

Oliguria without serum creatinine increase after living-donor liver transplantation is associated with adverse postoperative outcomes

Toshiyuki Mizota^{1,*}, Satoshi Minamisawa², Yuichi Imanaka², Kazuhiko Fukuda¹

¹Department of Anaesthesia, Kyoto University Hospital, 54 Shogoin-Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan

²Department of Healthcare Economics and Quality Management, Graduate School of Medicine, Kyoto University, Yoshida Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan

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* Corresponding author: Toshiyuki Mizota

Assistant Professor

Department of Anesthesia, Kyoto University Hospital, 54 Shogoin-Kawahara-Cho, Sakyo-Ku, Kyoto 606-8507, Japan

Tel: +81-75-751-3433; Fax: +81-75-752-3259

Email: mizota@kuhp.kyoto-u.ac.jp

Abstract

Background: Acute kidney injury (AKI) is a common complication after liver transplantation and is associated with significant morbidity and mortality. Although clinical guidelines recommend defining AKI based on serum creatinine increase and oliguria, the validity and utility of the oliguric component of AKI definition remains largely unexplored. This study examined the incidence and the impact on clinical outcomes of oliguria meeting the urine output criterion of AKI in patients undergoing liver transplantation. The authors hypothesized that oliguria was an independent risk factor for adverse postoperative outcomes.

Methods: This study retrospectively examined 320 patients who underwent living-donor liver transplantation at our centre. AKI stages were allocated according to recent guidelines based on serum creatinine or urine output within 7 days of surgery.

Results: The incidence of oliguria meeting the urine output criterion of AKI was 50.3%. Compared with creatinine criterion alone, incorporating oliguria into the diagnostic criteria dramatically increased the measured incidence of AKI from 39.7% to 62.2%. Compared with patients diagnosed without AKI using either criterion, oliguric patients without serum creatinine increase had significantly longer intensive care unit stays (median: 5 vs. 4 days, $P = 0.016$), longer hospital stays (median: 60 vs. 49 days, $P = 0.014$) and lower chronic kidney disease-free survival rate on postoperative day 90 (54.2% vs. 73.3%, $P = 0.008$).

Conclusion: Oliguria is common after liver transplantation, and incorporating oliguria into the diagnostic criteria dramatically increases the measured incidence of AKI. Oliguria without serum creatinine increase was significantly associated with adverse postoperative outcomes.

Introduction

Acute kidney injury (AKI) is a common complication after liver transplantation and is associated with significant morbidity and mortality¹⁻³. Although several studies have analysed the incidence, risk factors and outcomes of AKI after liver transplantation, multiple AKI definitions made it difficult to compare results. Therefore, researchers and clinicians must have a consensus for defining AKI.

To standardise the AKI definition, the risk, injury, failure, loss of function and end-stage renal failure guideline criteria were developed⁴. These were subsequently revised by the Acute Kidney Injury Network⁵ and the Kidney Disease Improving Global Outcomes (KDIGO) group⁶. Although these definitions involve increases in serum creatinine (SCr) and oliguria to diagnose AKI, in practice, the urine output criterion of AKI definition is frequently discarded because of difficulties in making consistent measurements^{7, 8}.

While some studies have investigated the role of urine output criterion in defining AKI⁹⁻¹³, the validity and utility of the oliguric component of AKI definition remains largely unexplored. Within the context of liver transplantation, previous studies did not explore the incidence or clinical significance of oliguria. Therefore, this study examined the incidence and impact on clinical outcomes of oliguria meeting the urine output criterion of AKI in patients undergoing liver transplantation. We hypothesized that oliguria was an independent risk factor in this patient group for worsened outcomes.

Methods

This study was approved by the ethics committee of the Kyoto University Hospital (approval number: R0060, 22 Jun, 2015), and written informed consent was waived. We analysed the medical records of adult (≥ 18 years old) patients who underwent living-donor liver transplantation (LDLT) at the Kyoto University Hospital from January 2006 to December 2014. Patients with fulminant hepatic failure were excluded. In addition, patients who had end-stage renal disease preoperatively [i.e. estimated glomerular filtration rate (eGFR) < 15 mL/min/m² as determined using a formula validated in Japan: $\text{eGFR} = 194 \times \text{SCr}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ (if female)¹⁴ or receipt of long-term haemodialysis] were also excluded because assessment of AKI was not relevant.

Patients were divided into five categories according to the indication of LDLT: hepatocellular carcinoma, hepatitis B/C cirrhosis, alcoholic cirrhosis, cholestatic liver disease (primary biliary cirrhosis or primary sclerosing cholangitis) and others. The following patient and operative variables were also collected: patient characteristics, Model for End-stage Liver Disease (MELD) score¹⁵, Child-Pugh classification, preoperative SCr, previous liver transplantation, blood type compatibility, graft-recipient weight ratio, intraoperative blood loss, amount of intraoperatively used blood products, intraoperative urine output and operative time. SCr concentration was measured using LABOSPECT 008 (Hitachi High-Technologies, Tokyo, Japan).

AKI was diagnosed and staged according to recent guidelines⁶ (Table 1). Data from daily SCr measurement within 7 days of surgery and urine output measured every 2 hours during postoperative intensive care unit (ICU) stay (within 7 days of surgery, in case postoperative ICU stay was > 7 days) were used to assign AKI stages. Preoperative SCr value was considered as a baseline value. We allocated AKI stages based on SCr criterion (AKI-Cr) and urine output criterion (AKI-UO), respectively; then the higher stage of AKI-Cr or AKI-UO was used for staging according to the standard AKI definition (AKI-com).

The basic immunosuppressive regimen consisted of calcineurin inhibitor (tacrolimus or cyclosporine) and low-dose corticosteroids¹⁶. Patients who received blood-type-incompatible

transplants had preoperative anti-CD20 antibody (rituximab 375 mg/m²) with preoperative plasma exchange, postoperative hepatic artery infusion of prostaglandin E1 (0.01 µg/kg/min) and methylprednisolone (125 mg/day), as well as postoperative cyclophosphamide (2 mg/kg/day) followed by mycophenolate mofetil (starting dose, 500 mg/day; maintenance dose, 1000 mg/day)¹⁷⁻¹⁹.

Adverse outcomes for analysis included all cause hospital mortality, time to ICU and hospital discharge, 90-day mortality and chronic kidney disease (CKD)-free survival (the proportion of patients who are alive and free of CKD) at 90 days after LDLT. CKD was defined as an eGFR of <60 mL/min/1.73 m² at 90 days after LDLT according to the criteria established by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative, which defined CKD as a glomerular filtration rate of <60 mL/min/1.73 m² for >3 months²⁰.

Statistical analyses

Data were analysed using the statistical program R (<http://cran.r-project.org>). The data are presented as median (interquartile range) and number (percentage), unless otherwise stated. Differences between groups were compared using the Mann–Whitney U test for continuous variables. For categorical variables, the Pearson chi-square test or Fisher exact test was used where appropriate. Time-to-event analyses were used to compare lengths of ICU and hospital stays. Patient data were censored at the time of death. Medians and interquartile range were obtained using the Kaplan–Meier analyses, and the log-rank test was used to assess differences between groups. Simple and multivariable logistic regression analyses were used to assess the impact of AKI-Cr or AKI-com on hospital mortality. In the multivariable analysis, adjustments were made for previously described risk factors (recipient age, MELD score > 30, re-transplantation and blood-type incompatibility)^{21, 22}. We calculated the odds ratios of AKI-Cr or AKI-com; and then those of each stage of AKI-Cr or AKI-com. The areas under the receiver operating characteristic curves (AUC–ROC) were calculated to assess the ability of AKI-Cr or AKI-com to predict hospital mortality. All statistical tests were

two-tailed and statistical significance was set at $P < 0.05$ (with Dunnett correction for multiple comparisons yields a P value of <0.017).

Results

Altogether, 373 adult patients underwent LDLT during the study period. Of these, 320 eligible patients were analysed after excluding 21 patients with fulminant hepatic failure, 31 patients who had end-stage renal disease preoperatively, and one patient whose data concerning urine output in ICU were missing. The ages of the patients ranged from 18 to 69 years, and 154 patients (48.1%) were female. 203 patients (63.4%) received diuretics [furosemide (0.8–4 mg/h) or human atrial natriuretic peptide (hANP, 0.06–0.3 mg/h)] during postoperative ICU stays; 88 (27.5%) received hANP only, 57 (17.8%) received furosemide only, and 58 (18.1%) received both. Additionally, 256 patients (80.0%) were administered dopamine during ICU stays.

Incidences of AKI by diagnostic criteria

Altogether, AKI-Cr occurred in 127 patients (39.7%), whereas AKI-UO was diagnosed in 161 patients (50.3%), 89 (55.3%) of whom also met the criterion for AKI-Cr (Fig. 1). Combining oliguric or SCr-based criteria to define AKI as per KDIGO guidelines, 199 patients (62.2%) were diagnosed as AKI; the AKI incidence increased about 1.6 times compared to that using SCr-based criterion alone. Table 2 shows the patient characteristics and perioperative variables stratified by the AKI status. The graft-recipient weight ratio was lower, and intraoperative blood loss and volume of blood transfused were higher in patients with both AKI-Cr and AKI-UO compared with patients diagnosed without AKI using either criterion. Patients with AKI-Cr only or those with AKI-UO only were comparable in demographics and operative variables to patients without AKI, except that more female patients were included in AKI-UO only group and this group tended to suffer from more blood loss. Most patients who developed AKI-UO received diuretics (furosemide or hANP) during ICU stays. Table 3 shows the association between the AKI status and distribution of AKI stages according to the standard AKI definition (AKI-com). More than half of patients with AKI-Cr only or AKI-UO only were allocated to stage 1 AKI according to the standard AKI definition; in contrast, most patients (73.0%) with both AKI-Cr and AKI-UO were allocated to stage 2–3 AKI.

Clinical outcomes according to AKI status

Overall, patients with both AKI-Cr and AKI-UO had a significant increase in hospital and 90-day mortality, prolonged ICU or hospital stays, and lower CKD-free survival rate at postoperative day (POD) 90. Neither AKI-Cr only nor AKI-UO only were significantly associated with an increase in hospital or 90-day mortality, but patients with AKI-UO only had longer ICU or hospital stays and lower CKD-free survival rate at POD 90 (Table 4).

To examine whether incorporating oliguria into the diagnostic criteria for AKI improved predictive ability, we compared the performance of AKI-Cr and AKI-com staging in predicting hospital mortality. After adjustment for known predictive factors (age, MELD score > 30, blood-type incompatibility and re-transplantation), both AKI-Cr and AKI-com were significantly associated with an increase in hospital mortality [AKI-Cr: odds ratio (OR) 2.07, 95% confidence interval (CI) 1.11–3.85; AKI-com: OR 2.53, 95% CI 1.23–5.22].

Multivariable logistic regression analysis including known predictive factors revealed that hospital mortality among patients with stage 3 AKI-Cr increased nearly 8-fold when compared to those without AKI-Cr (OR 7.87, 95% CI 3.26–19.00), whereas stages 1–2 AKI-Cr were not significantly associated with an increase in hospital mortality (Table 5). When AKI-com was used instead of AKI-Cr, stage-wise increase in hospital mortality was observed and stage 2 and stage 3 AKI-com were significantly associated with an increase in hospital mortality (stage 2: OR 2.71, 95% CI 1.14–6.46; stage 3: OR 8.66, 95% CI 3.33–22.60; Table 5).

The addition of AKI-Cr to the known predictive factors (age, MELD score > 30, blood-type incompatibility and re-transplantation) improved AUC-ROC for hospital mortality from 0.63 (95% CI 0.54–0.71) to 0.71 (95% CI 0.62–0.79); when AKI-com was used instead of AKI-Cr, the AUC-ROC was 0.74 (95% CI 0.66–0.81) (Fig. 2).

Discussion

To the best of our knowledge, this is the first study that investigates the incidence and the impact on clinical outcomes of oliguria in patients undergoing liver transplantation. An analysis of our cohort revealed the following: (1) oliguria meeting the urine output criterion of AKI occurred in 50.3% of LDLT recipients, (2) compared with AKI diagnosis using only SCr criteria, incorporating oliguria into the diagnostic criteria for AKI dramatically increased the number of patients diagnosed with AKI from 39.7% to 62.2%, and (3) although incorporating oliguria into the diagnostic criteria for AKI only marginally improved the prognostic performance for hospital mortality, oliguria without AKI-Cr was significantly associated with prolonged ICU or hospital stays and lower CKD-free survival rate at POD 90.

The incidence, risk factors or outcomes of AKI after deceased-donor liver transplantation (DDLT) have been extensively studied, but few studies have reported them in LDLT²³. The incidence of AKI-Cr after LDLT observed in this study (39.7%) was similar to those after DDLT reported in previous studies (39.4–56.6%)^{3,24,25}. These incidences of AKI were substantially higher than those in the rest of the population who underwent major non-cardiac surgery, with a reported incidence of approximately 7.5%^{26,27}. Receiving a graft from a living donor had a protective effect against AKI after liver transplantation²³. However, the high incidence of AKI-Cr observed in our study suggests that LDLT recipients, as well as DDLT recipients, are at extremely high risk of postoperative AKI.

Multivariable analysis revealed that severe AKI (stage 3 AKI-Cr and stage 2–3 AKI-com) was associated with substantial increase in hospital mortality. Moreover, the addition of AKI-Cr or AKI-com to the known predictive factors improved AUC-ROC for hospital mortality. These results suggest that the development of severe AKI has a significant impact on clinical outcomes after LDLT. However, we could not show significant association of stage 1 AKI-Cr or stage 1 AKI-com with increased mortality (odds ratio around 1.0). Clinical significance of small increase in SCr or temporary oliguria after liver transplantation needs to be elucidated in future studies.

Although the aetiology of AKI after liver transplantation is multifactorial (factors include surgery-related events, blood loss, hypotension, sepsis, calcineurin inhibitor-induced vasoconstriction and volume depletion)²⁸, maintaining cardiovascular stability during and after liver transplantation is vital to renal perfusion and therefore is considered to be important in order to prevent AKI. In our study, patients with both AKI-Cr and AKI-UO suffered from increased blood loss compared with those without AKI diagnosed through either criterion. Similarly, although not reaching statistical significance, those with AKI-UO who also did not meet SCr-based criterion for AKI tended to have more blood loss. Hemodynamic instability due to massive blood loss may have contributed to the development of AKI.

Applying the urine output criterion in addition to the SCr criterion dramatically increased the number of patients diagnosed with AKI (39.7% to 62.2%). A similar phenomenon was observed in critically ill patients^{9,10} or patients undergoing cardiac surgery^{12,13}. Because a significant proportion of patients exhibit oliguria without SCr increase, the inclusion or exclusion of the urine output criterion must result in either significant overdiagnosis or underdiagnosis of true AKI. To resolve this problem, studies are needed to elucidate the validity and utility of oliguria in diagnosing AKI. Several studies have investigated the specific role of the oliguric component of AKI definition. A study of more than 14,000 critically ill patients reported a 50–100% increase in AKI diagnosis when the urine output criterion was incorporated into the definition but with a diminished effect on mortality compared with the corresponding stage of AKI-Cr alone⁹. On the other hand, the additive predictive value of the oliguric component of AKI has been reported by some authors. Applying the urine output criterion in addition to the SCr criterion resulted in significant improvement in the predictive performance of mortality¹⁰ (AUC-ROC increased from 0.6 to 0.69). In patients who developed AKI, urine output alone was a better mortality predictor than SCr alone or the combination of both¹¹. Additional studies have produced varying estimates for the impact of the urine output criterion on both AKI incidence and outcomes^{12,13}. Possible explanations for the inconsistency of these results include differences in the study population. Differences in the definition of oliguria might also have

resulted in different estimates. Some studies used modified urine output criterion, for example, using 24 hour urine output to define oliguria instead of hourly urine output⁹.

In the setting of advanced liver disease, recent consensus definitions for AKI recommend the use of SCr only because of the limitations of urine output in this population²⁰. However, in our study, patients with oliguria who also did not meet SCr-based criterion for AKI had longer ICU or hospital stays and lower CKD-free survival rate at POD 90. These results suggest that oliguria without SCr increase had a significant impact on clinical outcomes after liver transplantation and discarding urine output criterion in diagnosing AKI may miss this clinically important sign.

The major limitation of this study is its retrospective design and small sample size. This study represents data from one institution. There was no standardised protocol for perioperative fluid or diuretic administration. Although hourly urine output is required to define AKI-UO according to recent guidelines, urine output measured every 2 hours was used to define oliguria instead because urine output is measured every 2 hours in our ICU. This modification may have affected the incidence or the impact on clinical outcomes of oliguria.

In conclusion, oliguria is common after liver transplantation and incorporating oliguria into the diagnostic criteria for AKI can dramatically increase the number of patients diagnosed with AKI. Compared with no AKI, AKI with oliguria without SCr increase was significantly associated with adverse postoperative outcomes including prolonged ICU or hospital stays and lower CKD-free survival rate at POD 90. Discarding urine output criterion in diagnosing AKI may miss this clinically important sign.

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Conflicts of interest

None.

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Tables

Table 1 Definition and staging for acute kidney injury⁶.

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline or ≥ 0.3 mg/dl increase	< 0.5 mL/kg/h for 6–12 h
2	2.0–2.9 times baseline	< 0.5 mL/kg/h for ≥ 12 h
3	3.0 times baseline or increase to 4.0 mg/dl or initiation of renal replacement therapy	< 0.3 mL/kg/h for ≥ 24 h or anuria for ≥ 12 h

Table 2 Patient characteristics and perioperative variables according to acute kidney injury status.

	No AKI (n = 121)	AKI-Cr only (n = 38)	AKI-UO only (n = 72)	AKI-Cr and AKI-UO (n = 89)
Age (years)	54 (42–59)	53 (48–60)	56 (47–61)	56 (46–60)
Female gender	48 (39.7%)	11 (29.0%)	45 (62.5%) *	50 (56.2%)
MELD score	15 (11–19)	14 (11–19)	17 (13–22)	16 (13–19)
Child-Pugh classification C	64 (52.9%)	20 (52.6%)	46 (63.9%)	57 (64.0%)
Pre-transplant SCr (mg/dL)	0.7 (0.6–0.8)	0.7 (0.6–0.7)	0.7 (0.6–0.9)	0.7 (0.5–0.9)
Pre-transplant serum albumin (g/dL)	2.8 (2.5–3.2)	2.8 (2.5–3.2)	2.9 (2.4–3.2)	2.8 (2.5–3.2)
Diabetes mellitus	25 (20.7%)	11 (15.3%)	8 (21.1%)	18 (20.2%)
Aetiology				
HCC	39 (32.2%)	15 (39.5%)	14 (19.4%)	35 (39.3%)
HBV/HCV	28 (23.1%)	11 (29.0%)	16 (22.2%)	20 (22.5%)
Alcoholic	5 (4.1%)	2 (5.3%)	6 (8.3%)	5 (5.6%)
Cholestatic liver disease	16 (13.2%)	4 (10.5%)	19 (26.4%)	12 (13.5%)
Others	33 (27.3%)	6 (15.8%)	17 (23.6%)	17 (19.1%)

Re-transplantation	4 (3.3)	3 (7.9%)	4 (5.6%)	3 (3.4%)
ABO-incompatible	29 (24.0%)	7 (18.4%)	17 (23.6%)	28 (31.5%)
Graft-recipient weight ratio (%)	0.95(0.82–1.14)	0.90 (0.77–1.15)	0.88 (0.78–0.98)	0.84 (0.69–1.02)*
Intraoperative blood loss (L)	5.5 (3.3–10.6)	6.5 (4.0–9.8)	7.8 (4.3–12.3)	7.9 (5.6–17.5)*
RBC use (mL)	1120 (560–2520)	1260 (560–2240)	1680 (945–2800)	1680 (840–3500)*
Intraoperative urine output (mL)	1451 (937–1968)	1203 (768–1507)	1317 (894–1920)	1202 (730–1677)
Operative time (min)	782 (712–920)	842 (748–1043)	805 (727–900)	837 (768–950)
Use of diuretics during ICU stays	45 (37.2%)	20 (52.6%)	61 (84.7%)*	77 (86.5%)*

*, $p < 0.017$ (significantly different with Dunnett correction) compared with no AKI. Data regarding graft-recipient weight ratio, intraoperative blood loss, or intraoperative urine output were missed in 18, 10 or 24 patients, respectively. Diuretics include furosemide and human atrial natriuretic peptide. AKI, acute kidney injury; AKI-Cr, acute kidney injury defined based on serum creatinine criterion; AKI-UO, acute kidney injury defined based on urine output criterion; SCr, serum creatinine; MELD, Model for End-stage Liver Disease; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; RBC, red blood cells; ICU, intensive care unit.

Table 3 The association between the AKI status and distribution of AKI stages according to the standard AKI definition.

	AKI-Cr only (n = 38)	AKI-UO only (n = 72)	AKI-Cr and AKI-UO (n = 89)
Stage 1	23 (60.5%)	51 (70.8%)	24 (27.0%)
Stage 2	10 (26.3%)	20 (27.8%)	39 (43.8%)
Stage 3	5 (13.2%)	1 (1.4%)	26 (29.2%)

AKI, acute kidney injury; AKI-Cr, acute kidney injury defined based on serum creatinine criterion; AKI-UO, acute kidney injury defined based on urine output criterion.

Table 4 Outcomes according to acute kidney injury status.

	No AKI (n = 121)	AKI-Cr only (n = 38)	AKI-UO only (n = 72)	AKI-Cr and AKI-UO (n = 89)
Hospital mortality	11/121 (9.1%)	4/38 (10.5%)	12/72 (16.7%)	23/88 (26.1%)*
Length of ICU stay (days)	4 (4–5)	5 (4–5)	5 (4–5) *	5 (4–6)*
Length of hospital stay (days)	49 (38–72)	48 (37–84)	60 (52–74) *	67 (45–NA)*
90-day mortality	6/120 (5.0%)	3/38 (7.9%)	9/72 (12.5%)	18/89 (20.2%)*
CKD-free survival at 90 days	88/120 (73.3%)	25/38 (65.8%)	39/72 (54.2%) *	41/89 (46.1%)*

*, $p < 0.017$ (significantly different with Dunnett correction) compared with no AKI. 90-day mortality and CKD-free survival at 90 days were missed in one patient without AKI using either criterion because he was lost to follow-up within 90 days after the surgery. Hospital mortality was missed in one patient with both AKI-Cr and AKI-UO because he was still hospitalized at the time of data collection. AKI, acute kidney injury; AKI-Cr, acute kidney injury defined based on serum creatinine criterion; AKI-UO, acute kidney injury defined based on urine output criterion; ICU, intensive care unit; CKD, chronic kidney disease.

Table 5 Odds ratios for hospital mortality according to definition criteria of AKI.

AKI-Cr		AKI-com	
n	Unadjusted OR	Adjusted OR for known risk factors	Adjusted OR for known risk factors
No AKI	193	1 (reference)	1 (reference)
Stage 1	62	0.94 (0.38–2.31)	1.14 (0.46–2.80)
Stage 2	36	1.19 (0.42–3.37)	2.55 (1.08–5.98)
Stage 3	29	8.53 (3.61–20.20)	9.37 (3.67–24.00)

Data are expressed as odds ratio (95% confidence interval). Known risk factors included recipient age, Model for End-stage Liver Disease score > 30, blood-type incompatibility, and re-transplantation. AKI, acute kidney injury; AKI-Cr, acute kidney injury defined based on serum creatinine criterion (without consideration of urine output); AKI-com, acute kidney injury defined based on both serum creatinine and urine output criteria; OR, odds ratio.

Figure legends

Fig. 1. Venn diagram of AKI status. AKI, acute kidney injury; AKI-Cr, acute kidney injury defined based on serum creatinine criterion; and AKI-UO, acute kidney injury defined based on urine output criterion.

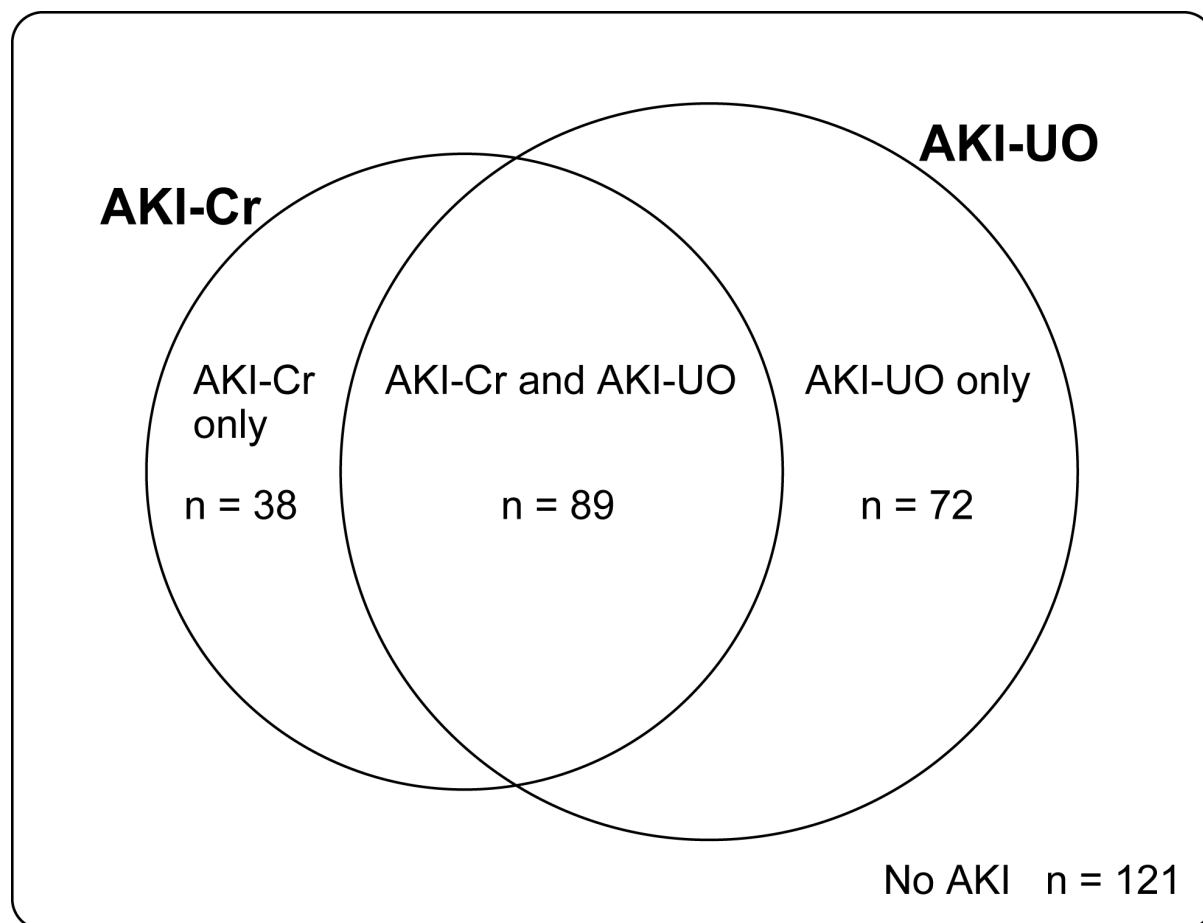


Fig. 2. The areas under the receiver operating characteristic curves for hospital mortality as predicted by known risk factors only, AKI-Cr combined with known risk factors and AKI-com combined with known risk factors. Known risk factors included recipient age, Model for End-stage Liver Disease score > 30, blood type incompatibility and re-transplantation. The AUC values and 95% CIs are listed within the figure. AUC, area under the curve; CI, confidence interval; AKI-Cr, acute kidney injury

defined based on serum creatinine criterion (without consideration of urine output); AKI-com, acute kidney injury defined based on both serum creatinine and urine output criteria.

