An Evidence Gap Map on Perioperative Mortality Ratios and Causes of Death in High-, Middle-, and Low-Income Countries

Study Protocol

Kevin McIntyre, Yun-Hee Choi PhD, Ava John-Baptiste PhD, **Daniel J. Lizotte PhD,** Jessica Moodie MSc, Dr. Saverio Stranges MD PhD FAFA, and Janet Martin PharmD

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1. Objectives of this Evidence Gap Map

The purpose of this evidence gap map (EGM) is to provide a single document that captures the current status of perioperative mortality ratios (POMR) and specific causes of death (CoD) in high, middle, and low income countries with regards to the three established bellwether procedures (caesarean section, laparotomy and treatment of an open fracture). This EGM will focus on the primary outcome of the incidence of specific causes of death across all countries, so as to enable the development of a series of multilevel meta-regression models investigating the incidence of specific causes of death.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | POMR | CoD1 POMR | CoD2 POMR | CoD3 POMR | CoD4 POMR | CoD5 POMR | CoD6 POMR | CoD7 POMR | etc |
| Overall |  |  |  |  |  |  |  |  |  |
| HDI Group 1 |  |  |  |  |  |  |  |  |  |
| HDI Group 2 |  |  |  |  |  |  |  |  |  |
| HDI Group 3 |  |  |  |  |  |  |  |  |  |
| Country 1 |  |  |  |  |  |  |  |  |  |
| Country 2 |  |  |  |  |  |  |  |  |  |
| Country 3 |  |  |  |  |  |  |  |  |  |
| Country 4 |  |  |  |  |  |  |  |  |  |
| Country 5 |  |  |  |  |  |  |  |  |  |
| Country 6 |  |  |  |  |  |  |  |  |  |
| etc |  |  |  |  |  |  |  |  |  |

Table 1: Example of an EGM for a Specific Bellwether Procedure

1. Inclusion Criteria

The following section describes the criteria for studies to be included into this EGM

* 1. Types of Studies and Research Designs

Only primary studies, will be included in this EGM.

In this context the term “primary study” is defined as follows:

* Studies that report on patient level data related to POMR, preferably with subgroups defined by suspected cause of death, predictor variables, and/or covariates
* These studies can use either experimental designs - i.e. randomized controlled trial (RCTs)-, quasi-experimental designs –e.g. propensity score matching, inverse probability weighting, or difference-in-differences, or observational designs – e.g. cohort study designs (prospective, retrospective or ambidirectional)
* Investigate a “bellwether” procedure. These procedures are defined by the *Lancet* Commission of Global Surgery (LCoGS) as Caesarean Section, Laparotomy and Treatment of an Open Fracture (Meara et al, 2015).
  1. Target Participant Characteristics

This EGM is focused on adult participants.

For the purposes of this EGM adult will be defined as ≥18 years old. Thus, this EGM will include:

* Studies whereby over 50 percent of the study’s participants meet this criterion. For example, a study may be investigating surgical outcomes in youth and have defined the age range of youth as 16-24. This paper would be included if the median age is 18 years or older.
* In the instance where median age cannot be determined, mean age will be used. A modification of the above criteria of over 50% of patients aged over 18 years (i.e. mean age ≥18 years) will be used.
* In the case where neither median nor mean age of the sample is reported the study will be excluded at the full-text screening stage.
  1. Minimum Sample Size

Studies will be included if they have 200 participants or more in their sample. This number was arrived at using the targeted POMR for LICs of 1.5% POMR and applying the rule of three for sample size estimation (Weiser and Gawande, 2015; Bainbridge et al, 2012). A POMR of 1.5% translates to one death for every 66.67 procedures (1/0.015). Thus, by applying the rule of three to the sample size calculation, this value is multiplied by three (66.67\*3) giving 200 as the minimum sample size acceptable for inclusion into the EGM.

Due to the lack of studies arising from LMICs (Bainbridge et al, 2012; Manchanda and Varma, 2004; Shroff et al, 2017) a sensitivity analysis will be planned, consisting of the inclusion of studies from LMICs that did not meet the minimum sample size threshold. More detail on this sensitivity analysis is provided in the planned subgroup and sensitivity analyses section (See Section 9, page 19).

* 1. Thematic Scope

This EGM will focus on the outcome of all-cause perioperative mortality ratio (POMR), and cause specific mortality ratios rather than any particular intervention leading to these outcomes. However, due to the extreme volume of surgical publications in addition to the need for each included publication to present specific cause of death data, eligibility for inclusion will be restricted to primary articles studying any of the three bellwether procedures that have been identified by the LCoGS (Meara et al, 2015). Thus, the scope of this EGM includes all eligible publications investigating bellwether procedures as defined by the LCoGS.

The ideal study would report POMR for all the specific bellwether procedures conducted at the institution, and suspected causes of death in the perioperative period.

* 1. Geographic Focus

This EGM will present evidence arising from High-, Upper-Middle-, Lower-Middle- and Low-Income Countries as defined by the World Bank Country and Lending Groups (World Bank, n.d.). Each country will be presented in the EGM with its own row to best show the existing evidence. Analyses will be conducted based upon the World Bank Country and Lending Group clusters. In the case that there is not enough evidence to conduct the analyses with four groups, the studies will be split into three groups (High Middle and Low) with the Upper-Middle and Lower-Middle groups being combined to create the new Middle group, or if this is still not adequate, two groups; high (HICs) and low- and middle-income countries (LMICs) using a 0.700 Human Development Index (HDI) cutoff point.

These cutoff points have been selected as there is evidence to show that a High versus LMIC grouping better explains differences in global trends in POMR compared to a crude analysis of POMR over time globally (Bainbridge et al, 2012).

* 1. Publication Period

Studies published from January 1, 2014 until September 1, 2021will be included with regular updating searches in the databases being conducted until May 1, 2022.This is important for the primary analysis to arise from the EGM that will model the incidence of POMR across time to investigate whether surgery is getting safer or not.

This publication period has been selected to complement a previous meta-analysis conducted on POMR in LMICs by Ng-Kamstra et al in 2018. This analysis examined POMR in LMICs between 2009 and 2015. To avoid overlap articles published in 2014 will be screened against Ng-Kamstra et al’s analysis to ensure that articles are not included in both meta-analyses.

* 1. Language Restrictions

Searches will be conducted in English, but studies written in any language will be considered for inclusion.

1. Included Interventions and Outcomes
   1. Interventions

All studies reporting outcomes of bellwether surgical interventions performed on adults, will be eligible for inclusion provided that they are reporting on a mixed surgical population (i.e. not one specific surgical subpopulation, such as geriatric patients, as to avoid confounding). This is because the EGM is interested in the safety of surgery in a global context, both in the geographical and rhetorical sense of the word.

* 1. Outcomes

This section outlines the various outcomes that will be incorporated in the EGM

* + 1. Perioperative Mortality Ratio (POMR)

Perioperative mortality will be defined as death from any cause before discharge (or a maximum of 30-days) following the administration of any type of anaesthesia for a surgical procedure conducted in an operating theatre (Davies et al, 2021). This definition will be used loosely. Thus we will also include longer time periods to allow for potential comparisons between in-hospital mortality, 30-day mortality, and longer time periods (e.g. 60-day or 90-day).

Thus, POMR will form the basis for the primary outcome that the EGM is focused on, cause specific POMRs.

* + - 1. Calculation of POMR

POMR will be calculated as the ratio of perioperative mortality, as defined above “divided by the total number of [surgical] procedures, per year, expressed as a percentage (Davies et al, 2021).

* + - 1. Definition of a Procedure

A procedure is defined by the WHO as “one that takes place in an operating room or theatre suite” (Watters et al, 2015). This definition notably excludes procedures that take place in “procedure rooms” such as many endoscopic procedures. By using the number of procedures as the denominator in the POMR, rather than patients, it takes into account people who have multiple procedures. Thus, the number of procedures can (and most likely will) be greater than the total number of patients who have undergone surgery. This rationale is similar to the maternal mortality rate which calculates its denominator based on the number of live births rather than on the number of women who have given birth (Watters et al, 2015). Since the numerator consists of number of people who died following surgery, this outcome can only be experienced by each patient once, even if they undergo multiple procedures. For this reason, POMR is classified as a ratio.

While the definition of POMR was updated by Davies et al in 2021 the definition of a procedure was not explicitly defined. Rather it was merely implied in the updated definition of POMR that a procedure must be conducted “in an operating theatre using any form of anaesthesia” (Davies et al, 2021). Therefore, for the purposes of this EGM and multilevel meta-regression, we will continue to use Watters et al’s 2015 definition as it meets the newer implied definition but remains more explicit.

If the number of procedures is not provided in the article, with instead the number of participants/patients reported, this value will be used as a proxy for number of procedures. Using procedures as the denominator is likely to lead to an underestimate of the dangers of surgery, but it is believed that this underestimate will be negligible.

* + - 1. Time points for Calculation of POMR

POMR is traditionally calculated at two time points: on the day of surgery (including intraoperative mortality) and before hospital discharge or at 30 days post-surgery, whichever comes first (Watters et al, 2015). These definitions have also been proposed by the Safe Surgery Saves Lives initiative at the WHO’s Patient Safety Programme (WHO, 2003). Recently Davies et al more explicitly state that the time point for POMR is “deaths before discharge (up to 30 days)” (2021).

For the purposes of the EGM we will be considering only a single time point for the primary analysis: 30-day mortality or hospital discharge as our primary objective. While this timeframe is vague in nature, this is due to the difficulties often experienced in obtaining accurate follow-up data after patients have been discharged, particularly in LMICs (Watters et al, 2015). Furthermore, there is data to suggest that death before discharge and 30-day mortality are reasonable correlated and thus death before discharge may be a viable proxy for the 30-day mortality proper (Watters et al, 2015).

As some articles may be unclear as to when they measured POMR or mortality in general, if 30-day mortality is not clearly reported, or mortality is measured at multiple other time points, the time closest to 30 days will be utilized for data analysis. This methodology was chosen to be consistent with other studies in the field (Bainbridge et al, 2012).

Furthermore, the 30-day mortality time point will be used for this study as the same-day time point is viewed as an indication of clinical judgment as to whether the patient should have undergone surgery at all, rather than the safety of the surgery itself (Watters et al, 2015). Thus, the authors believe that using this time point would reflect a different question than one that this EGM and following analyses are intending to investigate.

However, due to the limited amount of information surrounding cause of death for intraoperative, early period and late period mortality, as much information as possible will be gathered surrounding the timing of cause of death. This is because all information regarding time of death is still valid and useful for assessing other questions surrounding surgical safety, such as “clinical judgment” issues, and thus will be collected for the purposes of secondary objectives and collecting evidence for future work.

* + - 1. Other Benefits of Using POMR

A benefit of the POMR is that it transcends geographical and cultural barriers to allow for comparisons within as well as between countries in a similar way to the often-used maternal mortality rate (Watters et al, 2015). Another benefit of using the POMR is that in addition to providing a measure of surgical safety, it also indirectly provides an indication of surgical access since the number of procedures performed is the denominator of the POMR (Watters et al, 2015). This information becomes an even more useful measure when presented alongside the number of procedures per 100,000 people, as it then describes both the accessibility of surgical procedures as well as their safety (Watters et al, 2015).

* + - 1. POMR Risk Adjustment

In order for POMR to be comparable between various geographical/political boundaries, it must be adjusted for several variables which may distort the POMR due to their associations with both requiring surgery and their effect on the probability of perioperative mortality. These variables include age, emergency/elective status, American Society of Anesthesiologists (ASA) score, procedure/procedure group, and the Human Development Index (HDI) of the country (Watters et al, 2015). Additionally, if possible, data will be collected on, the proportion of each sex, whether the hospital performing the procedure was located either rurally or in an urban center, what type of hospital performed the procedure, and for procedures conducted in 2020 and beyond the proportion of patients who were confirmed to have SARS-CoV-2 infection for use in the model/sensitivity analyses.

The adjustment of POMR risk will be secondary to describing the unadjusted rates as analytic comparisons are useful only after the unadjusted trends in perioperative mortality ratios are understood within a jurisdiction. This is because the authors do not want to adjust away differences due to other factors when the unadjusted trend in deaths is important information regardless of why (e.g. initially it matters less why some areas may be seeing higher POMRs than others versus understanding overall how many people are dying in the perioperative period in total and what causes they are dying from).

* + - 1. Specific Causes of Death

Specific causes of death will be classified according to the WHO Global Health Estimates (GHE) system. A list of the corresponding causes of death can be found in Annex Table A of the Global Health Estimates Technical Paper “WHO methods and data sources for country-level causes of death 2000-2019” report (WHO, 2020).

We will use this system to classify cause of death. In the case that a death is listed that does not naturally map onto this system the most appropriate cause of death in the GHE system will be selected. These differences will be transparently and clearly presented.

1. Search Strategy

The search strategy will be conducted by searching for primary articles reporting on perioperative mortality among bellwether procedures as defined by Hanna et al, 2020. The search period will be from 2014-present (initial search conducted on September 1-2, 2021). This narrow timeframe will be supplemented by Ng-Kamstra et al’s 2018 meta-analysis investigating POMR in LMICs (2009-2014). This will provide more information for LMICs which are anticipated to have larger gaps in the evidence. In the case that there are not enough studies in the HICs cluster, the search will be expanded back to 2009 in line with Ng-Kamstra et al’s work.

The searched studies will then be screened sequentially through title\abstract and full-text phases to ensure that they meet the inclusion criteria. Included studies will then have their data extracted and compiled to create a database on POMR and specific cause of death POMR. This database will then be used to run the statistical analyses outlined in this protocol.

The primary articles will also be used to populate the EGM, to provide a visual guide to the demonstrate degree that this data exists and in what countries.

* 1. Search Terms and Strategy

See Appendix 1

1. Methodology: Searches, Screening, Coding and Quality Assessment
   1. Systematic Searches
      1. Database Searches

The search strategy outlined in the previous section will be conducted across several databases. The list of the proposed databases to be searched is found below. These include both peer-reviewed journals as well as various forms of grey literature.

* + - * Global Index Medicus
      * IRIS
      * MEDLINE
      * EMBASE
      * Cochrane CENTRAL
      1. Grey Literature Database Searches

In addition to the databases to be searched outlined in the previous section, the grey literature will also be searched for relevant articles, theses and dissertations. This grey literature will be searched for through some of the following sources:

* + - * Open Grey
      * OAIster
      * ProQuest Dissertations & Theses A&I
      * Open Access Theses and Dissertations (OATD)
      * E-theses online service (EThOS)
      * DART
      * Centre for Research Libraries Global Resource Network
      * EU Open Data Portal
      * Latin American Open Archives

Not all of these sources will necessarily be checked due to constraints on human resources. Specifics of what grey literature is searched will be transparently reported.

* + 1. Citation Tracking

Key articles identified by the research team will undergo forward and backward citation tracking to ensure that all relevant articles are captured in the search process.

* 1. Screening

All primary articles identified by the search strategy as well as the citation tracking methods will be compiled in DistillerSR reference management software (DistillerSR, 2021).

This artificial intelligence software will be used to assist with the screening process.

Articles will first be screened by title and abstract, then by full text. During the title/abstract screening a prespecified percent of studies (90%) will be set by the review team. This indicates that 90% of the articles found by the searches will be screened by humans using a prespecified and pilot tested flowchart form (see Appendix 2). The DistillerSR AI software will use machine learning to reorder the screening list such that articles with the highest probability of being included will constantly be brought to the top of the pile to ensure that the most relevant articles are being screened. After 90% of articles have been screened - or all articles to the point where the remaining articles have an incredibly low probability of inclusion as determined by the AI software (i.e. 2%) – then a search will be conducted through the remaining articles using the information gathered through the machine learning process to identify any potential articles remaining that may still meet the inclusion criteria. At this point the authors will continue on to level 2 screening (i.e. full text screening) as normal.

At each stage of screening irrelevant articles will be removed from the pool of eligible studies to be included in the EGM. Studies excluded from the EGM will still be maintained in a separate file for record keeping and transparency purposes. The removals will be documented in a PRISMA flow chart attached to the EGM.

The title and abstract screening stages will be conducted by a single author; however, the full text review will be conducted by two independent authors, with conflicts being resolved by consensus. In the case that consensus cannot be reached, a third author will be included to arbitrate.

* 1. Coding

A standardized data extraction form will be created in Microsoft Excel spreadsheet to organize the information being retrieved from each document. This data extraction form will be uploaded into DistillerSR to ensure that there is an auditable trail.

Data to be extracted consists of the title of the paper, the names of the authors, the year of publication, type of study design (e.g. RCT, quasi-experimental or observational), whether data was collected prospectively or retrospectively, the country of publication/where the surgeries took place, HDI value of that country at the time of the study (or closest available year), what type of surgery was being investigated, sample size, POMR, variance of the POMR, proportion of emergency surgeries, proportion of patients that were female/male, average ASA score (if available), proportion of COVID positive patients, level of hospital that the procedure was performed at, whether the institution was located in an urban or rural setting, and specific causes of death. Appendix 3 provides the proposed data extraction form.

* 1. Quality Appraisal of Primary Studies

If the number of papers deemed eligible for inclusion into the EGM is within a manageable upper limit, then the Risk of Bias in Non-Randomized Studies tool and the Risk of Bias Tool in Randomized Studies will be used as appropriate.

These tools were picked due to a combination of their validity, reliability, and ease to administer due to the expected large volume of articles that will meet the inclusion criteria for the EGM.

1. Screening and Coding Accuracy and Consistency
   1. Searching

The search strategy to be applied to each database will be individualized to the particular syntax necessary for the databases through consultation between the primary author and a medical librarian. Any necessary variations made to the search strategy will be recorded and preserved.

* 1. Test Screening

In order to test the screening process, a pilot testing was conducted on the screening flowchart by KM, analyzing 1,000 articles identified in the searches at the level 1 screening level (i.e. title/abstract screening). This flowchart was then tested again by the lead work-study student, employed to assist with the volume of articles captured, to ensure that it was capturing articles of interest.

* 1. Data Extraction

After the test full text screening process, articles meeting the inclusion criteria for the EGM will have data extracted and coded by the primary author before being independently reviewed by a secondary author for examination of the applicability, and reliability of the extraction. Conflicts will be resolved through consensus or, if consensus is not able to be reached, through the inclusion of a third author to arbitrate.

* 1. Title and Abstract Review of Primary Studies

Titles and abstracts of the searched studies will be screened to assess if they meet the inclusion criteria. The algorithm for determining whether a study will proceed to full-text review is outlined in Appendix 2.

* 1. Full Text Review of Primary Studies

All studies that are included on the basis of the title and abstract review will then be subjected to a full text review by the primary author. The algorithm for determining whether a study will be included in the EGM is provided in Appendix 2. A second author will also conduct full text review. Any disagreements will be resolved via consensus, or if consensus in not reachable, through the arbitration of a third author.

* 1. Data Extraction Consistency

After the full text screening process, articles meeting the inclusion criteria for the EGM will have data extracted and coded by the authors in the same manner as the testing. Conflicts will be resolved through consensus or, if consensus is not able to be reached, through the inclusion of a third author to arbitrate.

* 1. Quality Appraisal Accuracy

The quality appraisal will be conducted primarily by the first author. All quality appraisals will be transparently reported in supplemental files with reasoning for why each study was given the appraisal value that it was.

1. Resolving Issues Arising From Duplicates

Duplicate primary studies will be removed with the most recent version of the article being retained and the older version removed from the dataset. This will not necessarily apply to national dataset (e.g. NSQIP, NELA) since different articles may investigate different subpopulations at different time points. With respect to these studies we will attempt to access the databases directly to gather the information. Failing that, we will investigate individual studies and include on the basis of attempting to minimize patient overlap while maximizing temporal coverage (e.g. if one study examines laparotomies between 2000-2005 and a second one investigates them from 2006-2010, both studies will be included).

Since this EGM will collect primary studies from an overlapping time period as Ng-Kamstra et al, it is important that primary studies published during this period be carefully screened. In order to avoid biasing the results of the analyses that would occur due to counting these participants more than once, suspected duplicate studies will be thoroughly investigated to determine whether they are in fact duplicates. This will be done by comparing authors, publication dates, country that the study was conducted in, other methodological choices that would be expected to vary between studies.

This deduplication will be conducted in DistillerSR using the standard “duplication detection” settings and then running the “Smart Quarantine” procedure with the threshold for the level of match confidence set to 80%.

1. Primary Objective and Analysis Plan

The primary purpose of this EGM is to gather all existing relevant studies from 2015 onwards to describe the current major perioperative causes of death.

Additionally, another goal of this EGM is to gather sufficient data to conduct a multilevel meta-regression using a logistic regression technique to investigate the trends of cause of death within POMR over time as well as a general POMR model.

This approach will capitalize on the fact that in essence, a meta-analysis is a specialized case of a two-tiered multi-level model (Thompson, Turner & Warn, 2001). That is, the data involved in a meta-analysis is structured in such a way that participants are nested within studies, which have a certain amount of heterogeneity both within and between said studies (Thompson, Turner & Warn, 2001). In the case of investigating POMR on a global scale, HDI is considered to be a major covariate that must be controlled for (Bainbridge et al, 2012). Thus, this analysis proposes that a three-tiered multilevel model be used as the data collected from this EGM will be participants nested in studies which are nested in countries (which will be grouped into HDI levels) at a particular time. The levels can be conceptualized as follows:

Level One: Participant Level

Level Two: Study Level

Level Three: HDI group (defined by the country and date that the study was conducted)

These specifics can be applied to the general framework shown in the diagram below:

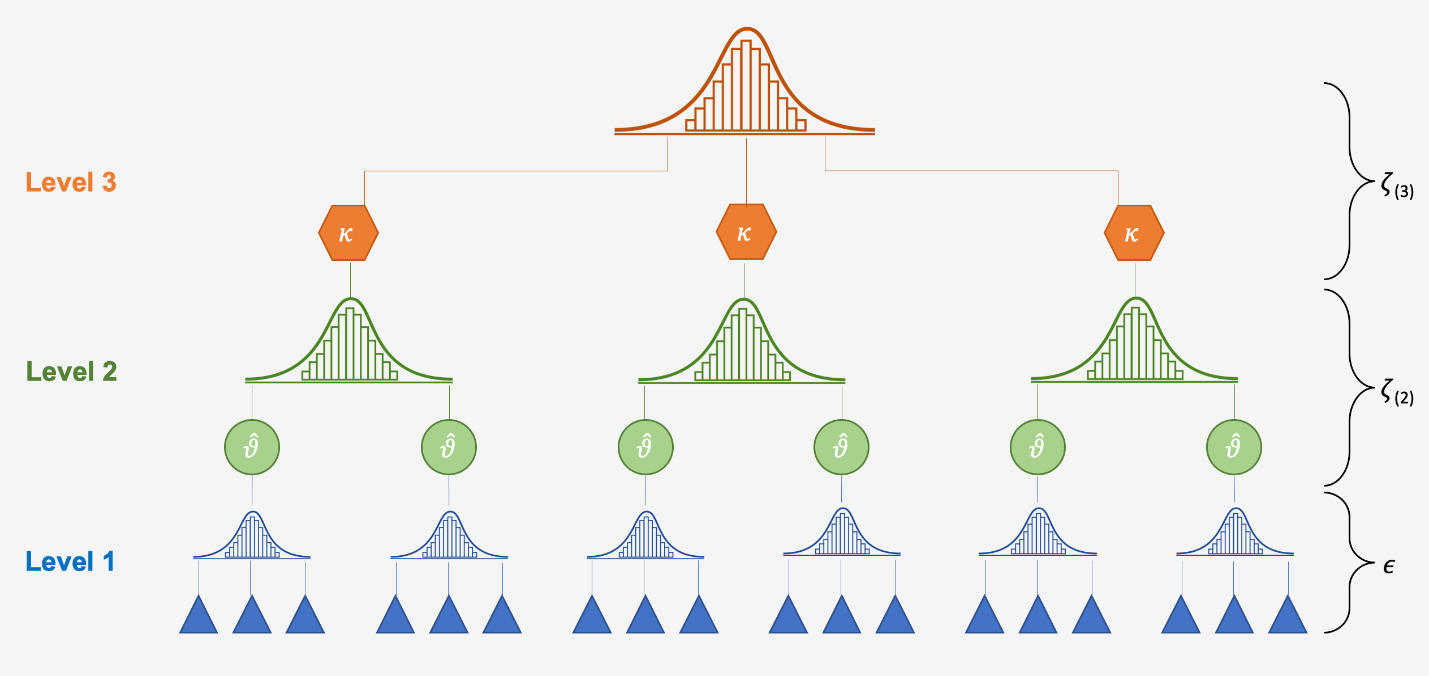


Fig. 1: Three-Tiered Multilevel Model Diagram (Harrer, Cuijpers, Furukawa & Ebert, 2019)

The primary objective of the multilevel meta-regression will be to determine the trend of all-cause POMR as well as POMR for each specific cause of death across time for each bellwether procedure as well as an overall model. An additional advantage of using a multilevel modeling technique for this analysis is that it inherently accounts for the expected interaction between year of surgery and HDI. This interaction is theoretically plausible and could be an important aspect of trends in global POMR. Hezam et al (2020) conducted two systematic reviews and meta-analysis using multiple bivariate meta-regressions to show that patterns of perioperative maternal mortality ratios across both HDI and year. However, no model was created that accounted for both these factors simultaneously, nor any potential interaction between them. Thus, by utilizing the proposed methods in this protocol this study plans to account for this possibility.

This interplay between HDI and time is can be easily explained through the use of the example of laparoscopic surgery. While laparoscopic surgery has a long and rich history, for the purposes of this example we purport that modern laparoscopic surgery in essence first became available in the early 1980s with it becoming commonplace in high income settings by the early 1990s1. Laparoscopic surgery is commonly used today due to the benefits that it provides; however, the use of laparoscopic surgery can be viewed as dependent on two interacting variables: Time and resources. Time is a fairly self-evident variable in this case. It is impossible for a surgical procedure to appear in a study before the invention of said procedure. Thus, regardless of the available resources in a given setting laparoscopic surgery could not have occurred there regularly prior to it becoming a common procedure (i.e. prior to 1980). Secondly, the resources available has a large impact on whether laparoscopic surgery will be undertaken. Even in 2021, there are many operating theatres which do not have the human and physical infrastructural resources to provide laparoscopic surgery. Thus, even though time is at its maximum value laparoscopic surgery is not universally available due to the lack of resources. These resources are proxied by the HDI variable in this analysis.Thus, for a study to provide laparoscopic surgery the technique must be available (i.e. time) and the center must have the resources to provide it (i.e. resources proxied by HDI). If either of these variables are not sufficiently met then a laparoscopic procedure cannot happen.

In addition to HDI and time, other covariates will include average age of the sample, proportion of emergency surgeries in the sample, average ASA score of the sample, proportion of each sex in the sample, proportion of COVID positive patients, hospital level and whether the facility was located in an urban or rural setting.

Furthermore, analyses indicating specific cause of death trends across time on each specific bellwether procedure/group will be conducted as well as the overall model.

* 1. Regression Equations

Below is the level specific and overall mixed model regression equations that accounts for the three tiers of nesting as well as the planned covariates that will be included in the adjusted models. This model will use a quasi-binomial logistic regression approach to handle proportions at either extreme (i.e. 0 and 1). We will also analyze the data in a sensitivity analyses using a null Bayesian model with an uninformative beta prior as a continuity correction. This will have the effect of transforming zero values and 1 values to slightly less extreme versions which will then allow for a logistic regression model to be fit from this corrected data.

**Level 1 – Individuals**

**Level 2 – Studies**

**Level 3 – Countries**

**Composite Equation**

1. Secondary Objectives and Analyses

The first of the secondary objectives is to investigate the relative rankings of specific causes of death across time to examine which causes of death are currently the most pressing issues requiring intervention. This data will be presented using Sankey graphs.

The following analyses are more specific in nature than the overall primary analysis and will be undertaken if there is sufficient data collected in order to run these more specific analyses. These analyses are proposed in order to break apart the large nature of both the major covariate of geography (of which HDI was a proxy in the initial analysis along with other constructs) and the outcome of POMR (which will be split into causes of death):

* Examining the POMR across time of countries of key interest to assess if these areas are following the overall trend reported in the primary analyses or if there are major differences.
* Combining the two existing analyses to look specifically at certain high priority causes of death in certain high priority countries, across time.

Thus, by taking a closer examination of these various exposures and outcomes, this EGM and multilevel analyses could create a directly useful first step for policy makers for such areas that have high POMRs or cause specific mortalities.

1. Planned Additional Analyses, Subgroup Analyses and Sensitivity Analyses

Due to the scope of this project and the foreseeable difficulty in accounting for many aspects that may also have an impact on the results of this study, several additional analyses, subgroup analyses and sensitivity analyses will be conducted to gather initial, exploratory evidence.

These analyses include:

* Sensitivity Analyses comparing RCTs to Observational study designs (data permitting)
* Sensitivity Analyses comparing prospective observational designs to retrospective observational study designs (data permitting)
* Sensitivity analysis conducted by removing studies at a high risk of bias to assess if these studies could potentially be biasing the results (If a RoB assessment was done)
* Sensitivity analysis conducted by removing all studies that did not explicitly state that they used the 30 day/hospital discharge time point to report POMR
* A sensitivity analysis will be done by removing all studies that exclusively investigated cancers. These studies will be initially included due to the heterogeneity of various cancers in both surgical methods and mortality risk, however, they remain highly correlated as they are all diseases of uninhibited cellular growth.
* A sensitivity analysis that removes studies from LMICs that did not meet the 200-person sample size restriction to investigate if this affects the results.
* Sensitivity analysis assessing impact on odds ratios when POMR is common (POMR ≥10%) versus rare (POMR<10%).
* Sensitivity analysis to assess the impact of multiple imputation for missing data (see missing data section for more information).
* Sensitivity analysis assessing the impact of using different time point cutoffs for the definition of POMR (e.g. In-hospital, 30-day, 60-day, 90-day).

1. Specification of Variables

This section will provide more information regarding the variables/data to be extracted from the primary articles that have not yet been discussed in detail.

* 1. Outcome Variable(s)

Due to the broad nature of this project several models will be developed. The primary models will investigate each identified cause of death POMR as an outcome variable.

A second analysis will investigate general POMR across time using a multilevel meta-regression model, with the levels of HDI serving as the level three variable.

* 1. Predictor Variable

The primary predictor variable that will be considered for the primary and secondary analyses will be year that the surgery took place during. In the case where the year that the surgery was conducted cannot be determined, either the median year (if there were several years of observation) or the calendar year 8 months prior to the publication date will be used so to allow for lag time due to the publication process.

* 1. Covariates

These variables have been included on the basis of a theoretical directed acyclic graph (DAG) (see Figures 3a and 3b in appendix 7) outlining the potential impact that each of these variables could have upon the measured relationship between the exposure of surgery and the outcome of POMR (i.e. the hypothesized causal mechanism). As demonstrated by Figure 3b each of the following covariates must be controlled for to close all backdoor pathways identified in the DAG. Note that this is a simplified model with the actual exposure being year that surgery was performed. It is therefore important to note that even though the adjustment for known confounders as identified in this DAG indicates that all backdoor paths will be closed, this is no guarantee that there are not other confounders which are not identified in the DAG. These confounders could introduce significant residual confounding into the results.

* + 1. Average Age of Participants

Due to the associations between the need for surgical procedures (including bellwether procedures), risk of perioperative mortality and age, the risk adjusted series of models will account for this confounder by incorporating the average age of each included primary article into the regression models.

* + 1. Proportion of Emergency Surgeries

Due to the association between the need for emergency surgery within the context of bellwether procedures, and the risk of perioperative mortality, the proportion of emergency surgery cases in each included primary article will be accounted for in the adjusted regression models.

* + 1. Average American Society of Anesthesiologists Score

Due to the confounding potential of severity of illness on the association between the exposure of undergoing a bellwether procedure and perioperative mortality, the average ASA score presented in each primary study will be used in the adjusted regression models.

This is dependent on the degree of missing data with regards to this variable. There is previous literature indicating that ASA scores are often not presented in publications and therefore, the use of multiple imputation will likely be necessary (see missing data section). If there is such a degree of missing data that multiple imputation cannot be used, then this variable will not be able to be adequately adjusted for and will unfortunately have to be dropped from the analysis.

* + 1. Proportion of Each Sex

Due to the wide variation in actual procedures that can fall under the definition of laparotomy (e.g. hysterectomy, and ooectomy), the adjusted models will account for the proportion of each sex in the studies.

* + 1. Human Development Index

The country that the procedure was performed in has a large potential to influence the risk of perioperative mortality. This could occur due to training standards of the surgeons, availability of specialists, availability of proper medical equipment, accessibility to timely surgery, and many more factors. Thus, the United Nations Human Development Index (HDI), a summary statistic that incorporates many aspects of a nation’s development will be used to group nations into categories (preferably four separate levels, however, as mentioned earlier if there is not enough data we will reduce the levels to as few as two).

The HDI value assigned to each study will be determined by the year and country that the study was conducted in. From these variables the HDI value will be assigned using freely available data from the United Nations Development Program. These HDI values are available for most countries from 1990-2020. If a study was conducted outside of this timeframe (or for a year in a country where HDI was not available), the closest available HDI will be given to the study.

* + 1. Urban Status

The geographical placement of the hospital where the procedure was performed could also potentially impact the risk of perioperative mortality in a variety of ways (e.g. through timely access, access to specialists, teaching hospital versus district hospital, etc.). Therefore, we plan to collect data on the geographic setting of the hospital where the procedures were performed. We will then dichotomize the hospitals into either rural or urban based on their proximity to large cities using a modification of the UNICEF definition (State of the World’s Children, 2012). This definition provides that while the definition for urban areas varies between countries and can even vary within countries over time, a threshold for using population size as the measurement for defining an area “an urban settlement is typically in the region of 2,000 people, although this varies globally between 200 and 50,000” (State of the World’s Children, 2012). However, due to the fact that large portions of the global population now live in urban areas (Figures 2a and b) it is estimated that the institutions captured in the primary literature will mostly (if not exclusively) be from regions with a population larger than 2,000 and likely even 50,000, the “rule of three” will again be used for this variable. Thus, institutions in urban areas will be considered any institution that is located in a settlement that has a recorded population of at least 150,000 people. While this is a crude measurement for a highly nuanced variable, it is hypothesized that this cutoff will provide a chance of dichotomizing the data into urban/rural in a meaningful way while still providing variation in the variable.

If no primary articles report data from institutions that do not meet the definition of urban (and thus there is no variation in the variable), the variable will be removed from the adjusted analyses.

* + 1. Hospital Level

What type of hospital a patient is treated at could have an impact on the surgery that they receive, the quality of surgery and thus the probability of POMR (World Health Organization, 2003). Oftentimes when patients present to district hospitals in need of surgical procedures the necessary surgery cannot be delayed while the patient is transferred to a higher level of care (secondary or tertiary-level hospital) (Maine et al, 2019; World Health Organization, 2003; Nwanna-Nzewunwa et al, 2016). This becomes even more dangerous because in many LMICs, district hospitals are not adequately resourced to provide quality surgical care due to a lack of equipment and/or properly trained staff (World Health Organization, 2003).. It should be noted that like rurality, the impact of the type of hospital that a patient is treated at seems to impact patients in LMICs more than those in HICs. This is exemplified by a 2009 study by Ghaferi, Birkmeyer and Dimick in the United States which found this effect to be negligible (Ghaferi and Dimick, 2009). They found complication rates to be comparable across facilities and subsequently no differences in the failure-to-rescue rates between hospital types were observed (Ghaferi and Dimick, 2009). Thus, despite this conflicting evidence, this variable will be kept for the multivariable analyses due to the hypothesized differential impact in LMICs.

* + 1. Procedure/Procedure Group

The procedure that a patient is undergoing clearly has an impact on the probability of perioperative mortality. Due to the potentially confounding effects of this variable, Watters et al (2015) and Watters et al (2016) both have

recommend adjusting for procedure in the analysis of POMR. It is obvious that surgical procedures will be performed at different rates between HDI groups and also that different procedures will have different POMRs (Regenbogen et al, 2008; Haynes et al, 2011; Glance et al, 2015); thus, the analyses utilized in investigating objectives 3 and 4 of this proposed thesis will account for the procedure/procedure group that the patients. The majority of analyses to be conducted in the first aspect of objective 1 and objective 2 will not adjust for this variable as it is not applicable. Analyses that combine the three bellwether procedures in objective 1 will utilize this variable, however, the stratified analyses on each procedure independently are inherently restricted to a single procedure group thereby eliminating the need to further adjust.

* + 1. COVID-19 Positivity Status and Time Since Diagnosis

Approximately 2% of participants in the CovidSurg dataset tested positive for COVID-19, which translates to roughly 3,000 participants (COVIDSurg Collaborative, GlobalSurg Collaborative, 2021). The CovidSurg group has found that the risk of POMR in the CovidSurg dataset is associated with the time between diagnosis with COVID-19 and surgery (COVIDSurg Collaborative, GlobalSurg Collaborative, 2021). Thus, for objectives 3 and 4 (analyses that will utilize the CovidSurg dataset), time since a patient tested positive for COVID-19 will be adjusted for.

* + 1. Follow-Up Time

Different studies follow surgical patients for different time periods. This can clearly have an impact on the number of patients who experience perioperative mortality. The most common timepoints included are in-hospital mortality, 30-day mortality and 90-day mortality. In order to minimize the bias that these varying follow-up times will have on the analysis, follow-up time will be included in the adjusted models as a categorical variable.

* 1. Model Specification and Diagnostics

Due to the potential complexity of the relationship between year and POMR, diagnostic tests will be undertaken to ensure that model fit is adequate.

This will be done to ensure that potentially important interactions are accounted for if necessary (e.g. age interacting with ASA status, age interacting with ASA status interacting with emergency status).

Furthermore, it is a distinct possibility that the linearity assumption may be violated due to the nature of the data being examined (e.g. the lower limit of 0 and upper limit of 1 for POMR could cause a floor/ceiling effect causing the data to deviate from a linear pattern at the extreme ends of the model, or cases of significantly changing POMR trends in HDI groups as Bainbridge et al, 2012 found some possible indications of with respect to a plateauing effect in recent years in LMICs).

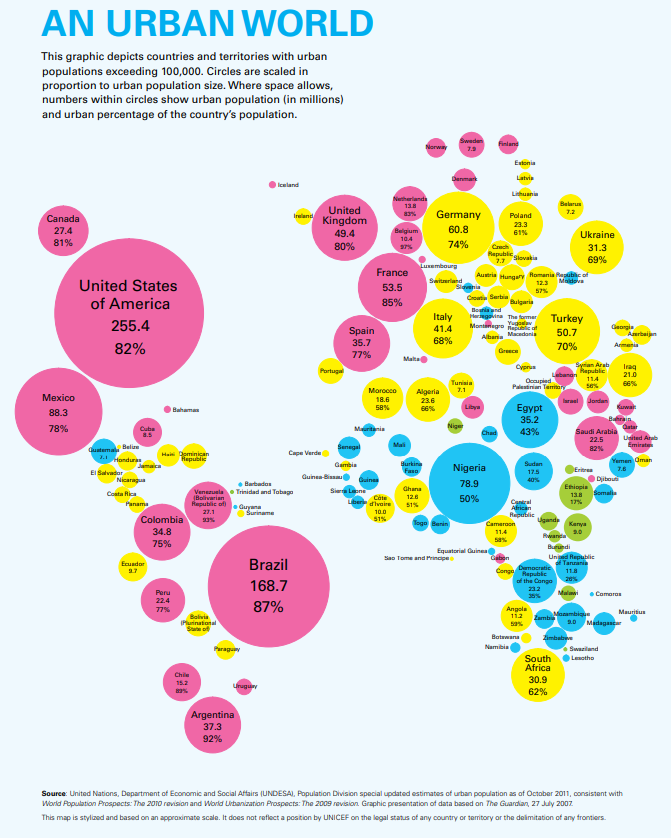


Figure 2a: Proportion of the World’s Population that Lives in Cities Larger than 100,000 people. (State of the World’s Children, 2012).

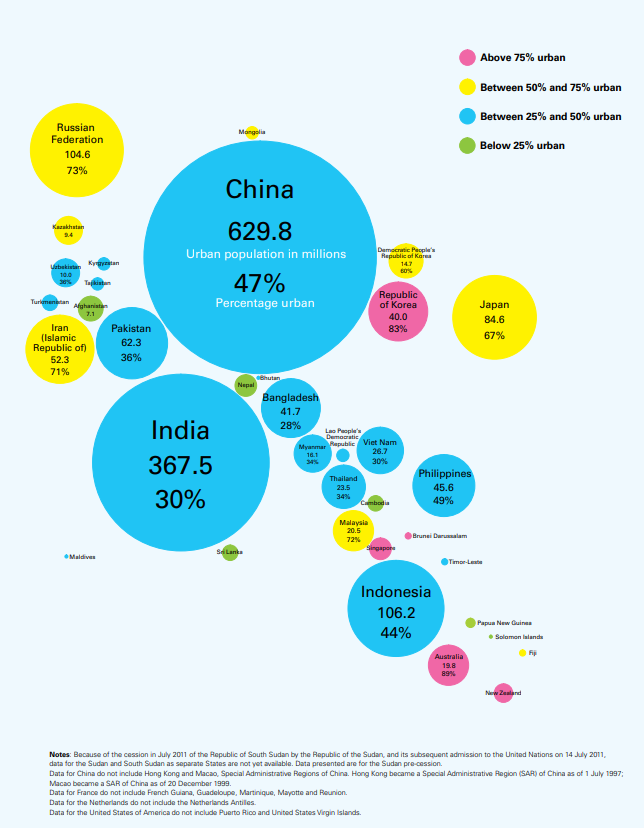


Figure 2b: Proportion of the World’s Population that Lives in Cities Larger than 100,000 people. (State of the World’s Children, 2012).

1. Missing Data

It is anticipated that there will be substantial missing data due to the variation in what variables are available for extraction from each primary article (e.g. ASA score will likely have a high proportion of missingness). To handle this, multiple imputations will be used with sensitivity analyses performed to investigate whether the imputations influenced the results.

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1. Appendix 1: Search Strategy
   1. Embase Search Strategy

Bellwether Search Strategy v13.0

Created in consultation with Jessica Moodie, MLIS

Database: Embase Classic+Embase 1947 to 2021 October 29

Date run November 1, 2021

|  |  |  |
| --- | --- | --- |
| # | Search String | Results |
| 1 | bellwether.mp. | 156 |
| 2 | open fracture/su [Surgery] | 3309 |
| 3 | ((open or compound) adj3 fracture\* adj5 (surg\* or reduction)).ti,ab. | 2419 |
| 4 | (open adj2 reduction).ti,ab. | 15806 |
| 5 | (c?esar?an\* or csection\* or c-section\*).ti,ab. | 104575 |
| 6 | general surgery/ | 19159 |
| 7 | \*abdominal surgery/ | 12022 |
| 8 | (abdom\* adj3 (surgery or surgical or surgeries or surgically or postsurg\* or post-surg\* or perisurg\* or peri-surg\* or operation\* or operating or operativ\* or operated or intraoperat\* or intra-operat\* or postoperat\* or post-operat\* or perioperat\* or peri-operat\*)).ti,ab. | 50899 |
| 9 | ((suture\* or epiploplast\* or omentoplast\*) adj5 (perforat\* adj3 ulcer\*)).ti,ab. | 211 |
| 10 | (small adj bowel\* adj3 (resection\* or anastomos\*)).ti,ab. | 4593 |
| 11 | (colostom\* or colectom\* or hemicolectom\*).ti,ab. | 41879 |
| 12 | (laparotom\* or duodenectom\* or jejunectom\* or ileectom\* or appendicectom\* or cholecystectom\* or minilaparotom\* or mini-laparotom\*).ti,ab. | 126045 |
| 13 | (gastroscop\* adj2 (intrasurgical\* or intraoperative\*)).ti,ab. | 80 |
| 14 | (peritoneal adj3 (adhesionlysis or lavage)).ti,ab. | 4255 |
| 15 | (inguinal adj herniorrhaph\*).ti,ab. | 1198 |
| 16 | (inguinal adj3 hernia\* adj3 (repair\* or surgery or surgical or surgeries or surgically)).ti,ab. | 8803 |
| 17 | (suture\* adj3 (gastric adj2 (tear\* or injur\* or perforat\*))).ti,ab. | 31 |
| 18 | or/1-17 | 365880 |
| 19 | ((an?esth\* or peri-an?esth\* or perian?esth\* or post-an?esth\* or postan?esth\* or surgery or surgical or surgeries or surgically or postsurg\* or post-surg\* or perisurg\* or peri-surg\* or operation\* or operating or operativ\* or operated or intraoperat\* or intra-operat\* or postoperat\* or post-operat\* or perioperat\* or peri-operat\* or theatre or hospital or inhospital) and (death\* or mortalit\* or fatal\* or expir\* or died)).mp. | 1242547 |
| 20 | pomr.mp. | 149 |
| 21 | or/19-20 | 1242644 |
| 22 | and/18,21 | 62988 |
| 23 | (exp animal model/ or animals/) not human/ | 2540222 |
| 24 | ((animal or animals or canine\* or dog or dogs or feline\* or hamster\* or lamb or lambs or mice or mouse or monkey or monkeys or murine or pig or pigs or porcine or piglet\* or primate\* or rabbit\* or rat or rats or rodent\* or sheep or veterinary\*) not (human or patient\*)).ti,kw,sh. | 5021818 |
| 25 | or/23-24 | 5159723 |
| 26 | 22 not 25 | 61468 |
| 27 | limit 26 to yr="2014 -Current" | 25166 |

* 1. Database: Ovid MEDLINE(R) ALL 1946 to Octboer 29, 2021

Date run: November 1, 2021

|  |  |  |
| --- | --- | --- |
| # | Search String | Results |
| 1 | bellwether.mp. | 136 |
| 2 | Fractures, Open/su [Surgery] | 3967 |
| 3 | ((open or compound) adj3 fracture\* adj5 (surg\* or reduction)).ti,ab. | 2011 |
| 4 | (open adj2 reduction).ti,ab. | 13360 |
| 5 | (c?esar?an\* or csection\* or c-section\*).ti,ab. | 67622 |
| 6 | General Surgery/ | 39970 |
| 7 | (abdom\* adj3 (surgery or surgical or surgeries or surgically or postsurg\* or post-surg\* or perisurg\* or peri-surg\* or operation\* or operating or operativ\* or operated or intraoperat\* or intra-operat\* or postoperat\* or post-operat\* or perioperat\* or peri-operat\*)).ti,ab. | 33871 |
| 8 | ((suture\* or epiploplast\* or omentoplast\*) adj5 (perforat\* adj3 ulcer\*)).ti,ab. | 146 |
| 9 | ("small bowel\*" adj3 (resection\* or anastomos\*)).ti,ab. | 2924 |
| 10 | (colostom\* or colectom\* or hemicolectom\*).ti,ab. | 24939 |
| 11 | (laparotom\* or duodenectom\* or jejunectom\* or ileectom\* or appendicectom\* or cholecystectom\* or minilaparotom\* or mini-laparotom\*).ti,ab. | 83682 |
| 12 | (gastroscop\* adj2 (intrasurgical\* or intraoperative\*)).ti,ab. | 44 |
| 13 | (peritoneal adj3 (adhesionlysis or lavage)).ti,ab. | 3169 |
| 14 | "inguinal herniorrhaphy".ti,ab. | 909 |
| 15 | (inguinal adj3 hernia\* adj3 (repair\* or surgery or surgical or surgeries or surgically)).ti,ab. | 6487 |
| 16 | (suture\* adj3 (gastric adj2 (tear\* or injur\* or perforat\*))).ti,ab. | 24 |
| 17 | or/1-16 | 268672 |
| 18 | ((an?esth\* or peri-an?esth\* or perian?esth\* or post-an?esth\* or postan?esth\* or surgery or surgical or surgeries or surgically or postsurg\* or post-surg\* or perisurg\* or peri-surg\* or operation\* or operating or operativ\* or operated or intraoperat\* or intra-operat\* or postoperat\* or post-operat\* or perioperat\* or peri-operat\* or theatre or hospital or inhospital) and (death\* or mortalit\* or fatal\* or expir\* or died)).mp. | 725821 |
| 19 | pomr.mp. | 108 |
| 20 | or/18-19 | 725895 |
| 21 | and/17,20 | 38028 |
| 22 | (exp Models, Animal/ or Animals/) not Humans/ | 4877339 |
| 23 | ((animal or animals or canine\* or dog or dogs or feline\* or hamster\* or lamb or lambs or mice or mouse or monkey or monkeys or murine or pig or pigs or porcine or piglet\* or primate\* or rabbit\* or rat or rats or rodent\* or sheep or veterinary\*) not (human or patient\*)).ti,kw,sh. | 6881358 |
| 24 | or/22-23 | 6899232 |
| 25 | 21 not 24 | 36647 |
| 26 | limit 25 to yr="2014 -Current" | 11612 |

* 1. Database: [Cochrane Central Register of Controlled Trials](https://www-cochranelibrary-com.proxy1.lib.uwo.ca/), Issue 9 of 12, September 2021

Date run: September 23, 2021

|  |  |  |
| --- | --- | --- |
| # | Search String | Results |
| 1 | MeSH descriptor: [Fractures, Open] this term only and with qualifier(s): [surgery - SU] | 68 |
| 2 | (((open or compound) NEAR/3 fracture\*) NEAR/5 (surg\* or reduction)):ti,ab,kw | 369 |
| 3 | (open NEAR/2 reduction):ti,ab,kw | 1083 |
| 4 | (cesarean\* OR csection\* OR c-section\*):ti,ab,kw | 11918 |
| 5 | MeSH descriptor: [General Surgery] this term only | 360 |
| 6 | (abdom\* NEAR/3 (surgery or surgical or surgeries or surgically or postsurg\* or post-surg\* or perisurg\* or peri-surg\* or operation\* or operating or operativ\* or operated or intraoperat\* or intra-operat\* or postoperat\* or post-operat\* or perioperat\* or peri-operat\*)):ti,ab,kw | 10335 |
| 7 | ((suture\* or epiploplast\* or omentoplast\*) NEAR/5 (perforat\* NEAR/3 ulcer\*)):ti,ab,kw | 4 |
| 8 | ("small bowel\*" NEAR/3 (resection\* or anastomos\*)):ti,ab,kw | 82 |
| 9 | (colostom\* OR colectom\* OR hemicolectom\*):ti,ab,kw | 2247 |
| 10 | (laparotom\* OR duodenectom\* OR jejunectom\* OR ileectom\* OR appendicectom\* OR cholecystectom\* OR minilaparotom\* OR mini-laparotom\*):ti,ab,kw | 9573 |
| 11 | (peritoneal NEAR/3 (adhesionlysis or lavage)):ti,ab,kw | 214 |
| 12 | ("inguinal herniorrhaphy"):ti,ab,kw | 297 |
| 13 | ((inguinal NEAR/5 (repair\* or surgery or surgical or surgeries or surgically))):ti,ab,kw | 2851 |
| 14 | (gastric NEAR/2 (tear\* OR injur\* OR perforat\*)):ti,ab | 215 |
| 15 | {OR #1-#14} | 36844 |
| 16 | ((an?esth\* OR peri-an?esth\* OR perian?esth\* OR post-an?esth\* OR postan?esth\* OR surgery OR surgical OR surgeries OR surgically OR postsurg\* OR post-surg\* OR perisurg\* OR peri-surg\* OR operation\* OR operating OR operativ\* OR operated OR intraoperat\* OR intra-operat\* OR postoperat\* OR post-operat\* OR perioperat\* OR peri-operat\* OR theatre OR hospital OR inhospital) AND (death\* OR mortalit\* OR fatal\* OR expir\* OR died)):ti,ab,kw | 65445 |
| 17 | (pomr):ti,ab,kw | 3 |
| 18 | {OR #15-#16} | 65446 |
| 19 | {AND #14, #17} | 3824 |
| 20 | {AND #14, #17} with Publication Year from 2014 to 2021, in Trials | 1786 |

* 1. Database: Global Index Medicus (https://www.globalindexmedicus.net/)

Date run: September 23, 2021

|  |  |  |
| --- | --- | --- |
| # | Search String | Results |
| 1 | (tw:(bellwether OR fracture\* OR cesarean\* OR caesarean\* OR cesarian\* OR caesarian\* OR "general surgery" OR "general surgeries" OR abdom\* OR laparotom\*) AND ((ti:(anesth\* OR anaesth\* OR perianesth\* OR perianaesth\* OR postanaesth\* OR postanesth\* OR surgery OR surgical OR surgeries OR surgically OR postsurg\* OR perisurg\* OR operation\* OR operating OR operativ\* OR operated OR intraoperat\* OR postoperat\* OR perioperat\* OR theatre OR hospital OR inhospital) AND (death\* OR mortalit\* OR fatal\* OR expir\* OR died)) OR (ab:(anesth\* OR anaesth\* OR perianesth\* OR perianaesth\* OR postanaesth\* OR postanesth\* OR surgery OR surgical OR surgeries OR surgically OR postsurg\* OR perisurg\* OR operation\* OR operating OR operativ\* OR operated OR intraoperat\* OR postoperat\* OR perioperat\* OR theatre OR hospital OR inhospital) AND (death\* OR mortalit\* OR fatal\* OR expir\* OR died)))) AND (year\_cluster:[2014 TO 2021]) | 4360 |
| Results by database: | | |
| WPRIM | | 2278 |
| LILACS | | 1159 |
| IMSEAR | | 571 |
| IMEMR | | 284 |
| AIM | |  |

* 1. Database: World Health Organization Institutional Repository for Information Sharing (iris) (https://apps.who.int/iris/)

Date run: September 23, 2021

|  |  |  |
| --- | --- | --- |
| # | Search String | Results |
| 1 | (("open fracture" OR bellwether OR abdom\* OR laparotom\* OR "general surgery" OR cesarean OR caesarean OR cesarian\* OR caesarian) AND (anaesth\* OR anesth\* OR perianesth\* OR perianaesth\* OR postanesth\* OR postanaesth\* OR surgery OR surgical OR surgeries OR surgically OR postsurg\* OR perisurg\* OR operation\* OR operating OR operativ\* OR operated OR intraoperat\* OR postoperat\* OR perioperat\* OR theatre)) AND (death\* OR mortalit\* OR fatal\* OR expir\* OR died) | 5039 |
| Filters: | | |
| Date issued: 2014 | | 175 |
| Date issued: 2015 | | 197 |
| Date issued: 2016 | | 155 |
| Date issued: 2017 | | 163 |
| Date issued: 2018 | | 158 |
| Date issued: 2019 | | 150 |
| Date issued: 2020 | | 208 |
| Date issued: 2021 | | 110 |
| **Total** | | 1316 |

1. Appendix 2: Screening protocol

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| This form was pilot tested on an initial search conducted September 2, 2021. One thousand results were then screened through the level one section of this form to ensure that it was capturing relevant studies. This form will be integrated with the DistillerSR software to help ensure consistency of screening and assist with the workflow and organization of the project.   |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | Screening Questions | Yes | | | No | | Unclear | | | | Notes | | Title/Abstract Screening  -Judgements to be made on whether to exclude the article in question based on the following questions  -If unclear whether to exclude or include the article include at this stage | | | | | | | | | | | | 1) Are the participants living humans? |  | | |  | |  | | | |  | | If NO exclude | | | | | | | | | | | | 2) Does the study include a bellwether procedure? (caesarean section, laparotomy – see list, or treatment of open fractures – see list) |  | | |  | |  | | | |  | | If NO exclude | | | | | | | | | | | | 3) Is the study investigating children/paediatrics?  -if there is a mix between adults and children is the mean age below 18?  -if it is unreported exclude |  | | |  | |  | | | |  | | If YES exclude | | | | | | | | | | | | 4) Does the study report mortality? (saying there was no mortality is acceptable) |  | | |  | |  | | | |  | | If NO exclude | | | | | | | | | | | | 5) Does the study report POMR or are you able to calculate POMR from the reported data? (i.e. deaths/patients operated on) |  | | |  | |  | | | |  | | If NO exclude | | | | | | | | | | | | 6) Are there ≥200 participants included in the study? |  | | |  | |  | | | |  | | If NO exclude (Unless the study is from an LMIC) | | | | | | | | | | | | 7) Is the study a full paper (i.e. NOT only an abstract) |  | | |  | |  | | | |  | | If NO exclude | | | | | | | | | | | | 8) Is the study a cohort Quasi-experimental or RCT study? (e.g. exclude case reports, case series, case control\*, qualitative studies, reviews and meta-analyses, editorials/opinion pieces – articles without data) | |  | | |  | | |  | | | | If NO exclude | | | | | | | | | | | | PROCEED TO FULL TEXT SCREENING FOR ARTICLES THAT HAVE NOT BEEN EXLCUDED | | | | | | | | | | | | Full Text Screening | | | | | | | | | | | | Repeat steps 1-8 to see if the full text provides more detail  -Proceed to question 9 | | | | | | | | | | | |  | | | | | | | | | | |  | |  | |  |  | | Screening Questions | Yes | | | No | | Unclear | | | | Notes |  |  | | | If NO exclude | | | | | | | | | | | | 9) If the study is an RCT are both/all arms undergoing a surgical procedure?  If study is not an RCT skip to question 11 |  | | |  | |  | | | |  |  | | If NO exclude ARMS of the trial that are not undergoing a surgical procedure | | | | | | | | | | |  | |  | |  |  | | 10) Does the study allow for POMR to be calculated from the remaining arms of the RCT? |  | | |  | |  | | | |  | | If NO exclude | | | | | | | | | | |  | |  | |  |  | | 11) Is the median (or mean if median is not available) age of the participants 18 years or older? |  | | |  | |  | | | |  | | If NO exclude | | | | | | | | | | |  | |  | |  |  | | 12) Is it possible to extract what countries the procedures/mortalities occurred in? |  | | |  | |  | | | |  | | If NO exclude | | | | | | | | | | |  | |  | |  |  | | 13) Does the study list specific causes of death for each perioperative death? |  | |  | | | |  | |  | |  | |  | |  |  | | If NO exclude If YES INCLUDE | | | | | | | | | | |  | |  | |  |  | |

1. Appendix 3: Data Extraction Form

[Draft Data Extraction Form](file:///C:\Users\Kevin\Desktop\Thesis\Proposal%20Drafts\Protocol%20Drafts\Thesis_Data_Extraction_Form.xlsx)

This form will be integrated into the DistillerSR platform to assist with data extraction.

1. Appendix 5: Quality Appraisal Process for Primary Studies

Both the ROBINS-I and RoB 2 risk of bias tools will be integrated into the DistillerSR platform to assist with the workflow and organization of the project.

* 1. Risk of Bias in Non-Randomized Studies – of Interventions (ROBINS-I)

Refer to following link: <https://methods.cochrane.org/bias/risk-bias-non-randomized-studies-interventions>

(Sterne et al, 2016)

* 1. Risk of Bias Tool for Randomized Trials (RoB 2)

Refer to following link: <https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials>

(Cochrane Bias, 2020)

1. Appendix 6: Planned R Code

setwd("H:")

install.packages("readxl")

library(readxl)

MR<-read\_excel("Meta-regressionExample.xlsx")

install.packages("metafor")

library(metafor)

MR$Year\_c<-as.factor(MR$Year)

MR$HDI\_c<-as.factor(MR$HDI)

MR$ASA\_c <- as.factor(MR$ASA)

### mixed-effects meta-regression model with all predictors/covariates

#Unadjusted Random Slope and Intercepts Multilevel Meta-regression Model Investigating (POMR ~ Year) split by HDI Group

Test\_MLMR\_1 <- rma.mv(POMR, VPOMR,

random = list(~1| Study\_ID,

~1|HDI),

mods = Year

tdist = TRUE,

data = MR2,

method = "REML")

summary(Test\_MLMR\_1)

#Adjusted Analysis Using Random Slopes and Intercepts Model Investigating (POMR ~ Year +ASA + Female + Emergency + Age + Urban) Split by HDI Group

MLMR2 <- rma.mv(POMR, VPOMR,

random = list(~1| Study\_ID,

~1|HDI),

mods = ~ Year + ASA + Female + Emergency + Age + Urban,

tdist = TRUE,

data = MR,

method = "REML")

summary(MLMR2)

1. Appendix 7: Directed Acyclic Graphs (DAG)/Theoretical Model

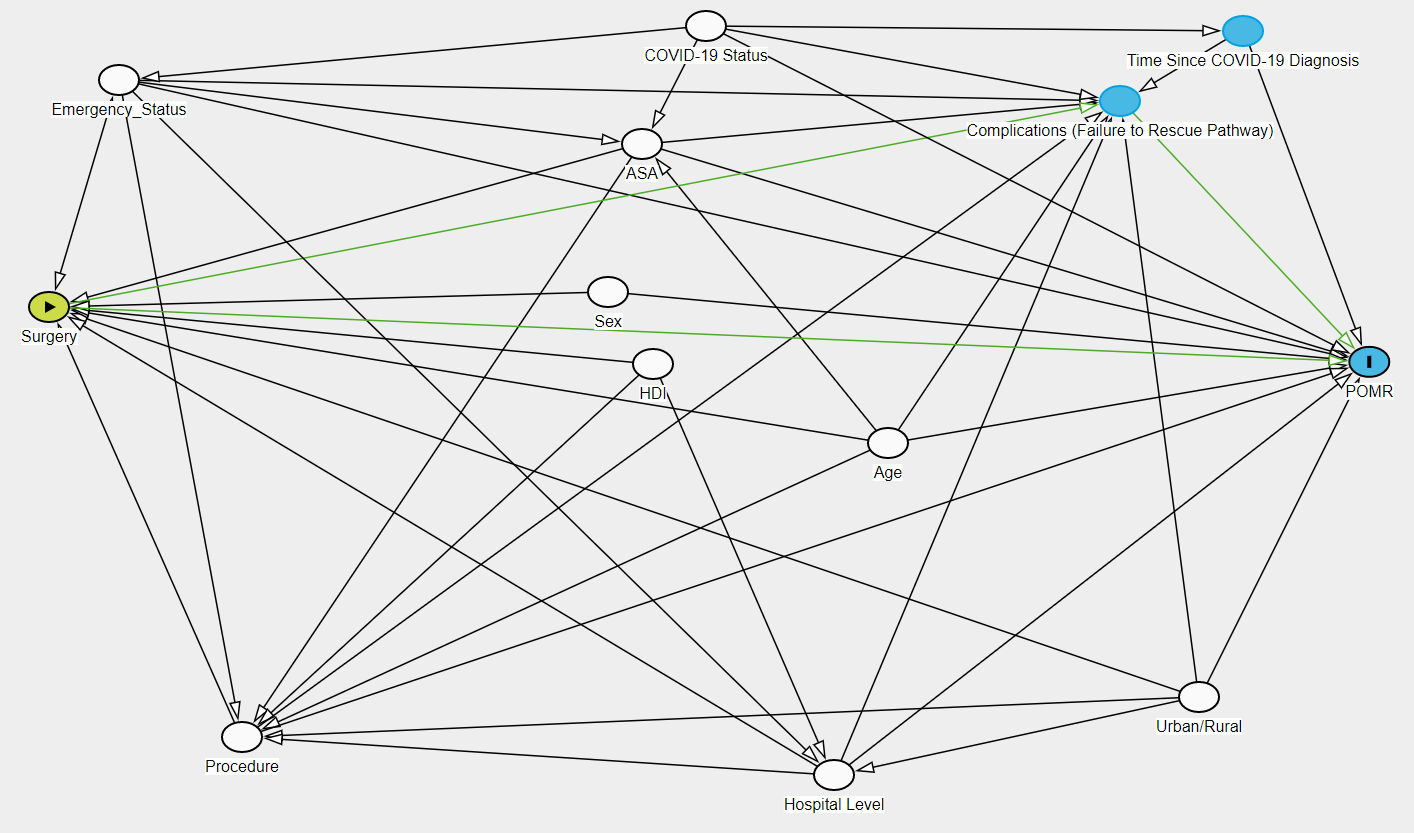


Figure 3b. DAG with Covariates Controlled For

* 1. Code for DAG

dag {

"COVID-19 Status" [adjusted,pos="0.490,-0.158"]

"Complications (Failure to Rescue Pathway)" [pos="0.767,-0.058"]

"Hospital Level" [adjusted,pos="0.576,0.841"]

"Time Since COVID-19 Diagnosis" [pos="0.849,-0.151"]

"Urban/Rural" [adjusted,pos="0.819,0.737"]

ASA [adjusted,pos="0.447,0.000"]

Age [adjusted,pos="0.612,0.398"]

Emergency\_Status [adjusted,pos="0.098,-0.086"]

HDI [adjusted,pos="0.455,0.293"]

POMR [outcome,pos="0.933,0.290"]

Procedure [adjusted,pos="0.180,0.790"]

Sex [adjusted,pos="0.425,0.197"]

Surgery [exposure,pos="0.052,0.217"]

"COVID-19 Status" -> "Complications (Failure to Rescue Pathway)"

"COVID-19 Status" -> "Time Since COVID-19 Diagnosis"

"COVID-19 Status" -> ASA

"COVID-19 Status" -> Emergency\_Status

"COVID-19 Status" -> POMR

"Complications (Failure to Rescue Pathway)" -> POMR

"Hospital Level" -> "Complications (Failure to Rescue Pathway)"

"Hospital Level" -> POMR

"Hospital Level" -> Procedure

"Hospital Level" -> Surgery

"Time Since COVID-19 Diagnosis" -> "Complications (Failure to Rescue Pathway)"

"Time Since COVID-19 Diagnosis" -> POMR

"Urban/Rural" -> "Complications (Failure to Rescue Pathway)"

"Urban/Rural" -> "Hospital Level"

"Urban/Rural" -> POMR

"Urban/Rural" -> Procedure

"Urban/Rural" -> Surgery

ASA -> "Complications (Failure to Rescue Pathway)"

ASA -> POMR

ASA -> Procedure

ASA -> Surgery

Age -> "Complications (Failure to Rescue Pathway)"

Age -> ASA

Age -> POMR

Age -> Procedure

Age -> Surgery

Emergency\_Status -> "Complications (Failure to Rescue Pathway)"

Emergency\_Status -> "Hospital Level"

Emergency\_Status -> ASA

Emergency\_Status -> POMR

Emergency\_Status -> Procedure

Emergency\_Status <-> Surgery

HDI -> "Hospital Level"

HDI -> Procedure

HDI -> Surgery

Procedure -> "Complications (Failure to Rescue Pathway)"

Procedure -> POMR

Procedure -> Surgery

Sex -> POMR

Sex -> Surgery

Surgery -> "Complications (Failure to Rescue Pathway)"

Surgery -> POMR

}