Author's response to reviews

Title: High prevalence of lack of knowledge of symptoms of acute myocardial infarction in Pakistan and its contribution to delayed presentation to the hospital

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Author's response to reviews: see over
Response to Reviewers

We thank both reviewers for their in-depth review of our manuscript. Their comments have certainly helped improve our manuscript.

A point-by-point response is listed below to each of the reviewer’s comments. Changes made in the manuscript.

Reviewer 1 – Sharon McKinley

Thank you for your encouraging remarks.

1. Should the sentences on p 6-7 re recruitment read “Every patient admitted to the hospital with a first AMI and surviving the initial 24 hours was screened for eligibility for the study. Eligible patients were approached by a trained medical research officer to seek informed consent, and enrolled in the study after obtaining informed consent.” The present description of enrollment does not make sense.

Thank you for the suggestion. The sentence has been revised accordingly. This has been mention on page 6 Para 2 line 2

2. The response rate was exceptionally high at 100% of patients approached. Was there any ethics committee of other institutional review process carried out to independently assess the procedure by which patients were approached and informed consent sought? Was there an approved written or verbal patient information statement that patients received before being asked to give informed consent?

High response rates are not unusual in our part of the world as can be seen from our previous experience [Husain, N, Psychol Med, 2000. 30(2): p. 395-402] & [Ismail, J. Heart, 2004. 90(3): p. 259-63]. Ethical approval of the study from the Ethical Review Committee of the Aga Khan University was sought as well as permission from the concerned hospital was taken. Informed consent form was read out clearly to the participant then verbal or written consent was requested and obtained. This has been mention on page 6 Para 2 line 1

3. What was the content of the interview that the patients participated in? Some of this is suggested in the results section and the tables and figures, but it is not clear if patients were presented with a list of possible reasons for delay or asked an open-ended question, or whether the few number of symptoms of heart attack that are reported were the only ones that patients were asked about. This last point is important as the authors’ main inference from the results they report is that knowledge of heart attack symptoms needs to be improved to decrease delay times, yet the number of symptoms they appear to have asked patients about is quite limited (i.e. no arm, shoulder or jaw pain/discomfort, no nausea, no sweating, no shortness of breath, no fatigue). The significance of some of these symptoms has become more evident since 2003 when data were collected for the study reported in the
manuscript. However there appear to be limitations to what the patients were asked to respond to as symptoms and reasons for delayed hospital presentation. If so these limitations need to be more fully acknowledged in the discussion of the results.

The main theme of the interview include information about socio demographic characteristics, Characteristic of AMI, Timing such as onset of pain, time of seeking first medical help and Possible factors lead to delay. This has been mentioned on page 8 Para 1 line and Para 2 line 1.

Regarding reasons for delay, subjects who sought medical care after six hours were questioned in open-ended fashion about possible reasons for the delay in seeking medical attention. This has been mention on page 9 Para 1 line 3.

An open ended question was asked about knowledge of symptom of heart attack from the study subjects. The purpose of an open-ended question was to assess unassisted recall. Possible symptoms of heart attack that were mentioned by patients were tabulated and four cardiac symptoms identified by the study group were chest pain, palpitations, shortness of breath and “ghabrahah” (uneasiness). The other symptoms mentioned were clearly not cardiac and the majority (81%) were unable to describe any symptom. Patients were NOT asked about specific symptoms. It is possible that some patients would identify more symptoms if recall was assisted, for example, by cues. This clarification has been added to the methods section and the limitation has been added to the discussion section. Our data is not inconsistent with previous work in which subjects have little knowledge of the symptoms of myocardial infarction beyond chest pain [Jafary, F.H., BMC Public Health, 2005. 5: p. 124]. This has been mention on page 8 Para 2 line 10.

4. The authors state in the methods that a p value of <0.05 was considered statistically significant in the analyses, yet they report (correctly) 95% confidence intervals for the ORs in the results (not p values). There should be consistency on the parameters stated for inferring statistical significance. More importantly, how do the authors justify their inferential statements in several places – the abstract, page 10, page 11, page 13, page 16 – about an interaction between higher education levels and tobacco smoking on delay times when this does not meet their a priori level of statistical significance, and has a tenuous logical link for which no other empirical support is offered.

Thank you for the suggestion. We agree and have introduced p values for the respective odds ratios in the table 2 page 28.

We agree that the proposed interaction was not specified a priori and the manuscript has been modified to reflect the potential nature of this interaction that warrants further study. This has been mentioned on page 14 Para 2 and line 8. Moreover, the reporting of interaction smoking and literacy has been deleted from the abstract.
5. How were continuous variables such as age and VAS pain scores categorized for the cross tabulation and regression analyses, especially pain levels which were found to be significant?

VAS was pre-defined that patients with VAS pain scores of 0-4 would be categorized as having mild pain, those from 4-7 moderate pain and those with scores of 8 more will be categorized as having severe pain moreover age was a priori categorized into younger and older categories. This has been mentioned on page 8 Para 2 and line 6.

6. Why is the sensitivity analysis not described in the statistical methods, and some of the data introduced in the discussion not reported in the results? In the discussion there needs to be reference to the body of research that shows that efforts to change knowledge do not necessarily lead to change in behaviour, particularly the REACT trial in the context of reducing delay in responding to heart attack symptoms.

Sensitivity analysis part has been added to statistical methods and result section. This has been mention on page 9 Para 2 line 9 and page 11 Para 1 line 1

We thank the reviewers for their important suggestion. A reference (number 47) to the REACT trial has been added in the final paragraph of the manuscript. This has been mention on page 17 Para 1 line 11

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct) There are quite a few English expression and presentation corrections that would be warranted if the methods issues described above are satisfactorily addressed by the authors.
Reviewer 2: Julie J. Zerwic

It is limiting that the only symptoms included were chest pain, palpitation, fidgetiness, and shortness of breath. Why were these symptoms the only ones included? How was the decision made to limit to these four symptoms? One concern is the use of fidgetiness as a symptom. Typically, fidgetiness would not be considered one of the four main symptoms of myocardial infarction. I wonder if this is a translation issue or if fidgetiness is truly the correct word. Why were only those with chest pain included? A discussion of the instrument, its reliability and validity should be included in the manuscript.

Thank you for the comment.

An open ended question was asked from patients regarding knowledge of symptom of heart attack. We wished to assess their unaided recall. Possible symptoms of heart attack that were mentioned by patients were tabulated and four cardiac symptoms identified by the study group were chest pain, palpitations, shortness of breath and “ghabrahat” (uneasiness). The other symptoms mentioned were clearly not cardiac and the majority (81%) were unable to describe any symptom. Patients were NOT asked about specific symptoms. It is possible that some patients would identify more symptoms if recall was assisted, for example, by cues. This clarification has been added to the methods section and the limitation has been added to the discussion section. This has been mentioned on page 8 Para 2 line 11

“Ghabrahat” is a unique symptom described by Indo-Asians that admittedly is poorly documented. The closest translation to this symptom is a vague sense of “uneasiness”, anxiety or feeling of doom. To clarify this further, this description has been incorporated in the methods section. This has been mentioned on page 8 Para 2 line 13

A structured questionnaire was used to collect data. Our questionnaire was not validated but different components of our questionnaire were taken from published studies. Moreover, the content validity of questionnaire items was examined by the clinical experts and peer review. The use of an unvalidated questionnaire has been acknowledged in the limitations section. This has been mentioned on page 7 Para 3 line 1

P p l

4 1 7 Citations 3,5,6 are not appropriate here because they focus on delay and not the benefits of early thrombolysis.

Thank you. Citations 3,5,6 has been deleted.

5 1 An article was published in the last year in Circulation (Moser was first author) that was a comprehensive review of the research on delay. This would be an appropriate article to cite in this section.

Moser et al’s article has been cited (reference number 14) in this section on page 4 Para 1
7 3 The discussion of independent variables is difficult to read. Perhaps a better way to organize the information would be to separate the variables into multiple sentences or give only the definitions absolutely necessary for the readers understanding.

Thank you for the comment. Discussion of independent variable has been revised on page 8 Para 1 line and par 2 line 1

7 2 How was it determined that knowing 1 out of the 4 symptoms was knowledgeable?

8 2 16 we agree that the choice of 1 out of 4 as a criterion for knowledgeable is arbitrary. Given our previous experience with knowledge in our population [Jafary, F.H., BMC Public Health, 2005. 5: p. 124] we felt that knowledge of at least one symptom was acceptable as knowledgeable, of course with caveats. WE have added the word “arbitrarily” in the text and acknowledged this limitation in the discussion. This has been mentioned on page 9 Para 1 line 2 and page 16 Para 1 line 4.

7 No information is provided about the measure used to collect the data. Was this a questionnaire that has established reliability and validity? Were the questions developed for this study? If so, how was validity established? How was delay captured? In other studies it has not been possible to identify symptom onset for all subjects because the patients (and family members) were not aware when symptoms started, therefore delay time could not be calculated. Sometimes it is possible to categorize subjects into the less than 2 hours and greater than 2 hours (for example) because an estimate of the time interval could be identified but the precise time could not. The strategies surrounding the calculation of delay must be provided to the reader. Fidgetiness is not an acknowledged symptom of MI. It is not clear if this might be an issue of translation. In addition, palpitations is not one of the most frequently experienced symptoms of MI. In contrast, diaphoresis is a common symptom and appears to be one of the symptoms that propels patients to seek treatment, but this was not apparently examined in this study. The justification of the four symptoms chosen in this study must be provided.

A structured questionnaire was used to collect data. Our questionnaire was not validated but different components of our questionnaire were taken from published studies. Moreover, the content validity of questionnaire items was examined by the clinical experts and peer review. The use of an unvalidated questionnaire has been acknowledged in the limitations section. This has been mentioned on page 7 Para 3 line 1

A paragraph has been added (on page 7 Para 2 line 6) in the methods section outlining how the time variables were calculated.

An open ended question was asked about knowledge of symptom of heart attack from the study subjects. Once again, the purpose of an open-ended question was to assess unassisted recall. Possible symptoms of heart attack that were mentioned by patients were tabulated and four cardiac symptoms identified by the study group were chest pain,
palpitations, shortness of breath and “ghabrahat” (uneasiness). The other symptoms mentioned were clearly not cardiac and the majority (81%) were unable to describe any symptom. Patients were NOT asked about specific symptoms. It is possible that some patients would identify more symptoms if recall was assisted, for example, by cues. This clarification has been added to the methods section and the limitation has been added to the discussion section. Our data is not inconsistent with previous work in which subjects have little knowledge of the symptoms of myocardial infarction beyond chest pain. This has been mentioned on page 8 Para 2 line 11

9 2 Why was 6 hours chosen as the time interval for a delayed presentation? Most studies use an earlier time interval (1 or 2 hours) based on the benefit of early reperfusion.

Although the benefits of thrombolytic therapy are maximal within the first couple of hours of presentation, we chose this time cut-off because evidence suggests that the benefits of fibrinolytic therapy dramatically decline beyond 6 hours following presentation. Our interest was to determine subjects who “miss” this therapeutic window and hence present with delay. A sensitivity analysis was performed using 2 hours as a cut-off. This has been mentioned on Page 7 Para 2 line 2

10 1 Delete reference to findings that are not significant. Also the OR of 1.7 appears in the table to correspond to a different CI.

Thank you for your comment. CI corresponding to OR of 1.66 has been corrected on page 10 Para 2 line 6.

10 2 Delete this paragraph if the interval chosen is 6 hours. Or change the interval to 2 hours but do not include both.

It was just a sensitivity analysis varying the cut points to see if we still get the same results. The other Reviewer has suggested to mention this sensitivity analysis in the analysis section and result section. This has been mention on page 9 Para 2 line 9 and page 11 Para 1 line 1

11 1 6 Delete discussion of finding that was not significant. If the authors feel this is very important then it could be included in directions for future studies. This section should be devoted to the main findings of the study.

Although by no means conclusive, our data suggests that there may be an interaction between smoking and education in that the so-called “protective” effect of literacy is washed away in the presence of smoking; those who smoke appear to present late regardless of their literacy status. As this possible interaction was not hypothesized of a priori, further study is warranted. This discussion part has been revised with same line on
Moreover, the reporting of interaction between smoking and literacy has been deleted from the abstract.

12.1 Data discussed in the manuscript should either be included in the results section or not included in the Discussion section.

Figure 2 has been added about distribution of knowledge of symptoms of heart attack.

Table 3 It is not clear how the percents are being presented. It seems like the percentages should sum across each cell. For example, illiterate smokers who delayed plus illiterate smokers who did not delay would equal 100%. However, the n=89 is listed as 36.5% and the larger n = 159 is only 33.4%.

Thanks for the comment. Percentages in Table 3 has been corrected.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

4.1-2 Limit the use of parenthetical additions, instead simply utilize the definition. Common use terms such as “door-to-needle” and “golden hour” are unnecessary in this manuscript. More relevant to describe this time interval (and use of these therapies) in Pakistan if known.

Thank you for the comments. “door-to-needle” and “golden hour” has been deleted.

6.1.7 Change “presences” to presence.

Presences has been changed to presence on page 2 Para 1 line 8.

6.2.2 The authors discuss mentally life threatening conditions. It is not clear what this means.

Actually we mean mentally retarded (defined as: a person who has both significantly low IQ and considerable problems in everyday functioning. This has been mentioned on page 2 Para 2 line 7.

7.2.3 Change “thrombolytics” to thrombolytic.

Thrombolytics has been changed to thrombolytic on page 7 Para 2 line 2.

8.1.8 Remove the word “as” after considered.

As word has been removed after considered on page 9 Para 2 line 8.
9 1 The breakdown of all of the patients who entered the ER is unnecessary. Only provide the patients that were considered for inclusion.

Unnecessary detail has been deleted

10 2 1 No need to say that the response rate was 100%.

Sentence “the response rate was 100% has been deleted

11 2 2 Need a % sign after 30.3

% sign has been added 30.3% on page 12 Para 2 line 2

12 1 Data discussed in the manuscript should either be included in the results section or not included in the

Figure has been added about distribution of knowledge of symptoms of heart attack

Discussion section.

13 1 1 The first sentence is difficult to read. Perhaps rewording would be helpful to enhance understanding and ease of reading.

14 1 1 the first sentence has been revised

14 2 12 Remove the word “be”
The word “be” has been deleted on page 12 Para 2 line 12

Figure 1 Delete. It is only necessary to describe subjects who were eligible to participate and this can be done in text

Figure 1 has been deleted

Table 1 Were all variables obtained from patient interview or were some of these variables identified from the medical record?

Couple of variables such as ECG findings, biomarkers, information about arrival of time at ER was collected from record file while other information was obtained from patient interview.

Figure 2 Where was this data presented in the Results section? This figure is not that helpful and could be eliminated.

Figure 2 has been deleted

Discretionary Revisions (which the author can choose to ignore)