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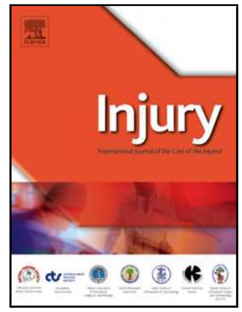
Sammy, I.A., Lecky, F.E., Sutton, A. et al. (2 more authors) (2016) Factors Affecting Mortality in Older Trauma Patients - A Systematic Review and Meta-analysis. Injury, 47 (6). pp. 1170-1183. ISSN 1879-0267

https://doi.org/10.1016/j.injury.2016.02.027



Title: Factors Affecting Mortality in Older Trauma Patients–A Systematic Review and Meta-analysis

Author: Ian Sammy Fiona Lecky Anthea Sutton Joanna Leaviss Alicia O'Cathain

PII:	S0020-1383(16)30026-2
DOI:	http://dx.doi.org/doi:10.1016/j.injury.2016.02.027
Reference:	JINJ 6630
To appear in:	*Injury, Int. J. Care Injured*
Received date:	30-7-2015
Accepted date:	29-2-2016

Please cite this article as: Sammy I, Lecky F, Sutton A, Leaviss J, O'Cathain A, Factors Affecting Mortality in Older Trauma PatientsndashA Systematic Review and Meta-analysis, *Injury* (2016), http://dx.doi.org/10.1016/j.injury.2016.02.027

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Authors:

Dr Ian Sammy (corresponding author)
TARN Doctoral Fellow
School of Health and Related Research
The University of Sheffield
Regent Court, 30 Regent Street
Sheffield S1 4DA
Tel: +44 (0) 114 222 4319
Email: ian.sammy@sheffield.ac.uk

Professor Fiona Lecky
Clinical Professor of Emergency Medicine
School of Health and Related Research
The University of Sheffield

Miss Anthea Sutton
Senior Information Specialist
School of Health and Related Research
The University of Sheffield

Dr Joanna Leaviss
Research Fellow
School of Health and Related Research
The University of Sheffield

Professor Alicia O'Cathain
Professor of Health Services Research
School of Health and Related Research
The University of Sheffield

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Word Count: 4,614 words (excluding Abstract, References, Tables and Figures)

Abstract

Introduction

Major trauma in older people is a significant health burden in the developed world. The aging of the population has resulted in larger numbers of older patients suffering serious injury. Older trauma patients are at greater risk of death from major trauma, but the reasons for this are less well understood. The aim of this review was to identify the factors affecting mortality in older patients suffering major injury.

Materials and Methods

A systematic review of Medline, Cinhal and the Cochrane database, supplemented by a manual search of relevant papers was undertaken, with meta-analysis.

Multi-center cohort studies of existing trauma registries that reported risk-adjusted mortality (adjusted odds ratios, AOR) in their outcomes and which analysed patients aged 65 and older as a separate cohort were included in the review.

Results

3609 papers were identified from the electronic databases, and 28 from manual searches. Of these, 15 papers fulfilled the inclusion criteria. Demographic variables (age and gender), pre-existing conditions (comorbidities and medication), and injury-related factors (injury severity, pattern and mechanism) were found to affect mortality.

The 'oldest old', aged 75 and older, had higher mortality rates than younger patients, aged 65 – 74 years. Older men had a significantly higher mortality rate than women (cumulative odds ratio 1.51, 95% CI 1.37 – 1.66). Three papers reported a higher risk of death in patients with pre-existing conditions. Two studies reported increased mortality in patients on warfarin (cumulative odds ratio 1.32, 95% CI 1.05-1.66). Higher mortality was seen in patients with lower Glasgow coma scores and systolic blood pressures. Mortality increased with increased injury severity and number of injuries sustained. Low level falls were associated with higher mortality than motor vehicle collisions (cumulative odds ratio 2.88, 95% CI 1.26-6.60).

Conclusions

Multiple factors contribute to mortality risk in older trauma patients. The relation between these factors and mortality is complex, and a fuller understanding of the contribution of each factor is needed to develop a better predictive model for trauma outcomes in older people. More research is required to identify patient and process factors affecting mortality in older patients.

Introduction

The factors affecting mortality in older people suffering major trauma are not well understood, though trauma in older patients is becoming a major public health issue worldwide. As population age increases globally, the proportion of people aged 65 years and older in Europe is expected to grow to at least 30% by 2050 (1). Research in the developed world suggests that older people are over-represented among major trauma victims (2-5).

Several studies worldwide have found higher mortality rates in older trauma patients compared to younger adults with similar injuries (4, 6). In the United Kingdom, Giannadous et al reported in 2008 that the mortality rate for patients aged ≥65 years presenting to a major trauma centre was significantly higher than in younger trauma patients (7). A variety of factors affect outcome from major trauma in older people. These include demographic factors, such as age, gender and social status; injury characteristics (injury pattern and severity); pre-existing medical conditions and the patients' physiological state on admission to hospital (8-17). Despite extensive research, there is no clear agreement on the relative impact of these diverse factors on mortality in older people with major trauma. For example, while some authors have reported a significant increase in mortality with the presence of pre-existing medical conditions, others have not (6, 18).

We therefore conducted a systematic review and meta-analysis of the research literature to identify the risk factors associated with increased mortality in older people suffering major trauma. The review sought to answer the following research question: 'Do differences in demographic, clinical and injury characteristics alter risk-adjusted mortality in older patients, 65 years and above, who have presented to the Emergency Department or the Emergency Services with major trauma?'

Materials and Methods

The methodology of this study is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) Statement for systematic reviews (19). The aim of this review was to identify factors affecting mortality in older patients, 65 years and above, who presented to the Emergency Department or the Emergency Services with major trauma. The objectives of the review were to quantify the degree to which each identified factor contributed to the risk of mortality in this age group, as measured by adjusted odds ratios of death.

Search Strategy

A systematic review of the literature was conducted through the Medline (via OvidSP), The Cochrane Library and Cinahl (via EBSCO) electronic databases. The electronic search was supplemented by a manual search of reference lists of relevant papers. All relevant papers up to June 2014 were included in the review. The search was updated in March 2015, using the same search strategy, and supplemented by manual searches of the reference lists of any new papers found. All searches were conducted independently by two of the authors (IS and FL). Any discrepancies were discussed between the two reviewers and a decision made regarding the inclusion of these papers.

The PICOS research question used for this review was:

> *'In older people admitted to hospitals in England and Wales with major trauma (population), what are the demographic, clinical and injury-related characteristics (intervention) that affect risk-adjusted mortality rates (outcome) when compared to those patients without these characteristics (comparator)'*

The following search strategy was used for all electronic databases:

> *(((((major injuries[Title/Abstract] OR major injury[Title/Abstract]) OR (multiple injured[Title/Abstract] OR multiple injures[Title/Abstract] OR multiple injuries[Title/Abstract] OR multiple injury[Title/Abstract])) OR Major Trauma[Title/Abstract]) OR Multiple Trauma[Title/Abstract]) AND (Elderly[Title/Abstract] OR "aged"[MeSH Terms])) NOT Hip*

Fracture$[Title/Abstract] AND (("1980/01/01"[PDAT] : "2014/12/31"[PDAT]) AND "humans"[MeSH Terms])

Studies were included if they were prospective multicenter cohort studies that included separate analyses of older major trauma patients, which reported odds ratios of death, adjusted for other significant covariates, such as injury characteristics (injury severity, injury pattern), demographic patient characteristics (age, gender) and clinical features (Glasgow coma score, systolic blood pressure). Studies with the appropriate methodology that used age cut-offs between 55 and 85 years to define 'older patients' were included in the review, once the other inclusion criteria were met. Outcome measures were in-hospital mortality or 30-day mortality. Only studies published in the English language or translated into English were included in the review. The search strategy was limited to papers published from 1980, as the first systematic database of major trauma patients (the Major Trauma Outcome Study) was developed in the early 1980s, and inclusion of studies from before this date risked increasing the degree of methodological heterogeneity in the review, due to different approaches to the assessment and reporting of trauma before this date (20, 21).

Studies were excluded if data on older patients were not analysed and reported separately. Single centre studies were excluded, to avoid the potential of provider bias due to the reporting of outcomes from an individual hospital. Studies that used prospectively collected data from established trauma registries were included, but studies that collected only historical data in a retrospective fashion were not. Prospective data collection was likely to be more reliable and less subject to inaccuracy than data collected retrospectively (22). Studies reporting exclusively on patients with hip fractures were excluded from this review, as the outcome of patients with isolated hip fractures is more a product of their pre-morbid medical state and their general medical and nursing care than their injury or trauma care per se (23, 24). As such, hip fracture patients are already excluded from many major trauma registries, including the TARN database in the UK (25).

Quality Assessment and Data Synthesis

The quality of selected papers was assessed against the STROBE ("strengthening the reporting of observational studies in epidemiology") guidelines for assessing cohort studies (26). A modified scoring system developed by Celso et al was used to grade the quality of each study (Appendix 1) (27). An a priori decision was made to include only studies with a CELSO score of 32 or above (an average of 4/5 per item). However, all eligible studies met this quality criterion and were included in the final review.

Meta-analysis was used to synthesise data from studies with broadly similar outcome measures and comparable populations. These included studies comparing gender, number of injuries sustained, mechanism of injury and pre-injury use of warfarin. Meta-analysis was not performed if the statistical heterogeneity between studies was high ('p' value for Cochran Q <0.10; I^2 >60%). For meta-analyses of more than 2 studies, where significant heterogeneity was found, stepwise exclusion of studies was performed to pool the effects of the studies with the least heterogeneity (28). For studies with high levels of statistical and methodological heterogeneity, a narrative synthesis of results was employed, without formal meta-analysis.

Results

Selection of Studies

Using the inclusion criteria, 3,609 papers were identified from electronic databases and a further 28 from manual searching of reference lists of relevant papers. Of these, 104 duplicate papers were identified, 3,471 excluded on initial screening of titles and abstracts and a further 45 excluded on screening of full text articles, leaving 15 eligible papers. Five (5) of these studies were included in the meta-analyses. The selection of studies is outlined in the PRISMA flow diagram shown in Figure 1.

Studies included in the meta-analysis were those comparing gender, number of injuries sustained, mechanism of injury and pre-injury use of warfarin. Those included in the narrative review compared age, injury pattern, injury severity, pre-existing medical conditions, Glasgow coma score and systolic blood pressure.

Description of Selected Studies

Table 1 lists all selected studies, with their main characteristics and findings. Of the 15 studies included in the review, several reported on more than one risk factor (see Table 2 and Table 1). Risk factors reported included the identification of an age cut-off at which mortality begins to rise significantly with increasing age (an 'inflexion point'); variations in mortality within age sub-groups of older people; gender; injury patterns; number of injuries; injury severity; injury mechanism; pre-existing medical conditions; pre-injury medication; Glasgow coma score and systolic blood pressure on admission to hospital.

Demographic Factors

Four studies specifically investigated the age at which risk-adjusted mortality increased significantly in major trauma patients, independent of other risk factors. The inflexion point for mortality with age occurred in the 4th or 5th decade (Table 1), apart from in Caterino's large American study which found an inflexion point at the 70-74 year age group (29-32).

Eight studies reported further differences in mortality between different age cohorts within the 65 and over age group (Table 3). Five of these studies reported age as a categorical variable, while in three it was a continuous variable. Three of the five studies that treated age as a categorical variable found a significant secondary increase in risk-adjusted mortality in the very old (≥75 years) (6, 33, 34). In contrast Curtis (2012) noted a secondary inflexion point at ≥85 years. Caterino's large study from the United States found a significant increase in mortality at 70-74 years old, but this was the only inflexion point in this study; the author did not note any initial increase in morality at a lower age, as seen in the other studies mentioned (31, 35). All three studies that treated age as a continuous variable found a significant and exponential increase in mortality with age (36, 37).

Four studies reported the relationships between risk-adjusted mortality and gender in older people with major trauma. Three of these studies reported an increased risk of death in men, while one (Sampalis, Quebec 2009) reported the opposite (6, 34, 38, 39). Figure 2 shows the Forest plot for the cumulative risk-adjusted mortality for gender, showing a significant increase in mortality in older men compared to older women (cumulative adjusted odds ratio 1.51; 95% CI 1.37 – 1.66). Bouamra's study could not be included in this meta-analysis as the older patients were divided into two separate age groups. Sampalis' study was also excluded, as its inclusion led to an unacceptably high level of statistical heterogeneity between the studies (I^2= 97%; 'p' value for Cochrane Q <.001). Sensitivity analysis of this meta-analysis showed that inclusion of Sampalis' study would have significantly altered the result, with the pooled results showing no significant difference in mortality rates between older men and women (cumulative adjusted odds ratio 1.07; 95% CI 0.57 – 2.00).

Injury Related Factors

Two studies reported on differences in risk-adjusted mortality for different injury patterns (Table 1). Using a reference of lower limb injuries, Aitken (2010) found a reduced mortality risk for patients with upper limb injuries (AOR 0.28; 95% CI: 0.14-0.56) and a slight reduction in mortality risk in patients with injuries to the abdomen, pelvis or thorax (AOR 0.64; 95% CI 0.44-0.99) (6). Richmond (2002) found a reduced risk of death in patients with extremity injuries, compared to a reference of head and neck injuries (AOR 0.58; 95% CI 0.4-0.9) (36).

Three studies investigated the impact of number of injuries on risk-adjusted mortality in older people. They all found an increased risk of death with increasing numbers of injuries (6, 36, 39). Sampalis (2009) and Richmond (2002) treated number of injuries as a discrete numerical variable while Aitken (2010) grouped patient into those having less than 3 injuries and those with 3 or more injuries. Figure 2 shows a Forest plot of the two studies reporting on the increase in risk-adjusted mortality for each additional injury sustained. The meta-analysis calculated a cumulative adjusted odds ratio for death of 1.08 for each additional injury sustained (95% CI 1.04 – 1.12). Seven

(7) studies reported on the relationship between injury severity and adjusted mortality in older people. All found an increased risk of death with increasing injury severity (Table 4) (6, 33, 36-40).

Sampalis (2009) in Quebec and Aitken (2010) in Queensland investigated the risk of mortality following falls compared to motor vehicle collisions in older people. Both investigators found higher risk-adjusted mortality in falls compared to motor vehicle collisions (Figure 2) (6, 39).

Pre-existing Conditions

Three studies investigated the impact of pre-existing medical conditions on mortality in older people with major trauma. In a cohort of patients aged 55 years and older, Yeung et al in Hong Kong identified the presence of one or more pre-existing medical conditions as a risk factor for increased mortality among older trauma patients (2.40 [95% CI 1.43 - 4.03]) (33). Richmond et al (2002), investigating trauma patients aged 65 and older, found no difference in the number of pre-existing medical conditions in survivors versus non-survivors. In light of this, the authors did not include pre-existing medical conditions in their multivariate analysis of mortality risk factors in this study (36). Grossman et al reported on the impact of 21 different pre-existing conditions on trauma outcome. Of these, Liver disease (AOR 5.11, 95% CI 3.09 - 8.21), renal failure (AOR 3.12, 95% CI 2.25 - 4.28), cancer (AOR 1.84, 95% CI 1.37 - 2.45), congestive heart failure (AOR 1.74, 95% CI 1.46 - 2.08) and COPD (AOR 1.49, 95% CI 1.22 - 1.80) had a significant impact on mortality. Other pre-existing medical conditions (including dementia, neurological conditions, other cardiac disease, diabetes, gastrointestinal disease, haematological disease, psychiatric disease, immunocompromise, arthritis, obesity, drug abuse, alcohol abuse and pulmonary disease) did not have a significant impact on mortality in older people with major trauma (Table 1).

Three studies investigating the impact of pre-injury medication on trauma in elderly patients fulfilled the inclusion criteria for this review. Efron et al demonstrated a protective effect of statin therapy on trauma mortality in older patients (AOR 0.33; 95% CI 0.12 – 0.92), while Grossman found pre-injury steroids significantly increased mortality (AOR 1.59; 95% CI 1.03 – 2.40) (37, 38). Howard et al (2009) found a significant increase in the adjusted odds of death in patients on warfarin, while Grossman's study did not (38, 41). Figure 2 shows the Forest plot for these studies. Cumulatively, they demonstrate a significant increase in risk-adjusted trauma mortality in older patients with pre-injury warfarin use (cumulative adjusted odds ratio 1.32; 95% CI 1.05 – 1.66).

Physiological Variables

All four studies assessing the impact of Glasgow coma score (GCS) on mortality found an increase in risk-adjusted mortality with lower GCS (33, 37, 40). In their study of older patients suffering gunshot wounds, Lustenberger et al found a significant increase in adjusted mortality in patients with a GCS of 3-8, compared to those with a higher GCS (AOR 13.47; 95% CI 10.35–17.53). Yeung's study of older trauma patients in Hong Kong compared risk-adjusted mortality in patients with different Glasgow coma scores. Using a reference of GCS 13-15, the adjusted odds ratio for mortality in patients with GCS 9-12 was 3.18 (95% CI 1.64 - 6.13); while the AOR for patients with GCS 6-8 was 6.23 (95% CI 3.16 - 12.29) and that for patients with GCS 3-5 was 23.18 (95% CI 10.70 - 50.24). Efron (2008) and Grossman (2002) both reported an increase in risk-adjusted mortality for each unit increase in GCS, with adjusted odds ratios of 0.66 (95% CI 0.58–0.76) and 0.78 (0.77–0.79), respectively. Due to the variation in reporting GCS in these studies, it was not possible to calculate a cumulative odds ratio for death with decreasing GCS.

Three eligible studies reporting the relationship between blood pressure and mortality in older trauma patients found an increase in risk-adjusted mortality with low blood pressure (Table 1). Lustenberger (2011) reported an adjusted odds ratio of 5.27 (95% CI 3.89–7.14) in older patients with gunshot wounds whose blood pressure was less than 90 mmHg (40). In contrast, Berry et al (2010) found that the inflexion point for increased mortality with decreased systolic blood pressure was 100 mmHg in patients aged 50 – 69 and 110 mmHg for patients age 70 and older (42). The adjusted odds ratios for these groups were 2.20 (95% CI 1.46–3.31) and 1.92 (95% CI 1.35–2.74), respectively. Grossman's study of older trauma patients found an increase in risk-adjusted mortality

(AOR 3.09; 95% CI 2.50-3.80), in patients with systolic blood pressures <90 mmHg (38). Due to the different cut-off points used in each study to define low blood pressure, meta-analysis was not performed on these studies.

Discussion

This systematic review identified a variety of risk factors that influence mortality in older trauma patients. These included demographic variables, pre-existing conditions, injury characteristics and physiological variables. Unfortunately the heterogeneity in study methodology, data analysis and reporting of results limited the utility of meta-analysis in this review, and its use was restricted to studies on gender, number of injuries, mechanism of injury and pre-injury use of warfarin.

Demographic Factors

Three of the four studies that attempted to identify an age at which mortality from trauma increased significantly reported an inflexion point for increasing mortality at around the 4^{th} to 5^{th} decade, ranging from 45 to 59 years (29, 30, 32). This concurs with the cut-off for age in most current predictive models for mortality in trauma. For example the TRISS methodology dichotomises age, with a cut off of 55 years (43). However, the one study that found a much higher inflexion point for mortality with age (Caterino, 2010) cannot be easily ignored; it is the only American study in this category, and has by far the largest cohort of patients (75,658 patients). It is possible that this difference in age groups may reflect local differences in populations, but equally this may be due to the impact of unmeasured confounding factors, such as mechanism of injury and the presence of pre-existing factors.

While most studies noted an increased mortality in older patients (those aged 65 and above), this review identified a number of studies which observed a second further sharp increase in mortality in the ‘oldest old’ trauma patients (those aged 75 and over and 85 and over). This suggests that the interpretation of age as a dichotomous variable is likely to be an over-simplification. Some registries, such as the TARN database, already categorise age into more than two groups, and this model preforms better than either a linear or a binary model of age in predictive modeling (34).

The majority of studies in the review that investigated the impact of gender on mortality in older trauma patients found that there was an increased risk of death in men compared to women. Sampalis' study, the only one reporting an increased risk of death in older women compared to men, included 4,717 patients, but was restricted to those involved in motor vehicle collisions or those with falls (39). Whether this may have influenced the outcome in this study is uncertain. It is unclear whether gender is a truly independent risk factor or if it reflects an increase in the number of comorbidities seen in older men compared to older women (44). Bouamra's updated predictive model for trauma mortality, based on UK TARN data, demonstrates an interaction between age and gender. The higher mortality in men is only seen in patients ≥65 years. This study did not attempt to include comorbidities in the analysis, so it is possible that this interaction reflects an increase in comorbidities in older men compared to older women (34). However, more recently, Bouamra and colleagues have further updated the TARN predictive model to include comorbidities as an independent covariate. The age/gender interaction persists in this newer model, suggesting that the influence of gender on trauma mortality is independent of comorbidities.

Injury Related Factors

Only two studies that compared mortality rates between patients with different injury patterns were eligible for inclusion in this review. The findings of these studies were inconsistent and contrasted with reports from other sources suggesting that head injuries in older people are associated with an increased risk of death compared to injuries to other body regions (45). Head injuries are clearly a leading cause of death in older trauma patients, and older patients with head injuries have also been shown to have higher mortality rates than younger patients (46, 47). However, the studies that investigated the impact of injury patterns in this review found no increase in risk-adjusted mortality in head injured older patients compared to those with other injury patterns.

Most current predictive models for major trauma generally incorporate the injury severity score (ISS) in their model, but the number of injuries sustained is not seen as a significant factor influencing outcome (34, 43). However, in this review injury severity and number of injuries were found to be independent predictors of mortality in older trauma patients (6, 36, 39). This may be due to the relative inability of older patients to compensate for the stresses of injury, and their propensity for multi-organ failure in response to major trauma (36, 48). In this setting, multiple injuries may be less well tolerated than in younger patients.

Several researchers have demonstrated that the risk of falls (particularly low level falls) increases with increasing age, while motor vehicle collisions remain an important cause of injury in both older and younger people (29, 36, 49, 50). In this review, two studies showed an increased risk of death in older patients with falls compared to those involved in motor vehicle collisions (Figure 2). The majority of falls in older people are low level falls, which traditionally has been viewed as 'low energy impact' injuries (51, 52). However, the findings of this review suggest that all falls in older people should be treated as high risk injuries.

Pre-existing Conditions

The three studies investigating the impact of pre-existing medical conditions which were eligible for inclusion in this review had widely differing results (33, 36, 38). This may in part be due to differing definitions of 'pre-existing conditions'. There is possibly also a difference in the prevalence and impact of pre-existing conditions on mortality in trauma patients between different countries. The complexity of the relationship between pre-existing conditions and trauma mortality is demonstrated by the results of Grossman's study, which provided a more detailed analysis of the impact of specific conditions, and showed that different conditions have different effects on outcome in trauma patients. Other studies not included in this review have also reported a positive association between pre-existing medical conditions and trauma mortality, but none of these studies analysed older people as a separate group (30, 44, 53). Bergeron, Gabbe, Bouamra and others have all acknowledged the need to include pre-existing medical conditions in predictive models of trauma mortality (34, 54, 55). As mentioned previously, Bouamra's latest iteration of the TARN predictive model for trauma mortality includes pre-existing medical conditions through the use of a modification of the Charlson comorbidity index.

The effect of anticoagulant and antiplatelet therapy on trauma mortality has attracted some interest among researchers. The two studies that fulfilled the inclusion criteria for this review (Howard et al, 2009 and Grossman et al, 2002) produced different results, though the cumulative risk-adjusted mortality from these papers showed a significant increase in mortality for older trauma patients on warfarin (41). This meta-analysis should be interpreted with caution, as there were important differences in the study populations; Howard's study only included head injured patients, while Grossman's study included all older trauma patients, which may have accounted for the difference in outcomes. However, several other studies have demonstrated a significant increase in mortality in trauma patients on Warfarin and antiplatelet therapy, though none fulfilled the inclusion criteria for this review (16, 56-58). In addition, a meta-analysis of the effect of warfarin on head injuries by Batchelor et al (2012), not restricted to older patients, concluded that warfarin use significantly increased mortality in these patients (59). These data suggest that the accurate documentation of warfarin use among older trauma patients is an essential part of clinical management as well as outcome prediction.

Physiological Variables

The impact of physiological variables on outcome in trauma patients has been extensively investigated, and forms one of the pillars of predictive modeling in major trauma (34, 43, 60). These physiological variables have also been investigated as risk factors for mortality in older trauma patients. Unfortunately, there has been no standardized approach to the definition of physiological variables in trauma research, so comparisons between studies are difficult.

For example, in this review of the studies investigating the effects of GCS on mortality, two studies analysed the GCS as a continuous variable reporting the change in adjusted odds per unit increase in GCS, while the others grouped GCS into categories. Furthermore, the limits of each category of GCS were not consistent between studies reporting GCS as a categorical variable (33, 40, 52). In light of this heterogeneity, it was not possible to conduct a meaningful meta-analysis of the studies reporting the effects of GCS on mortality in older people with major trauma.

Another factor that restricted the direct comparison of studies reporting on physiological risk factors was the lack of methodological homogeneity. Of the studies that reported the impact of systolic blood pressure on mortality, Lustenberger's cohort consisted exclusively of patients suffering gunshot wounds, while Berry's study reported on patients with isolated head injuries and the patients in Yeung's and Grossman's studies consisted of all older trauma patients (33, 40, 42). Direct comparisons between these studies would have been potentially misleading. Patients with gunshot wounds are likely to be hypotensive, while those with isolated head injuries may have higher than average blood pressures. It is therefore not surprising that Berry's cut-off for blood pressure was higher than that seen in Lustenberger's study. Meta-analysis was therefore not attempted on these studies.

Strengths and Limitations

This is the first systematic review of factors affecting trauma outcomes in older patients that has taken such a broad view of the topic. Hashmi et al (2014) conducted a systematic review and meta-analysis of factors affecting outcome in older trauma patients, but only considered physiological variables such as Glasgow coma score and systolic blood pressure (61). In contrast, our study highlights a wide range of factors affecting mortality in older trauma patients. While modeling of trauma outcomes has traditionally focused on a pre-defined spectrum of risk factors (such as injury severity, physiology and age), this review emphasizes the diversity of factors affecting trauma outcomes in older people. It is essential to consider all these risk factors when developing a new predictive model for mortality in older people with major trauma.

Inevitably, selection criteria for systematic reviews run the risk of excluding potentially useful and informative studies. Unlike Hashmi's review, which included single centre trials, this review was limited to multicenter studies. This was necessary, as the purpose of the review was to identify factors which independently influence trauma mortality. In this context, the inclusion of single centre studies risked introducing bias due to unrecognized process factors influencing outcomes in single hospital sites. However, this led to the exclusion of a small number of large single-center cohort studies that may have been directly relevant to this review, including two UK based studies: a review of elderly trauma by Giannoudis and a review of factors influencing trauma outcome in the elderly by Pickering et al (7, 62). In addition, several other single-centre studies investigating specific risk factors were also excluded. These included studies on the effects of warfarin on trauma outcomes in older people (63, 64) and the relation between comorbidities and outcome in older trauma patients (55).

Conclusion

This systematic review suggests that, in common with younger adults, increasing age and severity/number of injuries, alongside co-morbidity are predictors of increased early mortality after traumatic injury (6, 33, 35). However, there are additional factors affecting outcome in the elderly (such as gender, mechanism of injury, medications) which are not shown to be relevant in younger adults (34, 38, 39). In addition, some factors influencing mortality in younger adults (for example physiological derangement) may need to be assessed differently in older people (42). Unfortunately the evidence to describe if/ how these factors should be adjusted for in prognostic models is not definitive. There is a need for further robust prognostic studies to explore this.

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Figure and Table Legends

Figure 1: PRISMA recruitment flow diagram for systematic review of patient factors affecting mortality in older people with major trauma.

Figure 2: Forest plot of studies comparing risk-adjusted mortality in relation to different risk factors.

Table 1: Summary table for papers included in the systematic review of patient factors affecting mortality in older people with major trauma

Table 2: Studies and risk factors included in the review.

Table 3: A summary of the relationship between age and risk-adjusted mortality for patients 65 years and older.

Table 4: A summary table studies reporting the impact of injury severity on risk-adjusted mortality in older people with major trauma (*ICISS decreases with increased injury severity)

Table 1: SUMMARY TABLE FOR PAPERS INCLUDED IN THE SYSTEMATIC REVIEW OF PATIENT FACTORS AFFECTING MORTALITY IN OLDER PEOPLE WITH MAJOR TRAUMA

Paper	Year of Publication	Database	Type of study	Main Aim of Study	Patient Group (including sample size[n])	Comparator (including sample size[n])	Main Outcome Measure	Main Findings (95% CI)	Celso Score (Total = 40)
Aitken et al (Characteristics and outcomes of injured older adults after hospital admission.)	2010	Medline, CINHAL	Retrospective analysis of data from the Queensland Trauma Registry.	To describe the seriously injured adult population aged 65 and older; compare the differences in injury characteristics and outcomes in three subgroups aged 65 to 74, 75 to 84, and 85 and older	All patients aged 65 and older with major trauma entered into the Queensland Trauma Registry between 2003 and 2006 (n=6069)	Three cohorts compared: 65 - 74; 75 - 84 and 85 and older.	Adjusted odds ratio of death.	The study demonstrated an increasing mortality with age [reference age 65 – 74; AOR for 75-84 1.47 (1.07–2.02); AOR for ≥85 2.81 (1.97–3.99)], as well as with male gender [AOR 1.40 (1.07–1.84)], mechanism of injury [reference falls; motor vehicle collision AOR 0.47 (0.32–0.70)] and injury pattern [reference 1 injury; 2 injuries 1.49 (1.02–2.17); ≥3 injuries AOR 1.73 (1.18–2.53)].	38
Belzunegui et al (Major trauma registry of Navarre (Spain): the accuracy of different survival prediction models) Am J Emerg Med (2013)	2013	Medline	Prospective cohort study (multicentre study)	To determine which factors predict death among trauma patients who are alive on arrival at hospital, using regression modeling	All patients admitted to hospital with a NISS of >15, who sustained their injuries <24 hours prior to admission (n=378)	No comparators	Mortality at 30 days	The best-fit predictive model of mortality utilised an age cut-off of 59 years [AOR 4.35 (1.59 – 11.91)].	37

Berry et al (Redefining hypotension in traumatic brain injury)	2010	Manual search of citations from selected papers	Review of data from Los Angeles State trauma registry	To determine the age-adjusted optimal SBP in patients with isolated moderate to severe TBI	All adult trauma patients (age > 14 years) with blunt isolated moderate to severe TBI admitted between January 1998 and December 2005 to one of 13 trauma centres in the county of Los Angeles.	Patients were compared in age defined cohorts: 15 – 49; 60 – 69 and ≥ 70 years old.	Ten different models of mortality prediction were tested. The statistical fit of each model was assessed by the Akaike Information Criterion (AIC) and the Schwartz Criterion (SC). The discriminatory power of each model was assessed by the C-Statistic. Mortality rates for each age group in relation to systolic blood pressure were reported as risk adjusted odds ratios.	For each age group, mortality increased significantly when SBP dropped below 100 mmHg (50 – 69 years: AOR 2.20, 95% CI 1.46–3.31); and 110 mmHg (≥ 70 years : AOR 1.92, 95% CI 1.35–2.74) respectively.	38

Bouamra et al (A New Approach to Outcome Prediction in Trauma: A Comparison With the TRISS Model)	2006	Medline	A review of patient registered on the TARN database between 1996 and 2001	To determine whether an alternative to the TRISS model would better predict 30 day outcome with maximal case inclusion in the European Trauma Registry.	All patients entered onto the TARN database between 1996 and 2001 constituted the complete dataset (n = 100,399). The core dataset excluded patients with penetrating trauma, burns/inhalational injuries, age <16 years, intubated on arrival, transferred for definitive care and cases from outside England and Wales (n = 66,650)	The following pre-specified age cohorts were compared: 16–44, 45-54, 55-64, 65–74, ≥75 years)	The main aim of the study was to compare the accuracy of a new predictive model to that of the TRISS methodology. Coefficients for each risk factor and 95% confidence intervals were reported. Odds ratios were calculated from the coefficients.	Adjusted odds ratios reported for: Age group [Reference 16-24 years. 65-74 years 6.80 (5.56-8.33), >75 years 25.82 (20.00-33.33)]; Gender [Reference female. AOR 65-75 years age group 1.75 (1.29-2.69), >75 years age group 1.86 (1.32-2.33)]; Glasgow Coma Score [Reference 13-15. AOR for GCS 9-12: 2.97 (2.44-3.57), GCS 6-8: 4.63(3.58-5.88), GCS 4-5: 14.72 (12.5-20.0), GCS 3: 33.55 (33.3-50.0)	40

Caterino et al (identification of an age cut-off for increased mortality in patients with elderly trauma)	2011	Manual search of citations from selected papers	Cross Sectional study of a multicenter trauma registry	To determine the age cutoff at which trauma mortality increases	5 year groupings of patients, compared by age and ISS. (n=75658)	Cohorts of 5 year age bands: 16-29 (n=6400), 30-39 (n=9380), 40-49 (n=11084), 50-59 (n=8772), 60-69 (n=6925), 70-79 (n=9152), 80-89 (n=10912), ≥90 (n=3033)	Odds ratio of death adjusted for moderate or severe injury severity.	OR of death increased significantly at the 70 – 74 year age group, independent of injury severity. Using 70-74 age group as the reference, AOR for 16 – 19 year group was 0.52 (0.42 – 0.64) and AOR for 65 – 69 year group was 0.69 (0.54 – 0.89), with other age groups' AORs lying between these values. The AOR for the older age groups (using 70 – 74 years as a referent) were not significantly different (all 95% CIs crossed 1)	37
Curtis KA et al (Injury trends and mortality in adult patients with major trauma in New South Wales.)	2012	Medline	Retrospective Review of prospectively collected data	To identify the risk factors associated with death in major trauma patients in NSW, Australia	Patients suffering major trauma (ISS >15) in NSW (n=9769)	age cohorts: 16-24; 25-34; 35-44; 45-54; 55-64; 65-74(n=911); 75-84 (n=1214) and 85+ (n=613)	Adjusted odds ratio of death	AOR for overall mortality significantly higher for ages 65-74 [3.35 (2.57–4.38)]; 75-84[4.95 (3.88–6.32)] and ≥85[9.01 (6.85–11.87)].	37
Efron et al (Preinjury statin use is associated with improved in-hospital survival in elderly trauma patients.)	2008	Medline, CINHAL	Retrospective observational cohort study	To determine the effect of pre-injury treatment with statins on trauma mortality in older patients.	Patients 65 years and older presenting with moderate to severe trauma (AIS ≥3) who were on statins prior to injury.(n=1224)	Patients 65 years and older presenting with moderate to severe trauma (AIS ≥3) who were not on statins prior to injury. (n=2416)	Adjusted odds ratio of death	AOR of death for statin use was 0.33 (0.12-0.92). AOR of death for stain use in patients with no CVS disease was 0.30 (0.10- 0.9); AOR for each 1 year increase in age was 1.11 (1.06 - 1.14); AOR for every one point increase in NISS was 1.07 (1.05 – 1.09); AOR for each 1 point rise in GCS: 0.66 (0.58–0.76).	37

Fatovich, 2013, The effect of age, severity, and mechanism of injury on risk of death from major trauma in Western Australia	2013	Medline, CINHAL	Retrospective analysis of prospectively collected data	Compare adjusted mortality in older vs younger trauma patients	Elderly trauma patients (Aged 65 and over) with ISS ≥ 15. (n=820)	Trauma patients aged 15 – 64 with ISS ≥ 15. (n=3246)	In-hospital mortality (survival to discharge), adjusted for injury severity	Increased AOR with age. Inflexion point for increased mortality 47 years old.	36
Grossman MD et al (When is an elder old? Effect of preexisting conditions on mortality in geriatric trauma)	2002	CINHAL	Analysis of data from the Pennsylvania State trauma registry (1986-1999)	To carry out a descriptive study of geriatric trauma and examine the impact of comorbidity or preexisting conditions (PECs) on outcome.	All patients ≥65 years entered onto the registry between 1986 and 1999. (n=33,781)	Comparisons made with regard to physiology, comorbidities, injury severity, age and gender.	Risk adjusted mortality rates (AORs) for various covariates reported.	AOR significantly increased with age (1.068, 95%CI 1.061 -1.075), male gender (1.524, 95%CI 1.379 -1.686), SBP <90mmHg (3.09, 95%CI 2.50 - 3.80), decreasing GCS (1.282, 95%CI 1.265 - 1.298) and increasing ISS (1.098, 95%CI 1.093 - 1.104) AOR for comorbidities with a significant effect on mortality: CHF (1.74, 95% CI 1.46 - 2.08); Steroids (1.59 95% CI 1.03 - 2.40); Liver disease (5.11, 95% CI 3.09 - 8.21); Cancer (1.84, 95% CI 1.37 - 2.45); COPD (1.49, 95% CI 1.22 - 1.80); Renal failure (3.12, 95% CI 2.25 - 4.28)	37

Howard et al (Preinjury Warfarin Worsens Outcome in Elderly Patients Who Fall From Standing)	2009	Medline	Retrospective analysis of prospectively collected trauma registry data	To determine the effects on outcome of pre-injury warfarin in older trauma patients	Patients aged 65 and older with trauma entered onto the Pennsylvania Trauma Registry between 2003 and 2006, who were on warfarin prior to the injury (n=537)	Patients aged 65 and older with trauma entered onto the Pennsylvania Trauma Registry between 2003 and 2006, who were NOT on warfarin prior to the injury (n=2,254)	Adjusted odds ratios of death	For all patients on warfarin (referent = no warfarin), the AOR was 1.54 (95% CI 1.09 –2.19); for patients with a head injury AIS of 4 – 5, the AOR was 1.63 (95% CI 1.03–2.58). In the severe head injury group, the AOR was significantly higher for patients with a GCS of 14 – 15 [AOR 2.30 (1.12–4.70)], but not for patients with a lower GCS.	37
Kuhne et al (Mortality in severely injured elderly trauma patients--when does age become a risk factor?)	2005	Medline	Retrospective review of prospectively collected trauma registry data (Germany) between 1993 to 2003	To determine the age at which mortality rises significantly following major trauma	All patient with severe trauma (ISS ≥16) entered into the State trauma registry (n=5376)	Cohorts compare by 10-year age bands [15 - 55; 26-35; 36-45; 46 - 55; 56 - 65; 66 - 75 and >75]	Mortality adjusted for injury severity	The inflexion point for mortality was between the 45 – 54 year group and the 55 – 64 year group, independent of injury severity.	35

Lustenberger et al (Gunshot Injuries in the Elderly)	2011	Manual search of citations from selected papers	Review of data from the national trauma databank	To evaluate incidence of and outcomes after gunshot injury in the elderly age segment, to relate these outcomes to those in younger trauma patients, and to identify risk factors for death in the geriatric trauma population.	Patient admitted with gunshot wounds aged 55–64 years, (n = 1,676) 65–74 years, (n = 727 and) ≥75 years, (n = 787)	Patients were compared in cohorts of 10 years (55 – 64; 65 – 74 and ≥75 years)	Risk adjusted odds of death were reported. LOS in hospital and on ICU were also reported.	An increased risk of death [AOR] was seen in patiaents with a SBP <90 [5.27 (95% CI 3.89–7.14)]; GCS ≤ 8 [13.47 (95% CI 10.35–17.53); ISS ≥ 16 [5.50 (95% CI 4.23–7.16)]; Injury Severity [ISS 16-14: AOR 5.50 (4.23–7.16), reference ISS <16] and age [AOR 1.74 (1.50-2.03); Reference 55-64 years, comparators 65-74 and ≥75 years]	37

Richmond et al (Charactersitics and Outcomes of Serious Traumatic Injuries in Older Adults)	2002	Medline	Retrospecitive analysis of prospectively collected data	To characterize and compare the differences in injury characteristics and outcomes in older trauma patients.	Patients aged 65 and older entered into the Pennsylvania Trauma Registry between 1988 and 1997. 38,7070 patients	Patients were compared in three age groups: 65 – 74 years, 75 – 84 years and ≥85 years	Adjusted odds of death	Age treated as a continuous variable; AOR increased 1.05 for each additional year of age (95% CI 1.03 – 1.07). There was no difference in mortality between patients with and those without comorbidities. Other factors associated with increased AOR were number of injuries [AOR for each additional injury sustained: 1.11 (1.10 – 1.20)]; injury severity score (referent 0-9; 10 – 15: 2.76 [95%CI1.7-4.4]; 16 – 25: 4.65 [95% CI 2.5 – 7.4]; ≥26: 25.51 [95% CI 14.5 – 44.8]); body part injured (referent head/neck; extremity/pelvic girdle 0.58 [95% CI 0.4 – 0.9]	37

Sampalis et al (Assessment of mortality in older trauma patients sustaining injuries from falls or motor vehicle collisions treated in regional level I trauma centers)	2009	Manual search of citations from selected papers	A review of the Quebec Trauma Registry (QTR), which includes data from patients treated for injuries at 3 Level I, 29 Level II and 21 Level III trauma centers and the *Re´gie de l'Assurance Maladie du Que´bec* (RAMQ)	To describe the characteristics and outcomes and process – outcome associations of a cohort of older trauma patients treated in Quebec Level I trauma centers for injuries sustained in MVCs and Falls	Patient 65 years and older admitted to one of three level 1 trauma centres (n = 4717) in Quebec following a fall (n = 4111) or a motor vehicle crash (n = 606)	The cohorts were compared according to mechanism of injury primarily. For calculation of odds ratios, age was treated as a continuous variable.	Risk adjusted odds of death were reported.	Factors affecting mortality [AOR] included Male gender [AOR 0.57 (95% CI 0.45–0.71)]; Age (yrs) [AOR 1.06 (95% CI 1.04–1.07)]; ISS Category* [AOR 3.09 (95% CI 2.48–3.84)]; Number of Injuries (1–16) [AOR 1.07 (95% CI 1.03–1.12)]; Mechanism of Injury (Fall vs. Motor Vehicle Collision) [AOR 5.11 (1.84–14.17)] * ISS categories: 1–11, 12–24, 25–49, and 50–75.	37
Yeung et al (High risk trauma in older adults in Hong Kong: a multicentre study.)	2008	Medline	Retrospective analysis of prospectively collected data from a centralised trauma database.	To determine the injury characteristics of high risk older trauma patients and risk factors associated with increased mortality in this age group	Patients aged 55 years and older presenting to a trauma receiving hospital in Hong Kong, and entered into the Hong Kong trauma registry. (n=810)	The patients were compared in three age groups: 55 - 74; 75 - 84 nd 85 and above	All-cause mortality. Adjusted odds ratios of death were also quoted.	AOR significantly greater with Age [Reference 55 – 74; AOR for Age 75 – 84: 3.526 (2.034, 6.113); Age ≥85 4.230 (2.188, 8.180); presence of comorbidities [2.404 (1.433, 4.032)]; GCS [Reference 13 – 15; AOR for GCS 9 – 12: 3.175 (1.644, 6.129); GCS 6-8: 6.228 (3.157, 12.287); GCS 3 – 5: 23.184 (10.699, 50.239)] and ISS.	37

Author	Year	Country	Risk Factors Investigated											
			Demographics			Injury Factors				Patient Factors				
			Age cut-off	Age groups	Gender	Injury patterns	Number of injuries	Injury severity	Injury mechanism	Pre-existing conditions	Pre-injury medication	Glasgow coma score	Blood pressure	Studies in meta-analyses
Aitken	2010	Australia		√	√	√	√	√	√					√
Belzunegui	2013	Spain	√											
Berry	2010	USA											√	
Bouamra	2006	UK		√	√									
Caterino	2008	USA	√	√										
Curtis	2012	Australia		√										
Efron	2008	USA		√				√			√	√		
Fatovich	2012	Australia	√											
Grossman	2002	USA		√	√					√	√	√	√	√
Howard	2009	USA									√			√
Kuhne	2005	Germany	√											
Lustenberger	2011	USA						√				√	√	
Richmond	2002	USA		√		√	√	√		√				√
Sampalis	2009	Canada			√		√	√	√					√
Yeung	2008	Hong Kong		√				√		√		√		

Table 2: Studies and risk factors included in the review.

Study	Reference	55-64	65-74	75-84	≥85
		Age Groups in years			
		Adjusted Odds Ratios (95% Confidence intervals)			
Curtis (2012)	16-24	1.65 (1.24–2.19)	3.35 (2.57–4.38)	4.95 (3.88–6.32)	9.01 (6.85–11.87)
Aitken (2010)	65-74 years		(Reference)	1.47 (1.07–2.02)	2.81 (1.97–3.99)
Yeung (2008)	55-74 years			3.53 (2.03-6.11)	4.23 (2.19-8.18)
Boumra (2006)	16-44 years		6.80 (5.56-8.33)	25.81 (20.00-33.33)	

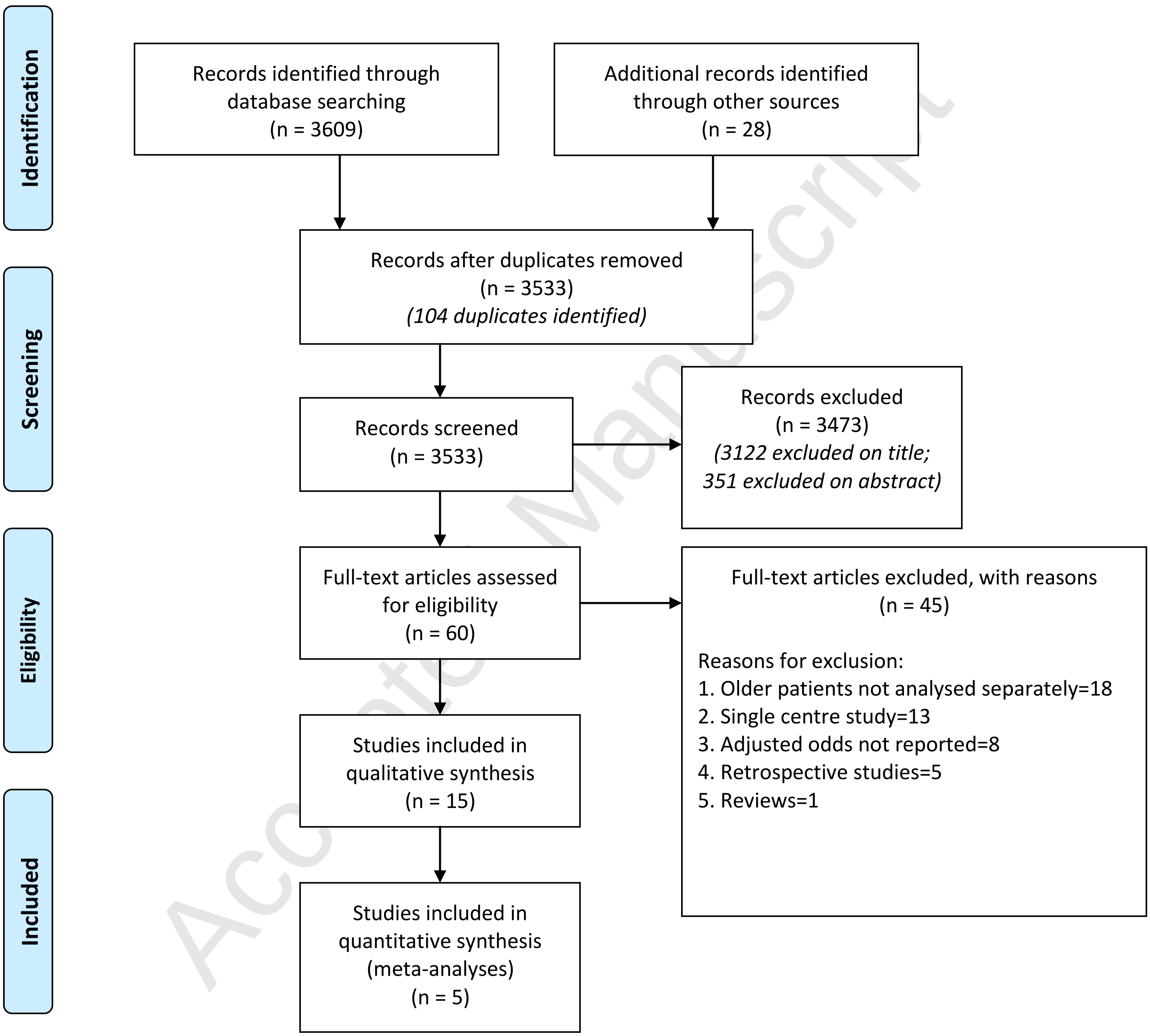
Caterino (2010)	Reference	70-74	75-79	80-84	85-89	≥90
		Age Groups in years				
		Adjusted Odds Ratios (95% Confidence intervals)				
	65-69 years	1.44 (1.12-1.85)	1.58 (1.25-2.00)	1.66 (1.32-2.10)	1.95 (1.63-2.48)	2.76 (2.13-3.57)

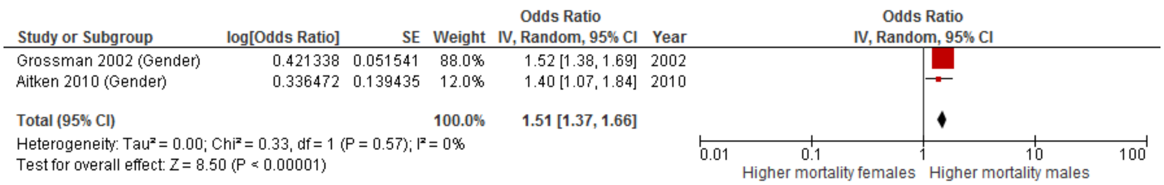
Studies with age as a continuous variable	
Efron (2008)	AOR for each 1 year increase in age: 1.11 (1.06 - 1.14)
Grossman (2002)	AOR for each 1 year increase in age: 1.07 (1.06 – 1.08)
Richmond (2002)	AOR for each 1 year increase in age: 1.05 (1.03 – 1.07)

Table 3: A summary of the relationship between age and risk-adjusted mortality for patients 65 years and older.

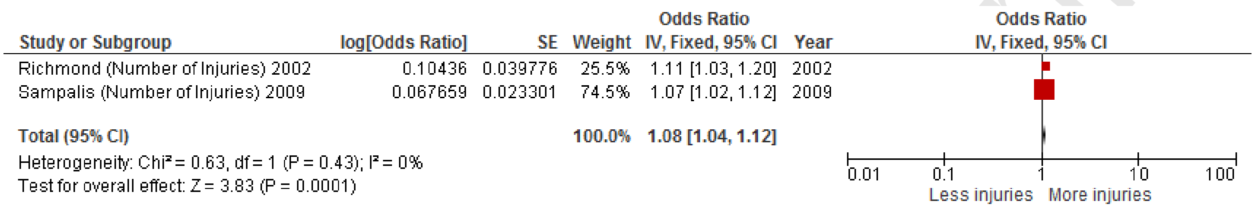
	Injury Severity Score					
Study	**1-9**	**10-15**	**16-24**	**25-39**	**40-49**	**≥50**
	Adjusted Odds Ratios (95% Confidence Intervals)					
Aitken (2010)	Reference	1.39 (0.88–2.21)	2.20 (1.37–3.54)	*(ISS ≥25)* 5.16 (2.94–9.06)		
Richmond (2004)	Reference	1.3 (1.0–1.8)	3.3 (2.5–4.4)	*(ISS ≥25)* 4.0 (2.7– 5.9)		
Lustenberger (2011)	*(ISS 1-15)* Reference		*(ISS ≥16)* 5.50 (4.23–7.16)			
Yeung (2008)	*(ISS 1 – 15)* Reference		2.17 (1.08-4.38)	14.30 (7.59-26.93)	37.12 (11.73-117.51)	57.94 (18.01- 186.43)
Sampalis (2009)	*ISS divided into 4 categories (1-11, 12-24, 25-49 and 50-75)* AOR for mortality between groups 3.09 (2.48–3.84)					
Efron (2008)	*Injury Severity estimated using NISS as a continuous variable* AOR for every one point increase in NISS: 1.07 (1.05 – 1.09)					
Grossman (2002)	*Injury Severity estimated using ISS as a continuous variable* AOR for every one point increase in ISS: 1.10 (1.09 - 1.11)					

Table 4: A summary table studies reporting the impact of injury severity on risk adjusted mortality in older people with major trauma.

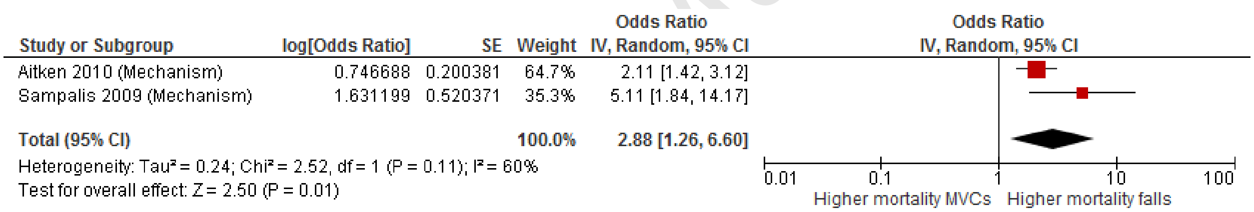

Identification
Screening
Eligibility
Included
Records identified through database searching (n = 3609)
Additional records identified through other sources (n = 28)
Records after duplicates removed (n = 3533) (104 duplicates identified)
Records screened (n = 3533)
Records excluded (n = 3473) (3122 excluded on title; 351 excluded on abstract)
Full-text articles assessed for eligibility (n = 60)
Full-text articles excluded, with reasons (n = 45)
Reasons for exclusion:
1. Older patients not analysed separately=18
2. Single centre study=13
3. Adjusted odds not reported=8
4. Retrospective studies=5
5. Reviews=1
Studies included in qualitative synthesis (n = 15)
Studies included in quantitative synthesis (meta-analyses) (n = 5)



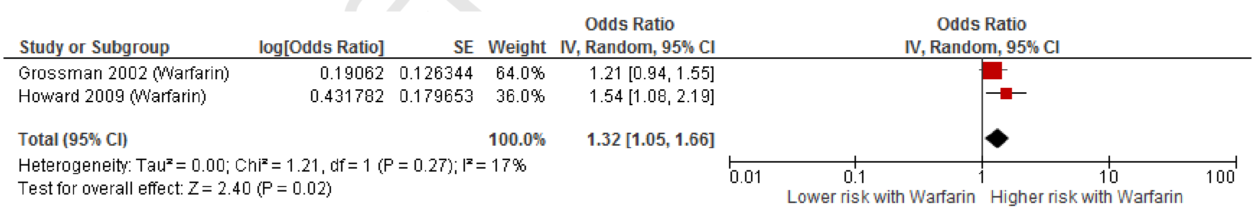
Meta-analysis of the impact of gender on mortality in older people with major trauma



Meta-analysis of the impact of number of injuries on mortality in older people with major trauma



Meta-analysis of the impact of mechanism of injury on mortality in older people with major trauma



Meta-analysis of the impact of pre-injury warfarin use on mortality in older people with major trauma