Biomarker-guided Intervention to Prevent Acute Kidney Injury After Major Surgery

The Prospective Randomized BigpAK Study

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Objective: To determine the impact of renal biomarker–guided implementation of the Kidney Disease Improving Global Outcomes (KDIGO) care bundle on the incidence of acute kidney injury (AKI) after major noncardiac surgery in a single-center unblinded randomized clinical trial.

Background: Early optimization of volume status and discontinuation of nephrotoxic medication before the occurrence of AKI may be the crucial step to reduce preventable AKI.

Methods: The urinary biomarker–triggered KDIGO care bundle (early optimization of fluid status, maintenance of perfusion pressure, discontinuation of nephrotoxic agents) was compared to standard intensive care unit (ICU) care in 121 patients with an increased AKI risk after major abdominal surgery that was determined by urinary biomarker (inhibitor of metalloproteinase-2 × insulin-like growth factor–binding protein 7) >0.3. Incidence of overall AKI, severity of AKI, length of stay, major kidney events at discharge, and cost effectiveness were evaluated.

Results: The overall stages of AKI were not statistically different between the 2 groups, but in patients with inhibitor of metalloproteinase-2 × insulin-like growth factor–binding protein 7 values of 0.3 to 2.0 a subgroup analysis demonstrated a significantly reduced incidence of AKI 13/48 (27.1%) in the intervention group compared to control 24/50 (48.0%, $P = 0.03$). Incidence of moderate and severe AKI ($P = 0.04$), incidence of creatinine increase >25% of baseline value ($P = 0.01$), length of ICU, and hospital stay ($P = 0.04$) were significantly lower in the intervention group. Intervention was associated with cost reduction. There were no significant differences regarding renal replacement therapy, in-hospital mortality, or major kidney events at hospital discharge.

Conclusions: Early biomarker-based prediction of imminent AKI followed by implementation of KDIGO care bundle reduced AKI severity, postoperative creatinine increase, length of ICU, and hospital stay in patients after major noncardiac surgery.

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Acute kidney injury (AKI) is a well-known complication in patients after major surgery.[1–3] Incidence rates of AKI after surgery vary between 13%[4] and 50%,[5] although AKI requiring renal replacement therapy (RRT) is relatively rare (2.3%–6.8%).[6] AKI does not only negatively affect patient morbidity and mortality[7] but also health care costs.[8,9] The impact of AKI requiring renal replacement is reflected by increased mortality rates[4] and poor patient outcome.[10] In contrast to already identified presurgical risk factors for postsurgical AKI, such as hypertension, diabetes mellitus, or preexisting chronic kidney disease,[2,5,3] the consequences of intra- and perioperative AKI management are still under debate. The advantages of conservative fluid administration for perioperative morbidity have been recently emphasized,[11–13] but patients may develop postoperative hypovolemia associated with AKI.[14]

In spite of increasing knowledge about caring for postoperative patients and the pathophysiological mechanisms of AKI, specific treatment options for AKI are limited. In previous studies, interventions were generally started after clinical evidence of changes in kidney function, such as elevated serum creatinine levels or decline in diuresis. However, no adequate therapeutic concepts have yet been established, because such "delayed approaches" may only address already existing kidney damage but not ongoing kidney injury. Therefore, increasing efforts should focus on the early detection and prevention of AKI. Instead of monitoring the traditional surrogate markers of kidney function [serum creatinine, estimated gromerular filtration rate (eGFR), or urine output], newly established biomarkers allow the detection of kidney injury before the manifestation of concurrent or subsequent clinical signs.

The insulin-like growth factor–binding protein 7 (IGFBP7) and the tissue inhibitor of metalloproteinase-2 (TIMP-2) are 2 urinary cell cycle arrest biomarkers used to predict AKI after major cardiac[15] and noncardiac surgery.[16] Both markers are involved in G1 cell cycle arrest that prevents cells from dividing in case of cellular stress.[17] We hypothesized that the biomarker-triggered Kidney Disease Improving Global Outcome (KDIGO) care bundle consisting of early optimization of fluid status, maintenance of perfusion pressure, and discontinuation of nephrotoxic agents may reduce postoperative AKI. To prove the hypothesis, we conducted a single-center randomized trial as a first step before preparing a multicenter randomized study in patients after major noncardiac surgery.

METHODS

Patients and Study Design

For this prospective randomized clinical study intensive care unit (ICU) patients after major elective noncardiac surgery, who were

at risk for AKI, were screened for urine biomarker TIMP-2 × IGFBP7 levels. Patients with levels above the cutoff (>0.3) were randomly allocated to either receive measures of KDIGO care bundle or standard care treatment. The study was conducted in a multidisciplinary surgical ICU of a tertiary care university hospital between May 1, 2015 and December 31, 2016. The study protocol was approved by the local Institutional Review Board (Ethics Committee, University of Regensburg, no. 15-101-0028). Written consent was obtained from eligible patients or from their legally authorized representatives. Deferred consent was used in patients for whom prospective informed consent was not feasible. Furthermore, the responsible ICU physician, who was not involved in the clinical study, had the authorization to withhold an intervention, if medically contraindicated. After recovery, patients had the right to affirm or withdraw their consent. The study is registered at ClinicalTrials.gov, number NCT02500394. Patients eligible for biomarker assessment had to be adults admitted to the ICU after major nonurgent noncardiac surgery (surgery duration of >4 h), who had intraoperatively received a jugular central venous line and a urinary catheter and who had at least 1 additional risk factor for AKI, such as age >75, critical illness, pre-existing chronic kidney disease (eGFR ≤60 mL/min), or intraoperative use of an intravenous radiocontrast agent. Critical illness was defined as ongoing requirement of inotropic support or mechanical ventilation at the time of ICU admission. Exclusion criteria were a preoperative episode of AKI during the same hospital stay, AKI during surgery before biomarker evaluation (because current data suggest a detrimental effect of increased fluid administration in early AKI on renal recovery),[18] pre-existing severe chronic kidney disease (estimated glomerular filtration rate of <15 mL/min), previous RRT or kidney transplantation, pregnancy, breastfeeding, or participation in other interventional trial.

Randomization and Intervention

Eligible patients were screened for increased levels of urinary TIMP-2 × IGFBP7 measured immediately after admission to the ICU and after 12 hours. Using the Astute Medical NephroCheck Test, a point of care unit-use immunofluorescence assay on the ASTUTE140 Meter with a 20-minute reaction time, AKI risk (TIMP-2 × _IGFBP7) was derived from (cTIMP-2 × _cIGFBP7)/1000 with a 0.3 (ng/mL)^2/1000 cut-off. In a preanalytical phase, the precision and accuracy of the test were checked, the SOPs prepared, and the laboratory staff trained for 24-hour test availability. The laboratory personnel processing the biomarker and creatinine assessment had no knowledge of patient allocation. Patients with elevated biomarkers at ICU admission (>0.3) were classified as having a high risk of AKI and were randomized in a ratio of 1:1 to intervention or standard care. Randomization was stratified by TIMP2 × IGFBP7 0.3 to 2.0 and TIMP-2 × IGFBP7 >2.0,[15] and block randomization was used within each stratum. Participants were allocated to the next sequential randomization number by sealed opaque envelopes.

Patients were randomized within 4 hours after ICU admission. The nature of the intervention did not allow masking of the study. Patients of the standard care group received standard ICU therapy that was based on the clinical condition of the individual patient without any information on the elevated biomarker. Standard care included a weekly assessment of the concurrent medication by an ICU pharmacist. We used the same balanced electrolyte infusion in both groups. The initial maintenance rate of continuous infusion was 100 mL/h in both groups. The standard care group received additional fluid infusion as a fluid bolus therapy (FBT) of 500 mL during 30 minutes to 1 hour, if deemed necessary by the responsible physician. Patients in the intervention group received a care bundle according to KDIGO recommendation that consisted of increased continuous intravenous fluid administration for 6 hours in combination with nephrology consultation (Supplemental Digital Content 1, http://links.lww.com/SLA/B318). Fluid administration was guided by central venous pressure (CVP). The algorithm of the fluid therapy was supported by clinical evidence and had a good cardiovascular safety profile.[19] Before the start of fluid intervention, fluid responsiveness was confirmed by one of the following dynamic tests: fluid challenge of 200 mL over 10 minutes, positive leg-raising test, or ultrasound assessment of the inferior vena cava. For patients weighing more than 100 kg, the infusion rate was limited to that calculated for patients weighing 100 kg. An additional fluid bolus of 500 mL was allowed in the intervention group, if deemed necessary by the responsible ICU team. Nephrology consultation conducted by a board-certified nephrologist took place after randomization and before the start of fluid intervention. If necessary, the nephrologist recommended adjustments of the current medication because of potential nephrotoxicity and advised on managing the hemodynamic, acid-base, electrolyte, and albumin status.

Outcomes

The primary endpoint was the incidence of AKI according to the KDIGO 2012 guidelines during the first 7 days after surgery.[20] Secondary outcomes included the incidence of moderate and severe AKI, increase in serum creatinine levels by ΔSCr >25% (because current data have shown a significant impact of small postoperative SCr changes on outcome in surgical patients),[21] hospital and ICU length of stay, the incidence of major kidney events (MAKEs) at discharge (defined as >50% increase in creatinine levels compared to baseline, use of RRT, and in-hospital death), changes in biomarker values during the first 12 hours after admission, subgroups analysis of biomarker strata, measures taken as a consequence of nephrology consultation, and cost-effectiveness analysis. SCr was measured before surgery, at admission to the ICU, on a daily basis during the ICU stay, and as indicated by the responsible physician during the stay at the general ward. Urine output was assessed hourly in the ICU. Cost-benefit analysis was based on specifications of InEK (Institut für das Entgeltsystem im Krankenhaus)—Institute for Payment System in Hospitals. Data for analysis were generate from the Verband der Universitätsklinika Deutschlands benchmark for university hospitals [Regensburg data set, departmental browser (FAB)] and internal occupancy statistics in reference year 2016.

Statistics

Sample Size Calculation

Sample size calculation had been based on the primary endpoint, the incidence of AKI during the first 7 days after surgery. According to our previously published data, we expected an AKI rate of 42% in the standard care group.[16] According to the literature and our clinical experience, we estimated a reduction in AKI to 20% in the intervention group.[19,22] To detect a difference of 42% versus 20% using a chi-square test with a power of 80% ($\beta = 0.2$) at a 5% significance level ($\alpha = 0.05$), a total of n = 138 (n = 69 per group) patients were required. However, as an interim patient analysis (n = 52) indicated that full study recruitment (n = 138) would be unable to detect a statistically significant difference in primary outcome, the study was prematurely terminated on 31st December 2016.

Statistical Analyses

Continuous data are presented as median (first quartile to third quartile) and categorical data as absolute frequencies (%). Baseline characteristics between the 2 study groups were compared with the nonparametric Mann-Whitney *U* test or the chi-square test. The primary endpoint was analyzed using a logistic regression model

with "occurrence of AKI" (yes vs no) as a dependent variable and "study group" as an independent variable. Odds ratio and corresponding 95% confidence interval (CI) are reported as effect estimates. Secondary endpoints (moderate and severe AKI, relevant SCr increase, and MAKE by discharge) were analyzed equivalently to the primary endpoint. ICU and hospital length of stay, biomarkers values, and laboratory variables were compared using the Mann-Whitney *U* test with the Hodges-Lehmann estimator and corresponding exact conditional nonparametric CIs as effect estimates. ICU length of stay was visualized by a Kaplan-Meier plot. A *P* value of <0.05 was considered statistically significant. All analyses were conducted using R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline Characteristics

Approximately 43% (N = 102) of 237 screened patients showed normal urine biomarker values and 57% (N = 135) had TIMP2 × IGFBP7 of >0.3. The overall occurrence of AKI was 43.0% (58/135) in the group with elevated TIMP-2 × IGFBP7 levels (>0.3); 37 (27.4%), 14 (10.4%), and 7 (5.2%) were classified as KDIGO stages 1, 2, and 3, respectively.

In total, 125 patients were randomized. However, 2 patients allocated to the intervention group had markedly elevated and not reproducible CVP values, 1 patient was not deemed to be fit by the responsible physician to receive increased maintenance fluid administration because of a substantial risk of developing cardiac insufficiency, and 1 patient allocated to the standard care group required urgent relaparotomy <12 hours after admission. Therefore, 60 patients were included in the intervention group and 61 patients in the standard care group for final assessment (Fig. 1). The baseline characteristics of the study participants were well balanced between the 2 groups (Table 1). The median laboratory turnaround time (from sample registration to results reporting) for urinary (TIMP2 × IGFBP7) was 69 minutes. Time between ICU admission and the start of randomization was 4 hours (median Q1, Q3: 3.0, 5.0). CVP remained stable during the 2 measurements: median of 6.0 mm Hg (Q1, Q3 3.0, 8.0) before intervention and 6.0 mm Hg (4.0, 8.0) after 3 hours. In the intervention group, the median amount of maintenance fluid was 212.5 mL/h (160, 320) at a rate of 3.0 mL/kg/h (2.5, 4.9) in the 0- to 3-hour interval and 200 mL/h (150, 250) at

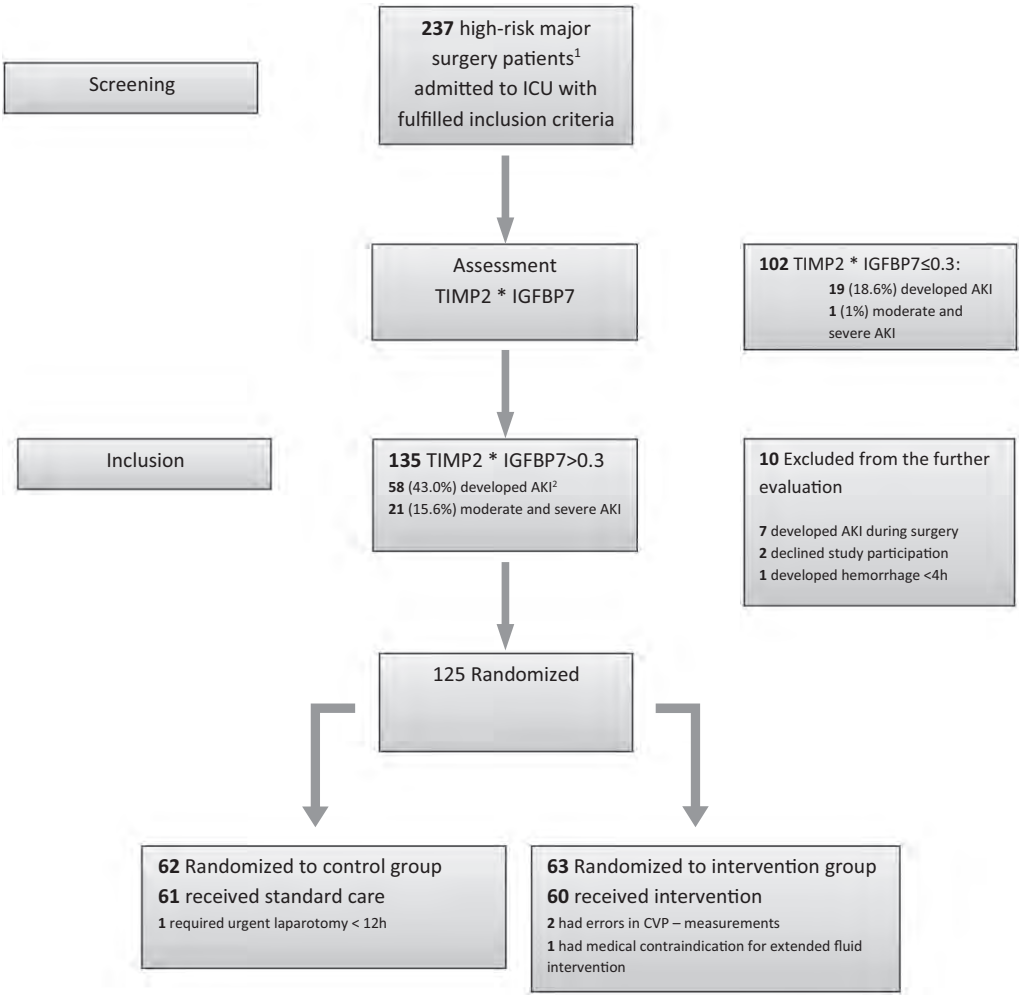

FIGURE 1. Study design and flow diagram. [1]High risk forAKI—elective major surgery >4 hours and 1 additional risk factor: age >75, critical illness, chronic renal disease, or use of radiocontrast agent during surgery. [2]AKI was defined according to KDIGO Criteria 2012.

TABLE 1. Baseline Characteristics for Patients Receiving Intervention Versus Standard Care

	Intervention n = 60	Standard Care n = 61	*P*
Age, median (IQR)	63 (55.25–73)	65 (57.5–74.5)	0.551
Sex (%)			0.957
Male	44 (73.3)	45 (73.8)	
Female	16 (26.7)	16 (26.2)	
BMI, median (IQR)	25.11 (22.66–28.72)	24.86 (23.47–30.03)	0.370
Weight, kg, median (IQR)	78 (64.1–85.75)	80 (69.5–88.7)	0.401
SAPS II, median (IQR)	31 (22–38)	32 (24.5–38)	0.474
Preoperative creatinine, mg/dL, median (IQR)	0.79 (0.69–1.04)	0.83 (0.69–1.00)	0.893
Preoperative GFR (CKD-EPI), mL/min/1.73 qm, median (IQR)	89.5 (69.0–101.0)	88.0 (70.5–98.0)	0.633
Urine output/4 h in mL/kg/h, median (IQR)	0.96 (0.63–1.31)	0.80 (0.55–1.14)	0.291
Baseline urine (TIMP-2) × (IGFBP7), $(ng/mL)^2/1000$, median (IQR)	0.96 (0.70–1.89)	0.86 (0.53–1.62)	0.129
Operative			
Hepatobiliary surgery (%)	22 (36.7)	18 (29.5)	0.405
Transplantation (%)	1 (1.7)	3 (5.0)	0.311
Pancreatic surgery (%)	13 (21.7)	7 (11.5)	0.131
Upper-GI surgery (%)	8 (13.3)	7 (11.5)	0.757
Colorectal surgery (%)	6 (10.0)	13 (21.3)	0.087
Vascular surgery (%)	2 (3.3)	6 (9.8)	0.152
Other abdominal surgery (%)	8 (13.3)	7 (11.5)	0.757
Risk factors			
Age >75 (%)	13 (21.7)	15 (24.6)	0.704
Contrast agent intraoperative (%)	2 (3.3)	6 (9.8)	0.152
Critical illness at admission (%)	56 (93.3)	58 (95.1)	0.682
Chronic kidney disease (%)	8 (13.3)	11 (18.0)	0.477

GI indicates gastrointestinal.

rate of 2.5 mL/kg/h (2.4, 3.1) in the 4- to 6-hour interval. The daily fluid balance for day 1 did not differ between the 2 groups, but on day 2 fluid balance was lower in the intervention group (864 vs 1342 mL), $P = 0.023$. Furthermore, the need for FBT in the first 24 hours was reduced in the intervention compared to the control group [1000 mL (Q1, Q3500, 2000) vs 2000 mL (1000, 2500)], $P < 0.001$. The creatinine values over the first 7 days after surgery and peak creatinine levels did not significantly differ between the 2 groups. However, delta creatinine defined as the ratio between peak SCr and baseline before surgery was lower in the intervention group at day 1 with a median difference of 0.08 (95% CI 0.02, 0.15) and during the 7 days (1.14) (1.05, 1.30) than in the standard care group (1.23) (1.11, 1.43) with a median difference of 0.1 (95% CI 0.02, 0.18), $P = 0.02$. Despite a similar urine output before randomization, this parameter differed between the groups after first 12 hours: 1.35 mL/kg/h (Q1, Q3, 0.94, 1.75) in the intervention group and 1.05 mL (0.84, 1.36) in the standard care group ($P = 0.01$) (Table 2). The postoperative use of albumin and diuretics was similar between the 2 groups.

Primary Endpoint

The overall stages of AKI according to KDIGO classification in the first 7 days after surgery were lower in the intervention group (31.7%) (19/60) than in the standard care group (47.5%) (29/61), $P = 0.076$, odds ratio (OR); 1.96 (95% CI, 0.93, 4.10) without statistical significance. But in patients with TIMP-2 × IGFBP7 values of 0.3 to 2.0 a subgroup analysis demonstrated significant reduced incidence of AKI 13/48 (27.1%) in intervention group compared to 24/50 (48%) in control patients ($P = 0.03$) (Fig. 2).

Secondary Endpoints

Biomarker guided KDIGO care bundle administration significantly reduced the incidence of moderate and severe AKI in the intervention group to 6.7% (4/60 patients) compared to 19.7% in the standard care group (12/60), $P = 0.04$; OR, 3.43 (1.04, 11.32). The incidence of SCr increase by >25% from baseline value was reduced to 40.0% (24/60) in the intervention group versus 62.3% (38/61) in the standard care group, $P = 0.01$; OR, 2.48 (1.19, 5.15). The length of ICU stay was significantly associated with the degree of postoperative change in creatinine levels (Δ creatinine) (Fig. 3). Patients in the intervention group generally had a shorter ICU stay compared to patients receiving standard care, the median difference was 1 (0, 2) day, $P = 0.035$ (Fig. 4). The median length of hospital stay decreased to 16 days[12,22] in the intervention group versus 21 days (15,39) in the standard care group, $P = 0.04$.

Finally, the relative decrease in urinary biomarkers TIMP2 × IGFBP7 values after 12 hours therapy was significantly higher in the intervention group: 2.66 (1.41, 7.04) compared to 1.84 (0.78, 3.19) in the standard care group; the median difference was −0.825 (95% CI −1.7, 0.08], $P = 0.03$. Interestingly, the subgroup analysis suggested significant effect of intervention predominantly in biomarker strata with TIMP2 × IGFBP7 0.3–2.0 (Fig. 2, Fig S1-3, http://links.lww.com/SLA/B318). There were no significant differences in the other secondary outcomes including the use of RRT, in-hospital mortality, as well as MAKE at discharge, although the secondary outcomes trended consistently in favor of intervention (Table 3).

All patients in the intervention group had undergone nephrology consultation before the start of any intervention. Recommendations on current potentially nephrotoxic medications were given for 21 patients (35%). For 6 patients (10%) higher target levels for mean arterial pressure were suggested because of significant pre-existing hypertension. Thirty-two patients (53%) received recommendations for improving acid-base balance, albumin levels, and electrolytes status. Thirteen patients (22%) did not require any nephrology recommendation. The overall-implementation rate of nephrological recommendations was 85% [76% for adjustment of medication (16/21 pts.), 100% for optimization of hemodynamics (6/6 pts.), and 87.5% for achievement of homeostasis (28/32 pts.)]. Reduction of length of ICU stay by 1 day was associated with cost savings of €2031 per patient receiving intervention, taking into account conduction of 2 biomarker tests per patient (Supplemental Digital

TABLE 2. Measures During the Evaluation Period for Intervention Versus Standard Care

	Intervention n = 60	Standard Care n = 61	Effect Estimate* (95%-CI)	*P*
First 12–24 hours after randomization				
Fluid bolus therapy/24 h, mL	1000 (500–2000)	2000 (1000–2500)	500 (500, 1000)	**<0.001**
Albumin dose /24 h, 100 mL	0 (0–1)	1 (0–1)	0 (0, 0)	0.106
Mean MAP/12 h, mm Hg	76.20 (72.18–80.1)	75.40 (70.0–82.30)	−0.55 (−3.2, 2.4)	0.748
Urine output /12 h, mL/kg/h	1.35 (0.94–1.75)	1.05 (0.84–1.36)	−0.25 (−0.46, 0.07)	**0.006**
Urine (TIMP-2) × (IGFBP7) at 12 h, $(ng/mL)^2/1000$	0.40 (0.18–0.95)	0.58 (0.28–1.26)	0.11 (−0.05, 0.28)	0.146
Diuretics dose, mg/48 h	30 (10–50)	30 (10–60)	0 (−10, 10)	0.593
Creatinine values, mg/dL				
Admission to ICU	0.83 (0.70–1.02)	0.85 (0.72–1.08)	0.05 (−0.05, 0.13)	0.336
Day 1	0.86 (0.72–1.05)	0.97 (0.76–1.17)	0.08 (−0.03, 0.19)	0.139
Relative change creatinine day 1 vs baseline	1.07 (0.94–1.17)	1.15 (1.03–1.28)	0.08 (0.02, 0.15)	**0.012**
Day 2	0.82 (0.67–1.13)	0.89 (0.70–1.38)	0.07 (−0.06, 0.2)	0.298
Day 3	0.81 (0.65–1.10)	0.80 (0.64–1.29)	0.03 (−0.09, 0.17)	0.602
Day 4	0.84 (0.63–1.20)	0.89 (0.69–1.46)	0.07 (−0.07, 0.23)	0.293
Day 5	0.76 (0.60–0.92)	0.78 (0.70–1.19)	0.1 (−0.04, 0.24)	0.191
Day 6	0.79 (0.61–1.14)	0.94 (0.69–1.55)	0.12 (−0.06, 0.3)	0.201
Day 7	0.82 (0.65–1.08)	0.83 (0.66–1.17)	0.03 (−0.14, 0.19)	0.812
Peak creatinine	0.92 (0.78–1.28)	0.99 (0.77–1.54)	0.06 (−0.07, 0.19)	0.357
Relative change creatinine peak vs baseline,	1.14 (1.05–1.30)	1.23 (1.11–1.44)	0.1 (0.02, 0.18)	**0.015**
Daily fluid balance on day 1 and day 2, mL				
Fluid intake d1, mL	3714 (3234–4080.5)	3738 (3101.5–4550)	9 (−344, 369)	0.948
Urine output d1, mL	1522.5 (1182.5–1980)	1240 (972.5–1652.5)	−250 (−425, −60)	**0.010**
Daily fluid balance d1, mL	1693.5 (1162.5–2275.8)	1715 (1055–2594)	92 (−313, 469)	0.645
Fluid intake d2, mL	4559 (3748.8–5257.8)	4736 (4123.3–5681.8)	254 (−228, 695)	0.331
Urine output d2, mL	2850 (2407.5–3187.5)	2480 (1975–3105)	−295 (−600, 35)	0.078
Daily fluid balance d2, mL	864 (392–1430)	1342 (730–2199)	405 (61, 764)	0.023*
Cumulative fluid balance d1 + d2, mL	2567 (1617–3706)	3207 (2015.5–4486)	558 (−66, 1196)	0.085

*Hodges-Lehmann estimate (95% CI). All data are presented as median (IQR).

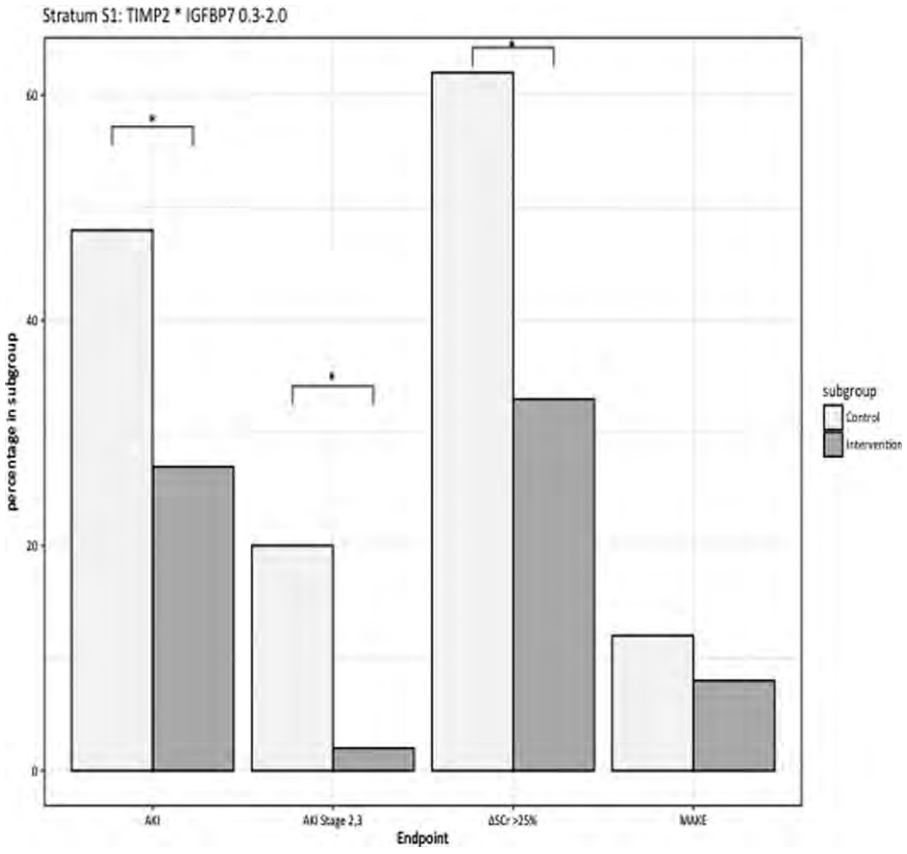

FIGURE 2. Incidence of primary and secondary study endpoints in biomarker stratum TIMP2 × IGFBP7 0.3–2.0 for control (light gray) and intervention (dark gray) group: AKI 24/50 versus 13/48, $P = 0.03$ (Chi-Quadrat test); AKI stage 2,3 10/50 versus 1/48, $P = 0.005$; ΔCr >25% 31/50 versus 16/48, $P = 0.005$; and MAKE 6/50 versus 4/48, P = n.s. Cr indicates creatinine; ΔCr, difference between peak Cr in the first 7 postoperative days and baseline Cr.

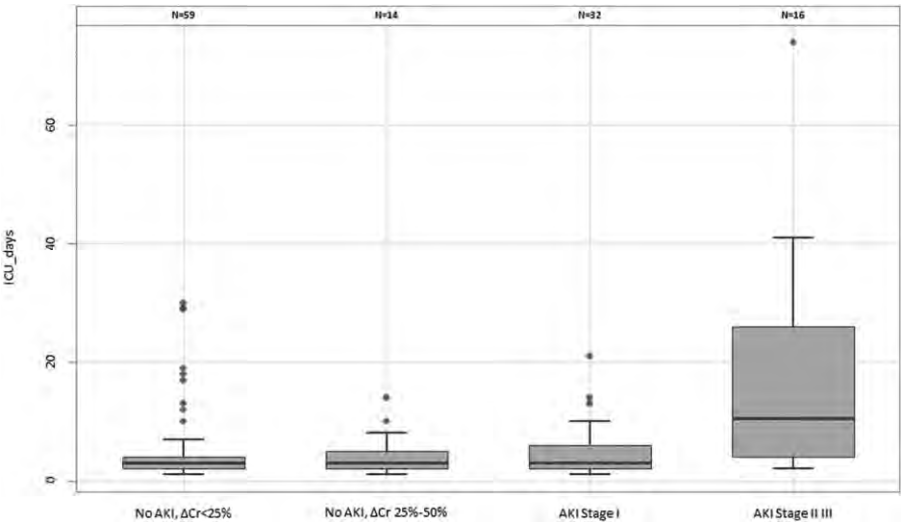

FIGURE 3. Length of ICU stay (medians and percentiles) by severity of acute kidney injury. Length of ICU stay (95% CI) gradually increases the more severe the acute kidney injury (ΔCr <25% vs ΔCr 25%–50% vs. ΔCr 50%–100% vs ΔCr >100%); $P = 0.001$, Kruskal-Wallis test; $P = 0.009$ for No AKI (ΔCR 0–50%) vs AKI (stage I, II, or III) patients (Mann-Whitney *U* test). Cr indicates creatinine; ΔCr, difference between peak Cr in the first 7 postoperative days and baseline Cr.

Content 2, http://links.lww.com/SLA/B318). There was no harm associated with the intervention.

DISCUSSION

In this prospective randomized clinical trial with patients after major noncardiac surgery, early biomarker-triggered implementation of KDIGO care bundle on optimizing volume status in combination with maintenance of adequate perfusion pressure and discontinuation of nephrotoxic agents through nephrology consultation significantly reduced the incidence of moderate and severe AKI. Furthermore postoperative increases in SCr (>25%) and length of stay were reduced. Finally, intervention that can be practiced in every ICU was associated with ICU-costs reduction.

Although a recent meta-analysis reported a pooled AKI incidence of 13.4% in an unselected population of patients after major abdominal surgery,[23] the incidence of all stages AKI in patients with elevated urinary levels (TIMP2 × IGFBP7) in our study was 43%; with 15.6% patients having moderate-severe AKI (equivalent to KDIGO stage 2–3). This effect is consistent with recent findings of the markedly improved detection of high-risk surgical patients for imminent AKI by use of a single urinary (TIMP2 × IGFBP7) test; furthermore, inclusion of such test significantly enhances the performance of clinical risk prediction models.[24]

Once an increased risk of AKI after surgery was detected by means of cell cycle biomarkers in our study, KDIGO care bundle was initiated, always taking into account, that hypervolemia was excluded before and during the intervention. We used the static preload parameter CVP for fluid administration despite the conflicting data on the role of CVP in fluid management. A recent large meta-analysis, however, has reported a reasonable prediction for

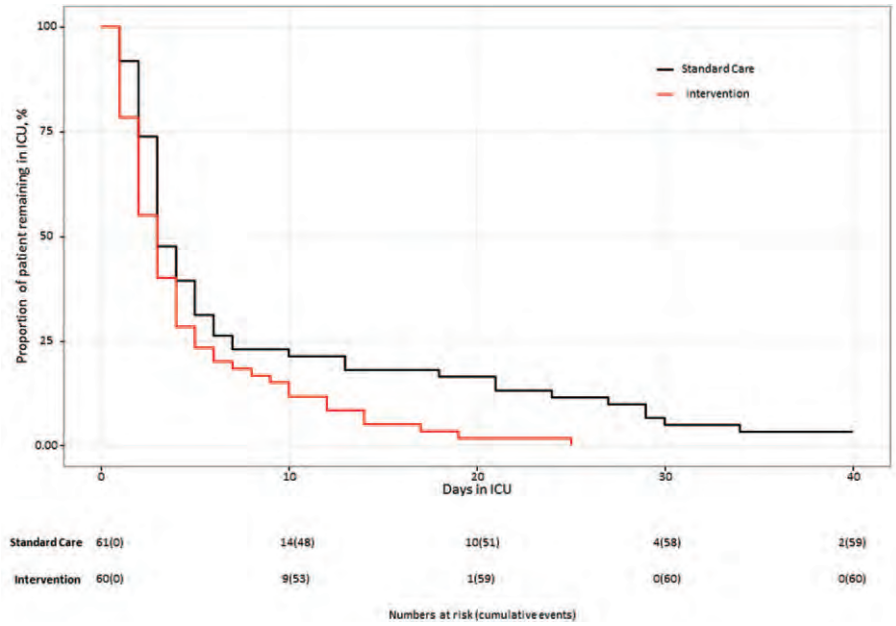

FIGURE 4. Kaplan-Meier plot visualizing patients' days in ICU comparing Standard Care Group and Intervention Group. $P = 0.035$ (Mann-Whitney *U* test). Cr indicates creatinine; ΔCr, difference between peak Cr in the first 7 postoperative days and baseline Cr.

TABLE 3. Clinical Outcomes for Intervention Group Versus Standard Care Group

	Intervention n = 60	Standard Care n = 61	Effect Estimate (95% CI)	*P*
Primary outcome				
Overall AKI (%)	19 (31.7)	29 (47.5)	1.96 (0.93, 4.10)*	0.076
Secondary outcomes				
AKI stage II and III (%)	4 (6.7)	12 (19.7)	3.43 (1.04, 11.32)*	**0.035**
Relevant Cr increase (ΔCr >25%) (%)	24 (40.0)	38 (62.3)	2.48 (1.19, 5.15)*	**0.015**
ICU length of stay, median (IQR) days	3 (2–5)	3 (2–7)	1 (0,2)†	**0.035**
Hospital length of stay, median (IQR) days	16 (12–22)	21 (15–39)	5 (0, 8)†	**0.036**
Requirement of RRT during hospital stay no (%)	2 (3.3)	4 (6.6)	2.04 (0.36, 11.55)*	0.663
In-hospital mortality (%)	4 (6.7)	5 (8.2)	1.25 (0.32, 4.90)*	0.981
MAKE by discharge (%)	5 (8.3)	8 (13.1)	1.66 (0.51, 5.40)*	0.399
Relative change urine (TIMP-2) × (IGFBP7) 12 h vs baseline, $(ng/mL)^2/1000$, median (IQR)	2.66 (1.41–7.04)	1.84 (0.78–3.19)	−0.825 (−1.7, 0.08)†	**0.028**

*Odds ratio (95% CI).
†Hodges-Lehmann estimate (95% CI).

fluid responsiveness with positive predictive values of >60% in range of CVP <6 mm Hg and negative predictive values >60% for CVP >9 mm Hg. These thresholds are very similar to those used in our protocol.[25] Before fluid administration was initiated, fluid responsiveness was tested.[26] In our intervention group, increased maintenance fluid infusion up to 5.0 mL/kg/h for 6 hours was triggered by elevated biomarker values and was given early after admission to the ICU. Interestingly, despite the additional fluid infusion during intervention, the intervention group did not have increased fluid administration. Daily fluid balance for day 1 did not differ between the 2 groups, but fluid balance was lower on day 2. Furthermore, the need for FBT in the first 24 hours was reduced in the intervention group. Although repeated FBT represents the current standard practice of fluid administration, recent studies have indicated only limited hemodynamic effects of such fluid boluses.[27] In a prospective study, an immediate hemodynamic effect on mean arterial pressure and heart rate was seen 10 minutes after FBT. However, these changes were not sustained at 1 and 2 hours after the administration of the fluid bolus. FBT was more commonly associated with adverse effects, such as increased respiratory rate and lower temperature due to the shift in intravascular volume to extravascular space.[28,29] Experimental data on sepsis also showed a greater plasma-expanding effect of slow infusion of albumin during 3 hours versus rapid albumin administration (30 min).[30,31]

We assume that the positive effect of intervention on reducing the incidence and severity of AKI, decrease in postoperative creatinine levels, and length of stay was caused by prediction of imminent AKI at the very early stage followed by ''optimal'' fluid resuscitation with less positive fluid balance and kidney protection. This effect was already present soon after intervention, indicated by significantly improved urine output on day 1, attenuated early (day 1) and total (7 days) increase in creatinine and significant reduction in cellular stress biomarkers (TIMP2 × IGFBP7) over the first 12 hours. Interestingly, effect of intervention on AKI was more pronounced in patients with TIMP2 × IGFBP7 level of 0.3 to 2.0. We hypothesize that the 0.3 to 2.0 range may represent preventable AKI while TIMP2 × IGFBP7 >2.0 is consistent with AKI that is becoming established and can only be managed. However, intervention still may be valuable in these patients since MAKE and length of stay trended downwards with the intervention.

Our study also has some important limitations. The 138 patients included in the calculation were not recruited over the estimated study duration, and this fact can overstate the effect size. The study design as a single-center study of patients after major noncardiac surgery may limit the generalizability of its results. However, a recent study has also shown reduced AKI frequency and severity in cardiac surgery patients after the implementation of KDIGO guidelines. Interestingly, this trial showed a nonsignificant trend toward a higher incidence in adverse kidney events (MAKE, requirement of RRT, and persistent renal dysfunction) in the intervention group.[32] In our study, these outcomes trended consistently in favor of intervention. However, the study was not powered to evaluate these parameters with statistical significance. Clearly, increasing the rate of continuous fluid administration is not suitable for all patients, especially those with high CVP values and negative dynamic test results of fluid responsiveness. Preventive strategies for these patients still need to be evaluated. Finally, this study was not blinded, which could contribute to measurement bias.

In summary, our study provides pilot data that need to be confirmed in an adequately powered multicenter trial. Further studies may also investigate the effect of a biomarker-guided KDIGO care bundle in different surgical subgroups and also address long-term AKI-related outcome parameters.

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Mitterrand proposed a new doctrin which was to avoid discussion on French national "problems" outside homeland, and since this time this doctrin is most of the time respected. Anyway, we agree with pleasure to address several comments raised by Karem Slim.

In his letter, Mr. Slim regrets the absence of details regarding the surgical access for the patients included in our trial. We would like to remind here that the cornerstone of our trial was indeed the lack of evidence regarding the outcome of ERP in laparoscopic patients, and that all included patients were operated on through a laparoscopic approach. On the same way, Mr. Slim is surprised by the use of postoperative carbohydrate loading in our study. We would also like to remind here that such postoperative carbohydrate loading was used in the LAFA trial, one of the few previously published randomized trials assessing the results of ERP in laparoscopic patients.[2,3] Finally, we would like to remind here that the full ERP was initially described including an epidural anesthesia in all patients, but this latter has since been shown to be associated with an increased rate of postoperative complication rate following colorectal cancer surgery and as therefore been abandoned by the majority of authors.

Most importantly, we do not look at the results of our trial as an advocacy against ERP but rather as a way to facilitate its implementation. Indeed, our results clearly show that large part of the benefit expected with ERP is obtained with a limited, and easily implemented, program including laparoscopic approach, and early postoperative feeding and mobilization. We are fully convinced that the concept of ERP is a major advance of modern surgery, leading to decreased postoperative morbidity and length of hospital stay. However, we also know, based on our own experience and on some reports from other teams,[4,5] that the implementation of a full ERP can be difficult and might discourage some surgeons. We therefore think that our trial might help the widespread of ERP among the majority of surgeons.

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Biomarker-guided Intervention to Prevent AKI or KDIGO Care Bundle to Prevent AKI in High-risk Patients Undergoing Major Surgery?

To the Editor:

We read the article on use of biomarkers for guiding intervention to prevent AKI by Göcze et al[1] with interest. We congratulate the authors for attempting to go a step further after validating the use of biomarkers in their previous study. However, we have a few questions. The first concerns the premise and the methods of this study. The study has been planned as a biomarker-guided intervention to prevent AKI after major surgery. Hence, one would have expected them to compare a group in which biomarkers guided intervention before onset of clinical changes, with another group in which clinical parameters such as serum creatinine and urine output guided intervention. However they have compared a group in which biomarkers guided intervention with no intervention at all. This essentially serves only to prove the utility of the intervention (KDIGO care bundles) in a subgroup of patients with a very high risk of AKI. But for this purpose, the authors could have taken all at-risk patients irrespective of the biomarker status and made the comparison. The need for using biomarkers to select patients is unclear and the title misleading.

Also, it appears unethical to administer fluids to patients who are elderly or already suffering from critical illness (the at-risk group) without measuring CVP or intravascular volume through other means such as IVC diameter.[2] At least some of the KDIGO care bundle guidelines are a part of routine ICU care.[3,4] Hence, what is also important is the extent to which the components of KDIGO were provided to the standard care group as a part of standard care. These interventions may be titrated to the serum creatinine levels or the urine output in the standard care group. If there was a 20% incidence of moderate to severe AKI, were nephrotoxic drugs withheld or dose modified in patients with mild AKI to prevent further progression in the control group? Furthermore, the authors state that patients in the standard care group were assessed by a pharmacist on a weekly basis for drugs. This is distinctly unusual for an ICU patient to have their drug charts assessed on a weekly basis. The drugs have to be reviewed at least on a daily basis. In a study which compares an intervention with standard of care, what constitutes the standard of care is very important before we attempt to prove the superiority or noninferiority of the intervention.

Also, the conclusions seem erroneous. The primary end point of AKI in 7 days was similar in the 2 groups. The authors conclude that in the subgroup of patients with TIMP-2xIGFBP7 values of 0.3 to 2.0, the incidence of AKI was significantly reduced [13/48 (27.1%) in intervention group compared to 24/50 (48%) in control patients ($P = 0.03$)]. However, one must be cautious while interpreting these results. The study never reached its required sample size. The study is underpowered even to provide definite evidence regarding its primary aim, let alone a secondary aim (subgroup stratification has been mentioned in the methods as a secondary aim and was not taken into account during sample size calculations). This is at best a hypothesis that needs to be subsequently tested in an adequately powered study.

Furthermore, the authors state that they have obtained deferred consent in some patients. Deferred consent is for critically ill patients, or those in delirium or coma. However, because the trial included patients undergoing elective surgery, why was deferred consent required in the first place? In addition, the sample size calculations seem unclear. If the interim analysis at 52 patients did in fact show that the sample size of 138 would be inadequate, what was the required size? If the size was clinically not feasible, why did the authors continue till 121 were randomized? This was only 17 patients short of the initially calculated number. It is difficult to understand why they continued to recruit and stopped at a number that's neither here nor there.

In the end, we feel that though the use of biomarkers and KDIGO care bundle both may have great potential to improve outcomes in AKI individually, a clearer research question, better formulation of study groups, and a justifiable level of care in the control arm would have helped us glean much more from the study.

The authors report no conflicts of interests.

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Biomarker-guided Intervention to Prevent AKI or KDIGO Care Bundle to Prevent AKI in High-risk Patients Undergoing Major Surgery?

We thank colleagues Singh and Kilambi[1] for their interest in our article[2] and their comments. One of their concerns was that the title of our study may be misleading. Singh and Kilambi questioned the need of biomarkers for selecting appropriate patients for intervention and suggested to administer the intervention to patients with clinical signs of AKI (serum creatinine and urine output) as control group to biomarker-guided strategy. However, we did not hypothesize that biomarker-guided intervention is better than an intervention guided on creatinine or urine output. The hypothesis of our study was that the biomarker-triggered Kidney Disease Improving Global Outcome (KDIGO) care bundle consisting of early optimization of fluid status, maintenance of perfusion pressure, and discontinuation of nephrotoxic agents reduces postoperative AKI. The main focus of our study was on the early detection of high-risk patients that is made possible by using a treatment strategy based on biomarkers instead of relying on the late clinical signs of AKI, such as a rise in serum creatinine or in the extent of diuresis. This novel approach to preventing AKI was compared to standard postoperative care to obtain first data.

Until recently, the major limitation to adopting KDIGO guidelines with regard to the role of biomarkers in patient selection was the lack of suitable methods for determining patients with a high risk of AKI. After the discovery and validation of cell cycle biomarkers, evidence in the literature has been steadily increasing that the inclusion of these markers in clinical or epidemiological prediction models significantly improves risk stratification. In several studies, the negative predictive value for [TIMP-2]•[IGFBP7] $\leq$0.3 was 97%.[3] Therefore, providing a KDIGO bundle for patients with a negative biomarker would significantly increase treatment costs with presumably little additional benefit.

On other contrary, to initiate the same protocol including fluid resuscitation in patients with already established AKI, as suggested by Singh and Kilambi, may have detrimental effects on renal recovery as has already been shown in earlier studies: patients with altered kidney function are at increased risk of fluid overload, and fluids may be harmful if oliguria is due to AKI.[4] These findings show the importance of a personalized treatment approach and the necessity to identify which patients may benefit from the intervention, rather than blindly testing the intervention in all patients.[5] Integrating a cellular injury biomarker in early patient assessment clearly represents a shift to more personalized medicine.

The control group in our study received standard intensive care that included all aspects of modern ICU therapy. Additional fluid infusion was administered if deemed necessary by the responsible physician. The concurrent medication was daily evaluated during the intensivist-led ward rounds and additionally once a week or on demand by the pharmacist responsible for the ICU. Withholding nephrotoxic medication and adapting dosages in patients with AKI is daily ICU routine and was conducted by the ICU medical team on a daily basis in our study. Although daily pharmacist attendance at intensivist-led multidisciplinary ward rounds is increasingly recommended, it is not yet standard procedure in the majority of German ICUs. Clearly, this fact has to be considered in the interpretation of our study results.

Deferred consent was used because 93.3% of patients in the intervention group and 95.1% of patients in the control group required inotropic support or mechanical ventilation after surgery; thus, these patients were critically ill at the time of enrollment. In addition, surgery duration of more than 4 hours was one of the requested inclusion criteria. It is clearly difficult to predict the duration of surgery before the procedure, even in elective surgical patients. On the contrary, despite the prolonged operation time, a significant number of patients still do not require postoperative ICU admission. The deferred consent option definitely improved the study logistics.

Although the interim analysis suggested that no difference in primary outcome will be achieved in the calculated sample size, we continued the study because of the structured study logistics and to avoid missing significant findings or clear trends in the secondary outcome parameters.

We acknowledge that our study is underpowered for the primary outcome. However, the findings in the subgroup analysis yielded the important information that even biomarker-positive patients are not identical with regard to the likelihood of benefitting from the intervention. Clearly, more research is needed, and – as stated in our summary – the present study provides pilot data that need to be confirmed in an adequately powered multicenter trial. Finally, we agree with Singh et al that biomarkers and the KDIGO bundle have both great potential to improve outcome in AKI, however, not individually but together.

The authors declare no conflicts of interest.

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The OSLO-COMET Randomized Controlled Trial of Laparoscopic Versus Open Resection for Colorectal Liver Metastases

To the Editor:

OSLO-COMET (OSLO laparoscopic versus open liver resection for colorectal metastases) is a landmark study in liver surgery.[1] The results generate important questions as to how the findings can be rapidly but safely incorporated into current liver surgical practice. The key findings of the study are that for patients requiring parenchyma-preserving liver resection for colorectal cancer liver metastatic disease, the laparoscopic approach was associated with fewer postoperative complications, was cost-effective, and was oncologically equivalent in terms of resection margin clearance. The authors state that the "results support the continued implementation of laparoscopic liver resection."[1] Their conclusions are supported by the findings of a systematic review of the worldwide published literature of laparoscopic liver resection which reported outcome in 9527 procedures.[2] This review reported 37 deaths (mortality rate 0.4%), and in comparison with open surgery, there were fewer complications, less blood loss, and a shorter hospital stay. The Louisville[3] and Morioka[4] international consensus conferences have shown that "minor" liver resections can be undertaken routinely as part of standard practice.

Bringing this cutting-edge evidence to routine care, a practical understanding of liver anatomy in relation to laparoscopic surgery is critical. Specifically, facility of laparoscopic access, and proximity to inflow and outflow structures (all principles of open liver surgery) are significant.

In this regard, laparoscopic left lateral sectionectomy and parenchyma-preserving laparoscopic resections of segments IVb, V, and VI (with or without prior laparoscopic or open liver resection) would be noncontroversial as standard of care. Extensions of the laparoscopic approach by the use of the left lateral decubitus position to facilitate mobilization of the right hemi-liver from the inferior vena cava are also increasingly used.

If OSLO-COMET's results are viewed in this context, it can be seen that the study focused on patients requiring relatively minor resections with median (interquartile range) pathologic weight of resected specimen being 83 (38–185) g and a median liver surgery complexity score of 1.99.

These comments are not criticisms of this important study, but emphasize the nature and scope of laparoscopic liver resections subjected to randomized evaluation in OSLO-COMET.

Further, when seeking to apply the evidence of the OSLO-COMET study, it is important to appreciate that this study was undertaken in a center with very considerable expertise in laparoscopic liver surgery, with the authors having undertaken 400 laparoscopic liver resections before the trial.

In conclusion, OSLO-COMET advances knowledge in liver surgery. When incorporating the results into current practice, 3 pragmatic points must be borne in mind. First, the scope of the findings translates only to patients requiring parenchyma-sparing hepatectomy for colorectal liver metastases. Second, it is accepted that patients should have the benefit of cutting-edge care; however, in the 21st century, it is not acceptable for patients to be the subject of an individual surgeon (or surgical team's) learning curve without their prior knowledge, and thus laparoscopic liver surgery should only be undertaken in recognized liver surgery units by trained liver surgeons. Third, it is important to appreciate that the findings do not apply to laparoscopic major hepatectomy. In current practice, this type of major resection should only be undertaken in the context of a randomized trial such as an international multicentre randomised controlled trial of open versus laparoscopic hemihepatectomy (The ORANGE II PLUS Trial).[5]

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Response: The OSLO-COMET Randomized Controlled Trial of Laparoscopic Versus Open Liver Resection for Colorectal Metastases

Reply:

We thank Chan et al for their valuable comments to our trial. We completely agree that the results of OSLO-COMET only are transferable to parenchyma-sparing liver resections of colorectal metastases.[1] We also agree that many of the resections in the trial are minor. However, a total of 136 of the 273 patients who underwent surgery had tumors located in the so-called "difficult segments" (segments 1, 4a, 7. and 8). The separation between "major" and "minor" resections might also need revision. The expression "technically major resections" has been introduced to better separate between "true" minor resections and those that are minor in volume but major in location.[2,3] This might be because the tumor is located close to major vessels, or in a part that is difficult to reach, such as the posterior parts of the right hemiliver. Furthermore, 36 patients in OSLO-COMET had previously undergone liver surgery, which may