

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

The impact of body mass index on survival of medical patients with sepsis: a prospective cohort study in a university hospital in China

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-021979
Article Type:	Research
Date Submitted by the Author:	29-Jan-2018
Complete List of Authors:	Zhou, Qingtao; Peking University Third Hospital, Department of pulmonary and critical care medicine Wang, Meng; Peking University Third Hospital, Department of pulmonary and critical care medicine Li, Shuo; Peking University Third Hospital, Emergency Department Zhang, Jing; Peking University Third Hospital, Department of pulmonary and critical care medicine Ma, Qingbian; Peking University Third Hospital, Emergency Department Ding, Yanling; Peking University Third Hospital, Department of pulmonary and critical care medicine Ge, Hongxia; Peking University Third Hospital, Emergency Department Shen, Ning; Peking University Third Hospital, Department of pulmonary and critical care medicine Zheng, Yaan; Peking University Third Hospital, Emergency Department Sun, Yongchang; Peking University Third Hospital, Department of pulmonary and critical care medicine
Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, INFECTIOUS DISEASES, THORACIC MEDICINE

SCHOLARONE™
Manuscripts



1
2
3
4 **1 The impact of body mass index on survival of medical patients with sepsis: a**
5
6 **2 prospective cohort study in a university hospital in China**
7

8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

3
4 Qingtao Zhou¹, Meng Wang¹, Shuo Li², Jing Zhang¹, Qingbian Ma², Yanling Ding¹,
5 Hongxia Ge², Ning Shen¹, Yaan Zheng², Yongchang Sun^{1*}

6
7 ¹ Department of Pulmonary and Critical Care Medicine, Peking University Third
8 Hospital, Beijing, China.

9 ² Emergency Department, Peking University Third Hospital, Beijing, China.

10
11 ***Corresponding author:** Yongchang Sun, Department of Respiratory and Critical
12 Care Medicine, Peking University Third Hospital, 49 North Garden Road, Haidian
13 District, Beijing 100191, P R China. Email: suny@bjmu.edu.cn

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23 **Abstract**

24 **Objective** To evaluate the impact of body mass index (BMI) on survival of a Chinese
25 cohort of medical patients with sepsis.

26 **Design** A single-center prospective cohort study conducted from May 2015 to April
27 2017.

28 **Setting** A tertiary care university hospital in China.

29 **Participants** 178 patients with sepsis admitted to the medical intensive care unit (ICU)
30 were included.

31 **Main outcome measures** The primary outcome was 90-day mortality. The secondary
32 outcomes were in-hospital mortality, length of ICU stay, and length of hospital stay.

33 **Results** The median age (interquartile range) was 78 (66-84) years and the majority of
34 patients (77.0%) were older than 65 years. The 90-day mortality was 47.2%. The
35 in-hospital mortality was 41.6%, and the length of ICU stay and hospital stay were 12
36 (5-22) and 15 (9-28) days, respectively. Compared with in-hospital survivors,
37 non-survivors had significantly lower BMI and PaO₂/FiO₂ (both p < 0.05), and higher
38 lactate, bilirubin, INR, sequential organ failure assessment (SOFA) score, and
39 APACHE II score (all p < 0.05). Those with healthcare-acquired infections,
40 hypotension, oliguria, septic shock, and intubation were also at increased risk of death
41 (all p < 0.05). Cox proportional hazard regression analysis identified that sequential
42 organ failure assessment (SOFA) score (HR = 1.229, p < 0.001), APACHE II score
43 (HR = 1.050, p < 0.001) and BMI (HR = 0.940, p = 0.029) were all independent
44 predictors of the 90-day mortality. Patients were divided into four groups based on

1
2
3
4 45 BMI (underweight, normal, overweight, and obese). Differences in survival among
5
6 46 the four groups were demonstrated by Kaplan-Meier survival analysis ($p = 0.008$),
7
8 47 with the underweight patients showing a lower survival rate.

9
10
11 48 **Conclusions** SOFA score, APACHE II score and BMI were independent factors
12
13 49 associated with survival in a Chinese cohort of medical patients with sepsis, while
14
15 50 underweight patients were at higher risk of death.

16
17
18 51
19
20 52 **Key words:** Sepsis; Septic shock; Body mass index; Critical care; Mortality

21
22
23 53
24
25 54 **Strengths and limitations of this study**

26
27
28 55 Our prospective observational cohort study was focused on medical patients with
29
30 56 sepsis.

31
32
33 57 The clinical characteristics and clinical outcomes of medical patients with sepsis were
34
35 58 analysed in a university hospital in China.

36
37
38 59 The impact of BMI on survival of medical patients with sepsis was evaluated.

39
40 60 Our analyses were limited by the use of weight ascertained at ICU admission, rather
41
42 61 than the patient's true outpatient weight.

43
44
45 62

46
47
48 63

49
50
51 64

52
53
54 65

55
56
57 66

67 **Introduction**

68 Sepsis is a major cause of morbidity and mortality worldwide ^[1]. Of these
69 patients, half are treated in the intensive care unit (ICU) ^[2]. In a national
70 population-based study of sepsis in Spain, medical diagnostic categories were the
71 majority of patients who developed sepsis, while only 26% of surgical patients
72 developed sepsis ^[3]. Many studies have analyzed the characteristics and clinical
73 outcomes of surgical patients with sepsis but few of these have focused on medical
74 patients.

75 Body mass index (BMI) is a simple index of weight-for-height that is commonly
76 used to classify whether adults are underweight, overweight and obese ^[4]. Several
77 studies have examined the effects of BMI on mortality with conflicting conclusions.
78 Lower mortality in the obese has been observed in some studies ^[5-9], but some
79 researchers believe that the true paradox may lie in the variations in sepsis
80 interventions, such as the administration of resuscitation fluids and antimicrobial
81 therapy ^[6]. In other studies, morbidly obese and underweight patients have been
82 shown to be associated with higher mortality ^[10,11]. Thus, the impact of BMI on
83 survival of patients with sepsis is still controversial.

84 As the relationship between BMI and clinical outcomes of sepsis is complex,
85 which may be related partly to differences in patient characteristics, we therefore set
86 out to evaluate prospectively the impact of BMI on survival in a cohort of medical
87 patients with sepsis admitted to the medical ICU in a university hospital.

88

89 **Patients and Methods**

90 **Design**

91 This was a prospective cohort study, which was conducted in the medical ICU of
92 a university-affiliated urban teaching hospital from May 2015 to April 2017.

93 **Subjects**

94 Hospitalized patients admitted to the medical ICU with sepsis acquired in the
95 community or in a hospital were eligible for the study if they met any of the following
96 criteria of severe sepsis [12]: (1) sepsis-induced hypotension, (2) lactate above upper
97 laboratory level limits, (3) urine output $<0.5 \text{ mL Kg}^{-1} \text{ h}^{-1}$ for more than 2 h despite
98 adequate fluid resuscitation, (4) acute lung injury with $\text{Pao}_2/\text{Fio}_2 < 250$ in the absence
99 of pneumonia as infection source, (5) acute lung injury with $\text{Pao}_2/\text{Fio}_2 < 200$ in the
100 presence of pneumonia as infection source, (6) creatinine $>2.0 \text{ mg/dL}$ ($176.8 \text{ }\mu\text{mol/L}$),
101 (7) bilirubin $>2 \text{ mg/dL}$ ($34.2 \text{ }\mu\text{mol/L}$), (8) platelet count $<100,000 \text{ }\mu\text{L}$, and (9)
102 coagulopathy (international normalized ratio >1.5).

103 Patients were excluded from the study if they met one of the following criteria: (1)
104 the patient had sepsis that required surgical treatment, or was caused by a surgical
105 procedure related infection, (2) age <18 years, (3) the patient had a positive HIV
106 antibody titer or had known/suspected tuberculosis at baseline, (4) expected lifespan
107 <3 months due to severe pre-existing comorbidities, (5) active Do Not Resuscitate or
108 Do Not Intubate order, and (6) pregnant.

109 All patients accepted treatment according to the international guidelines for
110 management of sepsis and septic shock [12,13]. We collected the following

1
2
3
4 111 demographic and clinical data: patient's gender, age, weight, height, primary site of
5
6 112 infection, community-acquired or hospital-acquired infection, hypotension, lactate
7
8 113 level, oliguria, $\text{PaO}_2/\text{FiO}_2$, serum creatinine, total bilirubin, platelets, international
9
10 114 normalized ratio (INR), Glasgow coma scale, SOFA score, acute physiology and
11
12 115 chronic health evaluation (APACHE) II score, septic shock, non-invasive ventilation,
13
14 116 intubation, positive blood culture, length of ICU stay, and length of hospital stay.
15
16
17 117 Those who survived to discharge were followed for at least 90 days.

18
19
20 118 BMI is defined as the weight in kilograms divided by the square of the height in
21
22 119 meters (kg/m^2). Using the World Health Organization (WHO) criteria for designation
23
24 120 of BMI ^[4], patients were classified as underweight ($\text{BMI} < 18.50 \text{ kg}/\text{m}^2$), normal
25
26 121 weight ($\text{BMI} = 18.50$ to $24.99 \text{ kg}/\text{m}^2$), overweight ($\text{BMI} = 25.0$ to $29.99 \text{ kg}/\text{m}^2$), and
27
28 122 obese ($\text{BMI} \geq 30.0 \text{ kg}/\text{m}^2$).

32 123 **Outcomes**

33
34
35 124 The primary outcome was 90-day mortality, while the secondary outcomes were
36
37 125 in-hospital mortality, length of ICU stay, and length of hospital stay.

38 126 **Statistical analysis**

39
40
41 127 Continuous variables were expressed as median (interquartile range) and
42
43 128 categorical variables as numbers (%). Clinical data were compared among the
44
45 129 in-hospital survivors and non-survivors. Continuous variables were compared using
46
47 130 the non-parametric Mann–Whitney U test, and categorical variables were compared
48
49 131 using the Chi squared test. Cox proportional hazard regression analysis was
50
51 132 undertaken to assess the factors associated with 90-day mortality. The variables
52
53
54
55
56
57
58
59
60

1
2
3
4 133 significantly associated with 90-day non-survival in the univariate analysis were used
5
6 134 in the Cox proportional hazard regression analysis.

7
8 135 Patients were divided into four groups based on BMI (underweight, normal,
9
10 136 overweight, and obese). Clinical data were compared between the four groups, where
11
12
13 137 continuous variables were compared using the non-parametric Kruskal-Wallis H test,
14
15 138 and categorical variables were compared using the Chi squared test. Kaplan-Meier
16
17 139 survival curves were constructed to show the survival probabilities at day-90
18
19
20 140 according to BMI classification, and compared using the log rank test.

21
22
23 141 All analyses were conducted using SPSS, version 22.0 (IBM, Armonk, NY,
24
25 142 USA). A p value <0.05 was considered significant.

26
27
28 143

29 30 144 **Results**

31
32
33 145 In total, 178 medical patients with sepsis were included in this study, with male
34
35 146 patients accounting for 65.2% (n=116). The median age (interquartile range) was 78
36
37 147 (66-84) years, and most patients were at least 65 years old (137/178 cases, 77.0%).
38
39 148 The most common primary site of infection was the lung (131 cases, 73.6%),
40
41 149 followed by abdomen (15 cases, 8.4%), urinary tract (13 cases, 7.3%), gastrointestinal
42
43 150 tract (12 cases, 6.7%) and other sites (7 cases, 3.9%). Septic shock patients accounted
44
45 151 for 33.1% (59 cases). Blood culture was positive in 38 patients (21.3%). The 90-day
46
47 152 mortality was 47.2% (84/178 cases), and the in-hospital mortality was 41.6% (74/178
48
49 153 cases). The length of ICU stay and the length of hospital stay were 12 (5-22) and 15
50
51 154 (9-28) days, respectively.

1
2
3
4 155 Compared with in-hospital survivors, non-survivors had significantly lower BMI
5
6 156 and PaO₂/FiO₂ (both p < 0.05), higher lactate, bilirubin, INR, SOFA score and
7
8 157 APACHE II score (all p < 0.05). Meanwhile, more patients died with
9
10 158 healthcare-acquired infections, hypotension, oliguria, septic shock, and intubation (all
11
12
13 159 p < 0.05) (table 1).

14
15
16 160 Cox proportional hazard regression analysis was conducted and the independent
17
18 161 factors for 90-day death were identified as SOFA score (HR = 1.220, p < 0.001),
19
20 162 APACHE II score (HR = 1.050, p < 0.001) and BMI (HR = 0.940, p = 0.029) (table
21
22
23 163 2).

24
25 164 Patients were divided into four groups based on BMI (underweight, normal,
26
27 165 overweight, and obese). The percentage of males (72.7%, 71.4%, 55.6%, and 18.2%,
28
29 166 p = 0.002), chronic obstructive pulmonary disease (24.2%, 21.4%, 0, and 27.3%,
30
31 167 p=0.017), hypotension (57.6%, 34.7%, 25.0%, and 9.1%, p = 0.007), septic shock
32
33 168 (57.6%, 30.6%, 25.0%, and 9.1%, p = 0.004), in-hospital mortality (60.6%, 41.8%,
34
35 169 30.6%, and 18.2%, p = 0.027) and 90-day mortality (66.7%, 48.0%, 36.1%, and
36
37 170 18.2%, p = 0.015) were statistically different among the four groups (table 3).

38
39
40
41 171 Kaplan-Meier survival curves were constructed to show the survival probabilities
42
43 172 at day-90 according to BMI classification and these were compared using the log rank
44
45 173 test, which also showed that higher BMI was associated with better prognosis
46
47
48 174 (p=0.008) (figure 1).

49
50
51
52 175

53 176 **Discussion**

1
2
3
4 177 This prospective observational cohort study was focused on medical patients with
5
6 178 sepsis admitted to the ICU, and the results showed that SOFA score, APACHE II score
7
8 179 and BMI were identified as independent factors for 90-day mortality by Cox
9
10 180 regression analysis. Mortality increased with increasing SOFA and APACHE II score,
11
12 181 which was consistent with previous studies^[14-16]. However, BMI was also found to be
13
14 182 an independent predictor of survival, where 90-day mortality decreased with an
15
16 183 increase in BMI. While studies examining the risk factors associated with outcomes in
17
18 184 sepsis reached inconsistent conclusions on the association of BMI with mortality, our
19
20 185 results confirmed a protective effect of higher BMI on mortality in patients with
21
22 186 sepsis caused by medical conditions.

23
24
25
26
27
28 187 Globally, the prevalence of obesity has reached epidemic proportions, especially
29
30 188 in developed countries. BMI is still a useful proxy of overall health because it is
31
32 189 highly correlated with body surface area, which is commonly used as a surrogate
33
34 190 measure in obesity classification. Even though it is widely accepted that obesity is a
35
36 191 risk factor for diabetes mellitus, hypertension, and cardiovascular diseases, the present
37
38 192 study and several other studies have indicated that overweight and obese patients with
39
40 193 sepsis tend to experience lower mortality. This has been called the “obesity paradox”
41
42 194 ^[5-9,17]. Although some researchers have expressed doubt that the true paradox may lie
43
44 195 in the variations in sepsis interventions ^[6,18], a meta-analysis concluded that
45
46 196 individuals who are considered overweight or obese have a reduced adjusted mortality
47
48 197 when admitted to the ICU with sepsis or septic shock ^[8]. Recently another
49
50 198 meta-analysis also concluded that being overweight was associated with lower
51
52
53
54
55
56
57
58
59
60

1
2
3
4 199 mortality (OR 0.87, 95% CI 0.77-0.97, $p = 0.02$) compared with obese (OR 0.89, 95%
5
6 200 CI 0.72-1.10, $p = 0.29$) and morbidly obese (OR 0.64, 95% CI 0.38-1.08, $p = 0.09$)
7
8 201 patients who did not exhibit significantly reduced mortality compared with normal
9
10 202 weight patients ^[19]. In a large and nationally representative sample of over 1,000
11
12 203 hospitals in the US, obesity was found to be significantly associated with a 16%
13
14 204 decrease in the odds of dying among sepsis patients who were hospitalized ^[20].

15
16
17
18 205 Underweight patients with sepsis may be more common in developing countries
19
20 206 than developed countries. In the present study, the percentages of underweight,
21
22 207 normal weight, overweight and obese patients were 18.4%, 55.3%, 20.1%, and 6.1%,
23
24 208 respectively, while those with sepsis in a study in Canada and the US represented
25
26 209 6.8%, 35.3%, 28.3%, and 29.0% ^[6]. Being underweight was found to be one of the
27
28 210 independent risk factors of mortality in a study on the correlation between surgical
29
30 211 site infection and mortality ^[10]. Furthermore, Lee et al ^[11] also reported that being
31
32 212 underweight was associated with mortality in patients with severe sepsis and septic
33
34 213 shock.

35
36
37
38
39
40 214 Consequently, previous studies on sepsis have shown that overweight and obese
41
42 215 patients have a decreased risk for mortality, and underweight patients may have a
43
44 216 higher mortality. However, BMI has not been shown to be an independent factor for
45
46 217 clinical outcomes by multivariable analyses. In our cohort of medical patients with
47
48 218 sepsis, which mainly included the elderly and less obese patients, BMI was identified
49
50 219 as an independent factor for survival. The mechanism of the correlation between BMI
51
52 220 and mortality of sepsis is unclear. There are several potential reasons that could
53
54
55
56
57
58
59
60

1
2
3
4 221 explain this. First, higher BMI resulted in more fat reserves, and patients could have a
5
6 222 greater capacity to cope with the inflammatory response during sepsis and
7
8 223 sepsis-associated acute lung injury ^[21-23]. Furthermore, they may be able to tolerate
9
10 224 extensive weight loss and dysfunction associated with critical illness ^[24]. Secondly, a
11
12
13 225 higher BMI can lead to an increased level of lipoproteins. High-density lipoproteins
14
15 226 may not only bind and inactivate lipopolysaccharide (LPS) or other harmful bacterial
16
17
18 227 products released during sepsis ^[25], but also modulate adhesion molecule expression,
19
20 228 upregulate endothelial nitric oxide synthase, and counteract oxidative stress ^[26].
21
22
23 229 Thirdly, higher BMI can lead to increased adipose tissue deposition. Adipose tissue is
24
25 230 increasingly being considered as a functional endocrine organ and associated with
26
27
28 231 increased renin-angiotensin system activity ^[27]. It appears to have protective
29
30 232 hemodynamic effects during sepsis and may decrease the need for fluid or
31
32
33 233 vasopressor support ^[18,28]. This may be the reason why the percentages of patients
34
35 234 with hypotension and with septic shock in the four groups decreased as BMI
36
37
38 235 increased in the present study.

39
40 236 It should be noted that in the majority of our patients (73.6%) sepsis was
41
42 237 associated with pulmonary infection, a much higher percentage as compared to other
43
44
45 238 studies. Ranieri et al ^[29] reported that the primary sites of infection in adults with
46
47
48 239 septic shock were lung (43.9%), abdomen (30.0%), urinary tract (12.3%), skin (5.5%)
49
50 240 and other sites (8.3%). Scheer et al ^[30] found that the most common primary site of
51
52
53 241 infection was different between medical and surgical patients. In medical patients,
54
55 242 lung was the most common primary site (42.0%-56.7%), while it was abdomen

1
2
3
4 243 (48.4%-64.4%) in surgical patients.
5

6 244 There were several limitations to our study. Firstly, the BMI of our patients
7
8 245 ranged from 12.11 to 32.46. Morbidly obese patients were not included in the study,
9
10 246 although morbidly obese patients are not common in this country. Secondly, the
11
12 247 present study used weight ascertained at ICU admission, rather than the patient's true
13
14 248 outpatient weight. This practice may misclassify the BMI category in as many as
15
16 249 21.9% of patients due to lack of fluid balance adjustment ^[31]. Lastly, although 178
17
18 250 patients were included in this prospective study, it was still difficult to avoid
19
20 251 sample-related bias, because a large proportion of our patients were older than 65
21
22 252 years.
23
24
25
26
27

28 253 **Conclusions**

29
30 254 To our knowledge, this is the first prospective cohort study that focused on
31
32 255 medical patients with sepsis, showing that SOFA score, APACHE II score and BMI
33
34 256 were independent predictors of survival, and more importantly, underweight patients
35
36 257 were at higher risk of death.
37
38
39

40 258

41 259 **Acknowledgements**

42
43 260 Not applicable.
44

45 261

46 262 **Authors' contributions**

47
48 263 QTZ, YCS, YAZ designed the study. QTZ, YCS, NS, YAZ, and QBM coordinated
49
50 264 the study. MW, JZ, YLD, SL, and HXG were responsible for patient screening,
51
52
53
54
55
56

1
2
3
4 265 enrollment, and follow-up. QTZ, MW, and YCS analyzed the data. QTZ drafted the
5
6 266 manuscript. YCS critically revised the manuscript. All authors had full access to all
7
8 267 study data, read and approved the final version of the manuscript.
9

10
11 268

12 13 269 **Funding**

14
15
16 270 None.
17

18
19 271

20 21 272 **Competing interests**

22
23 273 None declared.
24

25
26 274

27 28 275 **Ethics approval and consent to participate**

29
30 276 The study protocol was approved (approval number M2015021) by the ethics
31
32 277 committee of Peking University Third Hospital, Beijing, China. All patients or their
33
34 278 legally authorized representatives provided written informed consent to participate in
35
36 279 the study.
37
38
39

40
41 280

42 43 281 **Data sharing statement**

44
45 282 No additional data are available.
46

47
48 283

49 50 284 **References**

- 51
52 285 1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus
53
54 286 Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315:801-10.
55
56
57

- 1
2
3
4 287 2. Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med* 2013;369:2063.
5
6 288 3. Bouza C, López-Cuadrado T, Saz-Parkinson Z, et al. Epidemiology and recent trends of
7
8 289 severe sepsis in Spain: a nationwide population-based analysis (2006-2011). *BMC Infect Dis*
9
10
11 290 2014; 14:3863.
12
13 291 4. WHO classification of body mass index (BMI). [[http://apps.who.int/bmi/index.jsp?introPage=](http://apps.who.int/bmi/index.jsp?introPage=intro_3.html)
14
15 292 [intro_3.html](http://apps.who.int/bmi/index.jsp?introPage=intro_3.html)] Accessed on 2 March 2015.
16
17
18 293 5. Wurzinger B, Dünser MW, Wohlmuth C, et al. The association between body-mass index and
19
20 294 patient outcome in septic shock: a retrospective cohort study. *Wien Klin Wochenschr* 2010;122:
21
22 295 31-6.
23
24
25 296 6. Arabi YM, Dara SI, Tamim HM, et al. Clinical characteristics, sepsis interventions and
26
27 297 outcomes in the obese patients with septic shock: an international multicenter cohort study.
28
29 298 *Crit Care* 2013;17:R72.
30
31
32 299 7. Prescott HC, Chang VW, O'Brien JM Jr, et al. Obesity and 1-year outcomes in older
33
34 300 Americans with severe sepsis. *Crit Care Med* 2014;42:1766-74.
35
36
37 301 8. Pepper DJ, Sun J, Welsh J, et al. Increased body mass index and adjusted mortality in ICU
38
39 302 patients with sepsis or septic shock: a systematic review and meta-analysis. *Crit Care*
40
41 303 2016;20:181.
42
43
44 304 9. Gaulton TG, Marshall MacNabb C, Mikkelsen ME, et al. A retrospective cohort study
45
46 305 examining the association between body mass index and mortality in severe sepsis. *Intern*
47
48 306 *Emerg Med* 2015;10:471-9.
49
50
51 307 10. Giles KA, Hamdan AD, Pomposelli FB, et al. Body mass index: surgical site infections and
52
53 308 mortality after lower extremity bypass from the National Surgical Quality Improvement
54
55
56
57
58
59
60

- 1
2
3
4 309 Program 2005-2007. *Ann Vasc Surg* 2010;24:48-56.
- 5
6 310 11. Lee SM, Kang JW, Jo YH, et al. Underweight is associated with mortality in patients with
7
8 311 severe sepsis and septic shock. *Intensive Care Med Exp* 2015; 3:A876.
- 9
10
11 312 12. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines
12
13 313 for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013;41:580-637.
- 14
15
16 314 13. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International
17
18 315 Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med* 2017;
19
20 316 43:304-77.
- 21
22
23 317 14. de Carvalho MA, Freitas FG, Silva Junior HT, et al. Mortality predictors in renal transplant
24
25 318 recipients with severe sepsis and septic shock. *PLoS One* 2014;9:e111610.
- 26
27
28 319 15. Innocenti F, Tozzi C, Donnini C, et al. SOFA score in septic patients: incremental prognostic
29
30 320 value over age, comorbidities, and parameters of sepsis severity. *Intern Emerg Med* 2017 Feb
31
32 321 10. Doi:10.1007/s11739-017-1629-5.[Epub ahead of print]
- 33
34
35 322 16. Song JE, Kim MH, Jeong WY, et al. Mortality Risk Factors for Patients with Septic
36
37 323 Shock after Implementation of the Surviving Sepsis Campaign Bundles. *Infect*
38
39 324 *Chemother* 2016;48:199-208.
- 40
41
42 325 17. Atamna A, Elis A, Gilady E, et al. How obesity impacts outcomes of infectious diseases. *Eur*
43
44 326 *J Clin Microbiol Infect Dis* 2017; 36:585-91.
- 45
46
47 327 18. Taylor SP, Karvetski CH, Templin MA, et al. Initial fluid resuscitation following adjusted
48
49 328 body weight dosing is associated with improved mortality in obese patients with suspected
50
51 329 septic shock. *J Crit Care* 2018;43:7-12.
- 52
53
54
55 330 19. Wang S, Liu X, Chen Q, et al. The role of increased body mass index in outcomes of sepsis: a

- 1
2
3
4 331 systematic review and meta-analysis. *BMC Anesthesiol* 2017;17:118.
5
6 332 20. Nguyen AT, Tsai CL, Hwang LY, et al. Obesity and Mortality, Length of Stay and Hospital
7
8 333 Cost among Patients with Sepsis: A Nationwide Inpatient Retrospective Cohort Study. *PLoS*
9
10 334 *One* 2016; 11:e0154599.
11
12
13 335 21. Stapleton RD, Dixon AE, Parsons PE, et al. The association between BMI and plasma
14
15 336 cytokine levels in patients with acute lung injury. *Chest* 2010;138:568-77.
16
17
18 337 22. Stapleton RD, Suratt BT. Obesity and nutrition in acute respiratory distress syndrome. *Clin*
19
20 338 *Chest Med* 2014;35:655-71.
21
22
23 339 23. Zampieri FG, Jacob V, Barbeiro HV, et al. Influence of Body Mass Index on Inflammatory
24
25 340 Profile at Admission in Critically Ill Septic Patients. *Int J Inflam* 2015; 2015:734857.
26
27
28 341 24. Herridge MS, Cheung AM, Tansey CM, et al. One-year outcomes in survivors of the acute
29
30 342 respiratory distress syndrome. *N Engl J Med* 2003;348:683-93.
31
32
33 343 25. Wu A, Hinds CJ, Thiemermann C. High-density lipoproteins in sepsis and septic shock:
34
35 344 metabolism, actions, and therapeutic applications. *Shock* 2004;21:210-21.
36
37
38 345 26. Murch O, Collin M, Hinds CJ, et al. Lipoproteins in inflammation and sepsis. I. Basic science.
39
40 346 *Intensive Care Med* 2007; 33:13-24.
41
42
43 347 27. McGown C, Bierendinc A, Younossi ZM. Adipose tissue as an endocrine organ. *Clin Liver*
44
45 348 *Dis* 2014;18:41-58.
46
47
48 349 28. Salgado DR, Rocco JR, Silva E, et al. Modulation of the renin-angiotensin-aldosterone
49
50 350 system in sepsis: a new therapeutic approach? *Expert Opin Ther Targets* 2010; 14:11-20.
51
52
53 351 29. Ranieri VM, Thompson BT, Barie PS, et al. Drotrecogin alfa (activated) in adults with septic
54
55 352 shock. *N Engl J Med* 2012;366:2055-64.
56
57
58
59
60

- 1
2
3
4 353 30. Scheer CS, Fuchs C, Kuhn SO, et al. Quality Improvement Initiative for Severe
5
6 354 Sepsis and Septic Shock Reduces 90-Day Mortality: A 7.5-Year Observational Study. *Crit*
7
8 355 *Care Med* 2017;45:241-52.
9
10
11 356 31. O'Brien JM Jr, Philips GS, Ali NA, et al. The association between body mass index, processes
12
13 357 of care, and outcomes from mechanical ventilation: a prospective cohort study.
14
15
16 358 *Crit Care Med* 2012;40:1456-63.
17
18 359
19
20
21 360
22
23 361
24
25 362
26
27
28 363
29
30 364
31
32 365
33
34 366
35
36 367
37
38 368
39
40 369
41
42 370
43
44 371
45
46 372
47
48 373
49
50 374
51
52
53
54
55
56
57
58
59
60

375 **Table 1. Comparison of demographics and clinical data between groups defined by clinical**
 376 **outcome in 178 patients with sepsis**

Characteristics	Survivors (n=104)	Non survivors (n=74)	p value
Age (year)	78.0 (60.0-84.0)	78.0 (69.0-84.0)	0.291
Males	67 (64.4)	49 (66.2)	0.805
Body mass index (kg/m ²)	23.2 (20.4-26.1)	21.7 (18.4-24.2)	0.006
Comorbidities			
COPD	23 (22.1)	9 (12.2)	0.088
Diabetes mellitus	26 (25.0)	21 (28.4)	0.614
Hypertension	47 (45.2)	31 (41.9)	0.662
Cerebrovascular disease	30 (28.8)	15 (20.3)	0.194
Neoplasm	18 (17.3)	12 (16.2)	0.848
Liver disease	5 (4.8)	4 (5.4)	1.000
Heart failure	20 (19.2)	14 (18.9)	0.958
Chronic renal failure	18 (17.3)	11 (14.9)	0.664
Smoking (pack years)	0 (0-30.0)	0 (0-16.3)	0.509
Primary site of infection			
Lung	77 (74.0)	54 (73.0)	0.874
Abdomen	10 (9.6)	5 (6.8)	0.499
Urinary tract	7 (6.7)	6 (8.1)	0.728
Gastrointestinal tract	7 (6.7)	5 (6.8)	1.000

Other site	3 (2.9)	4 (5.4)	0.452
Community-acquired infection	85 (81.7)	50 (67.6)	0.030
Hypotension	22 (21.2)	41 (55.4)	<0.001
Lactate level (mmol/L)	1.8 (1.0-3.4)	2.7 (1.5-5.7)	0.001
Oliguria	8 (7.7)	16 (21.6)	0.007
PaO₂/FiO₂(mmHg)	198.5 (119.3-287.5)	152.5 (99.6-210.3)	0.006
Serum Creatinine (μmol/L)	97.0 (68.3-176.3)	108.5 (64.0-194.3)	0.868
Total bilirubin (μmol/mL)	13.1 (9.9-22.3)	18.0 (12.5-32.8)	0.015
Platelets (×10⁹/L)	161.0 (95.8-232.5)	123.0 (75.0-204.3)	0.067
INR	1.2 (1.0-1.4)	1.3 (1.1-1.6)	0.015
Glasgow coma scale	15.0 (10.0-15.0)	13.0 (10.0-15.0)	0.117
SOFA score	5.0 (4.0-7.0)	9.0 (7.0-11.0)	<0.001
APACHE II score	16.0 (12.0-22.0)	21.0 (17.0-30.0)	<0.001
Septic shock	21 (20.2)	38 (51.4)	<0.001
Non-invasive ventilation	28 (26.9)	24 (32.4)	0.426
Intubated	36 (34.6)	43 (58.1)	0.002
Positive blood culture	19 (18.3)	19 (25.7)	0.235
Length of ICU stay (days)	12.0 (6.0-22.0)	12.0 (3.0-25.0)	0.521
Length of hospital stay (days)	18.0 (10.0-30.0)	13.0 (3.0-25.0)	0.009

377 Data are presented as n (%) or median (interquartile range) unless stated otherwise. COPD: Chronic obstructive pulmonary disease; INR: International

378 normalized ratio; SOFA: Sequential organ failure assessment; APACHE: Acute physiology and chronic health evaluation.

379

380 **Table 2. Risk factors for 90-day mortality of patients with sepsis or septic shock by Cox**
 381 **regression analysis**

Variables	Hazard ratio (95% Confidence interval)	p value
Body mass index (kg/m ²)	0.940 (0.889-0.994)	0.029
Hypotension	0.781 (0.229-2.670)	0.694
Lactate level (mmol/L)	1.018 (0.943-1.098)	0.648
Oliguria	1.288 (0.715-2.321)	0.399
PaO ₂ /FiO ₂ (mmHg)	1.000 (0.997-1.002)	0.933
Septic shock	1.075 (0.320-3.615)	0.907
SOFA score	1.229 (1.123-1.345)	<0.001
APACHE II score	1.050 (1.022-1.080)	<0.001
Intubated	1.511 (0.931-2.452)	0.095

382 SOFA: Sequential organ failure assessment; APACHE: Acute physiology and chronic health evaluation.

383

384

385

386

387

388

389

390

391

392 **Table 3. Comparison of demographics and clinical data among groups defined by body mass**
 393 **index in patients with sepsis**

Characteristics	Underweight (n=33)	Normal (n=98)	Overweight (n=36)	Obese (n=11)	p value
Age (years)	79.0 (69.0-86.0)	78.0 (67.0-84.0)	73.0 (57.0-83.0)	77.0 (71.0-86.0)	0.162
Males	24 (72.7)	70 (71.4)	20 (55.6)	2 (18.2)	0.002
Comorbidities					
COPD	8(24.2)	21 (21.4)	0	3 (27.3)	0.017
Diabetes mellitus	8 (24.2)	25 (25.5)	9 (25.0)	5 (45.5)	0.530
Hypertension	14 (42.4)	38 (38.8)	19 (52.8)	7 (63.6)	0.265
Cerebrovascular disease	10 (30.3)	24 (24.5)	11 (30.6)	0	0.193
Neoplasm	7 (21.2)	14 (14.3)	8 (22.2)	1 (9.1)	0.547
Liver disease	2 (6.1)	5 (5.1)	2 (5.6)	0	0.879
Heart failure	8 (24.2)	17 (17.3)	5 (13.9)	4 (36.4)	0.319
Chronic renal failure	5 (15.2)	14 (14.3)	7 (19.4)	3 (27.3)	0.669
Smoking (pack-years)	0 (0-20.5)	0 (0-30.0)	0 (0-3.0)	0 (0-30.0)	0.561
Primary site of infection					
Lung	27 (81.8)	69 (70.4)	27 (75.0)	8 (72.7)	0.637
Abdomen	2 (6.1)	9 (9.2)	3 (8.3)	1 (9.1)	0.956
Urinary tract	1 (3.0)	9 (9.2)	2 (5.6)	1 (9.1)	0.656
Gastrointestinal tract	2 (6.1)	6 (6.1)	3 (8.3)	1 (9.1)	0.955
Other site	1 (3.0)	5 (5.1)	1 (2.8)	0	0.800

Community-acquired infection	25 (75.8)	76 (77.6)	26 (72.2)	8 (72.7)	0.925
Hypotension	19 (57.6)	34 (34.7)	9 (25.0)	1 (9.1)	0.007
Lactate level (mmol/L)	2.4 (1.6-7.2)	2.1 (1.0-4.3)	1.6 (1.2-3.3)	1.9 (0.6-2.9)	0.201
Oliguria	8 (24.2)	13 (13.3)	3 (8.3)	0	0.121
PaO₂/FiO₂ (mmHg)	180.0(113.5-251.0)	164.5(102.3-240.5)	188.0(140.5-268.5)	215.0(153.0-300.0)	0.340
Serum Creatinine (µmol/L)	89.0 (57.0-127.0)	118.5 (72.5-190.5)	91.0 (60.0-212.5)	86.0 (56.0-112.0)	0.136
Total bilirubin (µmol/mL)	18.0 (10.1-33.1)	14.4 (10.1-28.4)	17.2 (12.2-26.3)	15.2 (11.3-20.0)	0.819
Platelets (×10⁹/L)	139.0 (75.0-213.0)	147.0 (86.0-209.8)	182.5 (128.3-253.8)	115.0 (49.0-144.0)	0.056
INR	1.3 (1.1-1.6)	1.2 (1.0-1.5)	1.2 (1.1-1.3)	1.1 (1.0-1.2)	0.269
Glasgow coma scale	13.0 (10.0-15.0)	15.0 (12.0-15.0)	15.0 (11.0-15.0)	13.0 (10.0-15.0)	0.761
SOFA score	8.0 (5.0-11.0)	7.0 (5.0-9.0)	6.0 (4.0-8.0)	5.0 (5.0-8.0)	0.382
APACHE II score	18.0 (16.0-24.0)	19.0 (13.0-25.0)	18.0 (13.0-22.0)	14.0 (9.0-17.0)	0.060
Septic shock	19 (57.6)	30 (30.6)	9 (25.0)	1(9.1)	0.004
Non-invasive ventilation	7 (21.2)	30 (30.6)	10 (27.8)	5 (45.5)	0.466
Intubated	19 (57.6)	43 (43.9)	13 (36.1)	4 (36.4)	0.305
Positive blood culture	7 (21.2)	24 (24.5)	4 (11.1)	3 (27.3)	0.383
Length of ICU stay (days)	10.0 (4.0-25.0)	13.0 (7.0-25.0)	11.0 (4.0-19.0)	9.0(6.0-13.0)	0.461
Length of hospital stay (days)	13.0 (4.0-29.0)	16.0 (10.0-28.0)	16.0 (8.0-32.0)	13.0(8.0-20.0)	0.813
In-hospital mortality	20 (60.6)	41 (41.8)	11 (30.6)	2 (18.2)	0.027
90-day mortality	22 (66.7)	47 (48.0)	13 (36.1)	2 (18.2)	0.015

394 Data are presented as n (%) or median (interquartile range). COPD: Chronic obstructive pulmonary disease; INR: International normalized ratio; SOFA:

395 Sequential organ failure assessment; APACHE: Acute physiology and chronic health evaluation.

1
2
3
4 396
5
6 397
7
8 398
9
10
11 399
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Fig 1. Kaplan-Meier survival plot for 90-day survival of underweight, normal weight, overweight, and obese patients with sepsis.

For peer review only

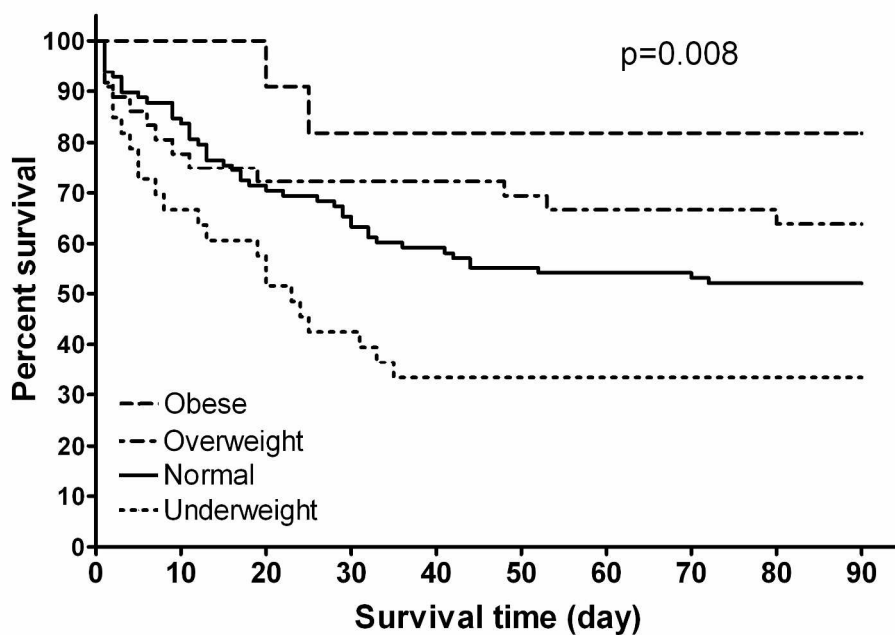


Fig 1. Kaplan-Meier survival plot for 90-day survival of underweight, normal weight, overweight, and obese patients with sepsis.

246x167mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5,6
		(b) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6,7
		(b) Describe any methods used to examine subgroups and interactions	6,7
		(c) Explain how missing data were addressed	N/A
		(d) If applicable, explain how loss to follow-up was addressed	N/A
		(e) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8,18-22
		(b) Report category boundaries when continuous variables were categorized	6
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The impact of body mass index on survival of medical patients with sepsis: a prospective cohort study in a university hospital in China

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-021979.R1
Article Type:	Research
Date Submitted by the Author:	12-Apr-2018
Complete List of Authors:	Zhou, Qingtao; Peking University Third Hospital, Department of respiratory and critical care medicine Wang, Meng; Peking University Third Hospital, Department of respiratory and critical care medicine Li, Shuo; Peking University Third Hospital, Emergency Department Zhang, Jing; Peking University Third Hospital, Department of respiratory and critical care medicine Ma, Qingbian; Peking University Third Hospital, Emergency Department Ding, Yanling; Peking University Third Hospital, Department of respiratory and critical care medicine Ge, Hongxia; Peking University Third Hospital, Emergency Department Shen, Ning; Peking University Third Hospital, Department of respiratory and critical care medicine Zheng, Yaan; Peking University Third Hospital, Emergency Department Sun, Yongchang; Peking University Third Hospital, Department of respiratory and critical care medicine
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Infectious diseases
Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, INFECTIOUS DISEASES, THORACIC MEDICINE

SCHOLARONE™
Manuscripts

1
2
3
4 **1 The impact of body mass index on survival of medical patients with sepsis: a**
5
6 **2 prospective cohort study in a university hospital in China**
7

8
9
3

10
11 4 Qingtao Zhou¹, Meng Wang¹, Shuo Li², Jing Zhang¹, Qingbian Ma², Yanling Ding¹,
12
13 5 Hongxia Ge², Ning Shen¹, Yaan Zheng², Yongchang Sun^{1*}
14

15
16
6

17
18 7 ¹ Department of Respiratory and Critical Care Medicine, Peking University Third
19
20 8 Hospital, Beijing, China.
21

22
23 9 ² Emergency Department, Peking University Third Hospital, Beijing, China.
24

25
26
10

27
28 11 ***Corresponding author:** Yongchang Sun, Department of Respiratory and Critical
29
30 12 Care Medicine, Peking University Third Hospital, 49 North Garden Road, Haidian
31
32 13 District, Beijing 100191, China. Email: suny@bjmu.edu.cn
33

34
35
14

36
37
15

38
39
16

40
41
17

42
43
18

44
45
19

46
47
20

48
49
21

50
51
22

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23 **Abstract**

24 **Objective** To evaluate the impact of body mass index (BMI) on survival of a Chinese
25 cohort of medical patients with sepsis.

26 **Design** A single-center prospective cohort study conducted from May 2015 to April
27 2017.

28 **Setting** A tertiary care university hospital in China.

29 **Participants** 178 patients with sepsis admitted to the medical ICU were included.

30 **Main outcome measures** The primary outcome was 90-day mortality. The secondary
31 outcomes were in-hospital mortality, length of ICU stay, and length of hospital stay.

32 **Results** The median age (interquartile range) of the patients was 78 (66-84) years.
33 The 90-day mortality was 47.2%. The in-hospital mortality was 41.6%, and the length
34 of ICU stay and hospital stay were 12 (5-22) and 15 (9-28) days, respectively. Cox
35 proportional hazard regression analysis identified that sequential organ failure
36 assessment (SOFA) score (HR = 1.229, $p < 0.001$), APACHE II score (HR = 1.050, p
37 < 0.001) and BMI (HR = 0.940, $p = 0.029$) were all independent predictors of the
38 90-day mortality. Patients were divided into four groups based on BMI [underweight
39 33 (18.5%), normal 98 (55.1%), overweight 36 (20.2%), and obese 11 (6.2%)]. The
40 percentage of males (72.7%, 71.4%, 55.6%, and 18.2%, $p = 0.002$), chronic
41 obstructive pulmonary disease (24.2%, 21.4%, 0, and 27.3%, $p = 0.017$), hypotension
42 (57.6%, 34.7%, 25.0%, and 9.1%, $p = 0.007$), septic shock (57.6%, 30.6%, 25.0%,
43 and 9.1%, $p = 0.004$), in-hospital mortality (60.6%, 41.8%, 30.6%, and 18.2%, $p =$
44 0.027) and 90-day mortality (66.7%, 48.0%, 36.1%, and 18.2%, $p = 0.015$) were

1
2
3
4 45 statistically different among the four groups. Differences in survival among the four
5
6 46 groups were demonstrated by Kaplan-Meier survival analysis ($p = 0.008$).

7
8 47 **Conclusions** BMI was an independent factor associated with survival in a Chinese
9
10
11 48 cohort of medical patients with sepsis, patients with lower BMI having a higher risk
12
13 49 of death.

14
15
16 50
17
18 51 **Key words:** Sepsis; Septic shock; Body mass index; Critical care; Mortality
19
20
21 52

22 23 53 **Strengths and limitations of this study**

24
25 54 Our prospective observational cohort study was focused on medical patients with
26
27
28 55 sepsis and conducted at a university hospital in China.

29
30 56 The impact of BMI on 90-day survival of medical patients with sepsis was evaluated
31
32
33 57 by Cox proportional hazard regression analysis and Kaplan-Meier survival analysis.

34
35 58 Our analyses were limited by the use of weight ascertained at ICU admission, rather
36
37
38 59 than the patient's true outpatient weight.
39
40
41 60

42
43 61

44
45 62

46
47 63

48
49 64

50
51 65

52
53 66
54
55
56
57
58
59
60

67 **Introduction**

68 Sepsis is a major cause of morbidity and mortality worldwide ^[1]. Of these
69 patients, half are treated in the intensive care unit (ICU) ^[2]. In a national
70 population-based study of sepsis in Spain, medical diagnostic categories were the
71 majority of causes in patients who developed sepsis, while only 26% of surgical
72 patients developed sepsis ^[3].

73 Body mass index (BMI) is a simple index of weight-for-height that is commonly
74 used to classify whether adults are underweight, overweight and obese ^[4]. Several
75 studies have examined the effects of BMI on mortality with conflicting conclusions.
76 Lower mortality in the obese has been observed in some studies ^[5-9], but some
77 researchers believe that the true paradox may lie in the variations in sepsis
78 interventions, such as the administration of resuscitation fluids and antimicrobial
79 therapy ^[6]. In other studies, morbidly obese and underweight patients have been
80 shown to be associated with higher mortality ^[10,11]. Thus, the impact of BMI on
81 survival of patients with sepsis is still controversial ^[12, 13].

82 As the relationship between BMI and clinical outcomes of sepsis is complex,
83 which may be related partly to differences in patient characteristics, we therefore set
84 out to evaluate prospectively the impact of BMI on survival in a cohort of medical
85 patients with sepsis admitted to the medical ICU in a university hospital.

86

87 **Patients and Methods**

88 **Design**

1
2
3
4 89 This was a prospective cohort study, which was conducted in the medical ICU of
5
6 90 a university-affiliated urban teaching hospital in China from May 2015 to April 2017.
7

8 91 **Subjects**

9
10 92 Sepsis was defined as the presence (probable or documented) of infection
11
12 93 together with systemic manifestations of infection^[14]. Hospitalized patients admitted
13
14 94 to the medical ICU with sepsis acquired in the community or in a hospital were
15
16 95 eligible for the study if they met any of the following criteria of severe sepsis^[14]: (1)
17
18 96 sepsis-induced hypotension, (2) lactate above upper laboratory level limits
19
20 97 (1.5mmol/L in this study), (3) urine output <0.5 mL Kg⁻¹ h⁻¹ for more than 2 h despite
21
22 98 adequate fluid resuscitation, (4) acute lung injury with Pao₂/Fio₂<250 in the absence
23
24 99 of pneumonia as infection source, (5) acute lung injury with Pao₂/Fio₂ <200 in the
25
26 100 presence of pneumonia as infection source, (6) creatinine >2.0 mg/dL (176.8 μmol/L),
27
28 101 (7) bilirubin >2mg/dL (34.2 μmol/L), (8) platelet count <100,000 μL, and (9)
29
30 102 coagulopathy (international normalized ratio >1.5).
31
32
33
34
35
36
37

38 103 Patients were excluded from the study if they met one of the following criteria: (1)
39
40 104 the patient had sepsis that required surgical treatment, or was caused by a surgical
41
42 105 procedure related infection, (2) age <18 years, (3) the patient had a positive HIV
43
44 106 antibody titer or had known/suspected tuberculosis at baseline, (4) expected lifespan
45
46 107 <3 months due to severe pre-existing comorbidities, (5) active Do Not Resuscitate or
47
48 108 Do Not Intubate order, and (6) pregnant.
49

50
51
52 109 All patients accepted treatment according to the international guidelines for
53
54 110 management of sepsis and septic shock^[14,15]. We collected the following
55
56
57
58
59
60

1
2
3
4 111 demographic and clinical data: patient's gender, age, weight, height, primary site of
5
6 112 infection, community-acquired or hospital-acquired infection, hypotension, lactate
7
8 113 level, oliguria, $\text{PaO}_2/\text{FiO}_2$, serum creatinine, total bilirubin, platelets, international
9
10 114 normalized ratio (INR), Glasgow coma scale, SOFA score, acute physiology and
11
12 115 chronic health evaluation (APACHE) II score, septic shock, non-invasive ventilation,
13
14 116 intubation, positive blood culture, length of ICU stay, and length of hospital stay.
15
16
17 117 Those who survived to discharge were followed for at least 90 days.

18
19
20 118 BMI is defined as the weight in kilograms divided by the square of the height in
21
22 119 meters (kg/m^2). Using the World Health Organization (WHO) criteria for designation
23
24 120 of BMI ^[4], patients were classified as underweight ($\text{BMI} < 18.50 \text{ kg}/\text{m}^2$), normal
25
26 121 weight ($\text{BMI} = 18.50$ to $24.99 \text{ kg}/\text{m}^2$), overweight ($\text{BMI} = 25.0$ to $29.99 \text{ kg}/\text{m}^2$), and
27
28 122 obese ($\text{BMI} \geq 30.0 \text{ kg}/\text{m}^2$).

32 123 **Outcomes**

33
34
35 124 The primary outcome was 90-day mortality, while the secondary outcomes were
36
37 125 in-hospital mortality, length of ICU stay, and length of hospital stay.

38 126 **Statistical analysis**

39
40
41 127 Continuous variables were expressed as median (interquartile range) and
42
43 128 categorical variables as numbers (%). Clinical data were compared among the
44
45 129 in-hospital survivors and non-survivors. Continuous variables were compared using
46
47 130 the non-parametric Mann–Whitney U test, and categorical variables were compared
48
49 131 using the Chi squared test. Cox proportional hazard regression analysis was
50
51 132 undertaken to assess the factors associated with 90-day mortality. The variables
52
53
54
55
56
57
58
59
60

1
2
3
4 133 significantly associated with 90-day non-survival in the univariate analysis were used
5
6 134 in the Cox proportional hazard regression analysis.

7
8 135 Patients were divided into four groups based on BMI (underweight, normal,
9
10 136 overweight, and obese). Clinical data were compared between the four groups, where
11
12 137 continuous variables were compared using the non-parametric Kruskal-Wallis H test,
13
14 138 and categorical variables were compared using the Chi squared test. Kaplan-Meier
15
16 139 survival curves were constructed to show the survival probabilities at day-90
17
18 140 according to BMI classification, and compared using the log rank test.

19
20
21
22
23 141 All analyses were conducted using SPSS, version 22.0 (IBM, Armonk, NY,
24
25 142 USA). A p value <0.05 was considered significant.

26 27 28 143 **Patient involvement**

29
30 144 No patients were involved in developing the hypothesis, the specific aims or the
31
32 145 research questions, nor were they involved in the design or implementation of this
33
34 146 study. No patients were involved in the interpretation of study results or write up of
35
36 147 the manuscript. There are no plans to involve patients in the dissemination of results.

37
38
39
40 148

41 42 149 **Results**

43
44
45 150 Figure 1 shows the patient-selection process. In total, 178 medical patients with
46
47 151 sepsis were included in this study, with male patients accounting for 65.2% (n=116).
48
49 152 The median age (interquartile range) was 78 (66-84) years, and most patients were at
50
51 153 least 65 years old (137/178 cases, 77.0%). The most common primary site of infection
52
53 154 was the lung (131 cases, 73.6%), followed by abdomen (15 cases, 8.4%), urinary tract
54
55
56
57
58
59
60

1
2
3
4 155 (13 cases, 7.3%), gastrointestinal tract (12 cases, 6.7%) and other sites (7 cases, 3.9%).
5
6 156 Septic shock patients accounted for 33.1% (59 cases). Blood culture was positive in
7
8 157 38 patients (21.3%). The 90-day mortality was 47.2% (84/178 cases), and the
9
10 158 in-hospital mortality was 41.6% (74/178 cases). The length of ICU stay and the length
11
12 159 of hospital stay were 12 (5-22) and 15 (9-28) days, respectively.

160 Compared with in-hospital survivors, non-survivors had significantly lower BMI
161 and $\text{PaO}_2/\text{FiO}_2$ (both $p < 0.05$), higher lactate, bilirubin, INR, SOFA score and
162 APACHE II score (all $p < 0.05$). Meanwhile, more patients died with
163 healthcare-acquired infections, hypotension, oliguria, septic shock, and intubation (all
164 $p < 0.05$) (table 1).

165 Cox proportional hazard regression analysis was conducted and the independent
166 factors for 90-day death were identified as SOFA score (HR = 1.220, $p < 0.001$),
167 APACHE II score (HR = 1.050, $p < 0.001$) and BMI (HR = 0.940, $p = 0.029$) (table
168 2).

169 Patients were divided into four groups based on BMI [underweight 33 (18.5%),
170 normal 98 (55.1%), overweight 36 (20.2%), and obese 11 (6.2%)] . The percentage of
171 males (72.7%, 71.4%, 55.6%, and 18.2%, $p = 0.002$), chronic obstructive
172 pulmonary disease (24.2%, 21.4%, 0, and 27.3%, $p=0.017$), hypotension (57.6%,
173 34.7%, 25.0%, and 9.1%, $p = 0.007$), septic shock (57.6%, 30.6%, 25.0%, and 9.1%,
174 $p = 0.004$), in-hospital mortality (60.6%, 41.8%, 30.6%, and 18.2%, $p = 0.027$) and
175 90-day mortality (66.7%, 48.0%, 36.1%, and 18.2%, $p = 0.015$) were statistically
176 different among the four groups (table 3).

1
2
3
4 177 Kaplan-Meier survival curves were constructed to show the survival probabilities
5
6 178 at day-90 according to BMI classification and these were compared using the log rank
7
8 179 test, which also showed that higher BMI was associated with better prognosis
9
10
11 180 (p=0.008) (figure 2).
12

13
14 181

15 182 **Discussion**

16
17
18 183 This prospective observational cohort study was focused on medical patients with
19
20 184 sepsis admitted to the ICU, and the results showed that, besides SOFA score and
21
22 185 APACHE II score, BMI was identified as an independent factor for 90-day mortality
23
24 186 by Cox regression analysis. The association of SOFA and APACHE II score with
25
26 187 mortality in this cohort was consistent with previous studies^[16-18]. However, BMI was
27
28 188 also found to be an independent predictor of survival, where 90-day mortality
29
30 189 decreased with an increase in BMI. While studies examining the risk factors
31
32 190 associated with outcomes in sepsis reached inconsistent conclusions on the
33
34 191 association of BMI with mortality, our results confirmed that BMI was an
35
36 192 independent predictor of mortality in patients with sepsis caused by medical
37
38 193 conditions.
39

40
41
42 194 Globally, the prevalence of obesity has reached epidemic proportions, especially
43
44 195 in developed countries^[19]. BMI is still a useful proxy of overall health because it is
45
46 196 highly correlated with body surface area, which is commonly used as a surrogate
47
48 197 measure in obesity classification. Even though it is widely accepted that obesity is a
49
50 198 risk factor for diabetes mellitus, hypertension, and cardiovascular diseases, the present
51
52
53
54
55
56
57
58
59
60

1
2
3
4 199 study and several other studies have indicated that overweight and obese patients with
5
6 200 sepsis tend to experience lower mortality. This has been called the “obesity paradox”
7
8 201 [5-9,20]. Although some researchers have expressed doubt that the true paradox may lie
9
10 202 in the variations in sepsis interventions [6,21], a meta-analysis concluded that
11
12 203 individuals who are considered overweight or obese have a reduced adjusted mortality
13
14 204 when admitted to the ICU with sepsis or septic shock [8]. Recently another
15
16 205 meta-analysis also concluded that being overweight was associated with lower
17
18 206 mortality (OR 0.87, 95% CI 0.77-0.97, p = 0.02) compared with obese (OR 0.89, 95%
19
20 207 CI 0.72-1.10, p = 0.29) and morbidly obese (OR 0.64, 95% CI 0.38-1.08, p = 0.09)
21
22 208 patients who did not exhibit significantly reduced mortality compared with normal
23
24 209 weight patients [12]. In a large and nationally representative sample of over 1,000
25
26 210 hospitals in the US, obesity was found to be significantly associated with a 16%
27
28 211 decrease in the odds of dying among sepsis patients who were hospitalized [22].

29
30
31
32
33
34
35 212 Underweight patients with sepsis may be more common in developing countries
36
37 213 than developed countries. In the present study, the percentages of underweight,
38
39 214 normal weight, overweight and obese patients were 18.4%, 55.3%, 20.1%, and 6.1%,
40
41 215 respectively, while those with sepsis in a study in Canada and the US represented
42
43 216 6.8%, 35.3%, 28.3%, and 29.0% [6]. Being underweight was found to be one of the
44
45 217 independent risk factors of mortality in a study on the correlation between surgical
46
47 218 site infection and mortality [10]. Furthermore, Lee et al [11] also reported that being
48
49 219 underweight was associated with mortality in patients with severe sepsis and septic
50
51 220 shock.
52
53
54
55
56
57
58
59
60

1
2
3
4 221 Consequently, previous studies on sepsis have shown that overweight and obese
5
6 222 patients have a decreased risk for mortality^[5-9,20,22], and underweight patients may
7
8 223 have a higher mortality^[10,11]. However, BMI has not been shown to be an independent
9
10 224 factor for clinical outcomes by multivariable analyses. In our cohort of medical
11
12 225 patients with sepsis, which mainly included the elderly and less obese patients, BMI
13
14 226 was identified as an independent factor for survival. The mechanism of the correlation
15
16 227 between BMI and mortality of sepsis is unclear. There are several potential reasons
17
18 228 that could explain this. First, higher BMI resulted in more fat reserves, and patients
19
20 229 could have a greater capacity to cope with the inflammatory response during sepsis
21
22 230 and sepsis-associated acute lung injury^[23-25]. Furthermore, they may be able to
23
24 231 tolerate extensive weight loss and dysfunction associated with critical illness^[26].
25
26 232 Secondly, a higher BMI can lead to an increased level of lipoproteins. High-density
27
28 233 lipoproteins may not only bind and inactivate lipopolysaccharide (LPS) or other
29
30 234 harmful bacterial products released during sepsis^[27], but also modulate adhesion
31
32 235 molecule expression, upregulate endothelial nitric oxide synthase, and counteract
33
34 236 oxidative stress^[28]. Thirdly, higher BMI can lead to increased adipose tissue
35
36 237 deposition. Adipose tissue is increasingly being considered as a functional endocrine
37
38 238 organ and associated with increased renin-angiotensin system activity^[29]. It appears
39
40 239 to have protective hemodynamic effects during sepsis and may decrease the need for
41
42 240 fluid or vasopressor support^[21,30].

43
44 241 In general, sex has not been found to be an independent predictor for survival in
45
46 242 patients with sepsis, which is the same as the results of our current study. But in some

1
2
3
4 243 special population, for example in liver cirrhosis patients with bloodstream infection,
5
6 244 male sex may be an independent risk factor for mortality^[31].
7

8 245 As the relationship between BMI and clinical outcomes of sepsis may be related
9
10 246 partly to differences in patient characteristics, we therefore set out to evaluate the
11
12 247 impact of BMI on survival in a cohort of medical patients with sepsis, which is
13
14 248 different from surgical septic patients. Ranieri et al ^[32] reported that the primary sites
15
16 249 of infection in adults with septic shock were lung (43.9%), abdomen (30.0%), urinary
17
18 250 tract (12.3%), skin (5.5%) and other sites (8.3%). Scheer et al ^[33] found that the most
19
20 251 common primary site of infection was different between medical and surgical patients.
21
22 252 In medical patients, lung was the most common primary site (42.0%-56.7%), while it
23
24 253 was abdomen (48.4%-64.4%) in surgical patients. It should be noted that in the
25
26 254 majority of our patients (73.6%) sepsis was associated with pulmonary infection, a
27
28 255 much higher percentage as compared to other studies. He et al^[34] reported that
29
30 256 pulmonary-sepsis showed worse outcome than abdominal-sepsis, and pulmonary
31
32 257 infection is a risk factor for one-year mortality and quality of life after sepsis.
33
34
35
36
37
38
39

40 258 There were several limitations to our study. Firstly, the BMI of our patients
41
42 259 ranged from 12.11 to 32.46. There was no morbidly obese patient in the current study.
43
44 260 In fact, morbidly obese people are rare in this country. Secondly, the present study
45
46 261 used weight ascertained at ICU admission, rather than the patient's true outpatient
47
48 262 weight. This practice may misclassify the BMI category in as many as 21.9% of
49
50 263 patients due to lack of fluid balance adjustment ^[35]. Thirdly, BMI was used to
51
52 264 determine the nutritional status of patients in this study. BMI is a simple index and
53
54
55
56
57
58
59
60

1
2
3
4 265 widely used in clinical practice, but other indices such as percent body fat might
5
6 266 better reflect body composition^[36]. Lastly, it was a single-center study with 178
7
8 267 participants, and a large proportion of our patients were older than 65 years, which
9
10
11 268 may have led to a sample-related bias.

12 13 269 **Conclusions**

14
15
16 270 To our knowledge, this is the first prospective cohort study that focused on
17
18 271 medical patients with sepsis, showing that BMI was an independent predictor of
19
20 272 survival, patients with lower BMI having a higher risk of death.
21
22

23 273

24 25 274 **Acknowledgements**

26
27
28 275 Not applicable.
29

30 276

31 32 33 277 **Authors' contributions**

34
35 278 QTZ, YCS, YAZ designed the study. QTZ, YCS, NS, YAZ, and QBM coordinated the
36
37 279 study. MW, JZ, YLD, SL, and HXG were responsible for patient screening,
38
39 280 enrollment, and follow-up. QTZ, MW, and YCS analyzed the data. QTZ drafted the
40
41 281 manuscript. YCS critically revised the manuscript. All authors had full access to all
42
43 282 study data, read and approved the final version of the manuscript.
44
45
46

47 283

48 49 50 284 **Funding**

51
52 285 None.
53
54

55 286
56
57
58
59
60

1
2
3
4 287 **Competing interests**

5
6 288 None declared.

7
8
9 289

10
11 290 **Ethics approval and consent to participate**

12
13 291 The study protocol was approved (approval number M2015021) by the ethics
14
15 292 committee of Peking University Third Hospital, Beijing, China. All patients or their
16
17 293 legally authorized representatives provided written informed consent to participate in
18
19
20 294 the study.

21
22
23 295

24
25 296 **Data sharing statement**

26
27
28 297 The authors declare that all data supporting the findings of this study are available
29
30 298 within the article.

31
32
33 299

34
35 300 **References**

- 36
37 301 1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus
38
39 302 Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315:801-10.
- 40
41 303 2. Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med* 2013;369:2063.
- 42
43 304 3. Bouza C, López-Cuadrado T, Saz-Parkinson Z, et al. Epidemiology and recent trends of
44
45 305 severe sepsis in Spain: a nationwide population-based analysis (2006-2011). *BMC Infect Dis*
46
47 306 2014; 14:3863.
- 48
49 307 4. WHO classification of body mass index (BMI). [[http://apps.who.int/bmi/index.jsp?introPage=](http://apps.who.int/bmi/index.jsp?introPage=intro_3.html)
50
51
52
53
54 308 [intro_3.html](http://apps.who.int/bmi/index.jsp?introPage=intro_3.html)] Accessed on 2 March 2015.

- 1
2
3
4 309 5. Wurzinger B, Dünser MW, Wohlmuth C, et al. The association between body-mass index and
5
6 310 patient outcome in septic shock: a retrospective cohort study. *Wien Klin Wochenschr* 2010;122:
7
8 311 31-6.
9
10
11 312 6. Arabi YM, Dara SI, Tamim HM, et al. Clinical characteristics, sepsis interventions and
12
13 313 outcomes in the obese patients with septic shock:an international multicenter cohort study.
14
15 314 *Crit Care* 2013;17:R72.
16
17
18 315 7. Prescott HC, Chang VW, O'Brien JM Jr, et al. Obesity and 1-year outcomes in older
19
20 316 Americans with severe sepsis. *Crit Care Med* 2014;42:1766-74.
21
22
23 317 8. Pepper DJ, Sun J, Welsh J, et al. Increased body mass index and adjusted mortality in ICU
24
25 318 patients with sepsis or septic shock:a systematic review and meta-analysis. *Crit Care*
26
27 319 2016;20:181.
28
29
30 320 9. Gaulton TG, Marshall MacNabb C, Mikkelsen ME, et al. A retrospective cohort study
31
32 321 examining the association between body mass index and mortality in severe sepsis. *Intern*
33
34 322 *Emerg Med* 2015;10:471-9.
35
36
37 323 10. Giles KA, Hamdan AD, Pomposelli FB, et al. Body mass index:surgical site infections and
38
39 324 mortality after lower extremity bypass from the National Surgical Quality Improvement
40
41 325 Program 2005-2007. *Ann Vasc Surg* 2010;24:48-56.
42
43
44 326 11. Lee SM, Kang JW, Jo YH, et al. Underweight is associated with mortality in patients with
45
46 327 severe sepsis and septic shock. *Intensive Care Med Exp* 2015; 3:A876.
47
48
49 328 12. Wang S, Liu X, Chen Q, et al. The role of increased body mass index in outcomes of sepsis: a
50
51 329 systematic review and meta-analysis. *BMC Anesthesiol* 2017;17:118.
52
53
54 330 13. Ng PY, Eikermann M. The obesity conundrum in sepsis. *BMC Anesthesiol* 2017;17:147.
55
56
57
58
59
60

- 1
2
3
4 331 14. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines
5
6 332 for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013;41:580-637.
7
8 333 15. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International
9
10 334 Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med* 2017;
11
12 335 43:304-77.
13
14
15 336 16. de Carvalho MA, Freitas FG, Silva Junior HT, et al. Mortality predictors in renal transplant
16
17 337 recipients with severe sepsis and septic shock. *PLoS One* 2014;9:e111610.
18
19 338 17. Innocenti F, Tozzi C, Donnini C, et al. SOFA score in septic patients: incremental prognostic
20
21 339 value over age, comorbidities, and parameters of sepsis severity. *Intern Emerg*
22
23 340 *Med* 2018;13:405-12.
24
25
26 341 18. Song JE, Kim MH, Jeong WY, et al. Mortality Risk Factors for Patients with Septic
27
28 342 Shock after Implementation of the Surviving Sepsis Campaign Bundles. *Infect*
29
30 343 *Chemother* 2016;48:199-208.
31
32
33 344 19. GBD 2015 Obesity Collaborators, Afshin A, Forouzanfar MH, et al. Health Effects of
34
35 345 Overweight and Obesity in 195 Countries over 25 Years. *N Engl J Med* 2017;377:13-27.
36
37
38 346 20. Atamna A, Elis A, Gilady E, et al. How obesity impacts outcomes of infectious diseases. *Eur*
39
40 347 *J Clin Microbiol Infect Dis* 2017; 36:585-91.
41
42
43 348 21. Taylor SP, Karvetski CH, Templin MA, et al. Initial fluid resuscitation following adjusted
44
45 349 body weight dosing is associated with improved mortality in obese patients with suspected
46
47 350 septic shock. *J Crit Care* 2018;43:7-12.
48
49
50 351 22. Nguyen AT, Tsai CL, Hwang LY, et al. Obesity and Mortality, Length of Stay and Hospital
51
52 352 Cost among Patients with Sepsis: A Nationwide Inpatient Retrospective Cohort Study. *PLoS*
53
54
55
56
57
58
59
60

- 1
2
3
4 353 *One* 2016; 11:e0154599.
- 5
6 354 23. Stapleton RD, Dixon AE, Parsons PE, et al. The association between BMI and plasma
7
8 355 cytokine levels in patients with acute lung injury. *Chest* 2010;138:568-77.
- 9
10
11 356 24. Stapleton RD, Suratt BT. Obesity and nutrition in acute respiratory distress syndrome. *Clin*
12
13 357 *Chest Med* 2014;35:655-71.
- 14
15
16 358 25. Zampieri FG, Jacob V, Barbeiro HV, et al. Influence of Body Mass Index on Inflammatory
17
18 359 Profile at Admission in Critically Ill Septic Patients. *Int J Inflamm* 2015; 2015:734857.
- 19
20
21 360 26. Herridge MS, Cheung AM, Tansey CM, et al. One-year outcomes in survivors of the acute
22
23 361 respiratory distress syndrome. *N Engl J Med* 2003;348:683-93.
- 24
25
26 362 27. Wu A, Hinds CJ, Thiemermann C. High-density lipoproteins in sepsis and septic shock:
27
28 363 metabolism, actions, and therapeutic applications. *Shock* 2004;21:210-21.
- 29
30
31 364 28. Murch O, Collin M, Hinds CJ, et al. Lipoproteins in inflammation and sepsis. I. Basic science.
32
33 365 *Intensive Care Med* 2007; 33:13-24.
- 34
35
36 366 29. McGown C, Birerdinc A, Younossi ZM. Adipose tissue as an endocrine organ. *Clin Liver*
37
38 367 *Dis* 2014;18:41-58.
- 39
40
41 368 30. Salgado DR, Rocco JR, Silva E, et al. Modulation of the renin-angiotensin-aldosterone
42
43 369 system in sepsis: a new therapeutic approach? *Expert Opin Ther Targets* 2010; 14:11-20.
- 44
45
46 370 31. Zhao H, Gu X, Zhao R, et al. Evaluation of prognostic scoring systems in liver cirrhosis
47
48 371 patients with bloodstream infection. *Medicine (Baltimore)* 2017;96(50):e8844.
- 49
50
51 372 32. Ranieri VM, Thompson BT, Barie PS, et al. Drotrecogin alfa (activated) in adults with septic
52
53 373 shock. *N Engl J Med* 2012;366:2055-64.
- 54
55 374 33. Scheer CS, Fuchs C, Kuhn SO, et al. Quality Improvement Initiative for Severe

- 1
2
3
4 375 Sepsis and Septic Shock Reduces 90-Day Mortality: A 7.5-Year Observational Study. *Crit*
5
6 376 *Care Med* 2017;45:241-52.
7
8 377 34. He XL, Liao XL, Xie ZC, et al. Pulmonary Infection Is an Independent Risk Factor for
9
10 378 Long-Term Mortality and Quality of Life for Sepsis Patients. *Biomed Res Int* 2016;
11
12 379 2016:4213712.
13
14
15 380 35. O'Brien JM Jr, Philips GS, Ali NA, et al. The association between body mass index, processes
16
17 381 of care, and outcomes from mechanical ventilation: a prospective cohort study.
18
19 382 *Crit Care Med* 2012;40:1456-63.
20
21
22 383 36. Waisbren E, Rosen H, Bader AM, et al. Percent body fat and prediction of surgical site
23
24 384 infection. *J Am Coll Surg* 2010;210:381-9.
25
26
27 385
28
29 386
30
31 387
32
33 388
34
35 389
36
37 390
38
39 391
40
41 392
42
43 393
44
45 394
46
47 395
48
49 396
50
51
52
53
54
55
56
57
58
59
60

397 **Table 1. Comparison of demographics and clinical data between groups defined by clinical**
 398 **outcome in 178 patients with sepsis**

Characteristics	Survivors (n=104)	Non survivors (n=74)	p value
Age (year)	78.0 (60.0-84.0)	78.0 (69.0-84.0)	0.291
Males	67 (64.4)	49 (66.2)	0.805
Body mass index (kg/m ²)	23.2 (20.4-26.1)	21.7 (18.4-24.2)	0.006
Comorbidities			
COPD	23 (22.1)	9 (12.2)	0.088
Diabetes mellitus	26 (25.0)	21 (28.4)	0.614
Hypertension	47 (45.2)	31 (41.9)	0.662
Cerebrovascular disease	30 (28.8)	15 (20.3)	0.194
Neoplasm	18 (17.3)	12 (16.2)	0.848
Liver disease	5 (4.8)	4 (5.4)	1.000
Heart failure	20 (19.2)	14 (18.9)	0.958
Chronic renal failure	18 (17.3)	11 (14.9)	0.664
Smoking (pack years)	0 (0-30.0)	0 (0-16.3)	0.509
Primary site of infection			
Lung	77 (74.0)	54 (73.0)	0.874
Abdomen	10 (9.6)	5 (6.8)	0.499
Urinary tract	7 (6.7)	6 (8.1)	0.728
Gastrointestinal tract	7 (6.7)	5 (6.8)	1.000

Other site	3 (2.9)	4 (5.4)	0.452
Community-acquired infection	85 (81.7)	50 (67.6)	0.030
Hypotension	22 (21.2)	41 (55.4)	<0.001
Lactate level (mmol/L)	1.8 (1.0-3.4)	2.7 (1.5-5.7)	0.001
Oliguria	8 (7.7)	16 (21.6)	0.007
PaO₂/FiO₂(mmHg)	198.5 (119.3-287.5)	152.5 (99.6-210.3)	0.006
Serum Creatinine (μmol/L)	97.0 (68.3-176.3)	108.5 (64.0-194.3)	0.868
Total bilirubin (μmol/mL)	13.1 (9.9-22.3)	18.0 (12.5-32.8)	0.015
Platelets (×10⁹/L)	161.0 (95.8-232.5)	123.0 (75.0-204.3)	0.067
INR	1.2 (1.0-1.4)	1.3 (1.1-1.6)	0.015
Glasgow coma scale	15.0 (10.0-15.0)	13.0 (10.0-15.0)	0.117
SOFA score	5.0 (4.0-7.0)	9.0 (7.0-11.0)	<0.001
APACHE II score	16.0 (12.0-22.0)	21.0 (17.0-30.0)	<0.001
Septic shock	21 (20.2)	38 (51.4)	<0.001
Non-invasive ventilation	28 (26.9)	24 (32.4)	0.426
Intubated	36 (34.6)	43 (58.1)	0.002
Positive blood culture	19 (18.3)	19 (25.7)	0.235
Length of ICU stay (days)	12.0 (6.0-22.0)	12.0 (3.0-25.0)	0.521
Length of hospital stay (days)	18.0 (10.0-30.0)	13.0 (3.0-25.0)	0.009

399 Data are presented as n (%) or median (interquartile range) unless stated otherwise. COPD: Chronic obstructive pulmonary disease; INR: International

400 normalized ratio; SOFA: Sequential organ failure assessment; APACHE: Acute physiology and chronic health evaluation.

401

402 **Table 2. Risk factors for 90-day mortality of patients with sepsis or septic shock by Cox**
 403 **regression analysis**

Variables	Hazard ratio (95% Confidence interval)	p value
Body mass index (kg/m ²)	0.940 (0.889-0.994)	0.029
Hypotension	0.781 (0.229-2.670)	0.694
Lactate level (mmol/L)	1.018 (0.943-1.098)	0.648
Oliguria	1.288 (0.715-2.321)	0.399
PaO ₂ /FiO ₂ (mmHg)	1.000 (0.997-1.002)	0.933
Septic shock	1.075 (0.320-3.615)	0.907
SOFA score	1.229 (1.123-1.345)	<0.001
APACHE II score	1.050 (1.022-1.080)	<0.001
Intubated	1.511 (0.931-2.452)	0.095

404 SOFA: Sequential organ failure assessment; APACHE: Acute physiology and chronic health evaluation.

405

406

407

408

409

410

411

412

413

414 **Table 3. Comparison of demographics and clinical data among groups defined by body mass**
 415 **index in patients with sepsis**

Characteristics	Underweight (n=33)	Normal (n=98)	Overweight (n=36)	Obese (n=11)	p value
Age (years)	79.0 (69.0-86.0)	78.0 (67.0-84.0)	73.0 (57.0-83.0)	77.0 (71.0-86.0)	0.162
Males	24 (72.7)	70 (71.4)	20 (55.6)	2 (18.2)	0.002
Comorbidities					
COPD	8(24.2)	21 (21.4)	0	3 (27.3)	0.017
Diabetes mellitus	8 (24.2)	25 (25.5)	9 (25.0)	5 (45.5)	0.530
Hypertension	14 (42.4)	38 (38.8)	19 (52.8)	7 (63.6)	0.265
Cerebrovascular disease	10 (30.3)	24 (24.5)	11 (30.6)	0	0.193
Neoplasm	7 (21.2)	14 (14.3)	8 (22.2)	1 (9.1)	0.547
Liver disease	2 (6.1)	5 (5.1)	2 (5.6)	0	0.879
Heart failure	8 (24.2)	17 (17.3)	5 (13.9)	4 (36.4)	0.319
Chronic renal failure	5 (15.2)	14 (14.3)	7 (19.4)	3 (27.3)	0.669
Smoking (pack-years)	0 (0-20.5)	0 (0-30.0)	0 (0-3.0)	0 (0-30.0)	0.561
Primary site of infection					
Lung	27 (81.8)	69 (70.4)	27 (75.0)	8 (72.7)	0.637
Abdomen	2 (6.1)	9 (9.2)	3 (8.3)	1 (9.1)	0.956
Urinary tract	1 (3.0)	9 (9.2)	2 (5.6)	1 (9.1)	0.656
Gastrointestinal tract	2 (6.1)	6 (6.1)	3 (8.3)	1 (9.1)	0.955
Other site	1 (3.0)	5 (5.1)	1 (2.8)	0	0.800

Community-acquired infection	25 (75.8)	76 (77.6)	26 (72.2)	8 (72.7)	0.925
Hypotension	19 (57.6)	34 (34.7)	9 (25.0)	1 (9.1)	0.007
Lactate level (mmol/L)	2.4 (1.6-7.2)	2.1 (1.0-4.3)	1.6 (1.2-3.3)	1.9 (0.6-2.9)	0.201
Oliguria	8 (24.2)	13 (13.3)	3 (8.3)	0	0.121
PaO₂/FiO₂ (mmHg)	180.0(113.5-251.0)	164.5(102.3-240.5)	188.0(140.5-268.5)	215.0(153.0-300.0)	0.340
Serum Creatinine (µmol/L)	89.0 (57.0-127.0)	118.5 (72.5-190.5)	91.0 (60.0-212.5)	86.0 (56.0-112.0)	0.136
Total bilirubin (µmol/mL)	18.0 (10.1-33.1)	14.4 (10.1-28.4)	17.2 (12.2-26.3)	15.2 (11.3-20.0)	0.819
Platelets (×10⁹/L)	139.0 (75.0-213.0)	147.0 (86.0-209.8)	182.5 (128.3-253.8)	115.0 (49.0-144.0)	0.056
INR	1.3 (1.1-1.6)	1.2 (1.0-1.5)	1.2 (1.1-1.3)	1.1 (1.0-1.2)	0.269
Glasgow coma scale	13.0 (10.0-15.0)	15.0 (12.0-15.0)	15.0 (11.0-15.0)	13.0 (10.0-15.0)	0.761
SOFA score	8.0 (5.0-11.0)	7.0 (5.0-9.0)	6.0 (4.0-8.0)	5.0 (5.0-8.0)	0.382
APACHE II score	18.0 (16.0-24.0)	19.0 (13.0-25.0)	18.0 (13.0-22.0)	14.0 (9.0-17.0)	0.060
Septic shock	19 (57.6)	30 (30.6)	9 (25.0)	1(9.1)	0.004
Non-invasive ventilation	7 (21.2)	30 (30.6)	10 (27.8)	5 (45.5)	0.466
Intubated	19 (57.6)	43 (43.9)	13 (36.1)	4 (36.4)	0.305
Positive blood culture	7 (21.2)	24 (24.5)	4 (11.1)	3 (27.3)	0.383
Length of ICU stay (days)	10.0 (4.0-25.0)	13.0 (7.0-25.0)	11.0 (4.0-19.0)	9.0(6.0-13.0)	0.461
Length of hospital stay (days)	13.0 (4.0-29.0)	16.0 (10.0-28.0)	16.0 (8.0-32.0)	13.0(8.0-20.0)	0.813
In-hospital mortality	20 (60.6)	41 (41.8)	11 (30.6)	2 (18.2)	0.027
90-day mortality	22 (66.7)	47 (48.0)	13 (36.1)	2 (18.2)	0.015

416 Data are presented as n (%) or median (interquartile range). COPD: Chronic obstructive pulmonary disease; INR: International normalized ratio; SOFA:

417 Sequential organ failure assessment; APACHE: Acute physiology and chronic health evaluation.

1
2
3
4 418 **Fig 1. Patient selection.**

5
6 419

7
8 420

9
10 421

11
12 422

13
14 423

15
16 424

17
18 425

19
20 426

21
22 427

23
24 428

25
26 429

27
28 430

29
30 431

31
32 432

33
34 433

35
36 434

37
38 435

39
40 436

41
42 437

43
44 438

45
46 439

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

440 **Fig 2. Kaplan-Meier survival plot for 90-day survival of underweight, normal weight,**
441 **overweight, and obese patients with sepsis.**

For peer review only

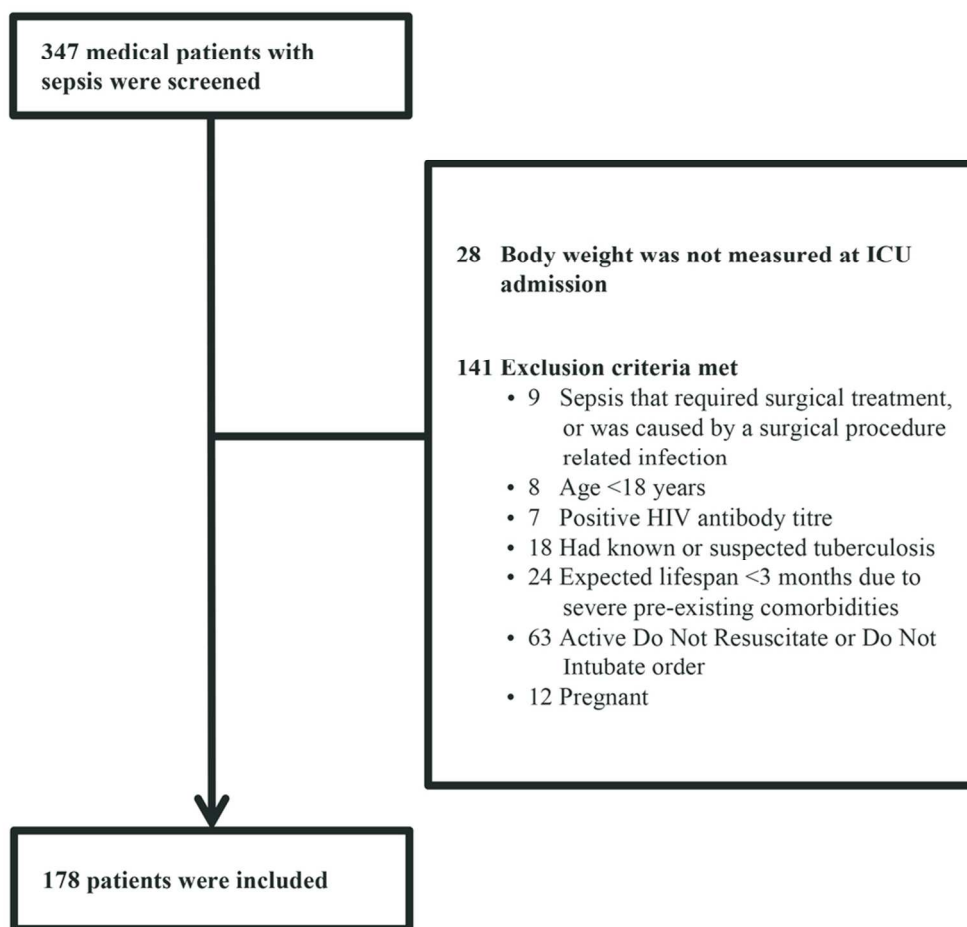


Fig 1. Patient selection.

90x90mm (300 x 300 DPI)

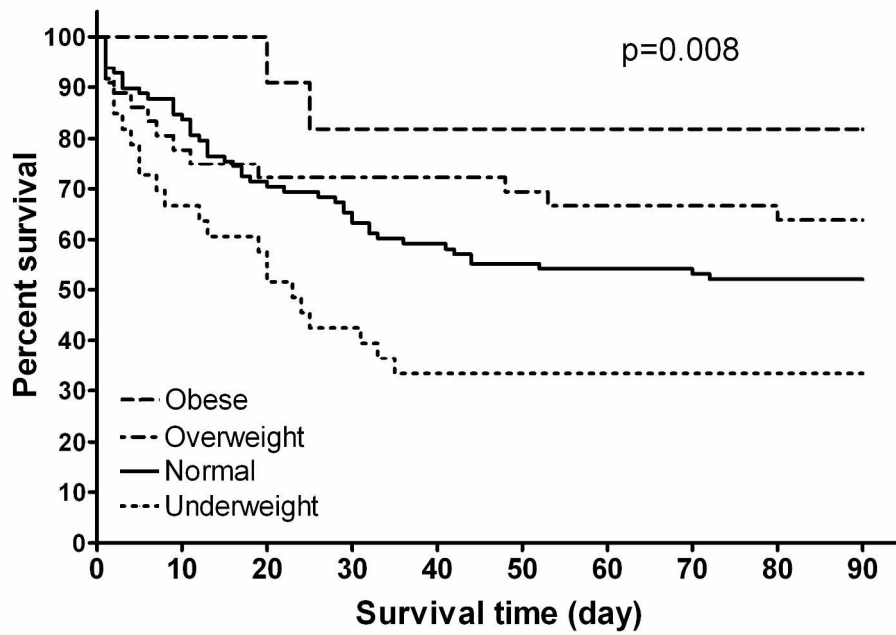


Fig 2. Kaplan-Meier survival plot for 90-day survival of underweight, normal weight, overweight, and obese patients with sepsis.

246x167mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(b) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6,7
		(b) Describe any methods used to examine subgroups and interactions	6,7
		(c) Explain how missing data were addressed	N/A
		(d) If applicable, explain how loss to follow-up was addressed	N/A
		(e) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7,8
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7,8
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8,19-23
		(b) Report category boundaries when continuous variables were categorized	6
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12,13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The impact of body mass index on survival of medical patients with sepsis: a prospective cohort study in a university hospital in China

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-021979.R2
Article Type:	Research
Date Submitted by the Author:	23-May-2018
Complete List of Authors:	Zhou, Qingtao; Peking University Third Hospital, Department of respiratory and critical care medicine Wang, Meng; Peking University Third Hospital, Department of respiratory and critical care medicine Li, Shuo; Peking University Third Hospital, Emergency Department Zhang, Jing; Peking University Third Hospital, Department of respiratory and critical care medicine Ma, Qingbian; Peking University Third Hospital, Emergency Department Ding, Yanling; Peking University Third Hospital, Department of respiratory and critical care medicine Ge, Hongxia; Peking University Third Hospital, Emergency Department Shen, Ning; Peking University Third Hospital, Department of respiratory and critical care medicine Zheng, Yaan; Peking University Third Hospital, Emergency Department Sun, Yongchang; Peking University Third Hospital, Department of respiratory and critical care medicine
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Infectious diseases
Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, INFECTIOUS DISEASES, THORACIC MEDICINE

SCHOLARONE™
Manuscripts

1
2
3
4 **1 The impact of body mass index on survival of medical patients with sepsis: a**
5
6 **2 prospective cohort study in a university hospital in China**
7

8
9
3

10
11 4 Qingtao Zhou¹, Meng Wang¹, Shuo Li², Jing Zhang¹, Qingbian Ma², Yanling Ding¹,
12
13 5 Hongxia Ge², Ning Shen¹, Yaan Zheng², Yongchang Sun^{1*}
14

15
16
6

17
18 7 ¹ Department of Respiratory and Critical Care Medicine, Peking University Third
19
20 8 Hospital, Beijing, China.
21

22
23 9 ² Emergency Department, Peking University Third Hospital, Beijing, China.
24

25
26
10

27
28 11 ***Corresponding author:** Yongchang Sun, Department of Respiratory and Critical
29
30 12 Care Medicine, Peking University Third Hospital, 49 North Garden Road, Haidian
31
32 13 District, Beijing 100191, China. Email: suny@bjmu.edu.cn
33

34
35
14

36
37
15

38
39
16

40
41
17

42
43
18

44
45
19

46
47
20

48
49
21

50
51
22

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23 **Abstract**

24 **Objective** To evaluate the impact of body mass index (BMI) on survival of a Chinese
25 cohort of medical patients with sepsis.

26 **Design** A single-center prospective cohort study conducted from May 2015 to April
27 2017.

28 **Setting** A tertiary care university hospital in China.

29 **Participants** 178 patients with sepsis admitted to the medical intensive care unit (ICU)
30 were included.

31 **Main outcome measures** The primary outcome was 90-day mortality. The secondary
32 outcomes were in-hospital mortality, length of ICU stay, and length of hospital stay.

33 **Results** The median age (interquartile range) was 78 (66-84) years and the majority of
34 patients (77.0%) were older than 65 years. The 90-day mortality was 47.2%. The
35 in-hospital mortality was 41.6%, and the length of ICU stay and hospital stay were 12
36 (5-22) and 15 (9-28) days, respectively. Cox proportional hazard regression analysis
37 identified that sequential organ failure assessment (SOFA) score (HR = 1.229, $p <$
38 0.001), APACHE II score (HR = 1.050, $p <$ 0.001) and BMI (HR = 0.940, $p =$ 0.029)
39 were all independently associated with the 90-day mortality. Patients were divided
40 into four groups based on BMI [underweight 33 (18.5%), normal 98 (55.1%),
41 overweight 36 (20.2%), and obese 11 (6.2%)]. The 90-day mortality (66.7%, 48.0%,
42 36.1%, and 18.2%, $p =$ 0.015) and in-hospital mortality (60.6%, 41.8%, 30.6%, and
43 18.2%, $p =$ 0.027) were statistically different among the four groups. Differences in
44 survival among the four groups were demonstrated by Kaplan-Meier survival analysis

1
2
3
4 45 (p = 0.008), with the underweight patients showing a lower survival rate.
5

6 46 **Conclusions** BMI was an independent factor associated with survival in a Chinese
7
8 47 cohort of medical patients with sepsis, patients with lower BMI having a higher risk
9
10
11 48 of death.
12

13
14
15
16 50 **Key words:** Sepsis; Septic shock; Body mass index; Critical care; Mortality
17

18
19
20
21 52 **Strengths and limitations of this study**
22

23 53 Our prospective observational cohort study was focused on medical patients with
24
25 54 sepsis and conducted at a university hospital in China.
26

27
28 55 The impact of BMI on 90-day survival of medical patients with sepsis was evaluated
29
30 56 by Cox proportional hazard regression analysis and Kaplan-Meier survival analysis.
31

32
33 57 Our analyses were limited by the use of weight ascertained at ICU admission, rather
34
35 58 than the patient's true outpatient weight.
36

37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

60

61

62

63

64

65

66

67 **Introduction**

68 Sepsis is a major cause of morbidity and mortality worldwide ^[1]. Of these
69 patients, half are treated in the intensive care unit (ICU) ^[2]. In a national
70 population-based study of sepsis in Spain, medical diagnostic categories were the
71 majority of causes in patients who developed sepsis, while surgical diagnoses were
72 identified in only 26% of cases ^[3].

73 Body mass index (BMI) is a simple index of weight-for-height that is commonly
74 used to classify whether adults are underweight, overweight and obese ^[4]. Several
75 studies have examined the effects of BMI on mortality with conflicting conclusions.
76 Lower mortality in the obese has been observed in some studies ^[5-9], but some
77 researchers believe that the true paradox may lie in the variations in sepsis
78 interventions, such as the administration of resuscitation fluids and antimicrobial
79 therapy ^[6]. In other studies, morbidly obese and underweight patients have been
80 shown to be associated with higher mortality ^[10,11]. Thus, the impact of BMI on
81 survival of patients with sepsis is still controversial ^[12, 13].

82 As the relationship between BMI and clinical outcomes of sepsis is complex, we
83 therefore set out to evaluate prospectively the impact of BMI on survival in a cohort
84 of medical patients with sepsis admitted to the medical ICU in a university hospital.

86 **Patients and Methods**

87 **Design**

88 This was a prospective cohort study, which was conducted in the medical ICU of

89 a university-affiliated urban teaching hospital in China from May 2015 to April 2017.

90 **Subjects**

91 Sepsis was defined as the presence (probable or documented) of infection
92 together with systemic manifestations of infection^[14]. Hospitalized patients admitted
93 to the medical ICU with sepsis acquired in the community or in a hospital were
94 eligible for the study if they met any of the following criteria of severe sepsis^[14]: (1)
95 sepsis-induced hypotension, (2) lactate above upper laboratory level limits
96 (1.5mmol/L in this study), (3) urine output $<0.5 \text{ mL Kg}^{-1} \text{ h}^{-1}$ for more than 2 h despite
97 adequate fluid resuscitation, (4) acute lung injury with $\text{Pao}_2/\text{Fio}_2 < 250$ in the absence
98 of pneumonia as infection source, (5) acute lung injury with $\text{Pao}_2/\text{Fio}_2 < 200$ in the
99 presence of pneumonia as infection source, (6) creatinine $>2.0 \text{ mg/dL}$ ($176.8 \text{ } \mu\text{mol/L}$),
100 (7) bilirubin $>2 \text{ mg/dL}$ ($34.2 \text{ } \mu\text{mol/L}$), (8) platelet count $<100,000 \text{ } \mu\text{L}$, and (9)
101 coagulopathy (international normalized ratio >1.5).

102 Patients were excluded from the study if they met one of the following criteria: (1)
103 the patient had sepsis that required surgical treatment, or was caused by a surgical
104 procedure related infection, (2) age <18 years, (3) the patient had a positive HIV
105 antibody titer or had known/suspected tuberculosis at baseline, (4) expected lifespan
106 <3 months due to severe pre-existing comorbidities, (5) active Do Not Resuscitate or
107 Do Not Intubate order, and (6) pregnant.

108 All patients accepted treatment according to the international guidelines for
109 management of sepsis and septic shock^[14,15]. We collected the following
110 demographic and clinical data: patient's gender, age, weight, height, primary site of

1
2
3
4 111 infection, community-acquired or hospital-acquired infection, blood pressure, lactate
5
6 112 level, urine output, PaO₂/FiO₂, serum creatinine, total bilirubin, platelets, international
7
8 113 normalized ratio (INR), Glasgow coma scale, SOFA score, acute physiology and
9
10 114 chronic health evaluation (APACHE) II score, non-invasive ventilation, intubation,
11
12 115 positive blood culture, length of ICU stay, and length of hospital stay. Those who
13
14 116 survived to discharge were followed for at least 90 days.

17
18 117 BMI is defined as the weight in kilograms divided by the square of the height in
19
20 118 meters (kg/m²). Using the World Health Organization (WHO) criteria for designation
21
22 119 of BMI ^[4], patients were classified as underweight (BMI < 18.50 kg/m²), normal
23
24 120 weight (BMI = 18.50 to 24.99 kg/m²), overweight (BMI = 25.0 to 29.99 kg/m²), and
25
26 121 obese (BMI ≥ 30.0 kg/m²).

30 122 **Outcomes**

31
32
33 123 The primary outcome was 90-day mortality, while the secondary outcomes were
34
35 124 in-hospital mortality, length of ICU stay, and length of hospital stay.

37 125 **Statistical analysis**

38
39
40 126 Continuous variables were expressed as median (interquartile range) and
41
42 127 categorical variables as numbers (%). Clinical data were compared between the
43
44 128 in-hospital survivors and non-survivors. Continuous variables were compared using
45
46 129 the non-parametric Mann–Whitney U test, and categorical variables were compared
47
48 130 using the Chi squared test. Cox proportional hazard regression analysis was
49
50 131 undertaken to assess the factors associated with 90-day mortality. The variables
51
52 132 significantly associated with 90-day non-survival in the univariate analysis were used
53
54
55
56
57
58
59
60

1
2
3
4 133 in the Cox proportional hazard regression analysis.

5
6 134 Patients were divided into four groups based on BMI (underweight, normal,
7
8 135 overweight, and obese). Clinical data were compared among the four groups, where
9
10 136 continuous variables were compared using the non-parametric Kruskal-Wallis H test,
11
12 137 and categorical variables were compared using the Chi squared test. Kaplan-Meier
13
14 138 survival curves were constructed to show the survival probabilities at day-90
15
16 139 according to BMI classification, and compared using the log rank test.

17
18
19
20 140 All analyses were conducted using SPSS, version 22.0 (IBM, Armonk, NY,
21
22 141 USA). A p value <0.05 was considered significant.

23 24 25 142 **Patient involvement**

26
27
28 143 No patients were involved in developing the hypothesis, the specific aims or the
29
30 144 research questions, nor were they involved in the design or implementation of this
31
32 145 study. No patients were involved in the interpretation of study results or write-up of
33
34 146 the manuscript. There are no plans to involve patients in the dissemination of results.

35 36 37 38 39 40 148 **Results**

41
42
43 149 Figure 1 shows the patient-selection process. In total, 178 medical patients with
44
45 150 sepsis were included in this study, with male patients accounting for 65.2% (n=116).
46
47 151 The median age (interquartile range) was 78 (66-84) years, and most patients were at
48
49 152 least 65 years old (137/178 cases, 77.0%). The most common primary site of infection
50
51 153 was the lung (131 cases, 73.6%), followed by abdomen (15 cases, 8.4%), urinary tract
52
53 154 (13 cases, 7.3%), gastrointestinal tract (12 cases, 6.7%) and other sites (7 cases, 3.9%).
54
55
56
57
58
59
60

1
2
3
4 155 Septic shock patients accounted for 33.1% (59 cases). Blood culture was positive in
5
6 156 38 patients (21.3%). The 90-day mortality was 47.2% (84/178 cases), and the
7
8 157 in-hospital mortality was 41.6% (74/178 cases). The length of ICU stay and the length
9
10
11 158 of hospital stay were 12 (5-22) and 15 (9-28) days, respectively.

12
13 159 Compared with in-hospital survivors, non-survivors had significantly lower BMI
14
15 160 and PaO₂/FiO₂ (both $p < 0.05$), higher lactate, bilirubin, INR, SOFA score and
16
17 161 APACHE II score (all $p < 0.05$). Meanwhile, more patients died with
18
19 162 healthcare-acquired infections, hypotension, oliguria, septic shock, and intubation (all
20
21 163 $p < 0.05$) (table 1).

22
23 164 Cox proportional hazard regression analysis was conducted and the independent
24
25 165 factors for 90-day death were identified as SOFA score (HR = 1.220, $p < 0.001$),
26
27 166 APACHE II score (HR = 1.050, $p < 0.001$) and BMI (HR = 0.940, $p = 0.029$) (table
28
29 167 2).

30
31 168 Patients were divided into four groups based on BMI [underweight 33 (18.5%),
32
33 169 normal 98 (55.1%), overweight 36 (20.2%), and obese 11 (6.2%)] . The percentage of
34
35 170 males (72.7%, 71.4%, 55.6%, and 18.2%, $p = 0.002$), chronic obstructive
36
37 171 pulmonary disease (24.2%, 21.4%, 0, and 27.3%, $p=0.017$), hypotension (57.6%,
38
39 172 34.7%, 25.0%, and 9.1%, $p = 0.007$), septic shock (57.6%, 30.6%, 25.0%, and 9.1%,
40
41 173 $p = 0.004$), in-hospital mortality (60.6%, 41.8%, 30.6%, and 18.2%, $p = 0.027$) and
42
43 174 90-day mortality (66.7%, 48.0%, 36.1%, and 18.2%, $p = 0.015$) were statistically
44
45 175 different among the four groups (table 3).

46
47 176 Kaplan-Meier survival curves were constructed to show the survival probabilities
48
49
50
51
52
53
54

1
2
3
4 177 at day-90 according to BMI classification and these were compared using the log rank
5
6 178 test, which also showed that higher BMI was associated with better prognosis
7
8 179 (p=0.008) (figure 2).
9

10
11 180

12 13 181 **Discussion**

14
15
16 182 This prospective observational cohort study was focused on medical patients with
17
18 183 sepsis admitted to the ICU, and the results showed that besides SOFA score and
19
20 184 APACHE II score, BMI was identified as an independent factor for 90-day mortality
21
22
23 185 by Cox regression analysis. The association of SOFA and APACHE II score with
24
25 186 mortality in this cohort was consistent with previous studies^[16-18]. However, BMI was
26
27
28 187 also found to be independently associated with survival, where 90-day mortality
29
30 188 decreased with an increase in BMI. While studies examining the risk factors
31
32
33 189 associated with outcomes in sepsis reached inconsistent conclusions on the
34
35 190 association of BMI with mortality, our results confirmed that BMI was independently
36
37
38 191 associated with mortality in patients with sepsis caused by medical conditions.
39

40 192 Globally, the prevalence of obesity has reached epidemic proportions, especially
41
42 193 in developed countries^[19]. BMI is still a useful proxy of overall health because it is
43
44
45 194 highly correlated with body surface area, which is commonly used as a surrogate
46
47
48 195 measure in obesity classification. Even though it is widely accepted that obesity is a
49
50 196 risk factor for diabetes mellitus, hypertension, and cardiovascular diseases, the present
51
52 197 study and several other studies have indicated that overweight and obese patients with
53
54
55 198 sepsis tend to experience lower mortality. This has been called the “obesity paradox”
56
57

1
2
3
4 199 [5-9,20]. Although some researchers have expressed doubt that the true paradox may lie
5
6 200 in the variations in sepsis interventions [6,21], a meta-analysis concluded that
7
8 201 individuals who were overweight or obese had a reduced adjusted mortality when
9
10 202 admitted to the ICU with sepsis or septic shock [8]. Recently another meta-analysis
11
12 203 also concluded that being overweight was associated with lower mortality (OR 0.87,
13
14 204 95% CI 0.77-0.97, $p = 0.02$) compared with obese (OR 0.89, 95% CI 0.72-1.10, $p =$
15
16 205 0.29) and morbidly obese (OR 0.64, 95% CI 0.38-1.08, $p = 0.09$) patients who did not
17
18 206 exhibit significantly reduced mortality compared with normal weight patients [12]. In a
19
20 207 large and nationally representative sample of over 1,000 hospitals in the US, obesity
21
22 208 was found to be significantly associated with a 16% decrease in the odds of dying
23
24 209 among sepsis patients who were hospitalized [22].

25
26
27
28
29
30 210 Underweight patients with sepsis may be more common in developing countries
31
32 211 than in developed countries. In the present study, the percentages of underweight,
33
34 212 normal weight, overweight and obese patients were 18.4%, 55.3%, 20.1%, and 6.1%,
35
36 213 respectively, while those with sepsis in a study in Canada and the US represented
37
38 214 6.8%, 35.3%, 28.3%, and 29.0% [6]. Being underweight was found to be one of the
39
40 215 independent risk factors of mortality in a study on the correlation between surgical
41
42 216 site infection and mortality [10]. Furthermore, Lee et al [11] also reported that being
43
44 217 underweight was associated with mortality in patients with severe sepsis and septic
45
46 218 shock. However, BMI has not been shown to be an independent factor for clinical
47
48 219 outcomes by multivariable analyses. In our cohort of medical patients with sepsis,
49
50 220 which mainly included elderly and less obese patients, BMI was identified as an

1
2
3
4 221 independent factor for survival, patients with lower BMI having a higher risk of death.
5
6 222 Thus, our findings would be helpful for evaluating the clinical outcomes of medical
7
8 223 patients with sepsis, although validation in further large sample, multi-center studies
9
10
11 224 is still needed.

12
13 225 The mechanism of the correlation between BMI and mortality of sepsis is unclear.
14
15 226 There are several potential reasons that could explain this. First, higher BMI resulted
16
17
18 227 in more fat reserves, and patients could have a greater capacity to cope with the
19
20 228 inflammatory response during sepsis and sepsis-associated acute lung injury [23-25].
21
22
23 229 Furthermore, they may be able to tolerate extensive weight loss and dysfunction
24
25 230 associated with critical illness [26]. Secondly, a higher BMI can lead to an increased
26
27
28 231 level of lipoproteins. High-density lipoproteins may not only bind and inactivate
29
30 232 lipopolysaccharide (LPS) or other harmful bacterial products released during sepsis
31
32
33 233 [27], but also modulate adhesion molecule expression, upregulate endothelial nitric
34
35 234 oxide synthase, and counteract oxidative stress [28]. Thirdly, higher BMI can lead to
36
37
38 235 increased adipose tissue deposition. Adipose tissue is increasingly being considered as
39
40 236 a functional endocrine organ and associated with increased renin-angiotensin system
41
42 237 activity [29]. It appears to have protective hemodynamic effects during sepsis and may
43
44
45 238 decrease the need for fluid or vasopressor support [21,30].

46
47 239 In general, sex has not been found to be an independent predictor for survival in
48
49
50 240 patients with sepsis, which is the same as the results of our current study. But in some
51
52 241 special populations, for example in liver cirrhosis patients with bloodstream infection,
53
54
55 242 male sex may be an independent risk factor for mortality [31].
56
57
58
59
60

1
2
3
4 243 As the relationship between BMI and clinical outcomes of sepsis may be related
5
6 244 partly to differences in patient characteristics, we therefore set out to evaluate the
7
8 245 impact of BMI on survival in a cohort of medical patients with sepsis, which is
9
10 246 different from surgical septic patients. Ranieri et al ^[32] reported that the primary sites
11
12 247 of infection in adults with septic shock were lung (43.9%), abdomen (30.0%), urinary
13
14 248 tract (12.3%), skin (5.5%) and other sites (8.3%). Scheer et al ^[33] found that the most
15
16 249 common primary site of infection was different between medical and surgical patients.
17
18 250 In medical patients, lung was the most common primary site (42.0%-56.7%), while it
19
20 251 was abdomen (48.4%-64.4%) in surgical patients. It should be noted that in the
21
22 252 majority of our patients (73.6%) sepsis was associated with pulmonary infection, a
23
24 253 much higher percentage as compared to other studies. He et al ^[34] reported that
25
26 254 pulmonary-sepsis showed worse outcome than abdominal-sepsis, and pulmonary
27
28 255 infection was a risk factor for one-year mortality and quality of life after sepsis.

29
30
31
32
33
34
35 256 There were several limitations to our study. Firstly, the BMI of our patients
36
37 257 ranged from 12.11 to 32.46. There was no morbidly obese patient in the current study.
38
39 258 In fact, morbidly obese people are rare in this country. Ten severe thinness patients
40
41 259 with BMI less than 16.0 were included in the present study, which maybe a small
42
43 260 danger that low BMIs represent a sample related bias. But the 90-day mortality and
44
45 261 in-hospital mortality of severe thinness patients were 70.0% and 60.0%, respectively,
46
47 262 which were not different from those of all 33 underweight patients (66.7% and 60.6%,
48
49 263 respectively). Secondly, the present study used weight ascertained at ICU admission,
50
51 264 rather than the patient's true outpatient weight. This practice may misclassify the BMI
52
53
54
55
56
57
58
59
60

1
2
3
4 265 category in as many as 21.9% of patients due to lack of fluid balance adjustment ^[35].

5
6 266 Thirdly, BMI was used to determine the nutritional status of patients in this study.

7
8 267 BMI is a simple index and widely used in clinical practice, but other indices such as

9
10 268 percent body fat might better reflect body composition^[36]. Lastly, it was a

11
12 269 single-center study with 178 participants, and a large proportion of our patients were

13
14 270 older than 65 years, which may have led to a sample-related bias.

15 16 17 18 271 **Conclusions**

19
20 272 To our knowledge, this is the first prospective cohort study that focused on

21
22 273 medical patients with sepsis, showing that BMI was independently associated with

23
24 274 survival, patients with lower BMI having a higher risk of death.

25
26
27
28 275

29 30 276 **Acknowledgements**

31
32 277 Not applicable.

33
34
35 278

36 37 279 **Authors' contributions**

38
39 280 QTZ, YCS, YAZ designed the study. QTZ, YCS, NS, YAZ, and QBM coordinated the

40
41 281 study. MW, JZ, YLD, SL, and HXG were responsible for patient screening,

42
43 282 enrollment, and follow-up. QTZ, MW, and YCS analyzed the data. QTZ drafted the

44
45 283 manuscript. YCS critically revised the manuscript. All authors had full access to all

46
47 284 study data, read and approved the final version of the manuscript.

48
49
50
51 285

52 53 286 **Funding**

1
2
3 287 None.
4
5

6 288
7

8 **289 Competing interests**
9

10 290 None declared.
11
12

13 291
14

15 **292 Ethics approval and consent to participate**
16

17
18 293 The study protocol was approved (approval number M2015021) by the ethics
19
20 294 committee of Peking University Third Hospital, Beijing, China. All patients or their
21
22 295 legally authorized representatives provided written informed consent to participate in
23
24 296 the study.
25
26
27

28 297
29

30 **298 Data sharing statement**
31

32
33 299 The authors declare that all data supporting the findings of this study are available
34
35 300 within the article.
36
37

38 301
39

40 **302 References**
41

- 42 303 1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus
43
44 304 Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315:801-10.
45
46
47 305 2. Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med* 2013;369:2063.
48
49
50 306 3. Bouza C, López-Cuadrado T, Saz-Parkinson Z, et al. Epidemiology and recent trends of
51
52 307 severe sepsis in Spain: a nationwide population-based analysis (2006-2011). *BMC Infect Dis*
53
54 308 2014; 14:3863.
55
56
57
58
59
60

- 1
2
3
4 309 4. WHO classification of body mass index (BMI). [[http://apps.who.int/bmi/index.jsp?introPage=](http://apps.who.int/bmi/index.jsp?introPage=intro_3.html)
5
6 310 [intro_3.html](http://apps.who.int/bmi/index.jsp?introPage=intro_3.html)] Accessed on 2 March 2015.
7
8 311 5. Wurzinger B, Dünser MW, Wohlmuth C, et al. The association between body-mass index and
9
10 312 patient outcome in septic shock: a retrospective cohort study. *Wien Klin Wochenschr* 2010;122:
11
12 313 31-6.
13
14
15 314 6. Arabi YM, Dara SI, Tamim HM, et al. Clinical characteristics, sepsis interventions and
16
17 315 outcomes in the obese patients with septic shock:an international multicenter cohort study.
18
19 316 *Crit Care* 2013;17:R72.
20
21
22 317 7. Prescott HC, Chang VW, O'Brien JM Jr, et al. Obesity and 1-year outcomes in older
23
24 318 Americans with severe sepsis. *Crit Care Med* 2014;42:1766-74.
25
26
27 319 8. Pepper DJ, Sun J, Welsh J, et al. Increased body mass index and adjusted mortality in ICU
28
29 320 patients with sepsis or septic shock:a systematic review and meta-analysis. *Crit Care*
30
31 321 2016;20:181.
32
33
34 322 9. Gaulton TG, Marshall MacNabb C, Mikkelsen ME, et al. A retrospective cohort study
35
36 323 examining the association between body mass index and mortality in severe sepsis. *Intern*
37
38 324 *Emerg Med* 2015;10:471-9.
39
40
41 325 10. Giles KA, Hamdan AD, Pomposelli FB, et al. Body mass index:surgical site infections and
42
43 326 mortality after lower extremity bypass from the National Surgical Quality Improvement
44
45 327 Program 2005-2007. *Ann Vasc Surg* 2010;24:48-56.
46
47
48 328 11. Lee SM, Kang JW, Jo YH, et al. Underweight is associated with mortality in patients with
49
50 329 severe sepsis and septic shock. *Intensive Care Med Exp* 2015; 3:A876.
51
52
53 330 12. Wang S, Liu X, Chen Q, et al. The role of increased body mass index in outcomes of sepsis: a
54
55
56
57
58
59
60

- 1
2
3
4 331 systematic review and meta-analysis. *BMC Anesthesiol* 2017;17:118.
5
6 332 13. Ng PY, Eikermann M. The obesity conundrum in sepsis. *BMC Anesthesiol* 2017;17:147.
7
8 333 14. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines
9
10 334 for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013;41:580-637.
11
12
13 335 15. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International
14
15 336 Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med* 2017;
16
17 337 43:304-77.
18
19
20 338 16. de Carvalho MA, Freitas FG, Silva Junior HT, et al. Mortality predictors in renal transplant
21
22 339 recipients with severe sepsis and septic shock. *PLoS One* 2014;9:e111610.
23
24
25 340 17. Innocenti F, Tozzi C, Donnini C, et al. SOFA score in septic patients: incremental prognostic
26
27 341 value over age, comorbidities, and parameters of sepsis severity. *Intern Emerg*
28
29 342 *Med* 2018;13:405-12.
30
31
32 343 18. Song JE, Kim MH, Jeong WY, et al. Mortality Risk Factors for Patients with Septic
33
34 344 Shock after Implementation of the Surviving Sepsis Campaign Bundles. *Infect*
35
36 345 *Chemother* 2016;48:199-208.
37
38
39 346 19. GBD 2015 Obesity Collaborators, Afshin A, Forouzanfar MH, et al. Health Effects of
40
41 347 Overweight and Obesity in 195 Countries over 25 Years. *N Engl J Med* 2017;377:13-27.
42
43
44 348 20. Atamna A, Elis A, Gilady E, et al. How obesity impacts outcomes of infectious diseases. *Eur*
45
46 349 *J Clin Microbiol Infect Dis* 2017; 36:585-91.
47
48
49 350 21. Taylor SP, Karvetski CH, Templin MA, et al. Initial fluid resuscitation following adjusted
50
51 351 body weight dosing is associated with improved mortality in obese patients with suspected
52
53 352 septic shock. *J Crit Care* 2018;43:7-12.
54
55
56
57
58
59
60

- 1
2
3
4 353 22. Nguyen AT, Tsai CL, Hwang LY, et al. Obesity and Mortality, Length of Stay and Hospital
5
6 354 Cost among Patients with Sepsis: A Nationwide Inpatient Retrospective Cohort Study. *PLoS*
7
8 355 *One* 2016; 11:e0154599.
- 10 356 23. Stapleton RD, Dixon AE, Parsons PE, et al. The association between BMI and plasma
11
12
13 357 cytokine levels in patients with acute lung injury. *Chest* 2010;138:568-77.
- 15 358 24. Stapleton RD, Suratt BT. Obesity and nutrition in acute respiratory distress syndrome. *Clin*
16
17 359 *Chest Med* 2014;35:655-71.
- 20 360 25. Zampieri FG, Jacob V, Barbeiro HV, et al. Influence of Body Mass Index on Inflammatory
21
22 361 Profile at Admission in Critically Ill Septic Patients. *Int J Inflam* 2015; 2015:734857.
- 25 362 26. Herridge MS, Cheung AM, Tansey CM, et al. One-year outcomes in survivors of the acute
26
27 363 respiratory distress syndrome. *N Engl J Med* 2003;348:683-93.
- 30 364 27. Wu A, Hinds CJ, Thiemermann C. High-density lipoproteins in sepsis and septic shock:
31
32 365 metabolism, actions, and therapeutic applications. *Shock* 2004;21:210-21.
- 35 366 28. Murch O, Collin M, Hinds CJ, et al. Lipoproteins in inflammation and sepsis. I. Basic science.
36
37 367 *Intensive Care Med* 2007; 33:13-24.
- 40 368 29. McGown C, Biredinc A, Younossi ZM. Adipose tissue as an endocrine organ. *Clin Liver*
41
42 369 *Dis* 2014;18:41-58.
- 45 370 30. Salgado DR, Rocco JR, Silva E, et al. Modulation of the renin-angiotensin-aldosterone
46
47 371 system in sepsis: a new therapeutic approach? *Expert Opin Ther Targets* 2010; 14:11-20.
- 50 372 31. Zhao H, Gu X, Zhao R, et al. Evaluation of prognostic scoring systems in liver cirrhosis
51
52 373 patients with bloodstream infection. *Medicine (Baltimore)* 2017;96(50):e8844.
- 54 374 32. Ranieri VM, Thompson BT, Barie PS, et al. Drotrecogin alfa (activated) in adults with septic

- 1
2
3 375 shock. *N Engl J Med* 2012;366:2055-64.
4
5
6 376 33. Scheer CS, Fuchs C, Kuhn SO, et al. Quality Improvement Initiative for Severe
7
8 377 Sepsis and Septic Shock Reduces 90-Day Mortality: A 7.5-Year Observational Study. *Crit*
9
10 378 *Care Med* 2017;45:241-52.
11
12
13 379 34. He XL, Liao XL, Xie ZC, et al. Pulmonary Infection Is an Independent Risk Factor for
14
15 380 Long-Term Mortality and Quality of Life for Sepsis Patients. *Biomed Res Int* 2016;
16
17 381 2016:4213712.
18
19
20 382 35. O'Brien JM Jr, Philips GS, Ali NA, et al. The association between body mass index, processes
21
22 383 of care, and outcomes from mechanical ventilation: a prospective cohort study.
23
24 384 *Crit Care Med* 2012;40:1456-63.
25
26
27 385 36. Waisbren E, Rosen H, Bader AM, et al. Percent body fat and prediction of surgical site
28
29 386 infection. *J Am Coll Surg* 2010;210:381-9.
30
31 387
32
33 388
34
35 389
36
37 390
38
39 391
40
41 392
42
43 393
44
45 394
46
47 395
48
49 396
50
51
52
53
54
55
56
57
58
59
60

397 **Table 1. Comparison of demographics and clinical data between groups defined by**
 398 **in-hospital clinical outcome in 178 patients with sepsis**

Characteristics	Survivors (n=104)	Non survivors (n=74)	p value
Age (year)	78.0 (60.0-84.0)	78.0 (69.0-84.0)	0.291
Males	67 (64.4)	49 (66.2)	0.805
Body mass index (kg/m ²)	23.2 (20.4-26.1)	21.7 (18.4-24.2)	0.006
Comorbidities			
COPD	23 (22.1)	9 (12.2)	0.088
Diabetes mellitus	26 (25.0)	21 (28.4)	0.614
Hypertension	47 (45.2)	31 (41.9)	0.662
Cerebrovascular disease	30 (28.8)	15 (20.3)	0.194
Neoplasm	18 (17.3)	12 (16.2)	0.848
Liver disease	5 (4.8)	4 (5.4)	1.000
Heart failure	20 (19.2)	14 (18.9)	0.958
Chronic renal failure	18 (17.3)	11 (14.9)	0.664
Smoking (pack years)	0 (0-30.0)	0 (0-16.3)	0.509
Primary site of infection			
Lung	77 (74.0)	54 (73.0)	0.874
Abdomen	10 (9.6)	5 (6.8)	0.499
Urinary tract	7 (6.7)	6 (8.1)	0.728
Gastrointestinal tract	7 (6.7)	5 (6.8)	1.000

Other site	3 (2.9)	4 (5.4)	0.452
Community-acquired infection	85 (81.7)	50 (67.6)	0.030
Hypotension	22 (21.2)	41 (55.4)	<0.001
Lactate level (mmol/L)	1.8 (1.0-3.4)	2.7 (1.5-5.7)	0.001
Oliguria	8 (7.7)	16 (21.6)	0.007
PaO₂/FiO₂(mmHg)	198.5 (119.3-287.5)	152.5 (99.6-210.3)	0.006
Serum Creatinine (μmol/L)	97.0 (68.3-176.3)	108.5 (64.0-194.3)	0.868
Total bilirubin (μmol/mL)	13.1 (9.9-22.3)	18.0 (12.5-32.8)	0.015
Platelets (×10⁹/L)	161.0 (95.8-232.5)	123.0 (75.0-204.3)	0.067
INR	1.2 (1.0-1.4)	1.3 (1.1-1.6)	0.015
Glasgow coma scale	15.0 (10.0-15.0)	13.0 (10.0-15.0)	0.117
SOFA score	5.0 (4.0-7.0)	9.0 (7.0-11.0)	<0.001
APACHE II score	16.0 (12.0-22.0)	21.0 (17.0-30.0)	<0.001
Septic shock	21 (20.2)	38 (51.4)	<0.001
Non-invasive ventilation	28 (26.9)	24 (32.4)	0.426
Intubated	36 (34.6)	43 (58.1)	0.002
Positive blood culture	19 (18.3)	19 (25.7)	0.235
Length of ICU stay (days)	12.0 (6.0-22.0)	12.0 (3.0-25.0)	0.521
Length of hospital stay (days)	18.0 (10.0-30.0)	13.0 (3.0-25.0)	0.009

399 Data are presented as n (%) or median (interquartile range) unless stated otherwise. COPD: Chronic obstructive pulmonary disease; INR: International

400 normalized ratio; SOFA: Sequential organ failure assessment; APACHE: Acute physiology and chronic health evaluation.

401

402 **Table 2. Risk factors for 90-day mortality of patients with sepsis or septic shock by Cox**
 403 **regression analysis**

Variables	Hazard ratio (95% Confidence interval)	p value
Body mass index (kg/m ²)	0.940 (0.889-0.994)	0.029
Hypotension	0.781 (0.229-2.670)	0.694
Lactate level (mmol/L)	1.018 (0.943-1.098)	0.648
Oliguria	1.288 (0.715-2.321)	0.399
PaO ₂ /FiO ₂ (mmHg)	1.000 (0.997-1.002)	0.933
Septic shock	1.075 (0.320-3.615)	0.907
SOFA score	1.229 (1.123-1.345)	<0.001
APACHE II score	1.050 (1.022-1.080)	<0.001
Intubated	1.511 (0.931-2.452)	0.095

404 SOFA: Sequential organ failure assessment; APACHE: Acute physiology and chronic health evaluation. The variables significantly associated with 90-day
 405 non-survival in the univariate analysis were used in the Cox proportional hazard regression analysis.

406

407

408

409

410

411

412

413

414 **Table 3. Comparison of demographics and clinical data among groups defined by body mass**
 415 **index in patients with sepsis**

Characteristics	Underweight (n=33)	Normal (n=98)	Overweight (n=36)	Obese (n=11)	p value
Age (years)	79.0 (69.0-86.0)	78.0 (67.0-84.0)	73.0 (57.0-83.0)	77.0 (71.0-86.0)	0.162
Males	24 (72.7)	70 (71.4)	20 (55.6)	2 (18.2)	0.002
Comorbidities					
COPD	8(24.2)	21 (21.4)	0	3 (27.3)	0.017
Diabetes mellitus	8 (24.2)	25 (25.5)	9 (25.0)	5 (45.5)	0.530
Hypertension	14 (42.4)	38 (38.8)	19 (52.8)	7 (63.6)	0.265
Cerebrovascular disease	10 (30.3)	24 (24.5)	11 (30.6)	0	0.193
Neoplasm	7 (21.2)	14 (14.3)	8 (22.2)	1 (9.1)	0.547
Liver disease	2 (6.1)	5 (5.1)	2 (5.6)	0	0.879
Heart failure	8 (24.2)	17 (17.3)	5 (13.9)	4 (36.4)	0.319
Chronic renal failure	5 (15.2)	14 (14.3)	7 (19.4)	3 (27.3)	0.669
Smoking (pack-years)	0 (0-20.5)	0 (0-30.0)	0 (0-3.0)	0 (0-30.0)	0.561
Primary site of infection					
Lung	27 (81.8)	69 (70.4)	27 (75.0)	8 (72.7)	0.637
Abdomen	2 (6.1)	9 (9.2)	3 (8.3)	1 (9.1)	0.956
Urinary tract	1 (3.0)	9 (9.2)	2 (5.6)	1 (9.1)	0.656
Gastrointestinal tract	2 (6.1)	6 (6.1)	3 (8.3)	1 (9.1)	0.955
Other site	1 (3.0)	5 (5.1)	1 (2.8)	0	0.800

Community-acquired infection	25 (75.8)	76 (77.6)	26 (72.2)	8 (72.7)	0.925
Hypotension	19 (57.6)	34 (34.7)	9 (25.0)	1 (9.1)	0.007
Lactate level (mmol/L)	2.4 (1.6-7.2)	2.1 (1.0-4.3)	1.6 (1.2-3.3)	1.9 (0.6-2.9)	0.201
Oliguria	8 (24.2)	13 (13.3)	3 (8.3)	0	0.121
PaO₂/FiO₂ (mmHg)	180.0(113.5-251.0)	164.5(102.3-240.5)	188.0(140.5-268.5)	215.0(153.0-300.0)	0.340
Serum Creatinine (µmol/L)	89.0 (57.0-127.0)	118.5 (72.5-190.5)	91.0 (60.0-212.5)	86.0 (56.0-112.0)	0.136
Total bilirubin (µmol/mL)	18.0 (10.1-33.1)	14.4 (10.1-28.4)	17.2 (12.2-26.3)	15.2 (11.3-20.0)	0.819
Platelets (×10⁹/L)	139.0 (75.0-213.0)	147.0 (86.0-209.8)	182.5 (128.3-253.8)	115.0 (49.0-144.0)	0.056
INR	1.3 (1.1-1.6)	1.2 (1.0-1.5)	1.2 (1.1-1.3)	1.1 (1.0-1.2)	0.269
Glasgow coma scale	13.0 (10.0-15.0)	15.0 (12.0-15.0)	15.0 (11.0-15.0)	13.0 (10.0-15.0)	0.761
SOFA score	8.0 (5.0-11.0)	7.0 (5.0-9.0)	6.0 (4.0-8.0)	5.0 (5.0-8.0)	0.382
APACHE II score	18.0 (16.0-24.0)	19.0 (13.0-25.0)	18.0 (13.0-22.0)	14.0 (9.0-17.0)	0.060
Septic shock	19 (57.6)	30 (30.6)	9 (25.0)	1(9.1)	0.004
Non-invasive ventilation	7 (21.2)	30 (30.6)	10 (27.8)	5 (45.5)	0.466
Intubated	19 (57.6)	43 (43.9)	13 (36.1)	4 (36.4)	0.305
Positive blood culture	7 (21.2)	24 (24.5)	4 (11.1)	3 (27.3)	0.383
Length of ICU stay (days)	10.0 (4.0-25.0)	13.0 (7.0-25.0)	11.0 (4.0-19.0)	9.0(6.0-13.0)	0.461
Length of hospital stay (days)	13.0 (4.0-29.0)	16.0 (10.0-28.0)	16.0 (8.0-32.0)	13.0(8.0-20.0)	0.813
In-hospital mortality	20 (60.6)	41 (41.8)	11 (30.6)	2 (18.2)	0.027
90-day mortality	22 (66.7)	47 (48.0)	13 (36.1)	2 (18.2)	0.015

416 Data are presented as n (%) or median (interquartile range). COPD: Chronic obstructive pulmonary disease; INR: International normalized ratio; SOFA:

417 Sequential organ failure assessment; APACHE: Acute physiology and chronic health evaluation.

1
2
3
4 418 **Fig 1. Patient selection.**

5
6 419

7
8 420

9
10 421

11
12 422

13
14 423

15
16 424

17
18 425

19
20 426

21
22 427

23
24 428

25
26 429

27
28 430

29
30 431

31
32 432

33
34 433

35
36 434

37
38 435

39
40 436

41
42 437

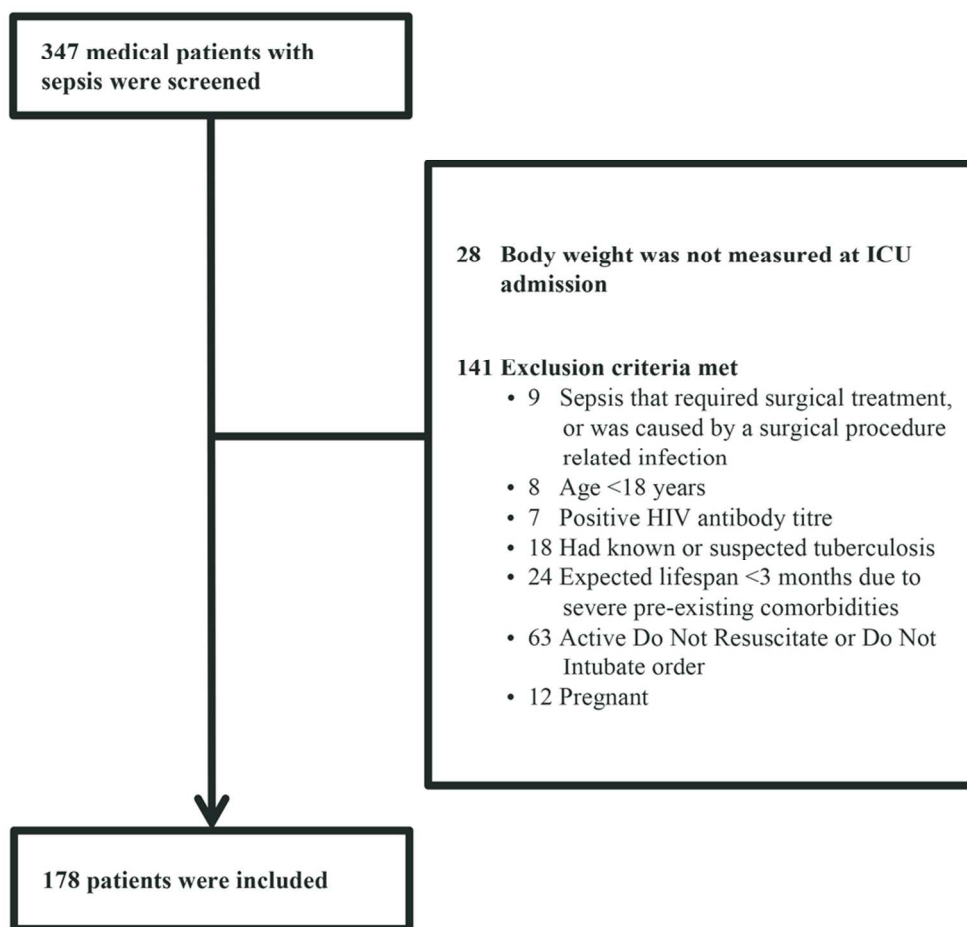
43
44 438

45
46 439

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

440 **Fig 2. Kaplan-Meier survival plot for 90-day survival of underweight, normal weight,**
441 **overweight, and obese patients with sepsis.**

For peer review only



39 Fig 1. Patient selection.

40 90x90mm (300 x 300 DPI)



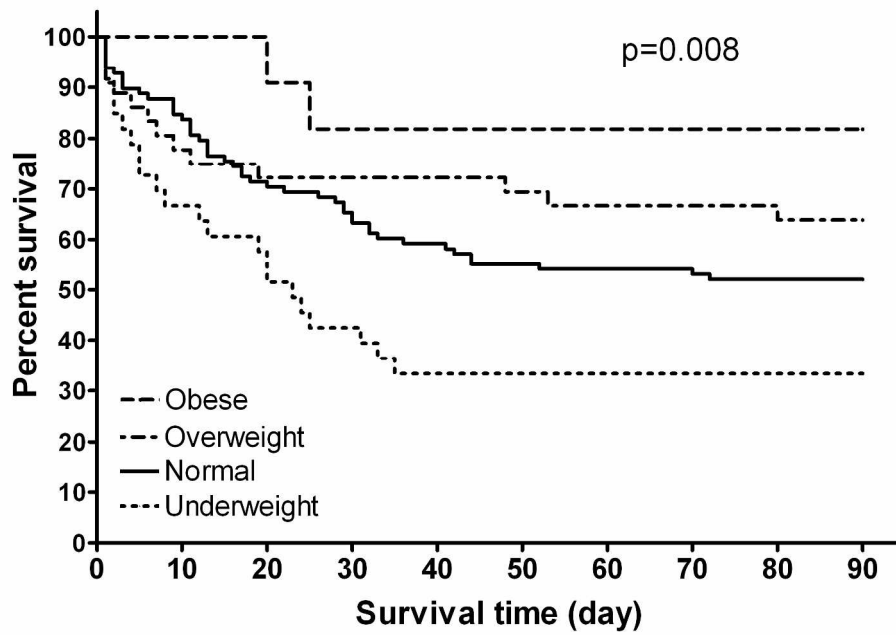


Fig 2. Kaplan-Meier survival plot for 90-day survival of underweight, normal weight, overweight, and obese patients with sepsis.

246x167mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4, 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4, 5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(b) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6,7
		(b) Describe any methods used to examine subgroups and interactions	6,7
		(c) Explain how missing data were addressed	N/A
		(d) If applicable, explain how loss to follow-up was addressed	N/A
		(e) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7,8
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7,8
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8,9
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8,19-25
		(b) Report category boundaries when continuous variables were categorized	6
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12,13
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13, 14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The impact of body mass index on survival of medical patients with sepsis: a prospective cohort study in a university hospital in China

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-021979.R3
Article Type:	Research
Date Submitted by the Author:	24-Jun-2018
Complete List of Authors:	Zhou, Qingtao; Peking University Third Hospital, Department of respiratory and critical care medicine Wang, Meng; Peking University Third Hospital, Department of respiratory and critical care medicine Li, Shuo; Peking University Third Hospital, Emergency Department Zhang, Jing; Peking University Third Hospital, Department of respiratory and critical care medicine Ma, Qingbian; Peking University Third Hospital, Emergency Department Ding, Yanling; Peking University Third Hospital, Department of respiratory and critical care medicine Ge, Hongxia; Peking University Third Hospital, Emergency Department Shen, Ning; Peking University Third Hospital, Department of respiratory and critical care medicine Zheng, Yaan; Peking University Third Hospital, Emergency Department Sun, Yongchang; Peking University Third Hospital, Department of respiratory and critical care medicine
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Infectious diseases
Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, INFECTIOUS DISEASES, THORACIC MEDICINE

SCHOLARONE™
Manuscripts

1
2
3
4 **1 The impact of body mass index on survival of medical patients with sepsis: a**
5
6 **2 prospective cohort study in a university hospital in China**
7

8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

3

4 Qingtao Zhou¹, Meng Wang¹, Shuo Li², Jing Zhang¹, Qingbian Ma², Yanling Ding¹,
5 Hongxia Ge², Ning Shen¹, Yaan Zheng², Yongchang Sun^{1*}

6
7 ¹ Department of Respiratory and Critical Care Medicine, Peking University Third
8 Hospital, Beijing, China.

9 ² Emergency Department, Peking University Third Hospital, Beijing, China.

10
11 ***Corresponding author:** Yongchang Sun, Department of Respiratory and Critical
12 Care Medicine, Peking University Third Hospital, 49 North Garden Road, Haidian
13 District, Beijing 100191, China. Email: suny@bjmu.edu.cn

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23 **Abstract**

24 **Objective** To evaluate the impact of body mass index (BMI) on survival of a Chinese
25 cohort of medical patients with sepsis.

26 **Design** A single-center prospective cohort study conducted from May 2015 to April
27 2017.

28 **Setting** A tertiary care university hospital in China.

29 **Participants** A total of 178 patients with sepsis admitted to the medical intensive care
30 unit (ICU) were included.

31 **Main outcome measures** The primary outcome was 90-day mortality while the
32 secondary outcomes were in-hospital mortality, length of ICU stay, and length of
33 hospital stay.

34 **Results** The median age (interquartile range) was 78 (66-84) years old and 77.0%
35 patients were older than 65 years. The 90-day mortality was 47.2%. The in-hospital
36 mortality was 41.6%, and the length of ICU stay and hospital stay were 12 (5-22) and
37 15 (9-28) days, respectively. Cox proportional hazard regression analysis identified
38 that sequential organ failure assessment (SOFA) score (HR = 1.229, $p < 0.001$),
39 APACHE II score (HR = 1.050, $p < 0.001$) and BMI (HR = 0.940, $p = 0.029$) were all
40 independently associated with the 90-day mortality. Patients were divided into four
41 groups based on BMI [underweight 33 (18.5%), normal 98 (55.1%), overweight 36
42 (20.2%), and obese 11 (6.2%)]. The 90-day mortality (66.7%, 48.0%, 36.1%, and
43 18.2%, $p = 0.015$) and in-hospital mortality (60.6%, 41.8%, 30.6%, and 18.2%, $p =$
44 0.027) were statistically different among the four groups. Differences in survival

1
2
3
4 45 among the four groups were demonstrated by Kaplan-Meier survival analysis ($p =$
5
6 46 0.008), with the underweight patients showing a lower survival rate.
7

8 47 **Conclusions** BMI was an independent factor associated with 90-day survival in a
9
10
11 48 Chinese cohort of medical patients with sepsis, with patients having a lower BMI at a
12
13 49 higher risk of death.
14

15
16 50

17
18 51 **Key words:** Sepsis; Septic shock; Body mass index; Critical care; Mortality
19

20
21 52

22 23 53 **Strengths and limitations of this study**

24
25 54 This prospective observational cohort study focused on medical patients with sepsis
26
27
28 55 and was conducted at a university hospital in China.

29
30 56 The impact of BMI on 90-day survival of medical patients with sepsis was evaluated
31
32
33 57 by Cox proportional hazard regression analysis and Kaplan-Meier survival analysis.
34

35 58 Our analyses were limited by the use of weight ascertained at ICU admission rather
36
37
38 59 than the patient's baseline outpatient body weight.
39

40
41 60

42
43 61

44
45 62

46
47 63

48
49 64

50
51 65

52
53 66
54
55
56
57
58
59
60

67 **Introduction**

68 Sepsis is a major cause of morbidity and mortality worldwide ^[1]. Of these
69 patients, half are treated in the intensive care unit (ICU) ^[2]. In a national
70 population-based study of sepsis in Spain, medical diagnostic categories made up the
71 majority of causes of sepsis, while surgical diagnoses were identified in only 26% of
72 cases ^[3].

73 Body mass index (BMI) is a simple index of weight-for-height that is commonly
74 used to classify whether adults are underweight, overweight and obese ^[4]. Several
75 studies have examined the effects of BMI on mortality with conflicting conclusions.
76 Lower mortality in the obese has been observed in some studies ^[5-9], but some
77 researchers believe that the true paradox may lie in the variations in sepsis
78 interventions, such as the administration of resuscitation fluids and antimicrobial
79 therapy ^[6]. In other studies, morbidly obese and underweight patients have been
80 shown to be associated with higher mortality ^[10,11]. Thus, the impact of BMI on
81 survival of patients with sepsis is still controversial ^[12, 13].

82 As the relationship between BMI and clinical outcomes of sepsis is complex, we
83 therefore set out to evaluate prospectively the impact of BMI on survival in a cohort
84 of medical patients with sepsis admitted to the medical ICU in a university hospital.

86 **Patients and Methods**

87 **Design**

88 This was a prospective cohort study, which was conducted in the medical ICU of

89 a university-affiliated urban teaching hospital in China from May 2015 to April 2017.

90 **Subjects**

91 Sepsis was defined as the presence (probable or documented) of infection
92 together with systemic manifestations of infection^[14]. Hospitalized patients admitted
93 to the medical ICU with sepsis acquired in the community or in a hospital were
94 eligible for the study if they met any of the following criteria of severe sepsis^[14]: (1)
95 sepsis-induced hypotension, (2) lactate above upper laboratory level limits
96 (1.5mmol/L in this study), (3) urine output $<0.5 \text{ mL Kg}^{-1} \text{ h}^{-1}$ for more than 2 h despite
97 adequate fluid resuscitation, (4) acute lung injury with $\text{Pao}_2/\text{Fio}_2 < 250$ in the absence
98 of pneumonia as infection source, (5) acute lung injury with $\text{Pao}_2/\text{Fio}_2 < 200$ in the
99 presence of pneumonia as infection source, (6) creatinine $>2.0 \text{ mg/dL}$ ($176.8 \text{ } \mu\text{mol/L}$),
100 (7) bilirubin $>2\text{mg/dL}$ ($34.2 \text{ } \mu\text{mol/L}$), (8) platelet count $<100,000 \text{ } \mu\text{L}$, and (9)
101 coagulopathy (international normalized ratio >1.5).

102 Patients were excluded from the study if they met one of the following criteria: (1)
103 the patient had sepsis that required surgical treatment, or was caused by a surgical
104 procedure related infection, (2) age <18 years, (3) the patient had a positive HIV
105 antibody titer or had known/suspected tuberculosis at baseline, (4) expected lifespan
106 <3 months due to severe pre-existing comorbidities, (5) active Do Not Resuscitate or
107 Do Not Intubate order, and (6) pregnant.

108 All patients accepted treatment according to the international guidelines for
109 management of sepsis and septic shock^[14,15]. We collected the following
110 demographic and clinical data: patient's gender, age, weight, height, primary site of

1
2
3
4 111 infection, community-acquired or hospital-acquired infection, blood pressure, lactate
5
6 112 level, urine output, PaO₂/FiO₂, serum creatinine, total bilirubin, platelets, international
7
8 113 normalized ratio (INR), Glasgow coma scale, SOFA score, acute physiology and
9
10 114 chronic health evaluation (APACHE) II score, non-invasive ventilation, intubation,
11
12 115 positive blood culture, length of ICU stay, and length of hospital stay. Those who
13
14 116 survived to discharge were followed for at least 90 days.

17
18 117 BMI is defined as the weight in kilograms divided by the square of the height in
19
20 118 meters (kg/m²). Using the World Health Organization (WHO) criteria for designation
21
22 119 of BMI ^[4], patients were classified as underweight (BMI < 18.50 kg/m²), normal
23
24 120 weight (BMI = 18.50 to 24.99 kg/m²), overweight (BMI = 25.0 to 29.99 kg/m²), and
25
26 121 obese (BMI ≥ 30.0 kg/m²).

30 122 **Outcomes**

31
32
33 123 The primary outcome was 90-day mortality, while the secondary outcomes were
34
35 124 in-hospital mortality, length of ICU stay, and length of hospital stay.

37 125 **Statistical analysis**

38
39
40 126 Continuous variables were expressed as median (interquartile range) and
41
42 127 categorical variables as numbers (%). Clinical data were compared between the
43
44 128 in-hospital survivors and non-survivors. Continuous variables were compared using
45
46 129 the non-parametric Mann–Whitney U test, and categorical variables were compared
47
48 130 using the Chi squared test. Cox proportional hazard regression analysis was
49
50 131 undertaken to assess the factors associated with 90-day mortality. The variables
51
52 132 significantly associated with 90-day non-survival in the univariate analysis were used
53
54
55
56
57
58
59
60

1
2
3
4 133 in the Cox proportional hazard regression analysis.
5

6 134 Patients were divided into four groups based on BMI (underweight, normal,
7
8 135 overweight, and obese). Clinical data were compared among the four groups, where
9
10 136 continuous variables were compared using the non-parametric Kruskal-Wallis H test,
11
12 137 and categorical variables were compared using the Chi squared test. Kaplan-Meier
13
14 138 survival curves were constructed to show the survival probabilities at day-90
15
16 139 according to BMI classification, and compared using the log rank test.
17
18
19

20 140 All analyses were conducted using SPSS, version 22.0 (IBM, Armonk, NY,
21
22 141 USA). A p value <0.05 was considered significant.
23
24

25 142 **Patient involvement**

26
27
28 143 No patients were involved in developing the hypothesis, the specific aims or the
29
30 144 research questions, nor were they involved in the design or implementation of this
31
32 145 study. No patients were involved in the interpretation of study results or write-up of
33
34 146 the manuscript. There are no plans to involve patients in the dissemination of results.
35
36
37

38 147

39 148 **Results**

40
41
42 149 Figure 1 shows the patient-selection process. In total, 178 medical patients with
43
44 150 sepsis were included in this study, with male patients accounting for 65.2% (n=116).
45
46 151 The median age (interquartile range) was 78 (66-84) years, and most patients were at
47
48 152 least 65 years old (137/178, 77.0%). The most common primary site of infection was
49
50 153 the lung (131 cases, 73.6%), followed by abdomen (15 cases, 8.4%), urinary tract (13
51
52 154 cases, 7.3%), gastrointestinal tract (12 cases, 6.7%) and other sites (7 cases, 3.9%).
53
54
55
56
57
58
59
60

1
2
3
4 155 Septic shock patients accounted for 33.1% (59 cases). Blood culture was positive in
5
6 156 38 patients (21.3%). The 90-day mortality was 47.2% (84/178 cases), and the
7
8 157 in-hospital mortality was 41.6% (74/178 cases). The length of ICU stay and the length
9
10
11 158 of hospital stay were 12 (5-22) and 15 (9-28) days, respectively.

12
13 159 Compared with in-hospital survivors, non-survivors had significantly lower BMI
14
15 160 and PaO₂/FiO₂ (both $p < 0.05$), higher lactate, bilirubin, INR, SOFA score and
16
17 161 APACHE II score (all $p < 0.05$). Meanwhile, more patients died with
18
19 162 healthcare-acquired infections, hypotension, oliguria, septic shock, and intubation (all
20
21 163 $p < 0.05$) (table 1).

22
23
24 164 Cox proportional hazard regression analysis was conducted and the independent
25
26 165 factors for 90-day death were identified as SOFA score (HR = 1.220, $p < 0.001$),
27
28 166 APACHE II score (HR = 1.050, $p < 0.001$) and BMI (HR = 0.940, $p = 0.029$) (table
29
30
31 167 2).

32
33
34 168 Patients were divided into four groups based on BMI [underweight 33 (18.5%),
35
36 169 normal 98 (55.1%), overweight 36 (20.2%), and obese 11 (6.2%)] . The percentage of
37
38 170 males (72.7%, 71.4%, 55.6%, and 18.2%, $p = 0.002$), chronic obstructive
39
40 171 pulmonary disease (24.2%, 21.4%, 0, and 27.3%, $p=0.017$), hypotension (57.6%,
41
42 172 34.7%, 25.0%, and 9.1%, $p = 0.007$), septic shock (57.6%, 30.6%, 25.0%, and 9.1%,
43
44 173 $p = 0.004$), in-hospital mortality (60.6%, 41.8%, 30.6%, and 18.2%, $p = 0.027$) and
45
46 174 90-day mortality (66.7%, 48.0%, 36.1%, and 18.2%, $p = 0.015$) were statistically
47
48 175 different among the four groups (table 3).

49
50
51 176 Kaplan-Meier survival curves were constructed to show the survival probabilities
52
53
54

1
2
3
4 177 at day-90 according to BMI classification and these were compared using the log rank
5
6 178 test, which also showed that higher BMI was associated with better prognosis
7
8 179 (p=0.008) (figure 2).
9

10
11 180

12 13 181 **Discussion**

14
15
16 182 This prospective observational cohort study focused on medical patients with
17
18 183 sepsis admitted to the ICU, and the results showed that besides SOFA score and
19
20 184 APACHE II score, BMI was identified as an independent factor for 90-day mortality
21
22
23 185 by Cox regression analysis. The association of SOFA and APACHE II score with
24
25 186 mortality in this cohort was consistent with previous studies^[16-18]. This study adds the
26
27
28 187 finding that BMI was independently associated with survival, where 90-day mortality
29
30 188 decreased with an increase in BMI. While studies examining the risk factors
31
32
33 189 associated with outcomes in sepsis reached inconsistent conclusions on the
34
35 190 association of BMI with mortality, our results confirmed that BMI was independently
36
37
38 191 associated with mortality in patients with sepsis caused by medical conditions.
39

40 192 Globally, the prevalence of obesity has reached epidemic proportions, especially
41
42 193 in developed countries^[19]. BMI is still a useful proxy of overall health because it is
43
44
45 194 highly correlated with body surface area, which is commonly used as a surrogate
46
47
48 195 measure in obesity classification. Even though it is widely accepted that obesity is a
49
50 196 risk factor for diabetes mellitus, hypertension, and cardiovascular diseases, the present
51
52 197 study and several other studies have indicated that overweight and obese patients with
53
54
55 198 sepsis tend to experience lower mortality. This has been called the “obesity paradox”
56
57
58
59
60

1
2
3
4 199 [5-9,20]. Although some researchers have expressed doubt that the true paradox may lie
5
6 200 in the variations in sepsis interventions [6,21], a meta-analysis concluded that
7
8 201 individuals who were overweight or obese had a reduced adjusted mortality when
9
10 202 admitted to the ICU with sepsis or septic shock [8]. Recently another meta-analysis
11
12 203 also concluded that being overweight was associated with lower mortality (OR 0.87,
13
14 204 95% CI 0.77-0.97, $p = 0.02$) compared with obese (OR 0.89, 95% CI 0.72-1.10, $p =$
15
16 205 0.29) and morbidly obese (OR 0.64, 95% CI 0.38-1.08, $p = 0.09$) patients who did not
17
18 206 exhibit significantly reduced mortality compared with normal weight patients [12]. In a
19
20 207 large and nationally representative sample of over 1,000 hospitals in the US, obesity
21
22 208 was found to be significantly associated with a 16% decrease in the odds of dying
23
24 209 among sepsis patients who were hospitalized [22].

25
26
27
28
29
30 210 Underweight patients with sepsis may be more common in developing countries
31
32 211 than in developed countries. In the present study, the percentages of underweight,
33
34 212 normal weight, overweight and obese patients were 18.4%, 55.3%, 20.1%, and 6.1%,
35
36 213 respectively, while those with sepsis in a study in Canada and the US represented
37
38 214 6.8%, 35.3%, 28.3%, and 29.0% [6]. Being underweight was found to be one of the
39
40 215 independent risk factors of mortality in a study on the correlation between surgical
41
42 216 site infection and mortality [10]. Furthermore, Lee et al [11] also reported that being
43
44 217 underweight was associated with mortality in patients with severe sepsis and septic
45
46 218 shock. However, BMI has not been shown to be an independent factor for clinical
47
48 219 outcomes by multivariable analyses. In our cohort of medical patients with sepsis,
49
50 220 which mainly included elderly and less obese patients, BMI was identified as an

1
2
3
4 221 independent factor for survival, patients with lower BMI having a higher risk of death.
5
6 222 Thus, our findings would be helpful for evaluating the clinical outcomes of medical
7
8 223 patients with sepsis, although validation in future large sample, multi-center studies is
9
10
11 224 still needed.

12
13 225 The mechanism of the correlation between BMI and mortality of sepsis is unclear.
14
15 226 There are several potential reasons that could explain this. First, higher BMI resulted
16
17
18 227 in more fat reserves, and patients could have a greater capacity to cope with the
19
20 228 inflammatory response during sepsis and sepsis-associated acute lung injury [23-25].
21
22
23 229 Furthermore, they may be able to tolerate extensive weight loss and dysfunction
24
25 230 associated with critical illness [26]. Secondly, a higher BMI can lead to an increased
26
27
28 231 level of lipoproteins. High-density lipoproteins may not only bind and inactivate
29
30 232 lipopolysaccharide (LPS) or other harmful bacterial products released during sepsis
31
32 233 [27], but also modulate adhesion molecule expression, upregulate endothelial nitric
33
34
35 234 oxide synthase, and counteract oxidative stress [28]. Thirdly, higher BMI can lead to
36
37
38 235 increased adipose tissue deposition. Adipose tissue is increasingly being considered as
39
40 236 a functional endocrine organ and associated with increased renin-angiotensin system
41
42 237 activity [29]. It appears to have protective hemodynamic effects during sepsis and may
43
44
45 238 decrease the need for fluid or vasopressor support [21,30].

46
47 239 In general, sex has not been found to be an independent predictor for survival in
48
49
50 240 patients with sepsis, which is the same as the results of our current study. But in some
51
52 241 special populations, for example in liver cirrhosis patients with bloodstream infection,
53
54
55 242 male sex may be an independent risk factor for mortality[31].
56
57
58
59
60

1
2
3
4 243 As the relationship between BMI and clinical outcomes of sepsis may be related
5
6 244 partly to differences in patient characteristics, we therefore set out to evaluate the
7
8 245 impact of BMI on survival in a cohort of medical patients with sepsis, which is
9
10 246 different from surgical septic patients. Ranieri et al^[32] reported that the primary sites
11
12 247 of infection in adults with septic shock were lung (43.9%), abdomen (30.0%), urinary
13
14 248 tract (12.3%), skin (5.5%) and other sites (8.3%). Scheer et al^[33] found that the most
15
16 249 common primary site of infection was different between medical and surgical patients.
17
18 250 In medical patients, the lung was the most common primary site (42.0%-56.7%),
19
20 251 while it was abdomen (48.4%-64.4%) in surgical patients. It should be noted that in
21
22 252 the majority of our patients (73.6%), sepsis was associated with pulmonary infection,
23
24 253 a much higher percentage as compared to other studies. He et al^[34] reported that
25
26 254 pulmonary-sepsis showed worse outcome than abdominal-sepsis, and pulmonary
27
28 255 infection was a risk factor for one-year mortality and quality of life after sepsis.

29
30
31
32
33
34
35 256 There were several limitations to our study. Firstly, the BMI of our patients
36
37 257 ranged from 12.11 to 32.46. There was no morbidly obese patient in the current study.
38
39 258 In fact, morbidly obese people are rare in this country. 10 severely underweight
40
41 259 patients with BMI less than 16.0 were included in the present study, which introduces
42
43 260 possible sample bias in patients in the low BMI category. However, the 90-day and
44
45 261 in-hospital mortality of these 10 severely underweight patients were 70.0% and 60.0%
46
47 262 respectively, not significantly different from that of all 33 underweight patients
48
49 263 (66.7% and 60.6%, respectively). Secondly, the present study used weight ascertained
50
51 264 at ICU admission, rather than the patient's baseline outpatient body weight. This
52
53
54
55
56
57
58
59
60

1
2
3
4 265 practice may misclassify the BMI category in as many as 21.9% of patients due to
5
6 266 lack of fluid balance adjustment ^[35]. Thirdly, BMI was used to determine the
7
8 267 nutritional status of patients in this study. BMI is a simple index and widely used in
9
10
11 268 clinical practice, but other indices such as percent body fat might better reflect body
12
13 269 composition^[36]. Lastly, it was a single-center study with 178 participants, and a large
14
15
16 270 proportion of our patients were older than 65 years, which may have led to a
17
18 271 sample-related bias.

272 **Conclusions**

273 To our knowledge, this is the first prospective cohort study that focused on
24
25 274 medical patients with sepsis, showing that BMI was independently associated with
26
27
28 275 90-day survival, with patients having a lower BMI at a higher risk of death.

276

277 **Acknowledgements**

278 Not applicable.

279

280 **Authors' contributions**

281 QTZ, YCS, YAZ designed the study. QTZ, YCS, NS, YAZ, and QBM coordinated the
282 study. MW, JZ, YLD, SL, and HXG were responsible for patient screening,
283 enrollment, and follow-up. QTZ, MW, and YCS analyzed the data. QTZ drafted the
284 manuscript. YCS critically revised the manuscript. All authors had full access to all
285 study data, read and approved the final version of the manuscript.

286

1
2
3
4 287 **Funding**

5
6 288 None.

7
8
9 289

10
11 290 **Competing interests**

12
13 291 None declared.

14
15
16 292

17
18 293 **Ethics approval and consent to participate**

19
20 294 The study protocol was approved (approval number M2015021) by the ethics
21
22 295 committee of Peking University Third Hospital, Beijing, China. All patients or their
23
24 296 legally authorized representatives provided written informed consent to participate in
25
26 297 the study.
27
28
29

30
31 298

32
33 299 **Data sharing statement**

34
35 300 The authors declare that all data supporting the findings of this study are available
36
37 301 within the article.
38
39

40
41 302

42
43 303 **References**

- 44
45 304 1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus
46
47 305 Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315:801-10.
48
49 306 2. Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med* 2013;369:2063.
50
51 307 3. Bouza C, López-Cuadrado T, Saz-Parkinson Z, et al. Epidemiology and recent trends of
52
53 308 severe sepsis in Spain: a nationwide population-based analysis (2006-2011). *BMC Infect Dis*
54
55
56
57
58
59

- 1
2
3
4 309 2014; 14:3863.
5
6 310 4. WHO classification of body mass index (BMI). [http://apps.who.int/bmi/index.jsp?introPage=
7
8 311 intro_3.html] Accessed on 2 March 2015.
9
10
11 312 5. Wurzinger B, Dünser MW, Wohlmuth C, et al. The association between body-mass index and
12
13 313 patient outcome in septic shock: a retrospective cohort study. *Wien Klin Wochenschr* 2010;122:
14
15 314 31-6.
16
17
18 315 6. Arabi YM, Dara SI, Tamim HM, et al. Clinical characteristics, sepsis interventions and
19
20 316 outcomes in the obese patients with septic shock:an international multicenter cohort study.
21
22
23 317 *Crit Care* 2013;17:R72.
24
25
26 318 7. Prescott HC, Chang VW, O'Brien JM Jr, et al. Obesity and 1-year outcomes in older
27
28 319 Americans with severe sepsis. *Crit Care Med* 2014;42:1766-74.
29
30
31 320 8. Pepper DJ, Sun J, Welsh J, et al. Increased body mass index and adjusted mortality in ICU
32
33 321 patients with sepsis or septic shock:a systematic review and meta-analysis. *Crit Care*
34
35 322 2016;20:181.
36
37
38 323 9. Gaulton TG, Marshall MacNabb C, Mikkelsen ME, et al. A retrospective cohort study
39
40 324 examining the association between body mass index and mortality in severe sepsis. *Intern*
41
42 325 *Emerg Med* 2015;10:471-9.
43
44
45 326 10. Giles KA, Hamdan AD, Pomposelli FB, et al. Body mass index:surgical site infections and
46
47 327 mortality after lower extremity bypass from the National Surgical Quality Improvement
48
49 328 Program 2005-2007. *Ann Vasc Surg* 2010;24:48-56.
50
51
52 329 11. Lee SM, Kang JW, Jo YH, et al. Underweight is associated with mortality in patients with
53
54 330 severe sepsis and septic shock. *Intensive Care Med Exp* 2015; 3:A876.
55
56
57
58
59
60

- 1
2
3
4 331 12. Wang S, Liu X, Chen Q, et al. The role of increased body mass index in outcomes of sepsis: a
5
6 332 systematic review and meta-analysis. *BMC Anesthesiol* 2017;17:118.
7
8 333 13. Ng PY, Eikermann M. The obesity conundrum in sepsis. *BMC Anesthesiol* 2017;17:147.
9
10 334 14. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines
11
12 335 for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013;41:580-637.
13
14
15 336 15. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International
16
17 337 Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med* 2017;
18
19 338 43:304-77.
20
21
22 339 16. de Carvalho MA, Freitas FG, Silva Junior HT, et al. Mortality predictors in renal transplant
23
24 340 recipients with severe sepsis and septic shock. *PLoS One* 2014;9:e111610.
25
26
27 341 17. Innocenti F, Tozzi C, Donnini C, et al. SOFA score in septic patients: incremental prognostic
28
29 342 value over age, comorbidities, and parameters of sepsis severity. *Intern Emerg*
30
31 343 *Med* 2018;13:405-12.
32
33
34 344 18. Song JE, Kim MH, Jeong WY, et al. Mortality Risk Factors for Patients with Septic
35
36 345 Shock after Implementation of the Surviving Sepsis Campaign Bundles. *Infect*
37
38 346 *Chemother* 2016;48:199-208.
39
40
41 347 19. GBD 2015 Obesity Collaborators, Afshin A, Forouzanfar MH, et al. Health Effects of
42
43 348 Overweight and Obesity in 195 Countries over 25 Years. *N Engl J Med* 2017;377:13-27.
44
45
46 349 20. Atamna A, Elis A, Gilady E, et al. How obesity impacts outcomes of infectious diseases. *Eur*
47
48 350 *J Clin Microbiol Infect Dis* 2017; 36:585-91.
49
50
51 351 21. Taylor SP, Karvetski CH, Templin MA, et al. Initial fluid resuscitation following adjusted
52
53 352 body weight dosing is associated with improved mortality in obese patients with suspected
54
55
56
57
58
59
60

- 1
2
3
4 353 septic shock. *J Crit Care* 2018;43:7-12.
5
6 354 22. Nguyen AT, Tsai CL, Hwang LY, et al. Obesity and Mortality, Length of Stay and Hospital
7
8 355 Cost among Patients with Sepsis: A Nationwide Inpatient Retrospective Cohort Study. *PLoS*
9
10 356 *One* 2016; 11:e0154599.
11
12
13 357 23. Stapleton RD, Dixon AE, Parsons PE, et al. The association between BMI and plasma
14
15 358 cytokine levels in patients with acute lung injury. *Chest* 2010;138:568-77.
16
17
18 359 24. Stapleton RD, Suratt BT. Obesity and nutrition in acute respiratory distress syndrome. *Clin*
19
20 360 *Chest Med* 2014;35:655-71.
21
22
23 361 25. Zampieri FG, Jacob V, Barbeiro HV, et al. Influence of Body Mass Index on Inflammatory
24
25 362 Profile at Admission in Critically Ill Septic Patients. *Int J Inflam* 2015; 2015:734857.
26
27
28 363 26. Herridge MS, Cheung AM, Tansey CM, et al. One-year outcomes in survivors of the acute
29
30 364 respiratory distress syndrome. *N Engl J Med* 2003;348:683-93.
31
32
33 365 27. Wu A, Hinds CJ, Thiemermann C. High-density lipoproteins in sepsis and septic shock:
34
35 366 metabolism, actions, and therapeutic applications. *Shock* 2004;21:210-21.
36
37
38 367 28. Murch O, Collin M, Hinds CJ, et al. Lipoproteins in inflammation and sepsis. I. Basic science.
39
40 368 *Intensive Care Med* 2007; 33:13-24.
41
42
43 369 29. McGown C, Bierendinc A, Younossi ZM. Adipose tissue as an endocrine organ. *Clin Liver*
44
45 370 *Dis* 2014;18:41-58.
46
47
48 371 30. Salgado DR, Rocco JR, Silva E, et al. Modulation of the renin-angiotensin-aldosterone
49
50 372 system in sepsis: a new therapeutic approach? *Expert Opin Ther Targets* 2010; 14:11-20.
51
52
53 373 31. Zhao H, Gu X, Zhao R, et al. Evaluation of prognostic scoring systems in liver cirrhosis
54
55 374 patients with bloodstream infection. *Medicine (Baltimore)* 2017;96(50):e8844.
56
57
58
59
60

- 1
2
3
4 375 32. Ranieri VM, Thompson BT, Barie PS, et al. Drotrecogin alfa (activated) in adults with septic
5
6 376 shock. *N Engl J Med* 2012;366:2055-64.
7
8 377 33. Scheer CS, Fuchs C, Kuhn SO, et al. Quality Improvement Initiative for Severe
9
10 378 Sepsis and Septic Shock Reduces 90-Day Mortality: A 7.5-Year Observational Study. *Crit*
11
12 *Care Med* 2017;45:241-52.
13 379
14
15 380 34. He XL, Liao XL, Xie ZC, et al. Pulmonary Infection Is an Independent Risk Factor for
16
17 Long-Term Mortality and Quality of Life for Sepsis Patients. *Biomed Res Int* 2016;
18 381
19 2016:4213712.
20 382
21
22 383 35. O'Brien JM Jr, Philips GS, Ali NA, et al. The association between body mass index, processes
23
24 of care, and outcomes from mechanical ventilation: a prospective cohort study.
25 384
26 *Crit Care Med* 2012;40:1456-63.
27 385
28
29 386 36. Waisbren E, Rosen H, Bader AM, et al. Percent body fat and prediction of surgical site
30
31 infection. *J Am Coll Surg* 2010;210:381-9.
32 387
33
34 388
35
36 389
37
38 390
39
40 391
41
42 392
43
44 393
45
46 394
47
48 395
49
50 396
51
52
53
54
55
56
57
58
59
60

397 **Table 1. Comparison of demographics and clinical data between groups defined by**
 398 **in-hospital clinical outcome in 178 patients with sepsis**

Characteristics	Survivors (n=104)	Non survivors (n=74)	p value
Age (year)	78.0 (60.0-84.0)	78.0 (69.0-84.0)	0.291
Males	67 (64.4)	49 (66.2)	0.805
Body mass index (kg/m ²)	23.2 (20.4-26.1)	21.7 (18.4-24.2)	0.006
Comorbidities			
COPD	23 (22.1)	9 (12.2)	0.088
Diabetes mellitus	26 (25.0)	21 (28.4)	0.614
Hypertension	47 (45.2)	31 (41.9)	0.662
Cerebrovascular disease	30 (28.8)	15 (20.3)	0.194
Neoplasm	18 (17.3)	12 (16.2)	0.848
Liver disease	5 (4.8)	4 (5.4)	1.000
Heart failure	20 (19.2)	14 (18.9)	0.958
Chronic renal failure	18 (17.3)	11 (14.9)	0.664
Smoking (pack years)	0 (0-30.0)	0 (0-16.3)	0.509
Primary site of infection			
Lung	77 (74.0)	54 (73.0)	0.874
Abdomen	10 (9.6)	5 (6.8)	0.499
Urinary tract	7 (6.7)	6 (8.1)	0.728
Gastrointestinal tract	7 (6.7)	5 (6.8)	1.000

Other site	3 (2.9)	4 (5.4)	0.452
Community-acquired infection	85 (81.7)	50 (67.6)	0.030
Hypotension	22 (21.2)	41 (55.4)	<0.001
Lactate level (mmol/L)	1.8 (1.0-3.4)	2.7 (1.5-5.7)	0.001
Oliguria	8 (7.7)	16 (21.6)	0.007
PaO₂/FiO₂(mmHg)	198.5 (119.3-287.5)	152.5 (99.6-210.3)	0.006
Serum Creatinine (μmol/L)	97.0 (68.3-176.3)	108.5 (64.0-194.3)	0.868
Total bilirubin (μmol/mL)	13.1 (9.9-22.3)	18.0 (12.5-32.8)	0.015
Platelets (×10⁹/L)	161.0 (95.8-232.5)	123.0 (75.0-204.3)	0.067
INR	1.2 (1.0-1.4)	1.3 (1.1-1.6)	0.015
Glasgow coma scale	15.0 (10.0-15.0)	13.0 (10.0-15.0)	0.117
SOFA score	5.0 (4.0-7.0)	9.0 (7.0-11.0)	<0.001
APACHE II score	16.0 (12.0-22.0)	21.0 (17.0-30.0)	<0.001
Septic shock	21 (20.2)	38 (51.4)	<0.001
Non-invasive ventilation	28 (26.9)	24 (32.4)	0.426
Intubated	36 (34.6)	43 (58.1)	0.002
Positive blood culture	19 (18.3)	19 (25.7)	0.235
Length of ICU stay (days)	12.0 (6.0-22.0)	12.0 (3.0-25.0)	0.521
Length of hospital stay (days)	18.0 (10.0-30.0)	13.0 (3.0-25.0)	0.009

399 Data are presented as n (%) or median (interquartile range) unless stated otherwise. COPD: Chronic obstructive pulmonary disease; INR: International

400 normalized ratio; SOFA: Sequential organ failure assessment; APACHE: Acute physiology and chronic health evaluation.

401

402 **Table 2. Risk factors for 90-day mortality of patients with sepsis or septic shock by Cox**
 403 **regression analysis**

Variables	Hazard ratio (95% Confidence interval)	p value
Body mass index (kg/m ²)	0.940 (0.889-0.994)	0.029
Hypotension	0.781 (0.229-2.670)	0.694
Lactate level (mmol/L)	1.018 (0.943-1.098)	0.648
Oliguria	1.288 (0.715-2.321)	0.399
PaO ₂ /FiO ₂ (mmHg)	1.000 (0.997-1.002)	0.933
Septic shock	1.075 (0.320-3.615)	0.907
SOFA score	1.229 (1.123-1.345)	<0.001
APACHE II score	1.050 (1.022-1.080)	<0.001
Intubated	1.511 (0.931-2.452)	0.095

404 SOFA: Sequential organ failure assessment; APACHE: Acute physiology and chronic health evaluation. The variables significantly associated with 90-day
 405 non-survival in the univariate analysis were used in the Cox proportional hazard regression analysis.

406

407

408

409

410

411

412

413

414 **Table 3. Comparison of demographics and clinical data among groups defined by body mass**
 415 **index in patients with sepsis**

Characteristics	Underweight (n=33)	Normal (n=98)	Overweight (n=36)	Obese (n=11)	p value
Age (years)	79.0 (69.0-86.0)	78.0 (67.0-84.0)	73.0 (57.0-83.0)	77.0 (71.0-86.0)	0.162
Males	24 (72.7)	70 (71.4)	20 (55.6)	2 (18.2)	0.002
Comorbidities					
COPD	8(24.2)	21 (21.4)	0	3 (27.3)	0.017
Diabetes mellitus	8 (24.2)	25 (25.5)	9 (25.0)	5 (45.5)	0.530
Hypertension	14 (42.4)	38 (38.8)	19 (52.8)	7 (63.6)	0.265
Cerebrovascular disease	10 (30.3)	24 (24.5)	11 (30.6)	0	0.193
Neoplasm	7 (21.2)	14 (14.3)	8 (22.2)	1 (9.1)	0.547
Liver disease	2 (6.1)	5 (5.1)	2 (5.6)	0	0.879
Heart failure	8 (24.2)	17 (17.3)	5 (13.9)	4 (36.4)	0.319
Chronic renal failure	5 (15.2)	14 (14.3)	7 (19.4)	3 (27.3)	0.669
Smoking (pack-years)	0 (0-20.5)	0 (0-30.0)	0 (0-3.0)	0 (0-30.0)	0.561
Primary site of infection					
Lung	27 (81.8)	69 (70.4)	27 (75.0)	8 (72.7)	0.637
Abdomen	2 (6.1)	9 (9.2)	3 (8.3)	1 (9.1)	0.956
Urinary tract	1 (3.0)	9 (9.2)	2 (5.6)	1 (9.1)	0.656
Gastrointestinal tract	2 (6.1)	6 (6.1)	3 (8.3)	1 (9.1)	0.955
Other site	1 (3.0)	5 (5.1)	1 (2.8)	0	0.800

Community-acquired infection	25 (75.8)	76 (77.6)	26 (72.2)	8 (72.7)	0.925
Hypotension	19 (57.6)	34 (34.7)	9 (25.0)	1 (9.1)	0.007
Lactate level (mmol/L)	2.4 (1.6-7.2)	2.1 (1.0-4.3)	1.6 (1.2-3.3)	1.9 (0.6-2.9)	0.201
Oliguria	8 (24.2)	13 (13.3)	3 (8.3)	0	0.121
PaO₂/FiO₂ (mmHg)	180.0(113.5-251.0)	164.5(102.3-240.5)	188.0(140.5-268.5)	215.0(153.0-300.0)	0.340
Serum Creatinine (µmol/L)	89.0 (57.0-127.0)	118.5 (72.5-190.5)	91.0 (60.0-212.5)	86.0 (56.0-112.0)	0.136
Total bilirubin (µmol/mL)	18.0 (10.1-33.1)	14.4 (10.1-28.4)	17.2 (12.2-26.3)	15.2 (11.3-20.0)	0.819
Platelets (×10⁹/L)	139.0 (75.0-213.0)	147.0 (86.0-209.8)	182.5 (128.3-253.8)	115.0 (49.0-144.0)	0.056
INR	1.3 (1.1-1.6)	1.2 (1.0-1.5)	1.2 (1.1-1.3)	1.1 (1.0-1.2)	0.269
Glasgow coma scale	13.0 (10.0-15.0)	15.0 (12.0-15.0)	15.0 (11.0-15.0)	13.0 (10.0-15.0)	0.761
SOFA score	8.0 (5.0-11.0)	7.0 (5.0-9.0)	6.0 (4.0-8.0)	5.0 (5.0-8.0)	0.382
APACHE II score	18.0 (16.0-24.0)	19.0 (13.0-25.0)	18.0 (13.0-22.0)	14.0 (9.0-17.0)	0.060
Septic shock	19 (57.6)	30 (30.6)	9 (25.0)	1(9.1)	0.004
Non-invasive ventilation	7 (21.2)	30 (30.6)	10 (27.8)	5 (45.5)	0.466
Intubated	19 (57.6)	43 (43.9)	13 (36.1)	4 (36.4)	0.305
Positive blood culture	7 (21.2)	24 (24.5)	4 (11.1)	3 (27.3)	0.383
Length of ICU stay (days)	10.0 (4.0-25.0)	13.0 (7.0-25.0)	11.0 (4.0-19.0)	9.0(6.0-13.0)	0.461
Length of hospital stay (days)	13.0 (4.0-29.0)	16.0 (10.0-28.0)	16.0 (8.0-32.0)	13.0(8.0-20.0)	0.813
In-hospital mortality	20 (60.6)	41 (41.8)	11 (30.6)	2 (18.2)	0.027
90-day mortality	22 (66.7)	47 (48.0)	13 (36.1)	2 (18.2)	0.015

416 Data are presented as n (%) or median (interquartile range). COPD: Chronic obstructive pulmonary disease; INR: International normalized ratio; SOFA:

417 Sequential organ failure assessment; APACHE: Acute physiology and chronic health evaluation.

1
2
3
4 418 **Fig 1. Patient selection.**

5
6 419

7
8 420

9
10 421

11
12 422

13
14 423

15
16 424

17
18 425

19
20 426

21
22 427

23
24 428

25
26 429

27
28 430

29
30 431

31
32 432

33
34 433

35
36 434

37
38 435

39
40 436

41
42 437

43
44 438

45
46 439

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

440 **Fig 2. Kaplan-Meier survival plot for 90-day survival of underweight, normal weight,**
441 **overweight, and obese patients with sepsis.**

For peer review only

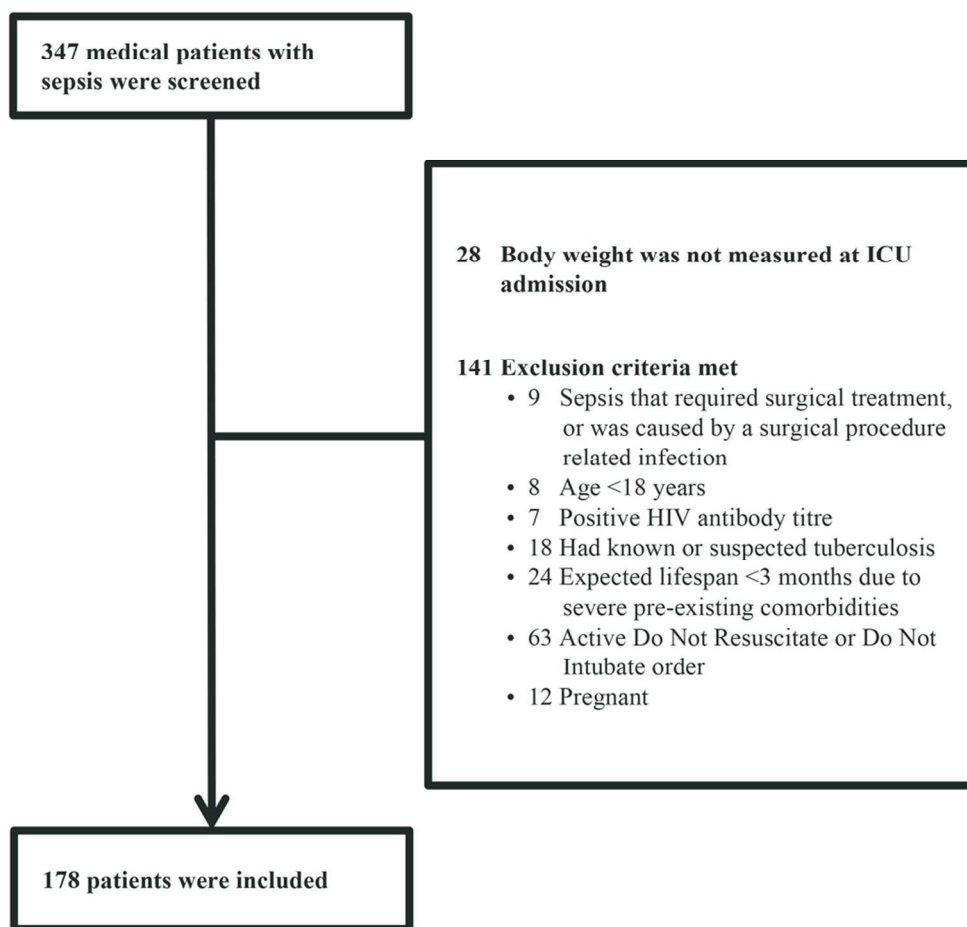


Fig 1. Patient selection.

90x90mm (300 x 300 DPI)

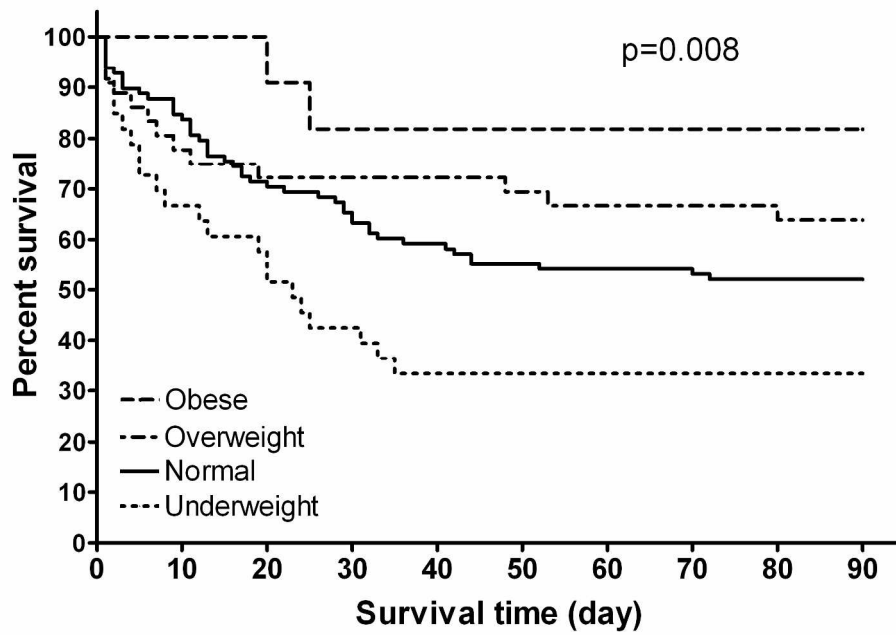


Fig 2. Kaplan-Meier survival plot for 90-day survival of underweight, normal weight, overweight, and obese patients with sepsis.

246x167mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4, 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4, 5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(b) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6,7
		(b) Describe any methods used to examine subgroups and interactions	6,7
		(c) Explain how missing data were addressed	N/A
		(d) If applicable, explain how loss to follow-up was addressed	N/A
		(e) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7,8
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7,8
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8,9
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8,19-25
		(b) Report category boundaries when continuous variables were categorized	6
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12,13
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.