PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prognostic Impact of Combined Non-severe Aortic Stenosis and Mitral Regurgitation on Clinical Outcomes: A Single-Center Retrospective Study
AUTHORS	Granot, Yoav; Sapir, Orly Ran; Laufer-Perl, Michal; Viskin, Dana; Banai, Shmuel; Topilsky, Yan; Havakuk, Ofer

VERSION 1 – REVIEW

REVIEWER	Lee, Seung-pyo Seoul National University Hospital, Department of Internal Medicine
REVIEW RETURNED	15-Jan-2024

GENERAL COMMENTS	This study by Granot et al. tried to describe the effect of MR in those with non-severe AS. The overall objective is clinically important and the authors have mostly done the analysis correctly. However, the manuscript have rooms for improvement, mainly in the way of writing the paper more clearly and also, analyzing their data more carefully as MR may be because of the heart failure (which is a primary outcome of the paper) itself. The specific comments are listed below. (Abstract) 1. Cut-off values of what in the second sentence? 2. Please state whether this study was a single-center or multi-center study, and also, whether this was a retrospective or prospective study. 3. How were the patients divided into and what statistical methods were used? (Introduction) 1. The overall objective/hypothesis of the study is different from the one stated in the Abstract. Moreover, it reads very vague. Please be more precise. 2. It is not clear to me whether the authors are trying to evaluate the effect of MR in the face of non-severe AS or the vice versa. Please be more specific and clear on this, rather than mixing everything into ‘multiple’ valvular heart disease. (Methods) 1. The Doppler echocardiography part is too long and also, generally not different with the contemporary guidelines. This could be significantly shortened. 2. I am not sure of the Israeli insurance system but how were heart failure hospitalization events accrued for the patients not followed at the authors’ institution? This can lead to huge bias if not properly defined in the first place.

	3. Why did the authors use CART to decide the most optimal cut-off AVA for heart failure hospitalization? Why not the ROC curve as in a majority of papers? More importantly, I would expect to see a graded impact of MR on clinical events according to a more granularized AVA, rather than just dividing the entire population into a simple cut-off of AVA 1.35. Is there any interaction between the MR grade and AVA? (Results) 1. With a median 3~3.5 years of follow-up in patients with non-severe AS, the mortality rate of 50% is exceptionally high when compared with large databases worldwide in AS (Sci Rep 2017;7(1):14723, J Am Coll Cardiol 2019;74(15):1851-63). How can this be explained? This should also be discussed. 2. It is not surprising that patients with more than mild MR would do worse. This would partially be explained by the possibility of having more significant functional MR (both ventricular and atrial) in this group, which is exactly explained by the higher prevalence of LV systolic dysfunction and AF in the first place. The authors are encouraged to segregate MR into primary and secondary to dissect this more carefully. 3. Another important question remains for the LV systolic dysfunction. I assume that non-severe AS was defined with the AVA but how non-severe AS was defined in those with LVEF <50% should be clearly stated and analyzed accordingly. (Discussion) 1. The first 4~5 sentences are a summary of the entire study but could be more clear. For example… 1.1. 'These patients have lower CO with worse diastolic function.' --> What is the comparator in this sentence? 1.2. 'AVA between 1.0-1.35cm² in the presence of >mild MR is associated with worse clinical outcomes even after adjusting for clinical and/or echocardiographic parameters.' --> Worse outcome when compared to those with AVA >1.35cm² in the presence of >mild MR or when compared to those with AVA between 1.0-1.35cm² in the presence of <=mild MR? 2. The third paragraph lists the existing papers that demonstrates the clinical outcome of AS patients with concomitant MR. However, the authors are strongly encouraged to summarize these papers succinctly and discuss how this is related to their own findings. 3. The authors may want to discuss their additional analysis results, following the recommendations of analyzing the data in the revision.

REVIEWER	Tomšič , Anton Leiden University
REVIEW RETURNED	24-Jan-2024

GENERAL COMMENTS	I read with great interest the study by Granot and colleagues. The authors address a very interesting topic, the combination of non-severe mVHD. The study is well written and the objective is clear. Here are my comments: 1. Do the authors have data on the aetiology of MR? Was is secondary or primary MV disease? 2. How symptomatic were this patientsn (NYHA class etc.)? There is no data on patient symptoms reported. 3. Is there data on the cause of death (cardic/non-cardiac) avaliable?

	4. The authors suggest that early intervention might help improve outcomes. However, I wonder if MR in these patients is more a sign of progressed disease and it is not clear if an intervention is justified as the risk-benefit ration might not be favourable in this cohort. Where do the authors stand on this matter? 5. The authors report a clear benefit of SAVR. Is data on surgery avaliable- was the MV addressed as well during surgery?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

(Abstract)

1. Cut-off values of what in the second sentence?

We have revised the relevant statement as follow:

"Here, we attempt to determine an aortic valve area (AVA) cut-off value associated with worse clinical outcomes in patients with combined non-severe AS and MR"

2. Please state whether this study was a single-center or multi-center study, and also, whether this was a retrospective or prospective study.

We have added this into our abstract as follow:

"Methods: Single center, retrospective analysis of consecutive patients who underwent echocardiography examination between…"

3. How were the patients divided into and what statistical methods were used?

This information is available in our Material and Methods /statistical analysis section:

"The AVA was divided into categories by means of a classification and regression model (CART) for the prediction of HF hospitalization, with a minimum of 100 cases in parent node and minimum of 50 cases in child node. The analysis selects the best predictor for splitting the data into child nodes. A P value is given for each branch."

We did not divide the cohort into a learning and validation, this is stated in our limitation section (Page 13, First paragraph)

(Introduction)

1. The overall objective/hypothesis of the study is different from the one stated in the Abstract. Moreover, it reads very vague. Please be more precise.

Thank you for this suggestion, we tried to improve our objective as shown in the introduction:

"Therefore, in this study, we chose to evaluate the presence and the impact of non-severe mVHD on patients' outcomes in a large tertiary center and seek an AVA cutoff value associated with worse clinical outcomes"

2. It is not clear to me whether the authors are trying to evaluate the effect of MR in the face of non-severe AS or the vice versa. Please be more specific and clear on this, rather than mixing everything into 'multiple' valvular heart disease.

Since this is a retrospective study, we can establish an association between combined non-severe aortic stenosis (AS) and mitral regurgitation (MR) with clinical outcomes. However, due to the observational nature of the design, we cannot definitively prove a causal relationship between the valvular abnormalities or their individual impact on outcomes.

While hemodynamic principles suggest potential interactions between AS and MR (e.g., AS worsens MR), our study design does not allow us to draw conclusions about causative pathways.

We have added this into our limitation paragraph (Page 13, Last paragraph):

“Third, due to the observational nature of the design, we cannot definitively prove a causal relationship between the valvular abnormalities or their individual impact on outcomes”

(Methods)

1. The Doppler echocardiography part is too long and also, generally not different with the contemporary guidelines. This could be significantly shortened.

We have edited the relevant section to make it more precise and shorter.

2. I am not sure of the Israeli insurance system but how were heart failure hospitalization events accrued for the patients not followed at the authors’ institution? This can lead to huge bias if not properly defined in the first place.

Indeed, while mortality cases were recorded regardless of the place they occurred, HF hospitalizations were available from our institution alone.

We added this into our revised manuscript (clinical data and outcome measures section):

“Hospitalization for heart failure (HF) which occurred at our medical center alone were retrieved from the electronic health record”

3. Why did the authors use CART to decide the most optimal cut-off AVA for heart failure hospitalization? Why not the ROC curve as in a majority of papers? More importantly, I would expect to see a graded impact of MR on clinical events according to a more granularized AVA, rather than just dividing the entire population into a simple cut-off of AVA 1.35. Is there any interaction between the MR grade and AVA?

The Reviewer is correct that a graded impact could be expected when looking at the interaction between AVA and MR.

Cohort studies like NEDA have the ability to divide the population into multiple graded cutoff values and only than compare each cutoff to a reference value.

As our cohort is much smaller in size, this option was not considered feasible.

There are other statistical ways to find a threshold effect (for example - Eur Heart J Cardiovasc Imaging . 2020 Jul 1;21(7):768-776. doi: 10.1093/ehjci/jez267) that are not available when using SPSS software. A classification tree allows an easy and intuitive way to divide, and thus was chosen as the preferred method here.

(Results)

1. With a median 3~3.5 years of follow-up in patients with non-severe AS, the mortality rate of 50% is exceptionally high when compared with large databases worldwide in AS (Sci Rep 2017;7(1):14723, J Am Coll Cardiol 2019;74(15):1851-63). How can this be explained? This should also be discussed.

While comparing two different cohorts can be quite difficult without the full data available, the most likely explanation to this is the advanced age of our cohort compared with other cohorts.

We have added this paragraph to our discussion section:

“Our cohort's all-cause mortality rate was higher compared to existing studies on severe [17] or moderate AS [18]. While baseline co-morbidities and the presence of MR in our cohort might contribute to this finding, the most likely explanation is the older age of our study population (80.1 vs. 77.8 years in severe AS and 74 years in moderate AS cohorts).”

2. It is not surprising that patients with more than mild MR would do worse. This would partially be explained by the possibility of having more significant functional MR (both ventricular and atrial) in this group, which is exactly explained by the higher prevalence of LV systolic dysfunction and AF in the first place. The authors are encouraged to segregate MR into primary and secondary to dissect this more carefully.

The Reviewer raises an important point. Unfortunately, Data regarding the etiology of MR are available in 59% (299 patients); in whom 22 had secondary and 277 had primary MR. Nevertheless, the combined outcome of all-cause mortality and/or HF hospitalization was similar between these 2 groups (i.e. 72.7% versus 71.5%, P=0.901).
We have added these data to our Results section (under 'patient clinical characteristics'):
"The study cohort included 2933 patients with non-severe AS. Of whom, 2427 had ≤mild MR and 506 >mild MR. Data regarding the etiology of > mild MR were available in 59% (299 patients), in whom 22 had secondary and 277 had primary MR."
Furthermore, as the Reviewer mentions, distinct clinical and hemodynamic features were indeed found in patients with more than mild MR, including rate of AF and lower ejection fraction.
These differences, however, were taken into consideration in our Cox regression model that adjusted for clinical (adjusted for Age, Sex, Atrial fibrillation, chronic renal failure Hypertension, Ischemic heart disease, COPD) and/or echocardiographic parameters (adjusted for Ejection fraction, Left ventricle end diastolic diameter, Left ventricle end systolic diameter, Aortic valve regurgitation grade, right ventricle size, right ventricle function). This information is available both in the statistical analysis section (Page 7, two last paragraphs) and under Table 4

3. Another important question remains for the LV systolic dysfunction. I assume that non-severe AS was defined with the AVA but how non-severe AS was defined in those with LVEF <50% should be clearly stated and analyzed accordingly.

We included in our study only patients with a valve area of >1cm^2, thus excluding both classical and paradoxical LFLG aortic stenosis.
However, discrepancies do exist between the European guidelines (which may reclassify these patients into the moderate AS category) and the American guideline which may allow intervention in this population:
J Am Coll Cardiol. 2023 Aug 22;82(8):721-734

Accordingly, we have added this sentence into our material and methods / Doppler echocardiography section (Page 5):
"Severe AS was defined as a peak velocity >4m/s, mean gradient >40mmHg or estimated AVA<1cm2. Both classical low flow-low gradient and paradoxical low-flow low gradient aortic stenosis were not included in the current study."
(Discussion)
1. The first 4~5 sentences are a summary of the entire study but could be more clear. For example…
1.1. 'These patients have lower CO with worse diastolic function.' --> What is the comparator in this sentence?
1.2. 'AVA between 1.0-1.35cm² in the presence of >mild MR is associated with worse clinical outcomes even after adjusting for clinical and/or echocardiographic parameters.' --> Worse

outcome when compared to those with AVA >1.35cm² in the presence of >mild MR or when compared to those with AVA between 1.0-1.35cm² in the presence of <=mild MR?

We have revised the first segment as follows (Discussion section, first paragraph):
"This study investigated the clinical outcomes of patients with combined non-severe aortic stenosis (AS) and low-grade mitral regurgitation (MR). We found two key findings:
- Patients with combined non-severe AS and low-grade MR had lower cardiac output and impaired diastolic function compared to those without these conditions.
- AVA between 1.0-1.35 cm² in the presence of more than mild MR was associated with worse clinical outcomes, even after accounting for other relevant factors. Conversely, patients with an AVA greater than 1.35 cm² had clinical outcomes comparable to those without AS, regardless of the degree of non-severe MR."

2. The third paragraph lists the existing papers that demonstrates the clinical outcome of AS patients with concomitant MR. However, the authors are strongly encouraged to summarize these papers succinctly and discuss how this is related to their own findings.

We have revised the first segment as follows (Discussion section, page 11, third paragraph):
"While previous studies demonstrated increased mortality risk in moderate AS compared to no or mild AS [10-12], the impact of combined non-severe AS and low-grade MR remained less explored. Similar to our finding, smaller studies found predictors of poor outcome in this population, including ≥moderate MR, as well as lower range AVA [13] or stage 2 cardiac structural abnormalities such as either LA enlargement or >mild MR (only 9 patients in total) [14-15]. Notably, Benfari et al. [16] showed that in patients with trans-aortic velocity>2.5m/s and AVA>1cm2, an MR ERO area >0.1cm² was associated with a higher rates of HF hospitalizations or death. Our study adds to this evidence by highlighting the specific association between AVA size and clinical outcomes in the context of non-severe AS and low-grade MR."

3. The authors may want to discuss their additional analysis results, following the recommendations of analyzing the data in the revision.

We hope our prior responses and modifications address your suggestions appropriately and enhance the manuscript to your satisfaction.

Reviewer: 2
Dr. Anton Tomšič , Leiden University
Comments to the Author:
I read with great interest the study by Granot and colleagues. The authors address a very interesting topic, the combination of non-severe mVHD. The study is well written and the objective is clear. Here are my comments:
1. Do the authors have data on the aetiology of MR? Was is secondary or primary MV disease?

The Reviewer raises an important point. Unfortunately, Data regarding the etiology of MR are available in 59% (299 patients); in whom 22 had secondary and 277 had primary MR. Nevertheless, the combined outcome of all-cause mortality and/or HF hospitalization was similar between these 2 groups (i.e. 72.7% versus 71.5%, P=0.901).
We have added these data to our Results section (under 'patient clinical characteristics'):
"The study cohort included 2933 patients with non-severe AS. Of whom, 2427 had ≤mild MR and 506 >mild MR. Data regarding the etiology of > mild MR were available in 59% (299 patients), in whom 22 had secondary and 277 had primary MR."

2. How symptomatic were this patientsn (NYHA class etc.)? There is no data on patient symptoms reported.

Unfortunately, clinical symptoms are not available in our database.

3. Is there data on the cause of death (cardic/non-cardiac) avaliable?

While mortality is recorded regardless of the place that is occurred, information about the cause of death is not currently available.

4. The authors suggest that early intervention might help improve outcomes. However, I wonder if MR in these patients is more a sign of progressed disease and it is not clear if an intervention is justified as the risk-benefit ration might not be favourable in this cohort. Where do the authors stand on this matter?

Since this is a retrospective study, we can establish an association between combined non-severe aortic stenosis (AS) and mitral regurgitation (MR) with clinical outcomes. However, due to the observational nature of the design, we cannot definitively prove a causal relationship between the valvular abnormalities or their individual impact on outcomes.
While hemodynamic principles suggest potential interactions between AS and MR (e.g., AS worsening MR), our study design doesn't allow us to draw conclusions about causative pathways.
It remains to be seen and investigated whether early intervention could improve these patients' clinical outcome.
We have revised our last paragraph in the discussion section to better reflect this notion:
“Our study suggests that combined non-severe aortic stenosis (AS) and low-grade mitral regurgitation (MR) may be associated with worse clinical outcomes, particularly when the aortic valve area (AVA) falls below 1.35 cm^2. This finding highlights the need for further investigation into the potential benefits of early intervention for these patients. Future studies could explore whether early intervention strategies, such as valve replacement or repair, can improve patients outcomes in this specific population.”

5. The authors report a clear benefit of SAVR. Is data on surgery avaliable- was the MV addressed as well during surgery?

Ten patients with combined >mild MR and an AVA<1.35cm^2 underwent an aortic valve intervention. Of whom, only one patients underwent also a mitral valve intervention.
We have added this information to our manuscript (Results section, Page 11, first paragraph)
The effect of surgical AV replacement in patients with >mild MR and AVA≤1.35cm^2 (n=10, one patient with concomitant mitral valve intervention) on outcomes is presented in tables S2,S3 and figure S2.

We would like to thank again the Editors and the Reviewers for their time and effort and we hope our revised manuscript will be suitable for publication.

VERSION 2 – REVIEW

REVIEWER	Lee, Seung-pyo Seoul National University Hospital, Department of Internal Medicine
REVIEW RETURNED	08-Mar-2024

GENERAL COMMENTS	The paper has been clarified much better than the previous version. I have no further comments.

REVIEWER	Tomšič , Anton Leiden University
REVIEW RETURNED	04-Mar-2024

GENERAL COMMENTS	I have no further comments.