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Diagnostic value of plasma NGAL and intraoperative diuresis for AKI after major gynecological surgery in patients treated within an intraoperative goal-directed hemodynamic algorithm

A substudy of a randomized controlled trial

Oliver Hunsicker, MD[a], Aarne Feldheiser, MD, PhD[a], Andreas Weimann, MD, PhD[b], David Liehre, MD[a], Jalid Sehouli, MD, PhD[c], Klaus-Dieter Wernecke, PhD[d], Claudia Spies, MD, PhD[a,*]

Abstract

Data on early markers for acute kidney injury (AKI) after noncardiovascular surgery are still limited. This study aimed to determine the diagnostic value of plasma neutrophil-gelatinase-associated lipocalin (pNGAL) and intraoperative diuresis for AKI in patients undergoing major abdominal surgery treated within a goal-directed hemodynamic algorithm.

This study is a post-hoc analysis of a randomized controlled pilot trial comparing intravenous solutions within a hemodynamic goal-directed algorithm based on the esophageal Doppler in patients undergoing epithelial ovarian cancer surgery. The diagnostic value of plasma NGAL obtained at ICU admission and intraoperative diuresis was determined with respect to patients already meeting AKI criteria 6 hours after surgery (AKI_{6h}) and to all patients meeting AKI criteria at least once during the postoperative course (AKI_{total}). AKI was diagnosed by the definition of the Kidney Disease Improving Global Outcome (KDIGO) group creatinine criteria and was screened up to postoperative day 3. Receiver operating characteristic curves including a gray zone approach were performed.

A total of 48 patients were analyzed. None of the patients had increased creatinine levels before surgery and 14 patients (29.2%) developed AKI after surgery. Plasma NGAL was predictive for AKI_{6h} (AUC_{AKI6h} 0.832 (95% confidence interval [CI], 0.629–0.976), $P=.001$) and AKI_{total} ($AUC_{AKItotal}$ 0.710 (CI 0.511–0.878), $P=.023$). The gray zones of pNGAL calculated for AKI_{6h} and AKI_{total} were 210 to 245 and 207 to 274 ng mL^{-1}, respectively. The lower cutoffs of the gray zone at 207 and 210 ng mL^{-1} had a negative predictive value (NPV) (i.e., no AKI during the postoperative course) of 96.8% (CI 90–100) and 87.1% (CI 78–97), respectively. Intraoperative diuresis was also predictive for AKI_{6h} (AUC_{AKI6h} 0.742 (CI 0.581–0.871), $P=.019$) with a gray zone of 0.5 to 2.0 mL kg^{-1} h^{-1}. At the lower cutoff of the gray zone at 0.5 mL kg^{-1} h^{-1}, corresponding to the oliguric threshold, the NPV was 84.2% (78–92).

This study indicates that pNGAL can be used as an early marker to rule out AKI occurring within 3 days after major abdominal surgery. Intraoperative diuresis can be used to rule out AKI occurring up to 6 hours after surgery.

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OH and AF contributed equally to this work.

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[a] Department of Anesthesiology and Operative Intensive Care Medicine (CCM, CVK), Charité - Universitätsmedizin Berlin, [b] Labor Berlin—Charité Vivantes Services GmbH, [c] Department of Gynaecology, European Competence Center for Ovarian Cancer, Charité— University Medicine Berlin, [d] Charité—University Medicine Berlin and SOSTANA GmbH Berlin, Berlin, Germany.

[*] Correspondence: Claudia Spies, Department of Anesthesiology and Operative Intensive Care Medicine (CCM, CVK), Charité - Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany (e-mail: claudia.spies@charite.de).

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Abbreviations: AKI = acute kidney injury, AUC = area under the curve, CI = confidence interval, FIGO = Fédération Internationale de Gynécologie et d'Obstétrique, pNGAL = plasma neutrophil-gelatinase-associated lipocalin, POD = postoperative day, ROC = receiver operating characteristic curves.

Keywords: acute kidney injury, creatinine, diuresis, goal-directed therapy, neutrophil gelatinase-associated lipocalin, sensitivity and specificity

1. Introduction

Perioperative acute kidney injury (AKI) is a serious and often under-appreciated complication associated with an increased morbidity, mortality, and healthcare costs.[1,2] AKI after major surgery has been shown to be an independent predictor for in-hospital mortality and even affects long-term survival in patients with preoperative normal renal function.[3,4]

In recent years, the understanding of AKI has changed as it has been shown that even small and temporary increased creatinine levels are related to short and long-term mortality.[5–9] While the urine output criteria for AKI diagnosis remained unchanged, the Kidney Disease Improving Global Outcome (KDIGO) group published revised diagnostic creatinine criteria, defining AKI as an abrupt decrease of kidney function within 48 hours and implied smaller changes of serum creatinine levels from baseline ($>0.3\,\text{mg dL}^{-1}$) as diagnostic criterion.[10] However, due to the intrinsic properties of serum creatinine limiting its use for early diagnosis,[11] there is still a substantial need for early biomarkers.[12]

In this regard, neutrophil gelatinase-associated lipocalin (NGAL) has emerged as a promising early biomarker of AKI. In animal models NGAL has been shown to be upregulated in the kidney very early after AKI.[13] Plasma NGAL primarily originates from the damaged kidneys via tubular back-leak and has been shown as an early marker to predict AKI in different hospital settings.[14–16] In the perioperative setting, pNGAL has been investigated after cardiovascular surgery,[17–20] but to date, data on predictive ability of pNGAL in patients after major noncardiovascular and nonvascular surgery are still limited.[21]

Furthermore, intraoperative diuresis as a functional kidney marker may help to identify patients at risk for AKI during the postoperative course.[22] A decreased diuresis as a criterion for AKI diagnosis has been implemented in the current diagnostic classifications for many years as it was supposed that a decrease in diuresis below oliguric threshold was directly related to a decreased glomerular filtration rate.[23,24] However, the association of intraoperative diuresis with perioperative AKI and its potential diagnostic value are still not evaluated.

We hypothesized that pNGAL and intraoperative diuresis might be used as early markers for the diagnosis of AKI occurring after noncardiovascular surgery.

This study aimed to investigate the diagnostic value of pNGAL obtained at admission to the intensive care unit and intraoperative diuresis with regard to AKI after noncardiovascular surgery.

2. Methods

This study is a post-hoc secondary analysis of a previously published randomized controlled trial comparing a balanced crystalloid with a balanced colloid within a goal-directed hemodynamic algorithm (BalaCriCo, ISRCTN 53154834).[25] Eligible patients were adults undergoing laparotomy for cytoreductive surgery due to primary ovarian cancer. The entire data were obtained from the per-protocol group of the BalaCriCo trial. Ethics approval was given by Ethics Committee of Charité—University Medicine Berlin (No. EK 12/581/08). The trial was conducted at Charité—University Medicine Berlin, Campus Virchow Klinikum, Berlin, Germany and written informed consent was obtained from all patients.

2.1. Intraoperative hemodynamic management

The hemodynamic management was performed according to an outcome-based goal-directed hemodynamic algorithm guided by the esophageal Doppler monitor (EDM, CardioQ-ODM, Deltex Medical, Chichester, UK) as published previously.[26]

2.2. Outcomes

AKI was defined as Kidney Disease Improving Global Outcome (KDIGO) stage 1 or higher using creatinine criteria and was screened up to postoperative day 3 (POD3).

The diagnostic value of pNGAL (obtained after surgery at admission to the intensive care unit) and intraoperative diuresis (cumulative diuresis at the end of surgery adjusted for duration of surgery and patients weight [$\text{mL kg}^{-1}\,\text{h}^{-1}$]) was determined with respect to patients, who were already meeting the KDIGO criteria 6 hours after surgery (AKI_{6h}); and patients who were meeting the KDIGO criteria at least once at any time point during the postoperative course up to POD3 (AKI_{total}).

2.3. Sampling and biomarker measurement

Regarding the measurements of plasma creatinine, blood samples were obtained at the day before surgery, at 1 and 6 hours after surgery and on postoperative day 1 (POD1) and 3 (POD3) (Fig. 1). Creatinine from heparin-plasma samples was measured using the analyzer COBAS 6000 (Roche Diagnostics, Mannheim, Germany). Plasma NGAL was measured at admission to the intensive care unit (sampling corresponded to 1 hour after the end of surgery (skin closing)). Plasma NGAL samples were centrifuged at 2000 g for 5 minutes and the supernatant was pipetted and stored at −80°C until measurement. The concentration of heparin-plasma NGAL was measured with a particle-enhanced turbidimetric immunoassay, NGAL-Test (BioPorto Diagnostics A/S) also on COBAS 6000 analyzer.

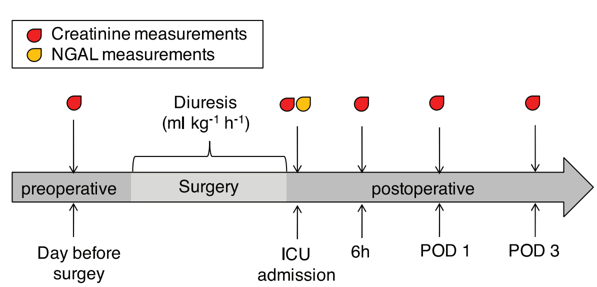

Figure 1. Blood sampling of creatinine and NGAL and assessment of diuresis.

2.4. Statistical analysis

Because of limited sample sizes and deviations from normal distribution of the observations, data were expressed as median (25%, 75% quartiles) or frequencies (%), respectively. Differences with respect to continuous data were tested using the exact Mann–Whitney *U* test for independent groups, while frequencies were tested by the Fisher exact test. Differences in continuous data with respect to time were analyzed using nonparametric analysis for longitudinal data in a 2-factorial design (1st factor: groups, 2nd factor: time).[27]

To assess the diagnostic value of pNGAL and intraoperative diuresis with respect to AKI_{6h} and AKI_{total} receiver operating characteristic (ROC) curves including a gray zone approach were calculated. This approach avoids a single cutoff that dichotomizes the population. In contrast, the gray zone approach provides 2 cutoffs: the lower cutoff of the gray zone will rule out AKI with near certainty and the upper cutoff will rule in AKI with near certainty.[28] Consequently, this approach allows clinical decision making with respect to AKI. First, the area under the curve (AUC_{ROC}) and 95% CIs were computed by averaging 1000 populations bootstrapped from the study population. Second, the best cutoff was determined maximizing the Youden index.[29] The best cutoff determination was conducted for a 1000 populations bootstrapped from the study population. The mean value and its 95% CI were then estimated. Finally, the gray zone was defined as 95% CI of the best cutoff.[30] For visualization, the gray zone was included into a boxplot presentation comparing patients without AKI and with AKI with respect to pNGAL and intraoperative diuresis.

A 2-tailed *P* value <.05 was considered statistically significant. All numerical calculations were performed with the R project for Statistical Computing, Version 3.0.1 (R-packages used: nparLD, foreign, gplots, pROC, ROCR).

3. Results

A total of 48 patients were analyzed according to the per-protocol group of the main study (Supplemental Digital Content—Figure S1, http://links.lww.com/MD/B782).

None of the patients had known chronic kidney disease or increased creatinine levels before surgery. According to KDIGO creatinine criteria, a total of 14 patients (29.2%) developed AKI after surgery. Ten patients (20.8%) had early AKI, diagnosed within 6 hours after admission to the intensive care unit, while all patients who developed AKI were diagnosed up to the first postoperative day (POD1). Ten patients had KDIGO stage 1 (20.8%), 1 patient stage 2 (2.1%), and 3 patients stage 3 (6.3%), respectively. On POD3, only 2 patients (4.2%) had still AKI, while all other patients had normalized creatinine values, no longer meeting KDIGO criteria. One patient in the AKI group (7.1%) needed renal replacement therapy.

In the publication of the main study a nonparametric longitudinal data analysis of the perioperative time courses of the plasmatic values of creatinine revealed no differences between the crystalloid and the colloid solution.[25] However, applying analyses with respect to KDIGO criteria revealed a higher frequency of patients in the AKI group who had been randomized to receive balanced colloid.

Perioperative characteristics of the study patients are shown in Table 1. Patients developing AKI had more severe cancer stage, longer duration of surgery, longer periods of preoperative fasting, and higher perioperative inflammatory markers but did not differ in intraoperative and postoperative hemodynamic variables (Table 1, Supplemental Digital Content—Figures S2–4, http://links.lww.com/MD/B782).

3.1. Diagnostic value of plasma NGAL

Plasma NGAL was higher in patients meeting the KDIGO criteria 6 hours after surgery and in patients meeting the KDIGO criteria at least once at any time point during the postoperative course (266 [242; 302] vs 174 [149; 200] ng mL^{-1}, $P=.001$ and 244 [184; 291] vs 175 [150; 200] ng mL^{-1}, $P=.023$) (Fig. 2). Plasma NGAL was predictive for AKI_{6h} (AUC_{AKI6h} 0.832 (95% confidence interval [CI], 0.629–0.976), $P=.001$) and AKI_{total} ($AUC_{AKItotal}$ 0.710 (CI 0.511–0.878), $P=.023$). The gray zones of pNGAL calculated for AKI_{6h} and AKI_{total} were 210 to 245 and 207 to 274 ng mL^{-1}, respectively. The lower cutoffs of the gray zone at 207 and 210 ng mL^{-1} had negative predictive values (NPV) of 96.8% (CI 90–100) and 87.1% (CI 78–97), and the upper cutoffs of the gray zone at 245 and 274 ng mL^{-1} had positive predictive values of 63.6% (CI 42–89) and 71.4% (40–100), respectively (Table 2).

3.2. Diagnostic value of intraoperative diuresis

Intraoperative diuresis was lower in patients meeting the KDIGO criteria 6 hours after surgery but did not differ between patients not meeting and meeting the KDIGO criteria at least once at any time point during the postoperative course (0.64 [0.41; 1.48] vs 1.85 [0.73; 2.68] mL, $P=.019$ and .83 [0.52; 1.68] vs 1.85 [0.67; 2.68] mL, $P=.083$) (Fig. 3). Intraoperative diuresis, adjusted for duration of surgery and patients' weight, was predictive for AKI_{6h} (AUC_{AKI6h} 0.742 (CI 0.581–0.871), $P=.019$) with a gray zone of 0.5 to 2.0 mL kg^{-1} h^{-1}. The lower cutoff of the gray zone at 0.5 mL kg^{-1} h^{-1}, coextensive with the known oliguric threshold, had a PPV of 40.0% (CI 14–71), and the upper cutoff of the gray zone at 2.0 mL kg^{-1} h^{-1} had a NPV of 100% (CI 100–100), respectively (Table 2). The lower cutoff at 0.5 mL kg^{-1} h^{-1} indicated a NPV of 84.2% (78–92). Intraoperative diuresis was not predictive for AKI_{total} ($AUC_{AKItotal}$ 0.661 (0.495–0.808), $P=.083$).

4. Discussion

The principal findings of the study are that pNGAL was predictive for AKI occurring 6 hours after surgery and even for AKI occurring within the first 3 days after surgery; that the lower cutoffs of the gray zone of pNGAL had high negative predictive values allowing to early rule out AKI after surgery; that intraoperative diuresis was also predictive for AKI occurring 6 hours after surgery, but not for AKI occurring within the first 3 days after surgery; and that the lower cutoff of the gray zone of intraoperative diuresis, coextensive with the known oliguric threshold, had a low positive predictive value, but a good negative predictive value also allowing to rule out AKI, but only with respect to AKI occurring 6 hours after surgery.

Whereas the primary nonparametric longitudinal analysis of the time course of renal markers in the main study[25] showed no statistical differences for plasmatic creatinine and pNGAL, intra- and postoperative diuresis, the classification of the patients according to the KDIGO criteria in this substudy of the BalaCriCo trial revealed a higher incidence and higher levels of AKI in the group of patients randomized to balanced hydroxyethyl starch. Even small increases of creatinine are related to worse outcome,[5–8] accordingly the analysis of the

Table 1

Perioperative data of the study patients.

	Non-AKI (n=34)	AKI (n=14)	*P* value
Age, y	53 (47; 59)	60 (48; 67)	.137
Body mass index, kg/m^2	24.9 (22.8; 28.4)	26.0 (24.3; 30.4)	.328
Randomized to balanced crystalloid, n, %	21 (87.5)	3 (12.5)	.024
Randomized to balanced colloid, n, %	13 (54.2)	11 (45.8)	
American Society of Anesthesiology (ASA)			
ASA Physical Status I, n, %	2 (5.9)	2 (14.3)	
ASA Physical Status II, n, %	16 (47.1)	8 (57.1)	.211
ASA Physical Status III, n, %	16 (47.1)	4 (28.6)	
Pre-existing Arterial Hypertension, n, %	10 (29.4)	3 (21.4)	.728
Pre-existing Diabetes mellitus, n, %	1 (2.9)	2 (14.3)	.200
FIGO classification			
Stadium 1, n, %	5 (17.2)	0 (0)	
Stadium 2, n (%)	6 (20.6)	0 (0)	
Stadium 3a, n, %	4 (13.8)	1 (9.1)	.020
Stadium 3b, n, %	5 (17.2)	3 (27.3)	
Stadium 3c, n, %	9 (31.0)	7 (63.6)	
Chronic medications			
Beta blocker, n, %	7 (20.6)	3 (21.4)	1.000
ACE inhibitors, n, %	4 (11.8)	3 (21.4)	.656
AT1 receptor antagonists, n, %	2 (5.9)	1 (7.1)	1.000
Statins, n, %	5 (14.7)	1 (7.1)	.656
Diuretics, n, %	5 (14.7)	1 (7.1)	.656
Other medications, n, %	6 (17.6)	3 (21.4)	1.000
POSSUM score[37]			
Possum physiologic score	14.0 (13.0; 17.0)	14.0 (13.0; 16.0)	.941
Possum operative score	31.0 (28.7; 33.3)	36.0 (30.0; 37.0)	.046
Possum score	46.0 (42.7; 50.2)	49.5 (46.7; 53.0)	.083
Risk prediction morbidity, %	91.5 (85.8; 96.2)	95.7 (91.7; 97.6)	.068
Risk prediction mortality, %	15.1 (9.4; 25.2)	22.9 (16.9; 33.9)	.092
Preoperative Creatinine, mg/dL	0.62 (0.57; 0.72)	0.58 (0.49; 0.64)	.097
Preoperative Creatinine Clearance (CKD-EPI), mL min^{-1} 1.73 m^{-2}	102.9 (96.2; 109.1)	103.3 (96.2; 105.9)	.991
Preoperative fasting of fluids, h	10 (7; 13)	14 (11; 20)	.038
Preoperative fasting of solids, h	21 (18; 25)	22 (18; 25)	.646
Duration of surgery, hh:min	3:48 (3:11; 4:52)	5:17 (4:24; 6:16)	.008
Baseline infusion, mL kg^{-1} h^{-1}	3.38 (2.29; 7.54)	3.20 (2.54; 5.13)	.765
Crystalloid infusion within GDT, mL/kg	48.7 (0; 50)	0 (0; 8.6)	.006
Colloid infusion within GDT, mL/kg	0 (0; 29.3)	46.3 (19.6; 50)	.007
Intraoperative diuresis, mL kg^{-1} h^{-1}	1.85 (0.67; 2.68)	0.83 (0.52; 1.68)	.083
Hospital length of stay, dd/hh	12/23 (10/23; 17/00)	15/23 (13/11; 22/22)	.068
Length of stay in ICU, dd/hh	00/18 (00/05; 01/14)	01/23 (00/17; 03/06)	.041
Total number of complications according to Clavien classification (number)	2.0 (1.0; 3.0)	3.5 (2.0; 6.0)	.014

Data are shown as median (25%; 75%) quartiles or as n (%) patients. *P* values calculated using the exact Wilcoxon–Mann–Whitney test and the Fisher exact test, or the exact Mantel–Haenszel test as appropriate. POSSUM=Physiologic and Operative Severity Score for the enumeration of Mortality and Morbidity.

study population following the KDIGO criteria is more appropriate than the nonparametric statistical analysis based on medians and quartiles in the intensive care environment.[31,32]

In recent years, perioperative AKI has been shown to be multifactorial determined and to date several patient and surgery-related factors risk factors have been identified.[2] It is supposed that most patients with AKI had episodes of hemodynamic instability during surgery followed by an ischemia-reperfusion injury.[33,34] In this regard, an intraoperative hemodynamic optimization has been stated as to date the most important preventive measure.[1,35] Interestingly, in our study population, which was treated within a goal-directed hemodynamic algorithm, we did not observe any differences in perioperative hemodynamic courses between AKI and non-AKI group. The longer period of preoperative fasting of clear fluids in the AKI group indicates to date underappreciated determinant for AKI.

There was still a lack regarding the diagnostic value of pNGAL after major noncardiovascular surgery. We investigated the diagnostic value of pNGAL with respect to AKI occurring in an early period after surgery (KDIGO criteria had to be applied 6 hours after surgery) and with respect to AKI occurring during a longer period (KDIGO criteria had to be applied within 3 days after surgery). Our results show that plasma NGAL had a good predictive value for patients experiencing early AKI and a fair predictive value for all patients developing AKI within the first 3 days after surgery. The minor predictive value of pNGAL for all the patients meeting the KDIGO criteria up to postoperative day 3 was referred to a reduced sensitivity whereas specificity was still preserved. A similar ROC curve configuration was found in ICU patients in regard to predict AKI within 48 hours and a further decrease of sensitivity was shown in the prediction of AKI within 5 days after obtaining plasma NGAL, while specificity was still acceptable.[36] The AUCs of pNGAL observed in our analysis are in good agreement with overall results from a systematic review in 7000 cardiac surgery patients.[15] From a clinical perspective we performed a gray zone approach that avoids a "black-or-

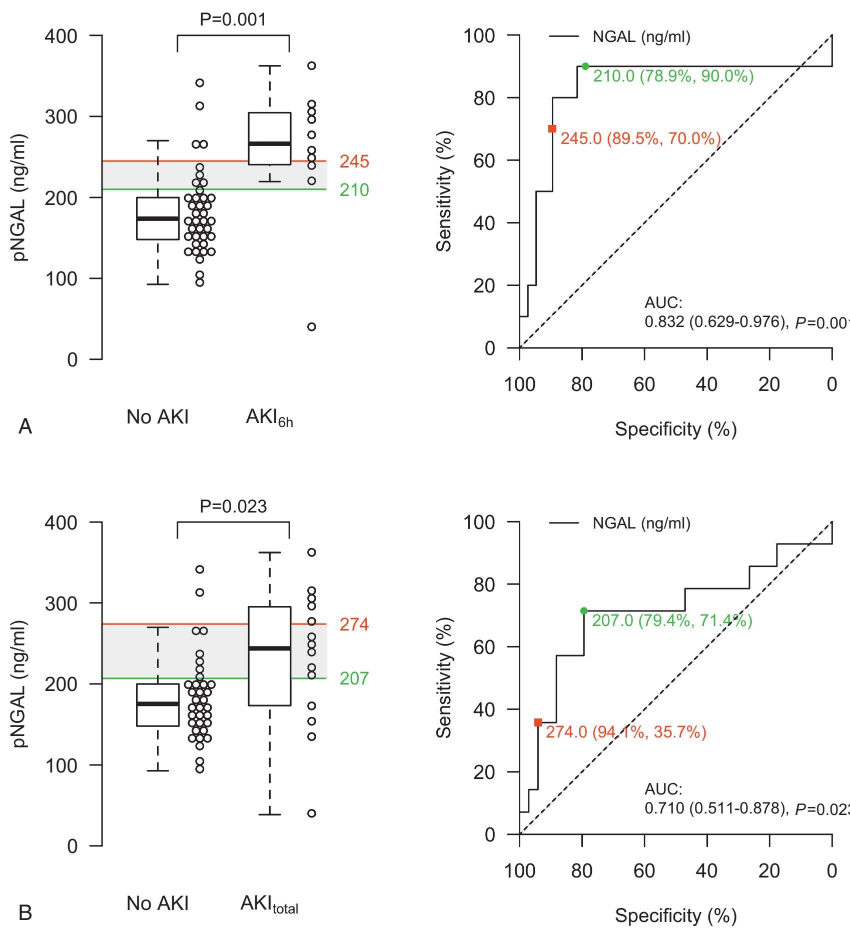

Figure 2. Comparison of pNGAL between patients without AKI and patients meeting the KDIGO criteria 6h after surgery (A); and patients meeting the KDIGO criteria at least once at any time point during the postoperative course up to POD3 (B). The boxplot presentation includes a gray zone approach obtained by the 95% confidence interval of the best cutoff calculated from receiver operating characteristic (ROC) curve. The corresponding ROC curve is shown with sensitivities and specificities of the lower and upper cutoff of the gray zone. AUC = area under the receiver operating characteristic curve.

white" decision of the ROC curve approach and allows better clinical decision making when evaluating a biomarker.[28,30] Furthermore, we calculated positive and negative predictive values of the cutoffs of the gray zone as sensitivities and specificities are of no practical use in clinical routine when it comes to helping the clinician estimate the probability of disease in individual patients.[37] Our results indicated that the lower cutoffs of the gray zone of 210 and 207 ng mL^{-1} were similar for early AKI and AKI occurring within the first 3 days. Both of these cutoffs had high negative predictive values indicating that approximately 9 of 10 patients will not develop AKI if pNGAL measured at ICU admission is below the lower cutoff. In contrast, the upper cutoffs gray zone had moderate positive predictive values allowing us to identify only approximately 7 of 10 patients who will develop AKI if pNGAL measured at ICU admission is above the upper cutoff. Thus, our results suggest that pNGAL can be used as an early marker to rule out AKI, but not to identify patients who will develop AKI within the first 3 days after major abdominal surgery.

Intraoperative diuresis as a functional kidney marker may help to identify patients at risk for AKI during the postoperative course. We found that intraoperative diuresis was predictive for early AKI, but not for AKI occurring within the first 3 days after surgery. Although intraoperative diuresis was higher in patients not developing early AKI, there was a wide distribution of values indicating that there are polyuric, normouric, and even oliguric patients who will not develop early AKI after surgery. In this regard, the lower cutoff of the gray zone, coexistent with the oliguric threshold at 0.5 mL kg^{-1} h^{-1}, showed poor positive predictive value suggesting that many oliguric patients do not develop AKI after surgery. These findings are consistent with findings regarding diuresis obtained during ICU stay in a mixed critical care population also reporting good negative and poor positive predictive values for episodes of oliguria.[38] Interestingly, oliguria can occur in patients with preserved hemodynamics due to excess ADH secretion despite lacking volume or osmolar stimulus.[39] In this context, it has been shown that oliguria is common during ICU stay, but most oliguric episodes are not followed by a significant creatinine increase and most AKI is not preceded by oliguric episodes.[38,40] However, our results also indicate a good negative predictive value at the oliguric threshold indicating that approximately 8 of 10 patients will not develop AKI if patients were not oliguric during the course of surgery. From a clinical point of view, intraoperative diuresis as functional kidney marker is only predictive for AKI occurring early after surgery. In this regard, the oliguric threshold can be used to rule out AKI, but cannot be used to identify patients developing AKI.

The study has some limitations and strengths. Post-hoc analyses of randomized controlled trials commonly have to handle heterogeneous data and the interventions usually

Table 2

Performance of lower and upper cutoff of the gray zone of intraoperative diuresis and pNGAL with respect to patients already meeting KDIGO criteria 6h after surgery (AKI_{6h}) and patients meeting KDIGO criteria at least once during the postoperative course (AKI_{total}).

	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
Intraoperative Diuresis				
AKI_{6h}				
<0.5 mL kg^{-1} h^{-1} (LC)	40.0 (10–70)	84.2 (71–95)	40.0 (14–71)	84.2 (78–92)
<2.0 mL kg^{-1} h^{-1} (UC)	100 (100–100)	44.7 (29–61)	32.2 (27–40)	100 (100–100)
AKI_{total}				
<0.6 mL kg^{-1} h^{-1} (LC)	28.6 (7–50)	76.5 (62–88)	33.3 (9–57)	72.2 (65–80)
<2.9 mL kg^{-1} h^{-1} (UC)	100 (100–100)	23.5 (9–38)	35.0 (31–40)	100 (100–100)
Pngal				
AKI_{6h}				
>210 ng mL^{-1} (LC)	90.0 (70–100)	78.9 (66–92)	52.9 (39–73)	96.8 (90–100)
>245 ng mL^{-1} (UC)	70.0 (40–90)	89.5 (79–97)	63.6 (42–89)	91.9 (85–97)
AKI_{total}				
>207 ng mL^{-1} (LC)	71.4 (50–93)	79.4 (65–91)	58.8 (42–80)	87.1 (78–97)
>274 ng mL^{-1} (UC)	35.7 (14–64)	94.1 (85–100)	71.4 (40–100)	78.1 (72–86)

LC = lower cutoff of the gray zone, NPV = negative predictive value, PPV = positive predictive value, UC = upper cutoff of the gray zone.

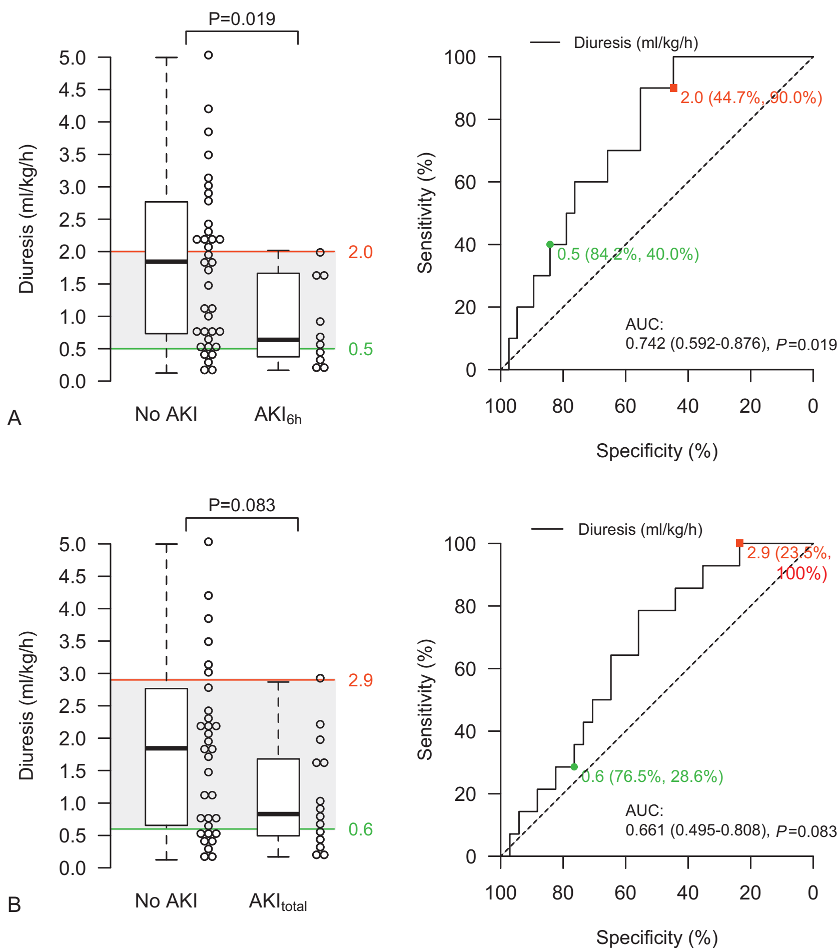

Figure 3. Comparison of intraoperative diuresis between patients without AKI and patients meeting the KDIGO criteria 6 hours after surgery (A); and patients meeting the KDIGO criteria at least once at any time point during the postoperative course up to POD3 (B). The boxplot presentation includes a gray zone approach obtained by the 95% confidence interval of the best cutoff calculated from receiver operating characteristic (ROC) curve. The corresponding ROC curve is shown with sensitivities and specificities of the lower and upper cutoff of the gray zone. AUC = area under the receiver operating characteristic curve.

constitute the most important confounding factors. In this regard, we cannot exclude that the results of this subanalysis have been biased by the interventions of the main study, but as analyses of the main study showed that there was no difference between the crystalloid and colloid group with respect to NGAL levels and there is not any evidence that the predictive ability of NGAL with respect to postoperative AKI might be influenced by the choice of the artificial infusion solution administered during surgery, the risk of bias is low. In addition, the sample size of the study is small which results from being a post-hoc secondary analysis of a pilot study and therefore the power of the specific analysis cannot be stated. The study population is a specific gynecological surgical selection of patients, but due to the well-defined surgical procedures, it provides an excellent surgical model in abdominal high-risk surgery.

In conclusion, pNGAL can be used as early marker to rule out AKI, but not to identify patients who will develop AKI within the first 3 days after major abdominal surgery. In patients with absence of intraoperative oliguria ($<0.5\,\text{mL}^{-1}\,\text{kg h}^{-1}$), risk for early AKI following surgery was low, whereas in oliguric patients, clinical risk factors especially with respect to age, duration of surgery, and surgical trauma need to be considered to assess the individual risk for AKI following surgery.

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