Project Review of *Comparing the performance of Acute Coronary risk stratification tools in an urban center*

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Document version

Version	Alterations
01	Initial version

1 ABBREVIATIONS

- ACS: Acute coronary syndrome
- GRACE: The Global Registry of Acute Coronary Events
- HEART: History, Electrocardiogram, Age, Risk factors, and initial Troponin
- MI: myocardial infarction
- NSTEMI: non-ST-segment elevation myocardial infarction
- STEMI: ST-segment elevation myocardial infarction
- TIMI: Thrombolysis in myocardial infarction
- VCS: Vancouver chest pain score

2 CONTEXT

Thank you for hiring my services! Together with this Project Review you have purchased an Analysis Plan for a "simple design" which means you want the methods appropriate for a UNIVARIATE analysis. In fact, given the number of individual questions and variables involved, several analyses will be required to answer them all.

This Project Review will evaluate the information on the current draft of your Protocol with regard to both the study design and analysis methods that are available to the research question.

3 EXECUTIVE SUMMARY / CONCLUSIONS

There is one crucial parameter missing from the current draft of the Protocol: the comparator groups.

Many options are available to fill in this gap and were briefly described in this document. The approach that requires the least amount of changes is the case-control study design.

This consists in dividing participants by outcome status (eg. MI/non-MI) and comparing the risk factors associated with each outcome. This is the design that best addresses the research question.

If there is no possibility of collecting data for both outcome diagnoses (MI and non-MI), then the data collected can only be used for a descriptive study.

4 PROJECT REVIEW

4.1 Research question

From the draft:

" (…) we want to directly compare the performance of these instruments and observe any differences in patients of varying ethnicity and sex".

This question investigates the relationship between three variables:

1. the occurrence of the main outcome (MI vs non-MI)
2. the instrument scores
3. sex/ethnicity

The main outcome (1) is interpreted as the response variable of the study. The two other variables (2 and 3) are predictor variables of that outcome.

Since a univariate analysis can only be used to investigate the association between one predictor and the response, careful considerations must be made regarding how the question can be addressed under this approach.

4.2 Overview of study design

This is a retrospective study to compare the risk of MI according to four diagnostic tools: GRACE, TIMI, HEART and VCS.

This type of data can be analyzed under either a cross-sectional or a case-control study designs, both explained in further detail in future sections.

From the draft:

"Study population: We will identify all patients admitted to the medical floor, stepdown unit or medical ICU at the North Central Bronx hospital who were admitted with the diagnosis of ACS through the electronic medical record system (…)"

This selection criterion poses the following issue to the analysis: if the ACS diagnosis is a selection criterion, then there are no groups in the study.

4.3 Univariate analyses: options available

Any comparison that might be evaluated requires comparator groups to be defined that are relevant to the research question. This is a crucial parameter that is still withstanding.

In what follows we will review the options available for specifying this parameter.

4.3.1 Comparator group options

There are two main ways in which the current draft can be complemented by specifying groups: classifying the participants included across outcomes (ACS or MI) or dichotomizing into score groups (high-risk scores vs others).

In the hope of keeping this project as simple as possible, I can choose that grouping factor for you as well as the analysis method (see section 4.3.1.2 below).

4.3.1.1 Cross-sectional comparisons

This approach groups the participants into exposures and evaluates if the exposure is associated with the occurrence of the outcome.

One way of defining these exposures would be to interpret both sex and ethnicity as exposures. The response variable can then be defined as the instrument scores, and the hypothesis tested would be whether or not different sexes/races have similar average scores (eg. with a t-test or ANOVA).

This interpretation, however, suffers from the following caveat: the choice of the response variable will be limited to either the outcome status or the diagnostic instruments' scores, and the specification above leaves out the outcome. The four instruments lie between the exposure and the main outcome of MI and there are two predictor variables (the score and the stratifying variable sex/ethnicity). With two predictors a univariate method cannot be employed properly (for an alternative, see Appendix). Thus, a simplification must be done on the research question to choose the response variable: either the response will be the outcome status or the instruments' scores.

Another way of defining exposure groups is to dichotomize the participants' scores into two groups: "high risk" vs "others". After dichotomizing the scores a significance test (like the chi-square test or the Fisher test) can be used to detect an association between the score group and the outcome status. As before, this leaves out the other variable from the question: sex and ethnicity.

4.3.1.2 Case-control

This approach inverts the question and groups the participants according to whether or not they have experienced the outcome (eg., MI vs non-MI, death vs survived, etc). Starting from the outcome one can inspect whether or not the cases had different characteristics at baseline. This is a classical retrospective design, to inspect prior risk factors.

The hypothesis that would be tested under this design is that participants that had the outcome had different baseline risks than the participants that did not experience the outcome. The effect being analyzed can be defined in two ways: using the dichotomized score groups (as above) the odds ratio is used as the effect.

This method of the odds ratios can be extended to deal with two predictors: to dichotomize the scores into groups and do a contingency table between MI status and score group, stratified by the final variable (first by sex, then by ethnicity). The two odds ratios calculated can be aggregated into a single effect and interpreted. This stratified approach fully addresses the research question, without resorting to multivariate analysis (see Appendix).

Alternatively, the numeric scores can be used in a significance test (eg., a t-test). The effect would be the average score difference between MI participants differs and non-MI participants. This second approach suffers from the same limitation as the cross-sectional design: the question has too many variables for a univariate analysis.

This is the least intrusive choice in the sense that it doesn't require major changes to the Protocol. Additionally, the way the research question is phrased alludes to a case-control design type of question. For those reasons, this will be considered the default choice for this consultation.

4.3.2 General considerations

You have 4 instruments: GRACE, TIMI, HEART and VCS. To evaluate the results of those instruments, you need a counterfactual, i.e., if you want to diagnose MI you need data from both MI and non-MI.

If you want to predict future NSTEMI/STEMI diagnoses, you can collect data from past patients with a known diagnosis of both MI and non-MI status. Based on these known diagnoses you can compare the error rates of each instrument (false positives and false negatives).

Two analysis options were provided above, with other ramifications possible. A single-arm design would limit the study to a descriptive nature, but that does not address the research question. In any case, both MI and non-MI participants must be included in the data to be analyzed.

When selecting participants it is desirable that non-MI participants match (or at least are similar to) the MI participants in regards to characteristics relevant to the question (age, sex, ethnicity, etc). Matching is often hard to implement and is often substituted by including all participants in the study period. If the two groups are too different from one another, there is a risk of bias in the analysis due to unbalanced baseline characteristics.

The analysis options discussed until now allow for the comparison between the four instruments but do not tackle the performance part of the question.

4.4 On the performance of the diagnostic instruments

In order to assess the performance, a metric must be chosen as the basis for the conclusion. Two commonly used metrics that you could choose from include the sensitivity and specificity. Accuracy is a less favored metric because it suppresses an important factor: it does not inform the types of errors being produced by the tests (false positives or false negatives). Although less common, that metric could be considered as well.

After choosing one performance metric, all four instruments can be assessed, their performances can be ranked and a conclusion can be drawn from the evidence in the data.

5 OBSERVATIONS AND LIMITATIONS

N/A

6 REFERENCES

N/A

7 APPENDIX

7.1 Alternative approach: Multivariate analysis

An alternative approach is to combine the values from all instruments in the same analysis, which would be assessed with a MULTIVARIATE analysis under a slightly more complex study design. This alternative would allow you to calculate a predictive model that draws from all risk factors in the decision process. Furthermore, this approach better approximates the complexities of the research question, without resorting to concessions and simplifications.

As you can imagine this would require major changes to your protocol, but if you want to change your request to do a multivariate analysis we can discuss what changes would be required to your original plan.

This is also the only way to use all other variables that will be collected for the study enumerated in Objective 1 of the Protocol in the same (predictive) analysis.