Title: **Obesity paradox and functional outcomes in sepsis: a multicenter prospective study**

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**Appendix**

**The Sepsis-3 Criteria for the diagnosis of Sepsis and Septic Shock**

**1. Screening for Sepsis Patients in the Emergency Departments or hospital1**

Quick Sequential Organ Failure Assessment (qSOFA) was used to screen patients with sepsis. A 'positive qSOFA' was defined if the patient satisfied two of the following conditions:

1) Systolic blood pressure ≤ 100 mm Hg

2) Respiratory rate ≥ 22 breaths/min

3) Altered mental status (i.e., Glasgow Coma Scale ≤ 14)

A positive qSOFA score suggests a high risk of poor outcome in patients with suspected infection. These patients were promptly assessed for evidence of organ dysfunction (i.e. calculation of the total SOFA score to confirm the diagnosis of sepsis).

**2. Criteria for Sepsis1,2**

A patient was diagnosed with sepsis if the patient satisfied the following two conditions:

1) Probable or confirmed diagnosis of infection

2) Acute change in total SOFA score of ≥2 consequent to the infection. The baseline SOFA score was assumed to be zero in patients not known to have pre-existing organ dysfunction.

**3. Criteria for Septic Shock1,2**

Septic shock was defined as persistent arterial hypotension that required vasopressors to maintain a mean arterial pressure ≥65 mmHg and a serum lactate level >2 mmol/L despite fluid resuscitation.

**References**

1.Seymour CW, Liu VX, Iwashyna TJ, et al: Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:762-74

2. Singer M, Deutschman CS, Seymour CW et al: The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315: 801-810

**Table S1. Baseline demographic and clinical characteristics of patients according to obesity status before and after propensity score matching**.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Before matching | | | | After matching | | | |
| Variables | Obese (n=1335) | | non-obese (n=5089) | | Obese (n=1335) | | non-obese (n=1335) | |
| Physiologic variables |  | |  | |  | |  | |
| Mean blood pressure, mmHg | 70 [60-89.7] | | 68.3[58.7-83.3]\*\*\* | | 70 [60-89.7] | | 69.7[60-89.3] | |
| Heart rate, beats/mina | 105.5±24.4 | | 106.9±24.9 | | 105.5±24.4 | | 106.8±23.7 | |
| Respiratory rate, breaths/min | 22 [20-26] | | 22[20-26] | | 22 [20-26] | | 22[20-26] | |
| White-cell count, 10³/uL | 11.2[6.2-16.7] | | 11.1[6.4-16.4］ | | 11.2[6.2-16.7] | | 10.9 [5.8-16.3] | |
| Platelet count, 10³/uL | 152 [86-228] | | 163[92-248]\*\* | | 152 [86-228] | | 148[80-233] | |
| Bilirubin level, mg/dl | 0.9[0.6-1.9] | | 0.8[0.5-1.6]\*\*\* | | 0.9[0.6-1.9] | | 0.9 [0.5-1.9] | |
| Creatinine level, mg/dl | 1.4[0.9-2.3] | | 1.3[0.8-2.1]\*\*\* | | 1.4[0.9-2.3] | | 1.3 [0.8-2.3]\* | |
| Glucose, mg/dL | | 146 [113-208.3] | | 137[106-191]\*\*\* | | 146 [113-208.3] | | 140[107-195] | |
| Antibiotics before current sepsis diagnosis | 399(29.9) | | 1364(26.8) | | 399(29.9) | | 398 (29.8) | |
| Pathogen identification |  | |  | |  | |  | |
| Gram positive bacteria | 235(17.6) | | 911(17.9) | | 235(17.6) | | 258 (19.3) | |
| Gram negative bacteria | 605(45.3) | | 2173 (42.7) | | 605(45.3) | | 598 (44.8) | |
| Atypical bacteria | 4 (0.3) | | 32 (0.6) | | 4 (0.3) | | 7 (0.5) | |
| Fungus | 51 (3.8) | | 200 (3.9) | | 51 (3.8) | | 55 (4.1) | |
| Virus | 29 (2.2) | | 89 (1.7) | | 29 (2.2) | | 27 (2.0) | |

**Data are presented as median [interquartile range] or number (%).**

adata are presented as mean±SD.

**Table S2. Comparison of the compliance of sepsis bundle elements of patients according to obesity status after propensity score matching.**

|  |  |  |  |
| --- | --- | --- | --- |
| Variables | Obese (n=1335) | non-obese (n=1335) | P |
| 1 hour bundle |  |  |  |
| Lactate measurement | 1072 (80.3) | 1000 (74.9) | 0.754 |
| Obtaining blood cultures | 894 (67.0) | 851 (63.7) | 0.080 |
| Antibiotic administration | 352 (26.4) | 348 (26.1) | 0.860 |
| Rapid administration of crystalloida | 1205 (90.3) | 1190 (89.1) | 0.340 |
| Application of vasopressorsb | 530 (39.7) | 536 (40.1) | 0.813 |
| 3 hour bundle |  |  |  |
| Lactate measurement | 1115 (83.5) | 1109 (83.1) | 0.756 |
| Obtaining blood cultures | 1144 (85.7) | 1136 (85.1) | 0.661 |
| Antibiotic administration | 888 (66.5) | 888 (66.5) | 1.000 |
| Rapid administration of crystalloida | 1208 (90.5) | 1195 (89.5) | 0.402 |
| Application of vasopressorsb | 715 (53.6) | 718 (53.8) | 0.907 |

a In patients with hypotension or lactate > 4 mmol/L

b In patients with hypotension during or after fluid resuscitation to maintain a mean blood pressure ≥ of 65 mmHg.

**Data are presented as number (%).**

**Table S3. Multivariate Cox regression analysis for hospital mortality in propensity-matched cohorts.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Univariate | | Multivariate | |
| Variables | HR(95%CI) | P | HR(95%CI) | P |
| Age | 1.01(1.01-1.02) | <0.001 |  |  |
| Obese | 0.77 (0.67-0.88) | <0.001 | 0.78 (0.68-0.90) | 0.001 |
| CCI | 1.08 (1.06-1.11) | <0.001 | 1.06 (1.03-1.09) | <0.001 |
| CFS | 1.08 (1.05-1.12) | <0.001 | 1.06 (1.03-1.10) | 0.001 |
| SOFA | 1.12 (1.10-1.14) | <0.001 | 1.11 (1.08-1.13) | <0.001 |
| Septic shock | 1.48 (1.27-1.72) | <0.001 | 1.21 (1.03-1.42) | 0.022 |

CI, confidence interval; CCI, Charlson Comorbidity Index; CFS, clinical frailty score; HR, hazard ratio; SOFA, Sequential Organ Failure Assessment.

**Table S4. Baseline characteristics of patients admitted to the ICU after propensity score matching.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Obese (n=711) | non-obese (n=723) | P |
| Age | 71[61-78] | 70[60-78] | 0.209 |
| Male | 383 (53.9) | 408 (56.4) | 0.329 |
| BMI | 27.3[26.0-29.3] | 21.0[18.9-23.0] | <0.001 |
| Cormorbidities |  |  |  |
| Cardiovascular disease | 182 (25.6) | 186 (25.7) | 0.956 |
| Diabetes | 319 (44.9) | 301 (41.6) | 0.216 |
| Chronic lung disease | 103 (14.5) | 94 (13.0) | 0.414 |
| Chronic kidney disease | 126 (17.7) | 139 (19.2) | 0.463 |
| Chronic liver disease | 84 (11.8) | 88 (12.2) | 0.835 |
| Solid malignancy | 190 (26.7) | 206 (28.5) | 0.454 |
| Hematological malignancy | 56 (7.9) | 54 (7.5) | 0.772 |
| Connective tissue disease | 11 (1.5) | 17 (2.4) | 0.271 |
| Chronic neurologic disease | 139 (19.5) | 144 (19.9) | 0.861 |
| CCI | 5 [3-7] | 5[4-7] | 0.196 |
| CFS | 4[3-6] | 4[3-7] | 0.103 |
| ECOG performance status | 2[1-3] | 2[1-3] | 0.092 |
| SOFA | 7[5-9] | 7[5-9] | 0.184 |
| Septic shock | 197 (27.7) | 207 (28.6) | 0.698 |
| Laboratory variables |  |  |  |
| Lactate level, mmol/L | 2.9[1.6-5.2] | 3.1[1.8-5.5] | 0.308 |
| C-reactive protein, mg/dL | 13.0[4.1-23.8] | 11.8[5.0-21.6] | 0.267 |
| Glucose, mg/dL | 151.5[115-225] | 144.5[108-210] | 0.163 |
| Primary site of infection |  |  | 0.353 |
| pulmonary | 242 (34.0) | 275 (38.0) |  |
| abdominal | 228 (32.1) | 210 (29.0) |  |
| urinary | 119 (16.7) | 127 (17.6) |  |
| Skin or soft tissue | 33 (4.6) | 27 (3.7) |  |
| Catheter related | 7 (1.0) | 9 (1.2) |  |
| Neurologic | 7 (1.0) | 2 (0.3) |  |
| Systemic infections without a primary site | 75 (10.5) | 73 (10.1) |  |
| Type of infection |  |  | 0.973 |
| Community acquired | 508 (71.4) | 516 (71.4) |  |
| Nosocomial | 203 (28.6) | 207 (28.6) |  |
| Multidrug-resistant organism | 181 (25.5) | 186 (25.7) | 0.338 |
| Combination antibiotic therapy | 474 (66.9) | 493 (68.3) | 0.564 |
| Adequate antimicrobial therapy | 635 (89.3) | 646 (89.3) | 0.921 |
| Source control of sepsis | 127 (17.9) | 143 (19.8) | 0.353 |
| Adjunctive corticosteroid therapy | 184 (25.9) | 213 (29.5) | 0.130 |

CI, confidence interval; CCI, Charlson Comorbidity Index; CFS, clinical frailty score; HR, hazard ratio; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment.

**Data are presented as median [interquartile range] or number (%).**

**Table S5. Clinical outcomes in patients admitted to the ICU after propensity matching.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Obese (n=711) | non-obese (n=723) | P |
| Primary outcomes |  |  |  |
| Hospital mortality | 236 (33.2) | 313 (43.3) | <0.001 |
| Hospital days | 17 [9-33] | 18 [8-35] | 0.240 |
| Secondary outcomes |  |  |  |
| ICU mortality | 177 (24.9) | 222 (30.7) | 0.014 |
| ICU days | 5 [2-11] | 5 [2-12] | 0.167 |
| home discharge | 336 (70.7) | 263 (64.1) | <0.001 |
| CFS at discharge | 5[3-7] | 5[3-7] | 0.026 |
| Frail (CFS ≥ 5) | 248 (52.2) | 247 (60.2) | 0.016 |

CFS, clinical frailty score; ICU, intensive care unit.

**Data are presented as median [interquartile range] or number (%).**

**Table S6. Cox analysis for hospital mortality in patients admitted to the ICU after matching.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Univariate | | Multivariate | |
|  | HR(95%CI) | P | HR(95%CI) | P |
| Age | 1.01 (1.00-1.01) | 0.069 |  |  |
| Obese | 0.81 (0.69-0.96) | 0.017 | 0.83 (0.70-0.98) | 0.031 |
| CCI | 1.06 (1.02-1.09) | 0.001 | 1.05 (1.02-1.08) | 0.004 |
| CFS | 1.03 (0.99-1.07) | 0.122 |  |  |
| SOFA | 1.11 (1.08-1.13) | <0.001 | 1.10 (1.08-1.13) | <0.001 |
| Septic shock | 1.36 (1.14-1.63) | 0.001 |  |  |

CI, confidence interval; CCI, Charlson Comorbidity Index; CFS, clinical frailty score; HR, hazard ratio; SOFA, Sequential Organ Failure Assessment.

**Table S7. Cox analysis for home discharge in patients admitted to the ICU after matching.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Univariate | | Multivariate | |
|  | HR(95%CI) | P | HR(95%CI) | P |
| Age | 1.00 (0.99-1.00) | 0.105 |  |  |
| Obese | 1.41 (1.20-1.65) | <0.001 | 1.36 (1.16-1.60) | <0.001 |
| CCI | 0.95 (0.91-0.98) | 0.001 |  |  |
| CFS | 0.88 (0.85-0.92) | <0.001 | 0.87 (0.84-0.91) | <0.001 |
| SOFA | 0.94 (0.92-0.97) | <0.001 | 0.94 (0.92-0.97) | <0.001 |
| Septic shock | 0.82 (0.68-0.99) | 0.041 |  |  |

CI, confidence interval; CCI, Charlson Comorbidity Index; CFS, clinical frailty score; HR, hazard ratio; SOFA, Sequential Organ Failure Assessment.

**Table S8. Organ dysfunction after propensity score matching.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Obese (n=711) | non-obese (n=723) | P |
| Day 3 |  |  |  |
| SOFA | 8 [5-12] | 10 [6-13] | <0.001 |
| Lactate | 1.5 [1-2.5] | 1.9 [1.2-3.3] | 0.001 |
| Vasopressors | 319 (23.9) | 390 (53.9) | 0.002 |
| MV | 284 (39.9) | 363 (50.2) | <0.001 |
| RRT | 147 (20.7) | 180 (24.9) | 0.141 |
| Day 7 |  |  |  |
| SOFA | 8 [5-11] | 9 [6-11] | 0.065 |
| Lactate | 1.4 [1-2] | 1.4 [1.1-2.2] | 0.578 |
| Vasopressors | 110 (8.2) | 132 (18.3) | 0.252 |
| MV | 179 (25.2)) | 223 (30.8) | 0.056 |
| RRT | 83 (6.2) | 81 (11.2) | 0.220 |

CI, confidence interval; CCI, Charlson Comorbidity Index; CFS, clinical frailty score; HR, hazard ratio; SOFA, Sequential Organ Failure Assessment; MV, mechanical ventilator; RRT, renal replacement therapy.

**Data are presented as median [interquartile range] or number (%).**

**Table S9. Interventions and complications during intensive care unit (ICU) stay in patients transferred to the ICU after propensity score matching.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Obese (n=711) | non-obese (n=723) | P |
| MV | 365 (51.3) | 441 (61.0) | <0.001 |
| MV duration | 6[2-14] | 7[3-16] | 0.550 |
| Tracheostomy at ICU dischargea | 43 (8.1) | 60 (12) | 0.035 |
| RRT | 226 (31.8) | 246 (34.0) | 0.367 |
| CPR | 41 (5.8) | 57 (7.9) | 0.112 |
| Major bleedingb | 20 (2.8) | 20 (2.8) | 0.957 |
| Arrhythmia | 148 (20.8) | 145 (20.1) | 0.721 |
| ARDS | 23 (3.2) | 43 (5.9) | 0.014 |
| UTI | 25 (3.5) | 20 (2.8) | 0.415 |
| BSI | 17 (2.4) | 22 (3.0) | 0.448 |
| VAP | 8 (1.1) | 17 (2.4) | 0.076 |

a We analyzed 534 patients in the obese group and 501 patients in the non-obese group who survived discharge from the intensive care unit.

bMajor bleeding was defined as a case requiring embolization, endoscopic hemostasis, or surgery.

MV, mechanical ventilator;ICU, intensive care unit; RRT, renal replacement therapy;CPR, cardiopulmonary resuscitation; ARDS, acute respiratory distress syndrome; UTI, Urinary Tract Infection; BSI, blood stream infections; VAP,ventilator - associated pneumonia.

**Data are presented as median [interquartile range] or number (%).**

**Table S10. Ethical approval of each center**

|  |  |  |
| --- | --- | --- |
| Institution | Institutional Review Board numbers | Approval date |
| Asan Medical Center | 2018-0675 | 6.12.2018 |
| Chonnam national university hospital | CNUH2029075 | 3.19.2019 |
| Chungnam national university hospital | 2019-11-048-001 | 1.3.2020 |
| Chungnam National University Sejong Hospital | 2020-08-017 | 8.27.2020 |
| Daegu Catholic University Medical Center | CR-18-163-L | 11.28.2018 |
| Hallym University Sacred heart hospital | 2018-09-004 | 10.5.2018 |
| Hanyang University Guri Hospital | 2020-08-015 | 9.4.2020 |
| Inje University Sanggye Paik Hospital | 2018-08-014 | 9.21.2018 |
| Jeju National University Hospital | 2018-06-012 | 7.17.2018 |
| Jeonbuk national university hospital | CUH 2018-10-027 | 3.13.2019 |
| Kangwon national university hostipal | 2018-08-004-001 | 11.7.2018 |
| Korea University Anam Hospital | 2 0 1 9 A N 0 0 2 7 | 1.17.2019 |
| Pusan National University Yangsan Hospital | 05–2019–092 | 7.11.2019 |
| Samsung Medical Center | 2018-05-108 | 5.24.2018 |
| Seoul National University Bundang Hospital | B-1810-500-402 | 10.11.2018 |
| Seoul national university hospital | H-1808-135-967 | 9.19.2018 |
| Severance Hospital | 4-2020-0706 | 8.5.2020 |
| Ulsan university hospital | UUH 2018-08-003 | 9.3.2018 |
| Yeungnam University Medical Center | 2020-08-051 | 9.17.2020 |

**Table S11. The number of patients enrolled from each hospital used in the analysis**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Before PSM | | After PSM | |
| Hospital No | Obese | Non-obese | Obese | Non-obese |
| A | 10 | 69 | 10 (0.7) | 9 (0.7) |
| B | 12 | 86 | 12 (0.9) | 22 (1.6) |
| C | 18 | 125 | 18 (1.3) | 26 (1.9) |
| D | 38 | 264 | 38 (2.8) | 54 (4.0) |
| E | 98 | 379 | 98 (7.3) | 115 (8.6) |
| F | 41 | 131 | 41 (3.1) | 35 (2.6) |
| G | 75 | 304 | 75 (5.6) | 79 (5.9) |
| H | 364 | 1370 | 364 | 390 |
| I | 1 | 4 | 1 (0.1) | 1 (0.1) |
| J | 6 | 18 | 6 (0.4) | 3 (0.2) |
| K | 84 | 350 | 84 (6.3) | 75 (5.6) |
| L | 2 | 12 | 2 (0.1) | 4 (0.3) |
| M | 187 | 626 | 187 (14.0) | 197 (14.8) |
| N | 171 | 541 | 171 (12.8) | 136 (10.2) |
| O | 97 | 264 | 97 (7.3) | 76 (5.7) |
| P | 49 | 186 | 49 (3.7) | 46 (3.4) |
| Q | 27 | 125 | 27 (2.0) | 34 (2.5) |
| R | 23 | 105 | 23 (1.7) | 13 (1.0) |
| S | 32 | 130 | 32 (2.4) | 20 (1.5) |

PSM; propensity score matching.

**Fig. S1** **Kaplan-Meier analysis in subgroup**

1. Subgroup analysis of mortality at 28 days according to obesity. Log rank χ2=8.83, p=0.003

**B.** Subgroup analysis of home discharge according to obesity. Log rank χ2=17.43, p <0.001

