PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Risk factors and clinical outcomes of functional decline during hospitalization in very old patients with acute decompensated heart failure: an observational study
AUTHORS	Yaku, Hidenori; Kato, Takao; Morimoto, Takeshi; Inuzuka, Yasutaka; Tamaki, Yodo; Ozasa, Neiko; Yamamoto, Erika; Yoshikawa, Yusuke; Kitai, Takeshi; Kato, Masashi; Ikeda, Tomoyuki; Furukawa, Yutaka; Nakagawa, Yoshihisa; Sato, Yukihito; Kuwahara, Koichiro; Kimura, Takeshi

VERSION 1 - REVIEW

REVIEWER	Dalane Kitzman Wake Forest School of Medicine USA PI of an NIH-funded clinical trial testing an intervention for physical decline from heart failure hospitalization
REVIEW RETURNED	28-Jul-2019

GENERAL COMMENTS	This is an outstanding paper on an extremely important topic. The sample size is very large, the methods are generally sound, and the manuscript is well written. Congratulations on an excellent study and report. Suggestions: Please add all cause death plus all cause hospitalizations as an outcome to analyze The functional decline stages that were utilize had very large gradations. There is a huge change in function mvoing from cane (0) to wheelchair (1) to bedridden! Even the baselin (cane) has significant disability. It would have been better to use a scale with more gradations and smaller gradations. Please add this statement to limitations section that “the Japanese long term care insurance categorization scheme is a coarse measure with very large gradations inherent in each single stage and therefore very likely substantially underestimated the prevalence of meaningful functional decline” Since there was an imbalance at baseline between the 2 groups please consider to re-do the analyses with inclusion of baseline status in the model (in other words, adjustment for the baseline value of the outcome measure). This should be in addition to and

	along with any other adjustment variables. This should be the main / primary analysis measure for all outcome measures Add to the last paragraph on page 18 (clinical and therapeutic implications) that one possible strategy could be immediate, tailored physical function rehabilitation during and after heart failure hospitalization. And please cite the ongoing NIH funded clinical trial (REHAB-HF) that is formally evaluating this strategy. The rationale/design paper was co-authored by Gordon R. Reeves and David Whellan (Am Heart Journal 2016). Please find this paper, review, and cite.

VERSION 1 – AUTHOR RESPONSE

RESPONSE TO THE REVIEWER 1

Response:

Thank you for your very valuable comments and suggestions.

We revised our manuscript in accordance with your comments and suggestions.

Reviewer 1's Comment:

This is an outstanding paper on an extremely important topic. The sample size is very large, the methods are generally sound, and the manuscript is well written. Congratulations on an excellent study and report.

Response:

We thank the reviewer for the positive and very careful assessment of our manuscript.

Please add all cause death plus all cause hospitalizations as an outcome to analyze.

Response

We appreciate your important comments. According to the reviewer's suggestion, we have added a composite of all-cause death or all-cause hospitalization to the secondary outcomes, and performed an additional analysis for the secondary outcome. As a result, the cumulative 1-year incidence of a composite of all-cause death or all-cause hospitalization in the functional decline group was significantly higher than that in the no functional decline group.

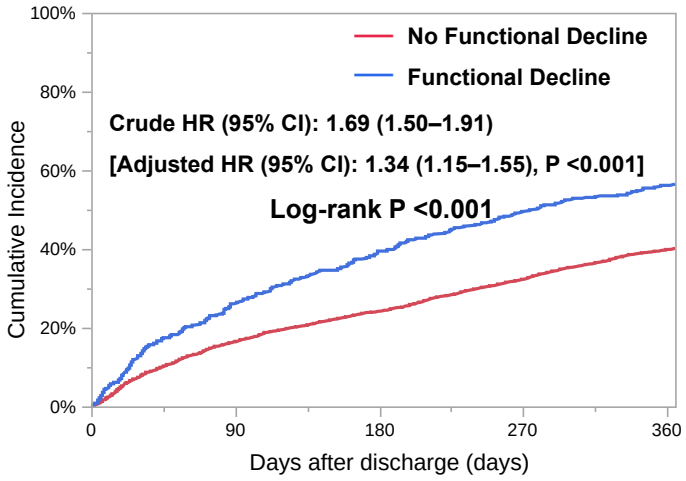
We have changed the statements as follows in the Method section:

"The secondary outcome measures were all-cause death, heart failure hospitalization, and a composite of all-cause death or all-cause hospitalization at 1-year." (Page 8, line 17 to Page 9, line 2)

We also have changed the statement in the Results as follows:

"The cumulative 1-year incidence of a composite of all-cause death or all-cause hospitalization was significantly higher in the functional decline group than in the no functional decline group. After adjusting confounders, the higher risk of the functional decline group relative to the no functional decline group remained significant (Figure 3 and eTable 3)." (Page 15, line 9–13)

All-cause death or All-cause hospitalization



Interval	0d	30d	180d	1y
No Functional Decline				
N of patients with at least 1 event		229	720	1186
N of patients at risk	3027	2764	2238	1582
Cumulative incidence		5.3 %	24 %	40 %
Functional Decline				
N of patients with at least 1 event		65	197	279
N of patients at risk	528	438	297	185
Cumulative incidence		13 %	40 %	57 %

The functional decline stages that were utilize had very large gradations. There is a huge change in function moving from cane (0) to wheelchair (1) to bedridden! Even the baseline (cane) has significant disability. It would have been better to use a scale with more gradations and smaller gradations. Please add this statement to limitations section that “the Japanese long term care insurance categorization scheme is a coarse measure with very large gradations inherent in each single stage and therefore very likely substantially underestimated the prevalence of meaningful functional decline”

Response

We appreciate your important comments. We have revised the statements as follows in the Limitations section:

“we adopted simple classification of functional status as ambulatory, use of wheelchair outdoor only, use of wheelchair indoor and outdoor, and bedridden state based on the definition of Japanese long-term care insurance. The categorization scheme is an easy to understand but coarse measure with very large gradations inherent in each single stage and therefore very likely substantially underestimated the prevalence of meaningful functional decline.” (Page 19, line 9–14 in the Limitations)

Since there was an imbalance at baseline between the 2 groups please consider to re-do the analyses with inclusion of baseline status in the model (in other words, adjustment for the baseline value of the outcome measure). This should be in addition to and along with any other adjustment variables. This should be the main / primary analysis measure for all outcome measures

Response

We appreciate the comment. According to the reviewer’s suggestion, we have re-analyzed the clinical outcomes using the 29 risk-adjusting variables with inclusion of clinically relevant additional baseline status (clinical signs, symptoms, and medications at discharge) listed in Table 1 in the multivariable

Cox proportional hazard models. The results were fully consistent with the results in the analysis by multivariable Cox proportional hazard models incorporating the 23 clinically relevant risk-adjusting variables.

We have changed the statements as follows in the Method section:

“We expressed the associations of the functional decline group with the no functional decline group for all outcome measures as hazard ratios (HRs) with 95% CIs by multivariable Cox proportional hazard models incorporating 29 clinically relevant risk-adjusting variables indicated in Table 1.” (Page 10, line 11–14)

We also have changed the statement in the Results as follows:

“After adjusting for baseline characteristics, the higher risk of the functional decline group relative to the no functional decline group remained significant (adjusted HR, 1.39; 95%CI, 1.18–1.62; P<0.001) (Figure 3 and eTable 3).” (Page 14, line 16 to Page 15, line 2)

In addition, we have changed the adjusted HRs and 95% CIs of the eTable 3.

Add to the last paragraph on page 18 (clinical and therapeutic implications) that one possible strategy could be immediate, tailored physical function rehabilitation during and after heart failure hospitalization. And please cite the ongoing NIH funded clinical trial (REHAB-HF) that is formally evaluating this strategy. The rationale/design paper was co-authored by Gordon R. Reeves and David Whellan (Am Heart Journal 2017). Please find this paper, review, and cite.

Response

We thank the reviewer for very careful assessment of our manuscript. According to the reviewer’s suggestion, we have revised the document as follows in the Discussion section:

“One possible strategy could be immediate, tailored physical function rehabilitation during and after heart failure hospitalization.” (Page 19, line 6–7 in the Discussion)

VERSION 2 – REVIEW

REVIEWER	Dalane W. Kitzman MD Wake Forest School of Medicine, USA I am PI of an NIH funded multicenter trial of a novel physical function intervention to improve physical function and prevent functional decline in older hospitalized ADHF patients (REHAB-HF).
REVIEW RETURNED	28-Nov-2019

GENERAL COMMENTS	The authors are congratulated for an excellent revision of an outstanding and extremely important manuscript. Upon additional review, I offer the following suggestions: 1) eTable 2 and eTable 3 are very important to the message of the manuscript. I’m assuming they are in the supplemental material because of journal style limitations. If possible, it would be good for these to be in the main manuscript, if the editors could allow.

	2) A unique and valuable aspect of your study is the age of the patients. Despite the fact that acute decompensated hospitalized heart failure is primarily a disorder of older persons, and that, as your data strongly confirm, age is a major risk factor for functional decline in these patients, there are scant data in very old persons (those age 75 or 80 years and greater). The majority of your patients are > age 80; that is remarkable. Suggest the authors highlight this somewhere in the manuscript. Some possibilities would be to add to the strenghts / limitations list at the front of the manuscript, and / or somewhere in the discussion (could use the verbiage above), and or add "in very old patients" in the title. 3) I believe the authors may have misunderstood my suggestion regarding adjustment for baseline variable. Please consider adjusting, first and foremost, for the Japanese insurance functional status category at baseline. In reality, this is the single most important adjustment variable, since one assumes that the functional status at baseline is likely a strong predictor of future functional decline. You could either add this to the model in additional to all the other variables you already have, or you could do a separate analysis with this being the sole adjustment. I believe that including baseline functional status is important, but given that you have included extensive other relevant baseline variables, it could be waived if the authors felt strongly or were for some reason unable to do this adjustment. 4) Either way, please add baseline functional category in your Forest-style plot that immediately follows the consort type diagram on page 40. The authors are again congratulated on an impressive study that has important implications for design of future management strategies for this high risk, vulnerable, and growing population.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Please state any competing interests or state 'None declared':

I am PI of an NIH funded multicenter trial of a novel physical function intervention to improve physical function and prevent functional decline in older hospitalized ADHF patients (REHAB-HF).

We appreciate the comment. We have added the competing interests ('None declared') in the manuscript. REHAB-HF is an outstanding HF exercise trial that is designed to fill the gaps left by the HF-ACTION trial. Thank you so much again for your valuable comment.

Please leave your comments for the authors below

The authors are congratulated for an excellent revision of an outstanding and extremely important manuscript.

We thank the reviewer for the positive assessment of our manuscript.

Upon additional review, I offer the following suggestions:

1) eTable 2 and eTable 3 are very important to the message of the manuscript. I'm assuming they are in the supplemental material because of journal style limitations. If possible, it would be good for these to be in the main manuscript, if the editors could allow.

We appreciate the comment. According to the reviewer's suggestion, we have included eTable 3 in the main manuscript as Table 3. On the other hand, eTable 2 showed the results of additional analysis on the risk factors for functional decline or in-hospital mortality in a total of 4056 patients. We, thus, would like to keep eTable 2 in its current form. However, we are pleased to include eTable 2 in the main manuscript if the editors and reviewers think it necessary.

2) A unique and valuable aspect of your study is the age of the patients. Despite the fact that acute decompensated hospitalized heart failure is primarily a disorder of older persons, and that, as your data strongly confirm, age is a major risk factor for functional decline in these patients, there are scant data in very old persons (those age 75 or 80 years and greater). The majority of your patients are > age 80; that is remarkable. Suggest the authors highlight this somewhere in the manuscript. Some possibilities would be to add to the strengths / limitations list at the front of the manuscript, and / or somewhere in the discussion (could use the verbiage above), and or add "in very old patients" in the title.

Thank you for your very valuable comments and suggestions. According to the reviewer's suggestion, we have added "very old patients" as follows in the Abstract, Strengths and limitations of this study, and Introduction section;

"To investigate the prevalence and risk factors of functional decline during hospitalization, and its relationship with post-discharge outcomes in very old patients with acute decompensated heart failure (ADHF) hospitalization." (Page 3, line 2-4 in the Abstract section)

"Independent risk factors of functional decline in very old patients with ADHF were related to both frailty and severity of HF. Functional decline during ADHF hospitalization was associated with unfavourable post-discharge outcomes." (Page 4, line 10-12 in the Abstract section)

"This study is the first large-scale contemporary multicentre observational study reporting the prevalence of functional decline in very old patients hospitalized for acute decompensated heart failure (ADHF)" (Page 5, line 7-8 in the Strengths and limitations of this study section)

"This study examines the risk factors of functional decline in very old patients hospitalized for ADHF" (Page 5, line 2-4 in the Strengths and limitations of this study section)

"In the rapidly aging societies, the number of very old patients hospitalized for acute decompensated heart failure (ADHF) is increasing" (Page 6, line 4-6 in the Introduction section)

"However, there is a scarcity of data regarding the risk factors of functional decline in very old patients hospitalized for ADHF." (Page 6, line 9-10 in the Introduction section)

"Therefore, we sought to clarify the risk factors for functional decline during hospitalization in very old patients with ADHF" (Page 6, line 13-14 in the Introduction section)

In addition, we have changed the title into "Risk factors and clinical outcomes of functional decline during hospitalization in very old patients with acute decompensated heart failure: an observational study"

3) I believe the authors may have misunderstood my suggestion regarding adjustment for baseline variable. Please consider adjusting, first and foremost, for the Japanese insurance functional status category at baseline. In reality, this is the single most important adjustment variable, since one assumes that the functional status at baseline is likely a strong predictor of future functional decline. You could either add this to the model in additional to all the other variables you already

have, or you could do a separate analysis with this being the sole adjustment. I believe that including baseline functional status is important, but given that you have included extensive other relevant baseline variables, it could be waived if the authors felt strongly or were for some reason unable to do this adjustment.

We appreciate your important comments. According to the reviewer's suggestion, we have used the 24 clinically relevant factors including the functional status at baseline listed in Table 1 as potential independent risk factors in multivariable logistic regression models, and also re-analyzed the clinical outcomes using the 30 risk-adjusting variables with inclusion of the functional status at baseline in the multivariable Cox proportional hazard models. We have changed the statements as follows in the Method section:

"We used 24 clinically relevant factors listed in Table 1 as potential independent risk factors in multivariable logistic regression models and estimated the odd ratios (ORs) and 95% confidence intervals (CIs)." (Page 10, line 8–10)

"We expressed the associations of the functional decline group with the no functional decline group for all outcome measures as hazard ratios (HRs) with 95% CIs by multivariable Cox proportional hazard models incorporating 30 clinically relevant risk-adjusting variables indicated in Table 1." (Page 10, line 12–15)

We also have changed the statement in the Abstract, Results, and Discussion as follows:

"The independent risk factors for functional decline included age ≥80 years (OR 2.71; 95% CI 2.09–3.51), women (OR 1.32; 95% CI 1.05–1.67), prior stroke (OR 1.67; 95% CI 1.28–2.19), dementia (OR 2.26; 95% CI 1.74–2.95), ambulatory before admission (OR 1.74; 95% CI 1.29–2.35), elevated body temperature (OR 1.91; 95% CI 1.31–2.79), New York Heart Association class III or IV on admission (OR 1.54; 95% CI 1.07–2.22), decreased albumin levels (OR 1.76; 95% CI 1.32–2.34), hyponatremia (OR 1.49; 95% CI 1.10–2.03), renal dysfunction (OR 1.55; 95% CI 1.22–1.98) after multivariable adjustment." (Page 3, line 15 to Page 4, line 4)

"After adjusting for baseline characteristics, the higher risk of the functional decline group relative to the no functional decline group remained significant (adjusted HR 1.46; 95% CI 1.24–1.71; P<0.001)." (Page 4, line 7-9)

"Among the baseline characteristics and status at hospital presentation, the following independent risk factors for functional decline during hospitalization were identified by the multivariable logistic regression analysis: age ≥80 years (OR 2.71; 95% CI 2.09–3.51), women (OR 1.32; 95% CI 1.05–1.67), prior stroke (OR 1.67; 95% CI 1.28–2.19), dementia (OR 2.26; 95% CI 1.74–2.95), ambulatory before admission (OR 1.74; 95% CI 1.29–2.35), elevated body temperature (OR 1.91; 95% CI 1.31–2.79), New York Heart Association class III or IV on admission (OR 1.54; 95% CI 1.07–2.22), decreased albumin levels (OR 1.76; 95% CI 1.32–2.34), hyponatremia (OR 1.49; 95% CI 1.10–2.03), renal dysfunction (OR 1.55; 95% CI 1.22–1.98) (Figure 2)." (Page 13, line 9–17)

"After adjusting for baseline characteristics, the higher risk of the functional decline group relative to the no functional decline group remained significant (adjusted HR, 1.46; 95%CI, 1.24–1.71; P<0.001) (Figure 3 and Table 3)." (Page 14, line 17 to Page 15, line 3)

"LVEF <40% (OR, 1.24; 95% CI, 1.00–1.52; P = 0.047) and acute coronary syndrome (OR, 1.76; 95% CI, 1.19–2.60; P = 0.005) that were not included in the risk factors for functional decline emerged as the risk factors for functional decline or in-hospital mortality (eTable 2). Meanwhile, among the risk factors for functional decline, women (OR, 1.13; 95% CI, 0.93–1.38; P = 0.22) was not included in the risk factors for functional decline or in-hospital mortality (Figure 2 and eTable 2)." (Page 16, line2–8)

“2) The independent baseline risk factors associated with functional decline included age ≥80 years, women, prior stroke, dementia, ambulatory before admission, elevated body temperature, NYHA class III or IV on admission, decreased albumin levels, hyponatremia, and renal dysfunction.” (Page16, line 15 to Page 17, line 1)

In addition, we have changed the adjusted HRs and 95% CIs of the Table 3.

4) Either way, please add baseline functional category in your Forest-style plot that immediately follows the consort type diagram on page 40.

We appreciate the comment. According to the reviewer’s suggestion, we have revised the figure.

The authors are again congratulated on an impressive study that has important implications for design of future management strategies for this high risk, vulnerable, and growing population.

Thank you so much again for your positive assessment of our manuscript.