**Serial Urinary tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein 7 and the Prognosis for Acute Kidney Injury over the Course of Critical Illness**

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**Supplemental Tables**

**Table S1**. Potentially nephrotoxic drugs considered

|  |
| --- |
| **Drug name / category** |
| Angiotensin-converting enzyme inhibitors |
| Angiotensin II receptor blockers |
| Acyclovir |
| Aminoglycosides |
| Amoxicillin with clavulanate |
| Calcineurin inhibitors |
| Cefepime |
| Nonsteroidal anti-inflammatory drugs |
| Phenytoin |
| Piperacillin with tazobactam |
| Vancomycin |

**Table S2**. Baseline patient characteristics for patients with at least one [TIMP-2]•[IGFBP7] > 0.3 and by number of consecutive [TIMP-2]•[IGFBP7] > 2.0.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Patients with  [TIMP-2]•[IGFBP7]>0.3 N=410 | Three Consecutive [TIMP-2]•[IGFBP7]≤2.0 N=314 | One Consecutive [TIMP-2]•[IGFBP7]>2.0 N=66 | Two Consecutive [TIMP-2]•[IGFBP7]>2.0 N=12 | Three Consecutive [TIMP-2]•[IGFBP7]>2.0 N=18 | p-value |
| Male | 256 (62%) | 195 (62%) | 41 (62%) | 7 (58%) | 13 (72%) | 0.87 |
| Age | 64 (53-74) | 65 (53-74) | 63 (54-74) | 68 (57-79) | 68 (52-74) | 0.77 |
| Race |  |  |  |  |  | 0.11 |
| White or Caucasian | 334 (81%) | 249 (79%) | 60 (91%) | 11 (92%) | 14 (78%) |  |
| Black or African American | 39 (10%) | 32 (10%) | 3 (5%) | 0 (0%) | 4 (22%) |  |
| Other or Unknown | 37 (9%) | 33 (11%) | 3 (5%) | 1 (8%) | 0 (0%) |  |
| Reason for ICU Admission |  |  |  |  |  |  |
| Cardiovascular | 128 (31%) | 97 (31%) | 21 (32%) | 3 (25%) | 7 (39%) | 0.87 |
| Neurological | 38 (9%) | 28 (9%) | 5 (8%) | 3 (25%) | 2 (11%) | 0.24 |
| Sepsis | 77 (19%) | 53 (17%) | 16 (24%) | 3 (25%) | 5 (28%) | 0.27 |
| Respiratory | 182 (44%) | 139 (44%) | 27 (41%) | 6 (50%) | 10 (56%) | 0.70 |
| Trauma | 31 (8%) | 24 (8%) | 5 (8%) | 0 (0%) | 2 (11%) | 0.85 |
| Surgery | 134 (33%) | 106 (34%) | 22 (33%) | 2 (17%) | 4 (22%) | 0.54 |
| Other | 68 (17%) | 54 (17%) | 11 (17%) | 1 (8%) | 2 (11%) | 0.90 |
| Medical History |  |  |  |  |  |  |
| COPD | 102 (25%) | 88 (28%) | 8 (12%) | 2 (17%) | 4 (22%) | 0.04 |
| Cancer | 107 (26%) | 80 (25%) | 18 (27%) | 2 (17%) | 7 (39%) | 0.56 |
| Chronic kidney disease | 34 (8%) | 26 (8%) | 2 (3%) | 2 (17%) | 4 (22%) | 0.03 |
| Liver disease | 20 (5%) | 12 (4%) | 6 (9%) | 1 (8%) | 1 (6%) | 0.17 |
| Heart failure | 68 (17%) | 51 (16%) | 11 (17%) | 2 (17%) | 4 (22%) | 0.88 |
| Coronary artery disease | 125 (30%) | 99 (32%) | 13 (20%) | 5 (42%) | 8 (44%) | 0.09 |
| Diabetes mellitus | 124 (30%) | 97 (31%) | 13 (20%) | 5 (42%) | 9 (50%) | 0.05 |
| Hypertension | 244 (60%) | 187 (60%) | 35 (53%) | 8 (67%) | 14 (78%) | 0.28 |
| Location prior to ICU admission |  |  |  |  |  | 0.50 |
| Emergency department | 158 (39%) | 124 (39%) | 25 (38%) | 4 (33%) | 5 (28%) |  |
| Operating room | 104 (25%) | 80 (25%) | 19 (29%) | 0 (0%) | 5 (28%) |  |
| Floor | 88 (21%) | 62 (20%) | 14 (21%) | 6 (50%) | 6 (33%) |  |
| Other ICU | 4 (1%) | 3 (1%) | 1 (2%) | 0 (0%) | 0 (0%) |  |
| Other Hospital | 49 (12%) | 38 (12%) | 7 (11%) | 2 (17%) | 2 (11%) |  |
| Unknown | 7 (2%) | 7 (2%) | 0 (0%) | 0 (0%) | 0 (0%) |  |
| Mechanical ventilation at enrollment | 341 (83%) | 259 (82%) | 55 (83%) | 11 (92%) | 16 (89%) | 0.90 |
| Baseline serum creatinine (mg/dL) | 0.8 (0.6-1.1) | 0.8 (0.6-1.0) | 0.8 (0.7-1.3) | 1.1 (0.6-1.5) | 1.0 (0.8-1.5) | 0.05 |
| APACHE III score | 71 (52-94) | 68 (51-88) | 78 (53-102) | 101 (88-126) | 113 (97-136) | <0.001 |
| Non-renal APACHE III score | 61 (43-85) | 58 (42-79) | 70 (43-87) | 85 (69-102) | 98 (87-105) | <0.001 |

**Table S3.** Outcomes by number of consecutive [TIMP-2]•[IGFBP7] >0.3 (A) and 2.0 (B)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| A |  | Three Consecutive Negative (≤0.3) | One positive (>0.3) | Two Consecutive Positive (>0.3) | Three Consecutive Positive (>0.3) | p-value |
|  | All Patients | [TIMP-2]∙[IGFBP7] | [TIMP-2]∙[IGFBP7] | [TIMP-2]∙[IGFBP7] | [TIMP-2]∙[IGFBP7] |
|  | N=530 | N=115 | N=128 | N=76 | N=211 |
| Stage 2-3 AKI within 7 days | 164 (30.9%) | 15 (13%) | 32 (25%) | 28 (36.8%) | 89 (42.2%) | <0.001 |
| RRT within 7 days | 25 (4.7%) | 4 (3.5%) | 3 (2.3%) | 3 (3.9%) | 15 (7.1%) | 0.169 |
| Death within 7 days | 33 (6.2%) | 5 (4.3%) | 5 (3.9%) | 6 (7.9%) | 17 (8.1%) | 0.330 |
| ICU length of stay (days) | 7 (4, 13.7) | 6.1 (3.6, 9.7) | 7.7 (4.1, 13.1) | 6.9 (3.0, 12.7) | 7.3 (4.1, 14.6) | 0.179 |
| Hospital length of stay (days) | 14.6 (8.7, 22.5) | 13.7 (8.3, 20.4) | 14.8 (9, 22.7) | 15.7 (9.2, 22.3) | 15 (8.6, 23.5) | 0.592 |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| B | Patients with | Three Consecutive | One Consecutive | Two Consecutive | Three Consecutive | p-value |
|  | [TIMP-2]∙[IGFBP7]>0.3 | [TIMP-2]∙[IGFBP7]≤2.0 | [TIMP-2]∙[IGFBP7]>2.0 | [TIMP-2]∙[IGFBP7]>2.0 | [TIMP-2]∙[IGFBP7]>2.0 |
|  | N=410 | N=314 | N=66 | N=12 | N=18 |
| Stage 2-3 AKI within 7 days | 148 (36.1%) | 84 (26.8%) | 38 (57.7%) | 9 (75%) | 17 (94.4%) | <0.001 |
| RRT within 7 days | 21 (5.1%) | 7 (2.2%) | 4 (6.1%) | 3 (25%) | 7 (38.9%) | <0.001 |
| Death within 7 days | 28 (6.8%) | 19 (6.1%) | 3 (4.5%) | 1 (8.3%) | 5 (27.8%) | 0.003 |
| ICU length of stay (days) | 7.3 (4.1, 14.6) | 7 (4, 12.8) | 8.6 (4.2, 15.6) | 10.5 (6.5, 26.3) | 9.9 (5.1, 18.3) | 0.102 |
| Hospital length of stay (days) | 15.1 (8.9, 22.9) | 14 (8.4, 22.3) | 16.8 (10, 23.8) | 31.9 (29, 35.6) | 24.9 (23.1, 32.8) | 0.001 |

Continuous variables are reported as median (25th, 75th percentiles), and categorical variables as number (percent).

P values compare outcome distributions among patients grouped by number of positive biomarkers and are calculated by Kruskal-Wallis test for continuous variables and log-rank test for categorical variables.

**Table S4.** Time of onset of stage 2-3 AKI relative to urine samples collected for [TIMP-2]•[IGFBP7] measurement

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Time of onset of stage 2-3 AKI | | | | | |
| Consecutive [TIMP-2]•[IGFBP7] > 0.3 | Within 1 week | Before enrollment | After enrollment | After first [TIMP-2]•[IGFBP7] > 0.3 | After second [TIMP-2]•[IGFBP7] > 0.3 | After third [TIMP-2]•[IGFBP7] > 0.3 |
| 0 (N=115) | 15 | 0 (0%) | 15 (100%) | N/A | N/A | N/A |
| 1 (N=128) | 32 | 5 (16%) | 27 (84%) | 23 (72%) | N/A | N/A |
| 2 (N=76) | 28 | 4 (14%) | 24 (86%) | 23 (82%) | 13 (46%) | N/A |
| 3 (N=211) | 89 | 17 (19%) | 72 (81%) | 70 (79%) | 47 (53%) | 34 (38%) |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Time of onset of stage 2-3 AKI | | | | | |
| Consecutive [TIMP-2]•[IGFBP7] > 2 | Within 1 week | Before enrollment | After enrollment | After first [TIMP-2]•[IGFBP7] > 2 | After second [TIMP-2]•[IGFBP7] > 2 | After third [TIMP-2]•[IGFBP7] > 2 |
| 0 (N=314) | 84 | 9 (11%) | 75 (89%) | N/A | N/A | N/A |
| 1 (N=66) | 38 | 9 (24%) | 29 (76%) | 22 (58%) | N/A | N/A |
| 2 (N=12) | 9 | 3 (33%) | 6 (67%) | 5 (56%) | 1 (11%) | N/A |
| 3 (N=18) | 17 | 5 (29%) | 12 (71%) | 10 (59%) | 4 (24%) | 1 (6%) |