Acute Kidney Injury in Liver Failure

CCCF 2017

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DISCLOSURES

• Current Sources of Funding
  NIH/NIDDK U01 58369
• US Acute Liver Failure Study Group (Co-PI)
Objectives

1. Describe the pathophysiological basis of hepatorenal syndrome
2. Review updated clinical definitions of AKI in cirrhosis and examine the role of etiology of AKI on natural history of cirrhotic patients in the presence/absence of liver transplant (LT).
3. Examine the potential role for novel biomarkers in assessing AKI in cirrhosis and in prognostication.
4. Review therapeutic interventions to manage and reverse hepatorenal syndrome (HRS-AKI) in cirrhosis.
5. Examine the benefits of CRRT in Acute Liver Failure (ALF)
Four related pathways initiated by hepatic decompensation:

1. Hyperdynamic circulation and ↓ PVR
2. Stimulation of neuro-hormonal compensation in the renal circulation (i.e., RAAS; SNS; ADH)
3. Cardiac dysfunction (cirrhotic cardiomyopathy) compounding circulatory derangements and kidney hypoperfusion
4. Inflammatory/vasoactive mediator induced direct renal injury and indirect effects on renal vascular circulation
Renal Blood Flow in Cirrhosis

n=70 cirrhotic patients

↓Renal BF before ascites, hyponatremia and AKI

Ring-Larsen et al Scand J Clin Lab Invest 1977
Traditional approach to AKI in Cirrhosis

AKI (serum creatinine >1.5 mg/dL)

- Volume depletion or Vasodilators
  - PRERENAL FAILURE
    - Shock
  - ACUTE TUBULAR NECROSIS

- Nephrotoxic drugs (NSAIDs)
  - NEPHROTOXICITY
    - Active sediment, proteinuria and/or hematuria
      - PARENCHYMAL NEPHROPATHY
        - Signs of infection
          - Septic Shock
        - Abnormal renal ultrasonography
          - HEPATORENAL SYNDROME

Ginès P et al., Lancet 2003
Box 1. Diagnostic criteria of hepatorenal syndrome (HRS) type of acute kidney injury (AKI) in patients with cirrhosis

HRS-AKI

- Diagnosis of cirrhosis and ascites
- Diagnosis of AKI according to ICA-AKI criteria
- No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin 1 g per kg of body weight
- Absence of shock
- No current or recent use of nephrotoxic drugs (NSAIDs, aminoglycosides, iodinated contrast media, etc.)
- No macroscopic signs of structural kidney injury*, defined as:
  - absence of proteinuria (>500 mg/day)
  - absence of microhaematuria (>50 RBCs per high power field),
  - normal findings on renal ultrasonography

*Patients who fulfil these criteria may still have structural damage such as tubular damage. Urine biomarkers will become an important element in making a more accurate differential diagnosis between HRS and acute tubular necrosis.

ICA, International Club of Ascites; NSAIDs, non-steroidal anti-inflammatory drugs; RBCs, red blood cells.
# Diagnosis and management of acute kidney injury in patients with cirrhosis: Revised consensus recommendations of the International Club of Ascites

Paolo Angeli¹,*, Pere Ginès²,₃,₄,₅, Florence Wong⁶, Mauro Bernardi⁷, Thomas D. Boyer⁸, Alexander Gerbes⁹, Richard Moreau¹₀,₁¹,₁₂, Rajiv Jalan¹³, Shiv K. Sarin¹⁴, Salvatore Piano¹, Kevin Moore¹⁵, Samuel S. Lee¹⁶, Francois Durand¹⁷,₁₈, Francesco Salerno¹⁹, Paolo Caraceni¹⁷, W. Ray Kim²⁰, Vicente Arroyo²,₃,₄, Guadalupe Garcia-Tsao²¹

<table>
<thead>
<tr>
<th>Subject</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline sCr</strong></td>
<td>A value of sCr obtained in the previous 3 months, when available, can be used as baseline sCr. In patients with more than one value within the previous 3 months, the value closest to the admission time to the hospital should be used. In patients without a previous sCr value, the sCr on admission should be used as baseline.</td>
</tr>
</tbody>
</table>
| **Definition of AKI** | - Increase in sCr ≥0.3 mg/dl (≥26.5 µmol/L) within 48 hours; or,  
  - A percentage increase in sCr ≥50% from baseline which is known, or presumed, to have occurred within the prior 7 days                                                                 |
| **Staging of AKI**    | - **Stage 1**: increase in sCr ≥0.3 mg/dl (26.5 µmol/L) or an increase in sCr ≥1.5-fold to 2-fold from baseline  
  - **Stage 2**: increase in sCr >2-fold to 3-fold from baseline  
  - **Stage 3**: increase of sCr >3-fold from baseline or sCr ≥4.0 mg/dl (353.6 µmol/L) with an acute increase ≥0.3 mg/dl (26.5 µmol/L) or initiation of renal replacement therapy |
| **Progression of AKI**| - **Progression**: Progression of AKI to a higher stage and/or need for RRT  
  - **Regression**: Regression of AKI to a lower stage                                                                                             |
| **Response to treatment** | - **No response**: No regression of AKI  
  - **Partial response**: Regression of AKI stage with a reduction of sCr to ≥0.3 mg/dl (26.5 µmol/L) above the baseline value  
  - **Full response**: Return of sCr to a value within 0.3 mg/dl (26.5 µmol/L) of the baseline value                                          |
<table>
<thead>
<tr>
<th>AKI Definition</th>
<th>AKI Stage</th>
<th>Serum Creatinine Criteria</th>
<th>AKI Stage</th>
<th>Urine Output Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RIFLE</strong> (2004)&lt;sup&gt;69&lt;/sup&gt;</td>
<td>1 (Risk)</td>
<td>↑ sCr ≥1.5 × baseline, within 7 d; or GFR ↑ &gt;25%; or urine output (UO) &lt;0.5 mL/kg/h × 6 h</td>
<td>2 (Injury)</td>
<td>↑ 1.5 × baseline or GFR ↑ &gt;25%</td>
</tr>
<tr>
<td></td>
<td>3 (Failure)</td>
<td></td>
<td></td>
<td>↑ 3 × baseline or sCr &gt;4 mg/dL (354 μmol/L) with an acute increase &gt;0.5 mg/dL (44 μmol/L) or GFR ↑ &gt;75%</td>
</tr>
<tr>
<td><strong>AKIN</strong> (2007)&lt;sup&gt;31&lt;/sup&gt;</td>
<td>1 (Risk)</td>
<td>↑ sCr ≥0.3 mg/dL (26.5 μmol/L) within 48 h; or ↑ sCr ≥1.5 × baseline, within 48 h; or UO &lt;0.5 mL/kg/h × 6 h</td>
<td>2 (Injury)</td>
<td>↑ ≥0.3 mg/dL (&gt;26.5 μmol/L) within 48 h or ≥1.5–2 × baseline</td>
</tr>
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<td></td>
<td>3 (Failure)</td>
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<td></td>
<td>↑ 3 × baseline or sCr &gt;4 mg/dL (354 μmol/L) with an acute increase &gt;0.5 mg/dL (44 μmol/L) or on RRT</td>
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<td><strong>KDIGO</strong> (2012)&lt;sup&gt;70&lt;/sup&gt;</td>
<td>1 (Risk)</td>
<td>↑ sCr ≥0.3 mg/dL (26.5 μmol/L) within 48 h; or ↑ sCr ≥1.5 × baseline, which is known or presumed to have occurred within the prior 7 d; or UO &lt;0.5 mL/kg/h for 6 h</td>
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<td><strong>ADQI</strong> (2010)&lt;sup&gt;12&lt;/sup&gt;</td>
<td>1 (Risk)</td>
<td>↑ sCr ≥0.3 mg/dL (26.5 μmol/L) within 48 h; or ↑ sCr ≥1.5 × baseline, which is known or presumed to have occurred within the prior 7 d; or UO &lt;0.5 mL/kg/h for 6 h</td>
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<td></td>
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<td><strong>ICA</strong> (2015)&lt;sup&gt;16&lt;/sup&gt;</td>
<td>1 (Risk)</td>
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<td><strong>AKI in cirrhosis</strong></td>
<td>3 (Failure)</td>
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<td></td>
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</tr>
</tbody>
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Angeli et al, J Hepatol 2015
Karvellas et al, Crit Care Clin 2015
Cirrhosis-associated AKI

- 50% increase in Cr level baseline in <6 months
- increase of 0.3 mg/dL in <48 hours.
- 337 cirrhotics admitted with infection
  - 30-day mortality was 10-fold higher if irreversible AKI present (vs. no AKI)
  - accurately predicted 30-day mortality, length of hospital stay, and organ failure (21).

Sensitivity 82%
Specificity 59%
NPV 93%
562 cirrhotic patients over 6 years
  - AKI, stratified into 4 groups

Incidence/mortality
  - Infection/sepsis (46%; 69%)
  - Hypovolemia (32%; 54%)
  - HRS (13%; 85%)
  - Parenchymal (9%; 27%)

90 day mortality → worse for HRS
  - adj-HR 3.48 (1.48-8.17)

HRS independently associated with 90 mortality after adjusting for MELD, Na and HE
Etiology and severity of AKI impact mortality in cirrhotic/ACLF patients

A: Stage 1 AKI, SCr < 1.5 mg/dl (low Urine output only)
B: Stage 1 AKI, SCr > 1.5 mg/dl
C: Stage 2/3 AKI (> 2x baseline)
# Methods of assessing renal function in liver disease

<table>
<thead>
<tr>
<th></th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum based methods</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Creatinine</td>
<td>• Universally available</td>
<td>• Affected by age, gender, muscle mass, steroids, medications</td>
</tr>
<tr>
<td></td>
<td>• Inexpensive</td>
<td>• Decreased generation in liver disease</td>
</tr>
<tr>
<td></td>
<td>• MELD/AKI scores, current HRS definitions use this</td>
<td>• Bilirubin effect on assay</td>
</tr>
<tr>
<td></td>
<td>• Affected by age, gender, muscle mass, sepsis</td>
<td>• Lack of standardization of creatinine assay</td>
</tr>
<tr>
<td></td>
<td>• Simple blood test</td>
<td>• Slow to rise in AKI</td>
</tr>
<tr>
<td>Serum Cystatin C</td>
<td>• Not affected by age, gender, muscle mass, sepsis</td>
<td>• Underestimates GFR post transplant</td>
</tr>
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<td></td>
<td>• Simple blood test</td>
<td>• Dilution as with all serum markers</td>
</tr>
<tr>
<td></td>
<td>• Appears to detect early kidney dysfunction and AKI earlier than serum creatinine</td>
<td>• Variable performance of Cystatin C</td>
</tr>
<tr>
<td>Urine based methods</td>
<td></td>
<td>• Variable expense</td>
</tr>
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<td>Urinary creatinine clearance</td>
<td>• Inexpensive</td>
<td>• Results may not be available on a timely fashion</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Serum based methods**

- **Serum Creatinine**
  - Universally available
  - Inexpensive
  - MELD/AKI scores, current HRS definitions use this
  - Affected by age, gender, muscle mass, steroids, medications
  - Decreased generation in liver disease
  - Bilirubin effect on assay
  - Lack of standardization of creatinine assay
  - Slow to rise in AKI

- **Serum Cystatin C**
  - Not affected by age, gender, muscle mass, sepsis
  - Simple blood test
  - Appears to detect early kidney dysfunction and AKI earlier than serum creatinine
  - Underestimates GFR post transplant
  - Dilution as with all serum markers
  - Variable performance of Cystatin C
  - Variable expense
  - Results may not be available on a timely fashion

**Urine based methods**

- **Urinary creatinine clearance**
  - Inexpensive
  - Avoids dilution issues of serum markers
  - Systematically Overestimates GFR in liver disease by 10-15% especially in pts with chronic kidney disease
  - Difficult to get accurate collections
It is difficult to demonstrate a reduction in GFR in cirrhosis with creatinine alone!

Fig. 1. Relationship between glomerular filtration rate (inulin clearance) and serum creatinine in patients with cirrhosis and ascites.
ARE THERE BETTER MARKERS THAN Creatinine and Urine output?

- Assessment of AKI?
- Differentiate etiology of AKI
  - Prerenal azotemia, hepatorenal syndrome, ATN
- Cirrhotics/Acute on Chronic Liver Failure (ACLF)
  - Determinants of mortality in absence of transplant
- Post-transplant
  - Predictors of renal recovery/reversibility of AKI
  - Predictors of mortal post transplant
Urinary neutrophil gelatinase-associated lipocalin as biomarker in the differential diagnosis of impairment of kidney function in cirrhosis

Claudia Fagundes, Marie-Noëlle Pépin, Mónica Guevara, Rogelio Barreto, Gregori Casals, Elsa Solà, Gustavo Pereira, Ezequiel Rodríguez, Elisabet García, Verónica Prado, Esteban Poch, Wladimiro Jiménez, Javier Fernández, Vicente Arroyo, Pere Giné

A B

Pre-renal azotemia
Chronic kidney disease
Hepatorenal syndrome
Acute tubular necrosis

Urine

Plasma

Urine NGAL (µg/g creatinine)

Plasma NGAL (ng/ml)

Fig. 1. Box-plot of (A) urine and (B) plasma neutrophil gelatinase-associated lipocalin (NGAL) levels according to the four different causes of impairment of kidney function. The boxes represent the 25th percentile (bottom line), median (middle line), and 75th percentile (top line) values, whereas the whiskers are the lowest datum still within 1.5 IQR of the lower quartile, and the highest datum still within 1.5 IQR of the upper quartile. The Kruskal–Wallis test for each marker was: urine NGAL (p <0.0001) and plasma NGAL (p = 0.31). \(^*p = 0.029\) vs. pre-renal azotemia. \(^{b}p <0.01\) vs. all other groups.

Urinary NGAL
HRS vs. PRA p=0.029
ATN vs. all others, p <0.01

PRA n=16
CKD n=14
HRS n=33
ATN n= 21
Kidney Biomarkers and Differential Diagnosis of Patients With Cirrhosis and Acute Kidney Injury

Justin M. Belcher,¹,²,³ Arun J. Sanyal,⁴ Aldo J. Peixoto,²,⁵ Mark A. Perazella,²,⁵ Joseph Lim,⁶ Heather Thiessen-Philbrook,⁷ Naheed Ansari,⁸ Steven G. Coca,¹,²,³ Guadalupe Garcia-Tsao,⁵,⁶ and Chirag R. Parikh,¹,²,³ for the TRIBE-AKI Consortium

Urinary biomarkers (renal tubular injury)
NGAL
IL-18
Kidney-injury molecule-1 (KIM-1)
L-FABP
Kidney Biomarkers and Differential Diagnosis of Patients With Cirrhosis and Acute Kidney Injury

Justin M. Belcher,1,2,3 Arun J. Sanyal,4 Aldo J. Peixoto,2,5 Mark A. Perazella,2,5 Joseph Lim,6 Heather Thiessen-Philbrook,7 Naheed Ansari,8 Steven G. Coca,1,2,3 Guadalupe Garcia-Tsao,5,6 and Chirag R. Parikh,1,2,5 for the TRIBE-AKI Consortium

Table 4. Association Between Biomarker Panel and the Diagnosis of ATN

<table>
<thead>
<tr>
<th>Relative Risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Markers Positive</td>
</tr>
<tr>
<td>1 Marker Positive</td>
</tr>
<tr>
<td>2 Markers Positive</td>
</tr>
<tr>
<td>3 Markers Positive</td>
</tr>
<tr>
<td>4 Markers Positive</td>
</tr>
</tbody>
</table>

Biomarker cutoffs: NGAL, 365 ng/mL; IL-18, 85 pg/mL; L-FABP, 25 ng/mL; Albumin 44 mg/dL.

*Unadjusted.

Abbreviations: ATN, acute tubular necrosis.
More likely to have CKD post LT if ATN present pre-LT
ATN (Non-HRS AKI) impacts post-LT mortality
Table 3. Statistically Significant Plasma Protein Differences Between nAKI, iAKI, and rAKI Validation Groups*

<table>
<thead>
<tr>
<th>Group and Protein Comparison</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>nAKI vs. iAKI</td>
<td></td>
</tr>
<tr>
<td>Cystatin C</td>
<td>0.004</td>
</tr>
<tr>
<td>NGAL</td>
<td>0.0363</td>
</tr>
<tr>
<td>TFF-3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VEGF</td>
<td>0.008</td>
</tr>
<tr>
<td>nAKI vs. rAKI</td>
<td></td>
</tr>
<tr>
<td>Cystatin C</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>KIM-1</td>
<td>0.0024</td>
</tr>
<tr>
<td>NGAL</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>OPN</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TIMP-1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TFF-3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VEGF</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>rAKI vs. iAKI</td>
<td></td>
</tr>
<tr>
<td>OPN</td>
<td>0.0091</td>
</tr>
<tr>
<td>TIMP-1</td>
<td>0.0194</td>
</tr>
</tbody>
</table>

Table 4. Logistic Regression Models Predicting Reversible AKI: Clinical and Protein Variables and Their Coefficients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Clinical-Covariate-Only Model</th>
<th>Protein-Only Model</th>
<th>Combined-Data Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age status (age &gt;57)</td>
<td>-2.77</td>
<td>-4.65</td>
<td></td>
</tr>
<tr>
<td>Diabetes (yes)</td>
<td>-2.46</td>
<td>-2.28</td>
<td></td>
</tr>
<tr>
<td>OPN</td>
<td>2.47</td>
<td>1.17</td>
<td></td>
</tr>
<tr>
<td>TIMP-1</td>
<td>0.80</td>
<td>3.54</td>
<td></td>
</tr>
</tbody>
</table>

OPN ~ osteopontin
TIMP-1 ~ tissue inhibitor of metaloproteinase-1

nAKI ~ no AKI
rAKI ~ reversible AKI post-LT
iAKI ~ irreversible AKI post-LT
Therapies for HRS-AKI

Splanchnic vasoconstrictor → Splanchnic and systemic vasoconstriction

Decreased renal vasoconstrictor systems → Decreased renal vasoconstriction

Increased GFR
A Randomized, Prospective, Double-Blind, Placebo-Controlled Trial of Terlipressin for Type 1 Hepatorenal Syndrome

ARUN J. SANYAL, THOMAS BOYER, GUADALUPE GARCIA-TSAO, FREDERICK REGENSTEIN, LORENZO ROSSARO, BEATE APPENROOT, ANDRES BLEI, VEIT GÜLBERG, SAMUEL SIGAL, PETER TEUBER, and The Terlipressin Study Group

N=56 Albumin 1 g/kg then 20-40 g/day
N=56 Terlipressin 1 mg IV q6h + Albumin

Treatment was continued to day 14 unless
• Success: ↓SCr level to ≤1.5 mg/dL for ≥ 48 hours by day 14
• Failure: Death, dialysis, or transplantation

HRS Reversal 34% vs 13% (p=0.008)

No mortality benefit
Terlipressin Plus Albumin Is More Effective Than Albumin Alone in Improving Renal Function in Patients With Cirrhosis and Hepatorenal Syndrome Type 1

Thomas D. Boyer,1 Arun J. Sanyal,2 Florence Wong,3 R. Todd Frederick,4 John R. Lake,5 Jacqueline G. O'Leary,6 Daniel Ganger,7 Khurram Jamil,3 Stephen Chris Pappas,8 and the REVERSE Study Investigators

N=99
Albumin 1 g/kg then 20-40 g/day
N=97
Terlipressin 1 mg IV q6h + Albumin

Treatment was continued to day 14 unless
• Success: ↓SCr level to ≤1.5 mg/dL for ≥ 48 hours by day 14
• Failure: Death, dialysis, or transplantation

HRS Reversal 24% vs 15% (p=0.13)

No mortality benefit
Terlipressin versus Norepinephrine in the Treatment of Hepatorenal Syndrome: A Systematic Review and Meta-Analysis

Antonio Paulo Nassar Junior¹, Alberto Queiroz Farias², Luiz Augusto Carneiro d’ Albuquerque³, Flair José Carrilho², Luiz Marcelo Sá Malbouisson¹

REVERSAL OF HRS: Norepinephrine vs. Terlipressin

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>Treatment</th>
<th>Control</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alessandria et al. 2007</td>
<td>0.84 (0.52, 1.36)</td>
<td>7/10</td>
<td>10/12</td>
<td>24.91</td>
<td></td>
</tr>
<tr>
<td>Sharma et al. 2008</td>
<td>1.00 (0.54, 1.86)</td>
<td>10/20</td>
<td>10/20</td>
<td>14.83</td>
<td></td>
</tr>
<tr>
<td>Singh et al. 2012</td>
<td>1.11 (0.56, 2.22)</td>
<td>10/23</td>
<td>9/23</td>
<td>11.94</td>
<td></td>
</tr>
<tr>
<td>Ghosh et al. 2013</td>
<td>1.00 (0.71, 1.41)</td>
<td>17/23</td>
<td>17/23</td>
<td>48.32</td>
<td></td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.904)</td>
<td>0.97 (0.76, 1.23)</td>
<td>44/76</td>
<td>46/78</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

NE vs. Terlipressin in HRS:
No difference in mortality or rates of HRS reversal
More importance was HRS reversal than agent
Cirrhosis vs. ALF: Not the same

Cirrhosis/Acute on Chronic Liver Failure
- Scarring/fibrosis
- Portal hypertension
- ACLF
  - Cirrhosis with acute deterioration in liver function over 2-4 weeks
    - Hepatic encephalopathy (HE)
    - Hepatorenal syndrome (HRS)
    - Variceal bleeding

Acute Liver Injury/Failure
- Hepatocyte necrosis
- Pro-inflammatory cascade
- NO portal hypertension
- No prior liver disease
- Encephalopathy and jaundice
- Complications
  - Cerebral edema, lactic acidosis, MSOF
CRRT: Ammonia clearance in ALF

Figures 1a and 1b. RRT on days 1 and 2 and ammonia dynamics from days 1 to 3 post study admission (n=340 ALF patients).
CRRT in ALF: Improved survival without LT

### TABLE 4. Association of Renal Replacement Therapy Use on Day 1 With 21-Day Post Study Admission Transplant-Free All-Cause Mortality for Patients With ALF (n = 1,186)

<table>
<thead>
<tr>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>aOR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Year of admission (2007-2016 vs. 1998-2006)</td>
<td>0.48 (0.34-0.68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>1.04 (1.03-1.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>APAP</td>
<td>0.28 (0.20-0.41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IMV</td>
<td>2.34 (1.60-3.42)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vasopressors</td>
<td>3.67 (2.38-5.67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>INR</td>
<td>1.28 (1.17-1.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.10 (1.00-1.21)</td>
<td>0.041</td>
</tr>
<tr>
<td>Ammonia (μmol/L)</td>
<td>1.004 (1.002-1.006)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RRT</td>
<td>0.99 (0.64-1.51)</td>
<td>0.95</td>
</tr>
<tr>
<td>IRR</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>CRRT</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
AKI in Liver Failure: Conclusions

- **HRS-AKI** impacts mortality significantly in the absence of liver transplant (LT).
- Vasoconstrictor therapies are associated with reversal of HRS but do not impact mortality in the absence of LT.
- **Non-HRS AKI (ATN):** ↑ rates of CKD and ↓ survival rates post-LT.
- Urinary and plasma biomarkers: may in the future assist in differentiating:
  - *Etiology of AKI* in cirrhotic patients (Urinary NGAL, IL-18, KIM-1)
  - *Reversibility of AKI post-LT* (osteopontin, TIMP-1)
- Acute liver failure: **CRRT** may improve outcome (decreased cerebral edema? Improved ammonia clearance), avoid IHD.