**Table S1.** Urinary [TIMP-2]\*[IGFBP7] over 10 time points after study inclusion in the first 22 patients

|  |  |  |  |
| --- | --- | --- | --- |
|  | **TIMP-2\*IGFBP7/1000 (ng/mL)2** | | |
| **h after inclusion** | **AKI 0/1 (IQR, n=6)** | **AKI 2/3 (IQR, n=7)** | **RRT (IQR, n=9)** |
| **0** | 0.190 (0.075, 0.293) | 0.400 (0.160, 1.060) | 6.210 (1.935, 11.680) |
| **12** | 0.180 (0.128, 0.360) | 0.410 (0.150, 7.280) | 3.585 (1.000, 31.220) |
| **24** | 0.055 (0.045, 0.132) | 0.225 (0.035, 8.733) | 4.715 (0.992, 21.210) |
| **36** | - | - | 0.910 (0.250, 1.810) |
| **48** | 0.100 (0.033, 0.355) | 0.070 (0.040, 0.550) | 0.470 (0.280, 26.65) |
| **60** | - | - | 1.330 (1.140, 1.520) |
| **72** | 0.125 (0.020, 0.313) | 0.130 (0.675, 0.350) | 0.120 (0.060, 1.270) |
| **96** | 0.100 (0.045, 0.208 | 0.220 (0.058, 0.533) | 0.280 (0.020, 2.210) |
| **120** | 0.040 (0.033, 0.100) | 0.190 (0.123, 0.888) | 0.350 (0.200, 2.010) |
| **168** | 0.050 (0.025, 0.323) | 0.925 (0.255, 1.513) | 0.080 (0.030, 0.130) |

AKI = acute kidney injure (AKI 0/1 = no or mild AKI, AKI 2/3 = moderate or severe AKI without RRT, RRT = need for RRT), IQR = interquartile range, [TIMP-2]\*[IGFBP7] = product of tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein

**Table S2.** Baseline characteristics (N=100)

|  |  |
| --- | --- |
| **Baseline characteristics** | **All patients (n=100)** |
| **Demographic characteristics** |  |
| **Age (yr), median (IQR)** | 66.00 (59.00, 74.75) |
| **Gender - no (%)** |  |
| **male** | 63 (63.0) |
| **female** | 37 (37.0) |
| **BMI (kg/m2), median (IQR)** | 27.13 (24.11, 31.44) |
| **Coexisting conditions - no (%)** |  |
| **CKD** | 33 (33.0) |
| **Hypertension** | 74 (74.0) |
| **Diabetes mellitus** | 33 (33.0) |
| **CHD** | 20 (20.0) |
| **Cancer** | 52 (52.0) |
| **SCr Baseline (mg/dL), median (IQR)** | 0.78 (0.61, 1.00) |
| **Time sepsis diagnosis to study inclusion (h), median (IQR)** | 10.00 (4.00, 13.88) |
| **Renal parameters, median (IQR)** |  |
| **Serum creatinine (mg/dL)** | 1.49 (0.93, 2.47) |
| **Cystatin C (mg/L)** | 1.65 (1.18, 2.41) |
| **Urea (mg/dL)** | 61.50 (41.00, 89.00) |
| **Proteinuria (g/l)** | 0.36 (0.16, 1.02) |
| **Albuminuria (mg/L)** | 37.00 (17.25, 232.50) |
| **Urinary creatinine (mg/dL)** | 40.39 (22.01, 67.08) |
| **Urinary osmolality (mosm/kg)** | 358.00 (323.00, 466.00) |
| **Inflammation parameters, median (IQR)** |  |
| **Leukocytes (1/nL)** | 12.97 (7.92, 22.06) |
| **CRP (mg/dL)** | 187.05 (144.45, 301.68) |
| **PCT (ng/mL)** | 7.09 (2.60, 28,26) |
| **Primary source of sepsis - no (%)** |  |
| **Abdomen** | 54 (54) |
| **Lung** | 22 (22) |
| **Urinary tract** | 6 (6) |
| **Others** | 7 (7) |
| **Combinations** | 11 (11) |
| **Scores, median (IQR)** |  |
| **SOFA** | 12.00 (9.00, 14.00) |
| **SAPS II** | 67.00 (51.00, 78.00) |
| **APACHE II** | 30.00 (25.00, 35.75) |

APACHE II = Acute Physiology and Chronic Health Evaluation II, BMI = body mass index, CHD = coronary heart disease, CKD = chronic kidney disease, CRP = C-reactive protein, IQR = interquartile range, N = number of analysed patients (see Fig. 1), PCT = procalcitonin, RRT = renal replacement therapy, SAPS II = Simplified Acute Physiology Score II, SOFA = Sequential Organ Failure Assessment.

**Table S3.** Outcome characteristics within seven days after study inclusion

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Outcome characteristics** | **All patients (n=94)** | **No RRT (n=75)** | **RRT (n=19)** | **P value** |
| **Renal parameters min. or max. values within 7d, median (IQR)** |  |  |  |  |
| **Serum creatinine max. (mg/dL)** | 1.64 (1.12, 2.89) | 1.46 (1.01, 2.26) | 3.12 (2.55, 3.87) | **<0.0001** |
| **Cystatin C max. (mg/L)** | 1.88 (1.37, 2.89) | 1.68 (1.26, 2.32) | 3.16 (2.62, 3.85) | **<0.0001** |
| **Urea max. (mg/dL)** | 61.00 (40.75, 89.00) | 56.00 (39.00, 72.00) | 98.00 (74.00, 127.00) | **<0.0001** |
| **Proteinuria max. (g/l)** | 0.85 (0.41, 1.26) | 0.67 (0.31, 1.17) | 2.17 (1.03, 5.86) | **<0.0001** |
| **Albuminuria max. (mg/L)** | 102.5 (52.00, 424.75) | 83.00 (46.00, 244.00) | 566.00 (353.00, 3401.00) | **<0.0001** |
| **Urinary creatinine min (mg/dL)** | 11.47 (7.18, 17.49) | 10.50 (6.60, 16.44) | 15.61 (12.5, 34.56) | **0.006** |
| **Urinary osmolality min (mosm/kg)** | 323.00 (287.00, 352.50) | 334.00 (292.00, 361.00) | 311.00 (280.00, 334.00) | **0.023** |
| **Inflammation parameters min. or max. values within 7d, median (IQR)** |  |  |  |  |
| **Leukocytes max. (1/nL)** | 19.86 (13.13, 29.66) | 19.58 (13.12, 30.46) | 20.54 (13.36, 28.04) | 0.918 |
| **CRP max. (mg/dL)** | 260.00 (196.18, 359.38) | 266.70 (214.20, 364.70) | 172.40 (153.40, 303.90) | **0.008** |
| **PCT max. (ng/mL)** | 9.55 (4.09, 31.97) | 10.34 (4.01, 31.87) | 6.62 (4.06, 43.30) | 0.907 |
| **Scores min. or max. values within 7d, median (IQR)** |  |  |  |  |
| **SOFA max.** | 13.00 (10.00, 16.00) | 12.00 (10.00, 14.00) | 18.00 (14.00, 20.00) | **<0.0001** |
| **SAPS II max.** | 72.50 (64.75, 83.25) | 71.00 (61.00, 67.00) | 91.00 (83.00, 100.00) | **<0.0001** |
| **APACHE II max.** | 34.50 (30.00, 39.00) | 34.00 (29.00, 37.00) | 41.00 (33.00, 43.00) | **0.001** |
| **Fluid record first 24h after inclusion, median (IQR)** |  |  |  |  |
| **24h fluid input (L)** | 5.98 (4.35, 8.70) | 5.75 (4.25, 8.12) | 9.34 (4.90, 12.93) | **0.014** |
| **24h diuresis (L)** | 2.55 (1.32, 3.52) | 2.85 (1.91, 3.81) | 0.68 (0.13, 1.41) | **<0.0001** |
| **24h fluid balance (L)** | +2.16 (+0.50, +5.88) | +2.00 (+0.47, +3.81) | +7.36 (+1.05, +11.47) | **0.007** |
| **Furosemide dose within 7d (mg)** | 245 (115, 420) | 260 (135, 390) | 110 (35, 1695) | 0.366 |
| **Sepsis status - no (%)** |  |  |  | **0.029** |
| **Sepsis** | 23 (24.5) | 22 (29.3) | 1 (5.3) |  |
| **Septic shock** | 71 (75.5) | 53 (70.7) | 18 (94.7) |  |
| **Ventilation - no (%)** |  |  |  | 0.442 |
| **None** | 6 (6.4) | 6 (8) | 0 (0) |  |
| **Non-invasive ventilation** | 5 (5.3) | 4 (5.3) | 1 (5.3) |  |
| **Invasive ventilation** | 83 (88.3) | 65 (86.7) | 18 (94.7) |  |
| **Vasopressor support - no (%)** |  |  |  | 0.070 |
| **None** | 8 (8.5) | 7 (9.3) | 1 (5.3) |  |
| **Monotherapy with norepinephrine** | 57 (60.6) | 49 (65.3) | 8 (42.1) |  |
| **Combination therapy with others** | 29 (30.09) | 19 (25.3) | 10 (52.6) |  |
| **Length of ICU stay (d), median (IQR)** | 21 (9, 43) | 21 (10,5) | 14 (3, 4) | 0.165 |
| **Mortality 30 days - no (%)** | 22 (23.4) | 11 (14.7) | 11 (57.9) | **<0.0001** |

APACHE II = Acute Physiology and Chronic Health Evaluation II, CRP = C-reactive protein, ICU = intensive care unit, IQR = interquartile range, N = number of analysed patients (see Fig. 1), PCT = procalcitonin, RRT = renal replacement therapy, SAPS II = Simplified Acute Physiology Score II, SOFA = Sequential Organ Failure Assessment.

**Table S4.** Spearman’s correlation analyses (inclusion values) of potential associations between novel biomarker levels and demographics, organ dysfunction and inflammation

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **N = 100** | **TIMP-2\*IGFBP7/1000 (ng/mL)2** | | | **suPAR (ng/mL)** | | |
|  | **r** | **CI** | **P value** | **r** | **CI** | **P value** |
| **Age (years)** | 0.1213 | -0.0828 - 0.3156 | 0.2292 | -0.04181 | -0.2418 - 0.1616 | 0.6796 |
| **BMI (kg/m2)** | 0.1498 | -0.0539 - 0.3415 | 0.1369 | 0.05191 | -0.1518 - 0.2513 | 0.6080 |
| **SCr (mg/dL)** | 0.3153 | 0.1210 - 0.4864 | **0.0014** | 0.4092 | 0.2258 - 0.5646 | **<0.0001** |
| **CysC (mg/dL)** | 0.3084 | 0.1134 - 0.4805 | **0.0018** | 0.5478 | 0.3887 - 0.6751 | **<0.0001** |
| **AST (U/L)** | 0.2529 | 0.05355 - 0.4328 | **0.0111** | 0.3095 | 0.1146 - 0.4815 | **0.0017** |
| **ALT (U/L)** | 0.1980 | 0.00856 - 0.3884 | 0.0531 | 0.1622 | -0.04555 - 0.3565 | 0.1143 |
| **AP (U/L)** | 0.1449 | -0.06108 - 0.3390 | 0.1547 | 0.3950 | 0.2076 - 0.5544 | **<0.0001** |
| **γGT (U/L)** | 0.1132 | -0.09091 - 0.3083 | 0.2620 | 0.2820 | 0.08479 - 0.4580 | **0.0045** |
| **Leucocytes (1/nL)** | 0.0248 | -0.1782 - 0.2257 | 0.8070 | 0.2561 | 0.05696 - 0.4356 | **0.0100** |
| **CRP (mg/L)** | 0.1740 | -0.0291 - 0.3633 | 0.0834 | -0.0207 | -0.2218 - 0.1822 | 0.8384 |
| **PCT (ng/mL)** | 0.3196 | 0.1256 - 0.4900 | **0.0012** | 0.3092 | 0.1143 - 0.4812 | **0.0017** |
| **SOFA Score** | 0.3865 | 0.2000 - 0.5459 | **<0.0001** | 0.3725 | 0.1843 - 0.5343 | **0.0001** |

ALT = alanine aminotransferase, AP = alkaline phosphatase, AST = aspartate aminotransferase, BMI = body mass index, CI = confidence interval, CRP = C-reactive protein, CysC = Cystatin C, γGT = gamma-glutamyl transferase, PCT = procalcitonin, SOFA = sequential organ failure assessment, suPAR = soluble urokinase-type plasminogen activator receptor, [TIMP-2]\*[IGFBP7] = product of tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein

**Table S5a.** Receiver-operating characteristic (ROC) analysis and best performing cut-off (highest Youden index) for all tested biomarkers

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Biomarkers**  **for RRT prediction** | **Patients (N)** | **RRT (N)** | **AUC (ROC)** | **CI 95%** | **Best**  **cut-off** | **Sensitivity (%)** | **Specificity (%)** | **P value** |
| **[TIMP-2]\*[IGFBP7] 24h** | 84 | 11 | 0.892 | 0.802 - 0.981 | ≥ 0.60 | 90.9 | 67.1 | **<0.0001** |
| **CysC (mg/L)** | 94 | 19 | 0.836 | 0.754 - 0.919 | ≥ 1.685 | 94.7 | 64.0 | **<0.0001** |
| **[TIMP-2]\*[IGFBP7] 12h** | 85 | 13 | 0.829 | 0.706 - 0.952 | ≥ 1.405 | 76.9 | 76.4 | **<0.0001** |
| **suPAR (ng/mL)** | 94 | 19 | 0.834 | 0.720 - 0.949 | ≥ 8.534 | 84.2 | 82.7 | **<0.0001** |
| **SCr (mg/dL)** | 94 | 19 | 0.800 | 0.701 - 0.898 | ≥ 1.925 | 78.9 | 72.0 | **<0.0001** |
| **[TIMP-2]\*[IGFBP7] 48h** | 76 | 7 | 0.800 | 0.584 - 1.000 | ≥ 0.675 | 71.4 | 84.1 | **0.009** |
| **SOFA Score** | 94 | 19 | 0.778 | 0.651 - 0.905 | ≥ 11.5 | 89.5 | 52.0 | **<0.0001** |
| **Urinary osmolality (mosm/kg)** | 94 | 19 | 0.771 | 0.674 - 0.867 | ≤ 353.0 | 89.5 | 62.7 | **<0.0001** |
| **[TIMP-2]\*[IGFBP7] 0h** | 94 | 19 | 0.745 | 0.595 - 0.895 | ≥ 3.22 | 68.4 | 82.7 | **0.001** |
| **Albuminuria (mg/L)** | 94 | 19 | 0.730 | 0.604 - 0.856 | ≥ 107 | 63.2 | 74.7 | **0.002** |
| **Proteinuria (g/L)** | 94 | 19 | 0.709 | 0.576 - 0.842 | ≥ 0.47 | 73.7 | 37.3 | **0.005** |
| **PCT (ng/mL)** | 94 | 19 | 0.577 | 0.429 - 0.725 | ≥ 2.175 | 94.7 | 24.0 | 0.303 |
| **Urinary creatinine (mg/dL)** | 94 | 19 | 0.492 | 0.354 - 0.629 | ≤ 52.62 | 78.9 | 41.3 | 0.914 |
| **CRP (mg/L)** | 94 | 19 | 0.070 | 0.255 - 0.531 | ≥ 252.55 | 31.6 | 64.0 | 0.150 |

AUC = area under the receiver-operating characteristic curve, CI = confidence interval, CRP = C-reactive protein, CysC = cystatin C, PCT = procalcitonin, RRT = renal replacement therapy, SCr = serum creatinine, SOFA = sequential organ failure assessment, suPAR = soluble urokinase-type plasminogen activator receptor, [TIMP-2]\*[IGFBP7] = product of tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein 7

**Table S5b.** Receiver-operating characteristic (ROC) analysis and best performing cut-off (highest Youden index) for all tested biomarkers (only patients with moderate to severe AKI at the time of study inclusion)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Biomarkers**  **for RRT prediction** | **Patients (N)** | **RRT (N)** | **AUC (ROC)** | **CI 95%** | **Best**  **cut -off** | **Sensitivity (%)** | **Specificity (%)** | **P value** |
| **[TIMP-2]\*[IGFBP7] 24h** | 41 | 9 | 0.861 | 0.734 - 0.988 | ≥ 0.6 | 100 | 56.2 | **0.001** |
| **[TIMP-2]\*[IGFBP7] 12h** | 43 | 11 | 0.803 | 0.649 - 0.956 | ≥ 1.405 | 81.8 | 62.5 | **0.003** |
| **suPAR (ng/mL)** | 50 | 17 | 0.800 | 0.657 - 0.944 | ≥ 8.534 | 82.4 | 75.8 | **0.001** |
| **[TIMP-2]\*[IGFBP7] 48h** | 37 | 7 | 0.793 | 0.570 - 1.000 | ≥ 0.665 | 71.4 | 80.0 | **0.017** |
| **SOFA** | 50 | 17 | 0.742 | 0.588 - 0.895 | ≥ 11.5 | 94.1 | 30.3 | **0.006** |
| **CysC (mg/L)** | 50 | 17 | 0.735 | 0.599 - 0.872 | ≥ 1.97 | 82.4 | 54.5 | **0.007** |
| **[TIMP-2]\*[IGFBP7] 0h** | 50 | 17 | 0.733 | 0.577 - 0.889 | ≥ 3.285 | 76.5 | 72.7 | **0.008** |
| **Albuminuria (mg/L)** | 50 | 17 | 0.698 | 0.541 - 0.855 | ≥ 107.00 | 70.6 | 66.7 | 0.080 |
| **SCr (mg/dL)** | 50 | 17 | 0.684 | 0.530 - 0.839 | ≥ 1.99 | 82.4 | 54.5 | **0.034** |
| **Proteinuria (g/L)** | 50 | 17 | 0.682 | 0.527 - 0.837 | ≥ 0.635 | 70.6 | 60.6 | **0.037** |
| **Urinary creatinine (mg/dL)** | 50 | 17 | 0.501 | 0.335 - 0.667 | ≤ 59.62 | 82.4 | 48.5 | 0.992 |
| **PCT (ng/mL)** | 50 | 17 | 0.494 | 0.307 - 0.680 | ≥ 2.215 | 94.1 | 12.1 | 0.943 |
| **CRP (mg/L)** | 50 | 17 | 0.353 | 0.192 - 0.514 | ≥ 93.45 | 88.2 | 12.1 | 0.091 |
| **Urinary osmolality (mosm/kg)** | 50 | 17 | 0.220 | 0.094 - 0.346 | ≤ 358 | 94.1 | 60.6 | **0.001** |

AUC = area under the receiver-operating characteristic curve, CI = confidence interval, CRP = C-reactive protein, CysC = cystatin C, PCT = procalcitonin, RRT = renal replacement therapy, SCr = serum creatinine, SOFA = sequential organ failure assessment, suPAR = soluble urokinase-type plasminogen activator receptor, [TIMP-2]\*[IGFBP7] = product of tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein 7

**Table S5c.** Receiver-operating characteristic analyses in comparison to standard parameters (deLong’stest) and best performing cut-off values for the prediction of renal replacement therapy (only patients with moderate to severe AKI at the time of study inclusion)

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Biomarker**  **For RRT prediction** | **Patients (N)** | **RRT (N)** | **AUC (ROC)** | **CI 95%** | **Best cut-off** | **Sensitivity (%)** | **Specificity (%)** | **DeLong**  **P value towards [TIMP-2]\*[IGFBP7] 24h** | | **DeLong**  **P value towards suPAR** |
| **[TIMP-2]\*[IGFBP7] 0h** | 50 | 17 | **0.73** | 0.58 - 0.89 | ≥ 3.29 | 76.5 | 72.7 | **0.0400** | 0.4853 | |
| **[TIMP-2]\*[IGFBP7] 12h** | 43 | 11 | **0.80** | 0.65 - 0.96 | ≥ 1.41 | 81.8 | 62.5 | 0.0734 | 0.9807 | |
| **[TIMP-2]\*[IGFBP7] 24h** | 41 | 9 | **0.86** | 0.73 - 0.99 | ≥ 0.60 | 100 | 56.2 | - | 04679 | |
| **[TIMP-2]\*[IGFBP7] 48h** | 37 | 7 | **0.79** | 0.57 - 1.00 | ≥ 0.67 | 71.4 | 80.0 | 0.2829 | 0.9525 | |
| **suPAR (ng/mL)** | 50 | 17 | **0.80** | 0.66 - 0.94 | ≥ 8.53 | 82.4 | 75.8 | 0.4679 | - | |
| **CysC (mg/L)** | 50 | 17 | **0.74** | 0.60 - 0.87 | ≥ 1.97 | 82.4 | 54.5 | 0.2264 | 0.4944 | |
| **SCr (mg/dL)** | 50 | 17 | **0.68** | 0.53 - 0.84 | ≥ 1.99 | 82.4 | 54.5 | 0.1355 | 0.2326 | |
| **Proteinuria (g/L)** | 50 | 17 | **0.68** | 0.53 - 0.84 | ≥ 0.64 | 70.6 | 60.6 | **0.0114** | 0.1828 | |
| **Albuminuria (mg/L)** | 50 | 17 | **0.70** | 0.54 - 0.86 | ≥ 107.00 | 70.6 | 66.7 | **0.0412** | 0.2704 | |
| **SOFA Score** | 50 | 17 | **0.74** | 0.59 - 0.90 | ≥ 11.50 | 94.1 | 30.3 | 0.2388 | 0.5808 | |

AUC = area under the receiver-operating curve, CI = confidence interval, CysC = cystatin C, N = number of analysed patients (see Fig. 1), RRT = renal replacement therapy, SCr = serum creatinine, SOFA = sequential organ failure assessment, suPAR = soluble urokinase-type plasminogen activator receptor, [TIMP-2]\*[IGFBP7] = product of tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein 7.

**Table S6a.** Receiver-operating characteristic analysis and best performing cut-off (highest Youden index) for the prediction of the combinatory endpoint “RRT or death” within 7d (N=100)

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Biomarkers for the prediction of “RRT or death”** | **Patients (N)** | **RRT +death**  **(N)** | **AUC (ROC)** | **CI 95%** | **Best cut-off** | **Sensitivity (%)** | **Specificity (%)** | **deLong’s (P value)**  **towards**  **[TIMP-2]\*[IGFBP7] 24h** | | **deLong’s (P value)**  **towards**  **suPAR** |
| **[TIMP-2]\*[IGFBP7] 0h** | 100 | 24 | **0.66** | 0.52 - 0.80 | 0.50 | 75.0 | 47.4 | **0.0110** | 0.2192 | |
| **[TIMP-2]\*[IGFBP7] 12h** | 91 | 18 | **0.74** | 0.62 - 0.87 | 0.59 | 77.8 | 58.9 | 0.2040 | 0.7662 | |
| **[TIMP-2]\*[IGFBP7] 24h** | 89 | 15 | **0.78** | 0.63 - 0.92 | 0.44 | 86.7 | 60.8 | - | 0.8635 | |
| **[TIMP-2]\*[IGFBP7] 48h** | 78 | 8 | **0.79** | 0.57 - 1.00 | 0.25 | 87.5 | 55.7 | 0.8698 | 0.7881 | |
| **suPAR (ng/mL)** | 100 | 24 | **0.76** | 0.65 - 0.88 | 7.06 | 70.8 | 69.7 | 0.8635 | - | |
| **CysC (mg/L)** | 100 | 24 | **0.79** | 0.69 - 0.88 | 1.69 | 83.3 | 63.2 | 0.8998 | 0.7619 | |
| **SCr (mg/dL)** | 100 | 24 | **0.72** | 0.62 - 0.83 | 1.89 | 70.8 | 69.7 | 0.5409 | 0.5951 | |
| **Proteinuria (g/L)** | 100 | 24 | **0.68** | 0.53 - 0.80 | 0.47 | 62.5 | 81.6 | **0.0425** | 0.01973 | |
| **Albuminuria (mg/L)** | 100 | 24 | **0.66** | 0.56 - 0.81 | 19.5 | 87.5 | 32.9 | 0.1122 | 0.2852 | |
| **SOFA Score** | 100 | 24 | **0.71** | 0.59 - 0.84 | 11.5 | 87.5 | 51.3 | 0.4754 | 0.5565 | |

AUC = area under the receiver-operating characteristic curve, CI = confidence interval, CysC = cystatin C, N = number of analyzed patients (see Fig. 1), RRT = renal replacement therapy, SCr = serum creatinine, SOFA = sequential organ failure assessment, suPAR = soluble urokinase-type plasminogen activator receptor, [TIMP-2]\*[IGFBP7] = product of tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein 7.

**Table S6b.** Receiver-operating characteristic analysis and best performing cut-off (highest Youden index) for the prediction of the combinatory endpoint “RRT or death” within 7d (only patients with moderate to severe AKI at the time of study inclusion)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Biomarkers for the prediction of “RRT or death”** | **Patients (N)** | **RRT +death**  **(N)** | **AUC (ROC)** | **CI 95%** | **Best cut-off** | **Sensitivity (%)** | **Specificity (%)** | **deLong’s (P value)**  **towards**  **[TIMP-2]\*[IGFBP7] 24h** | **deLong’s (P value)**  **towards**  **suPAR** |
| **[TIMP-2]\*[IGFBP7] 0h** | 53 | 19 | **0.69** | 0.53 - 0.84 | 3.01 | 68.4 | 67.6 | **0.0224** | 0.4395 |
| **[TIMP-2]\*[IGFBP7] 12h** | 46 | 13 | **0.75** | 0.60 - 0.90 | 1.41 | 76.9 | 60.6 | **0.0200** | 0.8974 |
| **[TIMP-2]\*[IGFBP7] 24h** | 44 | 11 | **0.81** | 0.67 - 0.95 | 1.80 | 72.7 | 72.7 | - | 0.2779 |
| **[TIMP-2]\*[IGFBP7] 48h** | 39 | 8 | **0.78** | 0.57 - 1.00 | 0.22 | 87.5 | 51.6 | 0.6177 | 0.6882 |
| **suPAR (ng/mL)** | 53 | 19 | **0.73** | 0.58 - 0.89 | 8.53 | 73.7 | 73.5 | 0.2779 | - |
| **CysC (mg/L)** | 53 | 19 | **0.69** | 0.55 - 0.83 | 1.59 | 94.7 | 41.2 | 0.1910 | 0.4774 |
| **SCr (mg/dL)** | 53 | 19 | **0.62** | 0.47 - 0.78 | 1.98 | 78.9 | 52.9 | 0.0693 | 0.1561 |
| **Proteinuria (g/L)** | 53 | 19 | **0.70** | 0.55 - 0.84 | 0.67 | 68.4 | 61.8 | **0.0250** | 0.4205 |
| **Albuminuria (mg/L)** | 53 | 19 | **0.70** | 0.55 - 0.84 | 107.00 | 68.4 | 64.7 | **0.0499** | 0.4549 |
| **SOFA Score** | 53 | 19 | **0.69** | 0.54 - 0.84 | 11.5 | 94.7 | 29.4 | 0.0912 | 0.4370 |

AUC = area under the receiver-operating characteristic curve, CI = confidence interval, CysC = cystatin C, N = number of analyzed patients (see Fig. 1), RRT = renal replacement therapy, SCr = serum creatinine, SOFA = sequential organ failure assessment, suPAR = soluble urokinase-type plasminogen activator receptor, [TIMP-2]\*[IGFBP7] = product of tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein 7.

**Table S7.** Additional Receiver-operating characteristic analysis of standard and novel urinary biomarkers for RRT prediction after normalization to urinary creatinine

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Biomarker** | **Patients (N)** | **RRT (N)** | **AUC (ROC)** | **CI 95%** | **P value** |
| **[TIMP-2]\*[IGFBP7] 0h/mmol UCr** | 94 | 19 | 0.768 | 0.626 - 0.909 | **<0.0001** |
| **[TIMP-2]\*[IGFBP7] 12h/mmol UCr** | 85 | 13 | 0.858 | 0.731 - 0.985 | **<0.0001** |
| **[TIMP-2]\*[IGFBP7] 24h/mmol UCr** | 84 | 11 | 0.887 | 0.785 - 0.990 | **<0.0001** |
| **[TIMP-2]\*[IGFBP7] 48h/mmol UCr** | 76 | 7 | 0.819 | 0.635 - 1.000 | **0.006** |
| **Proteinuria (g/L)/mmol UCr** | 94 | 19 | 0.724 | 0.598 - 0.849 | **0.003** |
| **Albuminuria (mg/L)/mmol UCr** | 94 | 19 | 0.746 | 0.638 - 0.853 | **0.001** |

AUC = area under the receiver-operating characteristic curve, CI = confidence interval, UCr = urinary creatinine, RRT = renal replacement therapy, [TIMP-2]\*[IGFBP7] = product of tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein 7.



**Figure S1.** Biomarker kinetics of [TIMP-2]\*[IGFBP7] over time and suPAR levels at baseline (no RRT vs. RRT).

RRT = renal replacement therapy, suPAR = soluble urokinase-type plasminogen activator receptor, [TIMP-2]\*[IGFBP7] = product of tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein 7.

**c** For [TIMP-2]\*[IGFBP7] measurement, three urinary samples were missing for 12 h, two for 24 h and six for 48 h in non-RRT patients, and one sample for 48 h in the RRT group (anuria, ongoing surgery, administration of toluidine blue / interference with the urinary immunoassay)

**d** Patient with the fulfilment of RRT criteria earlier than 12 h, 24 h and 48 h were excluded from the respective analysis of [TIMP-2]\*[IGFBP7] values at the corresponding time points (six patients <12 h, eight patients <24 h, 11 patients ≤ 48 h)



**Figure S2.** Biomarker kinetics of [TIMP-2]\*[IGFBP7] over time and suPAR at baseline (AKI 0 vs. AKI 1).

AKI 0 = no acute kidney injury, AKI 1 = mild acute kidney injury, suPAR = soluble urokinase-type plasminogen activator receptor, [TIMP-2]\*[IGFBP7] = product of tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein 7.