.5%.

When planning the study we decided to use a Mantel-Haenszel test stratifying for center effects. Therefore, the non-inferiority test is based on odds ratios. Nevertheless, rate differences are easier to interpret and, therefore, the non-inferiority margin for the odds ratio (1.082) is also reported on the basis of rate differences (0.5%).

To convert from rate differences to odds ratios if one rate is fixed, we used the non-inferiority margin for the odds ratio which correspond to the rate difference 0.5% with the proportion (estimated from a stratified approach) of 6.53% in the control group using the straight-forward calculation OR\* = 1.082 = ((0.0653 + 0.005)/(1-0.0653– 0.005)) / (0.0653/(1-0.0653)).

Power estimation indicated that a sample size around 100,000 patients suffices to reach a power above 80% assuming incidence rates of the composite endpoint below 10%.

Logistic regression adjusting for surgery type as fixed effect incorporating center and calendar year as random effect was used to test and estimate the treatment effect on the odds ratio scale with two-sided 95% confidence intervals for the primary analysis. Subgroup analyses performed were not pre-specified and are exploratory only. Accounting for center effects is very important for this kind of before-after multicenter study. Therefore, the following data are reported - results from a nonparametric approach that use stratification according to centers (Mantel-Haenszel test for binary endpoints, van Elteren test for quantitative markers, e.g., blood product use) or results from the random effect regression models (logistic regression for binary endpoints, linear regression for quantitative variables). No data are reported by just pooling data from all centers.

Further multivariable mixed effect models were calculated to evaluate endpoints that were adjusted for surgery type with a fixed model, and for treatment year and center with a random effect model, respectively. For the primary endpoint, also adjustment for age and gender as fixed effects were evaluated.

# Table S1. Details regarding included OPS codes

|  |  |  |
| --- | --- | --- |
| **Type of surgery** | **OPS code** | **Surgery on…** |
| Neurosurgery | 5-01 – 5-02 | Skull, brain and meninges |
| 5-03 | Spinal cord, spinal meninges and spinal canal |
| 5-04 – 5-05 | Nerves and nerve ganglions |
| Otorhinolaryngology | 5-18 | Auricles and acoustic meatus |
| 5-19 – 5-20 | Middle and/inner ear |
| 5-21 – 5-22 | Nose and sinuses |
| 5-23 – 5-24 | Teeth, gingiva and jaw |
| 5-25 | Tongues |
| 5-26 | Salivary gland |
| 5-27 | Face |
| 5-28 – 5-29 | Pharynx |
| 5-30 | Larynx |
| 5-31 | Trachea |
| Thoracic surgery | 5-32 – 5-33 | Lung and bronchus |
| 5-34 | Thoracic wall, pleura, mediastinum and diaphragm |
| Cardiac surgery | 5-35 | Heart valves, septum and major vessels |
| 5-36 | Coronary artery |
| 5-37 | Pericardium and heart rhythm surgery |
| Vascular surgery | 5-38 – 5-39 | Vascular surgery |
| Visceral and endocrine surgery | 5-06 | Thyroid gland |
| 5-07 | Other glands |
| 5-42 | Esophagus |
| 5-43 - 5-44 | Stomach |
| 5-45 - 46 | Small and large bowels |
| 5-47 | Appendix |
| 5-48 – 5-49 | Rectum and anus |
| 5-50 | Liver |
| 5-51 | Gall bladder and biliary tract |
| 5-52 | Pancreas |
| 5-53 – 5-54 | Hernia and others |
| Urology | 5-55 | Kidney |
| 5-56 | Ureter |
| 5-57 | Urinary bladder |
| 5-58 – 5-59 | Urethra and others |
| 5-60 | Prostate |
| 5-61 | Scrotum |
| 5-62 – 5-64 | Testicles, funiculus spermaticus, epididymis, ductus deferens, and penis |
| Gynecology | 5-65 – 5-67 | Ovary, tuba uterina, and cervix uteri |
| 5-68 – 5-69 | Uterus and others |
| 5-70 – 5-71 | Vagina and vulva |
| 5-87 – 5-88 | Mamma |
| Obstetric | 5-72 – 5-73 | Delivery |
| 5-74 | Sectio caesarea |
| 5-75 | Other obstetric surgery |
| Oral and maxillofacial surgery | 5-76 – 5-77 | Facial bones and jaw |
| Trauma/Orthopedic surgery | 5-78 | Other bones |
| 5-79 | Reposition of fractured/luxated bones |
| 5-80 | Open joint surgery |
| 5-81 | Arthroscopic joint surgery |
| 5-82 | Endoprothetic joint replacement |
| 5-83 | Spine |
| 5-84 | Hand |
| 5-85 | Muscle, tendon, fascia and bursa |
| 5-86 | Replantation and amputation of limbs |
| Other | 5-40 | Hematopoietic and lymphatic system |
| 5-41 | Spleen and bone marrow |

Surgical procedures were classified according to the German procedure classification (‘Operationen- und Prozedurenschluessel’ - OPS) that is the official classification for the encoding of surgeries, procedures and general medical measures in the inpatient sector and for surgical procedures in the outpatient sector based on the International Classification of Procedures in Medicine. The currently valid version is called ‘OPS 2015’.

We included all types of surgical procedures (OPS code from 5-01 to 5-99) with the exception of ophthalmologic surgery (OPS code 5-08 to 5-16), dermatologic surgery (OPS code 5-89 to 5-92), and non-specified surgery (OPS code 5-93 to 5-99).

# Table S2. Multiplicity table for the components of the primary endpoint



This table describes the multiplicity patterns for the individual components of the primary endpoint (including death, myocardial infarction, ischemic stroke, acute renal failure, pneumonia, and sepsis) until hospital discharge.

# Table S3. Primary endpoint for the four centers and subgroups of surgical procedures

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Center 1** |  | **Center 2** |  | **Center 3** |  | **Center 4** |  |
| **Variable** | **Pre-PBM** | **PBM** | **Pre-PBM** | **PBM** | **Pre-PBM** | **PBM** | **Pre-PBM** | **PBM** |
| **All patients** | **N=13,394** | **N=23,414** | **N=13,082** | **N=20,003** | **N=13,978** | **N=16,915** | **N=14,059** | **N=14,874** |
| Primary endpoint — % (no.)\* | 5.7 (759) | 5.3 (1,249) | 9.0 (1,180) | 8.1 (1,616) | 5.9 (828) | 6.2 (1,053) | 6.0 (838) | 6.0 (892) |
| Death | 3.2 (431) | 2.9 (670) | 2.6 (338) | 2.8 (559) | 2.4 (330) | 2.6 (444) | 1.5 (212) | 1.5 (220) |
| Myocardial infarction | 0.2 (32) | 0.2 (48) | 1.2 (161) | 1.3 (269) | 0.3 (41) | 0.3 (56) | 0.3 (43) | 0.3 (45) |
| Stroke# | 0.4 (49) | 0.3 (59) | 0.8 (99) | 0.6 (115) | 0.4 (61) | 0.4 (69) | 0.7 (99) | 0.7 (108) |
| Acute renal failure | 1.9 (257) | 1.6 (381) | 3.4 (445) | 2.2 (439) | 1.9 (271) | 1.4 (235) | 2.6 (360) | 1.6 (233) |
| Pneumonia | 1.5 (201) | 1.7 (389) | 4.2 (544) | 3.5 (691) | 2.8 (394) | 3.0 (507) | 2.2 (313) | 2.6 (389) |
| Sepsis | 1.0 (128) | 1.2 (287) | 2.6 (345) | 2.5 (498) | 1.6 (228) | 2.0 (340) | 2.1 (294) | 2.0 (291) |
|  |  |  |  |  |  |  |  |  |
| **Neurosurgery** | **N=1,557** | **N=2,663** | **N=1,964** | **N=2,918** | **N=1,723** | **N=2,196** | **N=1,891** | **N=2,109** |
| Primary endpoint — % (no.)\* | 7.3 (113) | 7.5 (199) | 11.5 (225) | 10.5 (306) | 8.8 (152) | 10.3 (227) | 8.7 (165) | 10.0 (210) |
| Death | 4.8 (75) | 4.2 (113) | 4.2 (82) | 5.0 (147) | 3.2 (55) | 3.7 (81) | 2.2 (42) | 3.2 (67) |
| Myocardial infarction | 0.5 (8) | 0.4 (10) | 1.4 (27) | 1.3 (37) | 0.2 (4) | 0.5 (10) | 0.4 (8) | 0.3 (7) |
| Stroke† | 0.3 (4) | 0.2 (4) | 0.2 (3) | 0.1 (3) | 0.2 (4) | 0.3 (6) | 0.4 (8) | 0.3 (7) |
| Acute renal failure | 0.6 (9) | 0.7 (18) | 1.8 (35) | 1.0 (29) | 1.0 (17) | 0.5 (12) | 2.4 (46) | 1.4 (29) |
| Pneumonia | 1.9 (29) | 2.4 (65) | 6.8 (134) | 4.9 (142) | 6.0 (104) | 5.9 (130) | 4.4 (84) | 5.5 (117) |
| Sepsis | 0.8 (13) | 1.2 (33) | 2.9 (56) | 1.6 (48) | 1.7 (29) | 3.0 (65) | 2.2 (42) | 2.1 (45) |
|  |  |  |  |  |  |  |  |  |
| **Otorhinolaryngology** | **N=2,022** | **N=3,365** | **N=1,902** | **N=2,617** | **N=2,571** | **N=2,985** | **N=2,762** | **N=2,734** |
| Primary endpoint — % (no.)\* | 7.2 (145) | 8.9 (299) | 15.8 (301) | 13.1 (344) | 8.9 (228) | 9.5 (285) | 7.6 (209) | 7.3 (200) |
| Death | 4.5 (90) | 3.9 (131) | 4.3 (82) | 4.1 (107) | 2.5 (64) | 3.0 (90) | 2.1 (58) | 1.5 (42) |
| Myocardial infarction | 0.2 (5) | 0.3 (11) | 2.2 (42) | 1.9 (50) | 0.4 (9) | 0.5 (15) | 0.4 (10) | 0.3 (7) |
| Stroke | 0.3 (6) | 0.4 (15) | 1.6 (30) | 0.9 (24) | 0.8 (20) | 0.5 (16) | 0.9 (24) | 0.8 (21) |
| Acute renal failure | 2.8 (56) | 3.6 (121) | 6.3 (120) | 4.5 (119) | 3.3 (86) | 2.7 (81) | 3.3 (90) | 2.0 (56) |
| Pneumonia | 3.3 (67) | 4.7 (158) | 11.0 (210) | 8.7 (227) | 6.0 (153) | 6.7 (201) | 4.3 (118) | 4.7 (129) |
| Sepsis | 2.3 (47) | 3.8 (128) | 8.0 (153) | 6.4 (167) | 3.3 (86) | 4.6 (136) | 4.2 (117) | 3.5 (97) |
|  |  |  |  |  |  |  |  |  |
| **Thoracic** | **N=595** | **N=923** | **N=309** | **N=500** | **N=451** | **N=583** | **N=596** | **N=603** |
| Primary endpoint — % (no.)\* | 21.0 (125) | 23.9 (122) | 34.6 (107) | 29.6 (148) | 23.7 (107) | 23.3 (136) | 27.9 (166) | 27.0 (163) |
| Death | 12.3 (73) | 13.2 (122) | 12.3 (38) | 13.4 (67) | 12.4 (56) | 11.8 (69) | 10.7 (64) | 8.0 (48) |
| Myocardial infarction | 0.0 (0) | 0.7 (6) | 1.0 (3) | 4.4 (22) | 0.7 (3) | 0.9 (5) | 1.2 (7) | 1.2 (7) |
| Stroke | 1.5 (9) | 0.7 (6) | 2.9 (9) | 2.0 (10) | 0.9 (4) | 0.9 (5) | 4.2 (25) | 3.6 (22) |
| Acute renal failure | 8.9 (53) | 11.3 (104) | 18.8 (58) | 11.0 (55) | 10.6 (48) | 7.0 (41) | 12.2 (73) | 8.0 (48) |
| Pneumonia | 7.7 (46) | 9.5 (88) | 20.1 (62) | 17.2 (86) | 13.5 (61) | 12.7 (74) | 13.6 (81) | 14.8 (89) |
| Sepsis | 3.5 (21) | 7.2 (66) | 11.7 (36) | 12.0 (60) | 6.7 (30) | 6.2 (36) | 13.3 (79) | 11.1 (67) |
|  |  |  |  |  |  |  |  |  |
| **Cardiac** | **N=1,580** | **N=2,690** | **N=1,318** | **N=2,070** | **N=1,550** | **N=1,900** | **N=1,182** | **N=1,244** |
| Primary endpoint — % (no.)\* | 13.9 (219) | 14.0 (377) | 18.0 (237) | 17.2 (356) | 14.3 (222) | 13.1 (249) | 23.1 (273) | 22.4 (279) |
| Death | 7.3 (115) | 6.9 (186) | 4.6 (61) | 4.7 (102) | 5.3 (82) | 5.3 (101) | 6.3 (75) | 4.7 (59) |
| Myocardial infarction‡ | 0.1 (1) | 0.2 (5) | 1.7 (22) | 2.1 (43) | 0.3 (4) | 0.4 (7) | 1.1 (13) | 1.6 (20) |
| Stroke | 1.4 (22) | 0.8 (21) | 1.4 (18) | 2.5 (51) | 1.9 (30) | 1.7 (32) | 4.7 (55) | 5.3 (66) |
| Acute renal failure | 7.2 (113) | 7.0 (189) | 7.8 (103) | 5.7 (119) | 6.2 (96) | 3.7 (71) | 9.8 (116) | 5.5 (68) |
| Pneumonia | 4.2 (66) | 5.6 (151) | 9.1 (120) | 8.5 (176) | 6.3 (97) | 5.9 (113) | 9.3 (110) | 11.3 (140) |
| Sepsis | 2.1 (33) | 3.6 (96) | 4.2 (56) | 4.9 (102) | 2.8 (44) | 2.7 (53) | 9.4 (111) | 6.4 (79) |
|  |  |  |  |  |  |  |  |  |
| **Vascular** | **N=965** | **N=1,843** | **N=863** | **N=1,184** | **N=1,250** | **N=1,572** | **N=1,299** | **N=1,224** |
| Primary endpoint — % (no.)\* | 20.1 (194) | 15.8 (292) | 27.0 (233) | 21.6 (256) | 15.3 (191) | 13.8 (217) | 15.7 (204) | 14.6 (179) |
| Death | 10.8 (104) | 8.6 (159) | 8.3 (72) | 7.7 (91) | 7.0 (88) | 6.6 (103) | 4.9 (64) | 4.1 (50) |
| Myocardial infarction | 0.6 (6) | 1.0 (19) | 4.2 (36) | 4.7 (56) | 0.7 (9) | 0.7 (11) | 1.0 (13) | 0.7 (9) |
| Stroke | 2.5 (24) | 1.6 (29) | 4.2 (36) | 2.8 (33) | 2.0 (25) | 1.2 (19) | 2.5 (33) | 2.9 (36) |
| Acute renal failure | 9.9 (96) | 6.1 (113) | 13.4 (116) | 6.7 (79) | 6.6 (82) | 4.3 (68) | 8.4 (109) | 4.7 (57) |
| Pneumonia | 6.2 (60) | 4.7 (86) | 10.3 (89) | 6.8 (81) | 5.7 (71) | 6.0 (94) | 4.8 (62) | 5.3 (65) |
| Sepsis | 5.0 (48) | 4.6 (85) | 9.0 (78) | 8.0 (95) | 4.1 (51) | 4.3 (68) | 6.5 (84) | 5.8 (71) |
|  |  |  |  |  |  |  |  |  |
| **Visceral and endocrine** | **N=3,175** | **N=5,631** | **N=2,170** | **N=3,547** | **N=2,187** | **N=2,649** | **N=1,632** | **N=1,822** |
| Primary endpoint — % (no.)\* | 8.1 (257) | 8.0 (453) | 16.0 (348) | 13.0 (461) | 10.8 (237) | 12.1 (320) | 13.1 (214) | 12.6 (230) |
| Death | 5.2 (166) | 4.9 (277) | 5.2 (113) | 5.4 (190) | 5.2 (113) | 6.3 (166) | 4.1 (67) | 4.6 (83) |
| Myocardial infarction | 0.4 (13) | 0.3 (17) | 1.9 (42) | 1.7 (59) | 0.4 (8) | 0.5 (13) | 0.3 (5) | 0.4 (7) |
| Stroke | 0.3 (9) | 0.2 (10) | 1.3 (29) | 0.4 (15) | 0.6 (13) | 0.7 (19) | 1.3 (21) | 1.0 (18) |
| Acute renal failure | 3.0 (95) | 2.8 (159) | 8.0 (174) | 4.9 (174) | 4.7 (102) | 3.7 (97) | 7.0 (114) | 4.5 (82) |
| Pneumonia | 2.0 (64) | 2.1 (120) | 5.8 (126) | 4.8 (171) | 5.6 (123) | 5.5 (145) | 4.6 (75) | 5.0 (91) |
| Sepsis | 2.0 (62) | 2.6 (148) | 5.8 (126) | 5.4 (192) | 5.2 (113) | 5.9 (155) | 6.8 (111) | 6.6 (121) |
|  |  |  |  |  |  |  |  |  |
| **Urology** | **N=1,359** | **N=2,441** | **N=940** | **N=1,569** | **N=1,288** | **N=1,649** | **N=1,204** | **N=1,584** |
| Primary endpoint — % (no.)\* | 3.9 (53) | 4.6 (113) | 8.4 (79) | 7.5 (117) | 6.2 (80) | 5.8 (95) | 7.5 (90) | 5.4 (85) |
| Death | 1.2 (16) | 1.7 (41) | 1.5 (14) | 2.2 (33) | 2.2 (28) | 1.9 (32) | 0.6 (7) | 0.7 (11) |
| Myocardial infarction | 0.4 (6) | 0.4 (9) | 0.5 (5) | 1.2 (19) | 0.3 (4) | 0.5 (8) | 0.4 (5) | 0.3 (4) |
| Stroke | 0.2 (3) | 0.1 (2) | 0.3 (3) | 0.4 (6) | 0.4 (5) | 0.4 (6) | 0.6 (7) | 0.3 (5) |
| Acute renal failure | 1.9 (26) | 2.2 (53) | 5.5 (52) | 3.4 (53) | 2.9 (37) | 1.9 (32) | 4.6 (55) | 2.5 (39) |
| Pneumonia | 0.6 (8) | 1.1 (27) | 2.9 (27) | 1.7 (26) | 2.0 (26) | 1.9 (31) | 1.2 (14) | 1.5 (24) |
| Sepsis | 0.6 (8) | 1.4 (34) | 2.6 (24) | 2.1 (33) | 2.3 (30) | 2.1 (34) | 3.1 (37) | 2.5 (40) |
|  |  |  |  |  |  |  |  |  |
| **Gynecology** | **N=700** | **N=1,303** | **N=690** | **N=985** | **N=1,602** | **N=1,775** | **N=1,037** | **N=1,111** |
| Primary endpoint — % (no.)\* | 1.1 (8) | 0.9 (12) | 1.4 (10) | 1.6 (16) | 0.5 (8) | 0.3 (5) | 0.9 (9) | 1.4 (16) |
| Death | 0.1 (1) | 0.4 (5) | 0.4 (3) | 0.3 (3) | 0.3 (5) | 0.1 (1) | 0.4 (4) | 0.3 (3) |
| Myocardial infarction | 0.0 (0) | 0.1 (1) | 0.0 (0) | 0.2 (2) | 0.0 (0) | 0.0 (0) | 0.0 (0) | 0.1 (1) |
| Stroke | 0.1 (1) | 0.1 (1) | 0.4 (3) | 0.0 (0) | 0.1 (1) | 0.0 (0) | 0.0 (0) | 0.2 (2) |
| Acute renal failure | 0.3 (2) | 0.3 (4) | 0.6 (4) | 0.3 (3) | 0.1 (2) | 0.1 (1) | 0.4 (4) | 0.5 (5) |
| Pneumonia | 0.7 (5) | 0.2 (3) | 0.6 (4) | 0.6 (6) | 0.1 (2) | 0.1 (2) | 0.1 (1) | 0.7 (8) |
| Sepsis | 0.1 (1) | 0.2 (2) | 0.3 (2) | 0.7 (7) | 0.1 (2) | 0.2 (4) | 0.2 (2) | 0.6 (7) |
|  |  |  |  |  |  |  |  |  |
| **Obstetric** | **N=1,350** | **N=2,529** | **N=1,526** | **N=2,282** | **N=798** | **N=986** | **N=471** | **N=511** |
| Primary endpoint — % (no.)\* | 0.3 (4) | 0.0 (0) | 0.3 (4) | 0.2 (5) | 0.3 (2) | 0.1 (1) | 0.6 (3) | 0.8 (4) |
| Death | 0.1 (1) | 0.0 (0) | 0.0 (0) | 0.0 (0) | 0.0 (0) | 0.0 (0) | 0.0 (0) | 0.0 (0) |
| Myocardial infarction | 0.0 (0) | 0.0 (0) | 0.0 (0) | 0.0 (1) | 0.0 (0) | 0.0 (0) | 0.0 (0) | 0.2 (1) |
| Stroke | 0.0 (0) | 0.0 (0) | 0.0 (0) | 0.0 (1) | 0.0 (0) | 0.0 (0) | 0.0 (0) | 0.0 (0) |
| Acute renal failure | 0.1 (2) | 0.0 (0) | 0.0 (0) | 0.0 (1) | 0.0 (0) | 0.0 (0) | 0.2 (1) | 0.2 (1) |
| Pneumonia | 0.1 (1) | 0.0 (0) | 0.1 (2) | 0.0 (1) | 0.0 (0) | 0.1 (1) | 0.2 (1) | 0.6 (3) |
| Sepsis | 0.0 (0) | 0.0 (0) | 0.1 (2) | 0.0 (1) | 0.3 (2) | 0.0 (0) | 0.2 (1) | 0.0 (0) |
|  |  |  |  |  |  |  |  |  |
| **Oral and maxillofacial** | **N=566** | **N=979** | **N=569** | **N=785** | **N=684** | **N=781** | **N=542** | **N=560** |
| Primary endpoint — % (no.)\* | 2.7 (15) | 1.7 (17) | 1.9 (11) | 1.3 (10) | 2.3 (16) | 2.2 (17) | 0.7 (4) | 0.9 (5) |
| Death | 0.9 (5) | 0.3 (3) | 0.2 (1) | 0.3 (2) | 0.3 (2) | 0.5 (4) | 0.2 (1) | 0.2 (1) |
| Myocardial infarction | 0.0 (0) | 0.0 (0) | 0.5 (3) | 0.3 (2) | 0.0 (0) | 0.3 (2) | 0.0 (0) | 0.0 (0) |
| Stroke | 0.2 (1) | 0.0 (0) | 0.4 (2) | 0.1 (1) | 0.1 (1) | 0.1 (1) | 0.0 (0) | 0.0 (0) |
| Acute renal failure | 0.5 (3) | 0.2 (2) | 0.2 (1) | 0.0 (0) | 0.7 (5) | 0.0 (0) | 0.2 (1) | 0.0 (0) |
| Pneumonia | 1.1 (6) | 1.1 (11) | 1.1 (6) | 0.5 (4) | 1.5 (10) | 1.9 (15) | 0.6 (3) | 0.5 (3) |
| Sepsis | 0.7 (4) | 0.5 (5) | 0.2 (1) | 0.1 (1) | 0.3 (2) | 0.4 (3) | 0.0 (0) | 0.2 (1) |
|  |  |  |  |  |  |  |  |  |
| **Trauma/Orthopedic** | **N=2,061** | **N=3,482** | **N=2,936** | **N=4,395** | **N=3,179** | **N=3,712** | **N=4,457** | **N=4,709** |
| Primary endpoint — % (no.)\* | 5.3 (109) | 6.1 (213) | 7.2 (210) | 6.7 (296) | 5.6 (179) | 5.7 (213) | 5.2 (230) | 4.8 (227) |
| Death | 2.8 (58) | 3.0 (104) | 2.5 (73) | 2.1 (93) | 2.1 (66) | 2.4 (89) | 1.5 (67) | 1.4 (64) |
| Myocardial infarction | 0.3 (7) | 0.3 (10) | 1.3 (39) | 1.9 (82) | 0.4 (12) | 0.6 (21) | 0.2 (10) | 0.4 (17) |
| Stroke | 0.4 (8) | 0.3 (9) | 0.3 (9) | 0.3 (14) | 0.3 (8) | 0.3 (10) | 0.7 (31) | 0.5 (25) |
| Acute renal failure | 1.7 (36) | 2.1 (74) | 2.7 (78) | 1.5 (67) | 1.4 (44) | 1.2 (45) | 2.5 (112) | 1.4 (65) |
| Pneumonia | 1.9 (39) | 2.4 (83) | 3.5 (102) | 2.9 (128) | 3.2 (101) | 3.0 (110) | 2.1 (93) | 1.9 (91) |
| Sepsis | 1.3 (27) | 1.9 (66) | 2.5 (74) | 2.3 (100) | 1.7 (53) | 1.6 (58) | 2.1 (95) | 1.8 (85) |
|  |  |  |  |  |  |  |  |  |
| **Others** | **N=664** | **N=1,170** | **N=547** | **N=865** | **N=901** | **N=1,107** | **N=732** | **N=688** |
| Primary endpoint — % (no.)\* | 4.8 (32) | 5.2 (60) | 7.9 (43) | 7.5 (65) | 2.8 (25) | 3.6 (40) | 3.6 (26) | 5.7 (39) |
| Death | 2.9 (19) | 2.5 (29) | 1.3 (7) | 2.5 (22) | 1.2 (11) | 1.6 (18) | 0.5 (4) | 1.2 (8) |
| Myocardial infarction | 0.2 (1) | 0.4 (5) | 1.3 (7) | 1.6 (14) | 0.4 (4) | 0.4 (4) | 0.1 (1) | 0.4 (3) |
| Stroke | 0.2 (1) | 0.2 (2) | 0.5 (3) | 0.2 (2) | 0.0 (0) | 0.1 (1) | 0.8 (6) | 0.3 (2) |
| Acute renal failure | 1.8 (12) | 1.2 (14) | 2.7 (15) | 2.8 (24) | 0.9 (8) | 1.0 (11) | 1.1 (8) | 1.9 (13) |
| Pneumonia | 1.5 (10) | 1.5 (17) | 4.0 (22) | 3.0 (26) | 1.7 (15) | 1.7 (19) | 1.0 (7) | 2.3 (16) |
| Sepsis | 1.7 (11) | 2.1 (24) | 2.9 (16) | 2.3 (20) | 1.1 (10) | 1.3 (14) | 1.1 (8) | 2.6 (18) |

\*The primary endpoint was a composite endpoint (including death, myocardial infarction, ischemic stroke, acute renal failure, pneumonia, and sepsis) until hospital discharge. Note that patients could have had multiple events.

†n=455 events in patients with surgery of skull, brain or meninges (OPS 5-01 and 5-02) were not considered as postoperative ischemic stroke due to pre-existing diagnose at or before hospital admission.

‡n=672 events in patients with coronary artery surgery (OPS 5-36) were not considered as postoperative myocardial infarction due to pre-existing diagnosis at or before hospital admission.

Please note that n=11,253 patients in the Pre-PBM (center 1 n=2,577/ center 2 n=2,169/ center 3 n=3,482/ 4 n=3,025) and n=14,589 in the PBM cohort (n=4,352/ n=3,033/ n=4,002/ n=3,202) had surgeries in more than one subgroup according the German procedure classification (‘Operationen- und Prozedurenschluessel’ – OPS).

# Table S4. Secondary endpoints for the four centers and subgroups of surgery

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Center 1** |  | **Center 2** |  | **Center 3** |  | **Center 4** |  |
| **Variable** | **Pre-PBM** | **PBM** | **Pre-PBM** | **PBM** | **Pre-PBM** | **PBM** | **Pre-PBM** | **PBM** |
| **All patients** | **N=13,394** | **N=23,414** | **N=13,082** | **N=20,003** | **N=13,978** | **N=16,915** | **N=14,059** | **N=14,874** |
| RBC |  |  |  |  |  |  |  |  |
| Patients transfused — % (no.) | 18.1 (2,429) | 14.6 (3,417) | 16.9 (2,215) | 15.7 (3,136) | 18.5 (2,592) | 16.6 (2,806) | 15.4 (2,171) | 14.0 (2,089) |
| Units per patient – no. | 1.29±5.70 | 1.00±4.63 | 1.23±5.40 | 1.06±4.92 | 1.23±4.95 | 1.10±4.82 | 1.09±4.71 | 0.87±3.76 |
| Preoperative Anemia – % (no./ total no.) | 40.2 (4,293/10,677) | 40.0 (7,119/17,813) | 37.0 (3,827/10,350) | 39.4 (6,150/15,602) | 27.6 (3,575/12,961) | 29.5 (4,630/15,720) | 33.7 (3,187/9,465) | 36.3 (3,658/10,087) |
| Anemia at discharge – % (no./total no.) | 75.6 (7,270/9,621) | 74.6 (12,262/16,436) | 70.8 (5,694/8,042) | 72.4 (9,223/12,743) | 68.9 (6,713/9,740) | 70.7 (8,764/12,404) | 66.6 (6,016/9,028) | 70.1 (6,786/9,686) |
| Length of stay on ICU – days / patients on ICU - % (no.) | 1.7±12.5 / 19.8 (2,654) | 2.0±12.3 /  18.6 (4,365) | 1.8±7.8 /  23.3 (3,046) | 1.9±9.0 /  23.3 (4,670) | 5.6±13.8 / 23.9 (3,336) | 5.7±13.0 / 23.9 (4,049) | 6.3±13.2 /  15.4 (2,162) | 5.6±12.8 /  14.9 (2,212) |
| Hospital length of stay –days | 10.5±13.7 | 10.6±14.6 | 10.6±14.1 | 10.5±15.0 | 10.1±14.2 | 9.9±13.2 | 10.2±13.7 | 9.8±13.3 |
|  |  |  |  |  |  |  |  |  |
| **Neurosurgery** | **N=1,557** | **N=2,663** | **N=1,964** | **N=2,918** | **N=1,723** | **N=2,196** | **N=1,891** | **N=2,109** |
| RBC |  |  |  |  |  |  |  |  |
| Patients transfused — % (no.) | 15.9 (247) | 15.2 (405) | 15.6 (307) | 15.3 (445) | 14.5 (249) | 13.2 (290) | 15.6 (295) | 13.9 (293) |
| Units per patient – no. | 0.92±3.68 | 0.83±3.77 | 0.77±2.76 | 0.76±2.73 | 0.85±3.82 | 0.64±3.02 | 0.97±3.80 | 0.74±3.12 |
| Preoperative Anemia – % (no./ total no.) | 33.6 (428/1275) | 31.4 (669/2,131) | 29.4 (521/1,774) | 30.9 (819/2,652) | 21.7 (360/1,662) | 25.2 (526/2,087) | 29.7 (388/1,308) | 31.7 (500/1,577) |
| Anemia at discharge – % (no./total no.) | 77.2 (838/1,085) | 74.4 (1410/1,896) | 73.8 (918/1,244) | 74.8 (1,566/2,093) | 57.9 (846/1,462) | 61.9 (1,148/1,856) | 64.5 (813/1,260) | 68.1 (1,017/1,493) |
| Length of stay on ICU – days / patients on ICU - % (no.) | 3.8±12.9 / 48.6 (757) | 4.7±17.2 /  47.5 (1266) | 2.2±6.9 /  37.1 (728) | 2.8±9.0 /  36.1 (1054) | 5.3±8.0 /  41.9 (722) | 5.1±7.7 /  40.6 (892) | 6.2±10.1 /  22.5 (426) | 6.6±9.1 /  19.4 (409) |
| Hospital length of stay -days | 13.2±12.8 | 13.5±13.6 | 13.0±12.5 | 13.4±15.1 | 12.9±11.5 | 11.8±10.3 | 12.9±13.6 | 12.1±13.8 |
|  |  |  |  |  |  |  |  |  |
| **Otorhinolaryngology** | **N=2,022** | **N=3,365** | **N=1,902** | **N=2,617** | **N=2,571** | **N=2,985** | **N=2,762** | **N=2,734** |
| RBC |  |  |  |  |  |  |  |  |
| Patients transfused — % (no.) | 13.0 (262) | 14.0 (472) | 14.8 (281) | 14.4 (378) | 12.8 (328) | 13.1 (390) | 9.5 (262) | 8.0 (219) |
| Units per patient – no. | 1.84±9.51 | 1.86±7.81 | 2.49±10.35 | 2.21±9.74 | 1.80±7.99 | 1.79±8.03 | 1.46±7.18 | 1.08±6.09 |
| Preoperative Anemia – % (no./ total no.) | 30.2 (423/1,400) | 28.8 (665/2,311) | 35.7 (390/1,091) | 37.8 (549/1,452) | 20.3 (467/2,301) | 22.1 (594/2,682) | 24.9 (373/1,496) | 26.2 (415/1,585) |
| Anemia at discharge – % (no./total no.) | 65.5  (626/956) | 67.4 (1075/1596) | 79.2  (537/678) | 75.6 (763/1,009) | 65.6  (645/983) | 64.7 (827/1,279) | 60.3 (520/862) | 63.2  (540/855) |
| Length of stay on ICU – days / patients on ICU - % (no.) | 5.8±30.1 / 14.0 (283) | 7.4±28.5 /  16.3 (550) | 5.9±16.7 /  23.2 (441) | 6.8±20.2 /  23.5 (614) | 20.5±32.8 /  15.9 (410) | 19.7±27.2 /  17.5 (523) | 21.5±27.0 /  10.2 (283) | 19.9±28.7 /  9.9 (271) |
| Hospital length of stay -days | 10.4±18.2 | 10.8±18.5 | 12.7±21.9 | 13.2±24.7 | 10.5±21.3 | 10.3±18.1 | 8.8±17.3 | 9.5±19.1 |
|  |  |  |  |  |  |  |  |  |
| **Thoracic** | **N=595** | **N=923** | **N=309** | **N=500** | **N=451** | **N=583** | **N=596** | **N=603** |
| RBC |  |  |  |  |  |  |  |  |
| Patients transfused — % (no.) | 42.0 (250) | 41.7 (385) | 46.6 (144) | 38.0 (190) | 43.0 (194) | 47.0 (274) | 49.2 (293) | 49.1 (296) |
| Units per patient – no. | 6.59±15.13 | 6.81±14.38 | 8.09±15.70 | 5.84±13.63 | 7.37±16.14 | 6.99±14.10 | 7.89±16.06 | 5.57±11.50 |
| Preoperative Anemia – % (no./ total no.) | 48.6 (256/527) | 49.3 (423/858) | 43.4 (129/297) | 43.1 (205/476) | 44.3 (198/447) | 42.1 (241/573) | 45.4 (256/564) | 46.0 (271/589) |
| Anemia at discharge – % (no./total no.) | 81.4 (432/531) | 81.5 (687/843) | 75.4 (215/285) | 76.3 (331/434) | 81.9 (352/430) | 83.7 (468/559) | 82.1 (462/563) | 85.6 (495/578) |
| Length of stay on ICU – days / patients on ICU - % (no.) | 9.3±34.8 / 39.0 (232) | 12.8±40.2 / 41.4 (382) | 9.8±18.2 /  67.0 (207) | 7.8±16.6 /  61.0 (305) | 12.8±35.3 /  53.2 (240) | 13.7±24.6 /  53.9 (314) | 13.2±25.3 /  60.9 (363) | 10.2±19.9 /  60.9 (367) |
| Hospital length of stay -days | 20.1±23.2 | 23.6±27.4 | 25.6±25.0 | 20.9±22.2 | 22.2±37.7 | 21.6±30.5 | 24.7±32.9 | 22.8±26.5 |
|  |  |  |  |  |  |  |  |  |
| **Cardiac** | **N=1,580** | **N=2,690** | **N=1,318** | **N=2,070** | **N=1,550** | **N=1,900** | **N=1,182** | **N=1,244** |
| RBC |  |  |  |  |  |  |  |  |
| Patients transfused — % (no.) | 53.2 (841) | 37.9 (1,019) | 45.9 (605) | 42.0 (870) | 73.2 (1,135) | 61.1 (1,161) | 67.4 (797) | 63.3 (787) |
| Units per patient – no. | 3.88±9.15 | 3.19±8.69 | 3.70±9.18 | 2.91±7.95 | 4.99±8.22 | 3.87±8.22 | 6.07±11.64 | 4.63±8.46 |
| Preoperative Anemia – % (no./ total no.) | 38.1 (571/1,500) | 33.8  (855/2,526) | 33.6 (437/1,299) | 34.1 (691/2,025) | 38.0 (588/1,547) | 35.6 (676/1,897) | 29.5 (337/1,144) | 32.4 (398/1,229) |
| Anemia at discharge – % (no./total no.) | 88.9 (13,34/1,500) | 87.4 (2,176/2,490) | 80.6 (1,044/1,295) | 83.8 (1,671/1,994) | 84.8 (1,307/1,542) | 89.8 (1,696/1,888) | 94.6 (1,039/1,098) | 97.1 (1,176/1,211) |
| Length of stay on ICU – days / % patients on ICU - % (no.) | 4.8±20.4 / 75.5 (2,032) | 6.2±22.3 /  79.9 (1,263) | 4.8±10.7 /  76.7 (1,011) | 5.2±12.8 /  77.2 (1,598) | 5.4±16.8 /  98.6 (1,528) | 5.0±13.9 /  95.3 (1,810) | 6.4±15.5 /  92.0 (1,087) | 5.0±14.9 /  90.7 (1,128) |
| Hospital length of stay -days | 14.9±15.0 | 16.3±16.9 | 17.4±15.9 | 16.7±18.9 | 17.4±24.9 | 16.1±18.9 | 18.1±23.3 | 17.3±21.4 |
|  |  |  |  |  |  |  |  |  |
| **Vascular** | **N=965** | **N=1,843** | **N=863** | **N=1,184** | **N=1,250** | **N=1,572** | **N=1,299** | **N=1,224** |
| RBC |  |  |  |  |  |  |  |  |
| Patients transfused — % (no.) | 50.4 (486) | 39.1 (721) | 41.4 (357) | 39.4 (467) | 40.2 (503) | 37.1 (585) | 29.6 (385) | 28.3 (346) |
| Units per patient – no. | 7.08±16.23 | 4.35±11.05 | 5.43±14.19 | 4.25±11.29 | 3.95±10.72 | 3.83±10.63 | 3.43±10.45 | 2.81±8.21 |
| Preoperative Anemia – % (no./ total no.) | 46.0 (444) | 43.6 (804) | 40.8 (352) | 42.3 (501) | 41.0 (512) | 37.3 (587) | 36.2 (470) | 37.3 (456) |
| Anemia at discharge – % (no./total no.) | 81.7 (788) | 78.8 (1,453) | 64.2 (554) | 68.4 (810) | 74.1 (926) | 75.9 (1,193) | 59.7 (776) | 65.3 (799) |
| Preoperative Anemia – % (no.) | 51.3  (444/865) | 50.4  (804/1,594) | 49.7  (352/708) | 50.4  (501/995) | 41.9 (512/1,222) | 38.5 (587/1,526) | 45.0 (470/1,044) | 46.0  (456/992) |
| Anemia at discharge – % (no.) | 90.7  (788/869) | 89.9 (1,453/1,617) | 82.9  (554/668) | 85.0  (810/953) | 82.5 (926/1,123) | 85.8 (1,193/1,391) | 81.9  (776/948) | 81.6  (799/979) |
| Length of stay on ICU – days / patients on ICU - % (no.) | 8.5±40.0 /  41.9 (404) | 6.1±27.8 /  34.9 (643) | 5.6±16.0 /  46.8 (404) | 5.0±15.5 /  50.3 (596) | 7.7±17.1 /  40.3 (504) | 9.7±23.7 /  41.0 (644) | 11.7±25.0 /  25.3 (329) | 12.6±27.3 /  23.0 (281) |
| Hospital length of stay -days | 22.7±26.0 | 20.5±26.2 | 19.3±25.2 | 19.5±24.4 | 16.0±24.3 | 16.7±25.6 | 16.7±24.4 | 15.8±24.2 |
|  |  |  |  |  |  |  |  |  |
| **Visceral and endocrine** | **N=3,175** | **N=5,631** | **N=2,170** | **N=3,547** | **N=2,187** | **N=2,649** | **N=1,632** | **N=1,822** |
| RBC |  |  |  |  |  |  |  |  |
| Patients transfused — % (no.) | 21.5 (682) | 18.2 (1,026) | 23.5 (509) | 21.7 (769) | 22.4 (490) | 21.7 (574) | 22.7 (370) | 22.1 (403) |
| Units per patient – no. | 2.15±8.70 | 1.71±6.59 | 2.32±8.86 | 1.90±7.28 | 2.49±8.88 | 2.60±9.46 | 2.57±8.44 | 2.27±7.83 |
| Preoperative Anemia – % (no./ total no.) | 50.5 (1,284/2,541) | 49.7 (2,262/4,547) | 48.7 (917/1,884) | 51.2 (1,562/3,049) | 28.6 (609/2,128) | 29.8 (773/2,594) | 42.1 (603/1,434) | 44.0 (704/1,599) |
| Anemia at discharge – % (no./total no.) | 75.5 (1,745/2,312) | 72.7 (2,976/4,094) | 67.6 (1,183/1,750) | 70.4 (2,063/2,929) | 63.2 (1,236/1,955) | 65.3 (1,589/2,435) | 68.2 (1,023/1,500) | 69.3 (1,190/1,718) |
| Length of stay on ICU – days / patients on ICU - % (no.) | 2.7±21.3 /  13.6 (431) | 3.4±20.5 /  12.7 (713) | 3.2±12.0/  25.0 (542) | 2.7±11.1 /  23.8 (845) | 9.4±16.4 /  27.7 (605) | 11.3±22.9 /  26.5 (703) | 13.4±19.4 /  19.5 (319) | 13.5±26.0 /  18.3 (333) |
| Hospital length of stay -days | 12.8±18.2 | 12.7±20.2 | 13.9±19.6 | 13.2±19.0 | 13.7±19.1 | 13.8±21.5 | 17.9±21.4 | 17.8±24.6 |
|  |  |  |  |  |  |  |  |  |
| **Urology** | **N=1,359** | **N=2,441** | **N=940** | **N=1,569** | **N=1,288** | **N=1,649** | **N=1,204** | **N=1,584** |
| RBC |  |  |  |  |  |  |  |  |
| Patients transfused — % (no.) | 16.9 (230) | 15.6 (382) | 18.5 (174) | 15.4 (242) | 18.9 (244) | 14.1 (233) | 13.0 (156) | 10.5 (166) |
| Units per patient – no. | 1.10±4.74 | 1.23±5.90 | 1.29±5.64 | 0.93±3.69 | 1.34±6.00 | 1.16±5.39 | 0.90±4.37 | 0.64±3.07 |
| Preoperative Anemia – % (no.) | 30.8 (419) | 34.0 (829) | 30.6 (288) | 26.3 (413) | 30.0 (386) | 28.5 (470) | 30.0 (361) | 30.2 (479) |
| Preoperative Anemia – % (no./ total no.) | 49.4 (671) | 48.9 (1,194) | 46.1 (433) | 46.3 (726) | 49.6 (639) | 50.2 (828) | 50.8 (612) | 47.3 (750) |
| Anemia at discharge – % (no./total no.) | 37.1 (419/1,128) | 45.1 (829/1,840) | 38.2  (288/753) | 33.3 (413/1,240) | 30.9 (386/1,251) | 29.7 (470/1,585) | 46.6  (361/774) | 49.8  (479/961) |
| Anemia at discharge – % (no.) | 74.8  (671/897) | 80.2 (1,194/1,489) | 74.1  (433/584) | 63.0 (726/1,153) | 63.1 (639/1,013) | 62.5 (828/1,325) | 75.6  (612/809) | 68.0 (750/1,103) |
| Length of stay on ICU – days / % patients on ICU - % (no.) | 0.9±8.3 /  7.1 (97) | 1.9±17.2 /  7.6 (185) | 1.4±7.3 /  17.4 (164) | 1.0±5.2 /  16.7 /262) | 6.2±17.7 /  12.7 (164) | 6.8±14.6 /  11.0 (181) | 9.6±18.6 /  5.1 (61) | 9.9±14.3 /  4.6 (73) |
| Hospital length of stay -days | 11.1±17.9 | 10.2±13.1 | 10.0±12.4 | 8.7±11.5 | 9.8±16.9 | 8.7±14.1 | 10.6±15.0 | 8.7±12.8 |
|  |  |  |  |  |  |  |  |  |
| **Gynecology** | **N=700** | **N=1,303** | **N=690** | **N=985** | **N=1,602** | **N=1,775** | **N=1,037** | **N=1,111** |
| RBC |  |  |  |  |  |  |  |  |
| Patients transfused — % (no.) | 8.9 (62) | 7.7 (100) | 7.4 (51) | 7.6 (75) | 3.3 (53) | 3.0 (54) | 3.8 (39) | 4.6 (51) |
| Units per patient – no. | 0.55±3.42 | 0.39±2.32 | 0.39±2.61 | 0.34±1.51 | 0.16±1.17 | 0.15±1.35 | 0.22±1.87 | 0.23±1.59 |
| Preoperative Anemia – % (no./ total no.) | 24.2  (144/594) | 37.9  (283/747) | 21.8  (111/510) | 29.3  (206/704) | 13.6 (200/1,468) | 16.1 (245/1,518) | 39.5  (128/324) | 47.0  (170/362) |
| Anemia at discharge – % (no./total no.) | 68.1  (294/432) | 61.3  (474/773) | 55.2  (186/337) | 57.2  (301/526) | 60.1  (282/469) | 60.7  (301/496) | 60.7  (284/468) | 61.7  (386/626) |
| Length of stay on ICU – days / patients on ICU - % (no.) | 0.3±3.5 /  1.8 (23) | 0.1±2.5 /  3.0 (21) | 0.2±1.1/  4.9 (34) | 0.3±2.1/  5.2 (51) | 2.6±3.0 /  2.1 (34) | 5.1±18.6 /  2.5 (44) | 4.8±6.4 /  1.5 (16) | 8.32±11.2 /  1.4 (16) |
| Hospital length of stay –days | 6.9±10.3 | 7.9±10.6 | 6.6±7.9 | 5.6±8.5 | 4.9±9.3 | 4.5±6.6 | 4.9±7.8 | 4.8±6.4 |
|  |  |  |  |  |  |  |  |  |
| **Obstetric** | **N=1,350** | **N=2,529** | **N=1,526** | **N=2,282** | **N=798** | **N=986** | **N=471** | **N=511** |
| RBC |  |  |  |  |  |  |  |  |
| Patients transfused — % (no.) | 1.9 (26) | 2.4 (61) | 2.7 (41) | 2.1 (47) | 2.3 (18) | 1.1 (11) | 4.7 (22) | 3.7 (19) |
| Units per patient – no. | 0.09±1.19 | 0.09±1.25 | 0.07±0.73 | 0.05±0.54 | 0.06±0.45 | 0.03±0.36 | 0.16±0.97 | 0.19±2.16 |
| Preoperative Anemia – % (no./ total no.) | 45.3 (560/1,236) | 46.5 (929/1,998) | 48.4 (552/1,140) | 55.0 (920/1,673) | 43.1  (261/605) | 45.8  (360/786) | 47.5  (168/354) | 54.0  (209/387) |
| Anemia at discharge – % (no./total no.) | 85.7 (1,120/1,307) | 84.2 (1,972/2,341) | 68.5  (486/709) | 73.4  (647/881) | 89.1  (671/753) | 88.0  (803/912) | 80.9  (372/460) | 82.5  (415/503) |
| Length of stay on ICU – days / patients on ICU - % (no.) | 0.0±0.1 /  0.4 (6) | 0.1±1.9 /  0.7 (17) | 0.0±0.8 /  0.8 (12) | 0.0±0.3/  0.4 (10) | 2.4±4.6 /  1.3 (10) | 1.6±1.1 /  0.9 (9) | 2.8±4.0 /  1.5 (7) | 12.0±22.4 /  0.8 (4) |
| Hospital length of stay -days | 6.1±7.0 | 5.6±6.0 | 4.4±6.1 | 4.4±6.5 | 5.8±7.0 | 5.6±6.4 | 6.8±5.8 | 6.7±7.6 |
|  |  |  |  |  |  |  |  |  |
| **Oral and maxillofacial** | **N=566** | **N=979** | **N=569** | **N=785** | **N=684** | **N=781** | **N=542** | **N=560** |
| RBC |  |  |  |  |  |  |  |  |
| Patients transfused — % (no.) | 8.1 (46) | 5.6 (55) | 5.1 (29) | 3.4 (27) | 7.0 (48) | 6.7 (52) | 1.8 (10) | 2.5 (14) |
| Units per patient – no. | 0.64±4.03 | 0.37±2.37 | 0.22±1.19 | 0.14±0.97 | 0.49±3.90 | 0.33±1.94 | 0.15±1.71 | 0.11±0.95 |
| Preoperative Anemia – % (no./ total no.) | 36.6 (104/284) | 35.6 (147/413) | 19.5 (76/390) | 21.8 (116/533) | 21.9 (119/543) | 25.5 (148/581) | 14.3 (50/349) | 20.7 (74/358) |
| Anemia at discharge – % (no./total no.) | 61.9 (190/307) | 53.8 (254/472) | 62.3 (99/159) | 62.3 (170/273) | 43.9 (179/408) | 47.5 (247/520) | 56.9 (70/123) | 60.7 (99/163) |
| Length of stay on ICU – days / patients on ICU - % (no.) | 1.4±10.4/  6.2 (35) | 0.9±7.6 /  4.7 (46) | 0.5±3.1 /  12.0 (68) | 0.4±2.9 /  9.3 (73) | 5.2±9.8 /  11.1 (76) | 4.0±8.3 /  11.1 (87) | 6.8±9.1 /  5.0 (27) | 4.7±7.7 /  5.9 (33) |
| Hospital length of stay -days | 8.2±11.8 | 7.0±8.9 | 7.9±10.0 | 6.9±7.8 | 8.7±10.7 | 7.9±8.6 | 6.2±5.4 | 6.1±7.1 |
|  |  |  |  |  |  |  |  |  |
| **Trauma/ Orthopedic** | **N=2,061** | **N=3,482** | **N=2,936** | **N=4,395** | **N=3,179** | **N=3,712** | **N=4,457** | **N=4,709** |
| RBC |  |  |  |  |  |  |  |  |
| Patients transfused — % (no.) | 19.9 (410) | 19.7 (686) | 22.5 (660) | 19.9 (876) | 17.6 (558) | 16.6 (617) | 17.5 (779) | 14.3 (673) |
| Units per patient – no. | 1.67±7.08 | 1.76±6.94 | 1.50±5.06 | 1.30±5.41 | 1.05±4.05 | 0.98±4.30 | 1.51±6.58 | 0.96±4.33 |
| Preoperative Anemia – % (no./ total no.) | 39.4 (582/1,476) | 36.4 (935/2,567) | 35.2 (876/2,492) | 37.0 (1,334/3,610) | 30.6 (887/2,896) | 36.3 (1,256/3,458) | 34.6 (1,081/3,124) | 36.9 (1,171/3,170) |
| Anemia at discharge – % (no./total no.) | 70.1 (1,059/1,511) | 69.1 (1737/2,515) | 73.6 (1,462/1,987) | 78.1 (2,336/2,992) | 72.3 (1,623/2,244) | 75.6 (2,203/2,915) | 58.8 (1,956/3,329) | 65.1 (2,123/3,261) |
| Length of stay on ICU – days / patients on ICU - % (no.) | 2.2±18.1 / 14.6 (300) | 3.2±20.0 /  14.6 (508) | 1.4±6.7 /  18.6 (547) | 1.5±8.0 /  19.4 (851) | 6.5±11.4 /  16.5 (525) | 6.3±11.8 /  15.1 (559) | 10.4±22.2 /  10.8 (481) | 8.5±17.6 /  8.9 (417) |
| Hospital length of stay –days | 12.9±17.1 | 14.0±18.8 | 13.8±15.2 | 13.5±17.4 | 12.7±14.7 | 12.7±14.4 | 12.5±17.1 | 11.2±14.6 |
|  |  |  |  |  |  |  |  |  |
| **Others** | **N=664** | **N=1,170** | **N=547** | **N=865** | **N=901** | **N=1,107** | **N=732** | **N=688** |
| RBC |  |  |  |  |  |  |  |  |
| Patients transfused — % (no.) | 22.6 (150) | 17.4 (204) | 23.0 (126) | 23.6 (204) | 11.4 (103) | 12.8 (142) | 10.7 (78) | 12.1 (83) |
| Units per patient – no. | 2.02±7.11 | 1.63±7.22 | 1.62±9.12 | 1.62±6.01 | 0.76±4.23 | 0.94±3.93 | 0.70±3.99 | 0.91±4.18 |
| Preoperative Anemia – % (no./ total no.) | 37.2  (212/570) | 42.4  (338/798) | 30.7  (132/430) | 41.1  (255/621) | 16.9  (147/872) | 20.8 (222/1,065) | 34.6  (149/431) | 38.8  (159/410) |
| Anemia at discharge – % (no./total no.) | 73.6  (332/451) | 73.1  (538/736) | 64.9  (251/387) | 72.0  (437/607) | 64.4  (313/486) | 70.2  (412/587) | 76.6  (281/367) | 77.5  (275/355) |
| Length of stay on ICU – days / patients on ICU - % (no.) | 1.4±9.3 /  9.8 (65) | 1.5±11.5 /  8.3 (97) | 1.5±5.2 /  33.6 (184) | 1.9±7.5 /  34.0 (294) | 3.4±8.1 /  14.9 (134) | 4.0±11.9 /  16.4 (181) | 6.6±12.9 /  8.6 (63) | 7.2±14.2 /  13.4 (92) |
| Hospital length of stay –days | 13.8±17.0 | 14.0±23.2 | 13.5±14.4 | 13.5±15.1 | 9.7±12.0 | 10.0±13.7 | 11.0±14.1 | 12.1±17.7 |

Please note that n=11,253 patients in the Pre-PBM (center 1 n=2,577/ center 2 n=2,169/ center 3 n=3,482/ 4 n=3,025) and n=14,589 in the PBM cohort (n=4,352/ n=3,033/ n=4,002/ n=3,202) had surgeries in more than one subgroup according the German procedure classification (‘Operationen- und Prozedurenschluessel’ – OPS). Here, mean ± standard deviations are given for each center.

ICU denotes intensive care unit.

# Table S5. Application of platelets, fresh frozen plasma, and coagulation factors\*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Variables** | **Pre-PBM (n=54,513)** | **PBM**  **(n=75,206)** | **Odds ratio Mantel-Haenszel**  **(95% CI)** | **Adjusted Odds ratio† (95% CI)** | **P- Value** | **P- Value†** |
| **Platelets** |  |  |  |  |  |  |
| Patients receiving platelets | 4.22% | 3.54% | 0.96 (0.81-0.90) | 1.03 (0.88-1.20) | <0.001 | 0.71 |
| Platelets units per patient | 0.19±0.05 | 0.17±0.05 |  |  | <0.001 | 0.47 |
| **Fresh frozen plasma** |  |  |  |  |  |  |
| Patients receiving plasma | 4.09% | 3.78% | 0.98 (0.93-1.04) | 0.97 (0.83-1.12) | 0.56 | 0.66 |
| Plasma units per patient | 0.52±0.07 | 0.50±0.07 |  |  | 0.58 | 0.60 |
|  |  |  |  |  |  |  |
| **Coagulation factors\*** | **Pre-PBM**  **(n=27,372)** | **PBM**  **(n=40,329)** |  |  |  |  |
| **Prothrombin complex concentrate** |  |  |  |  |  |  |
| Patients receiving Prothrombin complex concentrate | 5.48% | 4.88% | 0.83 (0.77-0.88) | 1.09 (0.93-1.28) | <0.001 | 0.30 |
| Prothrombin complex concentrate units per patient | 119.4±15.4 | 113.7±15.1 |  |  | <0.001 | 0.044 |
| **Fibrinogen** |  |  |  |  |  |  |
| Patients receiving Fibrinogen | 3.42% | 3.22% | 0.94 (0.86-1.03) | 0.93 (0.82-1.08) | 0.18 | 0.41 |
| Fibrinogen units per patient | 0.134±0.007 | 0.136±0.006 |  |  | 0.18 | 0.99 |
| **Recombinant factor VII** |  |  |  |  |  |  |
| Patients receiving recombinant factor VII | 0.16% | 0.13% | 0.85 (0.60-1.21) | 0.84 (0.58-1.21) | 0.42 | 0.34 |
| Recombinant factor VII per patient | 4.83±1.48 | 0.32±1.22 |  |  | 0.37 | 0.20 |

\*Two centers could not provide data on coagulation factors.

**†**Logistic or linear regression analyses adjusted for subgroups of surgery as fixed and for calendar year and for centers as random effect.

Data are given as ratios or means±standard error from an univariate mixed effect model considering centers as random effect.

# Figure S2. Multivariable analysis of the primary composite endpoint



Figure depicts results of the multivariable logistic regression analysis of the combined primary endpoint adjusted for a random effect based on the total study cohort. Adjusted odds ratios with confidence intervals are shown on a logarithmic scale. Factors with higher incidences of the combined primary endpoint have odds ratios above 1.

# Figure S3. Trends of patients without RBC transfusion for the four centers (Q3\_2012 - Q2\_2015)

Percentage of patients without any red blood cell (RBC) transfusion increased after implementation of Patient Blood Management. Definition of time periods is provided in the Material and Method section. 0 = indicates 3-months implementation period; Q, quarter.

# Figure S4. RBC utilization analyzed in age categories.

A) Percentage of patients transfused



B) Number of units per patients



Red blood cell (RBC) utilization before (Pre-PBM) and after the implementation of Patient Blood Management (PBM). Increasing age was associated with an increased use of RBC transfusion. PBM resulted in a decrease of red blood cell utilization in all subgroups of age. The figures show percentages from a pooled analysis.

# 

# Figure S5. RBC utilization according to preoperative hemoglobin levels.

A) Percentage of patients transfused according to preoperative hemoglobin level

****

B) Number of red blood cell units transfused per patient according to preoperative hemoglobin level

****

Percentage of patients transfused with red blood cell (RBC) units (A) and number of RBC units transfused per patient (B) are presented before (Pre-PBM) and after the implementation of Patient Blood Management (PBM) categorized according to the preoperative hemoglobin level. Moderate anemia was defined as hemoglobin levels <13g/dL in men and <12g/dL in women, severe anemia <10g/dL in men and <9g/dL in women, respectively.

# Figure S6. Changes in RBC utilization - Subgroup analysis of type of surgery for each center

**A) Center 1**

**B) Center 2**

**C) Center 3**

**D) Center 4**

Changes in red blood cell (RBC) utilization were calculated based on the mean number of RBC units per patient.

# Figure S7. Hemoglobin levels at hospital discharge



Percentage of patients (pooled analysis) with different hemoglobin ranges at the time of hospital discharge before (Pre-PBM) and after the implementation of Patient Blood Management (PBM). PBM slightly increased the proportion of patients with a discharged hemoglobin level of lower than 9 g/dL.