Author's response to reviews

Title: 30-day mortality after acute myocardial infarction in Tuscany (Italy): An observational study using hospital discharge data

Authors:
Chiara Seghieri (chiara.seghieri@sssup.it)
Maria Pia Fantini (mariapia.fantini@unibo.it)
Stefano Mimmi (stemimmi@gmail.com)

Version: 3 Date: 3 August 2012

Author's response to reviews: see over
Dear Dr Aldcroft,

Thank you for the opportunity to submit a revised version of our paper. Below we answer, point by point, the critiques of the reviewers. Our replies are in boldface and changes to the text are tracked in word. A native English speaker and editor of Edanz Group revised the language of the paper and recommended that we change the title to ‘30-day mortality after acute myocardial infarction in Tuscany (Italy): An observational study using hospital discharge data’.

We appreciate the time and effort of the reviewers for their thoughtful feedback. We feel that the revised version of this manuscript has benefited considerably from the review process. We hope that we have addressed adequately each of the issues raised. Please feel free to contact us with any additional questions or comments.

We look forward to your final decision on this paper.

Yours sincerely,

Chiara Seghieri
We thank the reviewer for the helpful comments.

Major considerations:

The paper could be significantly enhanced if the follow is addressed / considered:

1) Significant typographical and grammatical inaccuracies. Suggest close attention to proof reading and sentence construction.

The language has been revised by a native English speaker and editor.

2) Define and be consistent with the outcome (dependent) variable – 20-day or 30-day in-hospital mortality. These are very different things.

All the data in the paper refer to 30-day mortality and we do not mention or take into consideration 20-day mortality.

3) Suggest a clinical cardiologist to help position the paper – due the authors really mean a haemodynamic lab, rather a cardiac catheterisation lab – use universal definitions.

After consulting a clinical cardiologist, we have changed the term throughout the paper to “cardiac catheterisation laboratory”, defined as a laboratory operating in a hospital with in-house cardiovascular surgical support, in which both diagnostic and therapeutic procedures are performed on the heart and great vessels for a wide variety of cardiovascular diseases [Pepine CJ, et al. ACC/AHA guidelines for cardiac catheterization and cardiac catheterization laboratories. American College of Cardiology/American Heart Association Ad Hoc Task Force on Cardiac Catheterization. Circulation 1991;84:2213-47].

In the context we describe, there were 37 hospitals, 11 of which had a cardiac catheterisation laboratory. Of these, 10 operated 24-h 7 days a week, one was a 12-h laboratory operating 12 h for 7 days a week, and had an associated 24-h laboratory about 26 km away (P.9, Ln 9-11). This is consistent with the literature describing a reperfusion network of a neighbouring area in Italy [Saia F, et al. Optimisation of therapeutic strategies for ST-segment elevation acute myocardial infarction: the impact of a territorial network on reperfusion therapy and mortality. Heart 2009;95:370-6].
4) The definition of STEMI and NSTEMI is somewhat dubious from administrative data, though this probably cannot be improved with the data available.

In the present paper we have defined STEMI and NSTEMI according to the ICD-9-CM classification, as reported in the literature [Cannon CP. Update to International Classification of Diseases, 9th Revision codes: distinguishes STEMI from NSTEMI. Crit Path. Cardiol. 2005;4:185-6] (P.7, Ln 7-9).

Effective 2007 in Italy we adopted the ICD-9 CM codes for acute myocardial infarction that distinguish non-ST elevation myocardial infarction (NSTEMI; code 410.7) from ST elevation myocardial infarction (STEMI; codes 410.1 to 410.6, 410.8). Using data from two studies conducted in Tuscany and in Italy [Buiatti E, et al. Determinants of treatment strategies and survival in acute myocardial infarction: a population-based study in the Florence district, Italy: results of the acute myocardial infarction Florence registry (AMI-Florence). Eur Heart J. 2003;24:1195-203; Perugini E, et al. Epidemiology of acute coronary syndromes in Italy [Article in Italian]. G Ital Cardiol (Rome) 2010;11:718-29], we found that the fourth digit has a high sensitivity and specificity, as reported in our manuscript (P.7, Ln 12-14).

5) Conclusion in the abstract is inaccurate – the authors have not conclusively shown that they can reliably predict mortality risk. See other work in this area – consider external validation, internal validation (test retest, n-fold cross validation and boot strapping etc).

Thank you for noticing this point. We agree and have omitted the term “reliably” from the conclusion in the abstract.

6) Suggest stratification by sex, our experience is that there are significant interactions between outcome, AMI phenotype and sex.

Although the literature shows that AMI clinical characteristics differ between genders, we tested the interaction between outcome, AMI phenotype and sex which proved to be non-significant. This is now reported in the manuscript (P.10, Ln 14-15)
7) Why did the authors exclude patients who suffered and AMI up to 8 weeks prior – this doesn’t make sense.

We excluded patients who suffered from AMI in the previous 8 weeks to exclude sequelae of a previous episode, according to the ICD-9-CM classification which defines "8 weeks" as the limit for a single "episode of care" and have added this in the Methods (P.5, Ln 20-22).

8) Why exclude patients who were discharged within 2 days of admission – again include these patients unless absolutely necessary and then justify.

We used this criterion to increase the accuracy in case definition. Voluntary discharges or discharges to home within 2 days of admission may arise from errors in recording data or diagnosis. However, no patient met this criterion in the present study.

9) Consider using the GRACE variables for case-mix adjustment – though I appreciate that these may not be available in the administrative data.

We would have considered using the GRACE variables, but unfortunately the administrative data did not include them.

10) Explanation/methods of deriving adjusted mortality rates – remember this is a methodology journal. Also why and how for mean adjusted regional mortality rate.

We have now better and more fully described in the Statistical analysis section of the Methods how adjusted mortality rates were obtained.

11) Similar as above from the modelling – what was the model fit, and how good was it. Pseudo R2, ANOVA, F test, distribution of residuals, AIC BIC and so on.

Thank you for the suggestion to report fit indexes. We have now included the Pseudo R2, Wald chi square test, AIC and BIC in Tables 3 and 4. The analysis of residuals did not reveal the presence of influential observations.
12) Derive and state crude and adjusted mortality rates by hospital with and without a haemodynamic lab. Were the same adjustments made for each data source?

Yes, the adjustment was the same for both sources. The presence of a cardiac catheterization laboratory was included as a second level variable in the multilevel logistic regression model (P.8, Ln 5-6).

13) Tabulate patient-level co-morbidity differences by the 2 hospital types, and if possible the hospital-level differences – what were the additional hospital features that may explain the increased variation in outcomes?

We have reported in Table 1 the patient level differences between the two hospital types. However, we did not have details of other hospital characteristics because they are not available in the hospital discharge record database.

14) The authors quantify the % variation in hospital related outcome – please give more detail – the model outputs

We estimated the random variance ($\sigma^2$), which is a measure of hospital variation in outcome. When $\sigma^2$ is significantly higher than 0, there is a significant inter-hospital variability. Our data (Table 3) indicate that after adjusting for case mix, the hospital variance declined from 0.12 to 0.05 (P.10, Ln 6-8).

15) Re comparable mortality rates by AMI phenotype in the UK – see some of the papers below.

In the discussion section we cited the article [Gale CP, et al. Impact of missing data on standardised mortality ratios for acute myocardial infarction: evidence from the Myocardial Ischaemia National Audit Project (MINAP) 2004-7. Heart 2011 Feb 28] in which data on the mortality rates in England are reported: in 2004-2007 the 30-day unadjusted mortality rate was 6.0% (95% CI 5.8% to 6.2%) for STEMI and 6.7% (95% CI 6.6% to 6.9%) for NSTEMI patients (P.12, Ln 8-10).
16) The authors seem to suggest that variation may be related to hospital type but also treatments – need therefore to model the treatment effects to see if the variation reduces? I accept that they may not have these data.

We agree with the reviewer. However, unfortunately, the administrative data do not include information on PTCA timing and other medical treatment.

17) The authors elect to rank the hospital by performance – when there are many other ways of representing and analysing the data. Consider exploring this further. See reference below

We acknowledge the reviewer's suggestion to compare hospital performance using the alternative method of funnel plots. We have added to the paper a specific section reporting the results and figures with the funnel plots for STEMI and non-STEMI patients (P.11, Ln 14-18).

18) Suggest not including hospitals with less than 10 submissions/patients

Using multilevel methodology, we believe it is possible to include second level units with a low case load. We have added two references that address this point (P.7, Ln 22-23).

19) Table 2 and 3. Age per ?units, round to 2 decimal points

In Tables 2 and 3 we have specified the age in years. We have now rounded the figures to 2 decimal points.

20) Not sure if Figures 2 and 3 are necessary, or add to the paper – stated in text.

We agree with your suggestion to omit the two figures and have included the results in Table 5.

21) Table of descriptives is needed.

We have now included a table of patient characteristics as Table 1.
22) Discussion implication of missing data and any methods to overcome the biases inherent

Data on hospital discharges in Tuscany region are routinely entered into the regional HDR database. The information system collects demographic information and ICD-9-CM diagnoses and procedures. Data are routinely checked through computerized procedures for quality control. If quality criteria are not fulfilled and demographic data are incomplete, records are discarded. Therefore, in the present paper the use of procedures for managing missing data was not necessary (P.5, Ln 15-17).

23) Discuss the alternative analytical approaches – survival with hierarchy – frailty, imputation, and so on.

Thank you for your suggestion. We have now added in the Discussion possible alternative approaches (P.15, Ln 4-7).

24) Please read and include references:


Thank you for mentioning these relevant publications, which we have read and cited in our paper.
We thank the reviewer for the helpful comments.

Major Compulsory Revisions:

1. Description of the study population should be presented, e.g. mean age of study population, frequency of male/female gender and comorbidities.

We have now included the characteristics of the study population as Table 1 in the paper.

2. What does 30-day all-cause in-hospital mortality mean? 30-day all-cause mortality, regardless whether the patient is discharged before 30 days or not, is widely accepted as an indicator of quality control, because it allows inter-institutional comparison, whereas in-hospital mortality reflects institutional habits concerning postoperative patient care [Osswald BR, Eur J Cardiothorac Surg 1999;15:401-407, Drye EE et al, Ann Intern Med 2012;156:19-26].

30-day in-hospital mortality indicates a death occurring during the index admission or a death occurring in the course of any subsequent admission within 30 days of AMI onset. 30-day in-hospital mortality was our outcome of interest [Osswald BR, Eur J Cardiothorac Surg 1999;15:401-407, Drye EE et al, Ann Intern Med 2012;156:19-26]; this could be performed by record linkage hospital discharge records (P.6, Ln 10-11). We are aware that this outcome underestimates all-cause mortality after AMI, but unfortunately we could not analyse out-of-hospital deaths because they can be obtained from the mortality registry database available to researchers after a time lag of several years (P.6, Ln 14-16).

3. What was the mean hospital stay? If it was shorter than 30 days how was the follow-up of patients conducted. What was the rate of completeness of follow-up?

We have reported in Table 1 the mean hospital stay. The follow-up was done through a deterministic record linkage procedure of hospital discharge records. The period of follow-up was determined as 30 days from AMI onset, as mentioned above (P.6, Ln 10-11).

4. Confidence intervals for hospitals 36 and 37 are questionable with only 1 patient for each. Estimation of mortality is considered adequate in study population with at least more than 100 persons.
Small-volume hospitals should be either excluded or grouped into 1 category [see Ref. 9 of the authors’ Reference list], e.g. exclude hospital with less than 10 patients, and group into one category hospitals with 10 to 49 patients and into another with 50 to 99 patients.

Using multilevel methodology it is possible to include second level units with a low case load (P.7, Ln 22-23). We have added 2 references to the text that addresses this point. We agree that confidence intervals for hospital 36 and 37 are questionable and have omitted them in Table 5 in the revised version of the manuscript.

5. How the adjusted 30-day mortality rate was computed? 30-day mortality between hospitals should be compared using risk-standardized mortality rates (RSMR) [see Ref. 8, 9 of the authors’ Reference list].

Adjusted 30-day mortality rates were estimated through the multilevel logistic regression, i.e. using a direct standardization method. These rates were then transformed to RSMR as described in the methods section (P.8, Ln 22-24).

6. Provide definition of regional average mortality rate.

We now provided a definition in the methods section (P.8, Ln 21-22).

7. The observed 30-day mortality was twice as high as the overall adjusted 30-day mortality rates. Discuss the difference in terms of observed and expected outcomes and O/E ratio [see Ref. 8 of the authors’ Reference list].

We have reported the O/E ratios in Table 5 and discussed the results in the Discussion (P.12, Ln 22-P.13, Ln 1).

Minor Essential Revisions:

1. Why gender was included in all models, although it was not significant in all models and in section methods a p-value of 0.05 was provided for variable selection.

Considering that there are no clinical variables, we added gender as a proxy for clinical conditions related to sex. Specifically both gender and age were included in the model, even
when they were not significant. We have now set out more clearly this point in the methods section (P.8, Ln 4-5).

2. Number of patients, age, frequency of male/female gender should be reported in the abstract as well.

We have now added information on patient characteristics in the Abstract.

3. No explanation for abbreviations given in Table 2.

We added the definitions of the abbreviations used in the Tables.

4. In Table 2 nowhere is reported that odds ratios and confidence intervals are presented.

We have now reported this information in the captions to Tables 3 and 4.
#3 – VICTORIA DELGADO

We thank the reviewer for the helpful comments.

Major Compulsory Revisions

1.-The study population is not well described: there is no mention to important determinants of prognosis such as Killip class and revascularization treatment used. The fact that the hospital has catheterization laboratory does not mean that the results per se should be better. The authors should indicate the volume of revascularizations performed in each center, the presence of cardiovascular surgical team in situ and the use of thrombolysis or primary percutaneous coronary intervention.

Unfortunately the administrative data available did not allow us to obtain all this information, but we have included a description of the characteristics of our study population in Table 1.

2.-Also, the patients should indicate how many patients were transferred to reference hospitals for rescue primary coronary interventions and correct for the door-to-balloon time.

Unfortunately information on when patients transferred to reference hospitals received PTCA and door-to-balloon time is not available from the hospital discharge records database (P.14, Ln 3-5).

3.-The authors indicate that the main outcome is 30-day in-hospital mortality. But this is a strange formulation. I guess that the mean hospital length admission is <7 days. Therefore, the authors should rephrase it.

We apologize for being unclear. We have now better specified in the text that by ’30-day’ in-hospital mortality we mean deaths occurring during the index admission or in any subsequent admission within 30 days from the AMI onset date (P.6, Ln 8-10). The mean hospital stay is now provided in Table 1.

4.-Would it be more insightful providing cardiac mortality instead of all-cause mortality?
Unfortunately administrative data do not include information on cardiac mortality. Information on death causes can be obtained from the mortality registry that is made available to researchers only after a time lag of several years as we discuss under Limitations (P. 15, Ln 1-3).

5.- The Kaplan-Meier curves are not provided.

We decided to use throughout the text 30-day mortality as a dichotomous outcome, and have now explained why we did not carry out survival analysis (P.15, Ln 4-7). However, to answer your request, we compared the Kaplan-Meier curves for STEMI (mean survival=27.2 days, 95%CI 26.9-27.5) and NSTEMI (mean survival=28.7 days, 95%CI 28.5.8-28.9) and the difference proved to be significant (log-rank test 55.48, p<0.001).

6.- Transferring from other hospital was an exclusion criterion. This is confusing since patients who were transferred may have the longest delays to revascularization and therefore the worse outcome. Later on the authors seem to include these patients in the analysis. Could the authors please clarify?

With respect to the transferred patients, we agree with the reviewer that these patients should be included, because “excluding transfers may lead to an inaccurate depiction of the quality of healthcare services in regionalized healthcare systems for the timely inter-hospital that call transfer of patients with AMI” [Kosseim M, et al. Ranking hospitals according to acute myocardial infarction mortality: should transfers be included? Med Care. 2006 Jul;44(7):664-70.].

Since we assigned the outcome responsibility to the first admission hospital (P.4, Ln 4-5), we included in the analyses patients discharged between January 1st 2009 and November 30th 2009 that, during the hospitalization, were transferred to another ward or hospital. Patients whose index admission constitutes a transfer per se were excluded.

Minor Essential Revisions

There are several typo errors.

A native English speaker has reviewed the paper.