OUTCOMES OF DIFFERENT HEALTHCARE CONTEXTS FOR DIRECT TRANSPORT TO A TRAUMA CENTRE VERSUS INITIAL SECONDARY CENTER CARE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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INTRODUCTION

Trauma is the leading cause of death for all persons under the age of 44 years in developed countries.[1-4] Trauma from accidents and assaults was the fourth highest cause of death in the United States of America (USA) in 2007, accounting for 5.9% of all deaths[5] and the largest loss of productive years of life. The financial cost of trauma is estimated at more than US$224 billion annually, of which direct medical costs are estimated to be US$117 billion per year, accounting for approximately 10% of total healthcare costs. [5,6] In an attempt to reduce the unacceptable burden that serious trauma places on society, the concept of a system-wide approach to managing trauma is promoted.[7]

Trauma systems aim to provide comprehensive, multidisciplinary and integrated care to seriously injured patients. The fundamental tenet of trauma systems is to get “the right patient to the right hospital at the right time.”[8] Informed from systems in the USA, most developed countries have, or are developing, some form of trauma system.[2,9,10] The American College of Surgeons have criteria for categorizing hospitals into one of four levels on the basis of resources, trauma volume, and educational and research commitment. [11] Level I trauma centers operate 24 hours a day/7 days a week (24/7) to provide comprehensive trauma care, immediate availability of appropriate staff and equipment and are required to treat a pre-specified number of seriously injured patients per year.[12,13] Level II trauma centers provide comprehensive trauma care 24/7 either as a supplement to a level I trauma center or as the lead hospital in less population-dense or rural areas.[14] Surgeons must be available at short notice but volume performance standards are not mandatory. Level III hospitals provide initial evaluation of the patient and manage the initial care of the majority of injured patients. A general surgeon must be promptly available for major resuscitation.[12,13] Level IV centers provide initial evaluation and assessment of injured patients in rural environments, require 24/7 coverage by a physician, but have no specific requirement for availability of surgeons or other specialists. Individual states designate the centers within their jurisdiction and the American College of Surgeons verifies that individual hospitals meet the requirements for a specific level of trauma center. There is no clearly stated definition of serious (or severe) trauma, but minor trauma should not be transferred from secondary centers to level I/II trauma centers.[12] Criteria to determine who to transport to a trauma center in the US include physiological signs, anatomy of injury, mechanism of injury, and conditions that require special consideration.[7,12,15] Many countries have developed similar 3-,[16,17] 4-[18-20] or 5- [21] tiered trauma systems.

Within a trauma system, pre-hospital care is the first step in managing the trauma patient. Immediate goals are to prevent further injury, initiate resuscitation and provide timely and appropriate transport of the injured patient to the most appropriate care facility. However, EMS personnel are often faced with a decision as to whether to transport a patient directly to a Level-1 trauma center or to divert to a closer secondary center for initial resuscitation and stabilization prior to onward transfer to definitive care. Clinicians involved in the care of trauma patients tend to have strong views one way or the other as to which option is ‘best’. Several reports describe improved outcomes from trauma systems[22-27] but the evidence for routine direct transport to a Level I/II trauma center appears inconclusive.[20,28-31] A recent systematic review and meta-analysis[32] found no difference in mortality between transfer and direct admissions but significant heterogeneity across studies challenges valid interpretation of the pooled estimate. A source of heterogeneity is likely to be related to differences in the health care context within which trauma systems operate. For example, in the USA there is a focus on trauma center care ('scoop and run'), but in France prehospital care is largely delivered by mobile critical care teams ('stay and play').[14]

We conducted a systematic review to compare hospital mortality and other patient-centred outcomes for patients with serious trauma who were transported directly to a Level I/II trauma center ('direct' group) with those transported to a health care facility before transport to the Level I/II trauma center ('transfer' group) in different health care settings. The null hypothesis was that there was no difference in patient-centered outcomes between the two groups within similar health care contexts.

METHODS

Search strategy

To identify studies eligible for review, computerized searches of bibliographic databases were performed (author TW): MEDLINE (1966–2012), EMBASE (1980–2012), CINAHL (1982–2012) and the Cochrane Library (2004—2012). Terms were mapped to the appropriate MeSH/EMTREE subject headings and "exploded": ("ambulance" OR "emergency medical services" OR "pre-hospital care" OR "medical air services") AND ("trauma" OR "trauma center") AND ("outcomes" OR "mortality" OR "survival" OR "quality of life" OR "functional outcome"). Reference lists of relevant review articles and journals were hand-searched for relevant papers.

Potential studies were those that compared seriously (or severely) injured patients transported directly or firstly to a secondary hospital and then transferred by ambulance (road or air) to level I/II trauma centers. Papers that described outcomes from all trauma cases transported to a trauma center were excluded unless there was a description of the severely injured. Patients who were first admitted as an in-patient to the secondary hospital and later moved to the trauma center were excluded. Most of the papers excluded these patients. Meisler[33] included admissions but separation of admissions to transfers was unclear and the authors did not respond to our request for information. Papers were included if they were published in English and reported patient-centered outcomes, i.e. hospital mortality, survival, quality of life and functional outcomes. Studies with ambulance response times and intensive care unit (ICU) or hospital length of stay (LOS) as the only outcomes were not included. Studies were limited to comparative studies, with concurrent controls. Those that only compared transferred patients to outcomes of a reference population or mortality case reviews were excluded. [34-37] Papers had to be published in peer-reviewed journals but those published only in abstract form were excluded. No time limits on journal publication date were set. If reports described overlapping study populations, we retained the most recent or complete publication.[20,28,38-40] In some studies, only subsets of patients met the inclusion criteria, and only these subsets were included. For example, for studies that described outcomes for Injury Severity Score[41] [ISS] >15 and ISS=<15, only patients with ISS > 15 were considered.[42]

Study selection

Studies identified during the literature search were assessed for relevance to the review based on the information contained in the title, abstract and subject descriptor/MeSH heading (authors TW and JF). Full text articles were obtained if, after reviewing the abstract, the study was considered relevant or if the title and abstract were inconclusive. All citations selected by either author for abstract review were eligible for selection, and any subsequent disagreement regarding eligibility resolved by discussion and consensus involving a third author (IJ).

Data extraction

Data were extracted from studies that met the inclusion criteria: study design, patient characteristics, reported outcomes, direction (and magnitude) of support for the hypothesis, and relevance to the specific question asked. They were grouped into regions defined *a priori*, i.e. USA, Canada, Europe, Australia and New Zealand, Asia and other. They were assessed for methodological quality, i.e. confidence that the "trial design, conduct and analysis has minimized or avoided biases in its treatment comparisons",[43] by the two reviewers independently (authors TW and JF).

The Newcastle–Ottawa tool (NOS),[44] developed for the assessment of methodological quality of cohort studies, was also used to assess methodological quality. A star system for assessment provides a visual semi-quantitative assessment of study quality: the highest quality studies are awarded a maximum of one star for each item within the selection and outcome categories and a maximum of two stars for comparability. Studies had to achieve at least five of the nine stars to be included in this review.

Data synthesis

Narrative and tabular summaries of study characteristics, methods and results are presented, guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[45] The systematic review protocol was not registered. We proposed to assess heterogeneity first, and only estimate a pooled effect if the statistical heterogeneity was low. In the event of significant heterogeneity, forest plots would be simply used to provide a graphical representation of the data. Data were analysed using Review Manager (*RevMan*) version 5.1 (Cochrane Collaboration, Oxford, UK) and STATA (Release 12: StataCorp LP, College Station, TX, USA). Statistical significance was defined by a two-sided alpha of 0.05.

Publication bias

Mortality data from the studies were used to construct a funnel plot, to investigate the likelihood of overt publication bias. [46,47] Funnel plot asymmetry was tested using the Harbord test for small-study effects, a modified linear regression test for funnel plot asymmetry based on the efficient score and its variance, Fisher's information.[48] We also explored other reasons for asymmetry such as selection bias, methodological quality and heterogeneity.

Statistical heterogeneity was assessed using the Higgins I^2 test, [49] which estimates the variability due to heterogeneity rather than chance alone. Values less than 25% are considered low risk, 25- 50% moderate risk and I^2 values greater than 50% high risk of heterogeneity.[49] *A priori* sensitivity analyses were proposed to explore sources of heterogeneity in the main analysis. Pre-planned analyses included the following sub-groups: (1) patients with significant head injury (GCS=<8); (2) those from rural areas and (3) paediatrics only. We also used the Galbraith plot, a graphical representation of the study data used to show the effect of study outliers on heterogeneity. For 95% of studies, it is expected that this is within two units of the true or population effect.[50]

RESULTS

Study characteristics

The initial search revealed 5,001 studies, but 4,886 were excluded after deleting duplicates and reviewing the title and abstract, and 85 excluded after reviewing the paper (Figure 1). Thirty studies[17,18,20,21,28-30,42,51-71] met the selection criteria and were included in this systematic review. We excluded ten studies [72-81] because they included all trauma cases and did not describe the severely injured cohort and one study because of discrepancies in their data [33] We included the most recent paper of two published by Haas,[19,21] but performed a sensitivity analysis to examine the effect of including the 2010 paper rather than the 2012 paper.

Insert Figure 1 here

Study design

No randomized controlled trials (RCT) were found in our literature search. Observational cohort studies were used to compare outcomes for patients admitted directly to the level I/II trauma center or transferred from a secondary hospital. The majority of studies abstracted data from a trauma registry database.[18,20,28,30,53,55,59,60,64,65,67,70,71,82] Young [71] checked missing registry data with the patients' medical records. Registry data were collected prospectively and analysed retrospectively and in most studies patients who died at the scene were not included. Record linkage was used in two studies to link administrative databases with[51] and without[21] trauma registry data. Databases from other sources were used in nine studies[29,52,54,57,58,61-63,66] Retrospective review of medical records was performed in five studies.[17,42,56,68,69]

The majority of studies were conducted in single level I/II trauma centers and their catchment areas, but eight were multiple level I/II centers studies: three from the USA,[53,54,63] three from Canada[21,28,51] one from Italy[62] and one from Australia.[30] Four USA studies [67,70,71,83] and one Norwegian study[68] classed their catchment area as 'rural'.

Most of the studies (n=14, 47%) were from the USA[18,20,29,53-55,57,60,63,64,67,69-71] Three were from Canada,[21,28,51] six from Europe that included two from Norway,[17,68] two from the Netherlands,[58,82] one from Italy [62] and one from Switzerland,[65] four from Asia (Hong Kong,[42,66] Japan,[61] and Taiwan[56]), two from Australia and New Zealand[30,59] and one from South Africa.[52] The mean age of patients varied between regions, from an overall median age of 27 years in the South African study[52] to 44.9 years for the direct group and 45.9 years for the transfer group in the three Canadian studies.[21,28,51]

Trauma systems

There was considerable variation between studies in the structure, policies and practices of the respective trauma system (Table 1). In the USA, four-tiered systems were common[20,29,53,54,57,63,64,69,71] but this was not consistent. For example, at the time of the study, no formal tiered trauma system was described by several papers including from the USA,[18,67] Asia,[42,56] New Zealand,[59] and South Africa.[52] In Canada the trauma system varied by province.[21,28,51] Three-tiered systems were described in Europe,[17,58,68] and Australia.[30] Two-tiered systems were also described in Europe[62,65,82] and Japan.[61]

Insert Table 1 here

The **policy for the management of patients** with serious trauma also varied. In some trauma systems, patients with serious trauma were transported to a level I/II trauma center, bypassing closer secondary hospitals[20,54,57] whereas other systems transported patients to the nearest ED for stabilisation before transfer to a level I/II trauma center.[28,51,59,69,82] In some trauma systems the transfer policy varied according to the severity of the trauma or the proximity of the trauma center. For example, patients with serious injury, as triaged at scene by EMS personnel were transported to the trauma center if transportation was estimated to be less than 20 minutes.[18,30] Some studies did not indicate whether written protocols specifying direct transport or transport to a secondary center then transfer to a Level I/II trauma center were available.[29,52,56,63,67,71]

Transport was most often by road ambulance for studies that reported mode of transportation[18,20,28,30,42,54,58,61] or combination of road and air services.[17,51,52,55,57,59,62,67,71,84] Two studies, one from the USA[60] and the other from Norway[68] described air-based services only.

Missing data

Missing data were reported in ten studies,[18,21,42,53,54,59,63,64,68,82] which ranged from less than 1% to 33% and these cases were excluded from their analyses. de Jongh[82] reported 33% missing data but the proportion of these who had severe trauma was not reported. A large amount of pre-hospital blood pressure data was missing but was replaced by day 1 systolic blood pressure values taken from the in-hospital records and used in multivariate analyses to control for hypotension in a study on TBI.[54] Multiple imputation to account for missing data on comorbidity and mechanism of injury were undertaken by Rivara[29] in survival analysis of one-year follow-up, Garwe[53] in their propensity-adjusted survival analyses and Fatovich[30] in their regression modelling of mortality.

Methodological quality

The NOS[44] ranged from 5 to 9 (mean 7). No study was excluded because of methodological quality. Ethics Committee approval was only reported by 10 studies.[17,21,29,30,51-54,60,61]

Sample size

Of the 43,554 patients included in this review, 31,261 (72%) patients had a direct admission to a level I/II trauma center. Nineteen studies[17,42,51,52,56-62,64-66,68-71,82] had fewer than 1,000 patients, ten, (seven from the US,[18,20,53-55,63,67] two from Canada[21,28] and one from Australia[30]) had between 1,000 and 5,000 patients and one study from the US[29] had more than 10,000 patients. No study described their study power calculation. With the exception of four studies[51,52,56,60] that had a greater proportion of transfers than direct admissions, the proportion of direct admissions to transfers ranged from 6% to 48% (median 33%).

Publication bias

The funnel plot included all 30 studies. It was asymmetrical (p=0.16), with small studies showing no benefit from the transfer group possibly missing from the analysis (Figure A Supplementary Data). A sensitivity analysis was conducted, excluding outliers, but similar results were found.

Heterogeneity

In the meta-analysis of hospital mortality overall there was high heterogeneity (I^2 71%). This was decreased when grouping studies by region, ranging from 0% to 67% with the exception of the Canadian studies where the I^2 value of 91% was very high. Valid interpretation of the pooled estimates could not be made for those with high heterogeneity.

Studies used different definitions for 'serious' trauma. A definition of major trauma as an ISS greater than 15 was reported in eight studies,[18,21,30,42,55,62,71,82] trauma registry criteria plus other restrictions on entry requirements in six others.[20,28,29,53,63,67] In the studies of TBI, severe TBI was defined as a GCS < 9 [17,54,57] or Abbreviated Injury Scale (AIS) of 3 or greater of the head score. [58,59] Injury severity, as estimated from the mean ISS, was reported in several studies. The mean ISS for direct admissions versus transfer (paediatric studies excluded) in the USA studies[18,20,53-55,63,64,70,71] was 19.8 and 20 respectively. In five European studies, two reported mean ISS,[62,65] direct group 28.5 and transfer group 29.2 and three reported the median, [17,58,82] direct group 25 and transfer group 25. These were higher values than the other regions. No Asian study reported the mean or median ISS. The median ISS in the Australian and New Zealand studies was 20 in the direct group and 20.5 in the transfer group, similar to the USA studies. Cheddie[52] reported a median ISS of 25 in the direct group and 20 for the transfer group. Four studies[21,29,42,61] reported the proportion of patients with ISS >=16. In an USA study[29] 77% of patients in both groups had a NISS >= 16. In a second study from Japan[61] 68% of the direct group and 81% of the transfer group had an ISS >= 16. Haas[21] grouped their patient ISS into three categories, with a higher proportion of patients having higher ISS in the direct group but there was a greater number of patients with missing ISS in the transfer group. There was a higher proportion of patients with ISS > 40 in the direct group in a Hong Kong study.[42]

The Galbraith plot showed that eleven of the studies[18,20,21,28-30,54,57,60,66,69] were outside the 95% limits of studies that are expected to have effect estimates within two standard errors of the population effect confirming significant heterogeneity (Figure B Supplementary Data). Six of these studies[18,20,21,28 ,29,30] were large studies with sample sizes greater than 3,000 patients.

Patient mortality

Different time points were used for mortality assessment with hospital mortality that included the deaths in the Level I/II trauma center ED (and not the transferring hospitals' EDs) the most frequent time point for 13 US studies,[18,20,29,55,57,60,63,64,67,69-71] two Canadian studies,[28,51] one European study,[65] the four Asian studies,[42,56,61,66] the two Australian / New Zealand studies[59] and the South African study.[52] Cheddie[52] also reported hospital mortality for patients who survived longer than 12 hours. Hospital mortality was lower in the transfer group if patients who did not survive the first 12 hours were included but significantly higher when excluding these deaths. Including deaths at the secondary hospital, Fatovich[30] reported similar mortality between direct admissions and transfers when including deaths in the secondary hospitals but lower mortality in transfers when excluding these deaths. In a USA study, Garwe[53] reported higher 30-day mortality for transfers when including ED deaths in the secondary hospitals compared to lower mortality when excluding them. Thirty day mortality was reported by four studies (USA,[53] Canada, [21] Europe[58,82]). Haas[21] also reported ED, 24-hour, 48-hour and 7-day mortality. Other time points included ICU mortality reported by one Italian study,[62] two week mortality in an US study of TBI,[54] six-month mortality in a Norwegian study of TBI[17] and one-year survival in an USA study.[29]

The pooled estimate for the 30 combined studies showed a non-significant, reduced risk of dying for the transfer group compared to direct admissions to the Level I/II trauma center (OR 0.91, 95% CI 0.77-1.08) but there was high heterogeneity (I^2 71%). Large variation in the unadjusted mortality was reported, as shown in Figure 2.

Insert Figure 2 here

US Studies

In the studies conducted in the USA (Figure 2a) direct admission was slightly favored (OR 1.04, 95% CI 0.85-1.29) but there was high statistical heterogeneity (I^2=67%). For rural settings,[55,67,70,71] transfer was associated with lower mortality (OR 0.87, 95% CI 0.60-1.25, I^2 30%). Excluding studies that were conducted more than ten years ago and rural settings, there was no statistical heterogeneity (I^2=0%) and direct transport was favored (OR=1.23, 95% CI 1.03-1.47). For studies of TBI, there was a significant reduction in the risk of dying in the direct group (OR 2.05, 95% CI 1.09-3.85, I^2 65%)[54,57,69] but similar to the USA studies overall, high heterogeneity. Hartl's[54] study of TBI reported missing pre-hospital blood pressure data in 47% of patients. The missing values were substituted with day 1 values. Our meta-analysis did not assess the results from the multivariate analyses in the systematic review. Excluding this study, direct transport to a Level I/II trauma center was favored but the effect size was smaller (OR 1.02 95% CI 0.81-1.28). Two US studies[53,54] reported 24 hour to 14-day mortality and showed direct transfer was associated with a decreased risk in dying. Paediatric-specific studies were only reported in the USA. The study of TBI[57] supported direct admission and a study of severe trauma found transfer associated with reduced risk of dying.[60]

Canadian studies

The three studies from Canada (Figure 2b), conducted in three different provinces, had high statistical heterogeneity (I^2 = 91%,). The studies favoring transfer were conducted among burns patients in 2006[51] and injuries from motor vehicle crashes[21] between 2002 and 2010. The third Canadian study[28] favored direct transport to a level I trauma center and was conducted shortly after the introduction of trauma systems in Canada between 1993 and 1995. There was little difference in the pooled estimate when data from Haas[19] study data were used rather than the more recent paper.[21]

European studies

In Europe the pooled effect favored transfer (OR 0.91, 95% CI 0.64-1.30, I^2 = 30%) but this was not significant (Figure 2c). Excluding de Jongh's study[82] because of a third of eligible patients were excluded did not change the result substantially (OR 0.98, 95% CI 0.65-1.48). Moen[17] reported 6-month mortality and when this study was excluded, the pooled effect demonstrated a non-significant support for direct admission to the trauma center (OR 1.03, 95% CI 0.76-1.40, I^2 = 0%). Excluding the three severe TBI studies[17,58,68] the pooled effect favored direct transport to a Level I trauma center but the difference between direct and transfer modes was not significant (OR 1.05, 95% CI 0.71-1.56, I^2 = 26%).

Asian studies

The pooled estimate from the four Asian studies favored direct transport to a trauma center but statistical heterogeneity was high (I^2=73%). The study conducted by Poon and Li[66] of 104 patients with traumatic extradural haematoma had very wide confidence intervals. Excluding this study, conducted between 1985 and 1989, reduced statistical heterogeneity substantially and the pooled effect was associated with a reduced risk of dying in the transfer group (OR 0.75, 95% CI 0.50-1.13, I^2=0%), as shown in Figure 2d.

Australasian studies

In the two Australia / New Zealand studies, the pooled effect significantly favored transfers (OR 0.60, 95% CI 0.49-0.74, I^2 0%) and in the South African study there was also a tendency for patients transported first to a secondary hospital to have a reduced risk of dying (OR 0.98, 95% CI 0.61-1.59).

Fourteen studies (seven US,[18,20,29,53,54,63,67] three Canadian studies,[21,28,51]; two European,[17,82] one Asian[56] and one Australian study[30]) adjusted for independent predictors of mortality such as age, gender, ISS, mechanism of injury, comorbidity. Three USA studies[53,54,63] and two Canadian studies [21,28] reported an independent and significant increase in the risk of death in the transfer group. Garwe[53] examined mortality at 24 hours, >24 hours to 14 days and >14 days to 30 days but the increased risk of dying in the transfer group was only significant at >24 hours to 14 days. Harrington[18] reported higher unadjusted mortality in the transfer group but in the multivariate analysis directness of transport was not significant.

Other patient-centred outcomes

Other patient-centred outcomes were reported in six studies.[17,55,58,66,68] In two studies[17,68,69] the Glasgow Outcome Scale (GOS) was used to assess outcome: a score of 4–5 was categorised as a favorable outcome and GOS 1–3 as an unfavorable outcome. Moen[17] showed higher age, low field Glasgow Coma Scale and bilateral dilated pupils were independent predictors of unfavorable GOS at six months, but being in the transfer group did not predict patient outcome. Sollid[68] found no difference in the proportion of good GOS outcomes (58% transfer versus 53% direct group). The direct group had a worse GOS on-scene but did not differ overall (p=0.87) in Joosse's study.[58] Among patients with acute subdural haematoma functional recovery was higher in the direct group (33%) compared to 15% in the transfer group but severe disability was higher in the direct group (17%) versus 9% for the transfer group.[69]

Helling[55] assessed Functional Independence Measure Scores (FIM) Scores for feeding transfer ability, locomotion, verbal expression and social interaction.[85] Scores ranged from 1 (complete dependence) to 4 (complete independence). With the exception of verbal expression, the scores were higher in the direct group. Poon and Li[66] found moderate or severe disability was less in the direct group, 10% compared to 27% in the transfer group.

DISCUSSION

We found differences in health care context and associated case-mix both within countries and between countries were important, such as different proportions of penetrating and blunt trauma.[14] This may be influential, as the majority of the studies were from the USA. Pre-hospital triage decisions are likely to depend on the need for immediate resuscitation, geographic distances between the scene and closest local hospital or level I/II trauma center and the time intervals involved, the expertise of the attendants (volunteer, paramedic, physician), facilities available at the closest hospital; and individual EMS personnel preferences.[16]

Inconsistent results were found when pooling the data from all included studies[17,18,20,21,28-30,42,51-71,82]: favorable outcomes were significantly higher for patients directly transported to a level I/II trauma center in some studies, lower in other studies while the remaining studies found no difference. After adjustment for independent risk factors for death, the effect of transfer on outcomes also remained inconclusive.

The pooled estimates of all studies combined demonstrated significantly high statistical heterogeneity (I^2 71%); similarly reported in a recently published systematic review.[32] This statistical heterogeneity reflects the clinical heterogeneity of serious trauma. Several factors may explain some of the inconsistency of outcomes between studies such as trauma system structure, triage policies, pre-hospital care and the method of assessing patient outcomes. For example, there are differences in the EMS services provided. Paramedic based systems are common in the USA, Australia and the UK but may offer basic or advanced life support and administer different interventions. Pre-hospital physician-manned EMS are well developed in Scandinavia and other European countries and widely used to supplement paramedic-based EMS.[86] We hypothesized that the health care context could explain some of the heterogeneity and that similar health care contexts grouped together may enable a more valid interpretation of the meta-analysis.

We also found the association of “directness” to a level I/II trauma center on mortality for patients with serious trauma varied across different health care contexts. Some regions had high heterogeneity challenging the validity of the pooled estimates. Combining studies from the USA.[18,20,29,53-55,57,60,63,64,67,69-71] there was high heterogeneity but the studies were conducted at different time periods, ranging from 1969-1981[69] to 2006-2007[53] when trauma systems were at different stages of their evolution and this may influence patient outcomes.[87] In the last ten years (excluding rural trauma systems) there have been only four studies conducted in the USA[18,53,54,63] Combining these studies, we found no heterogeneity (I^2=0%). Direct admission to a level I/II trauma center was associated with a 23% reduction in mortality compared to transfers. We found high heterogeneity in the three Canadian studies[21,28,51] which is not surprising considering the different trauma systems operating in each of the three provinces. Sampalis' study[28] was conducted between 1993 and 1995, shortly after the introduction of their trauma system. When this study was excluded, there heterogeneity was low and a trend towards direct admission being associated with a reduced risk of mortality. The Canadian trauma system was modeled on the USA system and started in the early 1990s in Quebec. Other provinces have followed and as a consequence Canada has a relatively mature trauma system.

The six European studies [17,58,62,65,68,82] included in our systematic review have modified their trauma systems from the USA system to accommodate their health care contexts. The two Norwegian studies described outcomes of TBI and used different time points for assessment of mortality. The results from both studies favored transfer. Similarly, the combination of the six European studies in the meta-analysis demonstrated a non-significant trend for transfers being associated with a nine percent reduction in mortality and moderate heterogeneity. Exclusion of Moen's study [17] that reported six-month mortality, compared to hospital or 30-day mortality in the other studies, reduced heterogeneity. There was a non-significant, three percent reduction in mortality for direct admissions.

Considering the four Asian studies,[42,56,61,66] two described outcomes of TBI patients.[56,66] There was high heterogeneity when combing the studies. Poon and Li's study[66] of traumatic extradural haematoma conducted between 1988 and 1989 had very wide confidence intervals. When excluded from the meta-analysis, heterogeneity was low and there was a trend for lower risk of dying in the transfer group. This result was heavily weighted by Hsiao's TBI study which was surprising because other studies of TBI[54,57-59] have shown a survival advantage of direct admission.

Australia has tertiary referral centers in the major capital cities designated either major trauma hospitals (level 1) or metropolitan trauma hospitals (level 2); rural-based hospitals, which are larger regional centers and rural district hospitals, with a smaller number of beds, usually staffed by general practitioners, although occasionally surgeons are available.[9,16,88,89] Not all of the eight States and Terrorities have formal trauma systems. Only two studies met the selection criteria. There was a reduction in mortality for patient transfers in the meta-analysis that was heavily weighted by the Australian study conducted by Fatovich.[30] Further studies are required to see if this trend continues as trauma systems mature.

Trauma centers have been shown to have better outcomes[1,23] but the factors contributing to their success are largely unknown[31]. Shafi[90] reported institutional variations in patient outcomes but found no significant associations between centers by performance ranking or trauma center characteristics. Survival for patients with penetrating injuries with shock and severe TBI with mass effect was improved when managed at Level I trauma centers although the more rapid assessment or earlier intervention at the Level I trauma center were not important.[91] Increased expertise in managing these patients is important but processes of care likely to influence outcome are difficult to measure.[91]

The decision to advocate bypass of closer secondary hospitals if they have the expertise and resources to provide quality care and stabilise the patient prior to transfer to a trauma center remains uncertain. Patients who require immediate resuscitation may deteriorate during the extra time required to reach the more distant trauma center. Stabilising patients before being transported to definitive care at the level I/II trauma center may reduce the time patients suffer physiological derangement and its consequences. Garwe[92] found patients were less likely to be transported directly to a Level I trauma center if they were further away from the Level I trauma center, required advanced airway management or had higher GCS scores (less likely to have a head injury).[92]

Several studies in our review[19,20,63] excluded transfers from non-trauma centers, a source of potential bias. Deaths for direct admissions to a trauma center are typically included in the mortality rate but estimates of mortality are inherently biased because patients dying at the secondary hospital are not usually included.[29,30] It is preferable to include ED deaths at the transferring hospital but Fatovich [30] found the significant differences in crude hospital mortality were removed when including deaths at the secondary hospital, even after adjusting for this selection bias.

Mortality is known to vary with age, severity of illness and mechanism of injury, but these were not reported consistently and there was no independent adjustment for important risk factors in several of the studies in this systematic review. Two large studies from the USA[18,20] had a disproportionately large number of direct admissions and fewer patients transferred from a secondary center (16:1 and 12:1, respectively) suggesting compliance with a directive that serious trauma should be transported directly to the level I/II trauma center. Nevertheless, unadjusted mortality in the transfer group was lower in one[20] and higher in the other study[18] and when adjusted for potential risk factors no difference was found. Other studies also show considerable variability in risk-adjusted mortality between similarly designated trauma centers.[90,93,94]

There is also little information on the effect of the quality of resuscitation provided in the secondary hospital's ED before transfer to the level I/II trauma center on patient outcomes. Gomes[95] found that pre-hospital interventions to treat life-threatening events may significantly decrease mortality when compared to similar interventions performed later at the trauma center.

This systematic review has several limitations. It is possible that we have missed some papers, despite an exhaustive literature search. It is also possible that the results are confounded by the fact that patients transferred directly to a level 1 trauma center may be different to those not directly transported in a way that has not been identified by the studies, or that the prehospital transport decisions have led to a selection bias. Also, due to evolution in trauma care over decades, it is likely that the many variables important in trauma care have changed over time.

Ideally a RCT would be used to test the hypothesis but, to our knowledge, no RCT has been conducted. All the studies in this review were cohort studies that have inherent biases due to the non-random allocation of the intervention. However, the use of concurrent controls reduces the bias compared with before and after studies that use historical controls. By comparing the outcome of direct admissions with transfer patients from the same level I/II trauma center, the effect of patient care is less likely to confound the results.[96] A common study method was to use trauma registry data but trauma registries use different definitions for inclusion and systematically exclude patients who die before transfer[19] making comparison between studies difficult.

One method of standardising definitions is the *Utstein Trauma Template for Uniform Reporting of Data following Major Trauma*[97] that uses uniform documenting and reporting of data following serious trauma to evaluate outcomes and enable comparisons between studies. No studies in this systematic review used this template. For a definitive answer to the study question, it is likely that a comprehensive nationwide trauma registry, with systematic data collection methods from the prehospital environment to hospital discharge and beyond, will be needed so that the many variables may all be accounted for in comparisons between tens of thousands of patients. Until that time, this study may be the best available evidence in regards to this contentious topic that highlights the complexities of the research question.

CONCLUSION

The published scientific evidence does not provide a definitive answer about the effect of direct transport to a level I/II trauma center compared with initial transport to another hospital for stabilisation first. Consideration needs to be given to differences in the overall healthcare context, the quality of care available within the local trauma system (including pre-hospital services) and the local epidemiology of injury in the interpretation of research in this complex field. Adherence to the Utstein template for major trauma will facilitate interpretation of the results from different centers. The current evidence is unable to support or refute a conclusion that all trauma patients be routinely transported directly to a level I/II trauma center. Perhaps our main finding is that the heterogeneity is so great that it is not possible to definitively answer the study question at this time. This challenges currently accepted dogma. However, each patient's situation and injuries are unique.

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CONFLICT OF INTEREST STATEMENT

TAW is a NH&MRC Clinical Research Postdoctoral Fellow

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DF - no conflict of interest

IJ is the Clinical Services Director for St John Ambulance (Western Australia).

St John Ambulance (WA) played no role in the study design, conduct or interpretation of the results.

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FIGURE LEGEND

Figure 1. Flow diagram of study selection

Figure 2. Summary of the unadjusted mortality proportion for studies from USA, Canada, Europe, and Australia and New Zealand comparing the direct transport versus transport to a secondary center than transfer of trauma patients to level I/II trauma centers.

Supplementary Data

Figure A. Funnel plot to demonstrate presence of publication bias: the vertical axis plots the standard error and the horizontal axis plots the logit event (mortality) rate, defined as logit (*p*) = log (*p*) - log (1 - *p*), where *p* is the event (mortality) rate

Figure B. Galbraith plot to assess heterogeneity for the 30 studies evaluated

Table 1. Health care contexts (at the time study was conducted) of studies that compared direct transport of patients or transport to secondary center then transfer to the Level I/II Trauma Center

Study	Study location	Trauma guideline	Trauma system
United States			
Garwe et al. (2011)[49]	Oklahoma	Oklahoma's Trauma System matched patients on a regional basis with the closest facility with the capability to provide definitive care for each injury If necessary, interfacility transfer was coordinated after initial stabilization taking severity and time-sensitivity of injury into consideration Majority of patients in the transfer group (61%) were transported from the scene of injury to the initial hospital by basic life-support service EMS agencies	Mandatory, inclusive trauma system Single Level I TC, two Level II TCs, 29 Level III and 75 IV TCs (level III & IV primarily in rural area)
Harrington et al. (2005)[17]	Rhode Island	Protocols recommended transfer to TC for severely injured patients if transportation <20 minutes Allows for transport to nearest medical facility in patients injured outside this 20-minute radius Rhode Island currently has 88 licensed EMS transportation agencies, a majority of which are based in fire departments Approximately 100 rescue and ambulance squads in the state	No centralized trauma system One designated TC serves entire state of Rhode Island, portions of southeastern Massachusetts and eastern Connecticut Has in-house trauma attending and operating room facilities available within 5 minutes of patient arrival 24 hospitals transferred patients to TC during study – none possessed any level of trauma designation Some had an operating room available on call 24 hours per day, while others have no operating room availability in the evening/night.
Hartl et al. (2006)[50]	New York State	Patients with severe TBI (GCS score <9) transported directly to a facility with immediately available computed tomography (CT) scanning, prompt neurosurgical care, and ability to monitor ICP and treat	46 designated TCs in New York State, two exclusively paediatric TCs In 2000, 5 Level I TCs participating in study In 2004, 22 Level I and two Level II participating TCs

		intracranial hypertension	representing 54% of the total TCs in the state
Helling et al. (2010)[51]	Pennsylvania	Patients transported directly to the regional TC (Conemaugh Memorial Medical Centre), or to nearest hospital and then transferred	Level I regional resource TC located in Highlands area of western Pennsylvania, comprising largely rural communities No other designated TCs within the primary service area, closest TC (Level II) located 50 miles to the east in Altoona, Pennsylvania, a 60-minute travel distance by vehicle under normal conditions
Johnson (1996)[53]	Washington DC	Not described	Neurosurgical service, Level I paediatric TC, adjacent to level I adult TC. Age of children hospital admits not specified
Larson et al. (2004)[56]	Central and south-eastern Ohio	Most EMS personnel in referral area trained to use mechanism of injury and physiologic status of the patient as means of identifying need for rapid transport to TC Decision to transfer patient from outlying hospital to paediatric TC made by medical team at that institution Helicopter transport between hospitals made by consultation between referring physician and paediatric emergency medicine physician at Children's Hospital who acts as medical control for the air ambulance	Columbus Children's Hospital, ACS-verified Level I paediatric TC in mixed urban and rural area. Paediatric patients less than 19 years of age
Nathens et al. (2003)[19]	Central region - King County, Washington State	Decision to divert patients from the field directly to Level I TC made by medical control at closest Level I/II TC Advanced Life Support crew carries out virtually all interfacility transports	8 state-designated TCs: single Level I TC, three Level III TCs, and four Level IV TCs Average driving distance between the Level III/IV centres and Level I facility 16 miles (range11–24)
Nirula et al. (2010)[59]	Participating sites included Washington State, Seattle; Dallas, Texas;	Not described	Eight Level I trauma or burn centres participating in the Inflammation and the Host Response to Injury collaborative research program

	Denver , Colorado; Pittsburgh		
Obremskey & Henley (1994)[60]	King County, Washington State, Seattle	Decision to divert patients from the field directly to Level I TC made by medical control at closest Level I/II TC Advanced Life Support crew carries out virtually all interfacility transports	Single level I TC (Harborview Medical Centre), three Level III TCs, and four Level IV TCs
Rivara et al. (2008)[29]	King County, Washington State, Seattle	Not described	Single level 1 TC
Rogers et al. (1999)[63]	Vermont	Pre-hospital care provided by volunteer ambulance attendants with only emergency medical technician capabilities No written protocols defining a major trauma patient nor any protocols governing patient transfers	No formal trauma system Single level I TC serves rural areas in Vermont and upstate New York
Stone et al. (1986)[65]	Illinois	Policy for patients to be triaged to nearest comprehensive ED Patients transported by ambulance	Illinois developed a state-wide trauma system in the early 1970s. Cook County trauma unit and community hospitals
Timberlake (1987)[66]	Morgantown, West Virginia	Not described	University hospital designated as Level 1 TC
Young et al. (1998)[67]	Central and Western Virginia	Aeromedical critical care transfer program Patients referred to TC by road ambulance or helicopter, directly from scene or via interhospital transfer	Single TC (The University Virginia Health Science Centre) Classified **rural** area because no city >75,000 people
Canada			
Bell et al. (2012)[47]	British Columbia	Current transport protocol to designated TCs in BC is based on a tiered response Many trauma patients transferred to closest available medical centre before transfer to regional burn centre	Level I TC supported by supported in rural and remote areas of the province by local trauma hospitals In 2010, 3 designated adult level I / II TCs to every 1 burn centre[86]

		Transports of severely injured patients organized by the Ambulance Service and critical care transport team Ground ambulance for short distances or within urban areas, helicopters primarily transfer patients over distances < 300 km and fixed-wing aircraft transport patients over greater distances Transport modes depend on time of day and weather	
Haas et al. (2012)[20]	Ontario	Not described	Nine Level I or II adult TCs; all located in major urban areas No Level III, IV, or V TCs in the region [86] Approximately 150 acute care hospitals that do not participate in the provincial trauma system and trauma team not required, trauma transfer protocol, or ED personnel required to have dedicated training in the preliminary care of the injured patient (Advanced Trauma Life Support).
Sampalis et al. (1997)[28]	Montreal and Quebec	Policy 1993-1995 - all major trauma patients transported to nearest ED for stabilisation, then transferred to level I TC Pre-hospital services in Canada vary with advanced life support paramedics in large urban centres, BLS in some (e.g. Montreal) and others mixed BLS/ALS services	Three-tiered system, tertiary (level I TCs), secondary (level II TCs, surgical and ED staff with other specialists on-call) and primary TCs (stabilization centres with ED coverage and on-call surgeons) This study, 3 Level I TCs, 2 in Montreal and one in Quebec City
Europe			
de Jongh et al. 2008[79]	St. Elisabeth Hospital, Noord-Brabant province, Netherlands	Policy to transport trauma patients to nearest hospital and transfer to TC if further treatment required	Single regional level 1 TC with large neurosurgical unit 15 EDs in the region
Joosse et al. (2012)[54]	Academic Medical	Decision to transport patient to specialized neurosurgical trauma care is made on-scene by trained	Three levels: (1) TCs (Level I), (2) large general hospitals without neurosurgical facilities but capable of treating

	Centre, Amsterdam, Netherlands	ambulance nurses based on several clinical parameters (e.g. GCS score <9, abnormal pupillary reaction)	patients with major trauma (3) hospitals with restricted capacity for trauma care[87] University hospital Level I TC and 12 regional acute care hospitals categorized according to available facilities to provide trauma care
Moen et al. (2008)[16]	Mid Norway	Single level 1 TC Patients transported from scene of accident by the air ambulance, decision to transport to local or to University Hospital made by attending air ambulance anaesthesiologist Ground ambulances staffed by paramedics transport patients to nearest hospital to accident scene	3-level system of public hospitals in Norway Mid-Norway there are seven local district general hospitals, one central hospital and one university hospital with a neurosurgical department
Sollid et al. (2003)[64]	Three counties - Nordland, Troms & Finnmark, Northern Norway	Aircraft co-ordinated and directed from Air Ambulance Dispatch Centre located in University Hospital's ED Inter-hospital transfer between the 10 hospitals and TC by fixed wing aircraft staffed with pilots, a specialized nurse attendant and an anaesthetist when necessary	Single level I TC (University Hospital of North Norway) Trauma system includes nine district general hospitals, central hospital in Bodø and level I TC Advanced air ambulance service provides 24-hour access to pre- and inter-hospital transport Fixed-wing aircraft, rotorwing and helicopter air ambulances
Nardi et al. (1994)[58]	North-east Italy	Single EMS - controls all ambulances and HEMS Decision to call HEMS at discretion of ambulance crew on arrival to scene Transfer group rescued by EMTs with BLS training, transported to the nearest level 1 hospital for stabilisation and then transferred to TC (level 2 hospital) HEMS team experienced trauma care anaesthesiologist and directly transported to a TC after stabilisation in the field	12 first level hospitals and 4 second level institutions (equivalent to Level I TCs) in 3 Provinces
Osterwalder	North Eastern	Emergencies coordinated via hospitals, police, and	Single TC and 10 of 11 regional hospitals in the TC's greater

et al. (2002)[61]	Switzerland	Swiss Rescue Flight Guard Decision to transfer directly or indirectly to TC for patients from immediate catchment areas of regional hospitals depended on different criteria, e.g. type of alarm service (direct via Rescue Flight Guard, police, or hospital emergency service), hospital policy (three hospitals did not usually permit direct admission to TC) or chance Ambulance teams generally consisted of two emergency medical technicians Emergency medical technicians often accompanied by an emergency physician, anesthaesiologist, or anaesthetic nurse with experience in intubation	catchment area Nearest regional hospital is approximately 11.7 km away and the farthest is about 94 km away from the TC Police responsible for emergency services for St. Gallen city and surrounding area, the site, and the immediate catchment area of the TC Regional hospitals responsible for other regions
Asia			
Hsiao et al. (2010)[52]	Taiwan	EMS usually transport patient to the nearest hospital Bypassing the nearest hospital to another hospital occurred if requested by the patient or their family Advanced airway management and intravenous fluid resuscitation are rarely performed by emergency medical technicians Patients transported by EMS usually get oxygen supplement, immobilisation and BLS as needed	University-affiliated general hospital, similar to level 1 TC Rating system for emergency care facilities (including trauma care) among hospitals began after the period of this study
Kam et al. (1998)[37]	Hong Kong	Policy to transfer to nearest hospital 10% of ambulance crews have higher level of training e.g. IV fluid therapy, spinal immobilisation	Single general hospital, trauma level I/II Patients managed by Hospital Trauma Team in 1200-bed general hospital since formation of Team, August 1994
Nakahara et al. (2010)[57]	Southern Osaka, Japan	12 Fire Departments manage ambulance teams Small municipalities and adjacent municipalities form joint Fire Departments Trauma triage protocol with four-step algorithms, similar to the ACS protocol, introduced January 2001	Two levels of care described: critical care medical centre, equivalent to a level I TC, and non-critical care medical centre hospitals Catchment area - two medical districts

		If criteria for Step I or 2, patient transported to critical care medical centre If criteria for Step 3 met, transport to critical care medical centre or contact on-line medical control If criteria for Step 4 met, contact on-line medical control	
Poon & Li (1991)[62]	Hong Kong	Liberal transfer policy to transfer from general district hospital to teaching hospital Referring surgical team provided medical and nursing escorts for transfers	Teaching hospital with neurosurgical unit. all head injured patients in ED of TC admitted directly to neurosurgical care Single district general hospital
Australia and New Zealand			
Fatovich et al. (2011)[30]	Perth, Western Australia	Road transport by single ambulance service provider Trauma patients transported to appropriate facility as soon as possible, objective for scene time maximum of 20 minutes, allowing for access and extrication[82] Judgement is based on paramedic's assessment of patients and transport times to the various hospitals	Four tertiary hospitals, one exclusively paediatric, all located in Perth Outer ring of six secondary hospitals do not have the facilities for in-patient management of major trauma Major trauma patients initially transported to secondary hospital transferred to tertiary hospital for ongoing and definitive care
Kejriwal & Civil (2009)[55]	Auckland, New Zealand	Patients with TBI transported to closest regional hospital for airway, breathing and circulation assessment and stabilisation	Trauma care in New Zealand delivered in ad hoc trauma system
South Africa			
Cheddie et al. (2011)[48]	Durban, South Africa	Admissions direct from scene in consultation with pre-hospital care providers or by inter-hospital transfer Organised, statutory system of pre-hospital care	Single level I trauma unit and trauma ICU, Inkosi Albert Luthuli Central Hospital based on ACSCOT 1993 guidelines[8] Four level II registrar-based facilities

ACS American College of Surgeons
ALS Advanced life Support
ACSOTT American College of Surgeons Outcomes of trauma
BLS Basic Life Support
CT Computed tomography scanning
ED Emergency Department
EMS Emergency Medical Services

HEMS	Helicopter Emergency Medical Services
IV	intravenous
TC	Trauma Center
TBI	Traumatic Brain Injury

Figure 1. Flow diagram of study selection

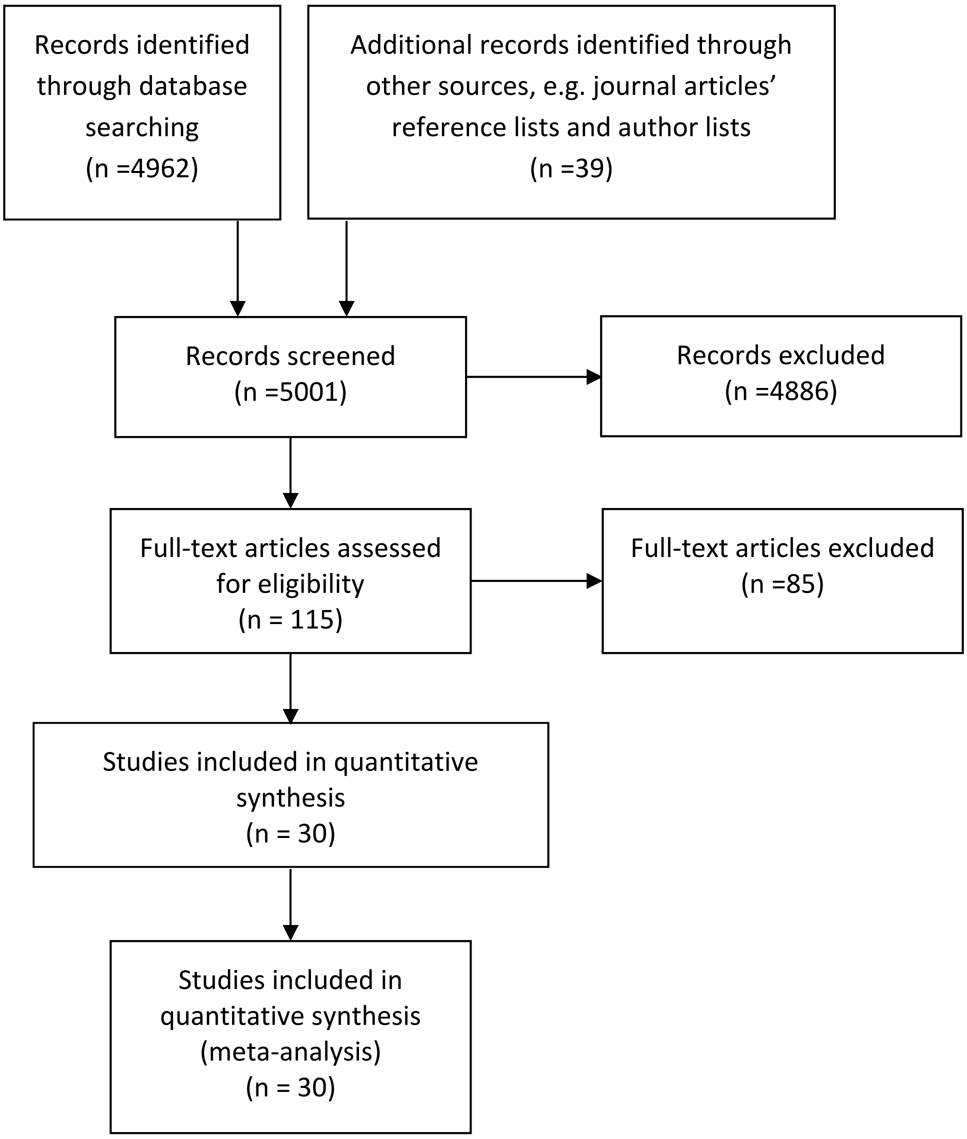


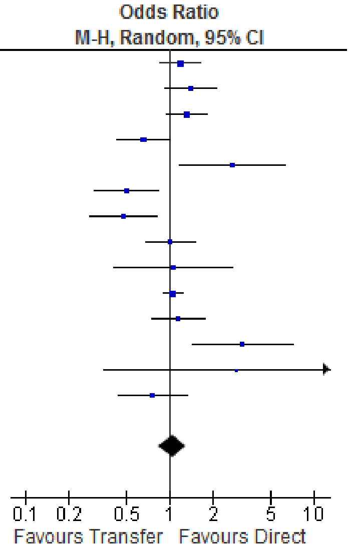
Figure 2. Summary of the unadjusted mortality proportion for studies from USA, Canada, Europe, and Australia and New Zealand comparing the direct versus indirect transport of trauma patients to level I/II trauma centres.

2a Studies conducted in the United States of America

Study or Subgroup	Transfer Events	Transfer Total	Direct Events	Direct Total	Weight	Odds Ratio M-H, Random, 95% CI
Garwe	63	600	125	1398	9.9%	1.19 [0.87, 1.64]
Harrington	28	280	237	3227	8.6%	1.40 [0.93, 2.12]
Hartl	65	254	179	864	9.8%	1.32 [0.95, 1.82]
Helling	29	267	189	1209	8.5%	0.66 [0.43, 1.00]
Johnson	21	42	15	56	4.2%	2.73 [1.17, 6.37]
Larson	43	278	32	120	7.2%	0.50 [0.30, 0.85]
Nathens	14	281	439	4439	6.9%	0.48 [0.28, 0.83]
Nirula	38	315	94	787	8.7%	1.01 [0.68, 1.51]
Obremskey	6	129	17	384	3.5%	1.05 [0.41, 2.73]
Rivara	239	2779	621	7570	12.0%	1.05 [0.90, 1.23]
Rogers	40	1061	53	1608	8.5%	1.15 [0.76, 1.75]
Stone	35	46	41	82	4.4%	3.18 [1.42, 7.11]
Timberlake	2	11	2	28	0.9%	2.89 [0.35, 23.63]
Young	28	151	38	165	6.8%	0.76 [0.44, 1.32]
Total (95% CI)		**6494**		**21937**	**100.0%**	**1.04 [0.85, 1.29]**
Total events	651		2082			

Heterogeneity: Tau² = 0.09; Chi² = 39.63, df = 13 (P = 0.0002); I² = 67%

Test for overall effect: Z = 0.40 (P = 0.69)

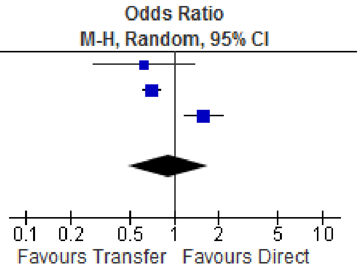


2b Studies conducted in Canada

Study or Subgroup	Transfer Events	Transfer Total	Direct Events	Direct Total	Weight	Odds Ratio M-H, Random, 95% CI
Bell	18	104	15	60	24.5%	0.63 [0.29, 1.36]
Haas	413	2003	761	2857	39.0%	0.72 [0.62, 0.82]
Sampalis	89	1608	99	2756	36.5%	1.57 [1.17, 2.11]
Total (95% CI)		**3715**		**5673**	**100.0%**	**0.92 [0.50, 1.72]**
Total events	520		875			

Heterogeneity: Tau² = 0.25; Chi² = 23.25, df = 2 (P < 0.00001); I² = 91%

Test for overall effect: Z = 0.25 (P = 0.80)

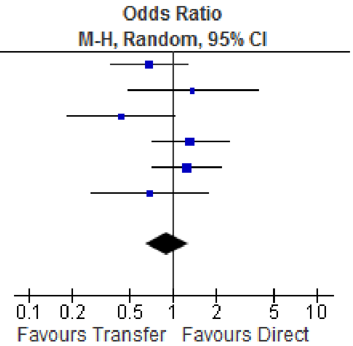


2c Studies conducted in Europe

Study or Subgroup	Transfer Events	Transfer Total	Direct Events	Direct Total	Weight	Odds Ratio M-H, Random, 95% CI
de Jongh	15	69	110	382	20.9%	0.69 [0.37, 1.27]
Joose	8	24	15	56	9.7%	1.37 [0.49, 3.85]
Moen	9	63	23	83	13.2%	0.43 [0.19, 1.02]
Nardi	31	82	31	98	20.8%	1.31 [0.71, 2.43]
Osterwalder	27	190	33	280	24.1%	1.24 [0.72, 2.14]
Sollid	10	38	16	47	11.3%	0.69 [0.27, 1.77]
Total (95% CI)		**466**		**946**	**100.0%**	**0.91 [0.64, 1.30]**
Total events	100		228			

Heterogeneity: Tau² = 0.06; Chi² = 7.17, df = 5 (P = 0.21); I² = 30%

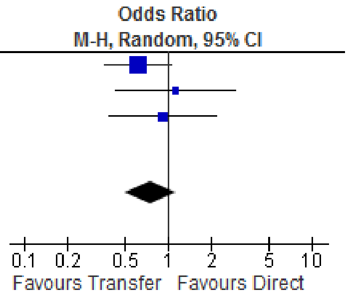
Test for overall effect: Z = 0.50 (P = 0.61)



2d Studies conducted in Asia

Study or Subgroup	Transfer Events	Transfer Total	Direct Events	Direct Total	Weight	Odds Ratio M-H, Random, 95% CI
Hsiao	86	167	55	87	59.0%	0.62 [0.36, 1.05]
Kam	14	27	21	43	18.0%	1.13 [0.43, 2.96]
Nakahara	7	53	49	343	23.0%	0.91 [0.39, 2.14]
Poon	8	33	1	71	0.0%	22.40 [2.67, 188.20]
Total (95% CI)		**247**		**473**	**100.0%**	**0.75 [0.50, 1.13]**
Total events	107		125			

Heterogeneity: Tau² = 0.00; Chi² = 1.41, df = 2 (P = 0.49); I² = 0%
Test for overall effect: Z = 1.36 (P = 0.17)



2e Studies conducted in Australia and New Zealand

Study or Subgroup	Transfer Events	Transfer Total	Direct Events	Direct Total	Weight	Odds Ratio M-H, Random, 95% CI
Fatovich	140	1078	394	2005	95.3%	0.61 [0.50, 0.75]
Kejriwal	7	73	17	97	4.7%	0.50 [0.20, 1.28]
Total (95% CI)		**1151**		**2102**	**100.0%**	**0.60 [0.49, 0.74]**
Total events	147		411			

Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 1 (P = 0.68); I² = 0%
Test for overall effect: Z = 4.84 (P < 0.00001)

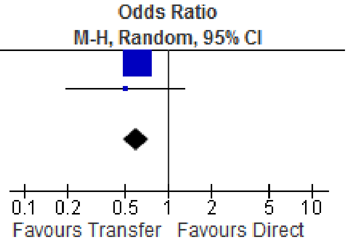


Table A. Comparison of cohort characteristics of direct admissions compared to those transported initially to a secondary hospital and subsequently transferred to level I/II trauma centre for patients with severe trauma

Study	Design	Participants	Group characteristics	Unadjusted mortality number of deaths (%)*and other patient outcomes Direct vs transfer	Adjusted mortality
United States of America					
Garwe et al., 2011[49] January 2006 - December 2007	Retrospective cohort study, State Trauma Registry data Linked data (10 cases missing) supplemented by manual record review Ethics approval	1,998 patients with major trauma Direct group 1,398 (70%) patients Transfer group 600 (30%) patients Include if transported alive by EMS to the closest trauma facility or Level I TC; arrived at the Level I TC within 24 hours of injury; and transferred patients only stopped at one intermediate facility before subsequent transfer to the Level I TC Non-fatal injuries included if patient hospitalised for 2+ days at Level I TC Excluded: patients whose closest facility a Level I TC, burn-related injuries, dying in ED within 2 hours (n = 64) of injury Missing information from 23 patients - excluded from	Direct group significantly more likely to be Black, to have penetrating injuries, to be injured during night hours and to be closer to the Level I TC Direct group also transported from scene of injury by advanced life support level EMS provider Transport group - disproportionate number of paediatric and elderly patients, tendency toward higher ISS scores and disproportionate number of patients with more severe (AIS score 3) head injuries in transfer group	*24 hour* 62 (4.4%) vs 21 (3.5%) *2-week* 115 (8.2%) vs 54 (9.0%) *30-day mortality* 125(9%) vs 63 (10.5%) Median ICU LOS both 4 days Hospital LOS 6 vs 7 days	24 hour mortality (HR, 1.7; 95% CI 0.6–4.8) direct vs transfer cohort >2 week-30 day-mortality (OR HR, 2.9; 95% CI, 1.3–5.6) direct vs transfer cohort >14 day to 30-day mortality (HR, 2.9; 95% CI, 0.7–12) direct vs transfer cohort Adjusted for propensity to be transported directly, age, injury severity score, severe head injury, emergency medical service or ED intubation, comorbid conditions, and time to definitive Level I trauma care

		mortality multivariable analyses, none of these died Data imputed for 70 patients missing initial scene SBP and for 39 missing initial scene GCS score			
Harrington et al. (2005)[17] 2001-2003 (27 months)	Trauma Registry queried and medical records reviewed No centralized trauma system Protocols recommended transfer to TC for severely injured patients if transportation <20 minutes Ethical approval not reported	3,507 adult patients ISS >15: 3,227 direct group and 280 transfer group 250 (5.5%) excluded: DOA or missing data	Similar in age but transfer group more severely injured, more severe head injury, and lower admission BP	Hospital mortality 237 (7%) vs 28 (10%) (*p*=0.72)	Significant variables age[2] (p< 0.001), ISS (p < 0.001), and GCS (p < 0.004). Time at referring hospital not significant. Logistic regression but OR not reported Adjusted for factors associated with mortality
Hartl et al. (2006)[50] 2000-2004	Data source-New York State TBI-trac database quality improvement programme Ethical approval	1,123 of 1449 patients with severe TBI (GCS<9) Direct group= 346 transfer group=95 Excluded (326 patients) GCS score >=9 on day 1 (71 patients), GCS motor score =6 on any day(14 patients), GCS score =3 with pupils bilaterally fixed and dilated and not paralysed (126 patients), daily or outcome GCS score >=4 with pupils bilaterally fixed and dilated or missing pupil information (79 patients), recorded time to study hospital > 24 hours (13 patients), transport time to study hospital < 10 minutes (17 patients) and missing outcome assessment (six patients)	No difference between groups with age, GCS, hypotension, pupillary abnormalities	*Two-week mortality* 179 (21%) vs 65 (26%) (*p*=0.1)	Direct transport (0) associated with significantly lower 2-week mortality than transfer (1) (OR 1.48, 95%CI 1.03-2.12, p=0.04) Adjusted for day 1 hypotension status, age < or >60 years, day 1 pupil status, initial GCS score, transport mode, time to admission, and pre-hospital intubation Large amount of missing pre-hospital BP data, day 1 SBP values from the in-hospital records used to control for hypotension in the analysis

		Included children Ground transport 64%			
Helling et al. (2010)[51] 2003-2008 (68 months)	Rural trauma system Trauma Registry queried No population-based trauma registry in Pennsylvania Ethic approval not reported	Direct group 2388 patients, transfer group 529 ISS >15: Direct group =1209 and transfer group =267 patients Included all deaths at the Level I TC Excluded transfers or discharges from Level I TC within 24 hours or who had an ISS < 9, transfers > 24 hours of treatment at secondary hospital Did not include deaths at secondary hospital Direct group 1,390 transported by ground and 733 by air, mode of transport not recorded for 265 patients. Transfer group 529 patients initially cared for at 20 secondary hospitals, one of which was a TC (Level II; n = 8) 348 transported by ground EMS and 177 by air No missing data reported	Transfer group slightly older (49 years +/- 25 years vs. 45 years +/- 23 years, *p* < 0.0001), slightly higher incidence of cardiac and hepatic comorbidity, fewer patients with upper and lower extremity AIS score > 3 (9% vs. 14%, *p* = 0.001 and 12% vs. 20%, *p* < 0.0001) and fewer patients with severe TBI (6% vs. 10%, *p* = 0.001)	Mortality 9% vs 6% *p* = 0.07 Mortality between ground (22 of 346) versus air transport (11 of 177) in transfer group (*p* = 0.96) Three referred patients died within 24 hours of arrival at the Level I TC For ISS >15: 189 (16%) vs 29 (11%), *p* = 0.06 For ISS >24: 168 (24%) vs 23 (21%) (p = 0.007) ICU LOS 5.3 vs 3.9 Hosp. LOS 6.4 vs 5.5 FIM Scores Feeding 3.75 vs 3.70 • Transfer ability 1.59 vs 1.46 • Locomotion 3.89 vs 3.83, • Verbal expression 3.28 vs 3.34 • Social interaction 3.88 vs 3.84	No adjusted analyses for potential confounders
Johnson et al. (1996)[53] 1985 – 1988	Prospective observational study, data collected by medical staff Ethics approval not reported	98 **children** with severe TBI: direct group 56 and transfer group 42 patients Age not reported for severe TBI Unable to be resuscitated in	Transfer group lower GCS Trauma score significantly lower in transfer group (9 direct vs 7 transfer) Transfer group lower proportion of MVA, falls,	15 (27%) vs 21 (50%) (*p*<0.05)	No multivariate adjustment for potential confounders

		ED not included Road transport 46%, helicopter 36%, private vehicle 18%	assault but higher proportion abuse and 'other' group		
Larson et al. (2004)[56] January 1991-June 1999	Retrospective analysis of trauma registry data Ethics approval	**Pediatric** trauma patients (<19 years of age) transported by helicopter, admitted to pediatric trauma center Included patients who suffered blunt or penetrating trauma 1,412 patients transported to trauma center by helicopter Excluded burns (n = 99), hanging (n = 7), drowning (n = 17), 19+ years (n=5), missing ISS (n = 63) Direct group =379 patients Transfer group after stabilisation = 842 patients Major (ISS > 15) trauma direct group=120 and transfer group 278 patients	Mean age, median ISS, and distribution of penetrating and blunt injuries did not differ significantly between the groups Transfer group sustained fewer injuries from MVAs, pedestrian versus MVA and more injuries from assaults, falls, and sports	Mortality direct group 33 (9%) vs 46 (6%) for transfer patients; p < 0.05 For major trauma, direct 32 (27%) vs 43 (16%, p < 0.05) for transfer group Direct patients with major trauma longer mean ICU LOS 149 hours vs 118 hours; p < 0.05) for transfer group	No multivariate adjustment for potential confounders
Nathens et al. (2003)[19] 1995-1998	Retrospective study, Trauma Registry review Ethics approval not reported	Direct group 4,439 patients, transfer group 281 patients from urban setting Trauma patients aged >=16, LOS>2 days Excluded burns	Transfer group similar age and sex but significantly more likely to be commercially insured, healthier and have blunt injuries. Also lower ISS , fewer patients with maximum AIS scores in the highest strata and TBI less severe	439 (10%) vs 14 (5%) (RR 0.50; 95% CI, 0.30–0.86)	RR of death transfer vs direct group (RR 1.05; 95% CI 0.61–1.80) Adjusted for age, gender, insurance status, comorbidity (cirrhosis, cardiovascular or cerebrovascular disease, COPD), mechanism of injury, ISS, severity of head injury (head AIS score), maximum AIS shock (SBP< 90 mm Hg) in ED of either the referring

					hospital or Level I facility.
Nirula et al. (2010)[59] April 2004 - June 2007	Secondary analysis Glue Grant Trauma Database - ongoing large multicentre prospective cohort study to evaluate inflammatory response to injury and posttraumatic multiple organ failure Patients admitted to any 1 of 8 participating institutions in United States Ethics approval not reported	787 patients in the direct group and 318 in the transfer group Patients aged 16+ years, **blunt trauma**, arrival to hospital within 6 hours of injury, hypotension (SBP<90) or elevated base deficit >=6), blood transfusion within 12 hours of injury, body region with an AIS score >=2 (excluded brain) and intact cervical spinal cord Excluded 91 (8%) patients who died within 24 hours of injury	Similar injury mechanisms, identical ISS, and similar APACHE II scores, but transfer group older, greater proportion of Caucasians, higher frequency of cardiac disease	12% both groups	Mortality increased for transfer group (OR 3.0, 95% CI 1.6-9.0) Adjusted for patient demographics, time from injury to TC, resuscitation volume, transfusions, TBI, initial SBP, comorbidities and injury severity
Obremskey & Henley (1994)[60] Jan-Jun 1990 (6 months)	Prospective study, trauma registry data Subgroup case control study Ethics approval not reported	513 trauma patients with **musculoskeletal injury** included in ISS and aged >12 years 384 direct group (admitted through ED), 129 transfer group (admitted from another hospital)	Similar injuries but significant differences in ISS, ICU LOS, total charges Transfer group higher ISS, no differences in RTS	17 (4.4%) vs (6) 4.7% (*p*=0.89)	No multivariate adjustment for potential confounders for mortality outcome 103 transfer patients and 103 controls from direct group matched on ISS and age, if >= 50 years statistically significant increase in LOS, reimbursement, and charges
Rivara et al. (2008)[29] 1999	Retrospective analysis of data for one participating site of National Study on Cost and Outcome of Trauma (NSCOT) database[23] prospective study of injured patients treated in 1 of 18 TCs and 51 large non-TCs Ethics approval	Patients with major trauma, ISS>15, 18 - 84 years with at least one AIS score >=3 injury Excluded if first presented for care >24 hours after injury or 89 patients admitted to secondary hospital prior to transfer to TC Direct group 7,570 patients Transfer group 2,779	No difference in proportion of males, NISS, but direct group younger, more likely to have penetrating injury, and fewer comorbid conditions	*Hospital mortality* 621 (8.2%) vs 239 (8.6%) (*p*= 0.66) *12-month mortality* 10% vs 11% (*p*= 0.29)	No increase in the adjusted risk of death w/in 1 year for transfer patients (HR 0.99, 95% CI 0.8, 1.3) Adjusted risk of death higher in transfer patients than direct group between 50 days and 365 days after injury (HR 1.3, 95% CI 0.8, 2.1), but not within first 50 days (HR 0.95, 95% CI 0.8, 1.2) but not

					statistically significant Adjusted for age group, gender, injury severity, injury mechanism, and comorbidities
Rogers et al. (1999)[63] Jan 1993- Jul 1996 (3.5 years)	Trauma registry data Most transfers by ground (94%) with few (6%) transferred by helicopter Ethics approval not reported	2,674 trauma patients: Age not specified Direct group 1,608 (61%) Transfer group 1,061 (39%)	Transfer group higher injury severity and acuity, more head/neck and multiple injuries	53 (3%) vs 40 (4%)	ISS and age contributed significantly (p <0.001) to mortality but transfer (0) vs direct group (1) (OR 0.84, 95%CI 0.46-1.50, *p* = 0.55) Adjusted for age, ISS transfer group and RTS
Stone et al. (1986)[65] 1969-1981 (12 1/2-years)	Clinical, operation and autopsy record review Transported to hospital by ambulance Ethics approval not reported	128 patients admitted with acute SDH Excluded haematomas complicating open depressed fractured skull, gunshot wound Male 91%, included children. Assault (58%), falls (34%) Direct group=82 patients Transfer group= 46 patients	Groups differed significantly by race, mode of injury, alcohol intoxication	41 (50%) vs 35 (76%) (*p*=0.004) Functional recovery 33% direct group vs 15% transfer group Severe disability/vegetative state 17% direct group vs 9% transfer group	No multivariate adjustment for potential confounders
Timberlake (1987)[66] January l, 1990 to December 31, 1994	Trauma registry queried and patients' hospital records reviewed Ethics approval not reported	39 (0.64%) patients with blunt pancreas injury Direct group = 28 (72%) Transfer group = 11 (28%) 2 (18%) patients underwent surgery prior to transfer	Mechanism of injury 34 (87%) MVA, 3 (8%) motorcycle crashes, 2 (5%) other No statistically significant differences between the groups other than delay to definitive care	Mortality direct group 2 (7%) cases and 2 (18%) in transfer group (p = 0.66) Hospital LOS for direct group 26 days and 20 days for transfer group	No multivariate adjustment for potential confounders
Young et al. (1998)[67] July 1994-October 1995 (15 months)	Trauma registry, medical records to verify missing data Ethics approval not reported	Direct group=165 (137 survived 24+ hours) Transfer group=151 (135 survived 24+ hours) Adult trauma patients, age>18 and ISS > 15	Direct group lower GCS, SBP on arrival to ED and RTS	*Hospital mortality* 38 (23%) vs 28 (19%) NS *Patients survived >24 hours* 10 (7%) vs 12 (9%) (p=0.63)	No multivariate adjustment for potential confounders

Canada					
Bell et al. (2012)[47] Jan. 1, 2001- Mar. 31, 2006	British Columbia Trauma Registry Prehospital and in-transit deaths and deaths in other facilities identified from provincial Coroner Service database Place of injury identified through data linkage with census records Ethics approval	Patients aged >= 18 years with severe thermal burns referred or transported directly to burns centre Excluded hospital admissions and deaths from hypothermia and intentional self-harm, patients treated and discharged on the same day or outpatients treated for burns in ED or burn clinic Direct group = 60 patients Transfer group = 104 patients Air transport direct group 7 (12%) patients, transfer group 63 (60%) patients No missing data reported	Significant difference in age, intubated before transport, use of fixed wing aircraft, rural cases, transport times between groups	*Bivariate analysis for continuous and discrete variables* *Relative risk (RR) of prehospital and in-hospital mortality and hospital stay by transport status Poisson regression model* *Patient hospital mortality after 72 hours: direct group = 11 (18.3%), transfer group = 9 (8.6%)* *In-hospital mortality 15 (25%) for direct admissions and 18 (17%) for transfers*	Covariates - site where definitive care delivered, age, sex, ISS, inhalation injury, intubation, mode of transport, transport time, burn total body surface area, rural and urban injury location, and injury mechanism After controlling for patient and injury characteristics, transfer group associated with in-hospital death (RR 1.32, 95% CI 0.54- 3.22) or hospital stay (RR 0.96, 95% CI 0.65-1.42) Rural populations experienced an increased risk of total mortality (RR 1.22, 95% CI 1.00-1.48)
Haas et al. (2010)[18] July 2002 - December 2007	Population-based study Retrospective cohort design Data source centralized administrative health databases, including National Ambulatory Care Reporting System Ethics approval	Severely injured patients aged 18+ years and surviving to ED Severe injury=ISS >15 or death within 24 hours of presentation Direct cohort=7481 (66%) patients Undertriage cohort =3917 patients initially triaged to non-TC: • 3469 (30%) =transfer group • 448 (4%). died before transfer could be accomplished =ED death group	Undertriage and direct cohorts similar demographic characteristics, but patients in direct cohort had more penetrating injuries and lower ISS Patients who died before successful transfer more likely to be female, older, have comorbidities, penetrating trauma, and severe head injuries	*30-day mortality* 1192(16%) vs 425 (12%) (unadjusted OR 0.74; 95% CI 0.65–0.83) *Including deaths at secondary hospital 30-day mortality, i.e. undertriage* 1192 (16%) vs 873 (22%) Unadjusted OR (1.51, 95% CI 1.37–1.67)	30 day-mortality (OR 0.91; 95% CI 0.80–1.04) in transfer cohort vs direct cohort Adjusted OR transfer vs direct cohort 1.24 (95% CI, 1.10–1.40) Adjusted for age; gender; Charlson score; mechanism of injury; ISS; and severe injury (AIS >=3) in the head, chest, and abdomen region

		Excluded: burns, foreign bodies, poisonings, toxic effects, suffocation, drowning, and complications of medical/ surgical care; presented with injury diagnosis code within 3 months of index event and patients DOA to ED or died within 30 minutes of ED presentation; died in ED after triaged non-urgent (CTAS 4 or 5) or admitted to non-trauma center			
Haas et al. (2012)[20] 2002-2010	Population-based, retrospective cohort study Data derived from administrative databases capturing all emergency department deaths and admissions in the region Ethics approval	MVA occupants, aged 18+,presenting to ED with severe injury ISS >= 15 or death within 24 hours of presentation Excluded discharges home from ED, patients with an injury-related ED visit in the 3 months before index event, died at scene, DOA or who died within 30 minutes of ED presentation, patients transferred more than once 6,341 MVA occupants: Direct group 2,857 patients (45%) transfer group within 24 hours 2,003 patients (57%) Missing ISS data - direct 54, transfer 136 patients Transport mode not reported	Transfer group older, lower ISS (more missing or low ISS because of greater number of early deaths within 24 hours of presentation) but included patients not transferred to trauma centre (n=1,481)	Unadjusted mortality ED 2% vs 4% 24-hour 6% vs 7% 48-hour 8% vs 9% 7-day 10% both groups 30-day 12% both groups	Compared to transfer group, adjusted mortality for direct group at 24 hours OR 0.58, 95% CI 0.41-0.84 48 hours OR 0.68, 95% CI 0.48-0.96 7 days OR 0.76, 95% CI 0.55-1.05 30 days OR 0.68, 95% CI 0.48-0.96)
Sampalis et al. (1997)[28] April 1993-Dec 1995 (33 months)	Prospective multicentre observational study Trauma Registry review	4,364 patients including children Included: injured within city limits, transported to hospital	Transfer group younger, more males, more head/neck injuries (56% vs 28%). Similar ISS, TRS, PHI	*Hospital mortality* 4.8% vs 8.9% (*p* <0.003) *Mortality after admission*	Adjusted overall mortality OR 1.57; 95% CI = 1.17-2.08, p=0.02 Adjusted for age, injury

	Ethics approval not reported	by local EMS; alive on arrival to hospital *PLUS* death as a result of the injury or hospital stay >3 days or ICU admission Direct group 2,756 (63%) Transfer group 1,608 (37%) Of the transfers, 437 (27%) from secondary centre and 1,171 (73%) from primary hospitals		3.6% vs 5.5% (*p* <0.003)	severity, sex, MOI, body region
Europe					
de Jongh et al., 2008[79] January 2000 - September 2006	Dutch trauma registry data, based on Major Trauma Outcome Study (MTOS)[81] Mixture of prospective and retrospective registry data from 12 of 15 EDs Compared outcomes with existing norms for England and Wales Ethics approval not reported	All trauma patients admitted from ED 17,023 records with complete information of 25,445 admissions from 12 EDs 451 patients major trauma ISS>15 transported to level I trauma centre (direct group=382, transfer group=69) Included trauma patients admitted immediately or following transfer from another hospital or DOA or died in ED Excluded patients with missing values for ISS (n=1395), GCS, outcome (mortality or length of stay n=4230), type of injury (blunt or penetrating), age (n=95) or transfer; patients who survived admission in the trauma centre and transferred within 30 days to another	Transfer group had more severe brain injury (75% vs 53% direct group)	*In-hospital death within 30 days direct group 110 (29%), transfer group 15 (22%)* *Compared with transfer group, unadjusted OR 1.5; 95% CI 0.8 - 2.7*	Adjusted for age, severe brain injury, ISS and GCS Direct group compared to transfer group adjusted OR 1.9; 95% CI 0.9 - 4.1

		institution (outcome unknown) Transport mode not described			
Joosse et al. (2012)[54] January 1, 2006 - December 31, 2009	Retrospective study Trauma registry used to identify patients Chart review GOS assessed by reviewing the latest hospital and general practitioner's correspondence Ethics approval not reported	Patients with severe TBI (AIS of the head score >=3) and underwent neurosurgery within 6 hours after admission to Level I trauma center Direct group n=56, transfer group (transferred to Level I trauma center after neuro-surgical intervention) n=24 Excluded patients operated for insertion of intracranial pressure monitoring device or external ventricular drains only, admitted for observation but requiring a secondary emergency operation, required surgery after clinical deterioration, or patients dying of uncontrollable bleeding outside the brain No missing data reported	Prehospital GCS score was higher in the transfer group (p = 0.02) Transfer group had lower score in almost all injury types	30-day mortality direct group 15 (27%) vs transfer group 8 (33%, *p* = 0.55) Direct group had a worse GOS on-scene but did not differ overall (p=0.87)	No multivariate adjustment for potential confounders
Moen et al. (2008)[16] 1998– 2002	Retrospective analysis Ambulance and hospital records Direct group: 79% air ambulance or ambulance with anaesthesiologist compared with 26% of the patients transported to local hospital (p<0.001) 95% of transfer group from secondary hospital to TC by air ambulance services Ethics approval	146 patients with severe TBI (GCS<=8) 83 patients in direct group, 63 patients in transfer group 9 patients bilaterally fixed dilated pupils, GCS = 3 and CT scan showing signs of herniation on admission and 2 patients died within 24 hours because of other injuries included in analyses of transportation, but excluded from analyses of surgical treatment, outcome and death	Transfer TBI group (43%) had fewer MVA injuries, higher field GCS, lower ISS, fewer pre-hospital intubations	*6-month mortality* 23 (31%) vs 9 (15%) (*p*<0.001)	6-month mortality not increased for transfer group (OR 0.43, 0.16, 1.14, p=0.09) Adjusted for age, GCS and pupillary abnormalities

		Median age 34 (1-88) years, Children included (19 patients<16 years)			
Nardi et al. (1994)[58] 1 August 1992 to 28 February1993	Prospective study, collected data entered into study database Single EMS - controls all ambulances and HEMS, Decision to call HEMS at discretion of ambulance crew on arrival to scene Ethics approval not reported	222 severe trauma patients from road traffic, work and sport accidents with ISS > 15, ICU admission 48+ hours in level I/II trauma center, received ventilatory support and alive at time of arrival of first rescuers Direct group ; 98 patients Transfer group 82 patients HEMS group: 42 patients transported by HEMS team	95% MVA No differences in age, sex, ISS or level I/II trauma center Mean ISS direct group 35.1 +/- 18.2, transfer group 33.4 +/- 19.6	Followed up to discharge from ICU Mortality: Direct group 31 (38%), 23 died before trauma center arrival Transfer group 31 (32%) Mean ICU LOS for ICU survivors Direct group = 15 days Transfer group = 13 days	No multivariate adjustment for potential confounders
Osterwalder et al. (2002)[61] June 15, 1990, and June 15, 1996	Prospective observational cohort study of trauma registry data Survival data from hospital, third-party medical records and citizen's registration offices Primary rescue for 300 (64%) injured patients by ground services, 170 (36%) rescued by helicopter Ethics approval not reported	Included **blunt trauma**, treatment in shock room, presence of injuries with minimum AIS 2+ in at least two of six defined body regions (without external system AIS-6), transfer to ICU or hospital stay 3+ days, or death after admission, ISS 8+ Direct group 280 patients Transfer group 190 patients	Groups differed in age, causes of the trauma (sport, falls) and rescue times	Mortality for direct group 33 (12%), and transfer group 27 (14%)	No multivariate adjustment for potential confounders
Sollid et al. (2003)[64] 1986-1995 (10 years)	Retrospective review of ambulance records, transfer notes, and hospital records Mode of transport: Direct group - ground 34%, rotor 38%, fixed wing 28% Transfer group: rotor 16%, fixed wing 84%	85 patients with severe TBI operated for intracranial mass lesions within 48 hours after injury Excluded: 33 patients operated for depressed or open skull fractures without intracranial mass lesions, 1 patient operated with	No differences in admission GCS scores, type of injury or the proportion of patients with multitrauma	16 (34%) vs 10 (26%) 2 to 76 months post-injury for 83 patients - direct group good outcomes 53% vs 58%	No multivariate adjustment for potential confounders

	Ethics approval not reported	diagnostic burr holes, *3* patients with unknown time of trauma, 15 patients operated > 48 hours after trauma and 9 re-operations Direct group=47 (55%) patients Transfer group=38 (45%) patients			
Asia					
Hsiao et al.,2010[52] July 2003 - June 2008	Clinical data collected retrospectively from medical charts Ethics approval not reported	254 patients with isolated severe TBI (GCS score 3~8 after initial ED resuscitation) Direct group =87 patients Transfer group=167 patients Excluded: loss of vital signs at the scene or any time before arrival at hospital; multiple traumas; penetrating brain injury; <18 years of age; and GCS score > 8 after drugs (including alcohol) were eliminated. Multiple trauma - any AIS score (other than to the head) > 2 or a sum of AIS scores other than to the head > 3	No significant difference between groups for sex, trauma mechanism, hypotension in ED, GCS Transfer group younger, lower percentage had hypertension and higher proportion hyperglycaemic	55 (63%) vs 86 (51%) (*p*=0.07)	Transfer not significantly correlated with mortality (OR 0.51, 95% CI 0.24 - 1.10) Adjusted for age, sex, trauma mechanism, temperature, BP, GCS score, airway management before arrival at the hospital, laboratory data, surgical intervention
Kam et al. (1998)[37] Aug 1994-Jul 1996 (24 months)	Retrospective review of case notes Policy to transfer to nearest hospital Ethics approval not reported	94/97 significantly injured patients 43/60 patients ISS >15 direct group and 27/34 ISS >15 transfer group No age restriction identified Transport mode road ambulance	No significant difference in sex, age, mode of injury or ISS between direct admission and transfer-in cases	21/43 (49%) vs 14/27 (52%) (*p*=0.81)	No multivariate adjustment for potential confounders

Nakahara et al. (2010)[57] October 2001 to September 2004	Review of medical center's computerized database Ethics approval	396 severe blunt trauma patients aged 15+ years, who had at least one severe injury with an AIS >=3 Excluded patients injured from another hospital and transferred to trauma center (n=4), no age (n=6), no ambulance team (n=51) no AIS scores (n=5), patients in cardiopulmonary arrest on arrival (n=58) Missing scene GCS data replaced with arrival GCS data (n=26) Direct group 343 patients Transfer group 53 patients	Transfer group had greater proportion of falls (17% vs 6%), ISS >15 (81% vs 68%) Transfer group had lower proportion GCS 3-5 (8% vs 31%)	Mortality 49 (14%) direct group vs 7 (13%) for transfer group	No multivariate adjustment for potential confounders
Poon and Li (1991)[62] Jan 1985 Dec 1989	Prospective study of neurosurgical data Ethics approval not reported	104 patients with traumatic extradural haematoma Direct group = 71 Transfer group =33	Transfer group more skull fractures 79% vs 70%, fewer posterior fossa lesions, 15% vs 19% Transfer group longer delay time of decreased conscious level to decompressive surgery: 3.2 vs 0.7 hours	Mortality direct group 1 (4%) vs 8 (24%) transfer group Moderate/severe disability direct group 10% vs 27% transfer group	No multivariate adjustment for potential confounders
Australia and New Zealand					
Fatovich et al. (2011)[30] 1 July 1997-30 June 2006	Trauma Registries from 4 TCs Trauma patients transported to appropriate facility as soon as possible, objective for scene time maximum of 20 minutes, allowing for access and extrication[82] Ethics approval	Patients with major trauma, i.e. ISS> 15 Direct group 2005 and transfer group 1078 patients Mean age (44 +/- 24 vs. 39 +/- 24 years, p<0.001) Included children Median ISS=24 (p=0.08) for	Transfer group significantly more head/neck injuries, less thoracic, abdominal and pelvis/ extremities injuries (p<0.001), less total number of regions injured (p<0.001) Groups differed in RTS on arrival to TC	*Hospital mortality* *395 (20%) vs 140 (13%) (p<0.001)* *Including deaths at secondary hospital:* *395 (20%) vs 214 (19%) (p=0.53)*	Adjusted OR for death in transfer group including ED deaths in secondary hospital 0.99 (95% CI 0.58-1.68) Adjusted for age, ISS, RTS, total regions injured and time

		both groups			
Kejriwal & Civil (2009)[55] 2004	Trauma Registry data Ethics approval not reported	198 adult patients in trauma registry with moderate or severe TBI, AIS score >=f 3 97 direct group and 73 transfer group Patients transferred >24 hours or without time of injury or time of arrival excluded (15%) Transport by road ambulance 89% direct group and 88% indirect group	Significant difference in age, MVA and multitrauma between TBI groups	17 (18%) vs 7 (10%) (*p*=0.1)	No multivariate adjustment for potential confounders
South Africa					
Cheddie et al. (2011)[48] March 2007 to December 2008	Data retrieved from hospital informatics system and an independent database in the trauma unit interhospital Ethics approval	407 severely injured patients: 118 (29%) direct from scene and 289 (71%) inter-hospital transfers Median age 27 years (range 1 - 83), 71% male Blunt injury accounted for 66% of admissions and MVC 87% Median ISS for cohort = 22 (survivors 18, deaths 29; p<0.001) Transfer group accepted at trauma centre for surgery and subsequent ICU management if surgical expertise unavailable at referral source, ICU admission following surgery at another institution, or for ICU management alone if surgery not required Excluded deaths in transfer	No significant differences in age, gender but significantly more penetrating trauma, less MVA-related injuries and lower ISS in transfer group (25 vs 20; p<0.02)	*Hospital mortality* *37 (31%) vs 70 (24%) (p=0.19)* *Patients surviving > 12 hours:* *13 (14%) vs 67 (23.5%) (p=0.04)* *No significant difference in mortality between ambulance vs. air transport*	No multivariate adjustment for potential confounders

		group before arriving at trauma centre Transport: direct group road 55%, helicopter 45% transfer: group road 100%	

AIS Abbreviated Injury Score [38]
CI Confidence Interval
DOA Dead on arrival
EDH Extradural haematoma
EMS Emergency Medical Services
ED Emergency Department
FIM Functional Independence Measure, ranged from 1 (complete dependence) to 4 (complete independence)
GCS Glasgow Coma Scale[83]
ICU Intensive care unit
ISS Injury Severity Score[36]
MOI Mechanism of injury
MTOS Major Trauma Outcome Study
MVA Motor vehicle accidents
NISS New Injury Severity Score[84]
LOS Length of stay
OR Odds Ratio
RTS The Revised Trauma Score is a physiologic index of injury severity assessed on arrival at the hospital. It is a weighted sum of coded values of the systolic blood pressure and unassisted respiratory rate
SDH Subdural haematoma
TBI Traumatic brain injury
TRISS The Trauma and Injury Severity Score (TRISS) methodology[85] combines age, physiologic, and anatomic characteristics to estimate patient survival probability
vs versus

Figure A. Funnel plot to demonstrate presence of publication bias: the vertical axis plots the standard error and the horizontal axis plots the logit event (mortality) rate, defined as logit (*p*) = log (*p*) - log (1 - *p*), where *p* is the event (mortality) rate

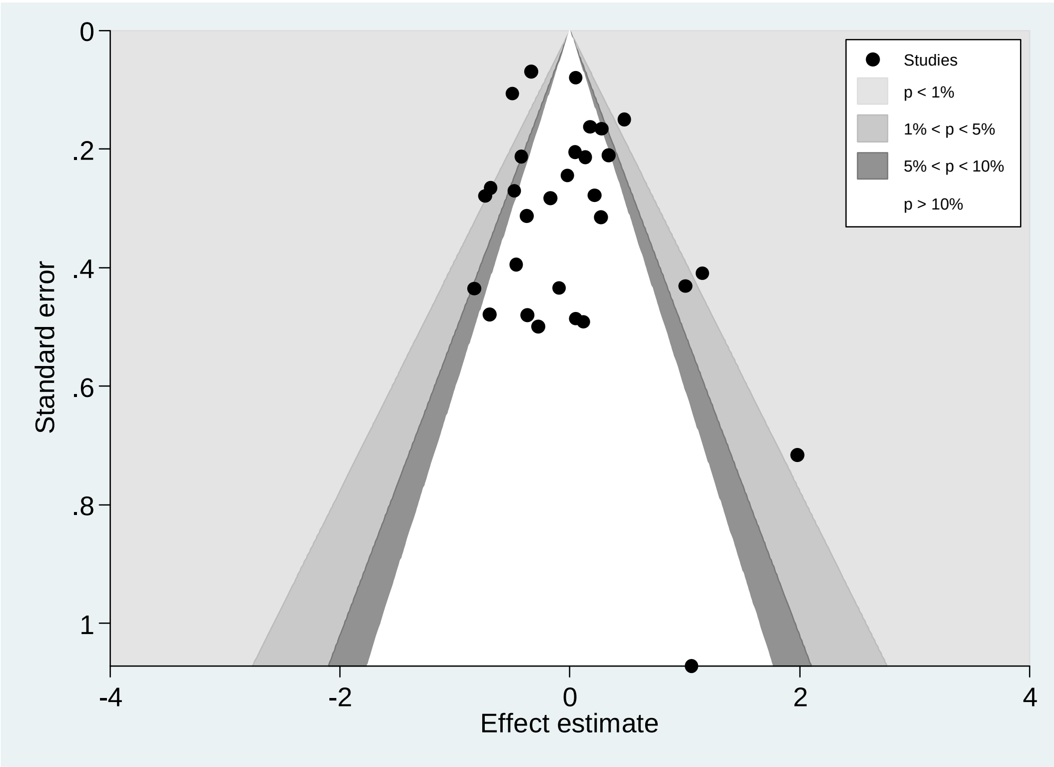
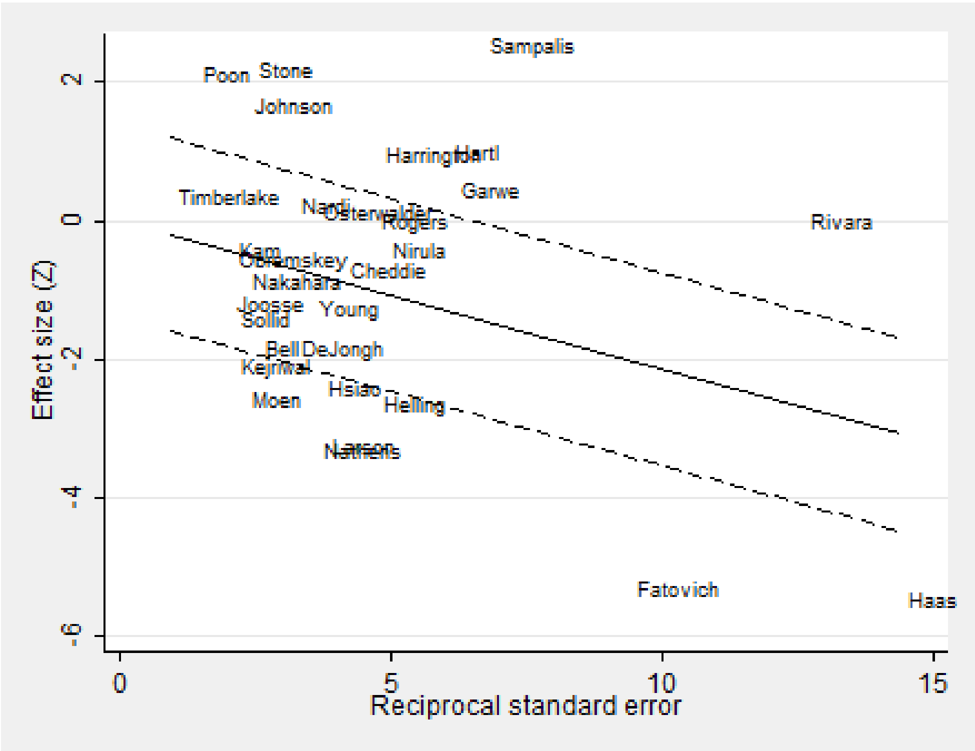


Figure B. Galbraith plot to assess heterogeneity for the 30 studies evaluated



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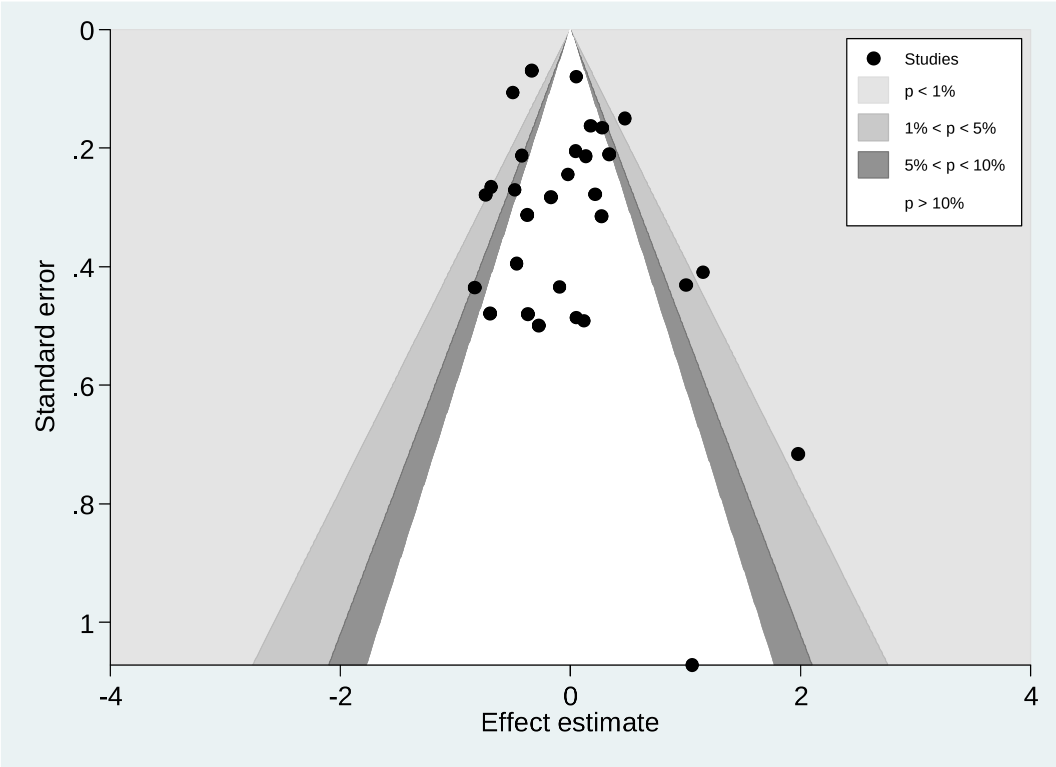

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