PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The impact of body mass index on survival of medical patients with sepsis: a prospective cohort study in a university hospital in China
AUTHORS	Zhou, Qingtao; Wang, Meng; Li, Shuo; Zhang, Jing; Ma, Qingbian; Ding, Yanling; Ge, Hongxia; Shen, Ning; Zheng, Yaan; Sun, Yongchang

VERSION 1 – REVIEW

REVIEWER	Tsukasa Ikeura The third Department of Internal Medicine, Kansai Medical University, Japan
REVIEW RETURNED	07-Mar-2018

GENERAL COMMENTS	The authors investigate the relation between BMI and mortality in patients with sepsis admitted to ICU. There are several key concerns: 1. As you know, C-reactive protein (CRP) is a common and helpful laboratory marker in diagnosis and monitor of infections. How about CRP as a predictive factor for mortality in patients with sepsis? As with SOFA score, APACHE II score and BMI, CRP was a factor associated with survival in the study? 2. In the discussion section, the authors mention one of reason why higher BMI is associated with better prognosis in patients with sepsis could be that patients with higher BMI have greater capacity to tolerate severe inflammation during sepsis because of more fat reserves. To validate the possible mechanism, the authors should show data regarding nutritional status of patients, such as the serum levels of triglyceride and albumin. 3. As the authors mention in the discussion section, a meta-analysis showing that higher BMI reduces mortality in patients with sepsis has already been published (Pepper DJ, et al. Crit Care. 2016 ;20:181). What do the authors think is novel information in the current study?

REVIEWER	Jochen Dobner Heinrich Heine Unviersity Düsseldorf Institute of Physical Biology, Germany
REVIEW RETURNED	07-Mar-2018

GENERAL COMMENTS	Zhou et. al. examine the influence of body mass index (BMI) on survival in medical patients with sepsis. They claim that body mass index is an independent predictor for beneficial outcome in patients with sepsis. To evaluate the influence of body weight on 90-day mortality they divided the patients into four groups and analyzed the outcome via Kaplan-Meier survival analysis.

	While the general message of the manuscript is plausible, there are some issues which need to be addressed (especially point 6): 1. The authors state that their analysis is limited by the use of the patients weight at ICU admission (lines 60-61). I think that there are other limitations that need to be named/discussed such as that the characterization solely focusing on body weight rather than the body composition in general may not always be the best choice and a potential source for misinterpretation. For example the consideration of total body fat content over weight alone may lead to different predictive usability (e.g. Waisbren, E., et al. (2010). "Percent body fat and prediction of surgical site infection." J Am Coll Surg 210(4): 381-389.). Another potential limitation is the relatively high age of examined patients (which actually *is* stated later in the text in line 218) as the immune system is known to alter over time. 2. The authors use the classification of BMI according to the WHO but do not include that there also is a classification for mild (BMI=17-18.49) moderate (BMI=16-16.99) and severe (BMI<16) thinness which would allow a more distinct analysis as especially underweight can be of critical impact. Also there is a slight discrepancy between the WHO stating the reference age >=20 whereas in the described study the cutoff age was <18 years of age (line 105). That should be explained/commented. 3. The authors state that BMI was a predictor for 90-day mortality. From the presented data it is clearly described that BMI is also a predictor for septic shock (lines 167-168). The question whether the relevant power of BMI in this scenario mainly lies in predicting the development of toxic shock which in turn leads to strongly decreased 90-day mortality needs to be discussed in more detail. 4. From the presented data and the study design it cannot be stated that BMI has a "protective effect" (line 185). It is rather an association and needs to be analyzed/discussed in further detail. 5. A short comment on the issue of sex, e.g. are there differences in predictive power between men and women, would be highly appreciated. 6. It needs either to be discussed why patients with a BMI as low as 12.11 are included in the study or they need to be excluded as it seems quite likely that a patient with such a low BMI will develop severe complications in a septic shock condition. 7. The sentence "Morbidly obese patients were not included in the study, although morbidly obese patients are not common in this country" (lines 245-246) needs to be changed into something more understandable. 8. Although the authors state that "it was still difficult to avoid sample-related bias" (lines 250-251) it seems not at all possible to exclude the sample-related bias completely. It

	should therefore be critically discussed as a limitation of the study. 9. In the table comparing the four groups according to BMI the mean and SD/95% CI should be included, especially regarding the underweight group. In general a more detailed description of the groups should be included.

REVIEWER	Pauline Yeung Ng Adult Intensive Care Unit, Queen Mary Hospital and The University of Hong Kong, Hong Kong
REVIEW RETURNED	08-Mar-2018

GENERAL COMMENTS	In this study, Zhou et al examines the impact of body weight as measured by BMI on survival during severe sepsis. In a single-center prospective cohort study including 178 patients admitted to a medical ICU, the authors conclude that patients who are underweight have a higher 90-day mortality (66.7% vs 48% for normal-weight vs 36.1% for overweight vs 18.2 for obese patients). In general, the manuscript is quite well-written. However, there are major methodological concerns with the statistical analysis that limits the conclusions drawn from this study. Major comments: - A major limitation of the study is the relatively small sample size for comparison of outcome across four patient groups. The authors did not present a sample size calculation. - Following this line of thought, adjustment for possible confounding is important to address potential biases across patient groups with small sample sizes. The authors used unadjusted analysis to identify factors associated with mortality, and subsequently included significant factors in the Cox proportional hazards model. However, as shown in Table 2, please explain why only some, but not all, factors significantly different between groups (e.g., community-acquired infection, total bilirubin) were included in the Cox regression model. - In the conclusion, the authors wrote that underweight patients were at a higher risk of death. Explain by which statistical method this result was determined, and with which reference group this comparison was made. The use of the log-rank test to compare the 90-day mortality between 4 groups of patients classified according to BMI does not help to determine which groups are significantly different. Consider performing further testing to arrive at more accurate and informative conclusions. - The body weight used for classification of patients in the current study was taken at the time of admission to ICU, instead of during a routine outpatient visit. There was a near significant trend for the lower body weight groups to have higher SOFA scores and APACHE II scores, speaking for the possibility that weight (upon ICU admission) was directly related to the disease severity, greatly limiting the interpretation of any subsequent analysis. Are the authors able to go back to outpatient medical records to retrieve a baseline body weight? - Similarly, there was possible bias in that weight may be a surrogate

	marker of underlying comorbidities, as the incidence of conditions such as COPD, neoplasm and liver disease is higher in the underweight than the overweight categories (Table 3). All these factors should be included in the adjusted confounder model for regression analysis. - One of the commonest confounder in any study examining the effect of body weight on clinical outcomes is cigarette smoking. Please explain how this may or may not be relevant in the current study. - Please include a study flow diagram that shows the number of patients screened and number of patients (and reasons) excluded from analysis. Minor comments: - Throughout the abstract and manuscript, the authors have opted to provide comparisons between in-hospital survivors vs non-survivors. It would be far more important to present these data for the different body weight groups, as this was the study exposure. - Similarly, the authors have presented the results that SOFA score and APACHE II score were significant predictors of survival from sepsis. This was not the primary hypothesis tested in the study, please explain whether adjustment for multiple testing was made, otherwise, de-emphasize these results. - The study did not include patients who are morbidly obese, which precludes comparison of the results with published studies / systematic reviews. - Abstract, Lines 44-47 - Consider presenting more detailed results from analysis of the four groups in the abstract, as the primary objective of this study was to evaluate the impact of BMI on survival. - Abstract, Conclusion - Main message unclear, please modify to answer the primary objective of the study. - Introduction, Lines 72-74 - Please delete or modify this statement, it is untrue, there are a lot of studies on medical patients with sepsis. - Introduction, Line 83 - Consider citing the latest systematic reviews on the effect of body weight in sepsis here [Wang S, Liu X, Chen Q, Liu C, Huang C, Fang X. The role of increased body mass index in outcomes of sepsis: a systematic review and meta-analysis. BMC Anesthesiol. 2017;17(1):118.] as well as editorial comments [E.g., Ng PY, Eikermann M. The obesity conundrum in sepsis. BMC Anesthesiol. 2017 Oct 25;17(1):147.] - Methods, Line 94 - Please clarify how ‘ sepsis’ was defined? - Methods, Line 96 - Please state exactly what the ‘upper laboratory level limit’ for lactate was. - Methods, Lines 124-125 - Consider including ICU mortality as a secondary outcome. - Results, Line 164-165 - Give exact numbers and frequencies (%) in each group. - Results, Line 164-170 - Please move this paragraph with results for the 4 patient groups to the earlier part of the Results section. Also, more detailed data and analyses are necessary. - Discussion, Lines 177-181 - Please de-emphasize or delete the discussion about SOFA score and APACHE score from this important opening paragraph, as explained above. - Discussion, Lines 187-188 - Insert relevant reference.

	- Discussion, Lines 214-216 - Insert relevant references. - Discussion, Lines 233-235 - Please delete this hypothetical statement as it was not tested in the study. - Discussion, Lines 236-243 - Explain why this paragraph on the site of infection is relevant to the primary study hypothesis of the association between BMI and mortality. - Discussion, Lines 245-246 - Do you mean '…although morbidly obese patients are NOT COMMON…' or 'NOT UNCOMMON'? - Limitations - Needs to be expanded. E.g., address sample size and power issue, presence of residual confounding. - Conclusions - Please delete the part about SOFA score and APACHE score, as explained above.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: Tsukasa Ikeura
Institution and Country: The third Department of Internal Medicine, Kansai Medical University, Japan
Please state any competing interests: I have neither competing interest nor state.
Please leave your comments for the authors below
The authors investigate the relation between BMI and mortality in patients with sepsis admitted to ICU.
There are several key concerns:
1. As you know, C-reactive protein (CRP) is a common and helpful laboratory marker in diagnosis and monitor of infections. How about CRP as a predictive factor for mortality in patients with sepsis? As with SOFA score, APACHE II score and BMI, CRP was a factor associated with survival in the study?
Response: Devran et al. reported that the 3rd day CRP value appears to be a predictor of mortality in patients with sepsis (Devran O, et al. Multidiscip Respir Med 2012; 7:47.), but most studies have shown that CRP is not a predictor of mortality (Su L, et al. Mediators Inflamm 2013, 2013:969875. Garnacho-Montero J, et al. Crit Care 2014; 18:R116. Ríos-Toro JJ, et al. PLoS One 2017; 12:e0175254). Therefore, CRP was not collected in our study.

2. In the discussion section, the authors mention one of reason why higher BMI is associated with better prognosis in patients with sepsis could be that patients with higher BMI have greater capacity to tolerate severe inflammation during sepsis because of more fat reserves. To validate the possible mechanism, the authors should show data regarding nutritional status of patients, such as the serum levels of triglyceride and albumin.
Response: We thank the reviewer for this helpful suggestion. The objective of this study was to evaluate the impact of BMI on survival of a Chinese cohort of medical patients with sepsis. We didn't collect the serum levels of triglyceride and albumin because both of them showed very weak correlation with BMI in previous studies. (Firdous S. J Coll Physicians Surg Pak 2014;24(5):308-13. / Liu BZ, et al. PLoS One 2016;11(6):e0157401.)

3. As the authors mention in the discussion section, a meta-analysis showing that higher BMI reduces mortality in patients with sepsis has already been published (Pepper DJ, et al. Crit Care. 2016 ;20:181). What do the authors think is novel information in the current study?
Response: In that meta-analysis, BMI was analyzed as a categorical variable. Compared to normal BMI, overweight or obese BMIs reduced mortality of septic patients, but underweight BMI and morbidly obese BMI did not. In our study, BMI was analyzed as a continuous variable and identified

as an independent predictor for survival in patients with sepsis for the first time. We have addressed this point in the discussion, please see lines 221-226.

Reviewer: 2
Reviewer Name: Jochen Dobner
Institution and Country: Heinrich Heine Unviersity Düsseldorf, Institute of Physical Biology, Germany
Please state any competing interests: None declared

Please leave your comments for the authors below

Zhou et. al. examine the influence of body mass index (BMI) on survival in medical patients with sepsis. They claim that body mass index is an independent predictor for beneficial outcome in patients with sepsis. To evaluate the influence of body weight on 90-day mortality they divided the patients into four groups and analyzed the outcome via Kaplan-Meier survival analysis.
While the general message of the manuscript is plausible, there are some issues which need to be addressed (especially point 6):
1. The authors state that their analysis is limited by the use of the patients weight at ICU admission (lines 60-61). I think that there are other limitations that need to be named/discussed such as that the characterization solely focusing on body weight rather than the body composition in general may not always be the best choice and a potential source for misinterpretation. For example the consideration of total body fat content over weight alone may lead to different predictive usability (e.g. Waisbren, E., et al. (2010). “Percent body fat and prediction of surgical site infection.” J Am Coll Surg 210(4): 381-389.). Another potential limitation is the relatively high age of examined patients (which actually is stated later in the text in line 218) as the immune system is known to alter over time.
Response: We agree with reviewer, and added discussion on these limitations, (lines 263-266). The limitation about high age has been stated, please see lines 266-268.

2. The authors use the classification of BMI according to the WHO but do not include that there also is a classification for mild (BMI=17-18.49) moderate (BMI=16-16.99) and severe (BMI<16) thinness which would allow a more distinct analysis as especially underweight can be of critical impact. Also there is a slight discrepancy between the WHO stating the reference age >=20 whereas in the described study the cutoff age was <18 years of age (line 105). That should be explained/commented.
Response: Because BMI is a continuous variable rather than categorical variable, it would be more accurate to analyze BMI as a continuous variable. Therefore, BMI was analyzed as a continuous variable in our study, and it was identified as an independent predictor for survival in patients with sepsis for the first time. Then Kaplan-Meier survival curves were constructed to show the survival probabilities at day-90 according to BMI classification, which also showed that higher BMI was associated with better prognosis. BMI is a simple index of weight-for-height that is commonly used to classify underweight, overweight and obesity in adults (http://apps.who.int/bmi/index.jsp?introPage=intro_3.html), and therefore patients younger than 18 years old were excluded.

3. The authors state that BMI was a predictor for 90-day mortality. From the presented data it is clearly described that BMI is also a predictor for septic shock (lines 167-168). The question whether the relevant power of BMI in this scenario mainly lies in predicting the development of toxic shock which in turn leads to strongly decreased 90-day mortality needs to be discussed in more detail.
Response: Cox proportional hazard regression analysis identified that SOFA score, APACHE II score and BMI were independent predictors of the 90-day mortality in our study, while septic shock was not an independent predictor, see table 2. The reason why the percentages of patients with hypotension and with septic shock in the four groups decreased as BMI increased in the present study was described in lines 236-240.

4. From the presented data and the study design it cannot be stated that BMI has a “protective effect” (line 185). It is rather an association and needs to be analyzed/discussed in further detail.
Response: We agree with the reviewer and have deleted “protective effect”, see lines 191-192.

5. A short comment on the issue of sex, e.g. are there differences in predictive power between men and women, would be highly appreciated.
Response: In general, sex has not been found to be an independent predictor for survival in patients with sepsis, which is the same as the results of our current study. But in some special population, for example in liver cirrhosis patients with bloodstream infection, male sex may be an independent risk factor for mortality (Zhao H, et al. Medicine (Baltimore) 2017;96:e8844.). We have added a short comment on this issue, see lines 241-244, please.

6. It needs either to be discussed why patients with a BMI as low as 12.11 are included in the study or they need to be excluded as it seems quite likely that a patient with such a low BMI will develop severe complications in a septic shock condition.
Response: The purpose of the current study was to evaluate the impact of BMI on survival of a cohort of medical patients with sepsis, therefore we should include all patients who met the inclusion criteria and did not meet exclusion criteria, regardless of BMI values.

7. The sentence “Morbidly obese patients were not included in the study, although morbidly obese patients are not common in this country” (lines 245-246) needs to be changed into something more understandable.
Response: We thank the reviewer for the suggestion. The sentence has been changed into “There was no morbidly obese patient in the current study. In fact, morbidly obese people are rare in this country”, see lines 259-260.

8. Although the authors state that “it was still difficult to avoid sample-related bias” (lines 250-251) it seems not at all possible to exclude the sample-related bias completely. It should therefore be critically discussed as a limitation of the study.
Response: In the current study, we included 33, 98, 36 and 11 patients in the underweight, normal, overweight and obese groups, respectively. In the post hoc power analysis, we set the ration of the four groups as 3:9:3:1, and according to our results the 90-day mortality was 66.7%, 48.0%, 36.1% and 18.2%, respectively. We used the Cochran-Armitage test for trend in proportions to calculate the power of this study in the PASS 14.0 software. Sample sizes of 27, 81, 27, and 9 for the four groups respectively can achieve 82.22% power to detect a linear trend using a two-sided Z test with continuity correction and a significance level of 0.05. In our study, the sample size of each group was larger than the calculated sample size, so we believe that this study has sufficient confidence to obtain statistically significant conclusions about differences among groups. The sample size limitation has been discussed in lines 266-268.

9. In the table comparing the four groups according to BMI the mean and SD/95% CI should be included, especially regarding the underweight group. In general a more detailed description of the groups should be included.
Response: In the table (table 3) comparing the four groups according to BMI, categorical variables were expressed as numbers (%). Because most continuous variables were non-normally distributed, so they were expressed as median (25th-75th percentile).

Reviewer: 3
Reviewer Name: Pauline Yeung Ng
Institution and Country: Adult Intensive Care Unit, Queen Mary Hospital and The University of Hong Kong, Hong Kong
Please state any competing interests: None declared

Please leave your comments for the authors below

In this study, Zhou et al examines the impact of body weight as measured by BMI on survival during severe sepsis. In a single-center prospective cohort study including 178 patients admitted to a medical ICU, the authors conclude that patients who are underweight have a higher 90-day mortality (66.7% vs 48% for normal-weight vs 36.1% for overweight vs 18.2 for obese patients).

In general, the manuscript is quite well-written. However, there are major methodological concerns with the statistical analysis that limits the conclusions drawn from this study.

Major comments:
- A major limitation of the study is the relatively small sample size for comparison of outcome across four patient groups. The authors did not present a sample size calculation.
Response: The current study was designed as a prospective cohort study without a sample size calculation. Finally, we included 33, 98, 36 and 11 patients in the underweight, normal, overweight and obese groups, respectively. In the post hoc power analysis, we set the ration of the four groups as 3:9:3:1, and according to our results the 90-day mortality were 66.7%, 48.0%, 36.1% and 18.2%, respectively. We used the Cochran-Armitage test for trend in proportions to calculate the power of this study in the PASS 14.o software. Sample sizes of 27, 81, 27, 9 for the four groups can achieve 82.22% power to detect a linear trend using a two-sided Z test with continuity correction and a significance level of 0.05. In our study, the sample size of each group was more than the calculated sample size, so we believe that this study has sufficient confidence to obtain statistically significant conclusions about differences among groups.

- Following this line of thought, adjustment for possible confounding is important to address potential biases across patient groups with small sample sizes. The authors used unadjusted analysis to identify factors associated with mortality, and subsequently included significant factors in the Cox proportional hazards model. However, as shown in Table 2, please explain why only some, but not all, factors significantly different between groups (e.g., community-acquired infection, total bilirubin) were included in the Cox regression model.
Response: Cox proportional hazard regression analysis was undertaken to assess the factors associated with 90-day mortality. The variables significantly associated with 90-day non-survival in the univariate analysis were used in the Cox proportional hazard regression analysis. See lines 131-134.

- In the conclusion, the authors wrote that underweight patients were at a higher risk of death. Explain by which statistical method this result was determined, and with which reference group this comparison was made. The use of the log-rank test to compare the 90-day mortality between 4 groups of patients classified according to BMI does not help to determine which groups are significantly different. Consider performing further testing to arrive at more accurate and informative conclusions.
Response: Cox proportional hazard regression analysis identified that BMI (HR = 0.940, p = 0.029) was an independent predictor of the 90-day mortality in our study. BMI was analyzed as a continuous variable, which means that patients with lower BMI were at higher risk of death. The sentence “underweight patients were at a higher risk of death” has been changed to “patients with lower BMI having a higher risk of death”, which is more accurate, please see lines 48-49 and line 272.

- The body weight used for classification of patients in the current study was taken at the time of admission to ICU, instead of during a routine outpatient visit. There was a near significant trend for the lower body weight groups to have higher SOFA scores and APACHE II scores, speaking for the possibility that weight (upon ICU admission) was directly related to the disease severity, greatly

limiting the interpretation of any subsequent analysis. Are the authors able to go back to outpatient medical records to retrieve a baseline body weight?
Response: There was a trend for the lower body weight groups to have higher SOFA scores, but the p value was 0.382. The APACHE II scores were 18, 19, 18 and 14 in underweight, normal, overweight and obese groups, respectively. Though the p value was near 0.05, there was no obvious trend for the lower body weight groups to have higher PAPCHE II scores.
Because body weight is not recorded for all outpatients in this hospital, we could not retrieve baseline body weight data for this study.

- Similarly, there was possible bias in that weight may be a surrogate marker of underlying comorbidities, as the incidence of conditions such as COPD, neoplasm and liver disease is higher in the underweight than the overweight categories (Table 3). All these factors should be included in the adjusted confounder model for regression analysis.
Response: Cox proportional hazard regression analysis was undertaken to assess the factors associated with 90-day mortality. The variables significantly associated with 90-day non-survival in the univariate analysis were used in the Cox proportional hazard regression analysis. All these factors have already been included in the regression analysis.

- One of the commonest confounder in any study examining the effect of body weight on clinical outcomes is cigarette smoking. Please explain how this may or may not be relevant in the current study.
Response: There were 58 smokers and 120 non-smokers in the current study, and their BMIs were 22.1±3.8 and 22.9±4.6, respectively, and the p value was 0.256.

- Please include a study flow diagram that shows the number of patients screened and number of patients (and reasons) excluded from analysis.
Response: A flowchart has been added, please see line 150 and figure 1.

Minor comments:
- Throughout the abstract and manuscript, the authors have opted to provide comparisons between in-hospital survivors vs non-survivors. It would be far more important to present these data for the different body weight groups, as this was the study exposure.
Response: We agree with the reviewer on this issue. Comparisons between in-hospital survivors vs non-survivors have been deleted in the abstract, but still remain in the manuscript in order to supply more information. Data for different body weight groups have been presented in the abstract, please see lines 39-45.

- Similarly, the authors have presented the results that SOFA score and APACHE II score were significant predictors of survival from sepsis. This was not the primary hypothesis tested in the study, please explain whether adjustment for multiple testing was made, otherwise, de-emphasize these results.
Response: It's true that SOFA score and APACHE II score were not the primary hypothesis tested in the study, though they were significant predictors of survival both in Unadjusted and adjusted multiple testing. Therefore, we have revised our conclusion to "BMI was an independent factor associated with survival in a Chinese cohort of medical patients with sepsis, patients with lower BMI having a higher risk of death" in the abstract. See lines 47-49, please.

- The study did not include patients who are morbidly obese, which precludes comparison of the results with published studies / systematic reviews.

Response: The BMI of our patients ranged from 12.11 to 32.46. There was no morbidly obese patient in our study, and the reason is that morbidly obese people are rare in China. This is a unique feature of our study population, which is different from data from developed countries.

- Abstract, Lines 44-47 - Consider presenting more detailed results from analysis of the four groups in the abstract, as the primary objective of this study was to evaluate the impact of BMI on survival.
Response: Data for different body weight groups have been presented in the abstract, please see lines 38-45.

- Abstract, Conclusion - Main message unclear, please modify to answer the primary objective of the study.
Response: We have revised our conclusion to “BMI was an independent factor associated with survival in a Chinese cohort of medical patients with sepsis, patients with lower BMI having a higher risk of death” in the abstract. See lines 47-49, please.

- Introduction, Lines 72-74 - Please delete or modify this statement, it is untrue, there are a lot of studies on medical patients with sepsis.
Response: The sentence “Many studies have analyzed the characteristics and clinical outcomes of surgical patients with sepsis but few of these have focused on medical patients” has been deleted. Thanks.

- Introduction, Line 83 - Consider citing the latest systematic reviews on the effect of body weight in sepsis here [Wang S, Liu X, Chen Q, Liu C, Huang C, Fang X. The role of increased body mass index in outcomes of sepsis: a systematic review and meta-analysis.
BMC Anesthesiol. 2017;17(1):118.] as well as editorial comments [E.g., Ng PY, Eikermann M. The obesity conundrum in sepsis. BMC Anesthesiol. 2017 Oct 25;17(1):147.]
Response: The two references have been added, see line 81, please.

- Methods, Line 94 - Please clarify how ‘ sepsis’ was defined?
Response: The definition of sepsis has been added, please see lines 92-93.

- Methods, Line 96 - Please state exactly what the ‘upper laboratory level limit’ for lactate was.
Response: The upper laboratory level limit of lactate was 1.5 mmol/L in our hospital, see line 97.

- Methods, Lines 124-125 - Consider including ICU mortality as a secondary outcome.
Response: The ICU mortality(38.8%) was similar to in-hospital mortality(41.6%) in our study, and therefore we don’t think that ICU mortality as a secondary outcome would add more information.

- Results, Line 164-165 - Give exact numbers and frequencies (%) in each group.
Response: We have added these data, see lines 169-170.

- Results, Line 164-170 - Please move this paragraph with results for the 4 patient groups to the earlier part of the Results section. Also, more detailed data and analyses are necessary.
Response: The results were described in terms of demographics, in-hospital outcomes, and 90-day follow-up data. BMI was identified as an independent factor of 90-day mortality by Cox analysis, and then patients were divided into four groups based on BMI in order to compare clinical data between groups and perform survival analysis. So we think it is appropriate to keep the paragraph as it was.
- Discussion, Lines 177-181 - Please de-emphasize or delete the discussion about SOFA score and APACHE score from this important opening paragraph, as explained above.
Response: We have de-emphasized the discussion on SOFA score and APACHE II score, see lines 184-187, please.

- Discussion, Lines 187-188 - Insert relevant reference.
Response: We have done so, please see line 195.

- Discussion, Lines 214-216 - Insert relevant references.
Response: We have done so, please see lines 221-223.

- Discussion, Lines 233-235 - Please delete this hypothetical statement as it was not tested in the study.
Response: We have deleted the last sentence of the corresponding paragraph.

- Discussion, Lines 236-243 - Explain why this paragraph on the site of infection is relevant to the primary study hypothesis of the association between BMI and mortality.
Response: As the relationship between BMI and clinical outcomes of sepsis may be related partly to differences in patient characteristics, we therefore set out to evaluate the impact of BMI on survival in a cohort of medical patients with sepsis, which is different from surgical septic patients. The most common primary site of infection is different between medical and surgical patients. It should be noted that in the majority of our patients (73.6%) sepsis was associated with pulmonary infection, and it was reported that Pulmonary-sepsis showed worse outcome than abdominal-sepsis, and pulmonary infection is a risk factor for one-year mortality and quality of life after sepsis. See lines 245-257, please.

- Discussion, Lines 245-246 - Do you mean '…although morbidly obese patients are NOT COMMON…' or 'NOT UNCOMMON'?
Response: We have reworded this statement. please see lines 259-260.

- Limitations - Needs to be expanded. E.g., address sample size and power issue, presence of residual confounding.
Response: The limitations of this study have been expanded, please see lines 258-268.

- Conclusions - Please delete the part about SOFA score and APACHE score, as explained above.
Response: The part about SOFA score and APACHE II score has been deleted, see lines 271-272, please.

VERSION 2 – REVIEW

REVIEWER	Tsukasa Ikeura The Third Department of Internal Medicine, Kansai Medical University, Japan
REVIEW RETURNED	18-Apr-2018

GENERAL COMMENTS	The authors revise the manuscript properly.

REVIEWER	Jochen Dobner Heinrich Heine Unviersity Düsseldorf, Institute of Physical Biology, Germany
REVIEW RETURNED	23-Apr-2018

GENERAL COMMENTS	The authors have responded to every point mentioned and the revised manuscript is thus very much improved. One issue though remains with the inclusion of patients with BMIs as low as 12.11 (lines 274-275 in the marked revised copy): "There were several limitations to our study. Firstly, the BMI of our patients ranged from 12.11 to 32.46". I wonder how many severely underweight patients

	were included and I would strongly recommend discussing this as there is often a U shaped distribution found (e.g. for risc of infection: Am J Epidemiol, 183 (2016), pp. 1008-1017 or influenza related pneumonia: Obes Rev, 14 (2013), pp. 839-857). As morbidly obese somehow represent the other extreme and could not be included in this study for mentioned reasons there is at least a small danger that low BMI(s) included in this study represent a sample related bias. I would therefore appreciate if the authors discuss that in the manuscript.

REVIEWER	Pauline Yeung Ng Adult Intensive Care Unit, Queen Mary Hospital and The University of Hong Kong, Hong Kong
REVIEW RETURNED	01-May-2018

GENERAL COMMENTS	Thank you for presenting an improved version of the manuscript. Major Comments: - The authors used the Cox proportional hazards model and showed that BMI (as a continuous variable) was associated with survival in patients with sepsis. However, in comparing the survival of the 4 BMI categories, please note that a log-rank test is unadjusted and hence results with regards to the 4 patient groups should discussed with this limitation in mind. - In general, the manuscript would benefit from English language editing. Minor Comments Abstract, Results - Please delete the detailed information about differences between the four BMI groups in lines 40-58, and only present data for the the primary outcome (i.e. 90-day mortality). Strengths and limitations, Lines 70-71 - Instead of repeating the statistical methodology used, please discuss, whether you think using the Cox and the Kaplan-Meier models was a strength or a limitation? Introduction, Lines 90-93 - Inaccurate citation of the study findings, which in fact showed 26% of patients with sepsis had surgical diagnostic categories. Introduction, Line 104 - Delete ‘which may be related partly to differences in patient characteristics’. Methods, Subjects, Line 139 - Instead of ‘hypotension’, please use ‘blood pressure’. Methods, Subjects, Line 140 - Instead of ‘oliguria’, please use ‘urine output’. Methods, Subjects, Line 142 - Delete ‘septic shock’ as repetitive with ‘blood pressure’. Results, Line 181 - Please define what ’abdomen’ as the site of infection refers to, as surgical cases were excluded from analysis. Results, Line 190 - How is ‘hypotension’ different from ‘septic shock’?

	Discussion, Line 221 - Rephrase as '…BMI was independently associated with mortality…', because a Cox proportional hazards model only tests associations and is not a predictor model. Discussion, Lines 251-259 - In addition to presenting the percentages of different BMI categories, please expand how this study contributes to the data on mortality of underweight patients. Discussion, Lines 266-267 - Please delete this over-generalized statement. Discussion, Lines 283-285 - Please delete this statement as the association of BMI with hypotension / septic shock was not statistically tested in the current study, even though there was a trend to association in univariate analysis. Discussion, Lines 286-297 - Discussion on sex and survival is irrelevant to the current study. Discussion, Lines 313-316 - Please discuss the limitation that weight ascertained at ICU admission may already reflect the severity of the underlying condition, or the patient's premorbid condition e.g. prolonged hospitalization and cachexia. Conclusions, Lines 332-333 - As explained above, please rephrase as '…showing that BMI was independently associated with survival…'. Table 1 - Clarify whether 'survivors' and 'non-survivors' in this table refer to the 'in-hospital' or '90 day' time definition. Table 2 - Please add in a footnote how the variables tested in the Cox regression analysis was determined (with reference to Methods, Lines 159-161). Table 3 - Would in fact order this table as Table 1, as it presents the patient demographics classified by the exposure tested (BMI).

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Tsukasa Ikeura

Institution and Country: The third Department of Internal Medicine, Kansai Medical University, Japan

Please state any competing interests: None declared.

Please leave your comments for the authors below

The authors revise the manuscript properly.

Response: Thank you very much.

Reviewer: 2

Reviewer Name: Jochen Dobner

Institution and Country: Heinrich Heine Unviersity Düsseldorf, Institute of Physical Biology, Germany

Please state any competing interests: None declared.

Please leave your comments for the authors below

The authors have responded to every point mentioned and the revised manuscript is thus very much improved. One issue though remains with the inclusion of patients with BMIs as low as 12.11 (lines 274-275 in the marked revised copy): "There were several limitations to our study. Firstly, the BMI of our patients ranged from 12.11 to 32.46". I wonder how many severely underweight patients were included and I would strongly recommend discussing this as there is often a U shaped distribution found (e.g. for risc of infection: Am J Epidemiol, 183 (2016), pp. 1008-1017 or influenza related pneumonia: Obes Rev, 14 (2013), pp. 839-857). As morbidly obese somehow represent the other extreme and could not be included in this study for mentioned reasons there is at least a small danger that low BMI(s) included in this study represent a sample related bias. I would therefore appreciate if the authors discuss that in the manuscript.

Response: The limitation of low BMIs was discussed, please see lines 258-263.

Reviewer: 3

Reviewer Name: Pauline Yeung Ng

Institution and Country: Adult Intensive Care Unit, Queen Mary Hospital and The University of Hong Kong, Hong Kong

Please state any competing interests: None declared

Please leave your comments for the authors below

Thank you for presenting an improved version of the manuscript.

Major Comments:

- The authors used the Cox proportional hazards model and showed that BMI (as a continuous variable) was associated with survival in patients with sepsis. However, in comparing the survival of the 4 BMI categories, please note that a log-rank test is unadjusted and hence results with regards to the 4 patient groups should discussed with this limitation in mind.

Response: Because BMI is a continuous variable rather than categorical variable, it would be more accurate to analyze BMI as a continuous variable. Therefore, BMI was analyzed as a continuous variable in our study, and it was identified as an independent factor for survival in patients with sepsis for the first time. Then Kaplan-Meier survival curves were constructed to show the survival probabilities at day-90 according to BMI classification, which also showed that higher BMI was associated with better prognosis. Though log-rank test is unadjusted, its result was consistent with that of Cox proportional hazards regression analysis.

- In general, the manuscript would benefit from English language editing.

Response: We had this manuscript copyedited by a professional English editing service that specializes in scientific papers.

Minor Comments

Abstract, Results - Please delete the detailed information about differences between the four BMI groups in lines 40-58, and only present data for the the primary outcome (i.e. 90-day mortality).

Response: Lines 40-58? I believe that you mean lines 40-45. We agree with you, the detailed information about differences between the four BMI groups was deleted.

Strengths and limitations, Lines 70-71 - Instead of repeating the statistical methodology used, please discuss, whether you think using the Cox and the Kaplan-Meier models was a strength or a limitation?

Response: BMI was analyzed both as a continuous variable (Cox proportional hazard regression analysis) and as a categorical variable (Kaplan-Meier survival curves), the results of the two analyses were consistent. Therefore, it is absolutely a strength of the present study.

Introduction, Lines 90-93 - Inaccurate citation of the study findings, which in fact showed 26% of patients with sepsis had surgical diagnostic categories.

Response: The sentence “only 26% of surgical patients developed sepsis” was changed to “surgical diagnoses were identified in only 26% of cases”, please see lines 71-72.

Introduction, Line 104 - Delete ‘which may be related partly to differences in patient characteristics’.

Response: The sentence was deleted, thank you.

Methods, Subjects, Line 139 - Instead of ‘hypotension’, please use ‘blood pressure’.

Response: The word “hypotension” was changed to “blood pressure”, please see line 111.

Methods, Subjects, Line 140 - Instead of ‘oliguria’, please use ‘urine output’.

Response: The word “oliguria” was changed to “urine output”, please see line 112.

Methods, Subjects, Line 142 - Delete ‘septic shock’ as repetitive with ‘blood pressure’.

Response: The word “septic shock” was deleted.

Results, Line 181 - Please define what 'abdomen' as the site of infection refers to, as surgical cases were excluded from analysis.

Response: Patients with abdomen infection who did not require surgical treatment were included in the study. Abdomen infection refers to peritonitis, liver abscess, and infection of biliary tract, etc.

Results, Line 190 - How is 'hypotension' different from 'septic shock'?

Response: Sepsis-induced hypotension is defined as a systolic blood pressure (SBP)<90 mmHg or mean arterial pressure (MAP)<70 mmHg or a SBP decrease>40 mmHg or less than two standard deviations below normal for age in the absence of other causes of hypotension. Septic shock is defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation. (Dellinger RP, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41:580-637.)

Discussion, Line 221 - Rephrase as '…BMI was independently associated with mortality…', because a Cox proportional hazards model only tests associations and is not a predictor model.

Response: The sentence was rephrased, please see lines 190-191.

Discussion, Lines 251-259 - In addition to presenting the percentages of different BMI categories, please expand how this study contributes to the data on mortality of underweight patients.

Response: The contribution of this study to the data on mortality of underweight patients was added, please see lines 219-221.

Discussion, Lines 266-267 - Please delete this over-generalized statement.

Response: The over-generalized statement was deleted.

Discussion, Lines 283-285 - Please delete this statement as the association of BMI with hypotension / septic shock was not statistically tested in the current study, even though there was a trend to association in univariate analysis.

Response: This statement had already been deleted in the previous revised manuscript (clean copy), sorry it was still shown on the marked copy.

Discussion, Lines 286-297 - Discussion on sex and survival is irrelevant to the current study.

Response: The discussion on sex and survival was added according to another reviewer's comment.

Discussion, Lines 313-316 - Please discuss the limitation that weight ascertained at ICU admission may already reflect the severity of the underlying condition, or the patient's premorbid condition e.g. prolonged hospitalization and cachexia.

Response: We agree with you that weight ascertained at ICU admission may already reflect the severity of the underlying condition or the patient's premorbid condition, but lack of evidence.

Conclusions, Lines 332-333 - As explained above, please rephrase as '…showing that BMI was independently associated with survival…'.

Response: The sentence was rephrased according to your suggestion, please see lines 273-274.

Table 1 - Clarify whether 'survivors' and 'non-survivors' in this table refer to the 'in-hospital' or '90 day' time definition.

Response: The "in-hospital clinical outcome" was added, see line 398, please.

Table 2 - Please add in a footnote how the variables tested in the Cox regression analysis was determined (with reference to Methods, Lines 159-161).

Response: The footnote was added, see lines 404-405, please.

Table 3 - Would in fact order this table as Table 1, as it presents the patient demographics classified by the exposure tested (BMI).

Response: The results were described in terms of demographics, in-hospital outcomes, and 90-day follow-up data. BMI was identified as an independent factor of 90-day mortality by Cox analysis, and then patients were divided into four groups based on BMI in order to compare clinical data between groups and perform survival analysis. So we think it is appropriate to keep the order of tables as it was.

VERSION 3 – REVIEW

REVIEWER	Jochen Dobner Heinrich Heine Unviersity Düsseldorf, Institute of Physical Biology, Germany
REVIEW RETURNED	28-May-2018

GENERAL COMMENTS	The authors again have addressed all points mentioned by the reviewers. I am very pleased how the manuscript is improved. Unlike reviewer 3 I do not think that discussion of sex and outcome in any way could be "irrelevant" as it is well-known that with regards to many diseases, sex might play a very important role. Therefore I would like this point remaining in the manuscript.

REVIEWER	Pauline Yeung Ng Adult Intensive Care Unit, Queen Mary Hospital, Hong Kong
REVIEW RETURNED	31-May-2018

GENERAL COMMENTS	The manuscript is ready for acceptance with the following grammatical / stylistic revisions:

	Abstract, Lines 33-34 - Please refrain from imprecise descriptions such as ‘the majority of’ and replace with ’77.0% patients were older than 65 years’. Abstract, Conclusions - Rephrase with ’BMI was an independent factor associated with 90-day survival in a Chinese cohort of medical patients with sepsis, with patients having a lower BMI at a higher risk of death.’ Strengths and limitations of this study, Line 58 - Rephrase with ‘…the patient’s baseline outpatient body weight’. Introduction, Lines 70-71 - Rephrase with ’…medical diagnostic categories made up the majority of causes of sepsis, while surgical diagnoses…’ Discussion, Lines 186-187 - Delete ‘However,’ and replace with ’This study adds the finding that BMI was independently associated with survival, where 90-day mortality…’ Discussion, Line 223 - Rephrase with ‘…validation in future large sample, multi-center studies…’ Discussion, Line 252 - Add ‘,’ after ’(73.6%)’ Discussion, Line 258-262 - Rephrase with ’10 severely underweight patients with BMI less than 16.0 were included in the present study, which introduces possible sample bias in patients in the low BMI category. However, the 90-day and in-hospital mortality of these 10 severely underweight patients were 70.0% and 60.0% respectively, not significantly different from that of all 33 underweight patients…’ Discussion, Line 264 - Rephrase with ‘…the patient’s baseline outpatient body weight’. Conclusions - Rephrase with ’…BMI was independently associated with 90-day survival , with patients having a lower BMI at a higher risk of death.’

VERSION 3 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:
Reviewer: 2
Reviewer Name: Jochen Dobner
Institution and Country: Heinrich Heine Unviersity Düsseldorf, Institute of Physical Biology, Germany
Please state any competing interests: None declared
Please leave your comments for the authors below
The authors again have addressed all points mentioned by the reviewers. I am very pleased how the manuscript is improved.
Unlike reviewer 3 I do not think that discussion of sex and outcome in any way could be "irrelevant" as it is well-known that with regards to many diseases, sex might play a very important role. Therefore I would like this point remaining in the manuscript.
Response: Thank you very much.

Reviewer: 3
Reviewer Name: Pauline Yeung Ng
Institution and Country: Adult Intensive Care Unit, Queen Mary Hospital, Hong Kong
Please state any competing interests: None declared
Please leave your comments for the authors below
The manuscript is ready for acceptance with the following grammatical / stylistic revisions:
Abstract, Lines 33-34 - Please refrain from imprecise descriptions such as 'the majority of' and replace with '77.0% patients were older than 65 years'.
Response: We thank the reviewer for this helpful suggestion. The sentence was changed according to the comment, please see lines 34-35.

Abstract, Conclusions - Rephrase with 'BMI was an independent factor associated with 90-day survival in a Chinese cohort of medical patients with sepsis, with patients having a lower BMI at a higher risk of death.'
Response: The sentence was rephrased according to the comment, please see lines 47-49.

Strengths and limitations of this study, Line 58 - Rephrase with '…the patient's baseline outpatient body weight'.
Response: The sentence was rephrased, please see line 59.

Introduction, Lines 70-71 - Rephrase with '…medical diagnostic categories made up the majority of causes of sepsis, while surgical diagnoses…'
Response: The sentence was rephrased, please see lines 70-71.

Discussion, Lines 186-187 - Delete 'However,' and replace with 'This study adds the finding that BMI was independently associated with survival, where 90-day mortality…'
Response: The sentence was rephrased, please see lines 186-187.

Discussion, Line 223 - Rephrase with '…validation in future large sample, multi-center studies…'
Response: The sentence was rephrased, please see line 223.

Discussion, Line 252 - Add ',' after '(73.6%)'
Response: It was done, please see line 252.

Discussion, Line 258-262 - Rephrase with '10 severely underweight patients with BMI less than 16.0 were included in the present study, which introduces possible sample bias in patients in the low BMI category. However, the 90-day and in-hospital mortality of these 10 severely underweight patients were 70.0% and 60.0% respectively, not significantly different from that of all 33 underweight patients…'
Response: The sentence was rephrased, please see lines 258-263.

Discussion, Line 264 - Rephrase with '…the patient's baseline outpatient body weight'.
Response: The sentence was rephrased, please see line 264.

Conclusions - Rephrase with '…BMI was independently associated with 90-day survival , with patients having a lower BMI at a higher risk of death.'
Response: The sentence was rephrased, please see lines 274-275.