PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The effect of albumin-globulin score and albumin/globulin ratio on survival in patients with heart failure: A retrospective cohort study in China
AUTHORS	Li, Kuan; Fu, Wanrong; Bo, Yacong; Zhu, Yongjian

VERSION 1 – REVIEW

REVIEWER	Tetsu Watanabe, MD, PhD Associated professor, Department of Cardiology, Pulmonology, and Nephrology, Yamagata University School of Medicine, Japan
REVIEW RETURNED	28-Mar-2018

GENERAL COMMENTS	General Comments: This retrospective observational study showed that albumin globulin ratio (AGR) is a feasible predictor of mortality in patients with heart failure. This study appears well conducted for design and contents. I have some points that need to be better clarified. Comments: 1. The authors should show how they determined cut-off value of AGR. They had better use tertile of AGR but not one cut-off value for Kaplan-Meier analysis. 2. Table 3 and Figure 2: This reviewer feels strange about these results. Commonly, heart failure mortality is increased with increasing rehospitalizations for worsening heart failure. Why AGR was not associated with rehospitalization? Although there were 120 cardiovascular deaths, were deaths due to progressive HF less than other causes? The authors should show proportion of each cause of death. 3. BNP don't distribute normally. They should examine whether continuous data distribute normally with Kolmogorov-Smirnov test and reanalyze with appropriate statistical analysis. Minor comments: 1. Page 7, bottom line: Abbreviations should be spelled out when they first appear.

REVIEWER	Darlington Obinnaya Okonko King's College London British Heart Foundation Center of Research Excellence, London, UK.
REVIEW RETURNED	09-Apr-2018

GENERAL COMMENTS	Li et al., show that the albumin/globulin ratio is associated with worst survival (but not rehospitalisation) in patients with de novo acute heart failure and diverse ranges of LVEF.

	This study has a major weakness that is potentially correctable. As the authors are aware, multiple parameters correlate with survival in heart failure and have been postulated to be of potential clinical use. Consequently, any new proposed prognostic marker must show that it provides incremental predictive information. Thus, the most important analyses that are missing are: (1) what is the incremental utility of AGR which can be demonstrated by showing that adding AGR to the baseline survival model in the multivariable Cox leads to a significant increase in the model chi-square value, or by calculating the net reclassification improvement (NRI) or the integrated discrimination index (IDI); (2) what is the incremental utility of the AGR compared to albumin or globulin alone. Why should clinicians measure both if measuring one is as prognostically good as the combined score. To answer this, the authors need to compare the area under the curve (AUC; or C-statistics) on ROC analysis for albumin and globulin versus AGR (perform a U-test). Could the authors also give the AUC for the cutoff of AGR of 1.48 used in the manuscript. Was this cutoff derived from ROC analysis or is it the median. If the AUC is modest (<0.7) then AGR is unlikely to be useful.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

General Comments: This retrospective observational study showed that albumin globulin ratio (AGR) is a feasible predictor of mortality in patients with heart failure. This study appears well conducted for design and contents. I have some points that need to be better clarified.

Comments:
1. The authors should show how they determined cut-off value of AGR. They had better use tertile of AGR but not one cut-off value for Kaplan-Meier analysis.
Answer, Thanks for your valuable suggestions. The cut-off value of AGR was determined by ROC. We have used both cut-off value and tertile to do the Kaplan-Meier analysis, respectively.
2. Table 3 and Figure 2: This reviewer feels strange about these results. Commonly, heart failure mortality is increased with increasing rehospitalizations for worsening heart failure. Why AGR was not associated with rehospitalization?
Answer, thanks. Because most of the participants in the current study are from rural China, their income is very low. When their status of heart failure became worse, they chose to ask the village doctor to treat them at home, so the rehospitalization rate was low, and it might be one potential reason that there is no relationship between AGR and rehospitalization.
3. BNP don't distribute normally. They should examine whether continuous data distribute normally with Kolmogorov-Smirnov test and reanalyze with appropriate statistical analysis.
Answer, thanks. We have tested the normality and analyzed those distributed non-normally with rank-sum test.
Minor comments:
1. Page 7, bottom line: Abbreviations should be spelled out when they first appear.
Answer, Thanks. We have spelled out those abbreviations.

Reviewer: 2

Li et al., show that the albumin/globulin ratio is associated with worst survival (but not rehospitalisation) in patients with de novo acute heart failure and diverse ranges of LVEF.

This study has a major weakness that is potentially correctable. As the authors are aware, multiple parameters correlate with survival in heart failure and have been postulated to be of potential clinical use. Consequently, any new proposed prognostic marker must show that it provides incremental predictive information. Thus, the most important analyses that are missing are:

(1) what is the incremental utility of AGR which can be demonstrated by showing that adding AGR to the baseline survival model in the multivariable Cox leads to a significant increase in the model chi-square value, or by calculating the net reclassification improvement (NRI) or the integrated discrimination index (IDI);
Answer, Thanks for your good comments. According to your comments, we calculated the NRI =0.320, which suggested that adding AGR to the baseline survival model is better.
(2) what is the incremental utility of the AGR compared to albumin or globulin alone. Why should clinicians measure both if measuring one is as prognostically good as the combined score. To answer this, the authors need to compare the area under the curve (AUC; or C-statistics) on ROC analysis for albumin and globulin versus AGR (perform a U-test). Could the authors also give the AUC for the cutoff of AGR of 1.48 used in the manuscript. Was this cutoff derived from ROC analysis or is it the median. If the AUC is modest (<0.7) then AGR is unlikely to be useful.
Answer, Thanks. The U-test suggested that the AUC of albumin and globulin are both lower than that of AGR (*P*=0.030 and 0.044, respectively), which means that AGR is better than simply testing one of them. Even though the AUC<0.7, it can also suggest in a certain extent that higher AGR is associated with favorable overall survival. Moreover, when we use tertile to investigate the effect of AGR on overall survival, we also found that higher AGR is associated with favorable overall survival.

VERSION 2 – REVIEW

REVIEWER	Tetsu Watanabe Yamagata university school of medicine, Japan
REVIEW RETURNED	30-Apr-2018

GENERAL COMMENTS	This paper is now well revised. There are no further comments.