RESEARCH ARTICLE

# Experience in Prehospital Endotracheal Intubation Significantly Influences Mortality of Patients with Severe Traumatic Brain Injury: A Systematic Review and Meta-Analysis

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## Abstract

### Background

Patients with severe traumatic brain injury (TBI) are at high risk for airway obstruction and hypoxia at the accident scene, and routine prehospital endotracheal intubation has been widely advocated. However, the effects on outcome are unclear. We therefore aim to determine effects of prehospital intubation on mortality and hypothesize that such effects may depend on the emergency medical service providers' skill and experience in performing this intervention.

### Methods and Findings

PubMed, Embase and Web of Science were searched without restrictions up to July 2015. Studies comparing effects of prehospital intubation versus non-invasive airway management on mortality in non-paediatric patients with severe TBI were selected for the systematic review. Results were pooled across a subset of studies that met predefined quality criteria. Random effects meta-analysis, stratified by experience, was used to obtain pooled estimates of the effect of prehospital intubation on mortality. Meta-regression was used to formally assess differences between experience groups. Mortality was the main outcome measure, and odds ratios refer to the odds of mortality in patients undergoing prehospital intubation versus odds of mortality in patients who are not intubated in the field. The study was registered at the International Prospective Register of Systematic Reviews (PROSPERO) with number CRD42014015506. The search provided 733 studies, of which 6 studies including data from 4772 patients met inclusion and quality criteria for the meta-analysis.

Prehospital intubation by providers with limited experience was associated with an approximately twofold increase in the odds of mortality (OR 2.33, 95% CI 1.61 to 3.38, p<0.001). In contrast, there was no evidence for higher mortality in patients who were intubated by providers with extended level of training (OR 0.75, 95% CI 0.52 to 1.08, p = 0.126). Meta-regression confirmed that experience is a significant predictor of mortality (p = 0.009).

## Conclusions

Effects of prehospital endotracheal intubation depend on the experience of prehospital healthcare providers. Intubation by paramedics who are not well skilled to do so markedly increases mortality, suggesting that routine prehospital intubation of TBI patients should be abandoned in emergency medical services in which providers do not have ample training, skill and experience in performing this intervention.

## Introduction

Severe traumatic brain injury (TBI) is a leading cause of death and morbidity in the first decades of life, with a tremendous burden on the society due to high costs of care and loss of productive life years [1–7]. Prehospital emergency care is the first step in the chain of survival, and effective treatment during this period is considered crucial for a beneficial outcome [8]. However, current prehospital TBI-treatment guidelines are based on low quality of evidence [9], and optimal treatment is a matter of on-going debate.

Airway obstruction is common at the accident scene in patients with severe TBI [10, 11], and resulting hypoxaemia and hypercapnia are known to trigger secondary injuries that adversely affect outcome [12, 13]. While isolated TBI *per se* does not necessarily lead to airway obstruction, a depressed level of consciousness associated with TBI may lead to airway obstruction due to displacement of the epiglottis, tongue or soft palate [14, 15]. Unconsciousness is also associated with compromised protective airway reflexes, which put the patient at increased risk of aspiration of gastric contents and blood [16, 17], especially when oropharyngeal bleeding is present. Additionally, head injury can induce apnoea [18], and other concomitant injuries such as chest trauma can also contribute to hypoxia [19].

For these reasons, securing the airway is considered a first treatment priority, and prehospital endotracheal intubation–as the "gold standard" of airway management–has often been advocated for comatose trauma patients with a Glasgow Coma Scale (GCS) score of ≤ 8 [20, 21]. However, despite theoretical advantages and despite widespread use by emergency medical services (EMS) around the world, there is little scientific evidence to support this practice [22]. In fact, it has even been suggested that prehospital endotracheal intubation may be associated with increased mortality [23]. Hypoxia due to prolonged or failed intubation attempts, increases in intracranial pressure during laryngoscopy, haemodynamic effects of drugs used to facilitate intubation, as well as inappropriate ventilation after endotracheal intubation might all contribute to unfavourable outcomes. In many paramedic based EMS systems, prehospital endotracheal intubation is performed by paramedics who only have basic training in this procedure and infrequently perform intubations in clinical practice. On the other hand, in other EMS systems, endotracheal intubation may be performed by highly trained critical care personnel or emergency physicians. In this context, it is likely that the incidence of adverse events is associated with the level of training and experience in airway management of the provider

who performs prehospital intubation (PHI). We therefore hypothesize that PHI by highly trained providers is beneficial, while the same intervention performed by less skilled personnel may be detrimental. We systematically reviewed the available literature and performed a stratified meta-analysis and meta-regression of eligible studies to assess effects of PHI on mortality in patients with severe TBI in the context of the EMS-providers' experience.

## Methods

### Protocol and registration

This study was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [24, 25] and MOOSE (Meta-Analysis of Observational Studies in Epidemiology) [26] guidelines. The search strategy, study selection, bias assessment, as well as data extraction and analysis techniques were specified a priori. The study was registered at the International Prospective Register of Systematic Reviews (PROSPERO) with number CRD42014015506 (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID= CRD42014015506).

### Eligibility criteria

Articles of interest were fully published controlled trials and observational studies comparing PHI versus non-invasive prehospital airway management in patients with suspected or confirmed severe TBI. Severe TBI was defined as a prehospital/admission Glasgow Coma Scale (GCS) $\leq$ 9 in the presence of a trauma mechanism or findings at physical examination suggestive of head injury, or a Head Abbreviated Injury Score (H-AIS) $\geq$ 3. Outcome of interest was mortality, and studies that reported or allowed calculation of an effect size were selected. Studies specifically investigating paediatric patients were excluded. Manuscripts reporting other patient populations were considered eligible as long as the data relating to the TBI population could be extracted.

A subset of studies was selected for the meta-analysis and meta-regression. Selection criteria were: (1) sufficient quality as described in detail below; (2) the overall study-level EMS-provider experience could be determined; and (3) mortality could be meaningfully compared between intubated and non-intubated patients, i.e., groups were drawn from the same population and are either directly comparable by design with respect to baseline characteristics and injury severity, or adjusted analyses were used to address imbalances between both cohorts.

When multiple publications with overlapping data met eligibility criteria for the meta-analysis, or when the same manuscript reported multiple eligible analyses of overlapping data, we used only one of the analyses to avoid duplicate inclusion of patients. In this case, the analysis in which the effect size was estimated with highest precision (i.e., with smallest standard error) was selected.

### Information sources and search strategy

We searched PubMed, Embase and Web of Science, without any restrictions, to identify eligible publications. This search was last updated on July 11th, 2015. For PubMed, the following search strategy was used: ("intubation, intratracheal"[Mesh] OR "intubation"[Mesh] OR "intubation"[All Fields]) AND ("brain injuries"[Mesh] OR "brain injuries"[All Fields] OR ("brain"[All Fields] AND "injuries"[All Fields]) OR ("head"[All Fields] AND ("injuries"[All Fields] OR "trauma"[All Fields])) OR ("traumatic"[All Fields] AND "brain"[All Fields] AND "injury"[All Fields]) OR ("traumatic brain injury"[All Fields]) OR ("head injury"[All Fields]) OR ("head trauma"[All Fields])) AND ("emergency medical services"[Mesh] OR "prehospital"[All Fields]). The search

terms were adapted accordingly for the other databases. Reference lists of pertinent publications were also screened for eligible studies.

## Study selection

Two investigators (SMB, PS) independently assessed publications for eligibility by screening abstracts of all identified studies. Full text articles were retrieved for all publications for which the relevance could not be determined based on title and abstract. Disagreements on eligibility were discussed among the investigators, and a third investigator (LAS) was appointed to resolve persisting disagreements.

## Data extraction

Data were extracted by one author (PS) using a standardized data collection sheet, and all data were checked for completeness and accuracy by a second author (SMB). We abstracted information from each included study on: (1) study characteristics, including design, population size, inclusion and exclusion criteria as well as time period and geographical area of patient inclusion; (2) patient characteristics, including age, gender and injury severity; (3) treatments in the intervention and control group; and (4) outcome measures. Studies were classified according to the level of training and experience in performing endotracheal intubations of the group of providers delivering prehospital care. Studies were labelled as "limited experience" if intubation was performed by personnel who usually have basic skills in this technique and who commonly only infrequently perform intubations in routine practice (e.g., emergency medical technicians and paramedics with limited scope of practice). "Extended experience" was selected if intubation was performed by prehospital emergency physicians or nurses/paramedics with an extended scope of practice and training (e.g., specially trained critical care paramedics/ nurses). Studies in which the patient population was intubated by a heterogeneous group of providers or in which the level of training could not be ascertained were classified as "indeterminate". Three reviewers (SMB, LAS, PS) independently assessed and scored the level of experience, and a level was only assigned by unanimous consensus.

Seven authors were contacted to obtain additional information, however only three responses were received.

## Assessment of study quality and risk of bias within studies

Quality assessment was independently performed by two authors (SMB and PS), and a third author (LAS) was consulted in case of disagreement. We used the Newcastle-Ottawa scale to assess the risk of bias of cohort studies [27]. A total of nine stars could be allocated per study for selection of participants, comparability of study groups and assessment of outcome. A total score of $\geq$ 7 stars with full score for "comparability" were required as eligibility for the meta-analysis.

Randomized controlled trials (RCT) were scored using the Cochrane Collaboration's tool for assessing risk of bias [28]. This tool is used to classify studies as "low", "unclear" and "high" risk of bias. Since blinding of EMS-providers and patients is not possible in studies comparing PHI versus other airway management, this respective item was omitted and studies were classified as "low" risk of bias if no other sources of bias could be identified. Trials with low risk of bias were considered eligible for the meta-analysis.

## Data synthesis and statistical analysis

The primary measure of the treatment effect was the odds ratio (OR) of mortality in patients undergoing PHI versus patients who were not intubated in the prehospital setting. No attempt was made to meta-analyse data across studies that did not meet the described criteria; these publications are only presented descriptively. A meta-analysis of eligible data was performed with STATA 13.0 (StataCorp, Texas). In accordance with our hypothesis that the effect of PHI on mortality differs with EMS-provider experience, and to accommodate for other potential between study heterogeneity, we used a random effects model [29]. Additionally, the analysis was stratified on the EMS-provider's level of experience. Heterogeneity was quantified as the percentage of total variation across studies that is attributable to heterogeneity rather than chance ($I^2$-statistic) [30]. Random effects meta-regression with EMS-provider experience as trial-level covariate was used to formally assess differences between groups of EMS-providers [31].

## Assessment risk of bias between studies

We addressed small-study bias in the meta-analysis by plotting the natural logarithm of the odds ratio against its standard error. Funnel plot asymmetry was assessed by Egger's regression asymmetry test [32].

## Results

### Study selection

The database search provided a total of 1202 articles. Screening of reference lists identified 11 additional articles. A total of 733 articles remained after removal of duplicates/triplicates. Based on review of the abstracts, 614 papers failed to meet the inclusion criteria. The full text of the remaining 119 articles was retrieved and assessed for eligibility. Of those, 95 articles were discarded because they did not meet the inclusion criteria. The remaining 24 studies were included in the systematic review, and six of those studies met the inclusion criteria for the meta-analysis. See Fig 1 for the PRISMA flow diagram.

### Study characteristics

Twenty-four studies reporting data from more than 30,000 patients were selected for the systematic review [33–56]. Due to partial geographic and temporal overlap of some of the studies (Table 1), the exact number of included individual patients could not be determined. Eighteen studies were performed in North America, four in Europe, one in Australia and one in Southwest Asia.

One of the studies is an RCT, and one study is a secondary cohort-analysis of an RCT that had been performed to address a different research question. All other studies are cohort studies (Table 1).

The Cochrane Collaboration's tool revealed a low risk of bias for the RCT. The Newcastle-Ottawa Scale rating ranged between four and nine stars for the cohort studies, with a median rating of 7 stars (Table 2).

### Patient and injury characteristics

Patients were predominantly male and typically had a mean or median age of around 35 to 45 years. In accordance with our study selection criteria, markers of injury severity generally reflect serious injury (Table 3).

## Treatments and level of experience of EMS providers

While all identified studies basically compared PHI versus no PHI, there were differences in how the intervention and control groups were defined. A portion of the analyses included intubation attempts or use of alternative airway devices after failed intubation in an intention-to-treat approach, while such attempts were excluded or not specifically reported in other analyses. In the PHI groups, patients were sometimes intubated with a "rapid sequence induction" approach using anaesthetic drugs and neuromuscular blocking agents, while patients in other studies were intubated without such medication, or medication use was not reported. The control group generally consisted of patients who were not intubated in the prehospital setting. However, a part of the studies specifically defined the control group as patients who required endotracheal intubation in the hospital. Table 4 summarizes treatments in the intervention- and control groups per study.

In seven studies, EMS-providers with extended experience performed PHI, and EMS-provider experience was considered limited in five studies (Table 4). Twelve studies were scored as "indeterminate" experience. One of these studies reported sub-analyses for a subset of patients intubated by EMS-personnel with limited experience.

## Summary of results from individual studies

In the 24 studies included in the systematic review, the observed unadjusted OR point estimates ranged between 0.12 and 64.7, while the adjusted estimates ranged between 0.38 and 5.0. In
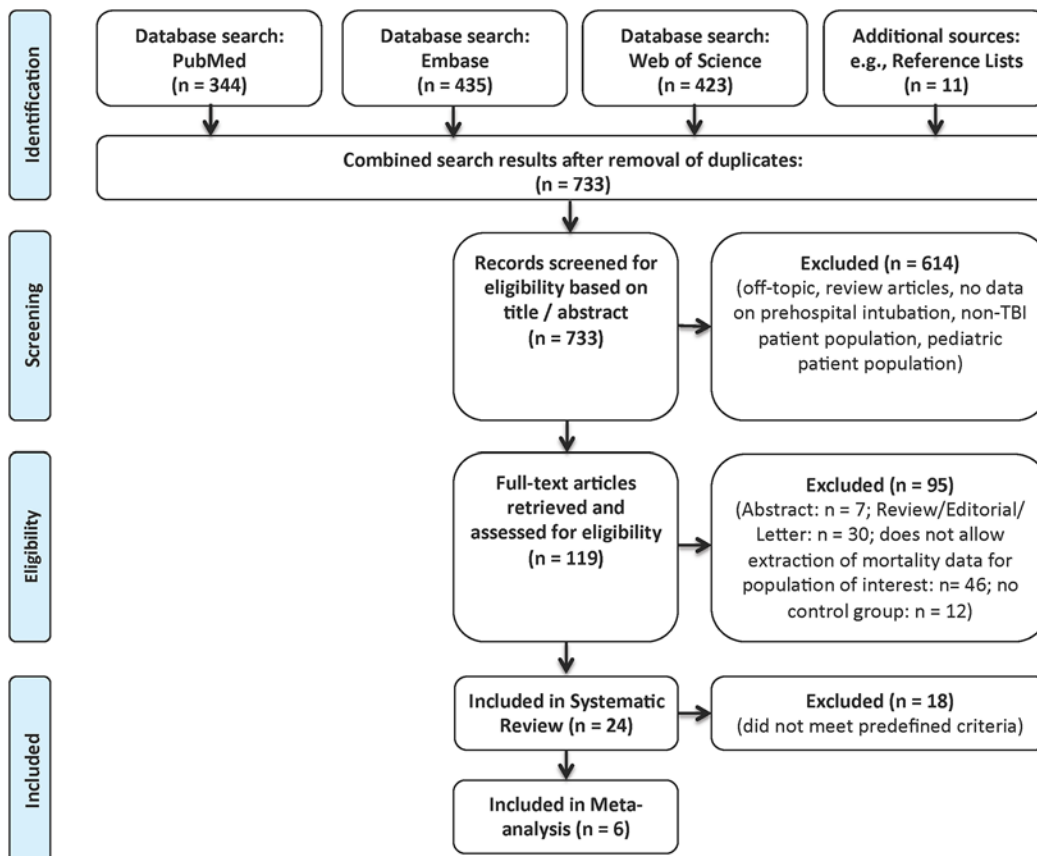


**Fig 1. PRISMA flow diagram.** PRISMA flow diagram summarizing identification, screening, eligibility and inclusion of studies.

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studies where PHI was performed by providers with limited level of training, reported adjusted ORs were between 1.96 and 5.0. In contrast, adjusted ORs were in the range between 0.38 and 0.87 when experienced providers performed intubation. Table 5 reports mortality data of individual studies and lists factors that have been used to adjust the estimates in the different studies.

**Table 1. Study characteristics.**

| First author (year) | Study design | Study Period | Region | Inclusion criteria[a] | Exclusion criteria[a] | n total[b] |
|---|---|---|---|---|---|---|
| Bernard (2010) [33] | Randomized controlled trial | 2004–2008 | Victoria, Australia | Age $\geq$ 15 years, evidence for head trauma, GCS $\leq$ 9, intact airway reflexes | Within 10 minutes of trauma hospital, no intravenous access, allergy to RSI drugs, transport planned by helicopter | 312 |
| Bochicchio (2003) [34] | Prospective cohort study | 2000–2001 | Maryland, USA | Adult trauma patients with GCS $\leq$ 8 and H-AIS $\geq$ 3 | Death within 48h of admission, failed intubation in the field (>2 attempts), long field extrications, transfer from outside institutions | 191 |
| Bukur (2011) [35] | Retrospective cohort study | 2005–2009 | Los Angeles County, USA | Age $\geq$ 14 years, H-AIS $\geq$ 3 and all other AIS < 3, intubation required either in the pre-hospital period or in the ED | Dead on arrival or in emergency room, non-survivable injuries (any AIS = 6), missing intubation data | 2366[c] |
| Davis (2003) [37] | Matched cohort study, prospectively enrolled intervention group matched to historical controls | Intervention: 1998–2000; Controls: "past 10 years, preference given to patients in past 5 years" | San Diego County, USA | Intervention: Apparent age $\geq$ 18, major trauma criteria (per county protocol) with suspected head injury, GCS $\leq$ 8, estimated transport time to ED > 10 minutes, intubation without RSI medication unsuccessful or impossible | Intervention: inability to obtain iv-access, violation of RSI protocol, CPR before administration of RSI drugs, inability to be intubated by prehospital personnel, transport to non-trauma centre, H-AIS < 2 or higher H-AIS defined by neck injury, death in the field or ED within 30 minutes | 836[d] |
| Davis (2004) [36] | Matched cohort study, prospectively enrolled intervention group matched to historical controls | Intervention: 1998–2002; Controls: NR | San Diego County, USA | See Davis (2003) | See Davis (2003) + incomplete oximeter-capnometer data | 236[d] |
| Davis (2005a) [39] | Retrospective cohort study | 1987–2003 | San Diego County, USA | Major trauma with GCS $\leq$ 8 and H-AIS $\geq$ 3 | H-AIS defined by non-head injury, incomplete data, interfacility transport | 2243[d] |
| Davis (2005b) [40] | Retrospective cohort study | 1987–2003 | San Diego County, USA | Major trauma with H-AIS $\geq$ 3, sub-analyses reported for patients with GCS $\leq$ 8 and/or H-AIS $\geq$ 4 | H-AIS defined by neck injury | 2474 to 9503[d] |
| Davis (2005c) [41] | Matched cohort study, prospectively enrolled intervention group matched to historical controls | Intervention: 1998–2002; Controls: NR | San Diego County, USA | See Davis (2003) | See Davis (2003) | 1056[d] |
| Davis (2006) [38] | Retrospective cohort study | 1992–2003 | San Diego County, USA | Adult major trauma victims with H-AIS $\geq$ 3 | H-AIS defined by non-head injury, CPR in the field, missing arrival ABG data | 3804[d] |
| Franschman (2011) [42] | Retrospective cohort study | 2003–2007 | Amsterdam and Nijmegen region, the Netherlands | Age $\geq$ 16 years, CT confirmed TBI and GCS $\leq$ 8 primarily admitted to one of two participating level I trauma centres | Missing airway management data | 274 to 335 |

*(Continued)*

**Table 1.** (*Continued*)

| First author (year) | Study design | Study Period | Region | Inclusion criteria[a] | Exclusion criteria[a] | n total[b] |
|---|---|---|---|---|---|---|
| Härtl (2006) [43] | Prospective cohort study | 2000–2004 | New York State, USA | Mechanism of injury consistent with TBI and GCS $\leq$ 8 for at least 6 h after injury | Death in ED or admitted with diagnosis of brain death, admission to study hospital >24h after injury, non-paralyzed patients with fixed and dilated pupils, missing pupil status, missing outcome assessment, GCS $\geq$ 9 on day 1, GCS motor score = 6 on any day, transport time < 10 minutes | 1123[e] |
| Irvin (2010) [44] | Retrospective cohort study. Only patients with isolated head injury are considered | 2000–2005 | numerous locations throughout the USA and Puerto Rico | GCS = 3 and H-AIS score assigned | Received paralytics or sedatives in the field, missing data for several predefined variables | 1504[f] |
| Karamanos (2014) [45] | Retrospective matched cohort study | 2003–2011 | Los Angeles County, USA | H-AIS $\geq$ 3 and/or GCS $\leq$ 8 | Extra-cranial AIS $\geq$ 3, cardiac arrest in the field, lack of immediate ABG obtained at admission | 220[c] |
| Klemen (2006) [46] | Cohort study | Intervention: 2000–2004; Controls: 1998–2004 | Maribor, Slovenia | GCS $\leq$ 8, H-AIS > 3, ISS > 15 | NR | 124 |
| Lenartova (2007) [47] | Prospective cohort study | 1999–2004 | five locations throughout Austria | GCS $\leq$ 8 following resuscitation or GCS score deteriorating to $\leq$ 8 within 48 hours of injury | Death on scene, death during transport to hospital or immediately after admission to the emergency room | 393 |
| Murray (2000) [48] | Retrospective cohort study, unmatched and matched analyses reported | 1995–1997 | Los Angeles County, USA | Field GCS $\leq$ 8 and H-AIS $\geq$ 3 | Missing documentation for outcome and intubation status, unsuccessful intubation excluded in some of the sub-analyses | 114 to 852 |
| Poste (2004) [49] | Matched cohort study, prospectively enrolled intervention group matched to historical controls. | Intervention: 1998–2002; Controls: NR | San Diego County, USA | See Davis (2003) + ground transport or air medical transport depending on sub-analysis | Inability to obtain iv access, CPR before administration of RSI medication, H-AIS < 2 or higher H-AIS defined by neck injury, inability to intubate, primary airway management by air-medical crew | 237 to 771[d] |
| Singbartl (1985) [50] | Prospective cohort study | NR | Bochum, Germany | Cerebral trauma, GCS $\leq$ 7 | NR | 147 |
| Sloane (2000) [51] | Retrospective cohort study | Intervention: 1988–1995; Controls: 1992–1995 | San Diego County, USA | Adult trauma patients, GCS $\leq$ 8, ISS $\geq$ 9, H-AIS $\geq$ 3, all other AIS $\leq$ 3 | Incomplete records, non-RSI, nasotracheal intubation, cricothyrotomy, intubation before arrival of aeromedical crews, interhospital transfer | 75[d] |
| Tuma (2014) [52] | Retrospective cohort study | 2008–2011 | Qatar | Age >14 years, field GCS $\leq$ 8 and H-AIS $\geq$ 3 and all other AIS $\leq$ 3 | Death within 24 hours due to haemorrhage or unclear cause, patients transferred from other hospital, intubation in OR or ICU | 160 |
| Vandromme (2011) [53] | Cohort study | 2006–2009 | Birmingham, Alabama, USA | Blunt mechanism, GCS $\leq$ 8 and CT-confirmed TBI, defined as Marshall Score of II-V | NR | 135 |
| Wang (2004) [55] | Retrospective cohort study | 2000–2002 | Pennsylvania, USA | Age $\geq$ 18, trauma with ICD-9-CM injury classification 800–995, H-AIS $\geq$ 3 | Interhospital transfer, no treatment by advanced life support rescuers, not intubated either in the field or in the ED | 4098 |

(*Continued*)

**Table 1.** (*Continued*)

| First author (year) | Study design | Study Period | Region | Inclusion criteria[a] | Exclusion criteria[a] | n total[b] |
|---|---|---|---|---|---|---|
| Wang (2014) [54] | Secondary analysis of a prospective RCT on hypertonic fluid resuscitation. | 2006–2009 | multiple locations throughout the USA and Canada | Age $\geq$ 15 years, blunt mechanism of injury, GCS $\leq$ 8 | Shock, pregnancy, out-of-hospital CPR, more than 2000 ml of crystalloid or any colloid or blood products prior to enrolment, severe hypothermia, drowning, asphyxia due to hanging, burns of more that 20% total body surface area, isolated penetrating head injury, inability to obtain venous access, prisoner status, intrafacility transfers, >4 h time interval between dispatch call and study intervention, death in the field or ED, neither advanced airway management in the field nor in the ED, missing key covariates | 1116 |
| Winchell (1997) [56] | Retrospective cohort study | 1991–1995 | San Diego County, USA | Blunt mechanism, GCS $\leq$ 8, admission to ICU or hospitalization for more than 3 days or death, depending on sub-analysis also H-AIS $\geq$ 4 and all other AIS $\leq$ 3, GCS = 3 or GCS 4–8. Intervention: apnoea or ineffective ventilation, no gag reflex. | Depending on sub-analysis: transport by ground or air | 50 to 1092[d] |

[a] In- and exclusion criteria for the population of interest.

[b] Number of population on which the analyses of interest (prehospital intubation versus no intubation in TBI patients) are based. If multiple analyses are presented in the manuscript, the range of the number of patients used in the analyses is reported.

[c] Data from the studies by Bukur and Karamanos report patients from the same region and overlapping time period.

[d] Data from the studies by Davis, Poste, Sloane and Winchell are all from the same region and overlapping time periods and partially report overlapping data.

[e] Total number of patients in study, unclear whether all are included in analysis of interest.

[f] Data are from the National Trauma Data Bank and might include some patients that have also been included to other studies that have been performed in the USA.

ABG: arterial blood gas

(H-)AIS: (head) abbreviated injury scale

CPR: cardiopulmonary resuscitation

CT: computed tomography

ED: emergency department

GCS: Glasgow Coma Scale

ICU: intensive care unit

ICD-9-CM: international classification of diseases, 9th revision, clinical modification

ISS: injury severity scale

NR: not reported

OR: operating room

RCT: randomized controlled trial

RSI: rapid sequence induction

TBI: traumatic brain injury

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## Pooled results: Meta-analysis, meta-regression and sensitivity analyses

Six analyses including data from 4772 patients met inclusion-criteria for the meta-analysis (Table 2). Overall, no significant association was observed between PHI and mortality (OR 1.35, 95% CI 0.78 to 2.33, p = 0.279, Fig 2). In studies in which intubation was performed by providers with limited experience, PHI was associated with higher odds of mortality (OR 2.33, 95% CI 1.61 to 3.38, p<0.001). In contrast, pooled results in the "extended experience" stratum showed no evidence for higher mortality in patients who were intubated in the prehospital setting (OR 0.75, 95% CI 0.52 to 1.08, p = 0.126). Meta-regression confirmed that EMS-provider experience is a significant predictor of mortality (p = 0.009). The funnel plot asymmetry regression test provided no evidence for small study bias (p = 0.312).

Substantial heterogeneity was observed between all studies ($I^2$ = 83.3%). After adjusting for experience in the meta-regression, residual heterogeneity was negligible ($I^2$ = 10.3%), suggesting that a large portion of the observed heterogeneity can be explained by differences in the level of experience.

We performed a sensitivity analysis excluding each of the studies one at a time and re-running the analyses without the excluded study. Odds-ratio estimates were of similar magnitude at each exclusion and all conclusions regarding significance remained the same, indicating that none of the included studies has undue influence on the overall results and conclusions (Table 6).

**Table 2. Quality Assessment.**

| First author (year) | Newcastle-Ottawa Quality Assessment Scale | | | | | | | | | Cochrane Collaboration's tool for assessing risk of bias | | | | | | | Meta-Analysis | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Selection | | | Comparability | | | Outcome | | | A | B | C | D | E | F | G | Eligible | Selected |
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | | | | | | | | | |
| Bernard (2010) [33] | | | | | | | | | | low | low | NA | low | low | low | low | Yes | Yes |
| Bochicchio (2003) [34] | * | * | * | * | - | - | * | - | - | | | | | | | | No | No |
| Bukur (2011) [35] | * | * | * | * | * | * | * | - | - | | | | | | | | Yes | No[a] |
| Davis (2003) [37] | - | - | * | * | * | * | * | * | * | | | | | | | | No | No |
| Davis (2004) [36] | - | - | * | * | * | * | * | - | * | | | | | | | | No | No |
| Davis (2005a) [39] | * | - | * | * | * | * | * | - | * | | | | | | | | No | No |
| Davis (2005b) [40] | * | * | * | * | * | * | * | - | * | | | | | | | | Yes | Yes[b] |
| Davis (2005c) [41] | - | - | * | * | * | * | * | * | * | | | | | | | | No | No |
| Davis (2006) [38] | * | * | * | * | - | - | * | - | * | | | | | | | | No | No |
| Franschman (2011) [42] | * | * | * | * | * | * | * | - | * | | | | | | | | Yes | Yes |
| Härtl (2006) [43] | * | * | * | * | * | * | * | * | - | | | | | | | | No[c] | No |
| Irvin (2010) [44] | - | * | * | * | * | * | * | * | - | | | | | | | | No[c] | No |
| Karamanos (2014) [45] | * | * | * | * | * | * | * | * | * | | | | | | | | Yes | Yes |
| Klemen (2006) [46] | * | * | * | * | (*)[d] | (*)[d] | * | * | * | | | | | | | | No | No |
| Lenartova (2007) [47] | * | * | * | * | - | - | * | * | * | | | | | | | | No | No |
| Murray (2000) [48] | * | * | * | * | (*)[e] | (*)[e] | * | * | * | | | | | | | | Yes | Yes[b] |
| Poste (2004) [49] | - | - | * | * | * | * | * | * | * | | | | | | | | No | No |
| Singbartl (1985) [50] | * | - | * | * | - | - | * | - | * | | | | | | | | No | No |
| Sloane (2000) [51] | - | - | * | * | - | - | * | * | - | | | | | | | | No | No |
| Tuma (2014) [52] | * | * | * | * | * | * | * | * | * | | | | | | | | Yes | Yes |
| Vandromme (2011) [53] | * | * | * | * | * | * | * | - | - | | | | | | | | No[c] | No |
| Wang (2004) [55] | * | * | * | * | * | * | * | * | * | | | | | | | | No[c] | No |
| Wang (2014) [54] | * | * | * | * | * | * | * | * | * | | | | | | | | No[c] | No |

*(Continued)*

**Table 2.** (*Continued*)

| First author (year) | Newcastle-Ottawa Quality Assessment Scale | | | | | | | | | Cochrane Collaboration's tool for assessing risk of bias | | | | | | | Meta-Analysis | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Selection | | | Comparability | | | Outcome | | | A | B | C | D | E | F | G | Eligible | Selected |
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | | | | | | | | | |
| Winchell (1997) [56] | * | * | * | * | - | - | * | * | * | | | | | | | | No | No |

[a] Not selected because of potential overlap with Karamanos (2014).

[b] Several analyses described in the manuscript were eligible; the one with the smallest standard error of the estimated OR was selected.

[c] Study eligible based on quality criteria, but EMS-provider experience was "indeterminate" (see Table 3).

[d] Several analysis presented; first hour survival and first day survival data are adjusted, however the analysis with the outcome of main interest (hospital mortality) is not adjusted.

[e] Several analyses are presented, among which one matched and one adjusted analyses. Both of these analyses earned two stars for comparability, while the cohorts are not comparable in the crude analyses.

Newcastle-Ottawa Quality Assessment Scale

Selection:    1. Representativeness of the exposed cohort (prehospital intubation)
                   2. Selection of the non-exposed cohort (no prehospital intubation)
                   3. Ascertainment of exposure
                   4. Demonstration that outcome of interest was not present at start of study

Comparability:    5. Comparability of cohorts on the basis of the design or analysis: most important factor
                          6. Comparability of cohorts on the basis of the design or analysis: additional factors

Outcome:    7. Assessment of outcome
                   8. Was follow-up long enough for outcomes to occur?
                   9. Adequacy of follow up of cohorts

Cochrane Collaboration's tool for assessing risk of bias: Domains

   A. Sequence generation
   B. Allocation concealment
   C. Blinding of participants and personnel
   D. Blinding of outcome assessors
   E. Incomplete outcome data
   F. Selective outcome reporting
   G. Other sources of bias

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## Discussion

### Summary of evidence

We performed a systematic review and meta-analysis to address effects of PHI on mortality in patients with severe TBI. The main finding is that effects of PHI depend on the level of experience of the EMS-providers who perform the intervention, and that PHI by EMS-personnel with limited experience in performing PHI is associated with increased mortality. When intubation is performed by well-trained personnel, we noted a trend towards improved survival, but the current evidence is insufficient to conclude that PHI by highly trained personnel reduces mortality.

### Strengths and limitations

Strengths of this systematic review include the comprehensive search strategy in three major databases without any restrictions, resulting in selection of 24 studies reporting data from more than 30,000 patients. The review was performed using pre-specified procedures according to published recommendations [24–26], and extracted data were double-checked to ensure

**Table 3. Patient and injury characteristics[a].**

| First author (year) | Patient age[b] | Male gender (%) | Isolated TBI? | Initial GCS[b] | H-AIS[b] | ISS[b] |
|---|---|---|---|---|---|---|
| Bernard (2010) [33] | Intervention: 40.0 ± 22 | Intervention: 75 | No | Intervention: 5 (3–7) | Intervention: 4.0 ± 1.4 | Intervention: 30.5 ± 14.8 |
| | Control: 41.4 ± 23 | Control: 77 | | Control: 5 (3–7) | Control: 3.9 ± 1.4 | Control: 30.1 ± 14.5 |
| Bochicchio (2003) [34] | Intervention: 35 ± 21 | Overall: 81 | No | Intervention: 4.0 ± 0.8 | Intervention: 4.9 ± 0.7 | Intervention: 20.1 ± 8 |
| | Control: 40 ± 15 | | | Control: 4.4 ± 2.1 | Control: 4.5 ± 0.9 | Control: 19.2 ± 9 |
| Bukur (2011) [35] | Intervention: 35.9 ± 18.2 | Intervention: 82 | Yes | Intervention: 3.3 ± 1.1 | Intervention: 4.8 ± 0.5 | Intervention: 26.7 ± 8.4 |
| | Control: 38.1 ± 24.2 | Control: 76 | | Control: 11.7 ± 4.2 | Control: 4.0 ± 0.8 | Control: 18.4 ± 7.0 |
| Davis (2003) [37] | Intervention: 37.1 | Intervention: 81 | No | NR | Intervention: 3.91 | Intervention: 27.6 |
| | Control: 36.8 | Control: 81 | | | Control: 3.92 | Control: 26.3 |
| Davis (2004) [36] | Intervention: 38.1 | Intervention: 81 | No | NR | Intervention: 3.92 | Intervention:26.2 |
| | Control: 36.9 | Control: 81 | | | Control: 3.92 | Control: 26.6 |
| Davis (2005a) [39] | Intervention. 33.0 | Intervention: 79 | No | Intervention: 4.1 | Intervention: 4.42 | Intervention: 32.9 |
| | Control: 37.5 | Control: 78 | | Control: 4.6 | Control: 4.42 | Control: 31.2 |
| Davis (2005b) [40] | Intervention: 35.3 | Overall: 76 | No | Intervention: 4.4 | Intervention: 4.6 | Intervention: 36.6 |
| | Control: 37.6[c] | | | Control: 8.0[c] | Control: 4.2[c] | Control: 28.3[c] |
| Davis (2005c) [41] | Intervention: 37.1 | Intervention: 81 | No | NR | Intervention: 3.91 | Intervention: 26.7 |
| | Control: 37.8 | Control: 81 | | | Control: 3.91 | Control 27.5 |
| Davis (2006) [38] | Intervention: 35.4 | Intervention: 79 | No | Intervention: 4.5 | Intervention: 4.5 | Intervention: 34.0 |
| | Control: 40.2 | Control: 77 | | Control: 10.3 | Control: 3.9 | Control: 24.4 |
| Franschman (2011) [42] | Intervention: 43 ± 21 | Overall: 70 | No | Intervention: 3 (3–3) | NR | Intervention: 32 (25–41) |
| | Control: 48 ± 20 | | | Control: 5 (3–7) | | Control: 25 (22–29) |
| Härtl (2006) [43] | Overall: 36.0 ± 20.6 | Overall: 75 | No | Overall: | NR | NR |
| | | | | GCS 3–5: 53.7% | | |
| | | | | GCS 6–8: 33.3% | | |
| | | | | GCS ≥ 9: 13.0% | | |
| Irvin (2010) [44] | Intervention: 37.9 ± 20.8 | NR | Yes | NR (should be 3, see inclusion criteria) | NR | Intervention: 31.6 ± 16.2 |
| | Control: 37.7 ± 20.0 | | | | | Control: 24.2 ± 16.0 |
| Karamanos (2014) [45] | Intervention: 35.3 ± 1.3 | Intervention: 86 | Yes | NR | NR | Intervention: |
| | | | | | | ISS ≤ 15: 5.5% |
| | | | | | | ISS = 16–24: 18.2% |
| | | | | | | ISS ≥ 25: 76.4% |
| | Control: 36.2 ± 1.5 | Control: 89 | | | | Control: |
| | | | | | | ISS ≤ 15: 8.5% |
| | | | | | | ISS = 16–24: 18.8% |
| | | | | | | ISS ≥ 25: 72.7% |
| Klemen (2006) [46] | Intervention: 44.8 ± 23.6 | Intervention: 77 | No | Intervention: 5 (3–8) | NR | Intervention: 24 (16–26) |
| | Control: 42.5 ± 21.3 | Control: 82 | | Control: 6 (4–8) | | Control: 23 (17–25) |
| Lenartova (2007) [47] | Overall: 48.9 ± 20.8 | Overall: 72 | No | Overall: 5.6 ± 2.9 | NR | Overall: 27.0 ± 12.7 |

*(Continued)*

**Table 3.** (*Continued*)

| First author (year) | Patient age[b] | Male gender (%) | Isolated TBI? | Initial GCS[b] | H-AIS[b] | ISS[b] |
|---|---|---|---|---|---|---|
| Murray (2000) [48] | Intervention: 34 | Intervention: 70 | No | NR | Intervention: | Intervention: 29.6 |
| | | | | | H-AIS = 3: 15% | |
| | | | | | H-AIS = 4: 15% | |
| | | | | | H-AIS = 5: 65% | |
| | | | | | H-AIS = 6: 5% | |
| | Control: 34 | Control: 78 | | | Control: | Control: 26.7 |
| | | | | | H-AIS = 3: 17% | |
| | | | | | H-AIS = 4: 30% | |
| | | | | | H-AIS = 5: 52% | |
| | | | | | H-AIS = 6: 1% | |
| | Attempted Intubation: 33 | Attempted Intubation: 79 | | | Attempted Intubation: | Attempted Intubation: 31.8 |
| | | | | | H-AIS = 3: 2% | |
| | | | | | H-AIS = 4: 23% | |
| | | | | | H-AIS = 5: 72% | |
| | | | | | H-AIS = 6: 4% | |
| Poste (2004) [49] | *Air transport cohort* | *Air transport cohort* | No | *Air transport cohort* | *Air transport cohort* | *Air transport cohort* |
| | Intervention: 38.0 | Intervention: 79 | | Intervention: 4.9 | Intervention: 3.91 | Intervention: 27.2 |
| | Control: 38.4 | Control: 79 | | Control: NR | Control: 3.92 | Control: 28.0 |
| | *Ground transport cohort* | *Ground transport cohort* | | *Ground transport cohort* | *Ground transport cohort* | *Ground transport cohort* |
| | Intervention: 37.2 | Intervention: 81 | | Intervention: 4.9 | Intervention: 3.91 | Intervention: 26.4 |
| | Control: 37.8 | Control: 81 | | Control: NR | Control: 3.91 | Control: 27.1 |
| Singbartl (1985) [50] | Overall: 41.2 | NR | No | Intervention: | NR | NR |
| | | | | GCS 3: 23.7% | | |
| | | | | GCS 4–5: 55.9% | | |
| | | | | GCS 6–7: 20.4% | | |
| | | | | Control: | | |
| | | | | GCS 3: 20.4% | | |
| | | | | GCS 4–5: 46.3% | | |
| | | | | GCS 6–7: 33.3% | | |
| Sloane (2000) [51] | Intervention: 26.2 | Intervention: 76 | Yes | Intervention: 5.2 | Intervention: 4.8 | Intervention: 31.4 |
| | Control: 36.2 | Control: 81 | | Control: 5.8 | Control: 4.7 | Control: 29.0 |
| Tuma (2014) [52] | Intervention: 30 ± 14 | Intervention: 95 | Yes | Intervention: median Glasgow motor score = 1 | NR | Intervention: 28 ± 8 |
| | Control: 34 ± 15 | Control: 98 | | Control: median Glasgow motor score = 3 | | Control: 27 ± 10 |
| Vandromme (2011) [53] | Overall: 38.0 | Overall: 77 | No | Intervention: 4.1 | Intervention: 4.4 | Intervention: 38.0 |
| | | | | Control: 5.9 | Control: 4.6 | Control: 33.7 |
| Wang (2004) [55] | Intervention: | Intervention: 74 | No | NR | Intervention: | Intervention: |
| | 18–30 years: 41.2% | | | | H-AIS = 3: 18.5% | ISS < 10: 1.1% |
| | 31–40 years: 17.1% | | | | H-AIS = 4: 25.1% | ISS = 10–15: 5.3% |

(*Continued*)

**Table 3.** (*Continued*)

| First author (year) | Patient age[b] | Male gender (%) | Isolated TBI? | Initial GCS[b] | H-AIS[b] | ISS[b] |
|---|---|---|---|---|---|---|
| | 41–50 years: 15.1% | | | | H-AIS = 5: 53.6% | ISS = 16–25: 23.3% |
| | 51–60 years: 8.4% | | | | H-AIS = 6: 2.7% | ISS = 26–35: 36.9% |
| | 61–70 years: 6.8% | | | | | ISS = 36–50: 25.3% |
| | 71–80 years: 6.3% | | | | | ISS = 51–70: 4.3% |
| | >80 years: 4.8% | | | | | ISS > 70: 3.7% |
| | Control: | Control: 75 | | | Control: | Control: |
| | 18–30 years: 33.6% | | | | H-AIS = 3: 28.0% | ISS < 10: 3.9% |
| | 31–40 years: 15.2% | | | | H-AIS = 4: 31.1% | ISS = 10–15: 9.9% |
| | 41–50 years: 16.4% | | | | H-AIS = 5: 39.7% | ISS = 16–25: 35.1% |
| | 51–60 years: 9.5% | | | | H-AIS = 6: 1.2% | ISS = 26–35: 34.2% |
| | 61–70 years: 7.8% | | | | | ISS = 36–50: 13.4% |
| | 71–80 years: 9.8% | | | | | ISS = 51–70: 1.8% |
| | >80 years: 7.3% | | | | | ISS > 70: 1.7% |
| Wang (2014) [54] | Intervention: 38.3 ± 18.1 | Intervention: 77 | No | Intervention: 5.0 ± 2.4 | Intervention: 3.8 ± 1.5 | Intervention: 29.4 ± 15.4 |
| | Control: 40.1 ± 19.0 | Control: 77 | | Control: 5.5 ± 2.4 | Control: 3.4 ± 1.9 | Control: 24.9 ± 14.8 |
| Winchell (1997) [56] | Intervention: 32.6 | NR | No/Yes[d] | Intervention: 4.8 | Intervention: 3.9 | Intervention: 27 |
| | Control: 33.5 | | | Control: 4.6 | Control: 3.6 | Control: 25 |

[a] For studies presenting data from several patient populations or several sub-analyses, the reported patient characteristics refer to the total patient population.

[b] Presented as mean, mean ± SD, mean (95% CI), median, median (IQR) or as percentage per category, as reported by the authors or as calculated from the available data.

[c] Multiple analyses with two different control groups (no prehospital invasive airway management, intubation in the emergency department) performed in the study. The presented data are for the subpopulation of patients intubated in the emergency department.

[d] Study reports sub-analyses for patients with isolated TBI.

GCS: Glasgow Coma Scale; H-AIS: head abbreviated injury scale; ISS: injury severity scale; NR: not reported; TBI: traumatic brain injury

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accuracy of the reported information. A sensitivity analysis was used to confirm that the results and conclusions reflect the current overall literature rather than being the result of undue influence of any individual study. Meta-regression was used as an adjunct to the stratified meta-analysis to formally determine the significance of EMS-provider experience.

The included studies were—except for one RCT—mostly cohort studies. Such studies are subject to inherent limitations of observational research, but generally provide similar estimates of treatment effects as RCTs if they are well designed [57, 58]. We included all observational studies in the systematic review to give a comprehensive overview of previously published literature, but we only pooled data across studies that met pre-specified quality criteria. This approach allowed to quantitatively summarize the best available evidence while precluding bias due to limited data quality.

We focused on mortality as outcome because it is of high clinical relevance and unambiguously defined. Other outcomes such as incidence of complications or functional neurologic recovery in survivors are also relevant, but are not consistently reported. The manuscripts that

**Table 4. Treatments.**

| First author (year) | Intervention | Control | Medication used for prehospital intubation | Intubated by | Level of training |
|---|---|---|---|---|---|
| Bernard (2010) [33] | Prehospital RSI (including attempts in an intention-to-treat approach) | Hospital intubation (prehospital intubation permitted if airway reflexes lost during transport) | Fentanyl, midazolam, succinylcholine, atropine if heart rate < 60/min, minimum 500 ml lactated Ringer's solution. After intubation: pancuronium, morphine infusion, midazolam infusion | Specially trained intensive care paramedics | Extended |
| Bochicchio (2003) [34] | Prehospital RSI | ED intubation | Midazolam (may be omitted), lidocaine, succinylcholine. After intubation: vecuronium if significant resistance to ventilation occurs | Ground paramedics and flight paramedics | Indeterminate |
| Bukur (2011) [35] | Prehospital intubation | ED intubation | NR | Paramedics | Limited |
| Davis (2003) [37] | Prehospital RSI or cricothyrotomy (after 3 unsuccessful intubation attempts) | No prehospital intubation | Midazolam if SBP > 120 mmHg, succinylcholine. After intubation: rocuronium, additional midazolam after 30 min if SBP remained > 120 mmHg, morphine every 10 minutes if SPB > 140 mmHg and heart rate > 100 BPM | Paramedics. A portion of intubations may have been performed by flight nurses or emergency medicine resident physicians | Indeterminate |
| Davis (2004) [36] | Prehospital RSI, combitube as salvage device or cricothyrotomy (after 3 unsuccessful intubation attempts) | No prehospital intubation | Midazolam if SBP > 120 mmHg, succinylcholine. After intubation: rocuronium, morphine every 10 minutes if SPB > 140 mmHg and heart rate > 100 BPM | Paramedics | Limited |
| Davis (2005a) [39] | Prehospital intubation by aeromedical teams, patients transported by helicopter | ED intubation, patients transported by ground ambulance | Patients may have been intubated using RSI medication; no details provided | Flight crews (certified flight nurses and emergency medicine resident physicians) | Extended |
| Davis (2005b) [40] | Prehospital tracheal intubation (depending on sub-analysis in- or excluding combitube, cricothyrotomy or nasotracheal intubation) | No prehospital invasive airway management | A portion of the patients (especially those intubated by flight crews) may have been intubated using RSI medication; no details provided | Depending on sub-analysis: Paramedics or paramedics and flight crews (flight nurses and emergency medicine resident physicians) | Indeterminate or limited depending on the sub-analysis |
| Davis (2005c) [41] | Prehospital RSI | No prehospital intubation | Midazolam if SBP > 120 mmHg, succinylcholine. After intubation: rocuronium additional midazolam after 30 min if SBP remained > 120 mmHg, morphine every 10 minutes if SPB > 140 mmHg and heart rate > 100 BPM | Paramedics, a portion of intubations were performed by flight nurses or emergency medicine residents | Indeterminate |
| Davis (2006) [38] | Prehospital invasive airway management including intubation, combitube insertion or cricothyrotomy | No prehospital invasive airway management | A portion of the patients were intubated using NMBA | Paramedics, a portion of intubations were performed by flight nurses or emergency medicine residents | Indeterminate |
| Franschman (2011) [42] | Prehospital intubation | No prehospital intubation | Different regimes, with or without RSI medications | Emergency physicians or ambulance nurses | Extended |
| Härtl (2006) [43] | Prehospital intubation | No prehospital intubation | NR | NR | Indeterminate |
| Irvin (2010) [44] | Prehospital intubation | No prehospital intubation | No sedatives or paralytic agents | NR | Indeterminate |

*(Continued)*

**Table 4.** (Continued)

| First author (year) | Intervention | Control | Medication used for prehospital intubation | Intubated by | Level of training |
|---|---|---|---|---|---|
| Karamanos (2014) [45] | Prehospital intubation | No prehospital intubation, oxygen by mask | NR | Paramedics | Limited |
| Klemen (2006) [46] | Prehospital RSI | No prehospital RSI | Various anaesthetic induction agents with or without succinylcholine | Emergency physicians | Extended |
| Lenartova (2007) [47] | Prehospital intubation | No prehospital intubation | NR | Predominantly emergency physician led teams (96%) | Extended |
| Murray (2000) [48] | Prehospital intubation (unsuccessful attempts either in- or excluded depending on sub-analysis) | No prehospital intubation (unsuccessful attempts either in- or excluded depending on sub-analysis) | None | Paramedics | Limited |
| Poste (2004) [49] | Successful prehospital RSI with endotracheal tube or combitube (after a maximum of 3 unsuccessful intubation attempts) | No prehospital intubation | Midazolam if SBP > 120 mmHg, succinylcholine. After intubation: rocuronium, morphine every 10 minutes if SPB > 140 mmHg and heart rate > 100 BPM | Paramedics | Limited |
| Singbartl (1985) [50] | Prehospital intubation | No prehospital intubation | NR | Emergency physicians and paramedics | Indeterminate |
| Sloane (2000) [51] | Prehospital RSI by aeromedical crews | ED RSI, transport by ground ambulance | Lidocaine, consider fentanyl, succinylcholine. After intubation consider vecuronium and fentanyl | Aeromedical physicians or flight nurses | Extended |
| Tuma (2014) [52] | Prehospital intubation | ED intubation | RSI, no details reported | Well trained critical care paramedics | Extended |
| Vandromme (2011) [53] | Prehospital intubation | ED intubation | NR | NR | Indeterminate |
| Wang (2004) [55] | Prehospital intubation, including combitube, cricothyrotomy or tracheotomy | ED intubation | Different regimes, with or without NMBA | Paramedics, flight paramedics, nurses, physicians | Indeterminate |
| Wang (2014) [54] | Prehospital advanced airway management including intubation, insertion of supraglottic airway devices or surgical airways | ED advanced airway management | Different regimes, with or without NMBA | NR | Indeterminate |
| Winchell (1997) [56] | Prehospital intubation. Ground paramedics: max. 3 attempts, aeromedical teams: cricothyrotomy if intubation could not be performed | No prehospital intubation | Either none (ground paramedics) or NMBA (flight crews) | Either paramedics or aeromedical crews (flight nurses, flight paramedics, occasionally physicians) | Indeterminate |

BPM: beats per minute

ED: emergency department

NMBA: neuromuscular blocking agents

NR: not reported

RSI: rapid sequence induction

SBP: systolic blood pressure

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**Table 5.  Mortality.**

| First author (year) | Time of mortality assessment | Sub-Analysis | Intervention | | Control | | Unadjusted OR (95% CI) | Adjusted OR (95% CI)[d] | Factors used for adjustment or matching |
|---|---|---|---|---|---|---|---|---|---|
| | | | Alive | Dead | Alive | Dead | | | |
| Bernard (2010) [33] | Hospital discharge | | 107 | 53 | 97 | 55 | 0.87 (0.55–1.39) | Considered equivalent to unadjusted | (Randomized Controlled Trial) |
| Bochicchio (2003) [34] | NR[a] | | 60[c] | 18[c] | 99[c] | 14[c] | 2.12 (0.98–4.58) | NR | NA |
| Bukur (2011) [35] | NR[a] | | 6[c] | 55[c] | 2019[c] | 286[c] | 64.7 (27.6–151.6) | 5.0 (1.7–13.7) | Mechanism of injury, admission SBP, admission GCS, H-AIS, ISS |
| Davis (2003) [37] | Hospital discharge | | 140[c] | 69[c] | 475[c] | 152[c] | 1.54 (1.09–2.17) | 1.6 (NR) | Adjustment: age, sex, H-AIS, Chest-AIS, Abdomen-AIS, scene time, admission SBP. Matching: age, sex, mechanism of injury, trauma centre, ISS, H-AIS, face AIS, chest AIS, abdomen AIS, extremities AIS, skin AIS |
| Davis (2004) [36] | Hospital discharge | | 35[c] | 24[c] | 139[c] | 38[c] | 2.51 (1.33–4.72) | NR | Age, sex, mechanism of injury, trauma centre, ISS, H-AIS, face AIS, chest AIS, abdomen AIS, extremities AIS, skin AIS |
| Davis (2005a) [39] | NR[a] | | 719 | 531 | 565 | 428 | 0.97 (0.82–1.15) | 0.70 (0.56–0.88) | Age, sex, mechanism of injury, preadmission hypotension, H-AIS, ISS, pre-intubation GCS |
| Davis (2005b) [40] | NR[a] | Population H-AIS ≥ 3. Control: no invasive PH airway management | 974 | 1256 | 6053 | 1220 | 6.40 (5.77–7.10) | 2.78 (2.38–3.13) | Age, sex, mechanism of injury, preadmission hypotension, H-AIS, ISS, pre-intubation GCS |
| | | Population GCS ≤ 8 and H-AIS ≥ 3. Control: no invasive PH airway management | 830 | 1221 | 1468 | 901 | 2.40 (2.12–2.71) | 1.35 (1.15–1.59) | " |
| | NR[a] | Population H-AIS ≥ 4. Control: no invasive PH airway management | 737 | 1163 | 3139 | 1103 | 4.49 (4.00–5.04) | 1.39 (1.19–1.64) | " |
| | | Population GCS ≤ 8 and H-AIS ≥ 4. Control: no invasive PH airway management | 652 | 1132 | 1083 | 843 | 2.23 (1.95–2.54) | 1.28 (1.09–1.52) | " |
| | | Population H-AIS ≥ 3, excludes intubation by aeromedical crews. Control: no invasive PH airway management | 250 | 695 | 4589 | 1063 | 12 (10.24–14.07) | 2.38 (1.92–3.03) | " |
| | | Population GCS ≤ 8 and H-AIS ≥ 3, excludes intubation by aeromedical crews. Control: no invasive PH airway management | 229 | 687 | 1236 | 798 | 4.65 (3.90–5.53) | 2.13 (1.69–2.63) | " |
| | | Population H-AIS ≥ 4, excludes intubation by aeromedical crews. Control: no invasive PH airway management | 196 | 641 | 2430 | 973 | 8.17 (6.85–9.74) | 2.27 (1.82–2.86) | " |

*(Continued)*

**Table 5.** (Continued)

| First author (year) | Time of mortality assessment | Sub-Analysis | Intervention | | Control | | Unadjusted OR (95% CI) | Adjusted OR (95% CI)[d] | Factors used for adjustment or matching |
|---|---|---|---|---|---|---|---|---|---|
| | | | Alive | Dead | Alive | Dead | | | |
| | | Population GCS ≤ 8 and H-AIS ≥ 4, excludes intubation by aeromedical crews. Control: no invasive PH airway management | 182 | 633 | 910 | 749 | 4.23 (3.49–5.12) | 1.96 (1.56–2.5) | " |
| | | Population H-AIS ≥ 3, Control: ED intubation | 1024 | 1390 | 1296 | 537 | 3.28 (2.88–3.73) | 2.13 (1.82–2.5) | " |
| | NR[a] | Population GCS ≤ 8 and H-AIS ≥ 3. Control: ED intubation | 870 | 1351 | 646 | 396 | 2.53 (2.18–2.95) | 1.47 (1.2–1.79) | " |
| | | Population H-AIS ≥ 4. Control: ED intubation | 769 | 1284 | 886 | 489 | 3.03 (2.62–3.49) | 1.45 (1.2–1.75) | " |
| | | Population GCS ≤ 8 and H-AIS ≥ 4. Control: ED intubation | 679 | 1250 | 512 | 372 | 2.53 (2.15–2.98) | 1.43 (1.16–1.75) | " |
| Davis (2005c) [41] | Hospital discharge | | 240[c] | 112[c] | 537[c] | 167[c] | 1.50 (1.13–1.99) | 2.0 (1.4–2.8) | Adjustment: age, sex, arrival SBP, H-AIS, ISS. Matching: age, sex, mechanism of injury, trauma centre, ISS, H-AIS, AIS for face, chest, abdomen, extremities and skin |
| Davis (2006) [38] | NR[a] | | 447 | 443 | 2368 | 546 | 4.30 (3.66–5.05) | NR | NA |
| Franschman (2011) [42] | Hospital discharge[b] | | 132 | 101 | 60 | 42 | 1.09 (0.68–1.75) | 0.63 (0.27–1.49) | Age, ISS, GCS, pupillary reflex, hypoxia, hypotension |
| Härtl (2006) [43] | Two week mortality | | NR | NR | NR | NR | NR | 0.82 (0.59–1.14) | Hypotension status on day 1, age category, pupil status on day 1, GCS (unclear whether initial value or at day 1) |
| Irvin (2010) [44] | Hospital discharge | | NR | NR | NR | NR | NR | 1.99 (1.35–2.93) | ISS, age, penetrating trauma, improvement en route |
| Karamanos (2014) [45] | Hospital discharge [b] | | 17 | 38 | 74 | 91 | 1.82 (0.95–3.48) | NR | Propensity scores calculated by logistic regression. All demographic and clinical variables that differed significantly between the groups were used in the model |
| Klemen (2006) [46] | Hospital discharge | | 39 | 25 | 35 | 25 | 0.90 (0.44–1.84) | NR | NA |
| | First day mortality | | 57 | 7 | 45 | 15 | 0.37 (0.14–0.98) | 0.38 (0.26–0.55) | Age, gender, mechanism of injury, GCS, ISS, initial SaO$_2$, SBP |
| | First hour mortality | | 62 | 2 | 47 | 13 | 0.12 (0.03–0.54) | 0.45 (0.34–0.56) | " |
| Lenartova (2007) [47] | 90 days after trauma | | 196[c] | 128[c] | 51[c] | 18[c] | 1.85 (1.03–3.31) | NR | NA |
| | ICU mortality | | 214[c] | 110[c] | 54[c] | 15[c] | 1.85 (1.00–3.43) | NR | NA |
| Murray (2000) [48] | Hospital discharge | Successful PH intubation vs. no prehospital intubation (as treated) | 15 | 66 | 415 | 356 | 5.13 (2.88–9.14) | NR | NA |
| | " | PH intubation attempts vs. no prehospital intubation attempts (intention-to-treat) | 25 | 113 | 405 | 309 | 5.92 (3.75–9.36) | 4.18 (2.06–8.93) | Gender, GCS, H-AIS, ISS, transport mode, associated injuries, mechanism of injury |

(Continued)

**Table 5.** (*Continued*)

| First author (year) | Time of mortality assessment | Sub-Analysis | Intervention | | Control | | Unadjusted OR (95% CI) | Adjusted OR (95% CI)[d] | Factors used for adjustment or matching |
|---|---|---|---|---|---|---|---|---|---|
| | | | Alive | Dead | Alive | Dead | | | |
| | " | Unsuccessful attempts excluded in both cohorts | 15 | 66 | 405 | 309 | 5.77 (3.23–10.3) | NR | NA |
| | " | Matched cohorts, unsuccessful attempts excluded in both cohorts | 9 | 48 | 17 | 40 | 2.27 (0.91–5.63) | NR | GCS, H-AIS, ISS group, significant associated injuries, age group, mechanism of injury, transport |
| Poste (2004) [49] | Hospital discharge | Ground transported patients | 172[c] | 85[c] | 406[c] | 108[c] | 1.86 (1.33–2.60) | NR | Age, gender, mechanism of injury, trauma centre, ISS, H-AIS, AIS for face, chest, abdomen, extremities and skin |
| | " | Air transported patients | 57[c] | 22[c] | 109[c] | 49[c] | 0.86 (0.47–1.56) | NR | " |
| Singbartl (1985) [50] | NR | NA | 48 | 45 | 31 | 23 | 1.26 (0.64–2.48) | NR | NA |
| Sloane (2000) [51] | Within 30 days after trauma | NA | 18 | 3 | 42 | 12 | 0.58 (0.15–2.32) | NR | NA |
| Tuma (2014) [52] | Within 30 days after admission | NA | 48[c] | 57[c] | 38[c] | 17[c] | 2.65 (1.33–5.29) | 0.55 (0.24–1.26) | Age, ISS, motor GCS, EMS time |
| Vandromme (2011) [53] | NR | NA | 34[c] | 30[c] | 42[c] | 29[c] | 1.28 (0.65–2.53) | NR | ED-GCS, ED SBP, ISS |
| Wang (2004) [55] | Hospital discharge | NA | 926 | 871 | 1652 | 649 | 2.39 (2.10–2.73) | 3.99 (3.21–4.93) | Age, sex, H-AIS, ISS, other severe injury, admission SBP, mechanism of injury, use of neuromuscular blocking agents, and a propensity score summarizing selected pre-existing medical conditions, social variables and in-hospital events. |
| Wang (2014) [54] | Within 28 days of after trauma | NA | 558 | 206 | 259 | 93 | 1.03 (0.77–1.37) | 1.57 (0.93–2.64) | Age, sex, ISS, mechanism of injury, initial SBP, initial GCS, highest field heart rate, out-of-hospital neuromuscular blockade use, mode of transport, H-AIS, parent trial intervention arm, study site |
| Winchell (1997) [56] | Hospital discharge | GCS ≤ 8, ground transport | 418 | 147 | 336 | 191 | 0.62 (0.48–0.80) | NR | NA |
| | " | GCS ≤ 8 and H-AIS ≥ 4, ground transport | 249 | 138 | 121 | 163 | 0.41 (0.30–0.56) | " | " |
| | " | GCS ≤ 8 and H-AIS ≥ 4, isolated TBI, ground transport | 159 | 47 | 73 | 72 | 0.30 (0.19–0.47) | " | " |
| | " | GCS = 3 and H-AIS ≥ 4, isolated TBI, ground transport | 53 | 37 | 27 | 59 | 0.32 (0.17–0.59) | " | " |
| | " | GCS = 4–8 and H-AIS ≥ 4, isolated TBI, ground transport | 106 | 10 | 46 | 13 | 0.33 (0.14–0.82) | " | " |
| | " | GCS ≤ 8, air transport | 280[c] | 151[c] | 56[c] | 15[c] | 2.01 (1.10–3.68) | " | " |
| | " | GCS ≤ 8 and H-AIS ≥ 4, air transport | 177[c] | 134[c] | 21[c] | 8[c] | 1.99 (0.85–4.62) | NR | NA |
| | " | GCS ≤ 8 and H-AIS ≥ 4, air transport | 80[c] | 36[c] | 13[c] | 4[c] | 1.46 (0.45–4.80) | " | " |

(*Continued*)

**Table 5.** (*Continued*)

| First author (year) | Time of mortality assessment | Sub-Analysis | Intervention | | Control | | Unadjusted OR (95% CI) | Adjusted OR (95% CI)[d] | Factors used for adjustment or matching |
|---|---|---|---|---|---|---|---|---|---|
| | | | Alive | Dead | Alive | Dead | | | |
| | " | GCS = 3 and H-AIS ≥ 4, isolated TBI, air transport | 22[c] | 24[c] | 2[c] | 2[c] | 1.09 (0.14–8.42) | " | " |
| | " | GCS = 4–8 and H-AIS ≥ 4, isolated TBI, air transport | 58[c] | 12[c] | 11[c] | 2[c] | 1.14 (0.22–5.81) | " | " |

[a] Time of mortality assessment is not explicitly mentioned. However, we strongly assume that it is hospital mortality because no follow-up beyond hospital discharge is reported. For the studies by Davis and colleagues, this assumption is further underlined by the fact that other studies that have been performed by the same study group in the same patient population also regularly report hospital mortality. Requests to the authors to clarify this issue have remained unanswered.

[b] Personal communication by the first author.

[c] Calculated from reported percentages. May not necessarily be exactly the actual number due to rounding or unreported omission of patients from the analysis.

[d] Calculation of the adjusted odds ratio may not necessarily be based on the same number of patients used for calculation of the unadjusted OR (e.g., due to missing covariates in some patients).

(H-)AIS: (head) abbreviated injury scale

CI: confidence interval

ED: emergency department

EMS: emergency medical services

GCS: Glasgow Coma Scale

ICU: intensive care unit

ISS: injury severity scale

NA: not applicable

NR: not reported

OR: odds ratio

SBP: systolic blood pressure

TBI: traumatic brain injury

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do report complications report different kinds of complications, precluding meaningful comparisons across studies. Functional recovery was infrequently reported and different ordinal scales or dichotomous scores such as "good" or "favourable" outcome were used. Follow-up periods for assessment of functional recovery were extremely variable, ranging from hospital discharge [37, 38, 41, 55, 56] to one year after the trauma [47], which additionally complicates comparison of functional outcome data across studies.

In this context, it must be mentioned that timing of mortality assessment was also not the same across studies. Among the six studies included in our meta-analysis, five report hospital mortality [33, 40, 42, 45, 48] and one reports mortality within 30 days [52]. We believe that these data can be meaningfully combined, because most patients who die in hospital commonly die within 30 days, and most patients who survive until hospital discharge will likely be alive at 30 days. As the sensitivity analysis shows, excluding the study that uses 30-day mortality and using only those studies that report hospital mortality would not alter any of the conclusions on the relationship between PHI and mortality.

A limitation of our systematic review is that the patient populations and treatments were not exactly the same across studies. We included not only studies reporting patients with confirmed TBI, but also studies in which TBI was suspected based on the GCS score in combination with trauma mechanism and/or and clinical findings. Prehospital healthcare providers do
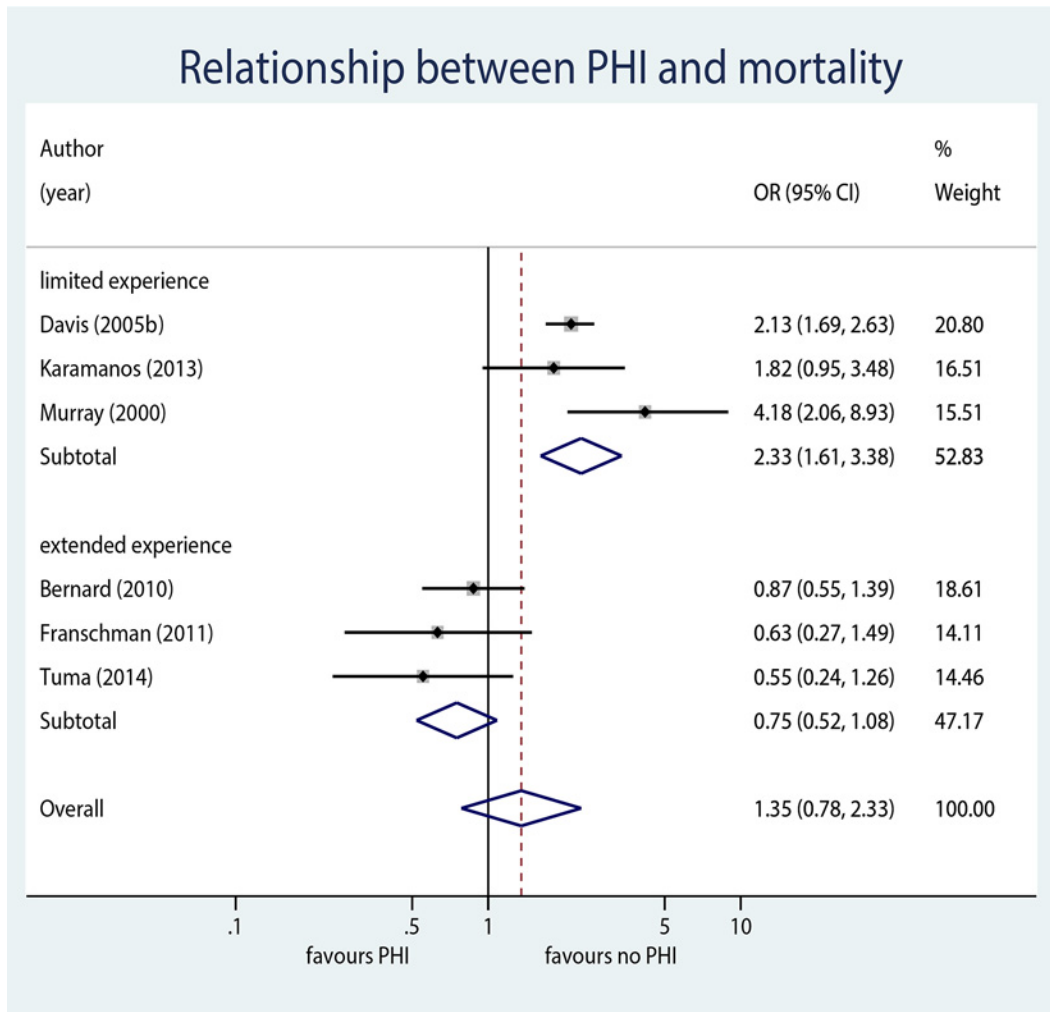
**Fig 2. Forrest plot.** Forrest plot summarizing the individual studies and pooled results of the meta-analysis. The relationship between prehospital intubation (PHI) and mortality is stratified by experience of prehospital healthcare providers.

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not know the actual diagnosis but have to treat patients based on the suspected diagnosis, and therefore, including these studies makes the results more applicable to the real-life situation. Other differences in in- and exclusion criteria, geographical differences, and differences in how the intubations were performed (with or without anaesthetic drugs) can all introduce heterogeneity and bias. We therefore used a random-effects model for the meta-analysis to accommodate for such heterogeneity, and indeed, substantial heterogeneity was observed. However, most of the heterogeneity vanished after adjusting for EMS-provider experience in the meta-regression, indicating that experience is the single most important factor in explaining those differences between the studies that are not attributable to chance.

It was necessary to assign a level of experience to each study. Experience is rather abstract and difficult to quantify, and we therefore used the pragmatic approach to dichotomize experience as "limited" or "extended". To avoid bias due to misclassification, three investigators performed this assessment and a level was assigned by unanimous consensus. With this careful approach, we can exclude that any study in which EMS-provider experience was actually "limited" may have been misclassified as "extended" experience or vice versa. The sensitivity

**Table 6. Sensitivity analysis.**

| Study excluded | N total | Limited experience stratum | | Extended experience stratum | | Total | | Heterogeneity I² | | Metaregression |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | | OR (95% CI) | p-value | OR (95% CI) | p-value | OR (95% CI) | p-value | overall | residual | p-value |
| None | 4772 | 2.33 (1.61–3.38) | < 0.001 | 0.75 (0.52–1.08) | 0.126 | 1.35 (0.78–2.33) | 0.279 | 83.3 | 10.3 | 0.009 |
| Davis (2005b) [40] | 1822 | 2.71 (1.20–6.12) | 0.017 | 0.75 (0.52–1.08) | 0.126 | 1.20 (0.60–2.37) | 0.606 | 80.1 | 22.7 | 0.040 |
| Karamanos (2013) [45] | 4552 | 2.72 (1.44–5.12) | 0.002 | 0.75 (0.52–1.08) | 0.126 | 1.27 (0.65–2.45) | 0.484 | 86.6 | 26.5 | 0.030 |
| Murray (2000) [48] | 3977 | 2.10 (1.70–2.58) | < 0.001 | 0.75 (0.52–1.08) | 0.126 | 1.10 (0.62–1.97) | 0.741 | 83.3 | 0.0 | 0.018 |
| Bernard (2010) [33] | 4460 | 2.33 (1.61–3.38) | < 0.001 | 0.59 (0.33–1.06) | 0.079 | 1.49 (0.81–2.74) | 0.195 | 80.5 | 11.9 | 0.030 |
| Franschman (2011) [42] | 4437 | 2.33 (1.61–3.38) | < 0.001 | 0.78 (0.52–1.17) | 0.234 | 1.53 (0.87–2.71) | 0.140 | 83.6 | 29.6 | 0.036 |
| Tuma (2014) [52] | 4612 | 2.33 (1.61–3.38) | < 0.001 | 0.81 (0.54–1.22) | 0.314 | 1.58 (0.91–2.73) | 0.103 | 82.1 | 20.8 | 0.031 |

CI: Confidence interval

OR: Odds ratio

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analysis suggests that the conclusions of our study are robust against a possible misclassification of any study that should in fact actually have been classified as "indeterminate".

The funnel plot regression asymmetry test did not provide evidence for small study bias. However, due to the rather small number of studies included in the meta-analysis and the limited power of such tests to detect bias at this sample size, we cannot completely exclude the possibility that our results might be affected by small study bias.

## Clinical implications

According to the "ABCDE" (Airway, Breathing, Circulation, Disability, Exposure) approach used in advanced trauma life support, securing the airway is a top priority in trauma patients with a threatened airway [59]. Patients with severe TBI have a high incidence of airway obstruction and hypoxia at the accident scene [10, 11], and there is a broad consensus that adequate prehospital airway management is crucial to prevent secondary injury [8]. Traditionally, early endotracheal intubation–as the gold standard of airway management–has been advocated for TBI patients with a GCS score ≤ 8, but this dogma is currently being challenged by publications that suggest higher mortality in patients who are prehospitally intubated. Von Elm and colleagues have previously addressed the relationship between PHI and mortality in a systematic review that included studies published up to 2007, and found that the available evidence was insufficient to allow recommendations on whether patients should or should not be intubated in the field [22]. Since then, several studies on the topic have been published. Our systematic review contains eight studies published after 2007, and four of the six studies in our meta-analysis were published in the last five years. Moreover, the previous systematic review did not address possible effects of EMS-provider experience, warranting the present investigation.

In line with the conclusions by Von Elm and colleagues, the pooled overall result of our meta-analysis provides no evidence for or against PHI, and does not allow an answer to the general question whether patients with severe TBI should be intubated in the field. However, we believe that the general overall effect is clinically less relevant because PHI may likely be either beneficial or detrimental, depending on the way it is performed, depending on side effects and complications, and depending on the ventilation strategy following intubation. Hence, an answer to the question whether or not to perform PHI should address additional factors that have previously received insufficient attention.

We hypothesized that the intubation skill of the EMS-provider is such a factor, because the incidence of adverse events related to poor intubation and ventilation performance may likely be higher when the intervention is performed by providers who are not well trained to do so. Indeed, our data provide strong evidence that PHI by EMS-providers with limited experience in performing intubations is associated with an approximately twofold increase in the odds of mortality. This suggests that the practice of routinely intubating patients with severe TBI should be abandoned in EMS systems in which providers have limited skills in performing this intervention.

We did not observe a clear association between PHI and mortality when intubation is performed by providers with extended experience. Additional studies are needed to assess whether the observed trend towards better survival is truly a contribution to better outcome or merely a play of chance. Such studies should preferably be adequately powered randomized controlled trials to test the null-hypothesis that prehospital intubation by personnel with ample experience in airway management has no effect on mortality (and possibly other outcomes such as functional recovery) in patients with severe TBI. Herein, the group of healthcare providers who perform intubations, the intubating technique including drugs used to facilitate intubation, as well as the ventilation targets following intubation should be well defined to minimize confounding. Patients with severe TBI form a heterogeneous group. Hence, such a study should either focus on a specific group of patients with well defined characteristics, or specific subgroups need to be defined a priori to allow analyses on whether the effects of prehospital intubation differ depending on patient and injury characteristics.

## Conclusions

Effects of PHI on mortality depend on the EMS-providers' skill. Prehospital intubation by providers with limited experience is associated with increased mortality, and such providers should not routinely perform PHI in TBI patients. Additional studies are needed to determine the relationship between PHI and mortality when intubation is performed by more experienced personnel.

## Supporting Information

**S1 PRISMA Checklist. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.**
(DOC)

**S1 Prospero Protocol. Prospective Register of Systematic Reviews (PROSPERO) protocol number CRD42014015506.**
(PDF)

## Author Contributions

## References

1. Langlois JA, Rutland-Brown W, Wald MM. The epidemiology and impact of traumatic brain injury: a brief overview. J Head Trauma Rehabil. 2006; 21: 375–8. PMID: 16983222

2. Maas AI, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. Lancet Neurol. 2008; 7: 728–41. doi: 10.1016/S1474-4422(08)70164-9 PMID: 18635021

3. McMillan TM, Teasdale GM, Stewart E. Disability in young people and adults after head injury: 12–14 year follow-up of a prospective cohort. J Neurol Neurosurg Psychiatry. 2012; 83: 1086–91. doi: 10.1136/jnnp-2012-302746 PMID: 22645256

4. Reilly P. The impact of neurotrauma on society: an international perspective. Prog Brain Res. 2007; 161: 3–9. PMID: 17618966

5. Tagliaferri F, Compagnone C, Korsic M, Servadei F, Kraus J. A systematic review of brain injury epidemiology in Europe. Acta Neurochir (Wien). 2006; 148: 255–68.

6. Thornhill S, Teasdale GM, Murray GD, McEwen J, Roy CW, Penny KI. Disability in young people and adults one year after head injury: prospective cohort study. BMJ. 2000; 320: 1631–5. PMID: 10856063

7. Tuominen R, Joelsson P, Tenovuo O. Treatment costs and productivity losses caused by traumatic brain injuries. Brain Inj. 2012; 26: 1697–701. doi: 10.3109/02699052.2012.722256 PMID: 23163250

8. Boer C, Franschman G, Loer SA. Prehospital management of severe traumatic brain injury: concepts and ongoing controversies. Curr Opin Anaesthesiol. 2012; 25: 556–62. doi: 10.1097/ACO.0b013e328357225c PMID: 22821147

9. Badjatia N, Carney N, Crocco TJ, Fallat ME, Hennes HM, Jagoda AS, et al. Guidelines for prehospital management of traumatic brain injury 2nd edition. Prehosp Emerg Care. 2008; 12 Suppl 1: S1–52. doi: 10.1080/10903120701732052 PMID: 18203044

10. Hussain LM, Redmond AD. Are pre-hospital deaths from accidental injury preventable? BMJ. 1994; 308: 1077–80. PMID: 8173428

11. Stocchetti N, Furlan A, Volta F. Hypoxemia and arterial hypotension at the accident scene in head injury. J Trauma. 1996; 40: 764–7. PMID: 8614077

12. Bratton SL, Chestnut RM, Ghajar J, McConnell Hammond FF, Harris OA, Hartl R, et al. Guidelines for the management of severe traumatic brain injury. I. Blood pressure and oxygenation. J Neurotrauma. 2007; 24 Suppl 1: S7–13. PMID: 17511549

13. Hammell CL, Henning JD. Prehospital management of severe traumatic brain injury. BMJ. 2009; 338: b1683. doi: 10.1136/bmj.b1683 PMID: 19454738

14. Safar P, Escarraga LA, Chang F. Upper airway obstruction in the unconscious patient. J Appl Physiol. 1959; 14: 760–4. PMID: 14440737

15. Boidin MP. Airway patency in the unconscious patient. Br J Anaesth. 1985; 57: 306–10. PMID: 3978013

16. Moulton C, Pennycook A, Makower R. Relation between Glasgow coma scale and the gag reflex. BMJ. 1991; 303: 1240–1. PMID: 1747645

17. Lockey DJ, Coats T, Parr MJA. Aspiration in severe trauma: a prospective study. Anaesthesia. 1999; 54: 1097–8. PMID: 10540100

18. Atkinson JL. The neglected prehospital phase of head injury: apnea and catecholamine surge. Mayo Clin Proc. 2000; 75: 37–47. PMID: 10630756

19. Blyth A. Thoracic Trauma. Bmj-Brit Med J. 2014;348.

20. Humphries RL. Head Injuries. In: Stone CK, Humphries RL, editors. Current Diagnosis & Treatment Emergency Medicine. 6 ed. New York: Mc Graw Hill; 2008. p. 313–27.

21. Salomone JP, Salomone JA. Prehospital Care. In: Feliciano DV, Mattox KL, Moore EE, editors. Trauma. 6 ed. New York: Mc Graw Hill; 2008. p. 121–38.

22. von Elm E, Schoettker P, Henzi I, Osterwalder J, Walder B. Pre-hospital tracheal intubation in patients with traumatic brain injury: systematic review of current evidence. Br J Anaesth. 2009; 103: 371–86. doi: 10.1093/bja/aep202 PMID: 19648153

23. Davis DP. Prehospital intubation of brain-injured patients. Curr Opin Crit Care. 2008; 14: 142–8. doi: 10.1097/MCC.0b013e3282f63c40 PMID: 18388675

24. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009; 62: e1–34. doi: 10.1016/j.jclinepi.2009.06.006 PMID: 19631507

25. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009; 339: b2535. doi: 10.1136/bmj.b2535 PMID: 19622551

26. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000; 283: 2008–12. PMID: 10789670

27.  Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [cited 2014 30.12.2014]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

28.  Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011; 343: d5928. doi: 10.1136/bmj.d5928 PMID: 22008217

29.  DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986; 7: 177–88. PMID: 3802833

30.  Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002; 21: 1539–58. PMID: 12111919

31.  Harbord RM, Higgins JP. Meta-regression in STATA. The Stata Journal. 2008; 4: 493–519.

32.  Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315: 629–34. PMID: 9310563

33.  Bernard SA, Nguyen V, Cameron P, Masci K, Fitzgerald M, Cooper DJ, et al. Prehospital rapid sequence intubation improves functional outcome for patients with severe traumatic brain injury: a randomized controlled trial. Ann Surg. 2010; 252: 959–65. doi: 10.1097/SLA.0b013e3181efc15f PMID: 21107105

34.  Bochicchio GV, Ilahi O, Joshi M, Bochicchio K, Scalea TM. Endotracheal intubation in the field does not improve outcome in trauma patients who present without an acutely lethal traumatic brain injury. J Trauma. 2003; 54: 307–11. PMID: 12579056

35.  Bukur M, Kurtovic S, Berry C, Tanios M, Margulies DR, Ley EJ, et al. Pre-hospital intubation is associated with increased mortality after traumatic brain injury. J Surg Res. 2011; 170: e117–21. doi: 10.1016/j.jss.2011.04.005 PMID: 21601884

36.  Davis DP, Dunford JV, Poste JC, Ochs M, Holbrook T, Fortlage D, et al. The impact of hypoxia and hyperventilation on outcome after paramedic rapid sequence intubation of severely head-injured patients. J Trauma. 2004; 57: 1–8. PMID: 15284540

37.  Davis DP, Hoyt DB, Ochs M, Fortlage D, Holbrook T, Marshall LK, et al. The effect of paramedic rapid sequence intubation on outcome in patients with severe traumatic brain injury. J Trauma. 2003; 54: 444–53. PMID: 12634522

38.  Davis DP, Idris AH, Sise MJ, Kennedy F, Eastman AB, Velky T, et al. Early ventilation and outcome in patients with moderate to severe traumatic brain injury. Crit Care Med. 2006; 34: 1202–8. PMID: 16484927

39.  Davis DP, Peay J, Serrano JA, Buono C, Vilke GM, Sise MJ, et al. The impact of aeromedical response to patients with moderate to severe traumatic brain injury. Ann Emerg Med. 2005; 46: 115–22. PMID: 16046940

40.  Davis DP, Peay J, Sise MJ, Vilke GM, Kennedy F, Eastman AB, et al. The impact of prehospital endotracheal intubation on outcome in moderate to severe traumatic brain injury. J Trauma. 2005; 58: 933–9. PMID: 15920406

41.  Davis DP, Stern J, Sise MJ, Hoyt DB. A follow-up analysis of factors associated with head-injury mortality after paramedic rapid sequence intubation. J Trauma. 2005; 59: 484–88.

42.  Franschman G, Peerdeman SM, Andriessen TM, Greuters S, Toor AE, Vos PE, et al. Effect of secondary prehospital risk factors on outcome in severe traumatic brain injury in the context of fast access to trauma care. J Trauma. 2011; 71: 826–32. doi: 10.1097/TA.0b013e31820cebf0 PMID: 21427618

43.  Härtl R, Gerber LM, Iacono L, Ni Q, Lyons K, Ghajar J. Direct transport within an organized state trauma system reduces mortality in patients with severe traumatic brain injury. J Trauma. 2006; 60: 1250–6. PMID: 16766968

44.  Irvin CB, Szpunar S, Cindrich LA, Walters J, Sills R. Should trauma patients with a Glasgow Coma Scale score of 3 be intubated prior to hospital arrival? Prehosp Disaster Med. 2010; 25: 541–6. PMID: 21181689

45.  Karamanos E, Talving P, Skiada D, Osby M, Inaba K, Lam L, et al. Is prehospital endotracheal intubation associated with improved outcomes in isolated severe head injury? A matched cohort analysis. Prehosp Disaster Med. 2014; 29: 32–6. doi: 10.1017/S1049023X13008947 PMID: 24330753

46.  Klemen P, Grmec S. Effect of pre-hospital advanced life support with rapid sequence intubation on outcome of severe traumatic brain injury. Acta Anaesthesiol Scand. 2006; 50: 1250–4. PMID: 17067325

47.  Lenartova L, Janciak I, Wilbacher I, Rusnak M, Mauritz W, Austrian Severe TBISI. Severe traumatic brain injury in Austria III: prehospital status and treatment. Wien Klin Wochenschr. 2007; 119: 35–45. PMID: 17318749

48.  Murray JA, Demetriades D, Berne TV, Stratton SJ, Cryer HG, Bongard F, et al. Prehospital intubation in patients with severe head injury. J Trauma. 2000; 49: 1065–70. PMID: 11130490

49. Poste JC, Davis DP, Ochs M, Vilke GM, Castillo EM, Stern J, et al. Air medical transport of severely head-injured patients undergoing paramedic rapid sequence intubation. Air Med J. 2004; 23: 36–40.

50. Singbartl G. Die Bedeutung der präklinischen Notfallversorgung für die Prognose von Patienten mit schwerem Schädel-Hirn-Trauma. Anasth Intensivther Notfallmed. 1985; 20: 251–60. PMID: 4083432

51. Sloane C, Vilke GM, Chan TC, Hayden SR, Hoyt DB, Rosen P. Rapid sequence intubation in the field versus hospital in trauma patients. J Emerg Med. 2000; 19: 259–64. PMID: 11033272

52. Tuma M, El-Menyar A, Abdelrahman H, Al-Thani H, Zarour A, Parchani A, et al. Prehospital intubation in patients with isolated severe traumatic brain injury: a 4-year observational study. Crit Care Res Pract. 2014; 2014: 135986. doi: 10.1155/2014/135986 PMID: 24527211

53. Vandromme MJ, Melton SM, Griffin R, McGwin G, Weinberg JA, Minor M, et al. Intubation patterns and outcomes in patients with computed tomography-verified traumatic brain injury. J Trauma. 2011; 71: 1615–9. doi: 10.1097/TA.0b013e31822a30a1 PMID: 21841511

54. Wang HE, Brown SP, MacDonald RD, Dowling SK, Lin S, Davis D, et al. Association of out-of-hospital advanced airway management with outcomes after traumatic brain injury and hemorrhagic shock in the ROC hypertonic saline trial. Emerg Med J. 2014; 31: 186–91. doi: 10.1136/emermed-2012-202101 PMID: 23353663

55. Wang HE, Peitzman AB, Cassidy LD, Adelson PD, Yealy DM. Out-of-hospital endotracheal intubation and outcome after traumatic brain injury. Ann Emerg Med. 2004; 44: 439–50. PMID: 15520702

56. Winchell RJ, Hoyt DB. Endotracheal intubation in the field improves survival in patients with severe head injury. Trauma Research and Education Foundation of San Diego. Arch Surg. 1997; 132: 592–7. PMID: 9197850

57. Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. N Engl J Med. 2000; 342: 1878–86. PMID: 10861324

58. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. N Engl J Med. 2000; 342: 1887–92. PMID: 10861325

59. American College of Surgeons Committee on Trauma. Advanced Trauma Life Support. 9 ed. Chicago, USA: American College of Surgeons 2012.