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Does frailty status predict outcome in major trauma in older people: a systematic review protocol

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LIST OF ABBREVIATIONS

AIS	Abbreviated Injury scale
ISS	Injury Severity Score
MOI	Mechanism of Injury
TBI	Traumatic Brain Injury
TARN	Trauma Audit and Research Network
ADL	Activities of Daily Living

ABSTRACT

Introduction

Across the world, major trauma is occurring increasingly in older people. Frailty is likely to be a factor that influences the severity of major trauma, and also the outcomes. We propose to conduct a systematic review of published literature to explore whether and to what degree frailty affects injury severity and outcome in major trauma in older people.

Method

A comprehensive electronic search will be conducted on Ovid Medline, PubMed, CINAHL and Ovid Embase. Grey literature will be searched using an online databases. The reference lists in selected studies will be hand searched to identify additional studies meeting the eligibility criteria. Google Scholar and Web of Science will be searched as a citation searching process from the relevant studies. Two independent reviewers will extract data from the selected studies using a piloted data extraction form. Joanna Briggs Institute (JBI) software will be used to manage and appraise the quality of the evidence. Grading of Recommendations Assessment, Development and Evaluation (GRADE) will be used to evaluate the overall outcomes certainty of these domains; risk of bias, imprecision, inconsistency, indirectness and publication bias. Meta-analysis will be conducted where possible, otherwise a synthesis without meta-analysis will be conducted taking into account of both the magnitude of any observed associations and the reliability of the findings. This protocol is reported following PRISMA-P.

Discussion

The concepts of both major trauma and frailty are relatively recent and so exploring their relationship could reveal new useful clinical insights that could be used to improve outcomes. We anticipate that much published literature may not use a formal measure of frailty, so we will also examine proxy measures of frailty such as disability and conduct a sensitivity analysis to determine the effect of doing so.

INTRODUCTION

Major trauma is defined as an injury or combination of life-threatening injuries that lead to long term disabilities (1). The age of people suffering major trauma is rising: the mean age of patients with major trauma rose from 36 to 54 years between 1993 to 2013 (2). In 2014, people aged >60 accounted for 30% of all major trauma in the United Kingdom (3). Demographic trends imply that major trauma will increasingly affect older people.

Specialised centres to manage patients with major trauma have developed in recent decades, improving outcomes by bringing together urgent pre-hospital care, orthopaedic surgeons, anaesthetics and others emergency care practitioners, to better meet the complex needs of these patients than traditional orthopaedic services alone (4). This has led to improve the provision of major trauma care in terms of interventions and diagnostic timings. Given the increasing age of patients with major trauma, the fact that the outcomes of major trauma in older people are poorer than in younger people (5) is a major challenge. There are two possible reasons for these poorer outcomes. One potential reason is that older people may sustain more severe injuries than younger people and, hence, have poorer outcomes. The other potential reason is that older people may have worse outcomes than younger ones even for the same Injury Severity Score (ISS), is due to age-associated vulnerability - frailty. Both reasons may be true.

Frailty is a relatively new concept describing an age-associated vulnerability state; it is understood to reflect the loss of homeostatic reserve secondary to the effects of the ageing process and the impact that age-associated disease has on cell, organ and system functioning. Fried et al. in 2001 operationalised frailty as a physiological syndrome with age that increases the risk of falls, mortality and disability, and which is not synonymous with comorbidity or disability (6). Rockwood operationalised frailty as an accumulation of functional deficits (7). Both operational models aim to distinguish between frail and robust groups of older people, and hence to offer a better indicator of the risks associated with age than chronological age per se. Both models predict that frailty is likely to adversely affect outcomes following injury, such as infections, poor wound healing, vascular events, delirium, increased and prolonged disability, institutionalisation and death (6, 8,

9).Consequently, it would be expected that the outcomes of major trauma will be worse in older people with frailty than in older people without frailty, even when matched for injury severity. It follows that the prognostic value of injury severity scores in older people would be modified by the patient's frailty status.

This systematic review will examine the current evidence about whether and to what degree injury severity is greater in older people with frailty than in those who are robust, and whether and to what degree outcomes are worse for matched injuries in people with frailty compared to those who are robust.

METHOD

Aims and objectives

The primary questions of this systematic review are:

- What is the published research evidence of the effect of frailty on the severity of major trauma?
- What is the published research evidence of the effect of frailty on the outcomes of major trauma in older people, having accounted for injury severity?

The secondary questions are:

- What is the published evidence showing that frailty is a better predictor than age of the incidence of major trauma and of the outcomes of major trauma in older people?
- Which frailty identification tool/tools studied in the published literature have the greatest predictive value?

Outcomes of interest

Primary outcomes:

- Mortality
- Discharge destination (new admission to a care home, readmission, nursing home)
- Frailty status /Activities of Daily Living (ADL)

Secondary outcomes:

- Mental health
  - Cognition
  - Delirium
  - Depression / anxiety

Protocol and Registration

This protocol is registered with the International Prospective Register of Ongoing Systematic Reviews (Alqarni AG, Ollivere B, Gladman JRF. Does frailty status predict outcome in major trauma in older people? A systematic review. PROSPERO 2021[1]), and is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (PRISMA-P) (10).

Eligibility Criteria

This review will include cohort and cross-sectional stud**y** design**s** including older patients (60 years of age and older) with major trauma which defined as an injury or combination of life-threatening injuries that lead to long term disabilities. For this study we will operationalise the definition of major trauma by defining it as an Injury Severity Score (ISS) of >/=9. Although some existing literature uses ISS 9-15 to define "moderate" injury and ISS>15 as "severe" or "major" injury, we expect that our inclusion of a wider range of injury severity than ISS>15 alone will best allow the effect of frailty upon the incidence and outcome of major trauma to be examined. Another alternative measurement is patients with injured organs who have single or multiple injuries using the Abbreviated Injury Scale (AIS)>3, where they are classified as severe. The use of AIS as measurement will help us to identify outcomes for matched injuries in people with frailty compared to robust. AIS and ISS are the most commonly used tools to define trauma; thus, lead us to limit our selection of trauma instruments. However, studies that have other anatomic trauma instruments such as New Injury Severity Score (NISS) will be included if they carry a similar severity to ISS>/= 9. Therefore, articles will be eligible if they concern major trauma (potentially life

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threatening or leading to long term disability), using ISS>9, AIS>3 or other trauma severity measurement that meets this definition as judged by the review team.

Eligible studies will measure both injury severity and frailty (or indicators of it) at baseline (to examine the relationship between injury severity and frailty) or injury severity, frailty, and one or more outcome of interest as listed above (to examine the relationship between frailty and outcomes accounting for injury severity).

Given the relative novelty of the frailty concept and the means to identify or measure it, it is anticipated that few studies will yet have used a formal measure of frailty using either the Fried or Rockwood approach or a clinical assessment to define frailty. For this reason, studies will also be eligible if an indicator of frailty is reported: prior disability / receipt of care, institutionalization, multi-morbidity or polypharmacy.

To summarise, the overall eligibility criteria will be:

- Cohort and cross-sectional study designs
- Age > 60 years old
- Major trauma and moderate trauma patients depending on ISS >/= 9, or similar measure as defined above
- Baseline measure of injury severity
- Baseline measure of frailty or proxy
- One or more measurements of outcome of interest
- Results describing relationship between baseline and outcomes

The review will be restricted to studies written in the English language. One justification for this restriction is that it is not yet clear that the associations we wish to study will be consistent across different countries and at this stage we may obtain a less confounded answer if we restrict to studies reported in the English language. A further justification is that we do not have the resources for extensive translation of papers. We will examine the potential for this restriction to produce bias by examining the effect of the restriction upon the citations found in the search and the extent of references to publications in languages other than English in the reference lists of included papers.

We will also restrict to papers published since 2010, because the concept of major trauma became in common use around 2010 and because outcomes prior to that time are likely to be different from more recent times.

Information Sources

A systematic literature search will be conducted using the following bibliographic databases: Ovid MEDLINE, PubMed, Ovid Embase and CINAHL. Moreover, Google Scholar and Web of Science will be searched as a citation searching process from the relevant studies.

Search Strategy

The search will use the synonyms of three terms: frailty, trauma and outcome. Singular and plural forms of key terms will be used. Differences in the United States (US) and UK spelling of words will be used to search for specific terms that have "z" instead of "s". The search strategy is shown in table mentioned in Appendix below and was devised with assistance of an experienced information specialist.

An electronic search of databases will be performed using the applicable search format in each database. Duplicate citations will be removed when the searches from each database are combined.

Study Selection

The list of references (titles and abstracts) obtained from the search will be screened, by two independent reviewers, against the eligibility criteria. Full text articles will be retrieved where there is uncertainty. Disagreements between reviewers will be resolved by consulting a third reviewer.

The reference lists in selected studies will be hand searched to identify additional studies meeting the eligibility criteria that were not identified through the electronic searches.

Data Extraction and Collection Processes

Two independent reviewers will extract data from the selected studies. A piloted data extraction form will be use. From each study, the following elements will be extracted:

1- Year of publication, authors and country
2- Design and setting and other factors (e.g., intervention studies)
3- Number of participants and age

4- Tool used to measure injury severity
5- Tool to measure frailty, or indicator of frailty
6- Baseline frailty/indicator
7- Injury severity
8- Relationship between baseline frailty/indicator and injury severity
9- Clinical outcomes, and when measured
10- Relationship between baseline frailty/indicator and clinical outcomes, when accounting/matched for injury severity
11- Relationship between age and injury severity
12- Relationship between age and clinical outcomes when accounting /matched for injury severity

The data extraction form will also be used to record the study certainty (GRADE) assessments.

Disagreements between the two reviewers will be arbitrated by a third independent reviewer.

Quality Assessment

Two independent reviewers will critically review all selected studies by using Joanna Briggs institute (JBI) critical appraisal checklist (11). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool will be used to assess the overall certainty of the findings. The GRADE domains for rating the evidence are risk of bias, imprecision, inconsistency, indirectness and publication bias (12). GRADE ratings are very low, low moderate or high degrees of certainty.

Data Synthesis

Meta-analysis

Meta-analysis will be undertaken when possible. It can be used if number of selected studies are homogeneous and have similarities in interventions, subjects involved and outcomes. In this case, summary outcome measures for meta-analysis of dichotomous

variables will include the odds ratio, relative risk, or similar statistics. For continuous variables, the mean difference or effect size will be recorded or calculated.

Synthesis without meta-analysis

Where meta-analysis is not possible Synthesis Without Meta-analysis (SWiM) will be performed. This will synthesise findings about the relationship between frailty and outcomes into categories which indicate the cumulative confidence of the evidence. For each research outcome of interest (e.g., does frailty status predict mortality for a given injury severity?) the GRADE assessments of all individual studies with pertinent results will be collated.

The next step is to synthesise the pooled evidence bases into three primary categories:

- No / insufficient evidence: no studies answering this question or only studies that are of "very low" certainty
- Weak evidence: there are studies, but they are all of "low" certainty
- Moderate or strong evidence: there are studies that are of moderate or high levels of certainty (the existence of studies of low or very low certainty will not affect this categorisation)

The next step is to divide the Weak and Moderate or strong categories according to effect size into four further sub-categories

- No effect
- Small effect
- Large or moderate effect
- Inconsistent effect (when studies of similar levels of certainty disagree)

Effect sizes will be calculated using Cohen's method, and classified as small effect = 0.2, medium effect = 0.5 and large effect = 0.8 (13).

Meta-bias

Cohort studies are open to biases resulting from the study selection criteria (14). This risk will be considered when reporting the evidence within each SWiM sub-category, by taking account of the number and diversity of studies used to derive the SWiM sub-category. Similar findings across different studies and settings will imply a lower risk of meta-bias than from a single focussed study.

Sensitivity analysis

Where possible, sensitivity analyses will compare the results from studies using direct measures of frailty to those using an indicator of frailty.

DISCUSSION

We anticipate that the findings of this study will yield insights that will improve the ability to estimate the prognosis of older people with major injury and hence to tailor their care more appropriately. We are not aware of any other literature on this topic.

We anticipate a number of challenges. One challenge is the definition of major trauma. Here we have distinguished the classification of major trauma (an injury or combination of life-threatening injuries that lead to long term disabilities) from the classification of injury severity (number and extent of damage to body regions). We have used an Injury Severity Score (ISS) >/= 9 in our definition of major trauma, even though an ISS score of 9-15 is often classified as moderate injury. We have included moderate injury in our definition of major trauma better to observe the effect of frailty upon its incidence and outcomes.

A further challenge is that we anticipate that studies about the outcome of major trauma may not have included formal measures of frailty. We have therefore decided to include studies measuring proxy measures of frailty. Whilst we realise that neither disability nor multi-morbidity are synonymous with frailty, in older people they are close approximations to frailty and justifiable proxy measures. If possible we will compare in a sensitivity analysis our findings from studies using a formal measure of frailty with results from studies using a proxy measure.

We will exclude papers not written in English. This is primarily to avoid confounding of our findings arising from studies conducted in very different settings, but also for convenience. We will examine the scope for this to have affected our findings by examining the number of papers excluded due to language considerations and by the number of non-English papers found in the reference lists of papers included in our study. This will lead to inability to do an IPD analysis and hence reliance on published analyses will be the only option.

We have anticipated that meta-analysis may not be possible due to the different way that injury severity and outcomes are recorded by planning to conduct a synthesis without meta-analysis that takes into account both the size of any associations between frailty and outcome, and the robustness of the studies. We do not plan to perform an independent patient data analysis, since this would require access to the raw data from investigators and would only be justified after this review has been conducted.

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APPENDIX 1. OVID MEDLINE DATABASE CONCEPTS

	Concept 1	Concept 2	Concept 3
Key concepts	**Frailty**	**Trauma**	**Outcome**
Controlled vocabulary terms / Subject terms	- Frail elderly/ - Frailty/ - Geriatric Assessment/	- Trauma Severity Indices/ - Trauma Nursing/ - Trauma Centers/ - Multiple Trauma/ - Injury Severity Score/	- Activities of Daily Living/ - Mortality/ - Hospital Mortality/ - Disability Evaluation/ - Disabled Persons/ - institutionalization/ - Dementia/ - Cognition Disorders/ - Cognitive Disfunction/ - Chronic Disease/ - Multimorbidity/ - Delirium/ - Emergence Delirium/ - Polypharmacy/
Free text terms / natural language terms	- frail* - (Prefrail or Pre frail or Pre-frail). - Prior frail - Receipt of care - Prior disability	- Trauma* - Polytrauma - Injur*	- Mortality - Institutionalization - Institutionalisation - Dement* - Cognition - Cognitive - Multimorbidity - Multimorbidities - Morbidity - Morbidities

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APPENDIX 2. PUBMED DATABASE CONCEPTS

	Concept 1	Concept 2	Concept 3
Key concepts	**Frailty**	**Trauma**	**Outcome**
Controlled vocabulary terms / Subject terms	- "Frailty"[MeSH Terms] - "Frail Elderly"[MeSH Terms]	- "Trauma Centers"[MeSH Terms] - "Multiple Trauma"[MeSH Terms] - "Trauma Severity Index"[MeSH Terms] -"injuries"[MeSH Subheading]	- "Activities of Daily Living"[MeSH Terms] - "Mortality"[MeSH Terms] - "Mortality"[MeSH Subheading] - "Hospital Mortality"[MeSH Terms]) - "Institutionalization"[MeSH Terms] - "Disabled Persons"[MeSH Terms] - "Disability Evaluation"[MeSH Terms] - "Cognition Disorders"[MeSH Terms] - "Cognition"[MeSH Terms] - "Chronic Disease"[MeSH Terms] - "Delirium"[MeSH Terms] - "Polypharmacy"[MeSH Terms]
Free text terms / natural language terms	- frail* - (Prefrail or Pre frail or Pre-frail). - Prior frail - Receipt of care - Prior disability	- Trauma* - Polytrauma - Injur*	- Mortality - Institutionalization - Institutionalisation - Cognition - Cognitive - Multimorbidity - Multimorbidities - Morbidity - Morbidities