Examining the Prognostic Utility of Frailty for Post-arrest Outcomes Following the Provision of Cardiopulmonary Resuscitation: A Systematic Review and Meta-Analysis Protocol

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Abstract

Background

Advanced knowledge of patient prognosis following a cardiac arrest is necessary to determine if resuscitation efforts are futile and ensure value-congruent care. Prior reviews have identified the prognostic factors associated with survival and recovery following cardiac arrest. However, few studies to date have examined the prognostic value of frailty in predicting post-arrest outcomes. The objective of this systematic review is to synthesize the available evidence reporting the association between frailty and patient outcomes following the provision of CPR in-hospital or out-of-hospital.

Methods

We searched the following electronic databases from inception until August 2020: Medline Epub Ahead of Print, In-Process and Other Non-Index citations, Pubmed exclusive of Medline citations, EMBASE, CINAHL and Web of Science. We plan to include observational studies that examine the association between frailty and any of the following outcomes: survival to hospital discharge, survival at one, three and twelve months post-arrest, return of spontaneous circulation, functional status at hospital discharge and one-month post-discharge, health-related quality of life at 90 days and one-year post-arrest, and discharge to continuing or long-term care. We plan to conduct a random-effects meta-analysis that pools the effect estimates from all eligible studies to obtain a summary estimate and confidence interval.

Discussion

The findings of this review can be used to determine if the evidence supports the consideration of frailty when discussing advanced directives and care planning with patients, families and caregivers. The findings of this review can also be used to inform future prognostic and clinical prediction models aiming to predict post-resuscitation outcomes.

Systematic Review Registration

This review has been submitted to the PROSPERO registry (submission ID: 212922)

Background

Cardiac arrest refers to a sudden loss of systemic blood circulation and tissue oxygenation due to inadequate or absent cardiac output. Cardiac arrest is classified as either out-of-hospital cardiac arrest (OHCA) or in-hospital cardiac arrest (IHCA), depending on the setting of the arrest. For every 1,000 hospital admissions, one to six patients will experience a cardiac arrest during their in-patient stay. Outside of the hospital setting, the global incidence rate for OHCA is 55 arrests per 100,000 person-years. Cardiac arrests require prompt initiation of cardiopulmonary resuscitation (CPR) to return systemic circulation to vital organs and to facilitate a successful recovery. Despite these efforts, the one-
year survival rate is 13% for individuals who experience IHCA and 7% for OHCA.\textsuperscript{5,6} Furthermore, the majority of survivors report physical disabilities, cognitive impairment or mental illness, potentially contributing to the decreased quality of life commonly reported post-arrest.\textsuperscript{7–9}

Advanced knowledge of patient prognosis following a cardiac arrest is necessary to determine if resuscitation efforts are futile and ensure value-congruent care. While prognostic factors of survival and recovery have been identified,\textsuperscript{10–13} few studies to date have examined the informational value of frailty in predicting post-arrest outcomes.\textsuperscript{10} Frailty is a multidimensional syndrome characterized by a heightened vulnerability to adverse health events and a diminished physiologic reserve, inhibiting homeostatic recovery from stressors.\textsuperscript{14,15} The growing geriatric population and the associated geriatric syndromes, including frailty, highlight the need for further exploration into the prognostic value of frailty.\textsuperscript{16} Frailty is associated with a greater risk for in-hospital and long-term mortality, health resource utilization, functional decline and a poor quality of life.\textsuperscript{17–21} Prior work has demonstrated that patients with frailty are less likely to survive a cardiac arrest or be discharged home following hospitalization.\textsuperscript{22–25}

A frailty measure or index could potentially provide a gauge of patient complexity and resilience. More specifically, frailty status can be used to guide clinical and shared decision-making when determining advanced care directives and goals of care. We propose to undertake a systematic review and meta-analysis of studies examining the association between frailty and patient prognosis following the provision of CPR, either in-hospital or out-of-hospital. This review is warranted, given the recent surge of publications examining the association between frailty and post-arrest outcomes. A systematic review allows for an appraisal of the evidence in its entirety, along with the exploration of between-study heterogeneity, so that we can better determine and stratify the prognostic utility of frailty.

**Objective**

The objective of this systematic review is to synthesize the available evidence reporting the association between frailty and patient outcomes following the provision of CPR in-hospital or out-of-hospital. Outcomes were selected based on recommendations from the Core Outcome Set for Cardiac Arrest (COSCA) initiative. The International Consortium for Health Outcome Measurement (ICHOM) Older Person Working Group was also used to guide outcome selection, bearing in mind that frailty and the risk of sudden cardiac death both increase with age.\textsuperscript{26–28}

**Research Question**

*Population:* Adults (≥ 18 years of age) who receive CPR

*Prognostic Factor:* Frailty

*Outcomes & Timing:* (a) Survival to hospital discharge,

(b) Survival at one, three, and twelve months post-arrest
(c) Return of spontaneous circulation (ROSC),
(d) Functional status at discharge and one-month post-discharge,
(e) Health-related quality of life (HRQoL) at 90 days and one-year post-discharge.
(f) Discharge from the index hospital visit to continuing or long-term care

Setting: In-hospital and out-of-hospital

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) was used to guide the reporting of this protocol and can be found in Appendix A. The PRISMA statement will be utilized to guide the reporting of this review to ensure transparency; a completed and detailed checklist will be provided with the publication. This systematic review will be conducted per Riley et al. and recommendations of the Prognosis Research Strategy (PROGRESS) Group. The critical appraisal and data extraction for systematic reviews of prediction modelling studies (CHARMS) checklist was used to frame the research question.

Data Sources and Search Strategy

We searched the following electronic databases from inception until August 2020: (a) Medline Epub Ahead of Print, In-Process and Other Non-Index citations, (b) Pubmed exclusive of Medline citations, (c) EMBASE, (d) CINAHL, and (e) Web of Science. We consulted an academic-affiliated librarian (RC) for the systematic literature search and developed a conservative search strategy for all prognostic factors reported in patients who experience a cardiac arrest, cognizant of the fact that search strategies focused on distinct factors or outcomes may overlook eligible articles. We included search terms informed by Haynes’ sensitive strategies for clinical prediction guides and etiology/risk, and by prior prognostic factor reviews. Text and MeSH terms for CPR and cardiac arrest will be utilized along with a combination of prognosis terms. A detailed search strategy can be found in Appendix B. Citation tracking will be conducted on all eligible studies to highlight any articles potentially missed by our search strategy. The search will be restricted to adults and non-animal studies. Further, we will exclude non-conference proceedings and conference abstracts as the limited methodological descriptions inhibit assessors from determining the risk of bias (ROB). Case studies and case series will also be excluded, given their lack of a comparison group.

Study Selection and Screening

We plan to include observational study designs (prospective and retrospective) that enrolled adults (≥ 90% of the sample aged 18 and older) who received CPR and reported an association between frailty and any of the outcomes mentioned above. Additionally, studies will be required to provide an explicit
definition or description of the frailty instrument used for inclusion in this review. We elected not to limit our search to older adults, given that frailty can also be found in younger populations. We plan to exclude studies if: (a) they were purposed to examine the efficacy of a specific clinical treatment, (b) they did not specify the timing of outcome measurement, (c) frailty was defined using a single measure (e.g., laboratory finding, radiographic imaging, etc.), (d) studies that only measured outcomes beyond one year from the date of cardiac arrest data (unless time-to-event analysis was completed), and (e) studies that only evaluated patients receiving a particular clinical therapy (e.g., therapeutic hypothermia, extracorporeal membrane oxygenation, etc.) Studies will not be excluded based on language, sample size, or time of publication. Studies with missing or insufficient data to generate effect estimates or estimates of precision (95% confidence intervals) will be excluded from the meta-analysis if the necessary information cannot be obtained from the appointed corresponding authors. In this situation, the data will be reported narratively.

Titles and abstracts will be imported into Covidence software (Melbourne, Australia), where citations will be screened and duplicates removed. Title, abstract, and full-text screening will be conducted independently and in duplicate by four reviewers (FM, RS, RHC, DM). A standardized and piloted form was created and will be utilized during title and abstract screening; this form is shown in Appendix C. Cases of disagreement over titles and abstracts will be included for full-text review. Any discourse between reviewers regarding study inclusion following full-text review will be resolved through discussion, and if necessary, through independent adjudication by a third study reviewer (F.F). If a decision cannot be determined regarding the study eligibility, reviewers will consult a content expert (J.M). Inter-rater agreement of full-text screening will be reported as a kappa statistic.

Data Extraction

Data will be extracted independently and in duplicate by four reviewers (FM, RHC, RS, DM). A standardized and pilot-tested data collection form will be created to ensure consistency of extraction. The following data from eligible studies will be extracted: author(s), year of publication, study design, single versus multisite, country of study, inclusion and exclusion criteria, recruitment time frame (months), follow-up length, total sample size, the proportion of adults ≥ 65 years of age, definition and timing of outcome, number of events, baseline demographics (e.g., age, sex, frailty status/score), the prognostic factors entered into the multivariable model, unit of change for continuous predictors, classification for categorical predictors, the unadjusted and adjusted point estimates of risk and lower and upper confidence intervals. All extracted data values will be rounded to two decimal places. Abstracted data will be recorded using Microsoft Excel.

Data Synthesis and Analysis

Data will be synthesized using R and the ‘meta’ package. We plan on generating point estimates and their respective 95% confidence intervals using relative risks, odds ratios or hazard ratios, where appropriate. Study results will be pooled according to the specific type of frailty instrument used, with
modified versions of scales included with the original version. Where more than one frailty measure is used in a study, each measure will provide specific information for that class of frailty instrument.

We plan to synthesize and report both univariable and multivariable estimates separately to determine if frailty is robust to the bias of confounding. If baseline risk estimates are not reported, the conversion is not possible, or we are unable to obtain this data from study authors, we will conduct subgroup analyses to compare studies based on the format of the effect estimate. Specifically, we will compare studies that provide information on baseline risk, where we can appropriately convert OR, RR, and HR to studies where conversion is not possible or appropriate. In the latter scenario, we will report the HR or OR. A hot-deck approach will be used to impute an associated variance for such variables. We will conduct a sensitivity analysis to determine the influence that data imputation has on pooled estimates. A random-effects model will be used for all statistical pooling, mindful of the fact that models of care and patient populations are likely to vary between regions.

**Risk of Bias within Studies**

We will examine the risk of bias of the individual studies using the Quality in Prognostic Studies (QUIPS) instrument. The risk of bias will be determined through the examination of six distinct domains: study participation, study attrition, prognostic factors, outcome measurement, study confounding, statistical analysis and reporting. The QUIPS tool will be modified to ensure better sensitivity in identifying overfit statistical models (e.g., < 10 events for each binary predictor). We will use the individual domains, rated as low or high risk of bias, to inform the overall risk of bias in each study. Five or six low-risk domains will result in a classification of low risk of bias, whereas two or more high-risk domains will result in a classification of 'high' risk of bias. Paired reviewers will independently assess each study using the modified QUIPS tool.

**Sources of Heterogeneity**

Statistical heterogeneity will be assessed through the visual inspection of forest plots, examining the consistency among point estimates and overlap among the associated confidence intervals, and the chi-square test for homogeneity. The inconsistency index ($I^2$) measure will only be used if the majority of studies include < 500 patients, given that prior work has demonstrated a lack of variance in the $I^2$ measure among studies with large sample sizes. Clinical and methodological heterogeneity will be examined to identify factors that may modify the association between frailty and the outcomes of interest and to determine the appropriateness of meta-analysis. Six effect modifiers are of interest: location of the arrest, etiology of the arrest, the use of advanced cardiac life support, the threshold used to define frailty within a measurement, adjustment for a minimum confounder set, and aspects related to the risk of bias within studies.

1. **Location.** Effect estimates will be compared between studies that focus primarily on IHCA and those that focus on OHCA.
2. **Etiology of Arrest.** Effect estimates will be compared between patients who arrest due to traumatic injury (e.g., blunt or penetrating trauma) versus those who arrest as a result of a medical condition (e.g., myocardial infarction).

3. **Basic versus Advanced Life Support.** Effect estimates will be compared between those who receive basic life support (e.g., chest compressions and ventilation) and those who received additional measures for advanced cardiac life support (e.g., epinephrine administration, endotracheal intubation, etc.)

4. **Measurement.** Effect estimates will be compared across studies that use the same instrument but differing thresholds to define frailty.

5. **Confounders.** Effect estimates will be compared across studies that statistically adjusted for patient age, studies that adjusted for both patient age and the presence of a shockable rhythm (per current Advanced Cardiac Life Support guidelines), and finally for studies without adjustment for these factors.

6. **Risk of Bias.** Effect estimates will be compared across studies with high and low risk of bias.

**Confidence in Estimates**

Overall confidence in estimates will be determined using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.\(^{43,45}\) Per GRADE recommendations, confidence will be rated as either high, moderate, low, or very low. In accordance with GRADE guidance for prognostic studies, observational studies will be considered high confidence until proven otherwise.\(^{43}\) For meta-analyses with more than ten studies, funnel plots will be produced to examine the distribution of positive and negative findings allowing for the detection of publication bias.\(^{43}\) An assessment of confidence will be given for each outcome individually. Congruency of pooled estimates between our sensitivity analysis (including imputed non-significant studies evaluating the predictor of interest) and our primary model (not including the imputed non-significant predictor) will be reported and taken into consideration when discussing our confidence in the estimates.

**Discussion**

A systematic review is warranted to better understand the current state and limitations of the literature to date, as well as to inform the direction and need for future research. The findings of this review can be used to determine if the evidence supports the consideration of frailty when discussing advanced directives and care planning with patients, families and caregivers. Further, the findings of this review can be used to inform future prognostic and clinical prediction models aiming to predict post-resuscitation outcomes. To our knowledge, no clinical prediction models to date have examined the informational value of frailty during model derivation. This information is needed to determine if the inclusion of frailty as a predictor or effect modifier can improve the discrimination and calibration of predictive models.
Older adults are at greater risk for sudden cardiac death and arrest when compared to younger adults. However, prior work has demonstrated that in geriatric populations, frailty and geriatric complexity are what drive health service use and clinical outcomes, rather than patient age. Though prior reviews report age as an important pre-arrest prognostic factor, we hypothesize that this relationship is likely confounded by frailty. Similarly, older patients without significant frailty may be at lower risk of morbidity and mortality than those with frailty, and therefore CPR may provide a greater benefit in this population. This is why Fernando et al. encouraged the examination of frailty in future reviews and studies examining post-arrest outcomes.

An anticipated challenge that may limit the findings of this study is heterogeneity in the frailty screening measures used between studies. The concept of frailty has long been studied in geriatrics and gerontology. However, it has only recently been adopted and applied in clinical practice. As a result, there is no universal consensus on a reference standard for instruments or indices measuring frailty. While a wide array of frailty measures and indices exist, the Clinical Frailty Scale appears to be the most commonly reported tool in studies examining frailty and cardiac arrest. The recent study and implementation of frailty screening in clinical practice may also limit the number of resuscitation studies examining frailty. A preliminary literature search revealed a minimum of five studies, supporting the feasibility of the proposed review.

In summary, we are aiming to synthesize the literature examining the relationship between frailty and patient outcomes following the provision of CPR for IHCA and OHCA. Our review will search for studies in both the hospital and community setting to broaden the clinical implications of our findings. Both adjusted and unadjusted results will be reported, and studies using the same frailty scales and instruments will be pooled together. This review will provide insight into associations between frailty and post-arrest outcomes, and the current state of the literature surrounding this relationship.

**Abbreviations**

COSCA: Core Outcome Set for Cardiac Arrest

CPR: Cardiopulmonary Resuscitation

CHARMS: Critical appraisal and data extraction for systematic reviews of prediction modelling studies

GRADE: Grading of Recommendations, Assessment, Development, and Evaluation

HRQoL: Health-related quality of life

I^2: Inconsistency index

ICHOM: International Consortium for Health Outcome Measurement

HR: Hazard Ratio
declarations

ethics approval and consent to participate: the proposed work has not received any funding.

consent for publication: the authors provide consent for publication.

availability of data and materials: all supplementary data is made available.

competing interest: the authors declare that they have no competing interests.

funding: no funding was used to support this work.

author contributions: fm conceptualized the study and created the first draft of the protocol. all authors provided meaningful feedback and revisions to the protocol. the authors have read and approved the final version of the protocol.

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