

Supplementary Online Content

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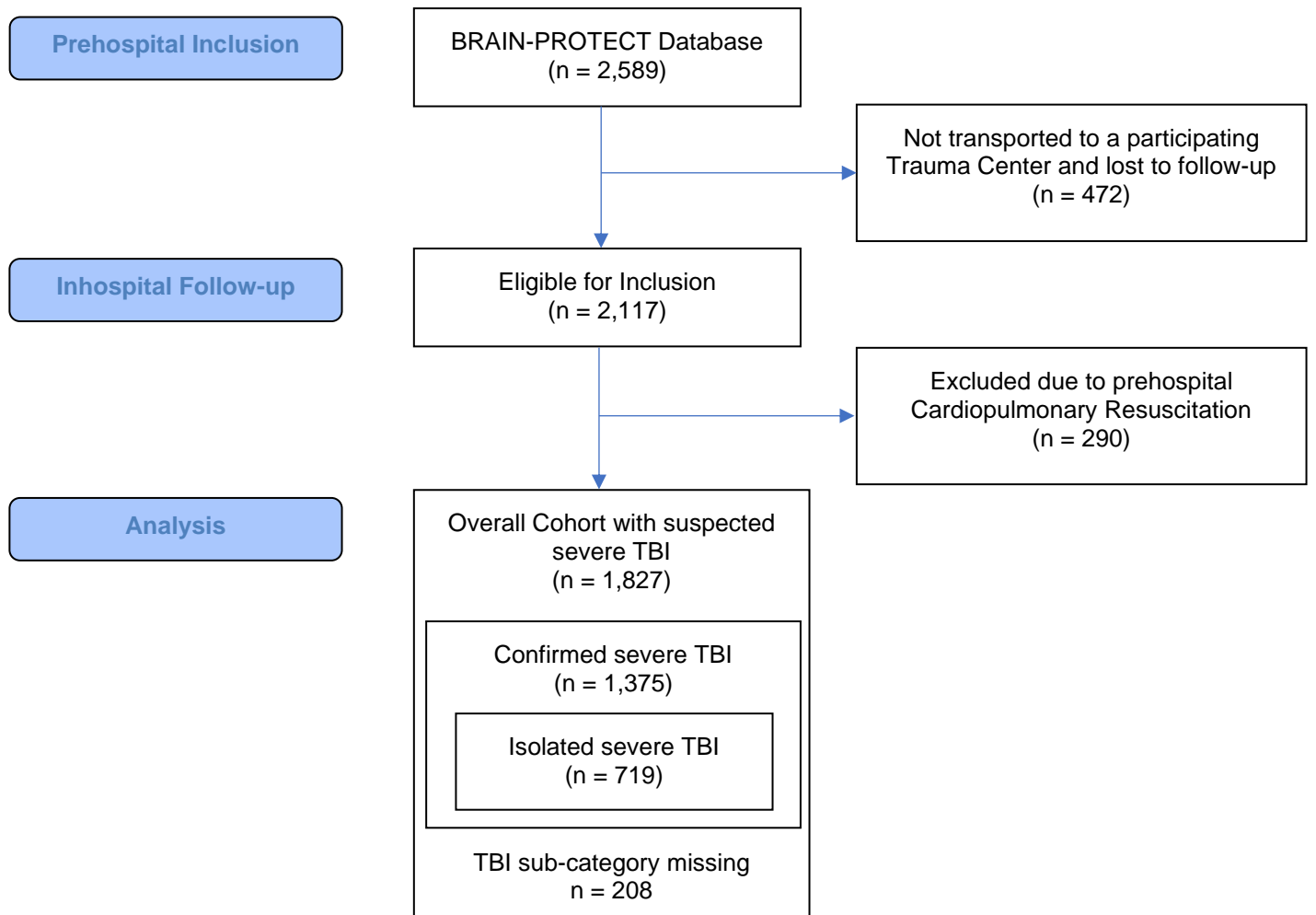
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This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure. Patient Flow Diagram



eTable 1. Characteristics of Patients Who Died Versus Survived Within 30 Days

	Survived (n=1,151)	Died (n=563)	P-value
Demographic and injury data			
Age (years)	35 [20, 55]	64 [41, 76]	< 0.001
Male sex (N (%))	823 (72%)	381 (68%)	0.10
Mechanism of Injury (N (%))			
Motor vehicle accident	222 (20%)	72 (13%)	< 0.001
Motorcycle accident	133 (12%)	30 (5%)	
Bicycle accident	255 (22%)	124 (22%)	
Pedestrian accident	84 (7%)	35 (6%)	
Other traffic accident	43 (4%)	7 (1%)	
Fall from height	341 (30%)	238 (43%)	
Firearm or stab injury	7 (1%)	26 (5%)	
Other	51 (4%)	20 (4%)	
Injury Severity Score	25 [16; 34]	30 [25; 41]	
Prehospital vital parameters at HEMS arrival			
GCS	6 [3, 7]	3 [3, 5]	< 0.001
Systolic blood pressure (mmHg)	139 (32)	150 (42)	< 0.001
Heart rate (min ⁻¹)	96 (28)	89 (30)	< 0.001
SpO ₂ (%)	98 [94, 99]	96 [92, 99]	< 0.001
In-hospital data			
GOS at discharge (N(%))			
Death	20 (2%)	552 (98%)	< 0.001
Vegetative state	32 (3%)	6 (1%)	
Severe disability	593 (54%)	5 (1%)	
Moderate disability	177 (16%)	0 (0%)	
Good recovery	269 (25%)	0 (0%)	
Primary Exposure			
Received TXA	412 (36)	241 (43)	0.005

Prehospital vital parameters represent the first documented values after arrival of Helicopter Emergency Medical Services (HEMS). Numeric variables are presented as mean (SD) or median [quartiles]. Percentages are column-percentages and may not necessarily add up to 100% due to rounding error, and may not necessarily use the total N of the respective column as reported in the top row as the denominator due to missing data (see Table 1 in the manuscript for missing data per variable). *Hospital length of stay (LOS) was only calculated for patients who were known to survive to discharge. GCS: Glasgow Coma Scale, GOS: Glasgow Outcome Scale, SpO₂: pulse-oximetric oxygen saturation, TXA: Tranexamic Acid.

eTable 2. Characteristics of Patients per Subgroup (Confirmed and Isolated TBI)

	Confirmed TBI (n=1,375)	Isolated TBI (n=719)
Demographic and injury data		
Age (years)	47 [23, 66]	53 [27, 68]
Male sex (N (%))	974 (71%)	478 (66%)
Mechanism of Injury (N (%))		
Motor vehicle accident	215 (16%)	62 (9%)
Motorcycle accident	135 (10%)	54 (8%)
Bicycle accident	327 (24%)	184 (26%)
Pedestrian accident	101 (7%)	49 (7%)
Other traffic accident	39 (3%)	16 (2%)
Fall from height	456 (34%)	279 (40%)
Firearm or stab injury	32 (2%)	27 (4%)
Other	53 (4%)	35 (5%)
Injury Severity Score	29 [22, 36]	25 [17, 27]
Prehospital vital parameters at HEMS arrival		
GCS	4 [3, 7]	5 [3, 7]
Systolic blood pressure (mmHg)	144 (36)	149 (35)
Heart rate (min ⁻¹)	93 (29)	88 (28)
SpO ₂ (%)	97 [93, 99]	98 [95, 99]
In-hospital data		
Hospital LOS (days)*	19 [9, 34]	14 [6, 25]
GOS at discharge (N(%))		
Death	521 (39%)	277 (39%)
Vegetative state	35 (3%)	16 (2%)
Severe disability	524 (39%)	236 (34%)
Moderate disability	130 (10%)	80 (11%)
Good recovery	126 (10%)	95 (13%)
Primary Exposure		
Received TXA	539 (39%)	243 (34%)
Primary Outcome		
Death at 30-days	511 (37%)	274 (38%)

Prehospital vital parameters represent the first documented values after arrival of Helicopter Emergency Medical Services (HEMS). Numeric variables are presented as mean (SD) or median [quartiles]. Percentages are column-percentages and may not necessarily add up to 100% due to rounding error, and may not necessarily use the total N of the respective column as reported in the top row as the denominator due to missing data (see Table 1 in the manuscript for missing data per variable). *Hospital length of stay (LOS) was only calculated for patients who were known to survive to discharge. GCS: Glasgow Coma Scale, GOS: Glasgow Outcome Scale, SpO₂: pulse-oximetric oxygen saturation, TXA: Tranexamic Acid.

eTable 3. Results of the Main Analysis: Full Cohort of Patients

Independent Variable	Odds Ratio (95% Confidence interval)	P-value
Prehospital Tranexamic Acid	1.18 (0.73; 1.90)	0.51
Anticoagulant Use	0.94 (0.57; 1.56)	0.81
Injury Mechanism [‡]		<0.001
Motor vehicle accident	Reference	
Motorcycle accident	0.61 (0.22; 1.66)	0.34
Bicycle accident	1.27 (0.55; 2.90)	0.58
Pedestrian accident	0.75 (0.22; 2.53)	0.64
Other traffic accident	0.40 (0.10; 1.63)	0.20
Fall from height	1.69 (0.75; 3.81)	0.21
Firearm or stab injury	8.71 (1.12; 67.57)	0.04
Other	0.89 (0.27; 2.95)	0.86
HEMS Provider anonymized [‡]		<0.001
W	Reference	
X	1.20 (0.62; 2.34)	0.59
Y	1.53 (1.15; 2.02)	0.003
Z	2.37 (1.85; 3.04)	<0.001
Sex (female versus male)	1.34 (0.84; 2.15)	0.22
Modified ASA score [‡]		<0.001
No systemic disease (ASA 1)	Reference	
Mild systemic disease (ASA 2)	1.72 (1.21; 2.43)	0.002
Severe systemic disease (ASA 3-4)	2.46 (1.49; 4.06)	<0.001
Systolic blood pressure [†]		0.93
Heart rate [†]		0.13
SpO ₂ [†]		0.01
Distance to trauma center [†]		0.04
ISS [†]		<0.001
ISS-by-time period interaction*		0.02
Time period*		0.80
GCS [†]		<0.001
Age [†]		<0.001

Adjusted odds ratios, 95% confidence intervals and P-values from the main analysis model for the full cohort of patients. ‡For categorical variables with more than two levels, the overall significance is displayed as well as odds ratio estimates and significance versus the reference category. †Non-categorical (numeric) variables were modelled using restricted cubic splines, only the overall significance is displayed as the odds ratio has no directly interpretable meaning. *Because the version of the Injury Severity Score (ISS) that was used across the Netherlands was changed during the observation period (as of 2015), an interaction term between the ISS and the time period was used to allow the relationship between the ISS and outcomes to vary depending on which version was used. HEMS: Helicopter Emergency Medical Service, ASA: American Society of Anesthesiologists physical status classification system; SpO₂: pulse-oximetric oxygen saturation, GCS: Glasgow Coma Scale.

eTable 4. Results of the Main Analysis: Confirmed Severe TBI

Independent Variable	Odds Ratio (95% Confidence interval)	P-value
Prehospital Tranexamic Acid	1.27 (0.68; 2.35)	0.45
Anticoagulant Use	0.78 (0.47; 1.29)	0.33
Injury Mechanism [‡]		<0.001
Motor vehicle accident	Reference	
Motorcycle accident	0.55 (0.19; 1.57)	0.26
Bicycle accident	1.11 (0.48; 2.55)	0.81
Pedestrian accident	0.79 (0.25; 2.48)	0.69
Other traffic accident	0.38 (0.09; 1.66)	0.20
Fall from height	1.55 (0.64; 3.75)	0.33
Firearm or stab injury	7.0 (0.87; 56.49)	0.07
Other	0.81 (0.24; 2.68)	0.73
HEMS Provider anonymized [‡]		<0.001
W	Reference	
X	1.12 (0.56; 2.24)	0.76
Y	1.38 (1.03; 1.86)	0.03
Z	2.66 (1.86; 3.80)	<0.001
Sex (female versus male)	1.28 (0.71; 2.29)	0.41
Modified ASA score [‡]		<0.001
No systemic disease (ASA 1)	Reference	
Mild systemic disease (ASA 2)	2.02 (1.50; 2.73)	<0.001
Severe systemic disease (ASA 3-4)	3.17 (1.72; 5.84)	<0.001
Systolic blood pressure [†]		0.59
Heart rate [†]		0.12
SpO ₂ [†]		0.008
Distance to trauma center [†]		0.009
ISS [†]		0.02
ISS-by-time period interaction*		<0.001
Time period*		0.001
GCS [†]		<0.001
Age [†]		<0.001

Adjusted odds ratios, 95% confidence intervals and P-values from the main analysis model for patients with confirmed severe TBI. [‡]For categorical variables with more than two levels, the overall significance is displayed as well as odds ratio estimates and significance versus the reference category. [†]Non-categorical (numeric) variables were modelled using restricted cubic splines, only the overall significance is displayed as the odds ratio has no directly interpretable meaning. *Because the version of the Injury Severity Score (ISS) that was used across the Netherlands was changed during the observation period (as of 2015), an interaction term between the ISS and the time period was used to allow the relationship between the ISS and outcomes to vary depending on which version was used. HEMS: Helicopter Emergency Medical Service, ASA: American Society of Anesthesiologists physical status classification system; SpO₂: pulse-oximetric oxygen saturation, GCS: Glasgow Coma Scale.

eTable 5. Results of the Main Analysis: Isolated Severe TBI

Independent Variable	Odds Ratio (95% Confidence interval)	P-value
Prehospital Tranexamic Acid	4.49 (1.57; 12.87)	0.005
Anticoagulant Use	0.62 (0.18; 2.18)	0.46
Injury Mechanism [‡]		<0.001
Motor vehicle accident	Reference	
Motorcycle accident	0.85 (0.16; 4.60)	0.85
Bicycle accident	0.93 (0.25; 3.44)	0.91
Pedestrian accident	0.63 (0.19; 2.16)	0.47
Other traffic accident	0.76 (0.23; 2.46)	0.64
Fall from height	2.26 (0.66; 10.40)	0.17
Firearm or stab injury	7.88 (0.63; 97.8)	0.11
Other	0.90 (0.20; 3.95)	0.89
HEMS Provider anonymized [‡]		0.04
W	Reference	
X	0.80 (0.15; 4.43)	0.80
Y	0.53 (0.20; 1.35)	0.18
Z	1.14 (0.66; 1.95)	0.64
Sex (female versus male)	0.98 (0.43; 2.24)	0.96
Modified ASA score [‡]		0.002
No systemic disease (ASA 1)	Reference	
Mild systemic disease (ASA 2)	1.61 (0.61; 4.28)	0.34
Severe systemic disease (ASA 3-4)	2.63 (1.49; 4.67)	0.001
Systolic blood pressure [†]		0.03
Heart rate [†]		0.002
SpO ₂ [†]		<0.001
Distance to trauma center [†]		<0.001
ISS [†]		0.29
ISS-by-time period interaction*		0.23
Time period*		0.14
GCS [†]		<0.001
Age [†]		<0.001

Adjusted odds ratios, 95% confidence intervals and P-values from the main analysis model for patients with isolated severe TBI. [‡]For categorical variables with more than two levels, the overall significance is displayed as well as odds ratio estimates and significance versus the reference category. [†]Non-categorical (numeric) variables were modelled using restricted cubic splines, only the overall significance is displayed as the odds ratio has no directly interpretable meaning. *Because the version of the Injury Severity Score (ISS) that was used across the Netherlands was changed during the observation period (as of 2015), an interaction term between the ISS and the time period was used to allow the relationship between the ISS and outcomes to vary depending on which version was used. HEMS: Helicopter Emergency Medical Service, ASA: American Society of Anesthesiologists physical status classification system; SpO₂: pulse-oximetric oxygen saturation, GCS: Glasgow Coma Scale.

Sensitivity Analyses

Additional sensitivity analyses for the primary outcome were performed *post-hoc* to address several aspects that may have impacted the conclusions based on the main analysis:

1. Given that injury severity and mechanism were accounted for with 3 variables in the main analysis model (as well as 3 variables for vital parameters that are also affected by trauma severity), we had initially not also adjusted for the pupillary response (reacting versus not reacting) or size (dilated versus normal). However, we acknowledge that the pupillary status may be systematically associated with TXA administration and is also a known predictor of mortality. We thus additionally adjust for potential confounding effects of pupillary response (reacting versus not reacting) and size (dilated versus normal), adding these variables to the main analysis model.
2. The main analysis model adjusts for a large number of covariates, with additional spline variables for continuous covariates. This may raise concerns about potential overfitting. While we considered rigorous adjustment for confounding highest priority in the main analysis, we now use a simpler model in the sensitivity analysis which only controls for patient age as well as injury severity (ISS and GCS), which we considered a priori the most important confounders in the dataset.
3. Same as model #2, with pupillary response (reacting versus not reacting) and size (dilated versus normal) added in.
4. Here, we present another simplified model in which the spline variables from the original model were replaced by the original variables, i.e., assuming a linear relationship between the non-categorical variables and the logit of mortality.
5. To address whether differences in TXA dose impacted our results and conclusions, patients who received a dose other than 1g as well as patients <18 years were excluded from the main analysis.
6. In the main analysis, we used a cutoff head-AIS value of ≥ 3 to define ‘confirmed’ and ‘isolated’ TBI, as a value of 3 represents serious injury by definition of the AIS scale. To test whether the results are sensitive to the choice of this cutoff value, we now perform a sensitivity analysis in which we use a head-AIS value of ≥ 4 (representing more severe injury) as cutoff to define ‘confirmed’ and ‘isolated’ severe TBI.
7. In the main analysis, we had not included the face-AIS in the definition of ‘isolated’ TBI. Head and face injuries commonly co-occur, and we would consider a patient with head and face injury as having an isolated TBI when no relevant extra-cranial injuries are present. Here, we included the face-AIS in the definition and consider patients with relevant face injuries as having non-isolated TBI.
8. To address non-independence of patients within hospitals with a fully specified model rather than focusing on marginal effects and adjusting the standard errors, we re-performed the analysis with the same covariates as the main analysis, now using a generalized linear mixed effects model with a logit link function and a random intercept for hospital.
9. Same as model #1, after multiple imputation (see main manuscript for details).
10. Same as model #2, after multiple imputation.
11. Same as model #3, after multiple imputation.
12. Same as model #4, after multiple imputation.
13. Same as model #5, after multiple imputation.
14. Same as model #6, after multiple imputation.
15. Same as model #7, after multiple imputation.
16. Same as model #8, after multiple imputation (should be viewed as an exploratory analysis, as the analysis of generalized mixed effects models after multiple imputation is not officially supported by Stata)

Results are presented on the next page

eTable 6. Results of Supplemental Sensitivity Analyses

Model	Full Cohort	P-value	Patients with confirmed TBI	P-value	Patients with isolated TBI	P-value
#1	1.45 (0.83; 2.53)	0.20	1.46 (0.77; 2.75)	0.25	5.79 (1.84; 18.22)	0.003
#2	1.07 (0.87; 1.31)	0.55	1.10 (0.87; 1.39)	0.43	1.60 (1.02; 2.51)	0.04
#3	1.13 (0.87; 1.48)	0.35	1.16 (0.88; 1.52)	0.29	1.42 (0.95; 2.14)	0.09
#4	1.13 (0.74; 1.74)	0.58	1.18 (0.77; 1.79)	0.45	2.90 (1.09; 7.71)	0.03
#5	1.23 (0.57; 2.65)	0.59	1.29 (0.51; 3.22)	0.59	4.35 (1.20; 15.82)	0.03
#6	1.18 (0.73; 1.90)	0.51	1.29 (0.56; 2.98)	0.55	4.21 (1.38; 12.82)	0.01
#7	1.18 (0.73; 1.90)	0.51	1.27 (0.68; 2.35)	0.45	4.72 (1.88; 11.88)	0.001
#8	1.18 (0.65; 2.13)	0.59	1.27 (0.69; 2.33)	0.45	4.49 (1.66; 12.15)	0.003
#9	1.05 (0.81; 1.36)	0.72	1.10 (0.90; 1.34)	0.34	1.90 (1.17; 3.11)	0.01
#10	1.05 (0.80; 1.38)	0.71	1.10 (0.87; 1.38)	0.44	1.60 (1.02; 2.51)	0.04
#11	1.00 (0.80; 1.26)	0.97	1.08 (0.91; 1.29)	0.39	1.57 (1.02; 2.41)	0.04
#12	1.00 (0.71; 1.41)	0.99	1.07 (0.77; 1.49)	0.69	2.01 (1.02; 3.96)	0.04
#13	1.06 (0.70; 1.60)	0.78	1.04 (0.72; 1.49)	0.84	1.99 (1.13; 3.50)	0.02
#14	1.17 (0.84; 1.65)	0.35	1.23 (0.87; 1.76)	0.25	2.44 (1.49; 4.00)	<0.001
#15	1.17 (0.84; 1.65)	0.35	1.20 (0.92; 1.55)	0.18	2.21 (1.41; 3.45)	0.001
#16	1.17 (0.84; 1.64)	0.36	1.19 (0.83; 1.69)	0.34	2.05 (1.17; 3.59)	0.01

For a detailed description of each model, please refer to the previous page. Results are reported as odds ratios and their 95% confidence interval.