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Prehospital Management of Traumatic Brain Injury across Europe: A CENTER-TBI Study

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Abstract

Background: Prehospital care for traumatic brain injury (TBI) is important to prevent secondary brain injury. We aim to compare prehospital care systems within Europe and investigate the association of system characteristics with the stability of patients at hospital arrival. **Methods:** We studied TBI patients who were transported to CENTER-TBI centers, a pan-European, prospective TBI cohort study, by emergency medical services between 2014 and 2017. The association of demographic factors, injury severity, situational factors, and interventions associated with on-scene time was assessed using linear regression. We used mixed effects models to investigate the case mix adjusted variation between countries in prehospital times and interventions. The case mix adjusted impact of on-scene time and interventions on hypoxia (oxygen saturation <90%) and hypotension (systolic blood pressure <100mmHg) at hospital arrival was analyzed with logistic regression. **Results:** Among 3878 patients, the greatest driver of longer on-scene time was intubation (+8.3 min, 95% CI: 5.6–11.1). Secondary referral was associated with shorter on-scene time (-5.0 min 95% CI: −6.2–−3.8). Between countries, there was a large variation in response (range: 12–25 min), on-scene (range: 16-36 min) and travel time (range: 15–32 min) and in prehospital interventions. These variations were not explained by patient factors such as conscious level or severity of injury (expected OR between countries: 1.8 for intubation, 1.8 for IV fluids, 2.0 for helicopter). On-scene time was not associated with the regional EMS policy (p = 0.58). Hypotension and/or hypoxia were seen in 180 (6%) and 97 (3%) patients in the overall cohort and in 13% and 7% of patients with severe TBI (GCS <8). The largest association with secondary insults at hospital arrival was with major extracranial injury: the OR was 3.6 (95% CI: 2.6–5.0) for hypotension and 4.4 (95% CI: 2.9–6.7) for hypoxia. **Discussion:** Hypoxia and hypotension continue to occur in patients who suffer a TBI, and remain relatively common in severe TBI. Substantial variation in prehospital care exists for patients after TBI in Europe, which is only partially explained by patient factors. **Key words:** traumatic brain injury; prospective; guidelines; practice; prehospital care

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Introduction

Traumatic brain injury (TBI) remains an important cause of death and disability globally (1). Although

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rates vary between countries, TBI is estimated to be responsible for around 300 hospital admissions and 12 deaths per 100,000 persons per year in Europe (2).

After the initial TBI, secondary insults, such as hypotension, hypoxia and intracranial hypertension may worsen the brain damage (3,4). Prehospital care for TBI focuses on preventing secondary brain injury by on-scene stabilization and rapid transportation to an appropriate hospital. There is no universally accepted and implemented international guideline aimed at avoiding secondary injury in the prehospital environment. While national guidelines do exist, these vary substantially. Moreover, the extent to which they are adopted and implemented is unclear, since real-life data on international variations in prehospital care are limited. Provider profiling of study centers in the CENTER TBI study (5–7), a large prospective observational cohort study of TBI across Europe and Israel, highlighted substantial reported variation in advanced life support capability of prehospital staff, degree of preference for stabilizing on scene versus immediate transport, and in preferred destination from scene (specialist center versus nearest hospital) (6). However, these reported preferences were based on clinicians' reports of local protocols rather than objective patient data.

Objective assessment of such data is important. There is a tradeoff between prehospital stabilization and prompt transportation to hospital. Stabilizing the patient in the prehospital environment with complex interventions can cause an important time delay reaching the hospital and starting appropriate diagnostic and tailored treatments. This delay could worsen outcome (8). Conversely other studies suggest that stabilizing patients on-scene for transportation to more distant specialist centers could improve outcomes (9–12). The decision between prehospital stabilization and immediate transport is made on-scene by prehospital staff based on clinical parameters, injury characteristics, skill levels available and the local policy.

The current study aimed to compare prehospital management of patients with TBI across Europe, and to investigate the association of prehospital care system characteristics with stability of patients at Emergency Department (ED) arrival.

METHODS

This study is reported according to the STROBE reporting guidelines (13). Ethical approval was obtained from all local institutional revision boards, according to various national standards (https://www.center-tbi.eu/project/ethical-approval).

Study Design

CENTER-TBI is a multicenter, longitudinal, prospective, observational study in 18 countries across Europe which enrolled patients between December 2014 and December 2017 (5). The core cohort includes patients presenting within 24 hours of injury, with a clinical diagnosis of TBI and an indication for computed tomography (6). Analyses in this manuscript were undertaken on the CENTER-TBI dataset (version 2.0), and accessed using a bespoke data management tool, Neurobot (details available on the SciCrunch Resource Identification Portal, using the Research Resource Identifier RRID/SCR_017004).

Prehospital data were collected by physicians and researchers at participating study centers. Unfortunately, no data was available on prehospital physiology. Response time was defined as time between injury and arrival of first EMS crew. On scene time was defined as time between first EMS crew arrival until the conveying crew left the injury scene. Travel time was the time between patient leaving the scene and arrival at first hospital (14). Major extracranial injury (MEI) was defined as any injury in all areas except head with an Abbreviated Injury Score (AIS) above 3.

Patient Selection

Patients with TBI who were transported by ambulance or helicopter to participating hospitals (n = 56), either directly or by secondary transfer, were included. For the center-level analysis, secondary transfer patients were excluded.

Statistical Analysis

We first compare baseline characteristics between patients that were immediately transported or that were stabilized on scene. This distinction was based on an a-priori defined cutoff of 20 minutes on scene. These two groups (patients who were immediately transported and those who were stabilized on scene) were compared concerning baseline characteristics. Continuous variables were described by the median and interquartile range (IQR). Categorical variables were described by the number of patients and the corresponding percentage.

Second, the drivers of on-scene time, as a continuous variable, were assessed using linear regression. The included predictors were demographic factors (age, sex), severity (GCS, pupil reactivity, major extracranial injury), situational factors (travel time – as proxy to travel distance, physician at scene, road traffic incident, high energy trauma), and interventions (intubation, IV fluids, CPR, ventilation). Within this analysis, we also assessed the adjusted between-country variation in prehospital times and prehospital interventions with mixed effects modeling. A random intercept for centers was applied to correct for between center differences. To assess the effect of between-center differences, the partial R^2 for the random intercept was calculated by comparing the R^2 of the model with and without random intercept.

Third, the adjusted impact of on-scene times and prehospital interventions (intubation, ventilation, IV fluids, secondary referral) on hypoxia (Saturation <90%) and hypotension (Systolic Blood Pressure <100mmHg) at arrival was assessed with a logistic regression. We adjusted for the following patient characteristics: age, GCS, pupil reactivity, major extracranial injury (15). We also measured the influence of these surrogate prehospital endpoints on functional outcome using ordinal logistic regression, which was adjusted for the aforementioned patient characteristics and utilized the imputed optimized 6-month Extended Glasgow Outcome Scale (GOS-E (6)) as the dependent variable. We allowed for a non-linear effect of systolic blood pressure and saturation with restricted cubic splines (3 degrees of freedom).

Fourth, the unadjusted and adjusted between country variation in prehospital times and rates of prehospital interventions (prehospital intubation, IV fluids, helicopter usage) across Europe were illustrated. Bar charts depict unadjusted variation whilst the aforementioned mixed effects model enabled illustration of adjusted variation. Values of the random intercept for country were visually depicted on a map of Europe. Furthermore, the variation was adjusted for the core variables of the prediction model developed in the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) study (age, number of reactive pupils, and Glasgow Coma Score at baseline) (15), and the CENTER-TBI stratum (ER/Admission/ICU) in which the patient was enrolled. Also, the median odds ratio (OR) was calculated, which quantifies the expected OR - of interventions performed or times taken - when two randomly picked countries are compared (16).

Additionally, the adjusted on-scene times were compared across centers which had indicated that they have a policy of immediate transportation, or a policy of stabilizing on scene based on the Provider Profiling questionnaires (17). Therefor mixed effects models were applied, with on-scene time as dependent variable, indicating on-scene policy as independent variable and country as random intercept. The on-scene times were adjusted for GCS, travel time to study center, intubation, pupils and sex.

The effects of continuous predictors were presented as the odds ratio for comparing the 75^{th} and the 25^{th} percentile of the specific variable. This was calculated by multiplying the regression coefficient and standard error by the width of the interquartile range of that variable.

We performed the multiple imputation method to impute the covariates for all regression analyses using the *mice* package in R. The following covariates were included in the imputation model: age, pupil reactivity, GCS, MEI, sex, prehospital intubation, IV fluids, CPR, ventilation, secondary referral and helicopter usage. The percentage of missing data can be found in Table 1. These results were compared with complete case analysis as a sensitivity analysis. The results of the complete case analysis of each analysis are shown in the supplemental material.

All analyses were performed using R (R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). The code applied can be found on https://github.com/bgravesteijn/Code_Core_prehospital.

Results

We included 3878 patients from 56 centers in 17 European Countries from a total of 4509 patients enrolled into the core CENTER TBI study. Patients who had self-presented to hospital without EMS activation (n = 616) or where prehospital details were missing or misreported (one country systematically misreported times, n = 15), were excluded (Figure S1).

On-Scene Time

The median on-scene time was 22 (IQR: 15-32) minutes, with 1744 (45%) patients having an on-scene time of less than 20 minutes, and 2118 (55%) more than 20 minutes (Table 1). Patients with TBI and longer on-scene times were more severely injured (GCS, pupil reactivity, MEI) and had more complex prehospital interventions (CPR, IV fluids, intubation and ventilation). The two characteristics with the largest association with longer on-scene time were prehospital tracheal intubation (+8.3 min, 95% CI: 5.6-11.1), and secondary referral (-5.0 min, 95% CI: −6.2 - −3.8). Other characteristics with

TABLE 1. Descriptive analysis of patients who received a short on-scene time (<20 min), or long on-scene time (>20 min)

	Overall	On-scene time "Short", <20 min, n = 1744	"Long", >20 min, n = 2118	p	Missing %
Age (median [IQR])	51 [31, 67]	52 [31, 67]	50 [31, 67]	0.518	0.0
Male (%)	2647 (68.3)	1125 (64.5)	1511 (71.3)	<0.001	0.0
MEI (%)	670 (17.3)	209 (12.0)	456 (21.5)	<0.001	0.0
Cause (%)				0.081	10
RTI	1589 (45.6)	699 (44.8)	883 (46.3)		
Fall	1657 (47.5)	756 (48.4)	895 (46.9)		
Violence	191 (5.5)	92 (5.9)	97 (5.1)		
Intentional self-harm	48 (1.4)	14 (0.9)	34 (1.8)		
Type (%)				0.020	1
Closed	3702 (96.5)	1683 (97.4)	2004 (95.7)		
Blast	5 (0.1)	3 (0.2)	2 (0.1)		
Crush	91 (2.4)	27 (1.6)	63 (3.0)		
Penetrating	39 (1.0)	15 (0.9)	24 (1.1)		
Rural area (%)	742 (19.9)	235 (14.0)	502 (24.6)	<0.001	4
Place (%)				0.001	2
Street	2070 (54.6)	985 (57.5)	1077 (52.2)		
Home	941 (24.8)	381 (22.2)	557 (27.0)		
Work/school	240 (6.3)	94 (5.5)	146 (7.1)		
Sport	236 (6.2)	106 (6.2)	129 (6.3)		
Military	2 (0.1)	0 (0.0)	2 (0.1)		
Public location	303 (8.0)	148 (8.6)	152 (7.4)		
Highest trained bystander (%)				<0.001	0.5
None	33 (0.9)	5 (0.3)	27 (1.3)		
Bystander	23 (0.6)	17 (1.0)	6 (0.3)		
Paramedic	1173 (30.4)	664 (38.3)	503 (23.9)		
Nurse	658 (17.1)	400 (23.1)	258 (12.3)		
Physician	1044 (27.1)	456 (26.3)	583 (27.7)		
Medical rescue team	926 (24.0)	193 (11.1)	729 (34.6)		
Secondary referral (%)	594 (15.3)	352 (20.2)	241 (11.4)	<0.001	0.0
Arrival Method (%)				<0.001	0.0
Ambulance	3141 (81.0)	1585 (90.9)	1547 (73.0)		
Helicopter	483 (12.5)	97 (5.6)	381 (18.0)		
Mobile medical team	254 (6.5)	62 (3.6)	190 (9.0)		
GCS motor, baseline (median [IQR])	6 [4, 6]	6 [6, 6]	6 [2, 6]	<0.001	2
GCS, baseline(median [IQR])	14 [8, 15]	15 [13, 15]	13 [6, 15]	<0.001	4
Pupils, baseline (%)				<0.001	5
Two reactive	3273 (88.7)	1545 (92.7)	1717 (85.4)		
One reactive	150 (4.1)	53 (3.2)	96 (4.8)		
None reactive	269 (7.3)	69 (4.1)	197 (9.8)		
CPR (%)	51 (1.3)	10 (0.6)	40 (1.9)	0.001	0.0
IV Fluids (%)	1469 (37.9)	442 (25.3)	1019 (48.1)	<0.001	0.0
Intubation (%)	885 (23.7)	123 (7.4)	754 (36.7)	<0.001	4
Supplemental oxygen (%)	1612 (46.3)	485 (31.8)	1118 (57.5)	<0.001	10
Ventilation (%)	815 (22.0)	114 (6.9)	693 (34.1)	<0.001	4
On-scene time (median [IQR])	22 [15, 32]	14 [10, 17]	30 [25, 40]	<0.001	0.4
Arrival time (median [IQR])	17 [10, 30]	16 [10, 30]	18 [10, 30]	0.276	41
Travel time (median [IQR])	18 [11, 28]	15 [10, 23]	20 [12, 32]	<0.001	42
Prehospital time (median [IQR])	62 [44, 90]	45 [32, 60]	80 [61, 109]	<0.001	3

MEI = major extracranial injury; RTI = road traffic incident; GCS = Glasgow coma scale; CPR = cardiopulmonary resuscitation; IV = intravenous.

smaller (though statistically significant) associations with longer on-scene times were travel time to the hospital (on average +0.6 min, 95% CI: 0.34 – 0.90), having a physician present at scene (+2.1 min, 95% CI: 1.1 – 3.2), administration of IV fluids (+1.5 min, 95% CI: 0.5 – 2.4), initiation of ventilatory support (+3.1 min, 95% CI: 0.4 – 5.7), and male gender (+1.4 min, 95% CI: 0.6-2.3) (Figure 1; Table 1, S1). The full model explained 36% of the variation in on-scene time (R^2). Of that variation explained, 42% was due to between center differences.

Predictors of Hypotension and Hypoxia

In total, 159 (5%) of the patients arrived at the ED with hypotension, 76 (2%) with hypoxia, and 21 (1%) with both. The proportions of hypoxia and hypotension were higher in severe TBI patients (defined as a GCS ≤ 8), 90 (11%) arrived with hypotension, 38 (5%) with hypoxia, and 17 (2%) with both (Table 2). Moreover, of the patients who were intubated on-scene, 92 (12%) had hypotension, 31 (4%) had hypoxia, and 14 (2%) had both.

The largest association with secondary insults on arrival was with major extracranial injury: the OR was 3.6 (95% CI: 2.6 – 5.0) for hypotension and 4.4 (95% CI: 2.9 – 6.7) for hypoxia. Other patient factors were also independently associated with arrival secondary insults including a higher GCS at scene, which was associated with less hypotension (OR 0.7, 95% CI: 0.5-0.9) and hypoxia (OR 0.6, 95%CI 0.4-0.8) on arrival; the presence of on scene unilaterally or bilaterally non-reactive pupils(s) predicted arrival hypoxia (OR: 1.9, 95% CI: 1.1 – 3.1). In terms of interventions, the requirement for IV fluids was associated with hypotension at arrival (OR 1.8, 95% CI: 1.3 – 2.5), while prehospital time (average OR 1.1 (1.01-1.20)) predicted hypoxia at arrival (Figure 2; Table 2 S1). The complete case analysis showed the same direction and range of effects (Figure 4 S1). The case mix adjusted variation by country in rates of arrival hypoxia and hypotension was small with a median OR of 1.11 and 1.05 respectively (Figure 6 S1).

The adjusted association of these surrogate endpoints with functional outcome was significant (Figure 5 S1): for saturation, lower values were associated with worse GOSE scores, plateauing at a saturation above 95%. For systolic blood pressure, lower (<100 mmHg) as well as higher (>180 mmHg) values were associated with worse functional outcome.

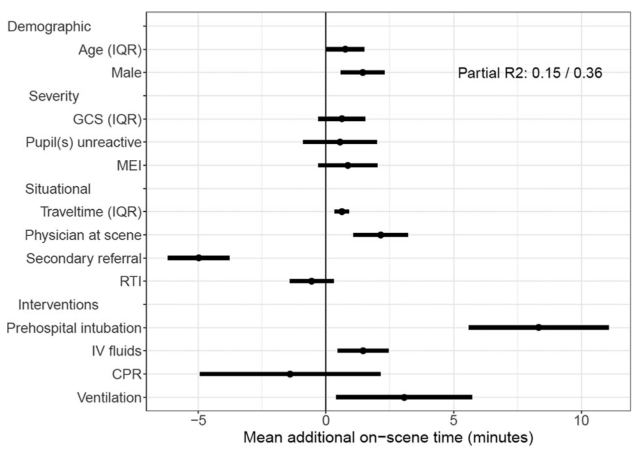

FIGURE 1. A forest plot showing the independent effects on on-scene time of demographic factors, injury severity, situational factors, and interventions given. The estimates can be interpreted as follows: this factor increases or decreases the on-scene time by x minutes, independent of the other factors displayed. This is the result of a multivariable mixed effects linear regression model with a random intercept for center conditional on country. The coefficients (and 95% confidence intervals) of the model are displayed. The partial R2 displayed is the percentage of the full model attributable to between country differences. RTI, Road traffic incident; MEI, major extracranial injury; GCS, Glasgow Coma Scale; IQR, interquartile range; CPR, cardiopulmonary resuscitation; IV, intravenous.

National Variation

There was large variation between prehospital times across European countries (unadjusted analyses, Figure 3). The shortest prehospital times for primary referrals were seen in Sweden (49 [IQR: 39-64]

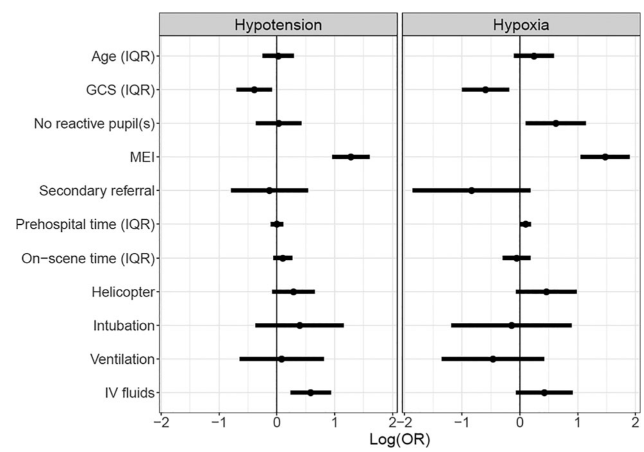

FIGURE 2. The effect of demographic factors, injury severity, situational factors, and interventions given on hypotension (systolic blood pressure < 100 mmHg) or hypoxia (oxygen saturation < 90%) at arrival at the emergency department. The effects are based on a logistic multivariable regression model.

TABLE 2. The number and percentage of patients with hypotension or hypoxia at arrival at the ED

	N	Hypotension + Hypoxia	Hypotension	Hypoxia	Neither
Overall	3348	21 (1%)	159 (5%)	76 (2%)	3092 (92%)
Intubated	759	14 (2%)	92 (12%)	31 (4%)	622 (82%)
Not intubated	2485	6 (0%)	62 (2%)	42 (2%)	2375 (96%)
Primary referral	2871	20 (1%)	140 (5%)	67 (2%)	2644 (92%)
Secondary referral	477	1 (0%)	19 (4%)	9 (2%)	448 (94%)
GCS >12	2096	4 (0%)	45 (2%)	26 (1%)	2021 (96%)
GCS 9-12	318	0 (0%)	17 (5%)	9 (3%)	292 (92%)
GCS <9	842	17 (2%)	90 (11%)	38 (5%)	697 (83%)

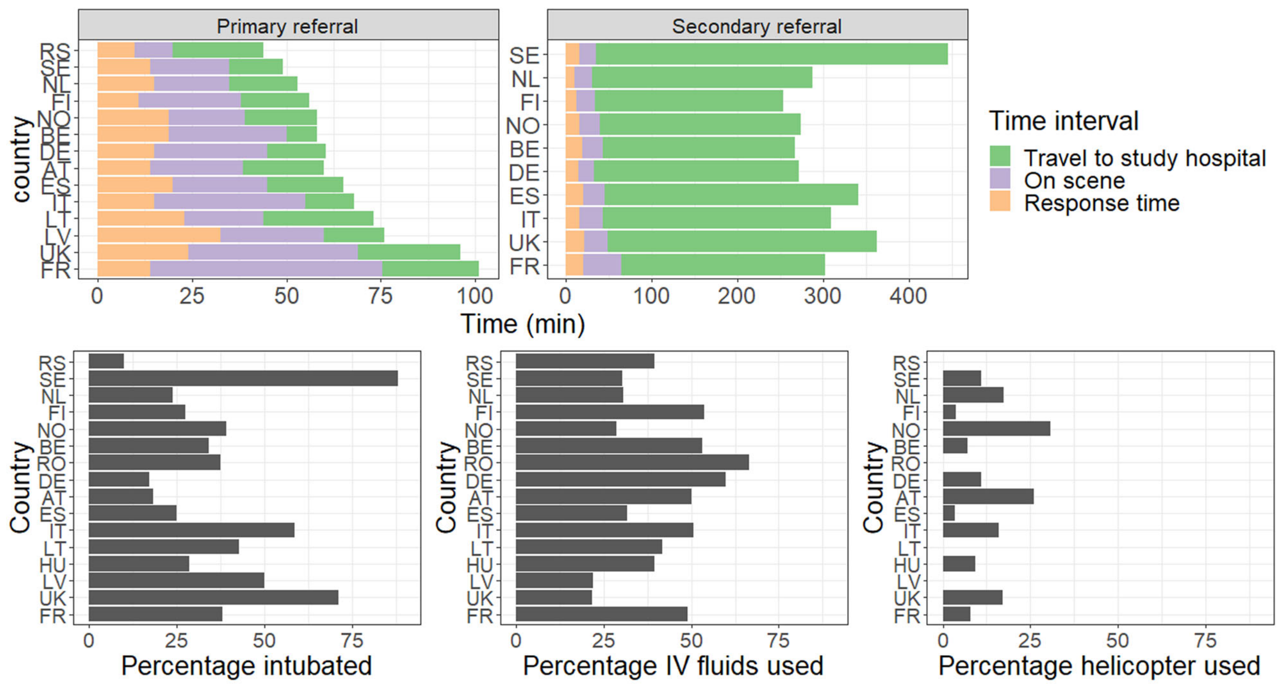

FIGURE 3. Bar charts showing the time spent in different prehospital phases per country (upper row), and the percentage of prehospital interventions (second row) used. In the upper row, only bars based on more than 10 patients are displayed.

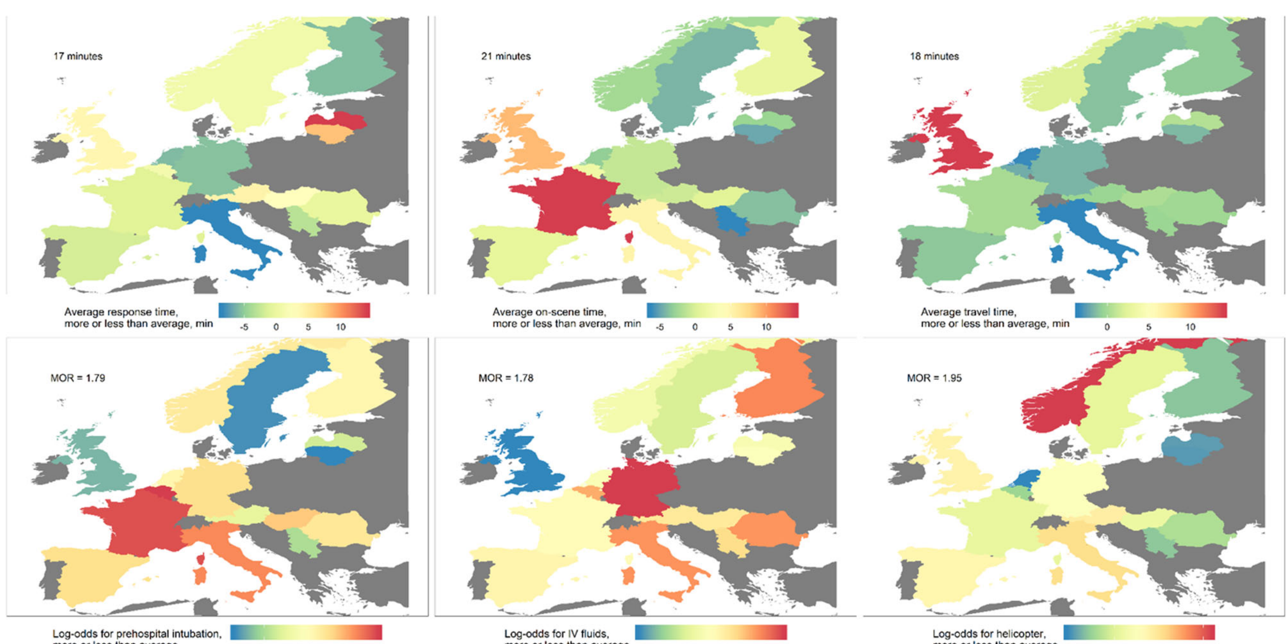

FIGURE 4. The adjusted variation in prehospital time (upper row), and use of key prehospital interventions (bottom row) across Europe. Every map shows the deviation per country from the overall average. In the upper row, the mean of the median time per country is shown. Moreover, secondarily referred patients are excluded from the analysis of travel times, because the time until arrival in the secondary hospital is unknown. The estimates of the random intercepts for each country are displayed. These are adjusted for the IMPACT core variables (age, pupils, and GCS), the CENTER-TBI stratum in which the patient was included, and the random variation at the center level.

minutes) and Serbia (44 [IQR: 28 – 85] minutes) whereas the longest prehospital times were seen in the United Kingdom (96 [IQR: 72 – 127] minutes) and France (101 [IQR: 74 – 146] minutes). Secondary referral extended the time until arrival at the study hospital to a greater degree (to hours rather than

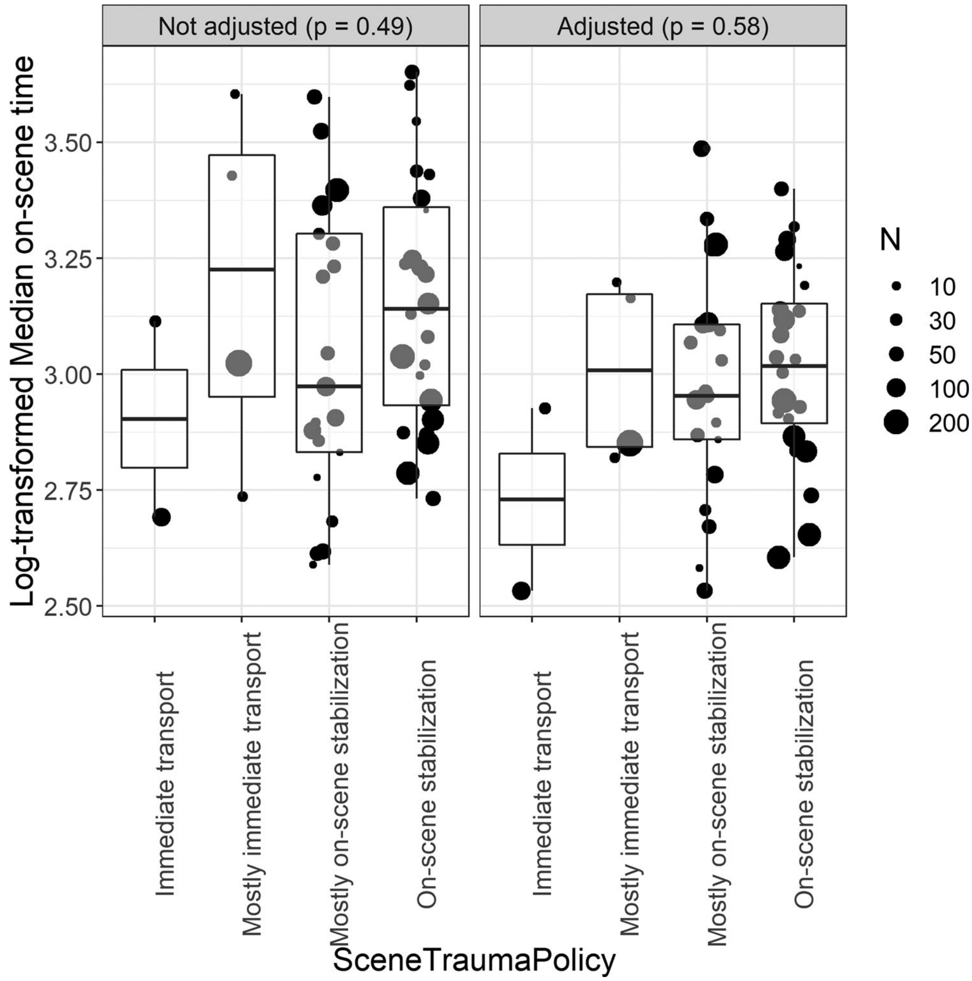

FIGURE 5. The unadjusted and adjusted log transformed median on-scene times. The bubbles represent the random intercept value for the model predicting on-scene time with center as random intercept. The right panel shows log transformed median on-scene times adjusted for GCS, traveltime, intubation, pupils, and sex (which were identified drivers of on-scene time).

minutes). In Sweden, the time to arrival at the study hospital for secondary referrals was the longest (446 [IQR: $340-560$] minutes). There was also large between-country variation in therapies the patients were provided with: intubation rates varied from 10% to 88%, iv fluid administration from 22% to 67%, and use of helicopters from 0% to 31%.

After adjusting for case mix, the variation in prehospital times and interventions within Europe remained substantial (Figure 4). The range of response times adjusted for injury severity was 12-25 minutes; the range of on-scene times was 16-36 minutes; and the range of travel times was 15-32 minutes. The range of response times adjusted for injury severity and prehospital interventions was 9-31 minutes; the range of on-scene times was 15-34 minutes; and the range of travel times was 14-32 minutes. The median odds ratio, expected when two randomly picked countries are compared, was 1.8 for prehospital intubation, 1.8 for IV fluids and 2.0 for helicopter. If prehospital times were also adjusted for the interventions that individual patients received, the model fit improved significantly (likelihood ratio tests, $p < 0.001$). However, the values of the random intercepts (which represent the average difference to the European average) did not differ from the models that only adjust for injury severity (Figure S7).

The unadjusted difference between the on-scene times of centers was not significantly different for patients from study hospitals reporting their EMS having a policy of stabilizing on scene versus a policy of immediate transport ($p = 0.49$) (17). After adjustment, the two centers reporting to have only a policy of immediate transport as part of provider profiling had on average the shortest average on-scene times (Figure 5). However, the overall difference in on-scene times between hospitals that reported the two different prehospital EMS policies was not significant ($p = 0.58$).

Discussion

To our knowledge this is the most comprehensive analysis comparing prehospital care for patients after TBI across Europe. Our multicenter, multinational, prospective cohort study suggests large variations across European countries in the prehospital care provided to patients who suffer a TBI, largely unexplained by patient characteristics. Despite the common availability of national guidelines for prehospital care, patients after TBI continue to present at the ER with hypotension and hypoxia, although these are less common than in the past (6% and 3% of cases, respectively). These physiological insults are commonest in severe TBI, where they occur in 13% and 7% of cases, respectively. The main determinant of such physiological instability on arrival at hospital were major extracranial injuries. We found that the main determinants of longer on-scenes time were interventional and situational rather than patient-related, for example on-scene intubation and primary referral to the study center.

However, we also determined that variation across Europe in prehospital times and interventions was only partly concordant with the prehospital policy (immediate transport or stabilize on scene) reported by clinicians in the CENTER TBI provider profiling exercise (6). We discovered that the probability of a patient with TBI being intubated at the injury scene, receiving IV fluids, or being transported by helicopter, was highly dependent on the country where the patient suffered the injury.

Not only did we see variation in prehospital interventions, but also in prehospital times. For on-scene times, this can partially be explained by the variation in provided interventions: for example, we found that prehospital intubation increased the on-scene time by 10 minutes, similar to an American retrospective study (18). Other interventions (IV-fluids, mechanical ventilation) also slightly increased the on-scene times. It is likely that the association of prolonged on-scene time and greater intervention may have been, in part, due to greater injury severity, requiring more on-scene stabilization before transfer. Although this explanation might be true for variations observed concerning the patient-level, the explanation for country-level variation in hospital times requires a different explanation: the diverse geographical landscapes of Europe, and the large between-center variation in the size and type of population of hospital catchment areas are more likely to drive the variation in prehospital times. Unsurprisingly, the use of helicopters was most prevalent in Norway which has large areas with low population density. Interestingly though, the longest total prehospital times (even after adjustment for patient and some situational factors) occurred in France and the United Kingdom. Potential explanations vary: France had the highest case-mix adjusted rates of prehospital intubation concordant with their surveyed response of stabilizing patients on scene; while the United Kingdom had the highest travel times from scene to hospital, perhaps reflecting traffic congestion and/or recent centralization of major trauma care to just 30 out of over 200 hospitals (8 of which participated in CENTER-TBI).

Despite large variation in performed interventions and prehospital times were observed, the rates of hypoxia and hypotension at arrival at the Emergency Department were lower than those in historical TBI studies: for example, even in severe patients, only 11% had hypotension at arrival, compared to 35% in a large historical study (3, 19) . In part, these lower rates may be explained by differences in case selection or definitions: While we only report documented hypoxia, the Traumatic Coma Data Bank also inferred hypoxia if there was clinically reported cyanosis or apnea. For example, we included intoxicated GCS < 9 patients in CENTER-TBI, similar to the study by Miller et al (20), who found a similar incidence of hypotension. Historically, TBI patients not in coma were generally not thought to have sustained a significant injury and imaging by CT scan was rarely conducted if intoxication was thought to be the root cause of a low GCS. Therefore, these patients were not included in historical TBI studies. The lower rates of hypoxia and hypotension at arrival can be explained by a higher inclusion rate of mild TBI patients with less severe extracranial injury than in previous studies. Our study reflects modern Emergency Medicine practice, which is to image all severities of TBI. However, there remains the possibility that prehospital care has simply improved over the last decades – in particular the almost universal use of supplemental oxygen, increased use of tracheal intubation, and the common use of prehospital IV fluids, may have markedly reduced the incidence of hypoxia and hypotension. However, there continues to be room for improvement - both physiological insults still occur at significant rates, particularly in patients after severe TBI.

A limitation of this international, multicenter trial is the proportion of missing data. This is unfortunately unavoidable in such a logistically challenging study. Since complete case analysis is both inefficient, and potentially biased, we imputed the data (21): both single imputation for the on-scene time, as well as multiple imputation for the main analyses were used. The single imputation was reliable, but not perfect: 60% of the variation could be explained by the model. The misclassification that could have occurred might have biased our results toward the null hypothesis. For the analysis with multiple imputed datasets, similar results were observed as the complete case analysis. This supports the validity of the selected imputation method.

Another limitation is that some prehospital physiological parameters (oxygen saturations and blood pressure) were not entered into the database. We used hypotension and hypoxia at arrival at the Emergency Department as a proxy for secondary insult. However, interventions such as intubation may have restored normal oxygen levels for some patients who were hypoxic at scene. There were some situational factors such as difficult extrication from the scene due to entrapment or stairs that may be valid factors for prolonging on scene times – and vary by country – that we could not account for using the data.

Finally, we acknowledge the fact that the centers that contributed patients to CENTER-TBI are a selected population of centers: these centers were mostly the equivalent of North American level 1 trauma centers (17). Our conclusions are based on extrapolation of the preferences and policies of these specialized centers toward the entire country.

Nevertheless, the prospective nature of the study, the large number of centers and countries, and the size of the CENTER TBI cohort do provide high external validity. Additionally, the data are acquired as "real-world" data, with lenient exclusion criteria. Therefore, we believe our results are applicable to the majority of settings.

We suggest that the large variation in administered prehospital interventions can be explained by two factors. First, the most relevant guidelines for prehospital management of TBI are national guidelines, which vary substantially across countries (7). However, even within countries, local policies vary according to the Provider Profiling questionnaires (22). Moreover, these local policies might not be concordant with practice, as research suggests that the adherence to guidelines is low (23). However, it is also possible that the prehospital guidelines are not (or not perceived as being) relevant to clinical practice in these contexts, and/or may be difficult to implement (24,25). Understanding and reconciling this discordance is essential if we are to provide a better evidence base for clinical practice in these contexts and ensure its appropriate adoption.

Second, the resources for prehospital care vary substantially across Europe. Even for prehospital intubation, for which the benefit - for severe TBI - has been shown in a randomized controlled trial (26), large variation was observed irrespective of patient factors (27): the practice variation is therefore likely to be also attributable (in part) to variation in resources. In many countries the academic basis for prehospital care is now only becoming a routine part of training for paramedics and other practitioners, whereas it has been established for Hospital based Emergency Medicine for at least 20 years. Some elements of prehospital care – such as helicopters - are costly, so research should also take account of cost-effectiveness. We need to identify prehospital interventions with proven clinical and cost effectiveness, prioritize their integration into guidelines then monitor adherence and impact on outcomes.

CONCLUSION

Across Europe, there are large variations in prehospital interventions for patients after TBI and in the associated on scene times. This variation is only partially explained by patient factors. Additional drivers of variation are likely to include EMS resource and organizational differences, and a low evidence base. While hypoxia and hypotension are less common than observed in past studies, they continue to occur in a substantial minority of patients after TBI, are particularly frequent following severe TBI or extracranial injury, and are associated with substantially worse outcomes. These data make a strong case for further research to facilitate the development and implementation of guidelines that support best practice in the prehospital care of patients with TBI.

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