Prognostic accuracy of clinical markers of postpartum bleeding in predicting mortality or severe complications in women giving birth: Protocol for a WHO individual participant data meta-analysis

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ABSTRACT

Background

Postpartum haemorrhage – excessive bleeding after birth – is a leading cause of maternal mortality and morbidity, but there is no universal consensus on what clinical markers constitute excessive bleeding. Identifying women who will deteriorate due to bleeding after birth is critical for treating them with a first-response bundle of effective interventions to avert death or severe morbidity. In clinical care, common clinical markers of severe postpartum bleeding include volume of blood loss and changes in vital signs such as pulse rate, blood pressure, and indices that combine these signs of haemodynamic changes. The aim of this study is to assess the prognostic accuracy of clinical markers of postpartum bleeding in predicting mortality or severe complications in women giving birth.

Methods

We will conduct an individual participant data (IPD) meta-analysis. To identify eligible datasets for producing estimates of prognostic accuracy of clinical markers in predicting maternal mortality or severe complications from bleeding after birth, a global call for data will be launched by WHO and literature reviews will be conducted. Individual datasets will be obtained by contacting chief or principal investigators or senior authors of potentially eligible datasets. All individual datasets obtained from these two sources will be checked against prespecified inclusion criteria and harmonized into a pooled database. The prognostic accuracy of each clinical marker will be meta-analysed by fitting two-level mixed logistic regression models, and a bivariate normal model for generating summary sensitivities and specificities. Methodological quality of each included study will be assessed using the Quality Assessment of Prognostic Accuracy Studies tool.

Ethics and dissemination:

This study will involve secondary analysis of existing de-identified data. To be included in the pooled database, each included study must have received ethics approvals from relevant committees and have a data sharing agreement between the data owner and WHO. The main manuscript will be submitted to an open-access journal.

Background

Worldwide, an estimated 287,000 women die from complications of pregnancy and childbirth every year (1). One of the leading causes of death is postpartum haemorrhage (PPH) (2). PPH is a common complication of childbirth, affecting millions of women every year (3). Yet nearly all PPH-related deaths are preventable. In high income countries (HIC), PPH-related mortality has nearly been eliminated (2). Efforts to improve PPH outcomes in low and middle income countries (LMICs) have been less successful: over 80% of maternal deaths from PPH occur in sub-Saharan Africa and South Asia (1). These inequities in PPH-related mortality are a stark reminder of the unfinished global agenda on maternal health and rights.

While some amount of bleeding after birth is expected, there is controversy about the exact amount of bleeding that should be considered excessive and therefore be designated as PPH (4). Contemporary clinical practice tends to rely on standardised volumetric thresholds of blood loss (e.g., ≥ 500 mL or ≥ 1000 mL) to distinguish 'normal' from 'excessive' bleeding (5,6). However, women's ability to tolerate bleeding after birth varies depending on physiological factors such as circulating blood volume and pre-delivery haemoglobin level. These physiological factors are influenced by upstream social determinants of health (e.g., good nutrition) and their distribution often exhibits social gradients (7). Consequently, a volume of blood loss that is well-tolerated by one woman might be catastrophic for another. Considering persistent inequities in PPH-related mortality, there is a need to assess if we can identify more accurately which women are at higher risk of dying or developing life-threatening complications, and who warrant treatment to reduce such risk.

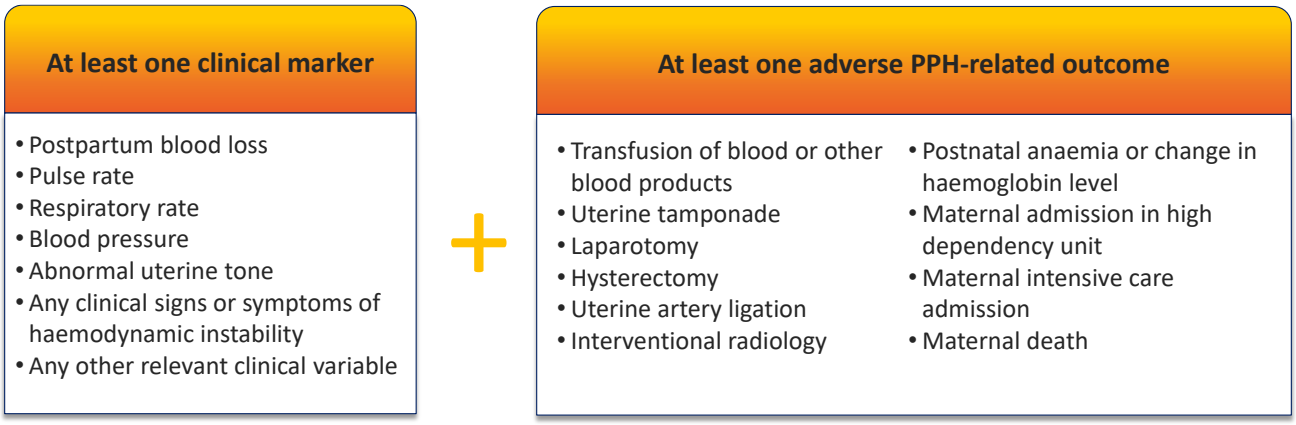
The aim of this study is to assess the prognostic accuracy of clinical markers of postpartum bleeding in predicting mortality or severe complications in women giving birth.

Methods

We will conduct an individual participant data (IPD) meta-analysis. This approach will permit granular assessments of prognostic performance of different thresholds for each clinical marker and exploration of prognostic accuracy across important population subgroups. WHO will establish a Steering Committee to provide methodological guidance and strategic inputs on the framing of the research question, and criteria for eligible datasets for the IPD. The data sharing standards for analysis will be made publicly available and any changes made to this protocol as informed by the available data will be reflected and explained in the final report of the analysis.

Eligible criteria for datasets

Figure 1. Eligibility criteria for clinical markers and outcome variables.



The eligibility criteria for datasets include the following:

1. Evidence of ethics committee approval before data collection
2. Data collected using a standardized protocol and/or through clinical/public health care encounter after 1990
3. Cohort design from observational or experimental studies
4. Data holder can sign a legal data sharing agreement with WHO
5. Data available on objectively measured blood loss by weighing blood loss (ideal) or via tools for fixed volumetric assessment such as calibrated drapes under participant's buttocks or measuring jars (acceptable), pulse rate, respiration rate, blood pressure, abnormal uterine tone, or any clinical signs and symptoms of haemodynamic instability [full list in Figure 1]. Studies with visually estimated blood loss are not eligible because of the inaccuracy of this method
6. Data available on clinical outcomes (e.g., blood transfusion, surgical interventions, morbidity, or mortality) [full list in Figure 1]
7. Dataset size of over 200 women
8. Dataset not exclusively of women diagnosed with postpartum haemorrhage

Data acquisition

A global call for data will be issued by WHO to acquire data and disseminated using all feasible WHO channels. The aim of the call will be to obtain datasets containing data on predictive clinical markers and outcomes. The call will include an online screening form to obtain information on the study eligibility criteria and principal investigators (PIs). For studies that appear to meet the eligibility criteria, WHO will contact the PIs and initiate the process of obtaining the datasets. All potentially eligible data will be sought irrespective of the data that was included in the published reports.

In addition to the call for data, we will search electronic databases [PubMed, MEDLINE, Embase, The Cochrane Library, generic data sharing platforms and WHO trial registers] from inception for eligible

studies. The searches will use the following terms for the populations of interest [pregnancy, birth, postpartum haemorrhage] combined with clinical markers [blood loss, pulse, blood pressure, shock index, haemoglobin, lactate] with no language restrictions. Authors of potentially eligible studies will be invited to respond to the global call for data.

Data collection and selection process

Authors of potentially eligible studies will be asked to provide additional details for further assessment. IPD will be requested for all potentially eligible studies, and PIs and their institutions will be invited to sign standard data-sharing agreements for this purpose. PIs will be asked to de-identify data and remove information that could lead to identification of individuals. The acquired de-identified data will be stored in a secure repository created by WHO specifically for this project. The management and updates of the repository will be the sole and exclusive responsibility of WHO and investigators collaborating with WHO will have access only to their own data. Two reviewers will review the submitted data and contact the principal investigators for any queries regarding the eligibility of the data. Study selection will be conducted independently by two reviewers, with disagreements resolved by discussion and consensus.

Data analysis

Data harmonization

The PIs will be provided with clear instructions about the required variables to share, the format, and the variable definitions. Once shared with WHO, the data variables in each dataset will be mapped against the required variables, and will be checked for accuracy, validity, and internal consistency against the study protocols and published reports. For the harmonized dataset, data will be recoded and transformed as required for consistency across datasets according to publicly available data sharing standards. Mapping and checking of all the files for each dataset will be verified by at least two reviewers. Consistency checks will be carried out through descriptive and distribution graphical analyses for each variable and by each outcome. Eligible predictive clinical markers and outcomes include those measured after birth and before hospital discharge. Clinical outcomes of interest include all-cause maternal mortality, transfusion of whole blood and/or blood products, need for mechanical or surgical intervention to stop bleeding [uterine tamponade, laparotomy, vessel ligation, compression sutures, interventional radiology, hysterectomy], maternal sepsis, organ system failure, high-dependency or intensive care admission, and postnatal anaemia.

Data handling

Data with different measurement units will be converted according to the international system of units. Derived values will be computed if their components are measured contemporaneously (e.g., body mass index from height and weight and shock index from pulse and blood pressure). For clinical markers measured at several time points (for example blood loss or blood pressure), we will extract measurements at 15, 30, 45, and 60 minutes after birth. For the primary analysis, we will use the most abnormal value before the diagnosis of PPH is made. For measured blood loss, we will extract the total blood loss following birth at the time of diagnosis, if available, and the total blood loss when measurement was stopped. Any additional blood loss from visual estimation will not be used as these are inaccurate. We will extract the outcomes of interest occurring after birth and until hospital discharge, irrespective of whether these were caused by excessive blood loss. A composite

outcome of maternal death and life-threatening complications including blood transfusion, mechanical or surgical interventions, or intensive care admissions for organ support will be generated. Available data will be checked for consistency and completeness by at least two reviewers.

Risk of bias and applicability

Risk of bias and applicability in the individual studies will be assessed independently by two reviewers using the Quality Assessment of Prognostic Accuracy (QUAPAS) tool (8). The QUAPAS tool assesses the risk of bias and concerns about applicability of studies across five domains: participants, index test, outcome, flow and timing, and analysis. We will modify the tool per our review question and adapt the signalling questions accordingly. We will consider all enrolled participants to be included in the analysis if data are available for >95% of all participants on the clinical markers and reported outcomes of interest, regardless of whether the data were included in the analysis for the primary paper. Conflicts will be resolved via discussion and consensus. We will calculate the number of eligible studies and participants we are able to obtain for our IPD and the total number of eligible studies and participants identified to assess the degree of selection bias in the final analysis.

Synthesis methods and approach to interpretation of the results

Participant data will be summarized descriptively. Dichotomous data will be presented as proportions and continuous data as medians and interquartile ranges. Outcomes will be presented as the incidence (proportion) of the composite outcome and its components (maternal death, blood transfusion, mechanical or surgical interventions, or intensive care admissions for organ support). Complete case analysis of data will be carried out.

We will use a two-stage approach to generate prognostic sensitivities, specificities, diagnostic odds ratios, positive and negative likelihood ratios and their confidence intervals for different thresholds of each clinical marker. In stage one, we will calculate the prognostic accuracy estimates per study. In stage two, we will use random-effects meta-analysis from a two-level mixed logistic regression model, with independent binomial distributions for the true positives and true negatives in each study, and a bivariate normal model for computing the summary sensitivities and specificities across studies (9). We will present results in tables and graphically with circles showing the individual study estimates, summary curve from the hierarchical summary receiver operating characteristic, a summary operating point (e.g., summary values for sensitivity and specificity), 95% confidence region for the summary operating point, and 95% prediction region (confidence region for a forecast of the true sensitivity and specificity in a future study). A clinical marker will be considered predictive if the diagnostic odds ratio suggests it is informative and for at least one threshold is >2.

For predictive clinical markers, we will explore whether the accuracy of predictions improve by using combinations of clinical markers within composite variables (e.g. blood loss >500 or shock index > 1). Combinations of clinical markers will be benchmarked against the single most predictive clinical marker. For blood loss we will consider incremental thresholds above the median blood loss. For other potentially important predictors we will use a pre-specified clinically relevant threshold for

each predictor (e.g., pulse >100 for tachycardia, blood pressure <100/60 mmHg for hypotension, or shock index >1 for shock). For combinations of clinical markers, different permutations will be explored including considering women at high risk for the composite outcome when all combined clinical markers are abnormal or at least one of them is abnormal. Lastly, combinations of clinical markers will also be explored among subgroups of participants if biologically plausible. For example, anaemic women may demonstrate abnormal clinical markers even with low measured blood loss and in this subgroup some combinations of clinical markers may be more predictive.

Heterogeneity will be explored through subgroup analyses conducted using the bivariate model by mode of birth (vaginal versus caesarean), World Bank classification by country income level at the time of data collection per dataset (high and upper-middle income versus low and lower-middle income), and individual baseline risk (high versus low), if sufficient data for the subgroups are available. Participants will be designated as high risk if they have any of the known risk factors for PPH (e.g., anaemia). We will explore the robustness of the findings through sensitivity analyses conducted by removing populations with different prognoses (e.g., participants that did not receive standard PPH prophylaxis with oxytocin) or using different test thresholds for initiating treatment (e.g., diagnosing and treating women with blood loss of 300 ml or more instead of the standard diagnostic threshold of 500 ml or more). Subgroup and sensitivity results will be examined by comparing the differences in sensitivities and specificities and prediction graphs. If we find no evidence of subgroup differences or that specific participant characteristics impact on the predictions, emphasis will be placed on presenting the predictions from the full dataset.

WHO will convene a technical consultation of an international group of experts to review the preliminary results and decide on the relative value they place on the sensitivity and specificity of predictive clinical markers for the composite outcome of interest. The preferred trade-offs between sensitivity and specificity will be achieved through consensus. The experts will review the outputs of this analysis and explore how these outputs will inform cost-effectiveness analyses and modelling.

Role of the funding source

The funder of the study will have no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Discussion

This IPD meta-analysis aims to provide evidence on the prognostic accuracy of clinical markers (such as measured blood loss, pulse rate, blood pressure, and shock index) that could predict mortality or life-threatening complications from postpartum bleeding. The findings will provide insight into what threshold and which clinical markers or combination of clinical markers can help to identify much earlier women at high risk of severe adverse outcomes.

IPD meta-analysis has several strengths over an aggregate meta-analysis. First, it permits granular analysis of various thresholds for each clinical marker. Second, the IPD approach allows further exploration of the prognostic accuracy for each clinical marker in important population subgroups, such as women giving birth vaginally or by caesarean section. Third, the IPD's individual-level analysis permits us to incorporate data from studies that were not purpose-designed to test the

prognostic accuracy of clinical markers, such as intervention studies where measurement of the clinical markers and outcomes are often more robust.

However, similar to aggregate meta-analysis, the IPD analysis may be limited by inconsistencies in the measurement and reporting of variables of interest across studies, as well as by differences in the selection of women in the available datasets (selection bias). We will document and report these potential sources of heterogeneity and bias through QUAPAS assessments and then explore their differences in prognostic accuracy by carrying out sensitivity and subgroup analyses where possible. There is also the potential for inclusion bias if we are not able to obtain data for all eligible studies so we will report the number of available datasets we were able to obtain for this study. Lastly, we expect that no datasets exist where women are naïve to treatment and so all women would have been treated upon PPH diagnosis. Therefore, the prognostic accuracy estimates will reflect the real-world study populations rather than a hypothetical population where all women are left untreated. Treatment is likely to reduce the incidence of both abnormal clinical markers and the composite outcome, biasing the estimated prognostic accuracy towards the null. We would need to consider this treatment paradox effect as we interpret the prognostic accuracy estimates and their clinical value.

To the best of our knowledge, this will be the first IPD meta-analysis to assess the prognostic accuracy of clinical markers for identifying women who are likely to deteriorate and experience life-threatening complications or die from postpartum bleeding. The findings from this study have the potential to inform future clinical practice, research and policy.

Author contributions

IG, AC, and OTO conceived the study idea and coordinated the development of the protocol. MP and AT contributed to the design of the methodology, including the statistical analysis plan. MP provided expertise and input relevant for individual participant data acquisition and harmonization. IG, AC, OTO advised on the clinical context and potential interpretation. All authors contributed to drafting and revising the manuscript, approved the final version for submission, and agreed to be accountable for all aspects of the work.

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We gratefully acknowledge the valuable guidance and support provided by the members of the Steering Committee established by the World Health Organization for this project. The committee contributed to the study methodology and provided strategic inputs on the framing of the research question, and criteria for eligible datasets for the IPD. We thank all members for their expert input and ongoing engagement throughout the development of this protocol. WHO is grateful to Professor Anna Lene Seidler for her review and input to this protocol.

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Competing interests
None declared.

Patient consent for publication
Not required.

Ethics and dissemination
This study will involve secondary analysis of existing study de-identified data. To be included in the pooled database, each included study must have received ethics approvals from relevant committees. The main manuscript will be submitted to an open-access journal.

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