

# **The AKI Prediction Score: A new prediction model for acute kidney injury after liver transplantation**

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## SUMMARY

AKI is a frequent complication after liver transplantation and associated with impaired long-term survival rates, CKD and higher costs. Although numerous risk factors have been previously identified, their cumulative impact on the development of AKI remains unknown. Our aim was therefore to design a new model to predict the frequency of post-transplant AKI. Risk analysis was performed in all patients undergoing primary liver transplantation in two centres (n=1230). A new model to predict severe AKI (KDIGO stage 2/3) was calculated based on weight of the factors in a multivariable regression analysis according to the Framingham risk scheme. Overall, 34% of the patients developed severe AKI, including 18% requiring postoperative RRT. Five factors were identified as strongest predictors: both recipient and donor BMI, DCD graft use, FFP requirements, and recipient WIT, leading to 0-25 score points with an AUC of 0.70 for the new AKI Prediction Score. Three risk classes were identified: low, intermediate and high risk. Recipients with intermediate/high risk had impaired long-term graft survival and more postoperative complications assessed with the CCI. Furthermore, severe AKI was less frequently observed if such recipients received a renal-sparing immunosuppression, compared to those receiving calcineurin inhibitor based immunosuppression (29 vs. 45%;  $p=0.007$ ). In conclusion, The AKI Prediction Score is a new and reliable instrument to identify recipients at risk for severe post-transplant AKI. This score is readily available at end of the transplant procedure, creating opportunities to engage in renal-sparing immunosuppression and early RRT.

## INTRODUCTION

AKI is a common issue after liver transplantation and various studies have reported incidence rates up to 60% (1–4). Post-transplant AKI is associated with the development of CKD and impaired survival rates (5–8). Furthermore, patients requiring temporary RRT have a prolonged hospital stay with subsequent requirement of more resources and higher costs (9). Several donor, recipient and surgical factors have been linked to a higher risk for the development of AKI after liver transplantation. Recipient factors include BMI, pre-transplant MELD-score and history of DM or hypertension (1,6,7). Older and steatotic grafts or DCD donors have been associated with a higher rate of post-transplant AKI (1,10,11). The duration of cold and warm ischemia and transfusion requirements are further known risk factors (12,13). Finally, postoperative events and the use of nephrotoxic immunosuppression can further aggravate the damage to the kidneys (14–17).

The multifactorial origin of AKI complicates the prediction of who is particularly at risk to develop AKI and who will also require RRT. The introduction of the ‘sickest first’ allocation following the MELD-score prioritizes patients with impaired pre-transplant renal function and such patients are more vulnerable for the additional renal damage during and after liver transplantation (18). In addition, the evolving use of marginal grafts over the last years, including DCD and steatotic grafts, increases the risk for AKI (1). Such livers are more prone to increased hepatic IRI and previous studies have shown that severe hepatic IRI is associated with hemodynamic instability and development of AKI after liver transplantation (12,13,19,20). The numerous risk factors for AKI and its significant impact on hospital resources and short- and long-term outcomes, highlights the need for a standardized prediction model for AKI after liver transplantation surgery. Therefore, the aim of this study is to develop a novel prediction score to identify recipients at risk for post-transplant AKI at the earliest possible point after liver transplantation.

## METHODS

### Data collection

The liver transplantation cohorts of the Queen Elizabeth Hospital in Birmingham, UK (2007–2015) and the Erasmus MC University Medical Centre in Rotterdam, the Netherlands (2008–2014) were used to develop this new prediction model. All consecutive adult patients who underwent primary, orthotopic deceased-donor liver

transplantation were included and their medical records were retrospectively assessed. Exclusion criteria were retransplantation, super-urgent transplantation, RRT prior to liver transplantation, domino transplants, combined liver-kidney transplantation, and machine perfusion of the graft.

### Study parameters

Donor, graft, recipient and surgical characteristics that were assessed as risk factor for AKI are highlighted in **Table 1**. The DRI and MELD-score were calculated according to previous studies (21,22). Post-transplant AKI was defined according to the KDIGO criteria (23): an increase in serum creatinine by  $\geq 26.5 \mu\text{mol/L}$  within 48 hours or an increase in creatinine to  $\geq 1.5$  times baseline within the first 7 postoperative days. AKI was classified into 3 stages: stage 1, increase  $\geq 26.5 \mu\text{mol/L}$  or increase of 1.5-1.9-fold from baseline; stage 2, increase of 2-2.9-fold; stage 3, increase  $>3$ -fold or increase in serum creatinine to  $\geq 354 \mu\text{mol/L}$  or initiation of RRT. The peak serum AST level in the first 72 hours was used as surrogate marker for hepatic IRI (12). EAD was defined according to the Olthoff criteria (24). Based on the Clavien-Dindo Classification, all postoperative complications requiring treatment during initial hospital admission were collected and used to calculate the CCI to comprehend all postoperative morbidity (25,26). A major postoperative complication was defined as a Clavien-Dindo Classification grade  $\geq 3\text{b}$  complication.

### Transplant practice and immunosuppression

DCD grafts are retrieved using the super-rapid donor cannulation technique (27). The preferred preservation fluid for liver procurement in both centres is heparinized UW solution under pressure via the aorta. In the UK, the portal system is also cannulated and flushed in the donor with 1 litre UW solution. Additional back-table flush is performed in both centres, including a flush of the biliary tract. The standard implantation technique in both centres include the piggyback cava anastomosis (classic or side-to-side cavo-cavostomy) without the use of veno-venous bypass. A portocaval shunt is performed in selected cases. Triple-therapy immunosuppression after liver transplantation is the standard of care in both centers. In Birmingham, the regimen consists of Tacrolimus, Azathioprine or MMF and prednisolone, all introduced at day 0. Prednisolone therapy is generally discontinued after three months. A renal-sparing protocol is considered in recipients with impaired renal function and consists of either low-dose Tacrolimus introduction combined with MMF or delayed introduction of Tacrolimus (on day 3-5) with MMF and Basiliximab on day 0 and 4. In Rotterdam, the immunosuppression regimen was modified during the study period. Until 2012 patients received a triple-therapy regimen of Tacrolimus, MMF and pred-

**Table 1** - Donor, recipient and surgical characteristics in the two cohorts.

Donor / Graft characteristics	Birmingham (n=1009)	Rotterdam (n=221)	P-value
Age (years)	52 (41-62)	53 (44-62)	0.207
Body mass index (kg/m <sup>2</sup> )	25.8 (23.1-28.7)	24.4 (22.5-26.6)	<0.001
Donor risk index	1.8 (1.5-2.2)	2.2 (1.8-2.5)	<0.001
DCD graft (%)	285 (28%)	67 (30%)	0.537
<b>Recipient</b>			
Age (years)	55 (47-62)	54 (44-61)	0.107
Male gender (%)	650 (64%)	148 (67%)	0.472
Body mass index (kg/m <sup>2</sup> )	26.6 (23.6-30.4)	25.5 (23.1-28.9)	0.001
Etiology of liver disease (%)			<0.001
ALD	276 (27%)	39 (18%)	
Hepatitis C	225 (22%)	31 (14%)	
Hepatitis B	40 (4%)	21 (10%)	
NASH	97 (10%)	30 (14%)	
PSC	118 (12%)	56 (25%)	
PBC	131 (13%)	11 (5%)	
AIH	30 (3%)	9 (4%)	
Other	92 (9%)	24 (11%)	
Hepatocellular carcinoma (%)	260 (26%)	63 (29%)	0.402
Biological MELD-score	13 (9-17)	16 (9-21)	<0.001
Serum creatinine (μmol/l)	78 (63-96)	76 (61-95)	0.271
Serum sodium (μmol/l)	138 (135-140)	138 (134-140)	0.775
<b>Medical history (%)</b>			
Hypertension	169 (17%)	18 (8%)	0.001
Diabetes mellitus	265 (26%)	57 (26%)	0.885
<b>Surgery</b>			
Cold ischemia time (hours)	7.8 (6.5-9.3)	6.4 (5.6-7.5)	<0.001
Recipient warm ischemia time (min)	38 (33-43)	28 (25-34)	<0.001
RBC transfusion (units)	2 (0-4)	3 (1-6)	<0.001
FFP transfusion (units)	6 (2-10)	4 (0-7)	<0.001

Continuous variables are displayed as median and interquartile range.

AIH, auto-immune hepatitis; ALD, alcohol-related liver disease; DCD, donation after circulatory death; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

nisolone (for three months), which were all introduced at day 0. From 2012, induction of tacrolimus is delayed until day 5, MMF is started on day 0 and Basiliximab given on day 0 and 4. Target peak trough levels for tacrolimus range between 7-10 ug/L during the first months in both centres.

## Development of the new risk score

To establish a clinically relevant risk score we decided to develop a prediction model, that is directly available at the end of the transplant procedure to timely adapt the immunosuppression regimen and consider early RRT. Therefore, we only include preoperative donor and recipient parameters and surgical factors, including the duration of ischemia periods. Previous studies, including our own, have shown, that mainly AKI grade 2 and 3 have an impact on long-term survival and the development of CKD (5,12,28). We have therefore chosen severe AKI (KDIGO stage 2 and 3) as outcome variable of our prediction model. As our own centre data was used, all datasets were complete and compensatory methods for missing values were not required. All significant factors in univariable regression analysis ( $p < 0.25$ ) were considered further. A backward stepwise approach was used for the multivariable logistic regression with a  $p$ -value  $> 0.05$  as exclusion threshold (29). Backward elimination is generally preferred as an automated predictor-selection procedure because it takes correlations among predictors into calculation (30). The five strongest predictors were included in the final model. A point system for the score was developed according to the Framingham risk scheme (31). For each predictor, the median of all values below (midpoint  $W_1$  reference –  $W_1$  reference) and above the threshold was calculated. The midpoint for the cohort below each threshold ( $W_{1-7}$  reference) was subtracted from the midpoint of all values above the threshold. The factor  $\beta$  was multiplied with the difference ( $W_{ij} - W_{\text{reference}}$ ), separately for each factor (31,32).

## Performance and validation of the new prediction model

The performance of the prediction model was evaluated by examining discrimination (ability to discriminate between patients who do and do not experience the event [severe AKI]) and calibration (the agreement between predicted probabilities from the model and observed outcomes). Discrimination was quantified by calculating the area under receiver-operating-characteristic curve (AUC) statistic. The Hosmer-Lemeshow test was used to determine the extent of agreement between the predicted and observed probabilities. We performed an internal validation using a bootstrapping procedure. This approach uses the entire data to develop the prediction model and accounts for model over fitting or uncertainty compensating for over optimism in the final prediction model. The bootstrapping in the current study was performed using 500 bootstrap resamples, each time selecting variables and developing a model within the sample.

## Additional statistics and ethical approval

Data were analysed with IBM SPSS Statistics version 24 (IBM Corporation, Armonk, New York, USA). Graphical images were constructed using GraphPad Prism version 7.04 (GraphPad Software, La Jolla, CA, USA). Median and IQR were used to analyse continuous variables and comparisons were made using the Mann-Whitney U test. Categorical variables were expressed in quantities and percentages. To compare categorical variables, the Chi-square test or the Fisher's exact test were used. Long-term survival rates were estimated using Kaplan-Meier methods, with comparisons between groups performed using log-rank tests. Completeness, plausibility and validity of the data were independently verified (by MK & AS), including objective review of all historical medical charts. All patients with complete data records were included. The local regulatory board approval was obtained prior to study initiation and database/chart review in Birmingham and Rotterdam.

## RESULTS

### Baseline characteristics and development of AKI

Overall, 1230 recipients were included in this study: 1009 recipients from Birmingham and 221 recipients from Rotterdam. The donor, recipient and surgical characteristics in both centres are displayed in **Table 1**. The recipient age was comparable in both centres (median Birmingham 55; Rotterdam 54 years;  $p=0.107$ ) and the recipient BMI was significantly higher in Birmingham (26.6 vs. 25.5;  $p=0.001$ ). The most common aetiologies of liver disease in Birmingham were alcohol-related liver disease (27%) and hepatitis C (22%), while in Rotterdam primary sclerosing cholangitis (25%) was the most common indication for transplantation, followed by alcohol-related liver disease (18%) (**Table 1**). Recipients in Rotterdam presented with a higher lab MELD-score (median 16 vs. 13;  $p<0.001$ ). Importantly, no differences were observed

**Table 2** - Development of AKI after liver transplantation in both cohorts.

	Birmingham (n=1009)	Rotterdam (n=221)	Total (n=1230)	P-value
No AKI	420 (42%)	129 (58%)	549 (45%)	
Overall AKI	589 (58%)	92 (42%)	681 (55%)	<0.001
AKI stage 1	195 (19%)	57 (26%)	252 (21%)	
AKI stage 2	134 (13%)	24 (11%)	158 (13%)	
AKI stage 3	260 (26%)	11 (5%)	271 (22%)	
Severe AKI (stage 2/3)	394 (39%)	35 (16%)	429 (25%)	<0.001
RRT	207 (21%)	6 (3%)	213 (18%)	<0.001

AKI, acute kidney injury; RRT, renal replacement therapy

for serum creatinine levels (median Birmingham 78  $\mu\text{mol/l}$ ; Rotterdam 76  $\mu\text{mol/l}$ ;  $p=0.271$ ) prior to liver transplantation. Donors in both centres were of same age, but had a significantly higher BMI in Birmingham (median 25.8 vs. 24.4;  $p<0.001$ ). In Birmingham, 28% of the transplants were performed with DCD grafts, compared to 30% in Rotterdam ( $p=0.537$ ). Both the duration of cold ischemia (median 7.8 vs. 6.4 hours;  $p<0.001$ ) and recipient WIT (38 vs. 28 min;  $p<0.001$ ) was longer in Birmingham. Overall, 681 (55%) of the recipients developed AKI (**Table 2**), which was more common in Birmingham (58% vs. 42%;  $p<0.001$ ). Additionally, in Birmingham liver recipients developed more severe form of AKI (39% vs. 16%;  $p<0.001$ ) and required postoperative RRT more frequently (21% vs. 3%;  $p<0.001$ ).

### Key predictors of severe AKI and the new AKI Prediction Score

Initially, we evaluated 18 donor, recipient and surgical factors and the multivariable logistic regression identified the following five parameters as significant predictors for development of severe AKI: donor BMI (as a surrogate marker for graft steatosis), the use of a DCD graft, recipient BMI, the duration of recipient WIT (implantation

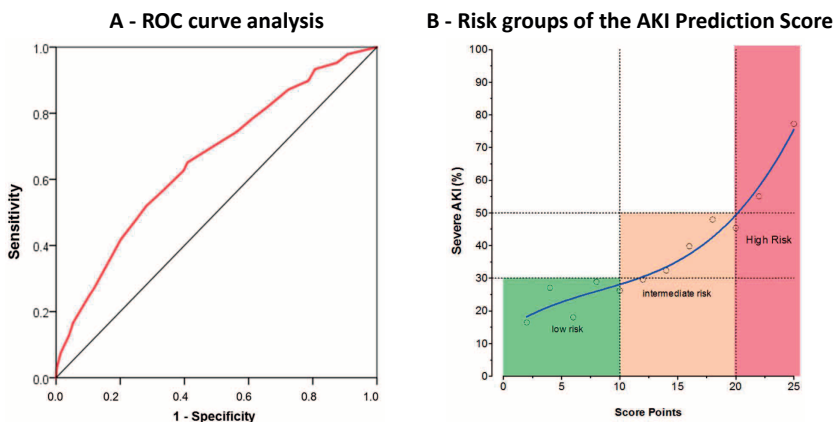
**Table 3 - Multivariable logistic regression analysis for development of CKD after liver transplantation.** The imputed data sets were combined and the point system was developed according to the Framingham risk scheme. For each predictor, the median of all values (Midpoint  $W_{\text{reference}}$  –  $W_{\text{reference}}$ ) below and above the threshold has been calculated. The Midpoint for the cohort below each threshold ( $W_{\text{reference}}$ ) is subtracted from the midpoint of all values above the threshold. The factor  $\beta_i$  is multiplied with the difference ( $W_{ij} - W_{\text{reference}}$ ), separately for each factor to develop the score points.

Parameter	Category	Regression Coefficient $\beta_i$	$p$ -value	Reference Value $W_i$ (Midpoint)	$\beta_i \times (W_{ij} - W_{\text{reference}})$	Risk Score
Donor BMI	$\leq 25 \text{ kg/m}^2$	0	0.030	22.85 ( $W_{2\text{reference}}$ )	0	0
	$> 25 \text{ kg/m}^2$	-0.306		28.26	3.111	3
DCD graft	no	0	$<0.001$	0 ( $W_{3\text{reference}}$ )	0	0
	yes	-0.801		1	0.801	1
Recipient BMI	$\leq 30 \text{ kg/m}^2$	0	0.002	24.93 ( $W_{6\text{reference}}$ )	0	0
	$> 30 \text{ kg/m}^2$	-0.477		32.6	3.659	4
No. of FFP	$\leq 3 \text{ U}$	0	$<0.001$	0 ( $W_{7\text{reference}}$ )	0	0
	4 - 6 U	-1.103		5	5.515	6
	7 - 10 U	-0.948		8	7.584	8
	$> 10 \text{ U}$	-0.636		16	10.176	10
Recipient WIT	$\leq 36 \text{ min}$	0	$<0.001$	30 ( $W_{9\text{reference}}$ )	0	0
	$> 36 \text{ min}$	-0.616		42	7.392	7
Total Score Points						0-25

$\beta$ , regression coefficient; DCD, donation after circulatory death; FFP, fresh frozen plasma; Recipient WIT, recipient warm ischemia time.



time) and FFP requirements during the transplant procedure (**Table 3**). Both donor and recipient age, preoperative MELD-score and serum creatinine levels were not identified as predictors. The score points, calculated for the AKI Prediction Score ranged from 0 to 25 points (**Table 3**). The strongest predictor was FFP requirements (0, 6, 8, or 10 points), followed by the duration of recipient WIT (0 or 7 points), recipient BMI (0 or 4 points), donor BMI (0 or 3 points) and the use of DCD graft (0 or 1 point). The C-statistic of this model was 0.70 (**Figure 1A**) and the Hosmer-Lemeshow Goodness-of-fit test had a p-value of 0.664. In addition, the cumulative incidence of severe AKI increased exponentially with each single point of the AKI Prediction Score and recipients were divided into three risk groups: low risk (0-10 points), intermediate risk (11-20 points) and high risk (>20 points). Sixty-two percent of the recipients in the high risk group developed severe AKI, compared to 39% and 23% in the intermediate and low risk group, respectively (**Figure 1B**).



**Figure 1-** (A) ROC curve analysis and (B) The incidence of severe AKI according to the risk groups of the AKI Prediction Score.

### The AKI Prediction Score and other outcomes

Hepatic IRI and subsequent early dysfunction of the graft are a known risk factors for AKI and we therefore analysed these outcomes according to the AKI Prediction Score. As expected, the surrogate marker for severity of hepatic IRI, peak serum AST levels increased significantly with the score (**Table 4**). In addition, EAD was observed in 32%, 40%, and 62% in the low, intermediate, and high risk group, respectively ( $p < 0.001$ ). Importantly, primary non-function (PNF) was more frequently observed in the higher risk groups (low 1%; intermediate 2%; high risk 5%;  $p = 0.002$ ). And 90-day graft loss occurred more often in recipients with an overall higher risk (low

**Table 4 - Other recipient outcomes after liver transplantation in relation to the risk groups of the AKI Prediction Score.**

AKI Prediction Score	Low risk	Intermediate risk	High risk	P-value
Peak AST (n=1098)	753 (304-1550)	1048 (374-2218)	1684 (886-3040)	<0.001
Early allograft dysfunction	175 (32%)	229 (40%)	70 (62%)	<0.001
Primary non function*	4 (1%)	11 (2%)	6 (5%)	0.002
Severe complication**	129 (24%)	170 (30%)	46 (41%)	0.001
Comprehensive Complication Index***	20.9 (0-40.5)	22.6 (8.7-43.3)	24.2 (8.7-48.1)	0.007
Comprehensive Complication Index >30	187 (34%)	218 (38%)	52 (46%)	0.049
ICU length of stay	2 (2-4)	3 (2-6)	4 (2-7)	<0.001
Hospital length of stay	12 (8-18)	11 (8-18)	13 (9-23)	0.264
90-day graft loss	38 (7%)	37 (7%)	18 (16%)	0.002

\* Severe graft dysfunction resulting in death or retransplantation within 7 days after initial liver transplantation

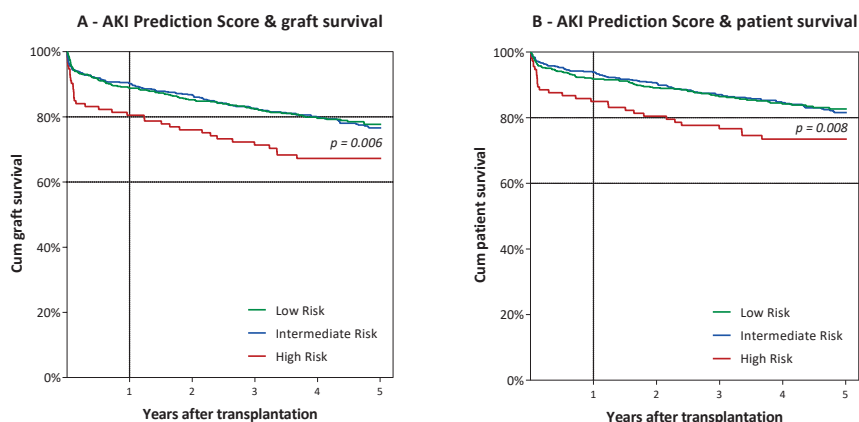
\*\* Defined as a Clavien Dindo classification grade 3B complication in the first 30 postoperative days

\*\*\* Comprehensive Complication Index in the first 30 postoperative days

Continuous variables are displayed as median and interquartile range.

AST, aspartate transaminase; ICU, intensive care unit; INR, international normalized ratio

7%; intermediate 7%; high risk 16%;  $p=0.002$ ). An additional analysis of postoperative complications showed that recipients with a higher AKI Prediction Score had more severe complications (low 24%; intermediate 30%; high risk 41%;  $p=0.001$ ). In accordance with the increasing overall risk, the sum of early post-transplant complications, as expressed by the 30-day CCI was significantly higher in the groups with

**Figure 2 - AKI Prediction Score risk groups and (A) graft survival and (B) patient survival after liver transplantation.**

more risk (low 20.9; intermediate 22.6; high risk; 24.2;  $p=0.007$ ). The long-term graft and patient survival followed a similar pattern. The 5-year graft survival for recipients in the low (79%) and intermediate risk (77%) group was similar, while recipients in the high risk group has a significant lower graft survival (67%) ( $p=0.006$ ) (**Figure 2A**). Comparable results were observed for patient survival after 5 years (low 83%; intermediate 82%; high risk 74%;  $p=0.008$ ) (**Figure 2B**).

### AKI Prediction Score and Immunosuppression

The majority of recipients (81%) received a Tacrolimus-based immunosuppression from day 0 and 19% started with a renal-sparing treatment with MMF from day 0 and Basiliximab on day 0 and 4 combined with a delayed introduction of Tacrolimus on day 3-5 (**Table 5**). Overall, recipients with a standard immunosuppression protocol had better pre-transplant kidney function (eGFR 89 vs. 77 mL/min/1.73 m<sup>2</sup>;  $p<0.001$ ). This difference was even more pronounced in recipients classified as intermediate and high risk ( $>10$  score points; eGFR 87 vs. 67 mL/min/1.73 m<sup>2</sup>;  $p<0.001$ ). We analysed the differences in immunosuppression for recipients with a low risk for AKI (0-10 points) compared to recipients with intermediate and high risk ( $>10$  points). In the Low Risk group, significantly less recipients experience AKI when they received the renal sparing regimen (11 vs. 30%;  $p<0.001$ ). A similar pattern was observed comparing the intermediate/high risk group (29% vs. 45%;  $p=0.007$ ).

**Table 5** - Development of acute kidney injury after liver transplantation according to immunosuppression regimens in different AKI Prediction Score risk groups.

	Pre-transplant eGFR (mL/min/1.73 m <sup>2</sup> )	No/mild AKI	Severe AKI	p-value*
<b>All recipients (n=1227)</b>				<0.001
Tacrolimus based	89	607 (61%)	389 (39%)	
MMF / Basiliximab / Delayed Tacrolimus	77	194 (83%)	40 (17%)	
<b>AKI Prediction Score: 0-10 points</b>				<0.001
Tacrolimus based	91	276 (70%)	118 (30%)	
MMF / Basiliximab / Delayed Tacrolimus	85	136 (90%)	16 (11%)	
<b>AKI Prediction Score: &gt;10 points</b>				0.007
Tacrolimus based	87	331 (55%)	721 (45%)	
MMF / Basiliximab / Delayed Tacrolimus	67	58 (71%)	24 (29%)	

\* p-value displays the statistical difference in severe AKI between the three immunosuppression regimens.

## DISCUSSION

Acute kidney injury in the setting of liver transplantation is increasingly recognized and in focus by many. We here present a new prediction model for the development of AKI after liver transplantation and show the following new findings. First, the AKI Prediction Score is an easy-to-use tool to assess the individual recipient risk of AKI development based on the combination of donor, recipient and surgical risk factors. Second, the new model stratifies recipients into three risk groups (low, intermediate and high risk) and correlated well with an impaired graft function and overall post-transplant morbidity and graft loss. Third, the AKI Prediction Score is readily available at the end of the transplant procedure, enabling doctors to use the score to avoid further nephrotoxicity through immunosuppression and therefore reduce complications and improve general outcomes.

Post-transplant AKI is an important risk factor for development of CKD, especially if candidates require RRT in the early post-transplant phase (5,6,10). Recipient with AKI also have an increased mortality-risk in the short and long-term (33–36). The high incidence of this complication and its multifactorial origin motivated us to develop a new score, that identifies recipients at risk for AKI combining donor, recipient and surgical characteristics. The strongest predictor in the new score was the requirement of FFP transfusions during the transplant procedure. This was not unexpected, as significant blood loss during the hepatectomy phase is common recipients which carry a higher risk due to coagulopathy and portal hypertension. Additionally, coagulopathy and fibrinolysis represent severe hepatic IRI and impaired early graft function (24,37,38). Other predictors in our model with negative impact on graft function and subsequent kidney injury were a higher donor BMI, a prolonged implantation of the graft (recipient WIT) and the use of a DCD graft. Such three factors have been previously identified as risk factors for AKI after liver transplantation by many (1,16,17,39). Donor BMI serves as surrogate marker of graft steatosis and fatty livers are known to be more susceptible to hepatic IRI (40–42). Prolonged graft implantation times impair the graft function further and lead to a more severe AKI, expectedly (1,12,39). In addition, the obligatory DWIT in DCD liver transplantation aggravates the injury to these grafts and the subsequent risk for postoperative AKI (8,28,43). The fifth predictor in the model was obesity of the recipient ( $\text{BMI} > 30 \text{ kg/m}^2$ ), which is a known factor to increase the risk for postoperative AKI in general and after liver transplantation (6,16,44,45). Although preoperative recipient serum creatinine levels and MELD-score have been identified as risk factors for AKI after liver transplantation in previous studies, they were found to predict AKI not significant predictors our

cohort. This could be the result of a generally increased use of marginal grafts in our centres, which might have a more significant impact on AKI (1). Also, recipients with HRS (with subsequent elevated serum creatinine levels) prior to liver transplantation, may improve their kidney function in the early period after liver transplantation.

In addition to the 25-point system of the score, we stratified the recipients into three clusters of low, intermediate and high risk, where severe AKI was observed in 23%, 39% and 63%, respectively. Post-transplant AKI was often simultaneously observed with severe hepatic IRI, EAD and other complications (10,13–15,19). Such results by others were also paralleled by our study. Graft injury and initial graft function, displayed by transaminase release and incidence of EAD, worsened with increasing score points. In addition, the incidence of PNF and other complications increased with higher risk in the AKI Prediction Score. Second, the overall postoperative morbidity was also in parallel with the risk of the three clusters with significantly more severe complications and a higher CCI during hospital stay. Third, recipients with a low and intermediate risk had comparable long-term graft and recipient survival rates, while recipients with a high risk according to the AKI Prediction Score, had impaired graft and recipient survival rates.

This is not the first score to predict the risk for AKI after liver transplantation, however it is the largest deceased-donor population and the first score assessing the impact of graft quality. In 2017, Park and colleagues developed a risk score for recipients of a living-donor transplant in a Korean centre (16). In general, the incidence of AKI is lower with the use of living-donor grafts and only 8% of the recipients had severe AKI in this cohort. This is in line with our results, where we observed that higher risk grafts induce more AKI in the recipients. In addition, the Park model required ten variables, including postoperative serum glucose levels and the type of immunosuppression regimen. Another risk score from a large Chinese multicentre study mostly included DCD grafts (17). The authors developed here a model involving postoperative predictors, such as the immunosuppression protocol and dopamine treatment. Importantly, both models used the old RIFLE-criteria (and not the most recent KDIGO-criteria) to classify AKI, which appear not as standard over the last years. However, both scores achieved a slightly better discrimination in the C statistic, however direct comparison appeared difficult, since too many variables were required and our score did not include any postoperative predictors. This is a major advantage of our AKI Prediction Score, as it is directly available at the end of the transplant procedure. This allows the physicians to adapt the immunosuppression in recipients with a higher risk of severe AKI. Our results showed that in recipients with more than score 10 points who receive

a renal sparing immunosuppression regimen had significantly less often severe AKI compared to recipients receiving a standard regimen with Tacrolimus starting at day 0. Another opportunity with timely AKI risk prediction is early initiation of RRT, given there is evidence that in critically ill patients an early initiation of RRT reduces mortality and fosters early recovery of renal function (46).

Our prediction model has several limitations. First, we only used five predictors in our score and a larger, more heterogeneous cohort might have identified more predictors. However, our two-centre cohort of two European centres yielded more than 1200 recipients and due to the use of our own datasets, we did not have any missing values, as common in large national registries. The five predictors are likely available in every transplant centre and cohort, making this score simple and easy to use. Next, severe AKI (KDIGO stage 2 & 3) is an arbitrary threshold, however previous studies have shown that severe forms of AKI have the strongest relation with long-term survival rates and development of CKD (5,12,28). Third, it should be noted we excluded recipients with severe pre-transplant renal dysfunction requiring RRT. Such recipients have a different risk pattern of post-transplant kidney problems and depending on their origin of their renal failure, they either receive peri-operative RRT or receive a combined liver-kidney transplant. Therefore, we considered these recipients not suitable as a baseline cohort to develop a new score.

In conclusion, the AKI Prediction Score is a new and simple tool to support transplant professionals in assessing the risk for recipients who develop AKI with good discriminative characteristics. This new model is highly predictive for other postoperative issues, including impaired graft function and severe complications. The great advantage of this score is that it is timely available at the end of the transplant procedure to avoid further postoperative renal injury.

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