

September 4, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 4097-review.doc).

**Title:** Predictive Value of Extravascular Lung Water Indexed to Predicted Body Weight and Actual Body Weight on In-hospital Survival Rate of Severe Sepsis Patients in A Medical Intensive Care Unit

**Author:** Fu-Tsai Chung, Shu-Min Lin, Horng-Chyuan Lin, Chih-Teng Yu, Meng-Heng Hsieh, Yueh-Fu Fang, Chien-Yin Liu, Chih-Hsi Kuo, Tsai-Yu Wang, Han-Pin Kuo.

**Name of Journal:** *World Journal of Anesthesiology*

**ESPS Manuscript NO:** 4097

The manuscript has been improved according to the suggestions of reviewers

Sincerely yours!

Dr. Fu-Tsai Chung, MD & Associate Professor

1. School of Medicine, College of Medicine, Chang Gung University
2. Chief of Medical Intensive Care Unit V, Chang Gung Memorial Hospital, Linkou
3. Pulmonary Disease Research Center, Chang Gung Memorial Hospital, Linkou
4. Graduate Institute of Clinical Medical Sciences, College of Medicine, Chang Gung University
5. Department of Thoracic Medicine, Chang Gung Memorial Hospital, Chang Gung University, #5 Fushing Street, Kweishan, Taoyuan, Taiwan.

Tel: +886 3-3281200 ext. 8467

Fax: +886 3-3272474

**E-mail:** [vikingchung@yahoo.com.tw](mailto:vikingchung@yahoo.com.tw) (F.T.C.)

***Comments from Reviewer #1:***

***1. I read with great interest the present manuscript in which the authors have tried to assess the prognostic value of extravascular lung water (EVLW) in medical ICU patients with severe sepsis. Even though the manuscript have several merits, there are also several shortcomings requiring modifications. 1. There are several grammatical and typographical errors. I would strongly suggest the authors to go thru the manuscript again to rectify these mistakes. 2. The data is very old (2005-06) and may be outdated in today's context with recent change in guidelines in patient management and other technological advances. 3. Why were patients with "Altered coagulation profile" were excluded? How was it determined which patients to be excluded? Coagulation abnormalities are very common in sepsis pts and excluding such pts may have caused selection bias. 4. Kindly specify the criteria used to "classify pt with severe sepsis" 5. Results: There is relatively small difference between the various variables tested and this gets compounded by the fact that the cut-off for p value was used as 0.1 rather than 0.05. 6. Discussion is very short. Maybe comparison with other similar studies like Crit Care Med 2008;36:69-73 and J Crit care 2012;27:376-83 will add more substance to it.***

**REPLY TO COMMENT:**

**We have to thank the reviewer's comments to improve the manuscript quality to fit the journal publication.**

1. The manuscript has been re-written, the errors were corrected as could as possible.
2. Despite the data was old, the issue about EVLW indexed to actual or predicted body weight to predict outcome in these patients remains few. We provided a prospective study data to contribute to this issue and may further conduct a larger scale study for this issue in the future.
3. It was wrong writing in the original manuscript. Actually, a high rate of these septic patients with elevated EVLW had coagulopathy; we have corrected it in revised manuscript.
4. We have added the statement "Severe sepsis was defined by the consensus committee of the American College of Chest Physicians and Society of Critical Care Medicine [7]" and a reference in the revised manuscript.
5. After discussion with a statistician, we found the power of EVLWI<sub>a</sub> to predict survival is similar to that of EVLWI<sub>p</sub>; therefore, we written our manuscript and conclusion as the statistician's recommendation. We also appreciated the statistician in the acknowledgement.
6. We had written the discussion in revised manuscript.

***Comments from Reviewer #2:***

***1. This manuscript has shown that extravascular lung water indexed to predicted body weight (EVLWIp) was a better predictor than that indexed to actual body weight (EVLWIa) on outcome in patients with severe sepsis. However, there is no new finding in this manuscript. Because, previous study has shown the same finding (Crit Care Med 2008;36:69-73). 1.What is your new finding? 2.Discussion is too short. Please compare the research of Mallat J et al. (J Crit care 2012;27:376-83) with your research.***

**REPLY TO COMMENT:**

Despite the data was old, the issue about EVLW indexed to actual or predicted body weight to predict outcome in these patients remains few. We provided a prospective study data to contribute to this issue and may further conduct a larger scale study for this issue in the future.

After discussion with a statistician, we found the power of EVLWIa to predict survival is similar to that of EVLWIp; therefore, we written our manuscript and conclusion as the statistician's recommendation. We also appreciated the statistician in the acknowledgement. We had also written the discussion in revised manuscript.

**Comments from Reviewer #3:**

**1. Review of the ms ESPS 4097. In this paper the authors report on the predictive value of extravascular lung water indexed to predicted body weight. The study was designed to compare the predicting value of extravascular lung water indexed to predicted body weight and actual body weight. The results are interesting and the possible clinical relevance of such investigations would merit publication, but there are several points of criticism which should be considered by the authors. 1. The authors should clarify/define “continuous cardiac output (CO) calibration” in case of EVLW measurement. Does it mean that repeated calibrations were performed with thermodilution, or the registration of pulse contour-derived cardiac output? 2. Also the description of the method in this paragraph is very confusing. “Following three consecutive central venous injections of 10 ml iced 0.9% saline solution” means that the average was taken at each measurement or altogether three measurements were performed? Please clarify; or rather rewrite the description of the PiCCO methods to be more comprehensible. 3. The discussion is somewhat diffuse and may be rewritten. For instance, paragraph 2 was copied from the introduction. The authors should not repeat their thoughts here, rather focus on the explanation of their results and provide further information that has not been mentioned already. 4. The manuscript has typos and grammatical errors that make it difficult to read. The authors should double check spelling, or at least, please use the spell check function of the word processor (e.g.: paragraph 2 on page 4: “Dr. Meyer and Hall though that” - in this case “though” should be “thought”, in the next two rows “in accurate” and “incase”, etc, etc). Besides, please choose if you want to use the unit or its abbreviation (hours or hr, on page 10). Also, units and values should not be written together.**

**REPLY TO COMMENT:**

We have to thank the reviewer's comments to improve the manuscript quality to fit the journal publication. The manuscript has been re-written, and the errors were corrected as could as possible. After discussion with a statistician, we found the power of EVLWIa to predict survival is similar to that of EVLWI<sub>p</sub>; therefore, we written our manuscript and conclusion as the statistician's recommendation. We also appreciated the statistician in the acknowledgement.

1. In revised manuscript, it has been corrected as “The EVLW measurement was based on transpulmonary thermodilution method. This method was recently introduced as part of the PiCCO plus system (Pulsion Medical System, Munich, Germany). This method only used a single indicator (cold saline solution).

Following central venous injection of 10 ml iced 0.9% saline solution, continuous cardiac output (CO) and EVLW measurements were obtained. CO and EVLW determinations were performed immediately following catheter insertion, and were employed as the hemodynamic parameters for managing the patients in the medical ICU with severe sepsis.” In the section of EVLW measurement of method.

2. As reply as 1.
3. We had written the discussion in revised manuscript.
4. We had written the discussion in revised manuscript.

***Comments from Reviewer #4:***

***1. This study assesses the prognostic value of extravascular lung water (EVLW) in medical ICU patients with severe sepsis. The authors conclude that EVLW indexed to predicted body weight (EVLIp) is a better predictor of survival than other indices. My main concern is relatively small difference between AUCs of the variables, especially those of EVLIp and EVLWia. I think the significance of the difference between EVLIp and other variables should be estimated with a statistical test.***

**REPLY TO COMMENT:**

We have to thank the reviewer's comments to improve the manuscript quality to fit the journal publication. After discussion with a statistician, we found the power of EVLWia to predict survival is similar to that of EVLWIp; therefore, we written our manuscript and conclusion as the statistician's recommendation. We also appreciated the statistician in the acknowledgement.

***Comments from Reviewer #5:***

***1. The only weakness is the lack of novelty of this study, as well as the clinical lightweight which is the main finding, given the small difference between EVLip and Evlia. Anyway, I think the study reaches the level to be published***

**REPLY TO COMMENT:**

We have to thank the reviewer's comments to improve the manuscript quality to fit the journal publication. After discussion with a statistician, we found the power of EVLWIa to predict survival is similar to that of EVLWI<sub>p</sub>; therefore, we written our manuscript and conclusion as the statistician's recommendation. We also appreciated the statistician in the acknowledgement.