PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prognostic Impact of Moderate or Severe Mitral Regurgitation (MR) Irrespective of Concomitant Comorbidities. A retrospective matched cohort study.
AUTHORS	Prakash, Roshan; Horsfall, Matthew; Markwick, Andrew; Pumar, Marsus; Lee, Leong; Sinhal, Ajay; Joseph, Majo; Chew, Derek

VERSION 1 - REVIEW

REVIEWER	Michele De Bonis San Raffaele Scientific Institute, Milan, Italy
REVIEW RETURNED	07-Apr-2014

GENERAL COMMENTS	The purpose of this study is very interesting and timely. The Authors tried to define the independent impact of mitral regurgitation on prognosis in a real world population of patients undergoing echocardiography, after accounting for age and comorbidities. Indeed, considering the current possibility of percutaneous treatment of mitral regurgitation, it would be particularly important to differentiate the patients who would benefit from the new emerging technologies from those in whom they would be futile or of limited value. The Authors'conclusions were that, in this study population, significant (3+ or 4+) MR in patients with multiple comorbidities increases death and heart failure re-hospitalization rate and reduces estimated median survival. This independent negative impact of MR, however, appears to diminish with increasing comorbidities, advanced age and left ventricular dysfunction which may play a more significant role in terms of patients outcome than MR itself. The paper is well written but there are many limitations which have been acknowledged by the Authors only in part. In the opinion of this reviewer, the main weakness of this retrospective and observational study is represented by the fact that both patients with organic and secondary MR were included. Although an interaction analysis was performed to evaluate the differing hazard ratios on survival associated with those two etiologies of MR, it is well known that degenerative and secondary mitral regurgitation are two completely different entities in terms of mechanisms, prognosis, surgical indications and outcomes. Even the severity of MR is defined somehow differently considering that the recent 2012 European guidelines on valvular heart disease recommend a cut-off EROA of 0.4 cm2 to define severe degenerative MR and 0.2 cm2 as threshold for severe secondary MR. In this study 0,4 cm2 was used for both groups. By considering together those two completely different types of MR, a major bias has been introduced, particularly in the context of a retrospective analysis with no propensity score or other modality of matching able to minimize the baseline heterogeneity of the two groups of patients.

	Indeed patients with and without significant MR were still significantly different in terms of many preoperative characteristics including atrial fibrillation, previous CABG, CHF history, LV dimensions and SPAP. Despite the strong statistical efforts, it is difficult to image that those baseline data had no impact on the different outcomes registered. In addition, according to the data reported in the manuscript, not all of those variables have been tested in the statistical model. Rather than trying to correct this major limitation by using sophisticated statistical method, the study should be re-designed or the population re-analysed in order to consider separately degenerative and secondary MR. In each etiology group two propensity matched subgroups (with and without significant MR) with minimal/no baseline differences should be obtained and then compared. In conclusion the aim of the study was ambitious and timely but the method used is not convincing and the risk is that the results obtained are very much influenced by the suboptimal study design.

REVIEWER	Govanni Benfari Section of Cardiology, University of Verona, Italy
REVIEW RETURNED	17-Apr-2014

GENERAL COMMENTS	The outcome of patients with mitral regurgitation in a real world clinical setting is undoubtedly an issue of great clinical interest. In this paper by R. Prakas et al. three tertile of patients with different level ventricular function and both cardiac and non-cardiac comorbidities are suitably taken into account. I only want to raise some aspects of this intriguing topic: 1) First of all, patients with mitral regurgitation of different ethiology are contemplated together. It is well known that severity threshold is significantly different among functional mitral regurgitation or mitral regurgitation due to other ethology. It may be interesting to analyse separately these two populations. 2) Mitral regurgitation severity is assessed with both semi-quantitative and quantitative methods. It is useful to know the proportion of patients in which the quantification of mitral regurgitation was feasible. This aspect is especially important in functional mitral regurgitation. 3) Another aspect that must be underlined is that ejection fraction alone has a relatively low sensibility to reveal initial systolic dysfunction. Indeed patients with functional mitral regurgitation frequently present a subclinical ventricular dysfunction. Authors can only partially dichotomize the prognostic value of mitral regurgitation respect to the ventricular function. More accurate technique such as tissue Doppler or strain rate can give more information in this context. Nonetheless authors have appropriately reclassified ejection fraction <60% as representing mild left ventricular impairment. 4) In order to better understand which variables are included in the multivariable models I would propose to list Table 3 models clearly separated.

REVIEWER	Jeevanantham Rajeswaran Cleveland Clinic, Cleveland, Ohio, USA
REVIEW RETURNED	08-May-2014

GENERAL COMMENTS	Statistical Review: 1. Need a 'consort like' diagram to better illustrate the inclusion/exclusion criteria in the study cohort 2. Clearly define the time zero for your time related event analyses 3. What was the goodness of follow-up? Any lost to follow-up? What is the total patient years available for time to event analysis? 4. In the Cox PH models, has proportional hazard assumption been met? 5. For the sub group analysis, how was the age cut off of 75 year chosen? That is, what are the criteria for the cut-off point? 6. In multivariable model for death (table 3), • What are other variables you considered in step wise selection? • Why the GFR cutoff at 30? Better to use GFR as a continuous variable, instead of using a dichotomized variable. • Are previous ACS and previous CAD are two different variables? If yes, why there is no previous CAD as a main effect in the model, along with your interaction? There is no descriptive for these variable in Table 1 • I assume Charlson index 1 and 2 are binary variables, if that is the case, what is the reference value for this variable in this model. Is it 0, or something else? In other word, what are the possible values for this index in your study cohort? • How was the missing values were handled in your multivariable model? 7. Re-hospitalization and death are time-related events, Odds ratio is not the appropriate statistics. You could have run a simple univariate cox PH (permitting proportional hazard) models for each of the outcome and reported the HR in Table 2. Odds ratios for in-hospital and short-term events are ok. 8. During the follow-up period, patients with significant MR may have undergone a MV procedure? How was this handled in your time to event models? 9. How were the repeated re-hospitalizations handled in Table 2? 10. Figure 1 and Figure 2: • is it No MR or (no or mild) MR? • Figures need confidence intervals or confidence bars at some selected time points • X axis, better change it to months or years

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name Michele De Bonis
Institution and Country San Raffaele Scientific Institute, Milan, Italy
Please state any competing interests or state 'None declared': None declared

The purpose of this study is very interesting and timely. The Authors tried to define the independent impact of mitral regurgitation on prognosis in a real world population of patients undergoing echocardiography, after accounting for age and comorbidities. Indeed, considering the current possibility of percutaneous treatment of mitral regurgitation, it would be particularly important to differentiate the patients who would benefit from the new emerging technologies from those in whom they would be futile or of limited value. The Authors'conclusions were that, in this study population, significant (3+ or 4+) MR in patients with multiple comorbidities increases death and heart failure re-hospitalization rate and reduces estimated median survival. This independent negative impact of MR, however, appears to diminish with increasing comorbidities, advanced age and left ventricular dysfunction which may play a more significant role in terms of patients outcome than MR itself.
The paper is well written but there are many limitations which have been acknowledged by the Authors only in part.
In the opinion of this reviewer, the main weakness of this retrospective and observational study is represented by the fact that both patients with organic and secondary MR were included. Although an interaction analysis was performed to evaluate the differing hazard ratios on survival associated with those two etiologies of MR, it is well known that degenerative and secondary mitral regurgitation are two completely different entities in terms of mechanisms, prognosis, surgical indications and outcomes. Even the severity of MR is defined somehow differently considering that the recent 2012 European guidelines on valvular heart disease recommend a cut-off EROA of 0.4 cm2 to define severe degenerative MR and 0.2 cm2 as threshold for severe secondary MR. In this study 0,4 cm2 was used for both groups. By considering together those two completely different types of MR, a major bias has been introduced, particularly in the context of a retrospective analysis with no propensity score or other modality of matching able to minimize the baseline heterogeneity of the two groups of patients. Indeed patients with and without significant MR were still significantly different in terms of many preoperative characteristics including atrial fibrillation, previous CABG, CHF history, LV dimensions and SPAP. Despite the strong statistical efforts, it is difficult to image that those baseline data had no impact on the different outcomes registered. In addition, according to the data reported in the manuscript, not all of those variables have been tested in the statistical model.
Rather than trying to correct this major limitation by using sophisticated statistical method, the study should be re-designed or the population re-analysed in order to consider separately degenerative and secondary MR. In each etiology group two propensity matched subgroups (with and without significant MR) with minimal/no baseline differences should be obtained and then compared. In conclusion the aim of the study was ambitious and timely but the method used is not convincing and the risk is that the results obtained are very much influenced by the suboptimal study design.

Authors response to Reviewer 1 : Dr Michele De Bonis
The authors would like to thank Dr Bonis for his review and invaluable comments.

Point 1 :
The point raised about the inclusion of two separate etiologies of MR into a single analysis is well taken. As pointed by Dr De Bonis, it is widely understood that both aetiologies of MR have different pathophysiologies, natural courses and treatment options. However, in the context of our study, despite the differences in age and underlying mechanisms leading to the development of mitral regurgitation, the interaction between MR and LV function remains centrally critical to understanding the potential clinical value of therapies that are specifically targeted at improving MR without direct effect on LV function. Recognizing the differing pathophysiology and clinical patient groups associated

with MR has specifically lead to the study design and analysis undertaken.

Specifically, we have:

i) ensured that all baseline characteristics (i.e LV function) have been controlled for by employing stringent matching processes.

ii) undertaken the classification of MR aetiology through independent expert echocardiographic adjudication, and

iii) It is important to for the reviewer to recognize that this is a matched design with a matched analysis. Therefore, the analysis of survival is constrained to the case and the control in each matched pair. Unlike non-conditional, non-matched approaches, this regression analysis ensures that patients with MR are specifically compared with their matched control (matched on those well recognised critical factors such as age, gender, and LV function). Please recognize that using the conditional model design, patients with functional MR who are older and have worse LV function cannot be compared with younger controls, which were selected to match with degenerative MR patients. Hence, survival of degenerative MR patients are compared with their age/gender/LV function matched controls only, and the same applies to the functional MR estimates. As a consequence, the differences in patient groups are directly addressed in the study design. Effectively, for each case and control, differences in survival are estimated within each pair, allowing summation of the effect on mortality and clinical events by aetiology of MR and overall.

iv) Further, performed an interaction analysis seeking to evaluate a differing hazard ratio associated with the degenerative or functional aetiology of MR on survival. No statistical interaction was observed within our analysis and therefore the overall analysis provides the most robust estimate of effect. Hence, the hazard ratio estimate applies to both degenerative and functional MR, and while the onset of severe MR varies between the two groups, the impact is similar and differing absolute impact on outcome dependent on age of onset and the presence of other co-morbidities as expressed in the model.

Point 2:
Dr De Bonis highlighted the point about the difference in preoperative characteristics between the patients' with and without MR. Apart from previous CABG, the other baseline characteristics that remain significantly different are history of AF, heart failure and echocardiographic parameters such as LV dimensions, pulmonary artery pressures. The latter differences are a reflection of the disease process observed in an individual with significant MR and are an expected observation in such populations. The authors believe that an analysis comparing patients with and without significant MR will often encounter these baseline differences. As such, it is highly implausible to isolate a population of patient with significant MR without those baseline characteristics. We accounted for this baseline differences during our statistical modelling and demonstrated that these differences (AF, heart failure, echo parameters) independently did not influence the major outcomes.

Point 3 :
Given the relative moderate sized population studied, reanalysing the population by separating the aetiologies of MR will only serve to reduce the respective patient populations further and as such will render the analysis less robust and generalizable. The authors chose to study MR in its totality whilst understanding the inherent differences of each aetiology of MR and as such employing rigorous statistical methods to correct for these differences. We again reiterate that using specifically-matched study design and matched-analysis methodology, together with the finding of no significant interaction between the type of MR and the hazard ratio for mortality provides a robust estimate of hazard ratio

for MR. Including both aetiologies in the study matched study design and assessing the interaction between aetiology and outcome in the context of patients with multiple comorbidities is important, as current emerging therapies for MR are including both aetiologies of MR. The results observed from our study may assist in designing future clinical trials evaluating emerging MR corrective technologies in highly comorbid patients.

Reviewer:2
Reviewer Name Govanni Benfari
Institution and Country Section of Cardiology, University of Verona, Italy

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

The outcome of patients with mitral regurgitation in a real world clinical setting is undoubtedly an issue of great clinical interest. In this paper by R. Prakas et al. three tertile of patients with different level ventricular function and both cardiac and non-cardiac comorbidities are suitably taken into account.
I only want to raise some aspects of this intriguing topic:

1) First of all, patients with mitral regurgitation of different ethiology are contemplated together. It is well known that severity threshold is significantly different among functional mitral regurgitation or mitral regurgitation due to other ethology.
It may be interesting to analyse separately these two populations.

2) Mitral regurgitation severity is assessed with both semi-quantitative and quantitative methods. It is useful to know the proportion of patients in which the quantification of mitral regurgitation was feasible. This aspect is especially important in functional mitral regurgitation.

3) Another aspect that must be underlined is that ejection fraction alone has a relatively low sensibility to reveal initial systolic dysfunction. Indeed patients with functional mitral regurgitation frequently present a subclinical ventricular dysfunction. Authors can only partially dichotomize the prognostic value of mitral regurgitation respect to the ventricular function. More accurate technique such as tissue Doppler or strain rate can give more information in this context. Nonetheless authors have appropriately reclassified ejection fraction <60% as representing mild left ventricular impairment.

4) In order to better understand which variables are included in the multivariable models I would propose to list Table 3 models clearly separated.

Authors response to reviewer 2: Dr Govanni Benfari.
The authors would like to thank Dr Benfari for his review and invaluable comments.

Point 1 : Dr Benfari raised an issue about combining both aetiologies of MR into a single analysis. The authors understand the issue raised and recognize the differences in natural history, treatment and outcomes for each aetiologies of MR. For this, we have undertaken an interaction analysis seeking to evaluate a differing hazard ratio associated with the degenerative or functional aetiology of MR on survival. No statistical interaction was observed within our analysis and therefore the overall analysis provides the most robust estimate of effect.

Point 2 : The quantification of MR by quantitative methods were feasible in 83.5% of the population studied. The remaining patients had severe MR confirmed by semi-quantitative methods.

Point 3 : We agree that latest echocardiographic techniques have improved the sensitivity of detecting mild degrees of LV dysfunction, often before a mild reduction of ejection fraction. In the present analysis, we did not employ these novel echocardiographic techniques and only utilized ejection fraction as a measure for LV function.

Reviewer: 3
Reviewer Name Jeevanantham Rajeswaran
Institution and Country Cleveland Clinic, Cleveland, Ohio, USA
Please state any competing interests or state 'None declared': None

Statistical Review:

1. Need a 'consort like' diagram to better illustrate the inclusion/exclusion criteria in the study cohort.

Authors response : We thank the reviewer for the comments. We have added a figure (Figure 1) to the manuscript to describe the acquisition of the patients and the final matched cohort.

2. Clearly define the time zero for your time related event analyses

Authors response : Time zero was the first identified echocardiogram with evidence of severe MR, this establishing the diagnosis among the patients with MR. Controls were identified as those undergoing clinically indicated echocardiography in the same temporal period. The text has been adjusted to make the clearer.

3. What was the goodness of follow-up? Any lost to follow-up? What is the total patient years available for time to event analysis?

Authors response: The follow-up of these patients was complete. Our State's data records all patients who interface with the public health system and routinely records all deaths and the time of death. All deaths are recorded with only a 3-month delay. The median time for follow-up was 31 months (interquartile range: 12-45 months). The total patient time available was 13028 months. These details have been added to the manuscript and expressed in months.

4. In the Cox PH models, has proportional hazard assumption been met?

Authors response : The proportional hazards assumption was met: the global test of the proportional hazards assumption was found to be non-significant. The text has been amended to reflect this 'The utility of the final model was assessed visually by plotting the Cox-Snell residuals against the Nelson-Aalen cumulative hazard. The fit of the model was found to be acceptable.

5. For the sub group analysis, how was the age cut off of 75 year chosen? That is, what are the criteria for the cut-off point?

Authors response : The age was arbitrarily chose by the authors as an age cutoff for advance age. This merely reflects a common clinically determined perception though it is accepted that the definition of advanced age is evolving.

6. In multivariable model for death (table 3),
• What are other variables you considered in step wise selection?

Authors response: We apologies for the removal of this text, that was in a previous version but removed in the interest of length. The text has now been reinstated in the statistical methods section.

• Why the GFR cutoff at 30? Better to use GFR as a continuous variable, instead of using a dichotomized variable.

Authors response: GFR cutoff of 30 is recognized to reflect severe renal impairment (GFR<30). The relationship between GFR and outcome is curvilinear and otherwise requires transformation limiting its interpretation. Modeling GFR as a continuous variable or a dichotomous variable does not impact the estimated hazard ratio or MR substantially.

• Are previous ACS and previous CAD are two different variables? If yes, why there is no previous CAD as a main effect in the model, along with your interaction? There is no descriptive for these variable in Table 1

Authors response : Previous CAD included previous ACS as well as patients with the recorded history of stable angina, prior PCI and prior CABG. We assessed these components in the model and found these “non-ACS) components to not have a significant influence on mortality (after accounting for LV function, and therefore they were removed.

Point 8 :
• I assume Charlson index 1 and 2 are binary variables, if that is the case, what is the reference value for this variable in this model. Is it 0, or something else? In other word, what are the possible values for this index in your study cohort?

Authors response : Charlson index reference is 0, with the 1 and 2 modeled as indicator variables. i.e. Charlson score 1 model {Prof, was the something more to be added to this example ?}

• How was the missing values were handled in your multivariable model?

Authors response : By the nature of our data collection, there were no missing variables since matching required the echocardiographic data and initial clinical data to be available. However, we recognize that relying on clinical data does represent the risk of non-identification of clinical characteristics (e.g. the non-identification of a prior ACS event). Such lack of identification of prior events is inherent to all clinical studies and presents a bias towards the null. Nevertheless, we had access to data extending back 20 years to enable the identification of such events enabling this risk to be minimized.

7. Re-hospitalization and death are time-related events, Odds ratio is not the appropriate statistics. You could have run a simple univariate cox PH (permitting proportional hazard) models for each of the outcome and reported the HR in Table 2. Odds ratios for in-hospital and short-term events are ok.

Authors response : We had attempted to provide an estimate of the relative increase in events “by” a certain timepoint but agree the odds ratio is unhelpful and suspect the univariate estimates of the hazard ratios may also present a more biased estimates of relative association. Hence we have removed the odds ratio and will relay on the adjusted survival model.

8. During the follow-up period, patients with significant MR may have undergone a MV procedure?

How was this handled in your time to event models?

Authors response : We thank the reviewer for the comments. Very few of the patients (9) underwent mitral valve surgery during the follow-up period. Nevertheless we modeled surgery as a time varying co-variate, and predictably, this was not significant and did not impact the estimate of hazard ratio for MR and as a consequence, we have omitted it.

9. How were the repeated re-hospitalizations handled in Table 2?

Authors response : Re-hospitalisation was handled as the time to first event, with subsequent admissions not considered in the survival analysis. The frequency of events was captured as the number of admissions a function of the duration of follow-up.

10. Figure 1 and Figure 2:
• is it No MR or (no or mild) MR?

Authors response : These figures represent no or mild MR: The legends have been changed to improve clarity

• Figures need confidence intervals or confidence bars at some selected time points

Authors response : The confidence intervals have been provided in the graphics.

• X axis, better change it to months or years

Authors response : The x-axis of the graphs have been changed to months.

VERSION 2 – REVIEW

REVIEWER	Michele De Bonis Department of Cardiac Surgery San Raffaele University Hospital Milan, Italy
REVIEW RETURNED	27-Jun-2014

GENERAL COMMENTS	Comment to the following Authors' reply: point 2) Dr De Bonis highlighted the point about the difference in preoperative characteristics between the patients' with and without MR. Apart from previous CABG, the other baseline characteristics that remain significantly different are history of AF, heart failure and echocardiographic parameters such as LV dimensions, pulmonary artery pressures. The latter differences are a reflection of the disease process observed in an individual with significant MR and are an expected observation in such populations. The authors believe that an analysis comparing patients with and without significant MR will often encounter these baseline differences. As such, it is highly implausible to isolate a population of patient with significant MR without those baseline characteristics. We accounted for this baseline differences during our statistical modelling and demonstrated that these differences (AF, heart failure, echo parameters) independently did not influence the major outcomes.

	Coment by De Bonis: The Authors agree on the fact that in their study history of AF, heart failure and echocardiographic parameters such as LV dimensions, pulmonary artery pressures are different at baseline in patients with and without significant MR. They believe that an analysis comparing patients with and without significant MR will often encounter these baseline differences. This reviewer agree with this consideration although in centers performing early mitral valve repair the vast majority of the patients with severe MR is undergoing surgery before the occurrence of LV dilatation/dysfunction, pulmonary hypertension, AF or symptoms. In those centers, therefore, it is very common to see patients still without any MR induced clinical or echocardiographic abnormality.

REVIEWER	Giovanni Benfari University of Verona, Department of Medicine, Section of Cardiology.
REVIEW RETURNED	25-Jun-2014

GENERAL COMMENTS	The present paper is valid and well written. I agree that more and more the relevance of mitral regurgitation requires to be evaluated in the context of cardiac and extra cardiac comorbidities. Dr. Prakash et al. demonstrate that mitral regurgitation of different etiologies leads to worse outcome in real world patients and that its prognostic impact diminishes with the increasing of comorbidities. This is an interesting and up to date topic, that worth to be highlighted especially in the context of novel percutaneous mitral regurgitation corrective technologies. Elderly patients and complex clinical settings will particularly need this comprehensive approach to define the most appropriate therapeutic management. In addition the study supports the idea that mitral regurgitation has a considerable prognostic value independently of left ventricular ejection fraction tertile. This is another issue of great clinical interest especially in the field of functional mitral regurgitation. Specifically designed trials and very sensible echocardiographic assessment may help to confirm the relative prognostic value of these two variables. I have previously raised the issues I thought to be important. The authors have dealt with these in a quite satisfactory way, even if they cannot fully resolve them. The paper analyze an interesting and up to date topic, that worth to be highlighted.

REVIEWER	Dr. Jeevanantham Rajeswaran Cleveland Clinic, Cleveland, Ohio, USA
REVIEW RETURNED	25-Jun-2014

- The reviewer completed the checklist but made no further comments.