PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Cohort profile of BIGPROMISE: a perioperative biobank of a high-risk surgical population
AUTHORS	Noordzij, P.; Ruven, Henk; Reniers, Ted; Idema, Rene; Thio, M.S.Y.; Cremer, Olaf; Hollema, Nynke; Smit, Kyra; Vernooij, Lisette; Dijkstra, Ineke M.; Rettig, T

VERSION 1 – REVIEW

REVIEWER	Fislage, Marinus Charité Universitätsmedizin Berlin, Dept of Anesthesiology and Intensive Care Medicine
REVIEW RETURNED	03-Nov-2023

GENERAL COMMENTS	Summary: In this cohort profile, Noordzij and colleagues present the rationale as well as preliminary results of the BIGPROMISE study. The study aims to identify biomarkers that are potentially useful in predicting a wide range of postoperative complications. Considering the increasing number of surgeries each year, the study's objective is relevant. An article in the style of a cohort profile further fits BMJ Open's publishing policy. Even though I generally support the publication of the work, I would suggest revising some major and minor issues. Thank you for inviting me to review the manuscript. Major Comments - The introduction section offers the opportunity to refer to previous studies assessing blood biomarkers in postoperative complications. Please inform your readers about existing evidence gaps and the potential contribution of your research to fill these. - Please ensure that you use the appropriate reporting guideline. In your case it should be STROBE. Please check. - There is no information on the sample size calculation given. Therefore, it is difficult to comprehend why a final cohort of 3000 patients is needed. Are the patients of the two hospitals representative of a broader population? - Analogously, some remarks on your statistical analysis plan would be helpful. - I appreciate that you explain your choice of biomarkers in detail. However, please elaborate on your choice of complications. I would like to know why you decided to omit neurological complications for instance. - The blood collection "after induction of general anaesthesia" appears to be rather late for serving as preoperative data. Blood sampling performed days before surgery seems more reasonable when aiming to adjust the perioperative, anaesthesiologic and surgical handling to eventually prevent

	postoperative complications. Furthermore, I suggest explaining how the knowledge of new biomarkers will enable clinicians to modify the treatment. Where do you see the potential clinical implications of your work? - While I appreciate the general description of the study's rationale, I expect a cohort profile to provide more information on the study cohort itself. Although the recruitment phase is ongoing, some preliminary results would be of interest for the readers, such as the patient's characteristics, missing data or maybe even some first results. The latter could help generating hypotheses on the association of biomarkers with postoperative complications. - Please consider including a limitations section to the discussion. Minor Comments (Page numbers are those assigned by the Editorial Manager; e.g., "Page 3 of 55") - The manuscript contains British and American spelling alike. I presume that for BMJ Open you probably should use British English consistently. Please check the guidelines for authors. - If you want to use the Oxford comma, please make sure to insert it consistently. - p. 10 lines 52-54: I would recommend removing the sentence on Roche's economic role. There is no need for this statement in this scientific paper. However, this marks a good opportunity to inform about the role of the funder. - p. 11 lines 10-12: The sentence seems unclear to me. What is this surgical risk you are referring to? You may want to add a few words to make it clearer. - P. 11 line 23: I would like to recommend the phrase "…questionnaires in Dutch,…" instead. However, this is only a recommendation and I should also disclaim that I am not a native speaker. - P. 11 line 37: Nonetheless, this phrase should definitely be "… consider participating…" - P. 11 line 60: When you are mentioning "preoperative laboratory results" these data are retrieved from the patients' records. If that is correct, I would opt to call these laboratory results "previous", "past", etc. instead of "preoperative". Otherwise, it might be easily confused with your newly obtained study data. - P. 12 lines 15-19: Please elaborate on the choice of time spans since it is controversial; especially regarding postoperative mortality. - P. 12 line 17: You may want to change the words "consist of" to avoid redundance. - P. 13 line 26: How do patients who consented to biobanking differ from the entire patient cohort? Is it only a fraction of your whole sample? If yes, it would be interesting to see the numbers presented in the results section. - I appreciate that you inform the reader about your way of thought, when it comes to each group of biomarkers. However, the pages 14-16 contain several claims that require supporting references. - P. 14 line 42: There is a typo "identity". I presume you mean "identify". - "Findings to date": Please expand this section. The more information for the reader, the better. - P. 18 line 31: Did the patients already give their informed for the collaborative use of their data?

	- Where patients involved in designing the study? - Discussion: Frankly, some parts of the discussion could be more informative. Which are the biomarkers that made it into clinical practice and the “few large, well-designed studies” (p.19 lines 56-59)? - P. 19 lines 35-42 and p. 20 lines 3-13 are redundant and could form a single sentence. - The list with the definitions of postoperative complications is very informative and important. Thank you! Again, I suppose you should probably use British (or American?) English consistently.

REVIEWER	Häggström, Christel Uppsala University, Department of Surgical Sciences
REVIEW RETURNED	14-Dec-2023

GENERAL COMMENTS	General comments Thank you for this cohort profile presenting an extensive data and biomarker collection from two hospitals in the Netherlands. I have some suggestions, which are also included in the submission guidelines, that can make the cohort profile more clear. Please doublecheck the guidelines at: https://bmjopen.bmj.com/pages/authors#cohort_profile Comments 1. In the cohort description section, please report numbers of individuals at each stage of the study i.e for each of the sampling and collection points given I Supplement table 1. Please give reasons for non-participation. A flow diagram is recommended to illustrate this. 2. Furthermore, give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders, and indicate number of participants with missing data for each variable of interest. Preferably a baseline table with some the basic characteristics of the currently recruited study population would be nice to have. 3. Could you provide some more information of the data collected, both prior to surgery, perioperative and during hospital admission. In possible, attach variable lists to the supplement. Similarly, questionnaires and copies of written consents and permissions can be added. 4. Please add a section for reporting patient and public involvement Minor comments Please state the role of the funders, if they had any role in study design, data collection and analysis, decision to publish, or preparation of manuscripts. In the abstract it is mentioned that the overall incidence of severe postoperative complications was 11%. Please add the timeframe for this figure.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Major Comments

Q - The introduction section offers the opportunity to refer to previous studies assessing blood biomarkers in postoperative complications. Please inform your readers about existing evidence gaps and the potential contribution of your research to fill these.

A – In the original manuscript we discussed previous studies on perioperative biomarkers in the discussion. We have added a paragraph to the introduction, in which we describe the limitations of current evidence and suggest opportunities for future research.

Q - Please ensure that you use the appropriate reporting guideline. In your case it should be STROBE. Please check.

A – We checked the STROBE guideline for cohort studies and added information on study size, future study design, and funding.

Q - There is no information on the sample size calculation given. Therefore, it is difficult to comprehend why a final cohort of 3000 patients is needed. Are the patients of the two hospitals representative of a broader population? Analogously, some remarks on your statistical analysis plan would be helpful.

A – We have added information on sample size to the manuscript and added a brief paragraph on future study design and our considerations for statistical analysis.

Q - I appreciate that you explain your choice of biomarkers in detail. However, please elaborate on your choice of complications. I would like to know why you decided to omit neurological complications for instance.

A – We use standardized end points in perioperative medicine (StEP) to define postoperative complications. For ‘neurological’ outcomes we used stroke (including severity). We chose not to include postoperative delirium / cognitive decline as postoperative outcome, because no consensus was reached by StEP investigators for postoperative CNS failure or incidence of postoperative delirium during the postoperative hospitalization period.

Q - The blood collection “after induction of general anaesthesia” appears to be rather late for serving as preoperative data. Blood sampling performed days before surgery seems more reasonable when aiming to adjust the perioperative, anaesthesiologic and surgical handling to eventually prevent postoperative complications. Furthermore, I suggest explaining how the knowledge of new biomarkers will enable clinicians to modify the treatment. Where do you see the potential clinical implications of your work?

A – For elective surgery, patients are often admitted to the hospital on the day of surgery or the evening before surgery. We chose the study time point for preoperative blood collection for logistical reasons and patient comfort. By drawing blood in the operating theatre we aim to reduce patient discomfort (and improve the number of patients that participate in the study), and reduce the number of missing samples.

We are convinced that the results of our preoperative biomarker samples will be representative of the preoperative phase and can be used to identify preoperative risk factors. In general patients undergo elective major surgery within 3-6 weeks after diagnosis. As preoperative biomarkers are often used to diagnose chronic disease it is unlikely that results have changed significantly over a short period of time. The results of our study can therefore be used to design future studies for preoperative interventions that aim to improve outcome.

Q - While I appreciate the general description of the study’s rationale, I expect a cohort profile to provide more information on the study cohort itself. Although the recruitment phase is ongoing, some preliminary results would be of

interest for the readers, such as the patient's characteristics, missing data or maybe even some first results. The latter could help generating hypotheses on the association of biomarkers with postoperative complications.
A – We have added new preliminary results to the body of text in the manuscript, and as a supplementary table.

Q - Please consider including a limitations section to the discussion.
A – We added limitations of our study to the discussion.

Minor Comments
(Page numbers are those assigned by the Editorial Manager; e.g., "Page 3 of 55")
Q - The manuscript contains British and American spelling alike. I presume that for BMJ Open you probably should use British English consistently. Please check the guidelines for authors.
A – Spelling was changed to British English and the manuscript was checked for spelling errors.

Q - If you want to use the Oxford comma, please make sure to insert it consistently.
Q - p. 10 lines 52-54: I would recommend removing the sentence on Roche's economic role. There is no need for this statement in this scientific paper. However, this marks a good opportunity to inform about the role of the funder.
A – We have changed this accordingly and added a statement on funding to the manuscript.

Q - p. 11 lines 10-12: The sentence seems unclear to me. What is this surgical risk you are referring to? You may want to add a few words to make it clearer.
A – Surgical risk refers to the risk of the surgical procedure.

A – The following suggested changes to the text have been performed.
- P. 11 line 23: I would like to recommend the phrase "…questionnaires in Dutch,…" instead. However, this is only a recommendation and I should also disclaim that I am not a native speaker.
- P. 11 line 37: Nonetheless, this phrase should definitely be "… consider participating…"
- P. 11 line 60: When you are mentioning "preoperative laboratory results" these data are retrieved from the patients' records. If that is correct, I would opt to call these laboratory results "previous", "past", etc. instead of "preoperative". Otherwise, it might be easily confused with your newly obtained study data.
Q - P. 12 lines 15-19: Please elaborate on the choice of time spans since it is controversial; especially regarding postoperative mortality.
A – We chose our primary endpoints according to standardized criteria (StEP): 30-day, and 1 year mortality. Mortality after 120 days is important for disability free survival, because at this time point the WHODAS questionnaire is filled out by patients.

- P. 12 line 17: You may want to change the words "consist of" to avoid redundance.

Q - P. 13 line 26: How do patients who consented to biobanking differ from the entire patient cohort? Is it only a fraction of your whole sample? If yes, it would be interesting to see the numbers presented in the results section.
A – 91% of all study patients consented to biobanking their blood samples. The results are added to the supplementary table.

Q - I appreciate that you inform the reader about your way of thought, when it comes to each group of biomarkers. However, the pages 14-16 contain several claims that require supporting references.
A – We have added several references to this paragraph, especially for renal pathophysiology in postoperative complications.

Q - P. 14 line 42: There is a typo “identity”. I presume you mean “identify”.
- “Findings to date”: Please expand this section. The more information for the reader, the better.
A – We have added additional preliminary results and a supplementary table to the manuscript.

A - P. 18 line 31: Did the patients already give their informed for the collaborative use of their data?
Q – Patients gave informed consent to use of their blood samples for future research that aim to improve perioperative care.

Q - Where patients involved in designing the study?
A – Patients were not involved in designing the study. We deliberately did not involve patients in the observational phase of BIGPROMISE. Our first objective was to understand biomarker responses and their association with postoperative complications. In the next phase, which will include targeted interventions in specific patients groups (e.g. according to type of surgery or age), to prevent and reduce complications, patients will be involved in designing the study. Especially to identify which complications are most relevant from their perspective.

A - Discussion: Frankly, some parts of the discussion could be more informative. Which are the biomarkers that made it into clinical practice and the “few large, well-designed studies” (p.19 lines 56-59)?
Q –We intend to say that despite the fact that many potential useful biomarkers are being developed by biopharmaceutical companies, often the added value of those markers for clinical practice remains unclear. Mainly, because studies that aim to demonstrate the added value are often underpowered, of have poor methodology.

- P. 19 lines 35-42 and p. 20 lines 3-13 are redundant and could form a single sentence.
- The list with the definitions of postoperative complications is very informative and important. Thank you! Again, I suppose you should probably use British (or American?) English consistently.

Reviewer 2
Comments
Q - 1. In the cohort description section, please report numbers of individuals at each stage of the study i.e for each of the sampling and collection points given I Supplement table 1. Please give reasons for non-participation. A flow diagram is recommended to illustrate this.
A – We added a flow diagram with the number of drop outs to the findings to date section. Reasons for non-participation are provided in the flow chart.

2. Furthermore, give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders, and indicate number of participants with missing data for each variable of interest. Preferably a baseline table with some the basic characteristics of the currently recruited study population would be nice to have.
A – We added a supplementary table with preliminary results that included demographics, ASA class, type of surgery and severe complications.

3. Could you provide some more information of the data collected, both prior to surgery, perioperative and during hospital admission. In possible, attach variable lists to the supplement. Similarly, questionnaires and copies of written consents and permissions can be added.
A- We added a supplementary table with preliminary results and a document which contains study variables (new Supplementary Table 1).

4. Please add a section for reporting patient and public involvement
A – We added this section.

Minor comments
Q - Please state the role of the funders, if they had any role in study design, data collection and analysis, decision to publish, or preparation of manuscripts.
A – Roche had no role in the design of our study, collection of data, preparation and publication of this manuscript. We added as statement to the 'Funding' paragraph.

Q - In the abstract it is mentioned that the overall incidence of severe postoperative complications was 11%. Please add the timeframe for this figure.
A – The timeframe was 30 days. We added this to the abstract.

VERSION 2 – REVIEW

REVIEWER	Fislage, Marinus Charité Universitätsmedizin Berlin, Dept of Anesthesiology and Intensive Care Medicine
REVIEW RETURNED	03-Mar-2024

GENERAL COMMENTS	Thank you for revising the manuscript which has generally improved. I just wish to add that I still think the article would benefit, if it was published as a "study rationale" instead of a cohort profile. While you describe your rationale in great detail, you only provide a few details on the patients' characteristics. This might be due to the current stage of the study. Please have a look at other cohort profiles at BMJ Open. Some minor comments: - Page 6 + 20: Here you write that the blood samples "are routinely collected". This can be misleading. Do you collect the blood samples for the purpose of the study or is it actually routinely collected data for clinical practice? If I understood it correctly, the latter is true and this fact should be emphasized consequently throughout the manuscript. - Page 10: My apologies for the misunderstanding. When addressing the term "surgical risk" I did not have a semantic question in mind. The purpose of this sentence is still unclear. Did you obtain these variables because you wanted to assess the surgical risk? Is this a general statement? I would still argue that a little bit of context is required here. - E.g., page 10: Please avoid using the word "demographic" when referring to patient characteristics.

	- Page 20: I would recommend using “perioperative neurocognitive disorders” instead of “postoperative cognitive disorders” as suggested in the “Recommendations for the Nomenclature of Cognitive Change Associated with Anaesthesia and Surgery—2018”. - Page 20: I am still convinced that you should help your readers here: Which are the biomarkers that made it into clinical practice and the “few large, well-designed studies”? Which are the markers which “made it from bench to bedside”? Please add some examples and references.

REVIEWER	Häggström, Christel Uppsala University, Department of Surgical Sciences
REVIEW RETURNED	19-Feb-2024

GENERAL COMMENTS	General comments Thank you for the revised version of this cohort profile. In particular, thank you for the addition of power calculations and more details of statistics that is planned to be used, and Supplemental tables 1 and 3. Comments The number of participants in the flowchart (supplemental figure 1) and in the table with baseline data (Supplementary Table 3) does not agree. Please doublecheck the numbers. In the supplementary table 3, it would be nice with some more information of when the data are retrieved from (in line whit the information given in Supplementary Table 1, and Supplementary Table 1_new). Page 17, It is written that BIGPROMISE enables diagnostic studies, which is inconsistent with the rest of the text. Please rephrase this sentence so that it is consistent with the study aim.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1

Q - The number of participants in the flowchart (supplemental figure 1) and in the table with baseline data (Supplementary Table 3) does not agree. Please double check the numbers.

A – The figure reports 1,754 patients compared to 1,750 patients in the baseline table. This can be explained by 4 patients who withdrew informed consent for blood sampling and analysis of their data. Therefore analysis was performed in the remaining 1,750 patients. I’ve uploaded a new (and hopefully more clearer) version of supplementary figure 1.

Q- In the supplementary table 3, it would be nice with some more information of when the data are retrieved from (in line whit the information given in Supplementary Table 1, and Supplementary Table 1_new).

A – All data regarding baseline characteristics of the BIGPROMISE cohort at January 1 st 2024 are retrieved from the study database. This is reported in the footnote of the supplementary table 3.

Q - Page 17, It is written that BIGPROMISE enables diagnostic studies, which is inconsistent with the rest of the text. Please rephrase this sentence so that it is consistent with the study aim.

A – The text has been rephrased.

Reviewer 2.

Q - I just wish to add that I still think the article would benefit, if it was published as a "study rationale" instead of a cohort profile. While you describe your rationale in great detail, you only provide a few details on the patients' characteristics. This might be due to the current stage of the study. Please have a look at other cohort profiles at BMJ Open.

A – We considered reporting our study as a 'study rationale', but found a cohort profile more appropriate since BIGPROMISE is also a biobank for perioperative research, which will results in a multiple research questions and subsequent studies on perioperative outcome that remain to be determined in the near future.

Q - Page 6 + 20: Here you write that the blood samples "are routinely collected". This can be misleading. Do you collect the blood samples for the purpose of the study or is it actually routinely collected data for clinical practice? If I understood it correctly, the latter is true and this fact should be emphasized consequently throughout the manuscript.

A – Blood samples are collected and stored for study purposes. We have changed the sentences accordingly.

Q - Page 10: My apologies for the misunderstanding. When addressing the term "surgical risk" I did not have a semantic question in mind. The purpose of this sentence is still unclear. Did you obtain these variables because you wanted to assess the surgical risk? Is this a general statement? I would still argue that a little bit of context is required here.

A – Patients undergoing 'major' surgery are eligible for study participation. Major surgery is not clearly defined in literature. We have made a selection of surgical procedures with high intrinsic risk of complications, i.e. apart from age, gender, frailty, comorbidities etc. I made some text edits to hopefully make this more clear.

Q - E.g., page 10: Please avoid using the word "demographic" when referring to patient characteristics.

A – I have changed this accordingly.

Q - Page 20: I would recommend using "perioperative neurocognitive disorders" instead of "postoperative cognitive disorders" as suggested in the "Recommendations for the Nomenclature of Cognitive Change Associated with Anaesthesia and Surgery—2018".

A - I have changed this accordingly.

Q - Page 20: I am still convinced that you should help your readers here: Which are the biomarkers that made it into clinical practice and the “few large, well-designed studies”? Which are the markers which “made it from bench to bedside”? Please add some examples and references.

A – I added an example of two cardiac biomarkers to the text and added a reference to the ESC guidelines.