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ORIGINAL ARTICLE

# Perioperative fluid retention and clinical outcome in elective, high-risk colorectal surgery

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**Abstract**
*Backgrounds and aims* There is some controversy regarding concepts currently propagated for an optimal perioperative fluid management in colorectal surgery. We wanted to analyze the association of net intraoperative and postoperative fluid balances with postoperative morbidity and length of stay.
*Materials and methods* We performed a retrospective analysis of data collected prospectively from March 1993 through February 2005. A subgroup from 4,658 patients was studied who had undergone major elective colorectal surgery during that time. This subgroup included 198 patients with a particularly high preoperative risk profile requiring immediate postoperative intensive care unit (ICU) admission. Fluid therapy was guided by established clinical end points. Results were adjusted for various confounding variables (extent of the operative trauma, individual response to the injury, type of analgesia, underlying disease, treatment era).
*Results/findings* After adjustment for relevant covariates, the magnitude of fluid balance was unimportant for morbidity and postoperative hospital length of stay. A high Apache II score after ICU admission, an increased perioperative blood loss, and palliative surgical procedures were associated with a significantly higher complication rate, whereas use of epidural analgesia improved morbidity and shortened hospital stay.
*Interpretation/conclusion* If guided by established standards, even large perioperative fluid retentions do not appear to be associated with a worse outcome after extended colorectal surgery. Epidural analgesia may provide a significant benefit in those high-risk patients.

**Keywords** Colorectal surgery · Fluid therapy · Complications · Hospital length of stay · Fast track

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## Introduction

There is currently some controversy regarding perioperative fluid management. There is no clear consensus or agreement as to whether the patient should be treated according to a liberal fluid regimen or a restrictive one [1, 2]. Over the last few years, several randomized trials tested the effects of different perioperative fluid volumes on outcome after major abdominal surgery [3–10]. Intravenous fluid restriction improved postoperative morbidity in four of these trials [4–7], worsened it in one [3], and was without effect in two [8, 9]. An individualized concept (transesophageal Doppler monitoring) lead to an enhanced intraoperative fluid load and was found to be associated with a better outcome in four studies [10].

It is difficult to estimate the true value of each of these studies. All of them lack a precise description of at least one

variable which is also known or suspected to be associated with outcome. These variables include the actual weight gain (net fluid balance), complementary concepts of either intraoperative or postoperative fluid management, the extent of the surgical trauma (e.g., estimated blood loss, operating time), and the type of anesthesia (epidural analgesia). A further important determinant for outcome is the individual postoperative response to a comparable surgical trauma. This response includes the systemic inflammatory response syndrome (SIRS) which may lead to subsequent organ dysfunction. The extent of postoperative physiologic derangement shows a significant interindividual variation [11, 12] which has not been addressed by any of the above studies.

It was the aim of the current retrospective study to analyze the precise interaction between intra- and postoperative net fluid balances, and postoperative morbidity in patients after major colorectal surgery. All patients had a particularly high preoperative risk profile and were scheduled for immediate postoperative intensive care unit (ICU) surveillance. We wanted to build prognostic models which controlled for confounders describing the extent of the operative trauma, the individual response to the injury, the type of analgesia, and underlying diseases.

## Materials and methods

### Setting and population

The analysis was conducted in the Department of Surgery (surgical ICU) and the Department of Anaesthesiology of the LMU University Hospital Klinikum Grosshadern in Munich, Germany. The study period extended from March 1, 1993—when a database was initiated in our institution for local bench marking—through February 28, 2005. Structural qualities of the surgical ICU (technical equipment, staffing, number of beds) remained largely unchanged during the observation period. The same two senior intensivists were in charge throughout the whole time, thereby maintaining comparable ICU processes, and admission, discharge, DNR order, and withdrawal of care policies. The retrospective analysis was approved by the local institutional review board. Baseline data and acute ICU outcomes of the entire patient population treated in our ICU between 1993 and 2005 were published recently [13–15].

We accomplished a retrospective search of all eligible patients, including all consecutive postoperative patients admitted to the ICU immediately after colorectal surgery. The following search criteria were applied: planned elective operation for malignant or benign lesions involving the colon or rectum, American Society of Anesthesiologists (ASA) score of 2–4, preoperative scheduling for immediate postoperative ICU surveillance, and conventional (non-laparoscopic) construction of an anastomosis. Patients who did not have construction of at least one colorectal anastomosis (patients with a rectal extirpation, and/or construction of a colostomy) were excluded from the analysis. Reasons for a scheduled postoperative ICU admission were either the expected large extent of the surgical procedure or an increased perioperative risk due to a significant preexisting cardiopulmonary disease.

### Data collection

Using different databases, we collected the following information for each patient: age, sex, ICU admission date, hospital discharge date (postoperative hospital length of stay), hospital discharge state (dead or alive), type of surgery (surgery for a benign disease, curative surgery for a malignant disease (carcinoma, sarcoma), palliative surgery for a malignant disease), ASA score, operating time, estimated amount of perioperative blood loss, number of perioperatively transfused autologous or homologous red cell units, total perioperative fluid balance (each during operation and in the recovery room), use of epidural analgesia, Apache II score in the first 24 h after ICU admission, fluid balance in the first 24 h after ICU admission, and the number of homologous red cell units transfused in the first 24 h after ICU admission. We furthermore collected the need for one (or several) reoperations which were required on the basis of specific postoperative pathologies. Reoperations had to be due to specific surgical complications (anastomotic leakage, abscess, peritonitis, bleeding). We also collected the frequency of a complicated postoperative course. The latter was diagnosed if one or several of the following complications were present until discharge/death: intraabdominal infection (enterocutaneous fistulae which were cannulated and imaged by radiography; abscesses, anastomotic leakages or peritonitis which were investigated by laparotomy, endoscopy or ultrasound/CT-guided transcutaneous catheter drainage), postoperative hemorrhage gross dehiscence of the abdominal wall, pneumonia (defined by chest radiography and sputum/tracheal aspirate culture), urinary tract infection (defined by more than 100,000 pathogens per milliliter in urine culture), central venous catheter infection (diagnosed when systemic infectious signs disappeared within 24 h of catheter removal or if more than ten colonies were detected in cultures from the catheter tip), and severe cardiopulmonary events (acute coronary syndromes, pulmonary embolisms, respiratory insufficiencies) requiring invasive diagnosis or invasive organ support (e.g., administration of catecholamines, artificial ventilation). Postoperative infectious complications were defined as the

appearance of systemic signs of infection (temperature >38.5°C, white cell count below $4.0\times10^9$/L or above $10.0\times10^9$/L) and a septic focus or bacteremia. Phlebitis or local soft tissue infections without systemic infectious signs were not included.

## Therapeutic principles

### *General care*

Major surgical principles associated with colorectal resections and construction of colorectal anastomoses were identical and standardized during the study period after we had established specific concepts in our institution in 1993 [16]. Also surgical pre- and postoperative care remained largely unchanged during the observation period and included mechanical bowel preparation, prophylactic use of drains and nasogastric tube, early mobilization, and early enteral nutrition (depending on the physical capability and gastrointestinal function of the patient). Selection of the type of anesthesia and general anesthesia management largely followed guidelines established in the mid-1990s [17]. On the other hand, a variety of new general, therapeutic strategies associated with intraoperative management and postoperative critical care (such as non-invasive ventilation, strict glycemic control, but also increased use of epidural anesthesia and a modified hemodynamic management (see below)) were applied successively between 1999 and 2002. These strategies corresponded to specific practice guidelines for critically ill patients (for review, see [18]). To account for these therapeutic changes, we also included the variable "treatment era" (after/before 2002) as a binary variable into the statistical analysis. None of our high-risk patients underwent an enhanced recovery program.

### *Intraoperative fluid therapy*

Five hundred milliliters of colloids was given for preloading in patients with an epidural analgesia. All patients were given maintenance fluids (crystalloids and colloids) of 8 to 10 mL $kg^{-1}$ $h^{-1}$ intraoperatively and for the first postoperative hours in the recovery room. Blood loss was replaced with additional crystalloid in a 3:1 ratio. Additional fluid was given as necessary to maintain urine output of at least 1 mL $kg^{-1}$ $h^{-1}$. Similarly, additional fluid was administered when mean arterial blood pressure decreased to less than 70% of preinduction values and was unresponsive to minor adjustments in the inhaled anesthetic concentrations. In patients who were no longer responsive to fluid administration, norepinephrine was started at a dose of 0.5 µg $kg^{-1}$ $min^{-1}$ with 0.3 µg $kg^{-1}$ $min^{-1}$ increments.

After 2002, this regimen was modified in patients with severe congestive heart disease. These patients had additional continuous esophageal Doppler monitoring during the time of the operation to guide fluid therapy. By giving extra colloids, we tried to maintain descending aortic flow time between 350 and 400 ms and to optimize stroke volume. To account for this modified concept, the variable "treatment era" (after/before 2002) was considered for statistical analysis.

### *Postoperative (ICU) fluid therapy*

Until 2002, fluid therapy was mostly based on measurements of heart rate, systolic blood pressure, and urine output. Initially, patients with a positive shock index (heart rate > systolic blood pressure) and urine output < 1 mL $kg^{-1}$ $h^{-1}$ received fluid resuscitation with colloid (hydroxyethyl starch, in 6% solution of normal saline) and crystalloids with the objective to normalize shock index and urine output. Fluids were given as long as blood pressure was responsive to therapy. Fluid administration was stopped when $SaO_2$ significantly decreased or if the $PaO_2/FiO_2$ ratio was <100. In the latter patients, and in those who were no longer responsive to fluid administration and who remained in clinical shock with oliguria and a positive shock index, norepinephrine was started at a dose of 0.5 µg $kg^{-1}$ $min^{-1}$ with 0.3−µg $kg^{-1}$ $min^{-1}$ increments, up to a maximal dose of 5.0 µg $kg^{-1}$ $min^{-1}$. If the treatment failed to correct abnormalities in blood pressure, epinephrine was added.

Therapeutic concepts were changed after 2002: Fluid administration was guided by mean arterial pressure and central venous pressure. Norepinephrine was added earlier in the course of therapy (as soon as CVP was >15 mmHg). Dobutamine was added at a dose of 5 µg $kg^{-1}$ $min^{-1}$ with 5 µg $kg^{-1}$ $min^{-1}$ increments if venous oxygen saturation was <70% (provided that $SpO_2$ was >95% and blood hematocrit >30%). The aim of therapy was to achieve and maintain mean arterial pressure (MAP) >70 mmHg, central venous oxygen saturation >=70%, and urine flow >0.7 mL $kg^{-1}$ $h^{-1}$. If the treatment failed to correct abnormalities in MAP, vasopressin was added.

### *Bleeding management*

Red cell transfusion was usually considered when hemoglobin concentration fell below 8–9 g/dL (acute or chronic drop). Lower concentrations were tolerated in patients below the age of 40 years if there was no bleeding complication. In patients with a high risk of cardiac complications, we tried to maintain a hemoglobin concentration around 10 g/dL. In patients with intra-/postoperative bleeding, we tried to rapidly correct bleeding disorders with the objective to normalize thromboplastin time (by administration of clotting factor concentrates) and partial thromboplastin time (by administering fresh frozen plasma) and to obtain a thrombocyte concentration >50 G/L (by administering thrombocyte concentrates).

### Statistical analysis

Categorical variables were expressed as percentage and continuous variables as median (range). Univariate comparisons between different patient groups were made by the chi-square statistics for binary variables (morbidity), by Wilcoxon tests for continuous variables, and by log-rank tests (Kaplan–Meier plots) for hospital length of stay. Univariate associations of different treatment eras with outcome were compared by one-way ANOVA. In all multivariate analyses (see below), the variable "treatment era 2002–2005" was forced into the model.

#### *Regression modeling of time to discharge*

Association of variables with the risk to be hospitalized at a certain postoperative day was examined in hospital survivors using Cox-type risk models. Only those variables were included which were known at the time when a patient entered the study (day 1 after operation) [19]. The assumption that the effect of a variable was linear in the continuous variables was tested by analyzing the effect of estimated coefficients of design variables (quartiles or sixtiles of the covariate distribution) on the duration of hospital length of stay [20]. In case of a non-linear effect, a logarithmic, exponential, power or quadratic transformation of the variable was tested. If these approaches failed in fitting the data, the covariate was divided in two classes according to median, quartiles, or sixtiles. That type of classification was used which yielded the separation with the largest difference [20].

For taking into account deviations of the proportional risk assumption for individual covariates, we created interactions between the predictors and the logarithm of hospital length of stay [21]. Mathematically, these interactions can be described as the product between the value of the predictor variable and the corresponding logarithm of hospital length of stay. If this interaction was significant ($p<0.10$), the predictors were considered as associated with a non-proportional risk, i.e., with a time-varying effect.

Subsequently, a multiple non-proportional risk model with backward stepwise elimination of variables was constructed to estimate adjusted effects on hospital length of stay and 95% confidence intervals. Statistical significance was defined as $p<0.05$.

#### *Regression modeling of morbidity*

Due to the low number of events, a meaningful separate analysis of mortality was not possible. Effects of variables on morbidity (incidence of a complicated postoperative course, or need for reoperations) were examined by logistic regression analysis. Also interactions and collinearities between certain variables (Apache II score on admission day and ASA score, perioperative blood loss and number of transfused red cell units) were evaluated. The assumption that the effect was linear in the continuous variables was tested by analyzing the effect of estimated coefficients of design variables (quartiles or sixtiles of the covariate distribution) on morbility [22]. In case of a non-linear effect, a logarithmic, exponential, power or quadratic transformation of the variable was tested. If these approaches failed in fitting the data, the covariate was divided in two classes according to median, quartiles, or sixtiles. That type of classification was used which yielded the separation with the largest difference [22].

Variables were entered into a stepwise multivariable logistic regression model to estimate adjusted odds ratios (ORs) and 95% confidence intervals (CI). Statistical significance was defined as $p<0.05$. Goodness of fit was evaluated by Hosmer–Lemeshow statistics.

The statistical analysis was performed using a SPSS Package (SPSS version 15.0.1, SPSS Inc., Chicago, IL, USA).

## Results

### Clinical results

During the 12-year period of this study, 4,658 patients had various types of colorectal operations in our institution. A subgroup of 198 high-risk patients with elective colorectal operations fulfilled our criteria for inclusion in the analysis and required ICU therapy. Baseline characteristics, clinical variables, and variables relating to the perioperative management are presented in Table 1. More than 2/3 of the patients were suffering from a malignant disease, and in 1/3 of the tumor patients only a palliative procedure was possible. Due to their tumor size, about 1/3 of the patients required extended intraabdominal resections involving also neighboring organs or structures, such as small bowel, kidney, bladder, spleen, or retroperitoneum. About 25% of the tumor patients were suffering from a recurrent disease. Epidural analgesia was used in 137 patients (69.2%), but was not associated with disease severity after ICU admission. Apache II score did not differ significantly between those patients who had an epidural analgesia and those who had not (yes 10 (2–28), no 10 (0–32), $p=0.379$).

Sixty-two patients (31.3%) had a complicated postoperative course due to at least one severe complication. Surgical complications were dominating in 49 patients (24.8%). To treat the latter, one or more reoperations had to be performed in 37 patients (18.7% of the whole cohort). The remainder of the surgical complications could be treated conservatively. Severe cardiopulmonary complications occurred in 15

**Table 1** Baseline characteristics, clinical variables, and variables of perioperative therapy (median, range)

| Variable | |
|---|---|
| Number of patients | 198 |
| Age | 69 (24–93) |
| Sex (% male) | 62.6 |
| Benign disease (%) | 31.8 |
| Curative surgery for malignant disease (%) | 48.0 |
| Palliative surgery for malignant disease (%) | 20.2 |
| Site of the anastomosis | |
| Ascending colon (%) | 29.3 |
| Transverse colon (%) | 12.1 |
| Descending/sigmoid colon (%) | 34.8 |
| Rectum (%) | 23.7 |
| ASA score 2 (%) | 39.5 |
| ASA score 3 (%) | 56.1 |
| ASA score 4 (%) | 4.5 |
| Operation and recovery room | |
| Epidural analgesia (%) | 69.2 |
| Operating time (min) | 330 (60–765) |
| Estimated blood loss (mL) | 900 (0–17,020) |
| Transfused red cell units (*n*) | 2 (0–22) |
| Fluid balance (mL) | 4,500 (450–23,050) |
| Intensive care unit (day 1) | |
| Apache II score | 10 (0–32) |
| Transfused red cell units (*n*) | 0 (0–9) |
| Fluid balance (mL) | 1,680 (−2,025–23,600) |

patients (7.5%). Of the whole cohort, 10.6% died in the hospital because of complications. Median of hospital length of stay in survivors was 15 days (range 4–110 days).

## Association of treatment era with outcome

There was no evidence that outcomes differed significantly between different treatment eras (Table 2). After adjusting for confounders, there was also no evidence that the treatment era after 2002 (when intensive care therapy had changed significantly) was an independent predictor of a better prognosis (independent variable "need for a reoperation": $p=0.529$, adjusted odds ratio 1.326, 95% confidence interval 0.551–3.188; independent variable "frequency of a complicated postoperative course": $p=0.620$, adjusted odds ratio 0.833, 95% confidence interval 0.404–1.718; independent variable "hospital length of stay in survivors": $p=0.825$, adjusted hazard ratio 0.966, 95% confidence interval 0.672–1.389).

## Association between fluid balance and outcome

### *Intraoperative fluid balance*

Crude intraoperative fluid balances correlated weakly with outcome. A complicated postoperative course or a reoperation was more common only in those patients who had a fairly large positive intraoperative fluid balance (above the 5. sixtile (=7,800 mL), Table 3). However, these associations were not significant and were also unimportant for the final prognostic models (frequency of a complicated postoperative course: $p=0.399$, adjusted odds ratio 0.661, 95% confidence interval 0.252–1.731; need for a reoperation: $p=0.602$, adjusted odds ratio 1.373, 95% confidence interval 0.417–4,518). There was a significant association between large positive intraoperative fluid balances (above the 4. sixtile (=6,000 mL)) and hospital length of stay in survivors (Fig. 1). This interaction also varied significantly over time. However, after adjusting for confounders (perioperative blood loss and operating time (=extent of the surgical trauma), Apache II score (=individual response to the injury), type of analgesia, and type of surgery, the association was no longer significant in the final prognostic model ($p=0.190$, adjusted hazard ratio 1.289, 95% confidence interval 0.882–1.884).

**Table 2** Association between treatment era and outcome

| | Treatment era | Values |
|---|---|---|
| Need for a reoperation (%) ($p=0.687$) | 1993–1996 | 30.0 |
| | 1996–1999 | 16.2 |
| | 1999–2002 | 25.0 |
| | 2002–2005 | 20.8 |
| Frequency of a complicated postoperative course (%) ($p=0.957$) | 1993–1996 | 30.0 |
| | 1996–1999 | 32.4 |
| | 1999–2002 | 37.5 |
| | 2002–2005 | 34.8 |
| Hospital length of stay in survivors (days) ($p=0.297$) | 1993–1996 | 13 (9–27) |
| | 1996–1999 | 16 (9–110) |
| | 1999–2002 | 15 (9–57) |
| | 2002–2005 | 15 (4–60) |

### *Fluid balance on day 1 after ICU admission*

At univariate analysis, we found a significant, non-linear (quadratic) association between the fluid balance on day 1 after ICU admission and the frequency of a complicated postoperative course (after quadratic transformation: $p<$

**Table 3** Univariate association between intraoperative fluid balance and morbidity

| Intraoperative fluid balance (5. sixtile) | <7,800 mL | >7,800 mL | *p* value |
|---|---|---|---|
| Frequency of a complicated postoperative course (%) | 34 | 38 | 0.684 |
| Need for a reoperation (%) | 19 | 28 | 0.315 |

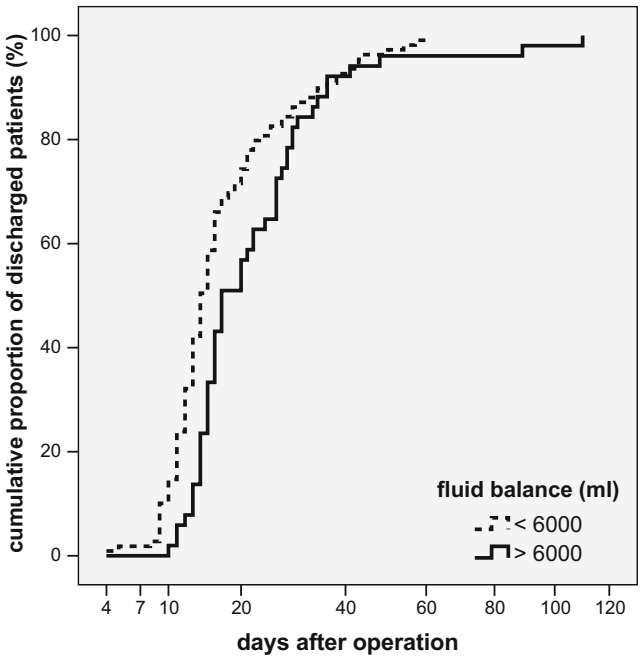


**Fig. 1** Univariate association between intraoperative fluid balance (4. sixtile) and the proportion of patients discharged at a specific day after operation (Kaplan–Meier plot for surviving patients, $p<0.05$ according to log-rank test)

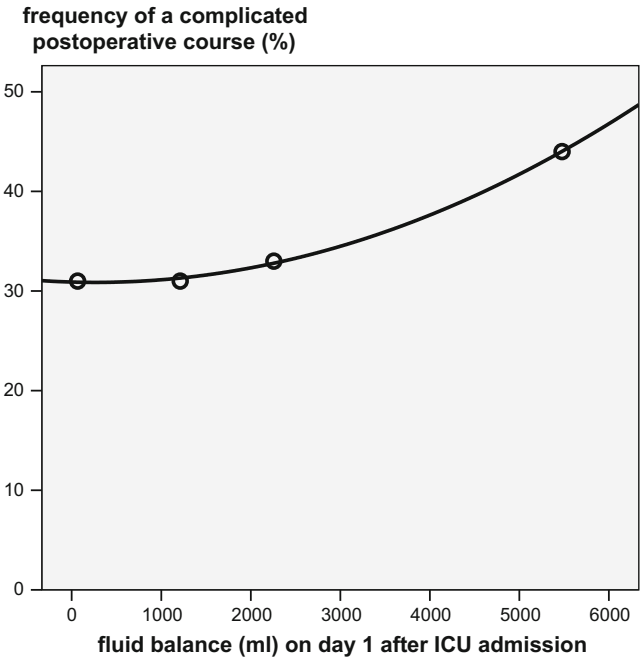


**Fig. 2** Univariate association between fluid balance on day 1 after ICU admission and the frequency of a complicated postoperative course. *Circles* represent mean values of 0–25%, 25–50%, 50–75%, and 75–100% quartiles of fluid balance. The association follows a quadratic equation ($p<0.05$)

0.05, unadjusted odds ratio 401.308, 95% confidence interval 2.092–7,6973.066; Fig. 2). Correspondingly, there were also significant non-linear associations between fluid balance and the risk to need a reoperation ($p<0.05$, unadjusted odds ratio 2.398, 95% confidence interval 1.003–5.733; Fig. 3) or—in survivors—to be hospitalized at a certain postoperative day ($p<0.05$, unadjusted hazard ratio 1.557, 95% confidence interval 1.009–2.402; Fig. 4). The latter association was only evident with fairly large positive fluid balances (above the 5. sixtile (=3,300 mL)).

However, after adjusting for confounders, we were unable to identify significant associations between even large fluid balances and the risk for a complicated postoperative course (after quadratic transformation of fluid balances: $p=0.100$, adjusted odds ratio 210.132, 95% confidence interval 0.719–61,445.186), the risk to need a reoperation ($p=0.113$, adjusted odds ratio 2.153, 95% confidence interval 0.835–5.552), or the risk to be hospitalized at a certain postoperative day ($p=0.285$, adjusted hazard ratio 1.286, 95% confidence interval 0.810–2.041).

## Prognostic factors for morbidity and hospital length of stay

All statistical approaches (final models) revealed that, besides fluid balances, neither age, site of the anastomosis, treatment era, nor sex was important for outcome. On the other hand, multivariate analysis identified the individual disease severity at ICU admission (Apache II score) and specific types of analgesia (non-epidural analgesia) as independent risk factors. The independent association with the type of analgesia was observed with all dependent variables examined (frequency of a complicated postoperative course, need for a reoperation, hospital length of stay (Tables 4, 5, and 6)). Apache II score interacted signifi-

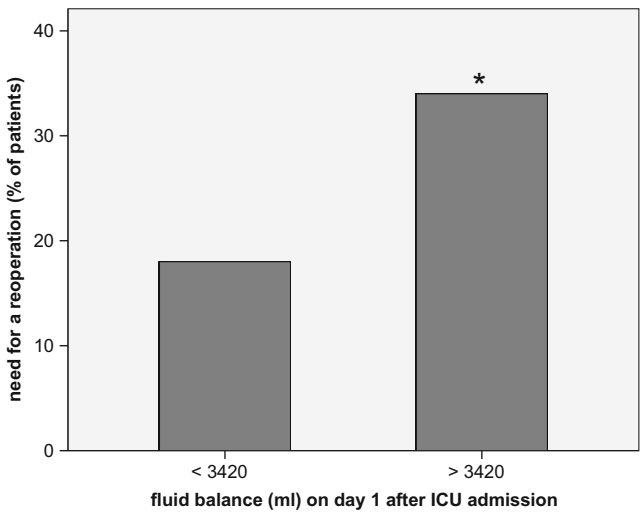


**Fig. 3** Univariate association between fluid balance (5. sixtile) on day 1 after ICU admission and the need for a reoperation ($p<0.05$)

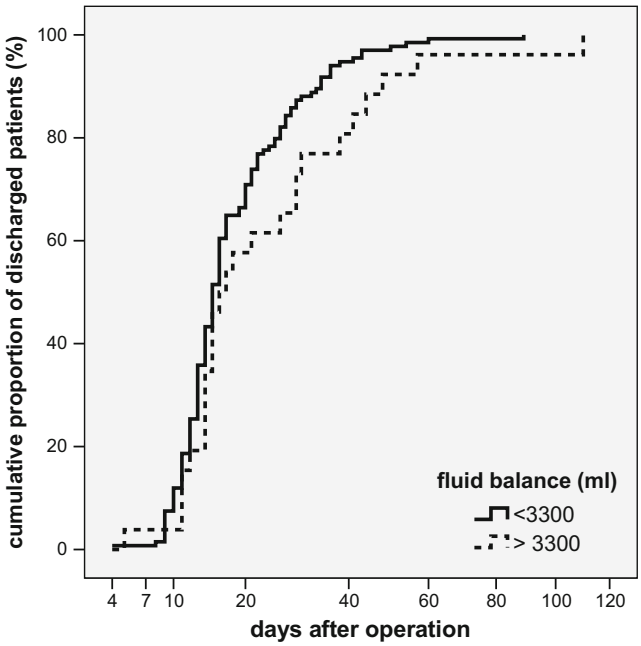


**Fig. 4** Univariate association between fluid balance (5. sixtile) on day 1 after ICU admission and the proportion of patients discharged at a specific day after operation (Kaplan–Meier plot for surviving patients, $p<0.05$ according to log-rank test)

cantly with the need for a reoperation and showed a strong linear association with the frequency of a complicated postoperative course. The interaction was weaker for hospital length of stay in survivors where Apache II score just failed to reach significance.

Furthermore, any increased perioperative blood loss appeared to be associated with a higher frequency of a complicated postoperative course (Table 4) and a higher risk for a prolonged hospital length of stay (Table 6). Palliative procedures were of particular relevance for severe surgical complications which required one or more reoperations (Table 5). A higher risk for a prolonged hospitalization was also seen in those patients who were affected by a particularly long operating time (Table 5). At univariate analysis, we found that the association of blood loss and operating time with hospital length of stay also varied significantly over time. However, these time-varying effects could not be confirmed at multivariate testing.

**Table 4** Morbidity analysis I (complicated postoperative course): the table presents independent risk factors according to the final logistic regression model

| | *p* value | Odds ratio | 95% confidence interval | |
|---|---|---|---|---|
| | | | Lower end point | Upper end point |
| Apache II score (per point) | 0.001 | 1.112 | 1.045 | 1.182 |
| Epidural analgesia | 0.049 | 0.485 | 0.236 | 0.996 |
| Estimated blood loss >380 mL | 0.029 | 2.579 | 1.099 | 6.053 |

*p* value for the Hosmer–Lemeshow statistics was 0.718

## Discussion

### Magnitudes of morbidity, mortality, and hospital length of stay

Our analysis describes the prognostic factors for postoperative morbidity and hospital length of stay in a cohort of 198 surgical high-risk patients representing 4.3% of all patients who had colorectal operations in our institution between 1993 and 2005. These high-risk patients had undergone different types and extents of large bowel resection and had been scheduled preoperatively for immediate postoperative ICU surveillance. We found that the acute prognosis of this highly selected, specific patient group did not change during the observation period and was limited. In about one third of the patients, the postoperative course was complicated; one or several reoperations were necessary in 18.7% of the patients, and 10.6% died during the index hospitalization. Postoperative morbidity and mortality in our cohort is clearly higher than that found by others in patients after elective colorectal resection. Following colorectal cancer surgery in unselected patients, postoperative general complication rate is about 15% [23], reintervention rate for intraabdominal complications 2–10% [24–26], and mortality 1–5% [23, 24, 26, 27].

The higher postoperative morbidity and mortality in the current study likely results from several facts: Almost two thirds of the patients in our series had an ASA score of 3 or 4, and about 20% of the patients had a palliative resection. Both variables are known risk factors for an increased postoperative morbidity including anastomotic leakage [23, 27]. Furthermore, the extent of the surgical injury (as measured by perioperative blood loss and duration of the operative procedure) was clearly higher in our cohort than in recent controlled studies [3, 5, 6]. The latter reported for elective colorectal operations an average operating time of 2–3 h, an estimated intraoperative blood loss of 300–500 mL, and no additional red cell unit transfusion. In our selected high-risk series, corresponding numbers were about 30% and 50% higher, and on average two red cell units had to be transfused. All these intraoperative variables are potential determinants of postoperative outcome [28–31]. Taken together, our patient population must be considered a high-risk group with respect to postoperative morbidity and mortality. Simultaneously, however, this high-risk group also received extremely variable amounts of perioperative fluids, thereby allowing us to analyze the

**Table 5** Morbidity analysis II (need for a reoperation): the table presents independent risk factors according to the final logistic regression model

| | *p* value | Odds ratio | 95% confidence interval | |
|---|---|---|---|---|
| | | | Lower end point | Upper end point |
| Epidural analgesia | 0.015 | 0.380 | 0.174 | 0.829 |
| Palliative operation for a malignant disease | 0.020 | 2.770 | 1.178 | 6.514 |
| Apache II score >14 points | 0.048 | 1.316 | 1.002 | 1.727 |

*p* value for the Hosmer–Lemeshow statistics was 0.980

interaction of fluid balances with outcome over a wide range.

## Prognostic relevance of fluid balances for morbidity and hospital length of stay

The extent to which the consequences of fluid therapy contribute to postoperative prognosis is still poorly understood and controversial [1, 32]. Thus far, numerous randomized studies tried to identify the potential role of varying fluid regimens for postoperative morbidity. Three different experimental categories exist. The first contains those studies which exclusively studied different peri- or postoperative fluid loads thereby largely ignoring the effect on physiologic variables [3–9]. The second category comprises those studies in which intraoperative fluid therapy was precisely guided by cardiac performance [10], and, finally, the third summarizes studies which evaluated fluid therapy in the context of a multimodal postoperative therapeutic concept [33, 34].

A key element of postoperative enhanced recovery programs is to avoid perioperative fluid excess. A recent metaanalysis of the subject revealed that such multimodal programs lead to a significant reduction of hospital length of stay and morbidity [33]. However, the selective importance of fluid therapy cannot be deduced from these studies since a variety of other perioperative measures are implemented simultaneously, thereby confounding the effect of fluid therapy.

Fluid therapy is also of central importance for optimization of intravascular volume and tissue perfusion in major abdominal surgery. Recent systematic reviews of the literature showed that the use of esophageal Doppler monitor for fluid replacement shortens hospital length of stay and results in fewer postoperative complications [10, 35]. To achieve predefined hemodynamic goals, significantly more fluids have to be given in the intervention group, and these extra fluids exclusively consist of colloids. Therefore, it is not known whether it is the larger fluid load per se, or just the type of fluid which is responsible for the improved prognosis. Furthermore, none of these studies considered the individual postoperative response to the surgical injury or the true perioperative weight gain/fluid retention as potential confounders.

Finally, seven studies examined selective effects of different intra- or postoperative fluid loads on outcome [3–9]. None of these studies used predefined hemodynamic goals but rather used fixed infusion rates thereby only guiding fluid therapy by the hour and by preoperative body weight. Only five studies [3, 5–8] monitored body weight or net water balances during the perioperative period. These studies found that fluid restriction largely prevented the perioperative increase of body weight. However, clinical results were mixed, and restrictive fluid administration was associated either with a better outcome [5–7], a worse outcome [3], or with no relevant clinical effect [8]. Unfortunately, the exclusively postoperative studies by Lobo et al. [7] and MacKay et al. [8] did not precisely

**Table 6** Analysis of hospital length of stay (after operation) in surviving patients

| | *p* value | Hazard ratio | 95% confidence interval | |
|---|---|---|---|---|
| | | | Lower end point | Upper end point |
| Apache II score >10 points | 0.085 | 1.335 | 0.961 | 1.854 |
| Operating time >460 min | 0.003 | 1.817 | 1.232 | 2.680 |
| Estimated blood loss >350 mL | 0.009 | 1.576 | 1.119 | 2.220 |
| Epidural analgesia | 0.032 | 0.681 | 0.479 | 0.967 |

The table presents independent risk factors according to the final Cox model. Hazard refers to the patient's risk of being hospitalized at a specific postoperative day

describe the extent of the surgical trauma (e.g., operating time), and the study by Brandstrup et al. [5] did not control for confounding effects of epidural analgesia.

The remaining two studies yielded contradictory results. The study by Nisanevich et al. [6] showed a borderline beneficial effect ($p=0.046$) of a restricted intraoperative fluid therapy on the total number of patients with complications. The effect was not seen for the total number of complications and could be largely attributed to a decreased frequency of postoperative wound dehiscence/infection (falling from 14.7% to 9.1%). Simultaneously, however, the number of patients receiving blood transfusions was also less in the restrictive protocol group (15.5% versus 25%), a difference known to be associated with significantly less surgical site (wound) infections after colorectal surgery [28, 36]. The most recent study by Holte et al. [3] found that hospital length of stay was actually longer after a restrictive perioperative fluid management ($p<0.03$), possibly because of a higher number of complications ($p<0.01$). However, the relatively small number of patients ($n=32$) limits the validity of these results. For both studies, it is not known whether the individual response to the surgical injury was comparable between the different treatment arms.

Our results suggest that the magnitude of net intra- or postoperative fluid balances alone is not an independent determinant of severe postoperative complications. Initially, large amounts of retained fluid were significantly associated with a risk for a prolonged hospital length of stay (Figs. 1 and 4) or with a risk to acquire one or more complications (Fig. 2) or to need a surgical reintervention (Fig. 3). However, these associations were only significant, when potential confounding variables were not included into the analysis. After correcting for the extent of surgical injury (by adjusting for operating time and blood loss), for the individual physiologic response to the injury (as measured by Apache II score), for the type of analgesia, and for the type of surgery (benign vs. malignant, curative vs. palliative), even large fluid balances were no longer predictive for a worse postoperative course (Tables 3, 4, and 5). Consequently, our results do not support the concept of a fixed, restrictive fluid therapy for perioperative care [32]. Furthermore, it appears indispensable to control important confounders exactly when the selective effects of different fluid regimens on clinical outcomes are to be examined.

## Prognostic factors for outcome

A key observation of our study was that Apache II score and epidural analgesia were significantly associated with outcome. On the other hand, we (and others) found that age, site of the anastomosis, or sex was not important for morbidity [23, 24, 27, 37, 38].

Due to its definition, Apache II score describes the extent of comorbidities together with the extent of the postoperative physiological derangement [39]. When measured during the immediate postoperative phase, Apache II score can be also taken as a summary indicator of the individual response to the surgical injury. This individual response is a major determinant for postoperative outcome [29]. Since there is a close correlation between Apache II score and postoperative, individual mediator release (SIRS), determination of Apache II score also accounts for the associated interindividual variability [40, 41].

Our analysis demonstrated that a high postoperative Apache II score predicts an increased risk for a complicated postoperative course and for a reintervention. The interaction between Apache II score and outcome was weaker in survivors where the predictive power of blood loss and operating time was dominating. Therefore, high Apache II scores appear to be of particular relevance for the risk to sustain a severe, potentially fatal postoperative complication.

The independent association between the type of analgesia and prognosis deserves a specific comment. Epidural analgesia decreased the risk for a worse outcome significantly, regardless which dependent variable was examined (frequency of a complicated postoperative course, need for a reoperation, hospital length of stay, Tables 3, 4, and 5). Older metaanalyses showed that epidural analgesia provides superior postoperative analgesia compared with parenteral opioids. Furthermore, in unselected surgical patients, this effect was also associated with reduced cardiopulmonary complication rates and mortality rates [42, 43]. However, the effect on mortality was not evident in two randomized studies [44, 45], and recent specific metaanalyses questioned (except an improved analgesia) any beneficial effect in unselected patients after colorectal surgery. Thus, epidural analgesia did not shorten the duration of hospital stay or reduce the rates of anastomotic leakage or of cardiopulmonary complications [46, 47]. Our results suggest that those conclusions may not be valid for high-risk patients undergoing extended colorectal resections. In such a situation, epidural analgesia appears to be beneficial and might be considered as a valuable alternative to conventional analgesia.

## Limitations of the study

This study is subject to a number of limitations. First, there are obvious limitations to the generalization of the data because they represent the experience of a single center and reflect a unique case mix, organization, and process of care. Second, a key role for outcome determination must be attributed to specific structures or process qualities. Since during the 12-year study period specific technical aspects of intraoperative and intensive care therapy changed in our

institution, we cannot completely exclude an effect of those potential confounders on the results of our study. On the other hand, univariate and multivariate analyses of treatment era did not reveal a specific association with patient outcome. To account for an occult bias as much as possible, treatment era was forced into all multivariate models. Furthermore, structures or peri-/intraoperative surgical procedures unrelated to organ supportive therapy remained largely unchanged in our institution. Third, the relative unimportance of perioperative fluid balances for prognosis may only exist in situations where fluid therapy is guided by established end points. We do not know whether an unrestricted fluid administration beyond those points might be detrimental. We do also not know whether fluid therapy would be equally unimportant for outcome in patients with a low perioperative risk and with less invasive operations. Finally, we could not examine associations between fluid balances and the risk for minor complications, such as bowel motility which might be particularly sensitive to a fluid overload.

We can also not exclude a certain selection bias with respect to the use of epidural analgesia, since we followed established exclusion criteria when deciding on the type of anesthesia [48]. On the other hand, epidural anesthesia became part of daily routine only after 2000, and before that time, the effect of such a selection bias must be considered minor. Furthermore, since all patients had an elective operation, anticoagulatory therapies were rarely a reason not to use an epidural analgesia.

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