Supplementary Online Content


**eTable 1.** Advanced Inclusion Criteria for Dialysis Initiation

**eTable 2.** Subgroup Analysis of Patients Assigned to the Delayed Group

**eTable 3.** Characteristics of Renal Replacement Therapy

**eTable 4.** Analysis of Pro- and Anti-inflammatory Markers

**eTable 5.** Cox Regression Analysis of Cytokines

This supplementary material has been provided by the authors to give readers additional information about their work.
## eTable S1: Advanced inclusion criteria for dialysis initiation

<table>
<thead>
<tr>
<th></th>
<th>Early (n=112)</th>
<th>Delayed (n=119)</th>
<th>Absolute difference Early - Delayed [95% CI]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severe Sepsis, No. (%)</strong></td>
<td>34 (30.4)</td>
<td>41 (34.5)</td>
<td>-4.1% [-16.2%, 8.0%]</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>Catecholamines &gt; 0.1 µg/kg/min, No. (%)</strong></td>
<td>96 (85.7)</td>
<td>108 (90.8)</td>
<td>-5.0% [-13.4%, 3.3%]</td>
<td>0.23</td>
</tr>
<tr>
<td><strong>Fluid overload or worsening pulmonary edema, No. (%)</strong></td>
<td>82 (73.2)</td>
<td>93 (78.2)</td>
<td>-4.9% [-16.0%, 6.1%]</td>
<td>0.38</td>
</tr>
<tr>
<td><strong>Non renal SOFA Score &gt; 2, No. (%)</strong></td>
<td>102 (91.1)</td>
<td>112 (94.1)</td>
<td>-3.1% [-9.8%, 3.7%]</td>
<td>0.38</td>
</tr>
<tr>
<td><strong>Number of advanced inclusion criteria, No. (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.50</td>
</tr>
<tr>
<td>1</td>
<td>10 (8.9)</td>
<td>7 (5.9)</td>
<td>3.1% [-3.7%, 9.8%]</td>
<td>0.38</td>
</tr>
<tr>
<td>2</td>
<td>28 (25.0)</td>
<td>23 (19.3)</td>
<td>5.7% [-5.0%, 16.4%]</td>
<td>0.30</td>
</tr>
<tr>
<td>3</td>
<td>48 (42.9)</td>
<td>55 (46.2)</td>
<td>-3.4% [-16.2%, 9.5%]</td>
<td>0.61</td>
</tr>
<tr>
<td>4</td>
<td>26 (23.2)</td>
<td>34 (28.6)</td>
<td>-5.4% [-16.6%, 5.9%]</td>
<td>0.35</td>
</tr>
</tbody>
</table>
Table S2: Sub-group analysis of the delayed group (n=119)

<table>
<thead>
<tr>
<th></th>
<th>Delayed (n=91)</th>
<th>Absolute indication* (n=17)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from KDIGO 2</td>
<td>25.0</td>
<td>27.0</td>
<td>0.97</td>
</tr>
<tr>
<td>to RRT, median (Q1, Q3), hours</td>
<td>(19.0, 40.0)</td>
<td>(14.0, 41.0)</td>
<td></td>
</tr>
</tbody>
</table>

**Primary endpoint**

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>90-day all cause mortality, No. (%)</td>
<td>53 (58.3)</td>
<td>9 (52.9)</td>
<td>0.91</td>
</tr>
</tbody>
</table>

**Key secondary endpoints**

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of RRT, median (Q1, Q3), days</td>
<td>36</td>
<td>12</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td>(7, -)</td>
<td>(5, 71)</td>
<td></td>
</tr>
<tr>
<td>ICU stay, median (Q1, Q3), days</td>
<td>17.0</td>
<td>9.0</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td>(9.8, 29.0)</td>
<td>(3.5, 39.0)</td>
<td></td>
</tr>
<tr>
<td>Hospital stay, median (Q1, Q3), days</td>
<td>43.0</td>
<td>38.0</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td>(25.5, 80.3)</td>
<td>(4.0, 92.5)</td>
<td></td>
</tr>
</tbody>
</table>

* Absolute indication for RRT: serum urea > 100 mg/dl; serum potassium > 6 mmol/l or with ECG abnormalities; serum magnesium > 4mmol/l d); urine production < 200 ml/12h or anuria (without diuretics, according to the KDIGO recommendations); and organ edema in the presence of AKI resistant to diuretic treatment (one attempt with loop diuretics prior to randomization)

1 Duration of RRT was censored at patients’ date of death or at day 90 where applicable, whatever occurred first.
**eTable S3: Characteristics of renal replacement therapy**

<table>
<thead>
<tr>
<th></th>
<th>Early (n=112)</th>
<th>Delayed (n=119)</th>
<th>Absolute difference Early - Delayed [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received RRT, No.</td>
<td>112</td>
<td>108</td>
<td></td>
</tr>
<tr>
<td>Blood flow per session,</td>
<td>110.15 ± 3.19</td>
<td>110.57 ± 5.27</td>
<td>-0.43 [-1.60, 0.75]</td>
</tr>
<tr>
<td>mean ± SD, ml/h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effluent volume per</td>
<td>26.6 ± 4.7</td>
<td>26.6 ± 5.8</td>
<td>0.0 [-1.5, 1.6]</td>
</tr>
<tr>
<td>session, mean ± SD, ml/kg/h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Session duration per day,</td>
<td>22.6 ± 1.7</td>
<td>22.4 ± 2.1</td>
<td>0.2 [-0.3, 0.8]</td>
</tr>
<tr>
<td>mean ± SD, hours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre filter BUN, mean ± SD</td>
<td>31.64 ± 11.53</td>
<td>39.54 ± 17.54</td>
<td>-7.91 [-11.86, -3.95]</td>
</tr>
<tr>
<td>Effluent UN, mean ± SD</td>
<td>30.06 ± 10.95</td>
<td>37.57 ± 16.66</td>
<td>-7.51 [-11.27, -3.75]</td>
</tr>
<tr>
<td>FUN/BUN-ratio, median (Q1, Q3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.96 (0.95, 0.97)</td>
<td>0.95 (0.95, 0.97)</td>
<td>0.05 [0.00, 0.01]</td>
</tr>
<tr>
<td>Urea mass removal rate [mg/min], median (Q1, Q3)</td>
<td>9.90 (7.42, 13.04)</td>
<td>11.82 (8.56, 16.60)</td>
<td>-1.76 [-3.22, -0.31]</td>
</tr>
<tr>
<td>Complications, Number of Individuals (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Air embolism</td>
<td>0</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>(0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheter insertion</td>
<td>4 (3.57)</td>
<td>2 (1.85)</td>
<td>1.72% [-2.56%, 5.99%]</td>
</tr>
<tr>
<td>complication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>2 (1.79)</td>
<td>1 (0.93)</td>
<td>0.86% [-2.19%, 3.91%]</td>
</tr>
<tr>
<td>Iatrogenic fluid or</td>
<td>2 (1.79)</td>
<td>0 (0)</td>
<td>1.79% [-0.67%, 4.24%]</td>
</tr>
<tr>
<td>electrolyte disturbance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0%</td>
</tr>
<tr>
<td>Seizures</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0%</td>
</tr>
<tr>
<td>Event</td>
<td>Control (0)</td>
<td>Case (0)</td>
<td>OR</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>-------------</td>
<td>----------</td>
<td>------</td>
</tr>
<tr>
<td>New onset of arrhythmia</td>
<td>1</td>
<td>0</td>
<td>0.89</td>
</tr>
<tr>
<td>Hypocalcemia (ionized calcium &lt; 1.0 mmol/L)</td>
<td>75</td>
<td>71</td>
<td>1.22</td>
</tr>
</tbody>
</table>

### Transition to other RRT modalities

<table>
<thead>
<tr>
<th>Transition Type</th>
<th>Control (0)</th>
<th>Case (0)</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No RRT</td>
<td>0 / 112</td>
<td>11 / 119</td>
<td>0.92</td>
<td>(-14.5%, -4.0%)</td>
</tr>
<tr>
<td>RRT w/o SLEDD/IHD</td>
<td>80 / 112</td>
<td>66 / 108</td>
<td>10.2</td>
<td>(-2.1%, 22.8%)</td>
</tr>
<tr>
<td>Transition to SLEDD alone,</td>
<td>25 / 112</td>
<td>32 / 108</td>
<td>-7.3</td>
<td>(-18.9%, 4.3%)</td>
</tr>
<tr>
<td>Transition to IHD alone,</td>
<td>2 / 112</td>
<td>2 / 108</td>
<td>0.1</td>
<td>(-3.6%, 3.5%)</td>
</tr>
<tr>
<td>Transition to SLEDD + IHD</td>
<td>5 / 112</td>
<td>8 / 108</td>
<td>-2.9</td>
<td>(-9.2%, 3.3%)</td>
</tr>
</tbody>
</table>

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### eTable S4: Analysis of pro- and anti-inflammatory markers

<table>
<thead>
<tr>
<th>Markers</th>
<th>Early, d0 (n=112)</th>
<th>Delayed, d0 (n=119)</th>
<th>Absolute difference Early - Delayed [95% CI]</th>
<th>p-value</th>
<th>Early, d1 (n=112)</th>
<th>Delayed, d1 (n=119)</th>
<th>Absolute difference Early - Delayed [95% CI]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIF, median (Q1, Q3), pg/ml</td>
<td>18471.6 (8423.4, 48146.4)</td>
<td>16675.2 (10155.6, 38407.2)</td>
<td>-98.4 [-4465.2, 4647.6]</td>
<td>0.79</td>
<td>14388.0 (6393.3, 28118.7)</td>
<td>15346.2 (7362.9, 30125.7)</td>
<td>-1132.2 [-4747.2, 2564.4]</td>
<td>0.89</td>
</tr>
<tr>
<td>IL-6, median (Q1, Q3), pg/ml</td>
<td>1218.3 (435.6, 2142.0)</td>
<td>871.1 (217.5, 1778.4)</td>
<td>224.9 [30.4, 467.9]</td>
<td>0.41</td>
<td>399.4 (116.5, 901.1)</td>
<td>989.3 (190.9, 2012.8)</td>
<td>-310.9 [-663.2, 93.3]</td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td>IL-8, median (Q1, Q3), pg/ml</td>
<td>344.0 (145.5, 568.1)</td>
<td>222.6 (71.8, 480.5)</td>
<td>73.0 [10.4, 143.5]</td>
<td>0.08</td>
<td>65.7 (28.0, 162.5)</td>
<td>215.5 (67.3, 373.7)</td>
<td>-105.9 [-160.6, 52.7]</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>IL-18, median (Q1, Q3), pg/ml</td>
<td>552.1 (270.7, 1137.7)</td>
<td>605.6 (309.7, 1386.1)</td>
<td>-49.4 [-178.8, 77.3]</td>
<td>0.46</td>
<td>518.4 (351.0, 1056.8)</td>
<td>603.9 (316.0, 1379.8)</td>
<td>-27.3 [-185.3, 101.9]</td>
<td>0.28</td>
</tr>
<tr>
<td>IL-10, median (Q1, Q3), pg/ml</td>
<td>51.6 (20.2, 211.2)</td>
<td>45.0 (17.2, 159.9)</td>
<td>3.9 [-7.9, 19.0]</td>
<td>0.68</td>
<td>27.0 (12.4, 73.1)</td>
<td>30.7 (13.0, 67.5)</td>
<td>-0.9 [-9.0, 6.5]</td>
<td>0.72</td>
</tr>
</tbody>
</table>

Day 0: blood samples were withdrawn at the time of randomization; day 1: blood samples were withdrawn 24 hours after randomization.
### eTable S5: Cox regression analysis of over-all mortality by cytokines

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 interleukin 6, per 1000pg/ml increase</td>
<td>1.24</td>
<td>1.04-1.48</td>
<td>0.02</td>
</tr>
<tr>
<td>Day 1 interleukin 8, per 1000pg/ml increase</td>
<td>2.01</td>
<td>1.34-3.00</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>