PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Diagnostic features, management, and prognosis of Type 2 myocardial infarction compared to Type 1 myocardial infarction: A systematic review and meta-analysis.
AUTHORS	White, Kyle; Kinarivala, Mansey; Scott, Ian

VERSION 1 – REVIEW

REVIEWER	Neumann, J University Heart Center, Hamburg
REVIEW RETURNED	29-Aug-2021

GENERAL COMMENTS	In the present manuscript, the authors provide a meta-analysis of 41 cohort studies aiming to identify differences between patients with type 1 and type 2 myocardial infarction. The main findings were as follows: comorbidities like chronic kidney disease and chronic heart failure were more common in type 2 MI patients and these patients presented more often with atypical symptoms of MI. Diagnostic assessment including coronary angiography and therapeutic measures like coronary interventions and cardioprotective medication were implemented less frequently in patients with type 2 MI. All-cause mortality was higher in patients with type 2 MI, while cardiovascular in-hospital mortality was comparable in type 1 and type 2 patients which indicates that mortality in type 2 MI patients is primarily driven by an increased number of non-cardiovascular deaths. The manuscript provides a well-written overview of type 2 MI patients. Even though these characteristics have been described before in various cohorts, a meta-analysis of this size on this entity has not been published before to the knowledge of the reviewer. M specific comments are: 1. The search has been performed until December 2020. Unfortunately, since that time several new papers have been published, which describe characteristics of patients with T2MI using large study populations (e.g. 10.1093/eurheartj/ehab581, 10.1093/eurheartj/ehaa035). Importantly, these analyses were based on the 4th Universal definition of MI. Thus, the authors should update their analyses. 2. The authors report on the different troponin assays used in the cohorts, but information regarding their sensitivity is lacking. Please provide more information on whether a high-sensitivity or conventional troponin assay was used. 3. The manuscript provides insufficient data on how the

	diagnosis of type 1 and type 2 MI was determined in the individual cohorts. Was the diagnosis retrospectively collected or adjudicated by the authors? Information regarding the proportions of type 1 and type 2 MI in the individual cohorts and the ranges within all cohorts in total would be helpful as well. The possibility of misclassifications and the limited comparability of the cohorts due to different definitions of type 2 MI should be stated in the limitations section. 4. In the results section the authors show similar median age ranges of type 1 and type 2 MI patients. In the discussion part however, type 2 MI patients are described as being older than type 1 MI. I suggest adding information on basic baseline characteristics like age and sex for example in Table 1. If possible, laboratory results such as haemoglobin and glomerular filtration rate (GFR) should be presented as well, especially since renal failure is described as a more common comorbidity in type 2 MI patients. 5. The cohorts summarized here recruited patients in very different settings with different pretest-probabilities and different incidence of MI. This is important for clinical interpretation of the findings and should be highlighted in the manuscript. Furthermore, the authors should add a column to describe the specific setting of recruitment.

REVIEWER	Chapman, Andrew Royal Infirmary of Edinburgh, British Heart Foundation Center for Cardiovascular Science
REVIEW RETURNED	04-Sep-2021

GENERAL COMMENTS	White et al report findings from a systematic review and meta-analysis evaluating precipitating factors, risk factors, investigations, management and outcomes for type 1 and type 2 myocardial infarction. They included studies that adjudicated the diagnosis according to the universal definition of myocardial infarction and reported data on at least one variable of interest. They applied random-effect meta-analysis, identifying 41 relevant studies. They demonstrate important differences in patient presenting symptoms, investigations, treatments and outcomes. This large study was pre-registered on PROSPERO and reports in accordance with PRISMA guidance. The assessment of bias appears well conducted. This is an important piece of work and will be impactful but I do have some comments for the authors to consider on the reporting of findings. Overall comment: Please consider reporting of outcomes and how this might impact on readability. There are an excessive number of forest plots presented in the supplement which detracts from the overall utility of your work. I would suggest you reduce to those you consider most relevant, or those where at least 50% of studies report the outcome of interest. For example you present meta-estimates for Fatigue in Figure S20 – comprising a

	single study. There is no rationale for this. Methods: Pleas explain rationale for random effects to the reader and include a statement on ethical approval. Results: It would be helpful to give geographical context to the cohort studies included. Results: Throughout the results the authors provide a median 'range'. Perhaps pedantic but it would be correct to report the median value (interquartile range) in parenthesis. Please update for age, troponin concentration and all other relevant variables. Results: Suggest moving the second paragraph on definition of MI to a supplemental appendix. Discussion: I think you could highlight the importance of your study better in the early discussion. This is a large pre-specified systematic review and meta-analysis in an important area. You included 131,000 patients from 41 cohort studies across many countries. This should be highlighted more prominently at the outset of discussion. How could outcomes be improved? What other studies would be beneficial? You have identified a huge treatment gap, is this important, should this be addressed now? Please review the CASABLANCA study. In this study the authors followed up patients were enrolled after peripheral or coronary angiography for incident myocardial infarction events. Therefore, patients had angiography prior to their T2MI event. There are important limitations to this study, not least that only those with a high pre-test probability of coronary or peripheral artery disease were enrolled. Whilst I agree that conflicting studies limit our ability to determine the utility of coronary angiography, this paragraph requires rephrasing.

REVIEWER	biffi, annalisa Milan Bicocca University
REVIEW RETURNED	29-Sep-2021

GENERAL COMMENTS	This paper discussed an interesting topic regarding the diagnostic features, management and prognosis of Type II myocardial infarction, however the manuscript has limitations and several points, which need to be clarified. -why have you mentioned just the type II of myocardial infarction in the title? -Could you please update the search strategy investigation up to now (or have a look if there are new published studies)? -I have not understood the meaning of weighted OR -In which way have you taken into account of the publication bias? -could you list the precipitating factors in the Method

	Section? -In the discussion section, may you clinically explain because some pre existing medical conditions, medical management and invasive interventions, outcomes, clinical features of Table S7, cardiac investigation of Table S8, are more frequent in T2MI compared to the T1MI? -Is it possible to specify the timing concerning the pre existing medical conditions (when did these conditions start to affect patients?)

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. J Neumann, University Heart Center, Hamburg

Comments to the Author:
In the present manuscript, the authors provide a meta-analysis of 41 cohort studies aiming to identify differences between patients with type 1 and type 2 myocardial infarction. The main findings were as follows: comorbidities like chronic kidney disease and chronic heart failure were more common in type 2 MI patients and these patients presented more often with atypical symptoms of MI. Diagnostic assessment including coronary angiography and therapeutic measures like coronary interventions and cardioprotective medication were implemented less frequently in patients with type 2 MI. All-cause mortality was higher in patients with type 2 MI, while cardiovascular in-hospital mortality was comparable in type 1 and type 2 patients which indicates that mortality in type 2 MI patients is primarily driven by an increased number of non-cardiovascular deaths.

The manuscript provides a well-written overview of type 2 MI patients. Even though these characteristics have been described before in various cohorts, a meta-analysis of this size on this entity has not been published before to the knowledge of the reviewer. My specific comments are:

1. The search has been performed until December 2020. Unfortunately, since that time several new papers have been published, which describe characteristics of patients with T2MI using large study populations (e.g. 10.1093/eurheartj/ehab581, 10.1093/eurheartj/ehaa035). Importantly, these analyses were based on the 4th Universal definition of MI. Thus, the authors should update their analyses.
REPONSE: Due to the current COVID workload in our clinical practice, and the loss of one author (MK) to another institution, we are not able to redo the search and the subsequent data extraction, data analysis, and re-write of the manuscript. In our review almost 20% of the studies used the 4th universal definition of MI. Re-doing the search and limiting studies to only those that used the fourth definition of MI would significantly impact on the breadth and generalizability of our review, which we feel is one of its strengths. Moreover, the10.1093/eurheartj/ehab581 reference by Wereski et al is a 2021 paper yet to appear in a print version and is a study of 1331 T1MI/T2MI patients; the reference 10.1093/eurheartj/ehaa035 by Hartikainen et al is a small study of 434 T1MI/T2MI patients (probably missed in our search as neither the title nor the abstract include the terms 'type 2 MI' or a synonym). Together they comprise 1765 patients and

both report findings very similar findings to those of our review, so we feel little is to be gained from updating the review to include a small number of additional studies given the current analysis has more than 130,000 patients. However we have made mention of two more recent studies in Discussion.

2. The authors report on the different troponin assays used in the cohorts, but information regarding their sensitivity is lacking. Please provide more information on whether a high-sensitivity or conventional troponin assay was used.
RESPONSE: The supplemental material on study characteristics has been updated to include the type of troponin used. Five of the 41 studies which accounted for 47% of all patients reported using high-sensitivity troponin assays. We did not feel separate subgroup analyses according to type of assay was warranted as: 1) 14 studies (34%) did not report the specific assay used; 2) the assays vary in their performance characteristics such as limits of detection and coefficients of variation; 3) the delta values and absolute levels used to confirm MI are not reported in most studies; 4) throughout the world countries vary in the extent to which they have adopted newer high sensitivity assays; and 5) the troponin value is only one of three variables (chest pain, ECG findings) used to diagnose T2MI.

3a. The manuscript provides insufficient data on how the diagnosis of type 1 and type 2 MI was determined in the individual cohorts. Was the diagnosis retrospectively collected or adjudicated by the authors?
RESPONSE: In our review we are dependent on each study's authors for the outcome definition used and methods employed to adjudicate each outcome.
3b. Information regarding the proportions of type 1 and type 2 MI in the individual cohorts and the ranges within all cohorts in total would be helpful as well. The possibility of misclassifications and the limited comparability of the cohorts due to different definitions of type 2 MI should be stated in the limitations section.
RESPONSE: The proportions are reported in the tables provided in the manuscript and supplemental material. The different definitions are the result of the evolving definition of T2MI over time and is unavoidable in our wide-ranging review. However, we note this as a limitation in Discussion.

4. In the results section the authors show similar median age ranges of type 1 and type 2 MI patients. In the discussion part however, type 2 MI patients are described as being older than type 1 MI. I suggest adding information on basic baseline characteristics like age and sex for example in Table 1.
RESPONSE: The reviewer is correct and highlighted an error in our discussion. The age of the patients did not differ between T1MI (60-82) and T2MI (62-79). We have changed the manuscript to more accurately reflect the data.
If possible, laboratory results such as haemoglobin and glomerular filtration rate (GFR) should be presented as well, especially since renal failure is described as a more common comorbidity in type 2 MI patients.
RESPONSE: Though we agree with the value of providing hemoglobin and eGFR of the patients, unfortunately these were not reliably reported in the included studies, therefore, this information can not be included. Furthermore, the definition used for chronic kidney disease (CKD) was invariably not provided and the authors took the publications at face value. In Discussion, we have stated the inability to provide this information as a limitation.

5. The cohorts summarized here recruited patients in very different settings with different pretest-probabilities and different incidence of MI. This is important for clinical interpretation of the findings and should be highlighted in the manuscript. Furthermore, the authors should add a column to describe the specific setting of recruitment.
REPONSE: The setting for each study has been added to the manuscript and supplemental material as suggested. While there may be inter-study differences in demographics and clinical practices, all the studies were undertaken in high income countries with reasonably well-developed healthcare systems, so we feel that the results as a whole are generalizable to such populations.

Reviewer: 2
Dr. Andrew Chapman, Royal Infirmary of Edinburgh

Comments to the Author:
White et al report findings from a systematic review and meta-analysis evaluating precipitating factors, risk factors, investigations, management and outcomes for type 1 and type 2 myocardial infarction. They included studies that adjudicated the diagnosis according to the universal definition of myocardial infarction and reported data on at least one variable of interest. They applied random-effect meta-analysis, identifying 41 relevant studies. They demonstrate important differences in patient presenting symptoms, investigations, treatments and outcomes.

This large study was pre-registered on PROSPERO and reports in accordance with PRISMA guidance. The assessment of bias appears well conducted.

This is an important piece of work and will be impactful but I do have some comments for the authors to consider on the reporting of findings.

Overall comment: Please consider reporting of outcomes and how this might impact on readability. There are an excessive number of forest plots presented in the supplement which detracts from the overall utility of your work. I would suggest you reduce to those you consider most relevant, or those where at least 50% of studies report the outcome of interest. For example, you present meta-estimates for Fatigue in Figure S20 – comprising a single study. There is no rationale for this.
RESPONSE: The comment from the reviewer, as well as the editor, is accepted. In the supplementary material we have removed 5 forest plots for which only single studies apply or where the total number of events/measures were less than 100. We would prefer not to apply a threshold of 50% of included studies having to report the outcome of interest, as we feel this would result in a significant loss of useful information that readers may be interested in seeing – best to report what the literature is showing, even if relatively few or small studies, rather than not include it at all.

Methods: Please explain rationale for random effects to the reader and include a statement on ethical approval.
RESPONSE: The random effects method was used because of anticipated heterogeneity in studies. This methodology has been previously described. The manuscript now highlights the rationale for using a random effects method with reference to a previous BMJ article detailing its use. As for ethical approval, the study is a systematic review of previously published research studies with no identifying patient information, and as such, no ethics approval was required.

Results: It would be helpful to give geographical context to the cohort studies included.
RESPONSE: We have adjusted the manuscript and supplemental material to include the geographical context of the cohort studies. We note that Reviewer 1, comment 5, made a similar request.

Results: Throughout the results the authors provide a median 'range'. Perhaps pedantic but it would be correct to report the median value (interquartile range) in parenthesis. Please update for age, troponin concentration and all other relevant variables.
RESPONSE: We report a range of median values as reported in individual studies. We do not believe we can report the IQR for these aggregated values. We would be happy to report the lowest and highest IQR reported across all studies though we are uncertain of its value.

Results: Suggest moving the second paragraph on definition of MI to a supplemental appendix.
RESPONSE: We would prefer to keep this here as it orientates the reader to the fact that the definition of T2MI has evolved from 2009 to 2020 and indicates that our review is representative of studies of each definition.

Discussion: I think you could highlight the importance of your study better in the early discussion. This is a large pre-specified systematic review and meta-analysis in an important area. You included 131,000 patients from 41 cohort studies across many countries. This should be highlighted more prominently at the outset of discussion.
RESPONSE: Thankyou for the comment and we have made adjustments to the manuscript.

How could outcomes be improved? What other studies would be beneficial? You have identified a huge treatment gap, is this important, should this be addressed now?
RESPONSE: We do make mention in Discussion of the urgent need for more research into why there are significant differences in drug and interventional management between T1MI and T2MI. We also make reference to the ACT-2 randomised trial that seeks to determine the downstream intervention effects of a routine vs more selective investigational approach (using CTCA or coronary angiography) in patients with T2MI. Further discussion of the reasons for the relative underuse of cardioprotective medications and non-invasive risk stratification investigations can only be speculative and is limited by the word count.

Please review the CASABLANCA study. In this study the authors followed up patients were enrolled after peripheral or coronary angiography for incident myocardial infarction events. Therefore, patients had angiography prior to their T2MI event. There are important limitations to this study, not least that only those with a high pre-test probability of coronary or peripheral artery disease were enrolled. Whilst I agree that conflicting studies limit our ability to determine the utility of coronary angiography, this paragraph requires rephrasing.
RESPONSE: Thank you for pointing this out to us and we have adjusted the manuscript to emphasize these studies represented a high-risk population as a result of case selection methods.

Reviewer: 3
Dr. Annalisa Biffi, Milan Bicocca University

Comments to the Author:
This paper discussed an interesting topic regarding the diagnostic features, management and prognosis of Type II myocardial infarction; however the manuscript has limitations and several points, which need to be clarified.

-why have you mentioned just the type II of myocardial infarction in the title?
RESPONSE: Thank you for the comment. We note that the research question was to compare T2MI to T1MI and that our title did not accurately reflect this comparison, and we have reworded accordingly.

-Could you please update the search strategy investigation up to now (or have a look if there are new published studies)?
RESPONSE: Please see the response to Reviewer 1, comment 1.

-I have not understood the meaning of weighted OR -In which way have you taken into account of the publication bias?
RESPONSE: Publication bias is a potential limitation of all systematic reviews. We did not think it appropriate or informative to construct funnel plots for every variable/outcome we have studied. The weightings of the odds ratios are determined by the random effects analytic model which considers both random error (intra-study variation) and inter-study differences (heterogeneity).

-could you list the precipitating factors in the Method Section?
RESPONSE: We were trying to ascertain what these were, as defined and reported in the studies, so we felt it would be inappropriate to pre-specify them a priori. Also, we could not be certain of what precipitants had been included in the studies prior to undertaking the review which further limits our ability to pre-specify them, although we surmised they would include various possibilities such as sepsis, hypotension, arrhythmia, etc.

-In the discussion section, may you clinically explain because some pre-existing medical conditions, medical management and invasive interventions, outcomes, clinical features of Table S7, cardiac investigation of Table S8, are more frequent in T2MI compared to the T1MI?
RESPONSE: The included studies did not provide any comments or explanations as to the differences between T1MI and T2MI cohorts, and accordingly we would only be speculating about the reasons for the differences as well. In Discussion we offer some thoughts as to whether the greater co-morbidity burden and medical complexity of T2MI vs T1MI may cause clinicians to hesitate in subjecting such patients to more invasive investigations or intensive treatments because of the risk of iatrogenic harm.

-Is it possible to specify the timing concerning the pre-existing medical conditions (when did these conditions start to affect patients?)
RESPONSE: We are unable to provide this information as it was not available in the included studies. This may represent are area of uncertainty and would best be considered as a separate research question.

VERSION 2 – REVIEW

REVIEWER	Neumann, J University Heart Center, Hamburg
REVIEW RETURNED	17-Nov-2021

GENERAL COMMENTS	Most of my comments have been addressed adequately. My specific comments are: - The authors need to check for double inclusion of patients, which probably has occurred for some participants (e.g. Baron 2016 used the same (but larger dataset) as Baron 2015. The same applies to Chapman 2018 and 2020). - The authors argue, that due to time constraints, they were not able to update their analyses towards more contemporary studies. They highlight, that they already cover many patients. However, the vast majority of participants is based from old and retrospective studies. This is an important, as the diagnosis of type 2 MI evolved substantially over time and strongly depends on the adjudication process (e.g. prevalence of T2MI in Sweden (Baron 2016, retrospective registry): 3.2%, and in Switzerland (Nestelberger 2017, prospective cohort with adjudication): 18.7%). In case the authors still decide not to update their findings, they should highlight this aspects more prominently in the discussion section. - The authors should highlight the wide range of settings, which were used for inclusion of participants.

REVIEWER	biffi, annalisa Milan Bicocca University
REVIEW RETURNED	24-Nov-2021

GENERAL COMMENTS	Thank you for the changes you made on the previous version of the study. I have few additional comments: -when I asked you about the publication bias I referred to the tendency to publish studies with significant results, for example. I suggest you to calculate the Egger test to evaluate the presence of publication bias. -then, you called the estimate "weightings of the OR". I think this could be confusing because if I read "weightings" I could think that those estimates are adjusted for some variables. So I suggest you to remove the word "weightings".

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Dr. J Neumann, University Heart Center, Hamburg

Comments to the Author:

Most of my comments have been addressed adequately. My specific comments are:

- The authors need to check for double inclusion of patients, which probably has occurred for some participants (e.g. Baron 2016 used the same (but larger dataset) as Baron 2015. The same applies to Chapman 2018 and 2020).

Response: We thank the reviewer for alerting us to this concern about duplication which we did not appreciate.
We agree the Baron 2016 paper appears to include the cohort that were the subject of the 2015 paper, while noting Baron 2015 states patients were 'Consecutive patients with AMI admitted to a cardiac or medical intensive care unit at all 73 hospitals in Sweden between 1 January and 31 December 2011 recorded in the SWEDEHEART registry..', while in Baron 2016 patients were 'Consecutive patients with AMI admitted to a cardiac unit at all 73 hospitals in Sweden between January 1, 2011 and December 31, 2013 recorded in SWEDEHEART registry.'
So there is a possibility that they were not exactly the same cohorts but we agree the majority of the patients from 2015 paper are included in the much larger sample of the 2016 paper. Consequently we have deleted the 2015 data from our datasets and recalculated the results.

However, the Chapman papers of 2018 and 2020 involved different cohorts and both papers should remain. Chapman 2018 states the patients were as follows: 'Consecutive hospital inpatients with elevated cardiac troponin I concentrations (≥0.05 μg/L) were identified at a tertiary cardiac center (Royal Infirmary of Edinburgh, Scotland, United Kingdom) during the validation (January 19, 2008–July 31, 2008) and implementation (January 19,2009–July 31, 2009) phases of a contemporary sensitive cardiac troponin I assay.
Chapman 2020 states the patients were as follows: 'High-STEACS (High-Sensitivity Troponin in the Evaluation of Patients With Suspected Acute Coronary Syndrome) is a stepped-wedge cluster randomized, controlled trial to evaluate implementation of a hs-cTn I assay and the recommendations of the Universal Definition of Myocardial Infarction in consecutive patients with suspected acute coronary syndrome, across 10 secondary and tertiary care hospitals in Scotland.' This trial ran from June 10, 2013 to March 3, 2016.

We have rechecked the other papers with similar authors (Putot et al 2018, 2019, 2020), Saaby et al (2013, 2014) and Sandoval et al (2014, 2017) and are satisfied these all involve separate patient cohorts.

As can be seen in the tracked changes version, while absolute values for some proportions, odds ratios and confidence intervals changed with the removal of the Barron 2015 dataset, the overall magnitude and direction of the estimates did not change to any clinically significant degree.

The authors argue, that due to time constraints, they were not able to update their analyses towards more contemporary studies. They highlight, that they already cover many patients. However, the vast majority of participants is based from old and retrospective studies. This is an important, as the diagnosis of type 2 MI evolved substantially over time and strongly depends on the adjudication process (e.g. prevalence of T2MI in Sweden (Baron 2016, retrospective registry): 3.2%, and in

Switzerland (Nestelberger 2017, prospective cohort with adjudication): 18.7%). In case the authors still decide not to update their findings, they should highlight this aspects more prominently in the discussion section.
- The authors should highlight the wide range of settings, which were used for inclusion of participants.

Response: This criticism of including old studies of both retrospective and prospective studies could be levelled at many systematic reviews of observational studies, and we acknowledge there is considerably heterogeneity in the setting and methods. It is for this reason we used random effects modelling in our meta-analyses. Changes over time in diagnostic definition affect many common conditions (such as type 2 diabetes, osteoporosis, hypertension) not just AMI, but this does not preclude investigators including studies spanning many years. Our study included studies undertaken between 2010 and 2018. In any event we believe this change in definition and heterogeneity in setting do not detract from the significant differences in patient characteristics, clinical features, management and outcomes our review has found between T1MI and T2MI, and which, because they were derived from different studies from different jurisdictions, serve as generalisable findings.

Reviewer: 3
Dr. Annalisa Biffi, Milan Bicocca University

Comments to the Author:

Thank you for the changes you made on the previous version of the study. I have few additional comments:

-when I asked you about the publication bias I referred to the tendency to publish studies with significant results, for example. I suggest you to calculate the Egger test to evaluate the presence of publication bias.

Response: We do not believe an Egger test is either appropriate or useful in the context of our review. Such tests are most relevant to binary outcomes of interventional trials which are assessing the presence or absence of an hypothesised effect when comparing a new treatment or intervention against a comparator, and Eggers test is being used to statistically assess the asymmetry in effect estimates resulting from the non-publication of negative trials. This is very different from a review of observational studies where management has already been decided and enacted, and where no hypotheses about treatment effects are being tested. Our review is a descriptive one, aimed at identifying if there are significant differences in a large range of measures (patient characteristics, clinical features, investigations, treatments, outcomes) between two cohorts of patients - T1MI and T2MI – and whose data, in most studies, were derived from registries or administrative datasets, not from clinical trials, and even in the latter, analyses of T1MI vs T2MI patients were secondary, not primary, analyses. We think it very unlikely that investigators have undertaken descriptive studies of these two populations and not reported their results on the basis that some a priori hypotheses about differences between the two populations were rejected ie.'negative' study. To support this, in none of our studies did investigators, in their Methods sections, hypothesise specific differences between T1MI and T2MI in the variables they chose to measure – they were

simply investigating to see if there were any significant differences. Finally, if an Eggers test is desired, which analyses should we choose to do this on? We prefer to defer this question about the need for Eggers test to the editors.

-then, you called the estimate "weightings of the OR". I think this could be confusing because if I read "weightings" I could think that those estimates are adjusted for some variables. So I suggest you to remove the word "weightings".

Response: We used the term 'weightings of the OR' in the sense of how the random effects modelling weighted the OR, but we appreciate this may be misinterpreted as weighting resulting from adjustment of predictor variables. We have reworded the sentence to make clear our emphasis on the modelling weights.

VERSION 3 – REVIEW

REVIEWER	Neumann, J University Heart Center, Hamburg
REVIEW RETURNED	01-Dec-2021

GENERAL COMMENTS	accept in the present version.

REVIEWER	biffi, annalisa Milan Bicocca University
REVIEW RETURNED	15-Dec-2021

GENERAL COMMENTS	-We thank the Author for the pleasure to review your meta analysis, however I have to evidence again the need to evaluate the presence of publication bias. Here some reference from the Cochrane Handbook: https://handbook-5-1.cochrane.org/chapter_10/10_4_3_1_recommendations_on_testing_for_funnel_plot_asymmetry.htm and here some meta analyses similar to your study, which investigated the publication bias: Gupta S, Vaidya SR, Arora S, Bahekar A, Devarapally SR. Type 2 versus type 1 myocardial infarction: a comparison of clinical characteristics and outcomes with a meta-analysis of observational studies. Cardiovasc Diagn Ther. 2017 Aug;7(4):348-358. doi: 10.21037/cdt.2017.03.21. PMID: 28890871; PMCID: PMC5582063. Xu Y, Fang H, Qiu Z, Cheng X. Prognostic role of neutrophil-to-lymphocyte ratio in aortic disease: a meta-analysis of observational studies. J Cardiothorac Surg. 2020 Aug 10;15(1):215. doi: 10.1186/s13019-020-01263-3. PMID: 32778122; PMCID: PMC7419193. Valentin G, Pedersen SE, Christensen R, Friis K, Nielsen CP, Bhimjiyani A, Gregson CL, Langdahl BL. Socio-economic inequalities in fragility fracture outcomes: a systematic review and meta-analysis of prognostic observational studies. Osteoporos Int. 2020 Jan;31(1):31-42. doi: 10.1007/s00198-019-05143-y. Epub

	2019 Aug 30. PMID: 31471664. -Moreover, I have read again your work, and I would ask you if you have considered the presence of some sources of heterogeneity (for example by realizing some subgroups analyses to evaluate them)

VERSION 3 – AUTHOR RESPONSE

Reviewer: 1
Dr. J Neumann, University Heart Center, Hamburg, Comments to the Author:
accept in the present version

Reviewer: 3
Dr. annalisa biffi, Milan Bicocca University Comments to the Author:
-We thank the Author for the pleasure to review your meta analysis, however I have to evidence again the need to evaluate the presence of publication bias. Here some reference from the Cochrane Handbook:

https://handbook-5-1.cochrane.org/chapter_10/10_4_3_1_recommendations_on_testing_for_funnel_plot_asymmetry.htm

and here some meta analyses similar to your study, which investigated the publication bias:

Gupta S, Vaidya SR, Arora S, Bahekar A, Devarapally SR. Type 2 versus type 1 myocardial infarction: a comparison of clinical characteristics and outcomes with a meta-analysis of observational studies. Cardiovasc Diagn Ther. 2017 Aug;7(4):348-358. doi: 10.21037/cdt.2017.03.21. PMID: 28890871; PMCID: PMC5582063.

Xu Y, Fang H, Qiu Z, Cheng X. Prognostic role of neutrophil-to-lymphocyte ratio in aortic disease: a meta-analysis of observational studies. J Cardiothorac Surg. 2020 Aug 10;15(1):215. doi: 10.1186/s13019-020-01263-3. PMID: 32778122; PMCID: PMC7419193.

Valentin G, Pedersen SE, Christensen R, Friis K, Nielsen CP, Bhimjiyani A, Gregson CL, Langdahl BL. Socio-economic inequalities in fragility fracture outcomes: a systematic review and meta-analysis of prognostic observational studies. Osteoporos Int. 2020 Jan;31(1):31-42. doi: 10.1007/s00198-019-05143-y. Epub 2019 Aug 30. PMID: 31471664.

Response: To assess for publication bias we performed funnel plots for two of our major outcomes, in-hospital all-cause mortality and one-year all-cause mortality. We chose these two outcomes as they are important outcomes for our analysis and were reported in more than seven of the included studies. These two funnel plots have been added to the online supplement, and show no asymmetry.

Of note, we developed funnel plots for all other outcomes which had been reported in

more than seven studies, and again found no evidence of publication bias, with no asymmetry around the pooled OR. These plots are available on request.

Reference has been made to publication bias and the funnel plots under Risk of bias in Methods and Results. We note that Gupta et al only reported one funnel plot for in-hospital mortality, Xu et al did not perform any tests of publication bias as they had too few studies, and Valentin et al simply stated: 'publication bias was explored using funnel plots, and no obvious asymmetry was found' with no other details.

-Moreover, I have read again your work, and I would ask you if you have considered the presence of some sources of heterogeneity (for example by realizing some subgroup analyses to evaluate them)

Response: We agree that given the high I2 values for most of our forest plots, significant between-study heterogeneity does exist, but in the absence of individual patient data which were unavailable to us, it is difficult to identify the exact source and type of heterogeneity. Sub-group analyses or meta-regression are used to analyse heterogeneity. We searched for studies that had performed subgroup analyses and re-reviewed the 8 studies that had over 500 patients with T2MI, as we felt that subgroup analysis with less than 500 patients would not be meaningful. None of these eight studies had performed any subgroup analysis. We did note and made mention in Discussion of two studies that performed sub-analyses based on risk stratification using validated risk scores or predictive models for mortality (Higuchi et al ref 26; Radovanovic et al ref 40) which, not surprisingly, noted higher mortality with higher risk scores. In regards to meta-regression, characterising the different sources of clinical, methodological or statistical heterogeneity in real-world observational studies is very difficult in the absence of well defined study parameters that are consistent in at least some studies, in contrast to randomised controlled trials, as noted in a recent reference we have cited. We note that the only other meta-analysis of observational studies of T2MI (Gupta et al, ref 6) made no attempt to analyse heterogeneity using L'Abbe plots or other methods. We have highlighted this as a limitation in our study in Discussion. Moreover, either form of analysis principally aims to assess whether certain patient types or characteristics are associated with, or predict, differences in certain outcomes. To this end, our study has tried to identify patient characteristics, investigation results and management regimens that better distinguish patients with T2MI from those with T1MI.

VERSION 4 – REVIEW

REVIEWER	biffi, annalisa Milan Bicocca University
REVIEW RETURNED	28-Jan-2022

GENERAL COMMENTS	I thank the Authors for the changes. I have no more suggestion regarding this manuscript.