**e-Table 1:** Underlying cardiovascular antihypertensive medication associations in the subgroup of patients

|  |  |
| --- | --- |
| **Cardiovascular antihypertensive medication** | **Number of patients** |
| **Monotherapy**  | 167 |
|  | BB | 79 |
|  | ACEi/ARB | 54 |
|  | CCB | 28 |
|  | Spironolactone | 6 |
| **Bitherapy** | 122 |
|  | BB and ACEi/ARB | 44 |
|  | ACEi/ARB and CCB  | 21 |
|  | BB & Spironolactone | 16 |
|  | ACEi/ARB and Diuretic | 14 |
|  | BB and CCB | 9 |
|  | ARB and Spironolactone | 5 |
|  | BB and Diuretic | 2 |
|  | Diuretic and CCB | 2 |
|  | Other associations\* | 9 |
| **Tritherapy** | 41 |
|  | BB & ACEi/ARB & CCB | 13 |
|  | BB & ACEi & diuretic | 9 |
|  | CCB & ACEi & Diuretic | 7 |
|  | BB & ACEi & spironolactone | 6 |
|  | CCB & ACEi/ARBs & spironolactone | 2 |
|  | Other associations\*\* | 4 |
| **Quadritherapy \*\*\*** | 13 |
| **Pentatherapy \*\*\*\*** | 2 |

BB = Betablocker, CCB = Calcium Channel Blocker, ACEi = angiotensin converting enzyme inhibitors, ARBs = Angiotensin II receptor blockers

\* diuretic & spironolactone (n=1), CCB & Spironolactone (n=1), miscellaneous medication (n=7)

\*\* CCB & BB & diuretic (n=1), miscellaneous medication (n=3),

\*\*\* BB & ACEi/ARBS & CCB & diuretic (n=6), miscellaneous association (n=7)

\*\*\*\* BB & ACEi/ARBS & CCB & diuretic & spironolactone (n=1), miscellaneous association (n=1)

**e-Table 2.** Characteristics of septic-shock patients admitted in ICU according to prior use of betablockers (BB) using propensity-matched analysis

|  |  |  |
| --- | --- | --- |
| **Variables** | **Non-matched cohort** | **Matched cohort** |
|  | **No betablocker (n=541)** | **Betablocker (n=194)** | **p** | **No betablocker (n=167)** | **Betablocker (n=167)** | **p** |
| **Age, years** | 65.02 (15.90) | 72.65 (11.81) | <0.001 | 72.56 (12.65) | 71.76 (11.77) | 0.549 |
| **Male sex** | 346 (64.0) | 120 (61.9) | 0.664 | 103 (61.7) | 102 (61.1) | 1.000 |
| **Weight, kg** | 67.29 (26.95) | 69.79 (27.68) | 0.280 | 69.85 (27.95) | 69.59 (27.57) | 0.931 |
| **Comorbid condition** |  |  |  |  |  |  |
| **Chronic heart failure** | 80 (14.8) | 74 (38.1) | <0.001 | 50 (29.9) | 64 (38.3) | 0.134 |
| **Arterial hypertension** | 142 (26.2) | 114 (58.8) | <0.001 | 98 (58.7) | 100 (59.9) | 0.911 |
| **Diabetes mellitus** | 91 (16.8) | 44 (22.7) | 0.089 | 34 (20.4) | 40 (24.0) | 0.510 |
| **Obesity** | 38 (7.0) | 20 (10.3) | 0.193 | 12 (7.2) | 16 (9.6) | 0.554 |
| **Cirrhosis** | 47 (8.7) | 31 (16.0) | 0.007 | 21 (12.6) | 27 (16.2) | 0.435 |
| **COPD** | 78 (14.4) | 36 (18.6) | 0.211 | 37 (22.2) | 34 (20.4) | 0.789 |
| **Chronic kidney failure** | 55 (10.2) | 35 (18.0) | 0.006 | 29 (17.4) | 31 (18.6) | 0.887 |
| **Immunosuppression** | 121 (22.4) | 32 (16.5) | 0.100 | 35 (21.0) | 27 (16.2) | 0.325 |
| **Characteristics on ICU admission** |  |  |  |  |  |  |
| **SAPS II** | 68.94 (21.39) | 69.87 (18.91) | 0.593 | 73.76 (20.20) | 69.66 (18.94) | 0.056 |
| **SOFA** | 9.88 (5.22) | 9.52 (5.04) | 0.403 | 9.90 (4.18) | 9.73 (5.17) | 0.745 |
| **Source of infection** |  |  | 0.049 |  |  | 0.986 |
| **Lung** | 275 (50.8) | 74 (38.1) |  | 73 (43.7) | 65 (38.9) |  |
| **Abdominal** | 65 (12.0) | 32 (16.5) |  | 24 (14.4) | 27 (16.2) |  |
| **Urinary tract** | 60 (11.1) | 32 (16.5) |  | 24 (14.4) | 25 (15.0) |  |
| **Skin and soft tissue** | 40 (7.4) | 15 (7.7) |  | 11 (6.6) | 13 (7.8) |  |
| **Catheter related** | 22 (4.1) | 9 (4.6) |  | 8 (4.8) | 8 (4.8) |  |
| **Other** | 22 (4.1) | 13 (6.7) |  | 11 (6.6) | 13 (7.8) |  |
| **Laboratory findings on admission** |  |  |  |  |  |  |
| **Lactate, mmol/L** | 3.19 (3.71) | 2.90 (3.32) | 0.351 | 3.29 (3.89) | 2.79 (3.41) | 0.213 |
| **WBC, (/mm3)** | 13.74 (15.28) | 14.56 (11.24) | 0.494 | 15.32 (12.25) | 14.86 (11.65) | 0.727 |
| **Serum creatinine level, µmol/L** | 173.17 (154.28) | 194.34 (137.11) | 0.093 | 194.28 (139.72) | 196.70 (143.65) | 0.876 |
| **ICU management** |  |  |  |  |  |  |
| **Cumulative fluid balance on 24h, mL** | 2768.08 (2586.56) | 2486.02 (2397.91) | 0.187 | 2728.47 (2827.03) | 2508.00 (2336.73) | 0.438 |
| **Cumulative norepinephrine dose on 24h, mg/kg/h** | 0.89 (1.32) | 0.89 (1.24) | 0.940 | 0.82 (1.01) | 0.93 (1.28) | 0.373 |
| **Stress-dose corticosteroid** | 260 (48.2) | 97 (50.0) | 0.736 | 75 (44.9) | 85 (50.9) | 0.324 |
| **Acute Kidney Injury (AKIN3) in 7 first days** | 200 (37.0) | 78 (40.2) | 0.477 | 73 (43.7) | 70 (41.9) | 0.825 |
| **RRT during ICU stay** | 254 (47.1) | 85 (43.8) | 0.478 | 91 (54.5) | 73 (43.7) | 0.063 |
| **Mechanical ventilation** | 452 (83.5) | 154 (79.4) | 0.230 | 146 (87.4) | 132 (79.0) | 0.057 |
| **Outcomes** |  |  |  |  |  |  |
| **ICU mortality** | 182 (33.6) | 66 (34.0) | 0.994 | 66 (39.5) | 52 (31.1) | 0.137 |

Variables are expressed as median (interquartile range) or number (percentage) as appropriate. ICU: intensive care unit, COPD: chronic obstructive pulmonary disease, SAPS2: Simplified Acute Physiology Score 2, SOFA: Sequential Organ Failure Assessment, WBC: white blood cell, AKIN: Acute Kidney Injury Network classification, RRT: Renal replacement therapy

**e-Table 3.** Characteristics of septic-shock patients admitted in ICU according to prior use of Renin Angiotensin System Blocker (SRAB) using propensity-matched analysis

|  |  |  |
| --- | --- | --- |
| **Variables** | **Non-Matched** | **Matched cohort** |
|  | **No SRAB (n=543)** | **SRAB (n=192)** | **p** | **No SRAB (n=166)** | **SRAB (n=166)** | **p** |
| **Age, years** | 64.66 (15.83) | 73.77 (11.27) | <0.001 | 72.11 (11.51) | 73.55 (11.56) | 0.256 |
| **Male sex** | 336 (61.9) | 130 (67.7) | 0.176 | 106 (63.9) | 111 (66.9) | 0.645 |
| **Weight, kg** | 67.03 (25.73) | 70.55 (30.73) | 0.130 | 66.77 (28.03) | 70.04 (31.08) | 0.315 |
| **Comorbid conditions** |  |  |  |  |  |  |
| **Chronic heart failure** | 88 (16.2) | 66 (34.4) | <0.001 | 60 (36.1) | 56 (33.7) | 0.730 |
| **Arterial hypertension** | 82 (15.1) | 174 (90.6) | <0.001 | 74 (44.6) | 151 (91.0) | <0.001 |
| **Diabetes mellitus** | 75 (13.8) | 60 (31.2) | <0.001 | 46 (27.7) | 54 (32.5) | 0.402 |
| **Obesity** | 34 (6.3) | 24 (12.5) | 0.009 | 18 (10.8) | 21 (12.7) | 0.733 |
| **Cirrhosis** | 64 (11.8) | 14 (7.3) | 0.109 | 10 (6.0) | 10 (6.0) | 1.000 |
| **COPD** | 67 (12.3) | 47 (24.5) | <0.001 | 39 (23.5) | 41 (24.7) | 0.898 |
| **Chronic kidney failure** | 55 (10.1) | 35 (18.2) | 0.005 | 29 (17.5) | 31 (18.7) | 0.887 |
| **Immunosuppression** | 115 (21.3) | 38 (19.8) | 0.745 | 37 (22.3) | 31 (18.7) | 0.497 |
| **Characteristics on ICU admission** |  |  |  |  |  |  |
| **SAPS II** | 67.49 (21.13) | 73.98 (18.90) | <0.001 | 71.22 (20.21) | 74.64 (18.69) | 0.111 |
| **SOFA** | 9.78 (5.44) | 9.79 (4.33) | 0.989 | 10.07 (6.43) | 9.98 (4.29) | 0.880 |
| **Source of infection** |  |  | 0.405 |  |  | 0.744 |
|  **Lung** | 252 (46.4) | 97 (50.5) |  | 85 (51.2) | 82 (49.4) |  |
|  **Abdominal** | 67 (12.3) | 30 (15.6) |  | 23 (13.9) | 26 (15.7) |  |
|  **Urinary tract** | 66 (12.2) | 26 (13.5) |  | 20 (12.0) | 23 (13.9) |  |
|  **Skin and soft tissue** | 43 (7.9) | 12 (6.2) |  | 10 (6.0) | 11 (6.6) |  |
|  **Catheter related** | 25 (4.6) | 6 (3.1) |  | 6 (3.6) | 6 (3.6) |  |
|  **Other** | 28 (5.2) | 7 (3.6) |  | 13 (7.8) | 6 (3.6) |  |
| **Laboratory findings on admission** |  |  |  |  |  |  |
| **Lactate, mmol/L** | 3.15 (3.55) | 2.99 (3.76) | 0.584 | 3.70 (4.23) | 2.94 (3.59) | 0.080 |
| **WBC (/mm3)** | 13.37 (14.68) | 15.61 (13.17) | 0.064 | 15.50 (12.51) | 15.23 (13.42) | 0.848 |
| **Serum creatinine level, µmol/L** | 167.94 (147.23) | 209.29 (154.35) | 0.001 | 185.40 (132.08) | 215.04 (160.65) | 0.067 |
| **ICU management** |  |  |  |  |  |  |
| **Cumulative fluid balance on 24h, mL** | 2675.20 (2547.45) | 2747.12 (2523.90) | 0.737 | 2965.67 (2601.58) | 2882.50 (2527.24) | 0.768 |
| **Cumulative norepinephrine dose on 24h, mg/kg/h** | 0.87 (1.29) | 0.95 (1.31) | 0.480 | 1.08 (1.63) | 1.01 (1.35) | 0.696 |
| **Stress-dose corticosteroid** | 261 (48.2) | 96 (50.0) | 0.738 | 82 (49.4) | 86 (51.8) | 0.742 |
| **Acute Kidney Injury (AKIN3) in 7 first days** | 205 (37.8) | 73 (38.0) | 1.000 | 72 (43.4) | 68 (41.0) | 0.739 |
| **RRT during ICU stay** | 243 (44.9) | 96 (50.0) | 0.259 | 85 (51.2) | 85 (51.2) | 1.000 |
| **Mechanical ventilation** | 441 (81.2) | 165 (85.9) | 0.171 | 141 (84.9) | 142 (85.5) | 1.000 |
| **Outcome** |  |  |  |  |  |  |
| **ICU mortality** | 180 (33.1) | 68 (35.4) | 0.630 | 62 (37.3) | 58 (34.9) | 0.732 |

Variables are expressed as median (interquartile range) or number (percentage) as appropriate. ICU intensive care unit, COPD chronic obstructive pulmonary disease, SAPS2 Simplified Acute Physiology Score 2, SOFA Sequential Organ Failure Assessment, WBC white blood cell, AKIN Acute Kidney Injury Network classification, RRT Renal replacement therapy

**e-Table 4.** Characteristics of septic-shock patients admitted in ICU according to prior use of Calcium Channel Blocker (CCB) using propensity-matched analysis

|  |  |  |
| --- | --- | --- |
| **Variables** | **Non-Matched** | **Matched** |
|  | **No CCB (n=632)** | **CCB (n=103)** | **p** | **No CCB (n=90)** | **CCB (n=90)** | **p** |
| **Age, years** | 65.81 (15.60) | 74.55 (10.64) | <0.001 | 74.12 (11.05) | 74.32 (10.59) | 0.902 |
| **Male sex** | 396 (62.7) | 70 (68.0) | 0.355 | 56 (62.2) | 60 (66.7) | 0.640 |
| **Weight, kg** | 67.37 (26.31) | 71.44 (31.62) | 0.164 | 68.02 (30.58) | 71.02 (32.22) | 0.523 |
| **Comorbid conditions** |  |  |  |  |  |  |
| **Chronic heart failure** | 124 (19.6) | 30 (29.1) | 0.039 | 25 (27.8) | 26 (28.9) | 1.000 |
| **Arterial hypertension** | 154 (24.4) | 102 (99.0) | <0.001 | 89 (98.9) | 89 (98.9) | 1.000 |
| **Diabetes** | 100 (15.8) | 35 (34.0) | <0.001 | 26 (28.9) | 31 (34.4) | 0.522 |
| **Obesity** | 42 (6.6) | 16 (15.5) | 0.004 | 13 (14.4) | 15 (16.7) | 0.837 |
| **Cirrhosis** | 72 (11.4) | 6 (5.8) | 0.126 | 4 (4.4) | 4 (4.4) | 1.000 |
| **COPD** | 92 (14.6) | 22 (21.4) | 0.105 | 16 (17.8) | 20 (22.2) | 0.576 |
| **Chronic kidney failure** | 69 (10.9) | 21 (20.4) | 0.011 | 13 (14.4) | 18 (20.0) | 0.430 |
| **Immunosuppression** | 127 (20.2) | 26 (25.2) | 0.295 | 12 (13.3) | 23 (25.6) | 0.060 |
| **Characteristics on ICU admission** |  |  |  |  |  |  |
| **SAPS II** | 69.16 (20.95) | 69.38 (19.62) | 0.920 | 78.93 (18.32) | 70.09 (18.12) | 0.001 |
| **SOFA** | 9.78 (5.35) | 9.79 (3.91) | 0.988 | 10.96 (4.06) | 9.57 (3.71) | 0.018 |
| **Source of infection** |  |  | 0.468 |  |  | 0.943 |
|  **Lung** | 300 (47.5) | 49 (47.6) |  | 44 (48.9) | 40 (44.4) |  |
|  **Abdominal** | 77 (12.2) | 20 (19.4) |  | 15 (16.7) | 18 (20.0) |  |
|  **Urinary tract** | 79 (12.5) | 13 (12.6) |  | 14 (15.6) | 13 (14.4) |  |
|  **Skin and soft tissue** | 50 (7.9) | 5 (4.9) |  | 7 (7.8) | 5 (5.6) |  |
|  **Catheter related** | 27 (4.3) | 4 (3.9) |  | 3 (3.3) | 3 (3.3) |  |
|  **Other** | 31 (4.9) | 4 (3.9) |  | 2 (2.2) | 3 (3.3) |  |
| **Laboratory findings on admission** |  |  |  |  |  |  |
| **Lactate, mmol/L** | 3.12 (3.57) | 3.05 (3.83) | 0.855 | 3.60 (4.73) | 3.22 (4.03) | 0.558 |
| **WBC (/mm3)** | 13.73 (14.50) | 15.32 (13.21) | 0.300 | 16.06 (13.84) | 15.71 (13.83) | 0.868 |
| **Serum creatinine level, µmol/L** | 177.09 (149.64) | 189.17 (153.40) | 0.451 | 215.89 (145.47) | 192.00 (159.36) | 0.295 |
| **ICU management** |  |  |  |  |  |  |
| **Cumulative fluid balance on 24h, mL** | 3851.69 (2237.16) | 3597.35 (2050.20) | 0.282 | 4033.44 (2855.11) | 3675.56 (1993.75) | 0.331 |
| **Cumulative norepinephrine dose on 24h, mg/kg/h** | 0.87 (1.27) | 0.98 (1.47) | 0.453 | 0.93 (1.18) | 1.03 (1.52) | 0.611 |
| **Stress-dose corticosteroid** | 311 (49.4) | 46 (44.7) | 0.436 | 50 (55.6) | 41 (45.6) | 0.233 |
| **Acute Kidney Injury (AKIN3) in 7 first days** | 230 (36.4) | 48 (46.6) | 0.061 | 35 (38.9) | 46 (51.1) | 0.134 |
| **RRT during ICU stay** | 293 (46.5) | 46 (44.7) | 0.809 | 51 (56.7) | 39 (43.3) | 0.101 |
| **Mechanical ventilation** | 512 (81.0) | 94 (91.3) | 0.017 | 81 (90.0) | 82 (91.1) | 1.000 |
| **Outcome** |  |  |  |  |  |  |
| **ICU mortality** | 209 (33.1) | 39 (37.9) | 0.400 | 35 (38.9) | 34 (37.8) | 1.000 |

Variables are expressed as median (interquartile range) or number (percentage) as appropriate. CCB Calcium Channel Blocker, ICU intensive care unit, COPD chronic obstructive pulmonary disease, SAPS2 Simplified Acute Physiology Score 2, SOFA Sequential Organ Failure Assessment, WBC white blood cell, AKIN Acute Kidney Injury Network classification, RRT Renal replacement therapy

**e-Table 5.** Comparison of characteristics of septic-shock patients admitted in ICU depending on their comorbid hypertensive condition

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **No hypertension (n=479)** | **Hypertension (n=256)** | **p** |
| **Age, years** | 64 [54 ;75] | 77 [66 ;82] | <0.0001 |
| **Male sex** | 299 (62.42 %) | 167 (65.2) |  |
| **Comorbid condition** |  |  |  |
|  **Chronic heart failure** | 76 (15.8) | 78 (30.5) | <0.0001 |
|  **Mellitus Diabetis** | 61 (12.7) | 74 (28.9) | <0.0001 |
|  **Obesity** | 24 (5) | 34 (13.3) | 0.0001 |
|  **Cirrhosis** | 59 (12.3) | 19 (7.4) | 0.044 |
|  **COPD** | 60 (12.5) | 54 (21.1) | 0.003 |
|  **Chronic kidney failure** | 47 (9.8) | 43 (16.8) | 0.009 |
|  **Immunosuppression** | 103 (21.6) | 50 (19.5) | 0.57 |
| **Characteristics on ICU admission** |  |  |  |
|  **SAPS II** | 66 [51 ;83] | 73 [58.75;88] | <0.0001 |
|  **SOFA** | 9 [6 ;13] | 10 [6.25;13] | 0.35 |
| **Source of infection** |  |  |  |
|  **Lung** | 233 (48.6) | 116 (45.3) | > 0.9 |
|  **Abdominal** | 53 (11.1) | 44 (17.2) |  |
|  **Urinary tract** | 56 (11.7) | 36 (14.1) |  |
|  **Skin and soft tissue** | 33 (6.9) | 22 (8.6) |  |
|  **Catheter related** | 20 (4.2) | 11 (4.3) |  |
|  **Other** | 27 (5.6) | 8 (3.1) |  |
|  **Unknow** | 57 (11.9) | 19 (7.4) |  |
| **Laboratory findings on admission** |  |  |  |
|  **Lactate, mmol/L** | 2 [1;4] | 1.95 [1;4.1] | 0.84 |
|  **WBC** | 10 [3.8;17.3] | 14 [7.7;20] | <0.0001 |
|  **Serum creatinine level, µmol/L** | 128.5 [80;202.8] | 166 [109.5;254.5] | <0.0001 |
| **ICU management** |  |  |  |
|  **Cumulative fluid balance on 24h, mL** | 2300 [1000;4142] | 2300 [1000;4075] | 0.90 |
|  **Cumulative norepinephrine dose on 24h, mg/kg/** | 0.4165 [0.1797;0.9868] | 0.4385 [0.205;1.087] | 0.26 |
|  **Acute Kidney Injury (AKIN3) in 7 first days** | 173 (36.1) | 105 (41) | 0.20 |
|  **RRT during ICU stay** | 210 (44) | 129 (50.4) | 0.10 |
|  **Mechanical ventilation** | 380 (79.3) | 226 (88.3) | 0.002 |
| **Outcome** |  |  |  |
|  **ICU mortality** | 152 (31.7) | 96 (37.5) | 0.12 |
|  |  |  |  |

Variables are expressed as median (interquartile range) or number (percentage) as appropriate. ICU intensive care unit, COPD chronic obstructive pulmonary disease, SAPS2 Simplified Acute Physiology Score 2, SOFA Sequential Organ Failure Assessment, WBC white blood cell, AKIN Acute Kidney Injury Network classification, RRT Renal replacement therapy