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The relationship of pre-hospital time to in-hospital trauma mortality in a physician staffed Emergency Medicine System

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Abstract

IMPORTANCE: The relationship between total prehospital time and mortality in physician staffed trauma systems remains uncertain.

OBJECTIVE: The objective was to describe the relationship of total pre-hospital time and in-hospital mortality in a prehospital physician staffed trauma system in France with the hypothesis that total prehospital time is associated with an increased mortality.

DESIGN, SETTING, AND PARTICIPANTS: Retrospective cohort study from 2011 to 2016. The relationship between death and prehospital time was assessed with a multivariable model adjusted with confounders. Data for this study were derived from two distinct regional trauma registries in France, one urban, one rural with both having a physician staffed Emergency Service. A total of 10216 consecutive adult trauma patients admitted to one of the regional trauma referral centers in the study period were included.

MAIN OUTCOMES AND MEASURES: Total Prehospital Time (TPT) was the primary exposure variable, recorded as arrival of the physician-lead prehospital care-team on scene to arrival at the hospital. The main outcome of interest was all cause in-hospital mortality.

RESULTS: Patients had a mean age of 41 years, were mostly men (78%) affected by predominantly non-penetrating injury (91%) with a median ISS of 17. 67% of patients had at least one body region with an AIS

score ≥3. 10% (n=406) presented in shock (systolic pressure <90 mmHg) and 27% (n=1378) with severe head injury AIS≥3. Unadjusted Increasing prehospital time 30-minute categories were associated with a markedly and constant increase in the risk of in-hospital death. Odds of death increased of 9% for each ten-minute increase in prehospital time (OR (95% CI) 1.09 (1.07-1.11). After adjustment the relationship between prehospital time and in-hospital death was halved but still significant (OR (95% CI) 1.04 (1.01-1.07)).

CONCLUSIONS AND RELEVANCE: Increasing total pre-hospital time is associated with increasing in-hospital all-cause mortality in trauma patients a physician staffed EMS after adjustment for case complexity. Pre-hospital time is a management objective in analogy to physiological targets. These findings plaid for a further streamlining of prehospital trauma care and the need to define the optimal *intervention to time-ratio*.

Introduction

The concept of time as essential determinant of outcome in the early care of trauma patients is a prevailing doctrine [1,2], symbolized in the catchphrase: the *Golden Hour* of Trauma [3,4]. The concept of trauma as time-sensitive disease has guided education and policy for decades in the international trauma community. Despite this cultural penetrance [5], evidence in favor remains elusive and the concept controversial [6–10].

The concept of trauma as a time-sensitive disease was developed and nurtured in a specific Emergency Medical System (EMS), mainly a paramedic-based system in North America. The international trauma community transposed this concept to diverse specific settings, even if the respective context was different from the North American system [11]. Data on system performance

from physician-staffed EMS are far less abundant than data from EMS systems. On the one side physician-staffed-EMS (ps-EMS) are considered to add complexity to a complex situation, to perform more interventions resulting in longer Total Pre-hospital Time (TPT).[12,13]. On the other side, proponents of the physician-led critical care team advocate a more tailored provision of advanced pre-hospital critical care. The ensuing debate oscillates between dichotomist concepts such as *scoop and run* or *stay and play*[11,13,14]. The reality is probably less easy to frame.

Based on this rationale and considering the comparative lack of data for ps-EMS, it appeared justified to reconsider the association of pre-hospital total time and in-hospital mortality in a physician-staffed EMS. The objective was to describe the relationship of total pre-hospital time and in-hospital mortality in a large and representative cohort of trauma patients from two regional and geographically very distinct trauma systems in France, one urban and one rural-mountainous. We hypothesized that total prehospital time is associated with a mortality increase in a physician staffed EMS system.

Material and Methods

A strobe checklist for this retrospective cohort study is provided in the appendix.

Ethical approval

This is an observational study using data from two prospective multicenter regional trauma registries, the TraumaBase©(TB), from the Paris area, Ile-de-France, and TRENAU (TR), from the region Rhône-Alpes. Both registries have obtained approval from the Institutional Review Board (Comité de Protection des Personnes, Paris VI and Clermont-Ferrand) from the Advisory Committee for Information Processing in Health Research (*Comite Consultatif Pour le Traitement de l'information en matière de recherche dans le domaine de la santé* CCTIRS, 11.305bis and 15.038bis) and from the National Data Protection Agency (*Commission Nationale de l'Informatique et des Libertés* CNIL, 911461 and CNIL 915372), waiving the need for informed consent. Both registries dispose of

algorithms for consistency and coherence and professional data monitoring. Datamonitoring for the TraumaBase© is assured by the Biostatistics Laboratory of Paris 7, and for the TRENAU registry by professional statisticians employed by the network.

Setting

The structure and triage in both trauma systems have been previously described [15,16]. In summary, Physician-staffed Mobile Intensive Care Units (MICU) provide the prehospital care in both systems. A MICU team provides the equivalent of ATLS-based pre-hospital interventions (sedation, prehospital anesthesia, advanced airway management, chest decompression…). The TraumaBase© Ile-de France covers an urban area of 12000 km2 with a population of 12 million inhabitants and 15 million visitors per year. Eight physician staffed EMS (SAMU, Service Aide Medicale Urgente) organized into 43 MICU (see above), 37 SAMU and 6 Brigade de Sapeurs de Pompiers (Paris Fire Brigade), and six designated level-1 centers provide almost exclusively the trauma care; no lower care centers have been designated. The TRENAU area covers an area of 18,000 Km2 in the Northern French Alps with a population of two million inhabitants and a high seasonal variation (8 million tourists each year). Care in the TRENAU network is provided by three SAMUs and a total of 14 designated trauma hospitals with two level-I, one level-II and eleven level-III centers. The TRENAU network disposes of specific management and triage guidelines [15]. Within the Paris network, national triage[17] and management guidelines apply such as those for shock[18]. At any given time, clinical management was left to the discretion of the responsible physician (pre-hospital or in-hospital). Both networks and registries are financially supported by the respective Regional Health Authorities Ile-de-France and Rhône-Alpes (Agence Régionale de Santé, ARS).

Study Populations

All consecutive trauma patients triaged to one of the six regional, designated Paris level-1 trauma centers or to one of the 14 centers participating in the TRENAU network were screened for inclusion.

Patients not managed by a physician-staffed mobile unit or not transported to a participating hospital (death on scene or not transported) or transferred from a hospital outside of the respective system were not included. Only patients directly admitted to level-1 or level-2 centers (TRENAU) were included. The enhanced care teams in both systems are able to provide a full spectrum of ATLS trauma care, including airway management with rapid sequence induction for intubation, sedation and analgesia, fluid therapy, vasoactive medication, fracture and dislocation reduction, chest decompression, hemorrhage control (tourniquets, splinting, compression…), red blood cell concentrate transfusion, etc. They currently do not provide thoracotomy or blood component therapy other than red blood cell concentrates occurring in less than 3% of cases in both systems.

We defined early critical pre-hospital trauma interventions as any of the following: pre-hospital intubation, vasopressor use, osmotherapy and fluid resuscitation > 1000 mL. Shock was defined as a systolic arterial pressure <90mmHg.

The eTable 1 provides the complete list of, epidemiological, clinical (pre-hospital and in-hospital), physiological and biological variables that were recorded for each patient. In brief, both data collection follow the style Utstein major trauma revised [19]. Calculation of the following scores completed this information, and 2005 version of Injury Severity Score (ISS).

Exposure variable and outcome criteria

Total Prehospital Time (TPT) was the primary exposure variable, recorded as arrival of the physician-lead prehospital care-team on scene to arrival at the hospital. Arrival on scene, leaving scene and arrival at the admitting hospital are systematically recorded in both registries, based on pre-hospital intervention run sheets and/or dispatch center data; exact timing of injury is not recorded in both registries.

The main outcome of interest was all cause in-hospital mortality. Patients who died within 24 hours were retained in the analysis to minimize survivor bias. Cause-specific of death, “death from bleeding” and death from “head injury” were considered as secondary end-points. The causes of death were based on a judgment by a physician reviewing all evidence at routine case closure in both registries. The physician performing case closure was not part of the working committee of this study.

Statistical analysis

Sample size

The retrospective nature of the study predetermines the sample size. A post-hoc power calculation was performed to assess internal validity of the analysis. Internal validity was assessed in terms of discrimination by the area under the curve and calibration by overall calibration, ratio exposed/observed and calibration slope.

Statistical methods

Continuous variables were presented with mean and standard deviation or with median and interquartile range when appropriate. Categorical variables were presented with frequency and percentage.

The relationship between death and prehospital time was assessed graphically by plotting the risk of death on prehospital time. A Generalized linear mixed model (GLM) with random effect by registry and EMS system explored the relationship between death and prehospital time with a logit function. We assessed graphically the departure of linearity in the relationship between death and time and added the polynomial terms in the GLM if needed.

We fitted the best model according to likelihood ratio test and Akaike information criterion (AIC). In addition, a Generalized additive model (GAM) assessed and explored the linearity of the relationship

between death and time. GAM is a flexible model of GLM with a link function based on smoothing splines. The amount of smoothing is controlled by the number of equivalent degrees of freedom. We assessed graphically the smooth function to fix the equivalent degrees of freedom for prehospital time. We assessed the deviance variation that occurs depending on the use of the linear term or the smoothing term in the equation.

To control for potential variables associated with case complexity, a GLM and GAM model was applied in multivariable analysis to adjust for the confounders age, gender, severity of anatomic injury pattern (ISS), systolic blood pressure (SBP) and Glasgow Coma Scale (GCS) in a parsimonious method. These five variables are strongly correlated with prehospital interventions such as airway. The more severely a patient is in shock (SBP), or likelihood of traumatic brain injury (GCS), the more severely injured he is (ISS). The High injury load may trigger more interventions and longer prehospital times. In consequence, for the sake of simplicity and to avoid collinearity, the models did deliberately not include prehospital interventions.

Two-sided p values < 0.05 were considered significant. All statistical analyses were performed using Stata SE, v.14.0 (StataCorp).

Missing data

Multiple imputation of missing values to predict total prehospital time was not feasible. Several variables were not routinely collected in both registries (distance between scene of accident and hospital, dispatching decision, etc.). Measurement errors in variables that are not routinely collected could lead to inappropriate predictions when applied to multiple imputation. Data were unlikely to be missing at random and this could lead to a bias towards the null when applying multiple imputation. For this reason, a complete case analysis was performed. Patients with and without

missing data on TPT were compared to assess comparability between the groups in term of demographic characteristics, prehospital condition, injury severity, in-hospital death.

Results

In total 6,441 patients were screened for inclusion from January 2011 to December 2016 in the Traumabase database and 8,888 from the TRENAU database from January 2009 to December 2016. The main reason to exclude patients were missing data (see flowchart, eFigure1, missing data eTable 2). In total 10,126 patients from both samples, 5,059 and 5,067 respectively, were retained for complete case analysis.

Patients had a mean age of 41 years, most were men (78%) affected by predominantly non-penetrating injury (91%) with a median ISS of 17, with 67% of patients with at least one body region with an AIS score ≥3. 10% (n=406) presented in shock (systolic pressure <90 mmHg) and 27% (n=1378) with severe head injury AIS≥3 (detailed data, please refer to Table 1).

The median Total-Pre-hospital Time (TPT) was 73 [IQR, 54-100] minutes in the Traumabase cohort and 60 [IQR, 45-80] in the TRENAU cohort (eTable 3). The median TPT was 65 [IQR, 49-90] for the combined cohort with 43% cases presenting a TPT shorter than 60 minutes. Three quarters of patients were transported by land and 90% were admitted to a designated trauma center. TPT increased with the number of pre-hospital interventions performed Orotracheal intubation and vasopressor use was more frequent in the Traumabase network, orotracheal intubation 23% versus 29%, fluid > 1000ml 26% versus 38%, vasopressor 10% versus 13% (eTable 4).

Primary outcome

Unadjusted GLM and GAM showed a significant progressive increase of all-cause mortality with TPT

(figure 1 A and B). Increasing TPT 30-minute categories were associated with a markedly and constant increase in the risk of in-hospital death (table 2). Odds of death increased by 9% for each ten-minute increase in TPT (OR (95% CI) 1.09 (1.07-1.11), table 3). When adjusted for confounders, the relationship between TPT and in-hospital death 4% (figure 2) but still significant (OR (95% CI) 1.04 (1.01-1.07), table 3).

Secondary outcome

Increasing TPT 30-minute categories were associated with a progressive and constant increase in the risk of death due to head injury (table 2). This relationship was also observed, though less marked, when considering death from bleeding (table 2). Unadjusted odds of death due to head injury increased by 9% for each ten-minute increase in TPT (OR (95% CI) 1.09 (1.07-1.11), table 3, while unadjusted odds ratio of death due to bleeding increased by 4% (1.04 (1.01-07) respectively, table 3). When adjusting for confounders, the relationship between TPT and in-hospital death due to head and bleeding injury showed a non-significant increase (table 3).

Discussion

The main finding of this study is that longer TPT is independently associated with increasing all-cause in-hospital mortality in a physician-staffed trauma system. To the best of our knowledge this is the first study reporting such an association in a physician staffed EMS in Europe.

The increase of mortality with increasing TPT appears as common sense. However, existing comparative data on TPT and mortality in physician staffed EMS are limited and conflicting [20,21]. Although time would be considered as an independent exposure variable, it remains invariably dependent on exposure variables such as physiology and severity and pre-hospital interventions. Concordantly, it was justifiable to assume that TPT could only be the result of multifactorial complexity thereby challenging its independent association with outcome. Nevertheless, by accounting for complexity (age, ISS, GCS and shock), time remained an independent exposure

variable corroborating studies conducted in North America [22]. Although other studies suggest that a physician-led team exerts a positive impact on outcome [12,22] even when TPT is longer.

The association of TPT and mortality implies that time is an independent exposure that should be a management objective. Observed TPT were comparable to other European physician staffed EMS [13,23,24] but longer than in paramedic staffed EMS [25]. A propensity matched analysis reported that critical prehospital interventions were associated with a decrease in mortality without impacting TPT [14]. Time needs to be kept as short as possible, maintaining a trade-off in favor of critical interventions to be performed in the safest way possible. We suggest to call this the optimal *intervention to time ratio*. This ratio implies, the time every pre-hospital intervention requires, must be counterbalanced by a gain in survival it could generate. A recent cohort study of trunk trauma [5] revealed an increased mortality for shocked patients with incompressible trunk trauma, long before any definitive hemorrhage control is possible, advocating eventually in favor of advanced pre-hospital resuscitation-and hemorrhage control. However, TPT results from all elements constituting the rescue chain: extrication, intervention[26], communication with command/dispatch and receiving center and transport time. The whole process needs streamlining to keep TPT as short and safe as possible to only address the targeted and individualized essential needs of each patient.

When looking at the specific causes of death, the adjusted model (Table 3, figure 2) showed a non-significant effect of time on hemorrhage-associated mortality. The critical relationship of time and trauma hemorrhage was recently observed, demonstrating peak mortality from hemorrhage at 37 minutes[27]. This circumstance might have weakened the relationship with death by hemorrhage in the model. Both registries only include patients that arrive alive at hospital. Ball et al. indicated that with shorter TPT, more patients arrived alive, but then died subsequently [28]. Future studies need to address this question and include all patients deceased on scene. In opposition to previous reports [29], the adjusted model did not show a significant association of TPT and TBI-induced mortality.

Affirmation of TBI as the cause of death is difficult since head injured patients commonly have other confounding causes of death (hemorrhage, thoracic trauma). Moreover, a substantial proportion of TBI patients ultimately die after withdrawal of treatment and are registered as such, which may have biased the true proportion of death due to TBI.

This study has several strengths. Data were extracted from two established registries with robust data management robust. Data were derived from two geographically and structurally distinct regions with different trauma systems. The TRENAU system qualifies as *inclusive* with three designated levels of care [16]. The Paris system tends to be *exclusive* with six designated level-1 centers absorbing the most regional trauma cases [17]. These characteristics apply to other European EMS supporting the external validity and generalizability of the observations made. The present model appears robust and generalizable. As eFigure 2 illustrates, mortality retains a coherent and consistent relationship to well documented predictors and confounders.

This study carries a number of limitations linked to its design. Based on a prospective data collection and with adequate control of potential confounders, it appeared however appropriate to examine the hypothesis in a sufficiently large real-life cohort. A physician closing the case determined the cause of death, a subjective bias cannot be excluded in analogy to most existing registries, unless postmortem CT scans and/or systematic autopsies become standard. Only patients that arrived alive in hospital were included in the study a feature shared with most established trauma registries and as exposed may have weakened the relationship of hemorrhage induced mortality and time. The choice of adjustment variables may seem arbitrary and the number of variables limited. However, the adjustment aimed to compensate for case complexity and case-mix in a simple but robust way. Cases with shock (SBP<90mmHg) and/or TBI (low GCS) and high injury load (ISS) and elderly patients account for the greater part of this complexity, since they may require pre-hospital resuscitation. Hence, the models did not include any specific prehospital interventions as they are well correlated and share a high collinearity with any of the four adjustment variables in the model and are part of the so-called causal pathway. Pre-hospital interventions in France focus on advanced airway

management, fluid and vasoactive therapy and simple hemostatic measures (eTable 4). At the time of the study, blood product use was rare and advanced surgical techniques exceptional. We decided to perform complete case analysis instead of performing multiple imputation. We cannot exclude that exclusion of observations led to selection bias. Multiple imputation is not always superior to complete case analysis, in particular if missing data are not missing at random; imputation may generate a bias towards the null[30]. In this study, it seems inappropriate to impute data on prehospital time without precise geographical location as ambulances in France are currently not systematically equipped with GPS systems. Missing data led to exclude 23% of patients from both registries. However, apart from a slight difference in the mechanism of injury, excluded patients shared the characteristics and severity of injury similar to the included patients. Finally, this study included cases from a large urban and a rural-mountainous area, supporting the generalizability of the results to most of Europe and mature trauma systems. These results may less apply to very remote isolated regions and or systems with a high incidence of penetrating injury.

Conclusion

This study demonstrates an independent relationship of in-hospital all-cause mortality in trauma with total prehospital time in a physician staffed EMS in France even after adjustment for case complexity. These results imply that pre-hospital time management is to become a management objective. Both findings plaid for further streamlining of prehospital trauma care and the need to define the optimal *intervention to time-ratio*.

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477 **Table 1. Patient characteristics according to regional database.**

	Total	Paris_ Ile de France (TRAUMABASE)	Northern French Alps (TRENAU)
	N=10,126	N=5,067	N=5,059
Age, mean (sd)	41 (18)	38 (17)	42 (18)
Sex male, N (%)	7,937 (78)	3,998 (79)	3,939 (78)
Penetrating injury, N (%)	861 (9)	568 (11)	293 (6)
Circumstances, N (%)			
Road Traffic injury	5,598 (55)	3,014 (60)	2,549 (51)
Falls	3,053 (30)	1,231 (24)	1,805 (36)
Stabbing	605 (6)	399 (8)	201 (4)
Gun shot	250 (2)	169 (3)	80 (2)
Prehospital SBP, mean (sd)	117 (32)	109 (34)	126 (26)
Prehospital SBP <90 mmHg, N (%)	1,259 (13)	946 (19)	313 (7)
Prehospital GCS, N (%)			
3-8	1,518 (15)	889 (18)	629 (13)
9-13	963 (10)	517 (10)	446 (9)
13-15	7,453 (75)	3,648 (72)	3,805 (77)
ISS, mean (sd)	17 (14)	18 (15)	17 (13)
0-15, N (%)	5,313 (53)	2,679 (53)	2,634 (53)
16-24, N (%)	2,034 (20)	1,013 (20)	1,021 (20)
25-34, N (%)	1,757 (17)	818 (16)	939 (19)
≥35, N (%)	966 (10)	554 (11)	412 (8)
Overall AIS score ≥3, N (%)	6,737 (67)	3,302 (65)	3,435 (68)
Severe head injury (AIS Head ≥3), N (%)	2,724 (27)	1,346 (27)	1,378 (27)

Secondary transfer, N (%)			
In-hospital Mortality, N (%)	968 (10)	566 (11)	402 (8)

AIS=abbreviated injury scale, GCS=Glasgow Coma Scale, ISS=Injury severity score, SBP=systolic blood pressure

Table 2. Primary and secondary outcome according to pre-hospital time.

	Total	Overall in-hospital death		Death due to head injury		Death due to bleeding	
		N	% (95%CI)	N	% (95%CI)	N	% (95%CI)
TPT[a]							
0-29 min	514	27	5.3 (3.6-7.6)	13	2.5 (1.5-4.3)	8	1.6 (0.8-3.1)
30-59 min	3,535	244	6.9 (6.1-7.8)	129	3.7 (3.1-4.3)	53	1.5 (1.1-2.0)
60-89 min	3,459	344	9.9 (9.0-11.0)	179	5.2 (4.5-6.0)	63	1.8 (1.4-2.3)
90-119 min	1,624	208	12.8 (11.3-14.5)	109	6.7 (5.6-8.0)	36	2.2 (1.6-3.1)
120-179min	870	121	13.9 (11.8-16.4)	55	6.3 (4.9-8.1)	19	2.2 (1.4-3.4)
180 + min	124	24	19.4 (13.3-27.3)	16	12.9 (8.0-20.0)	3	2.4 (0.8-7.2)
Total	10,126	968	9.6 (9.0-10.1)	501	5.0 (4.5-5.4)	182	1.8 (1.5-2.1)
P value for Homogeneity test			<0.001		<0.001		0.467

[a]TPT = Total Prehospital Time, arrival of the physician-lead prehospital care-team on scene to arrival at the hospital

Table 3. Relationship between outcome and prehospital time.

	GLM OR (95% CI)[a]	P Value
Univariate analysis		

Overall death	1.09 (1.07-1.11)	<0.001
Death due to head injury	1.09 (1.06-1.11)	<0.001
Death due to bleeding	1.04 (1.00-1.09)	0.043
Multivariable analysis		
Overall death	1.04 (1.01-1.07)	0.007
Death due to head injury	1.03 (1.00-1.07)	0.153
Death due to bleeding	1.00 (0.99-1.02)	0.239

Generalized linear model with random effect by registry and EMS system

[a] Odds ratio for increase of 10 minutes in prehospital time.

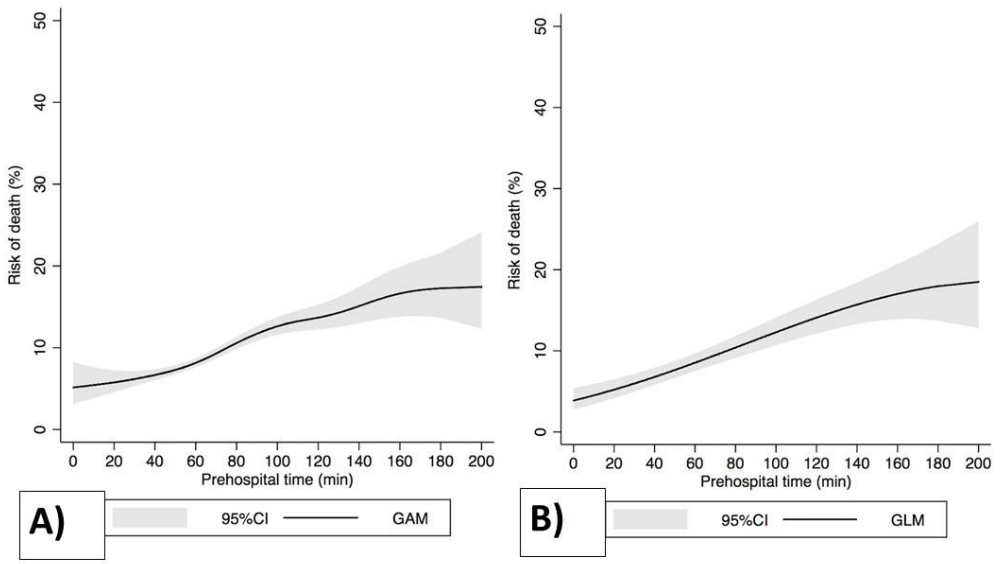


Figure 1: A) Unadjusted Generalized Additive Mixed Model representing the risk of death from all cause according to prehospital time truncated at 200 minutes. Area Under the Curve: 0.59 (0.57-0.61), Internal overall calibration E/O: 1.00 (0.94-1.06), Calibration slope: 1.03 (0.82-1.23). B) Unadjusted Generalized Linear Mixed Model representing the risk of death from all cause according to prehospital time truncated at 200 minutes. Area Under the Curve: 0.59 (0.57-0.61), Internal overall calibration E/O: 1.01 (0.94-1.07), Calibration slope: 0.99 (0.79-1.19).

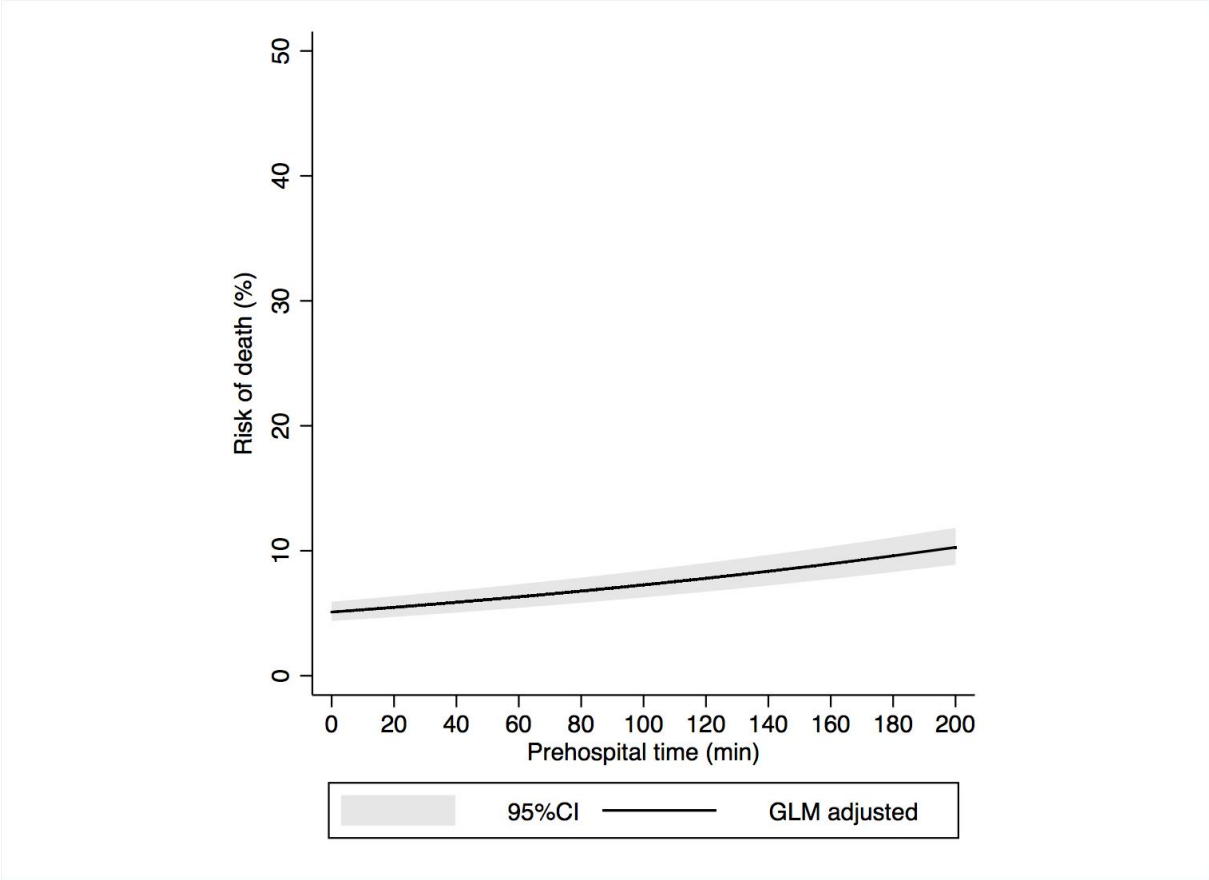
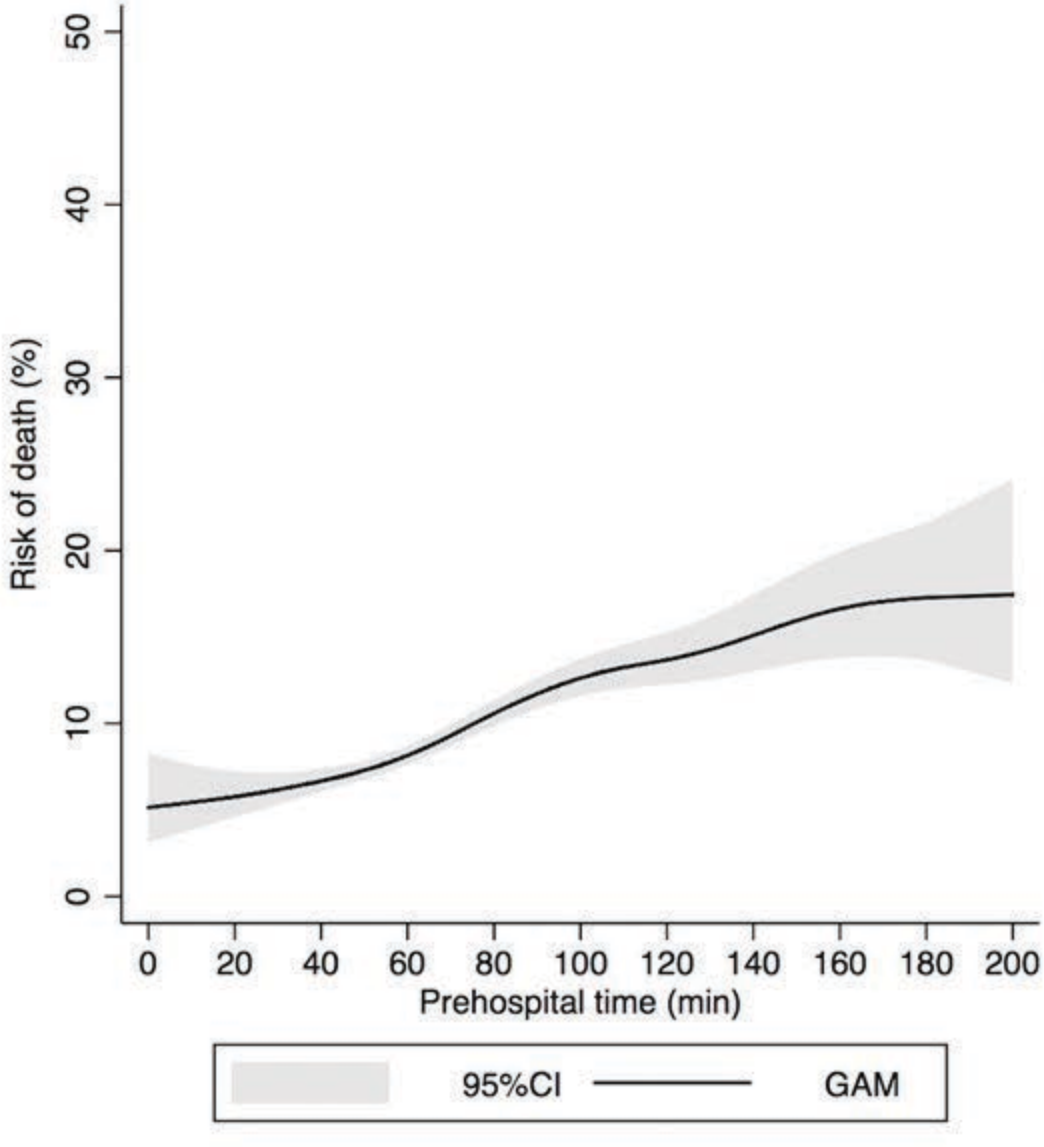
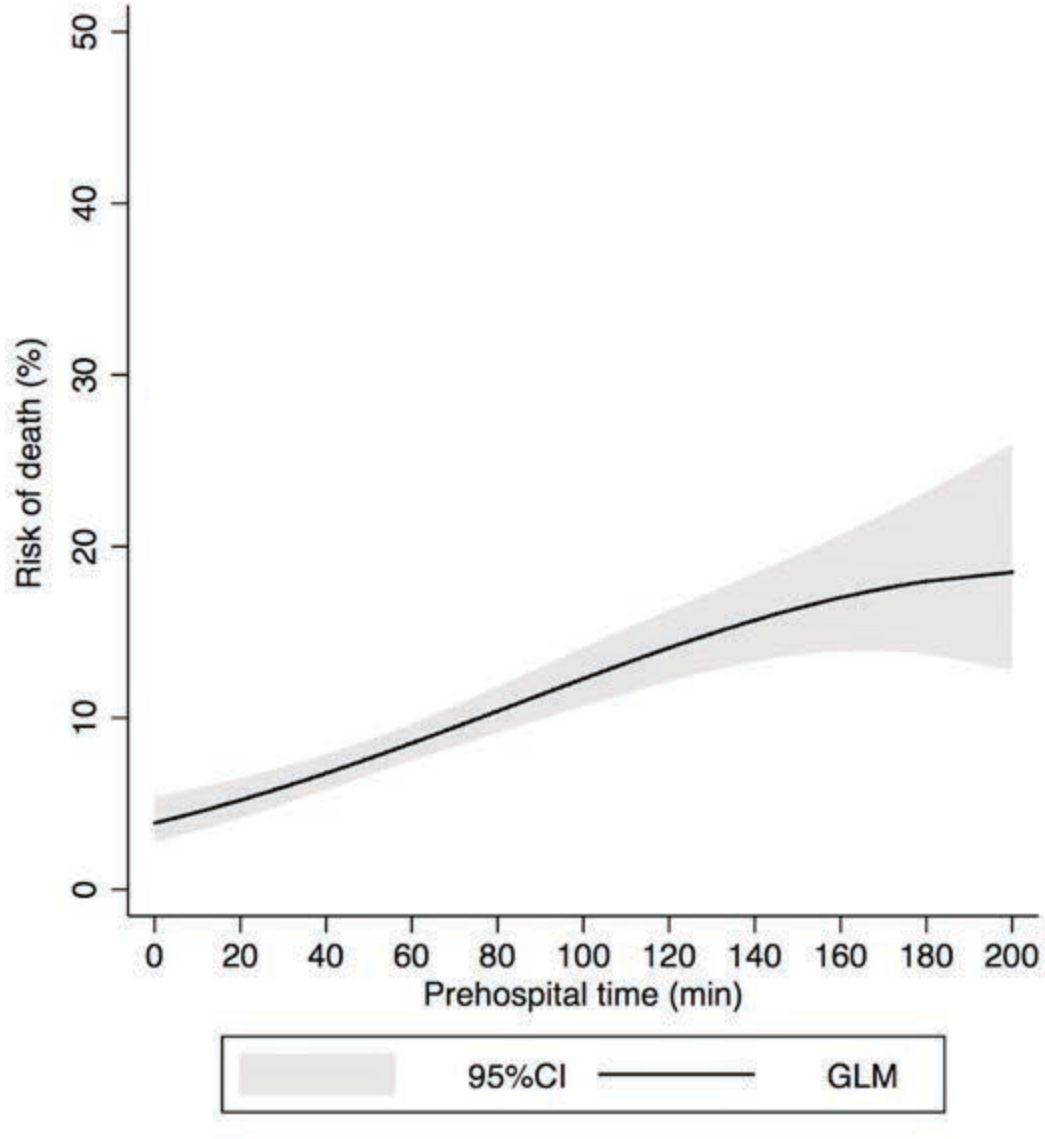
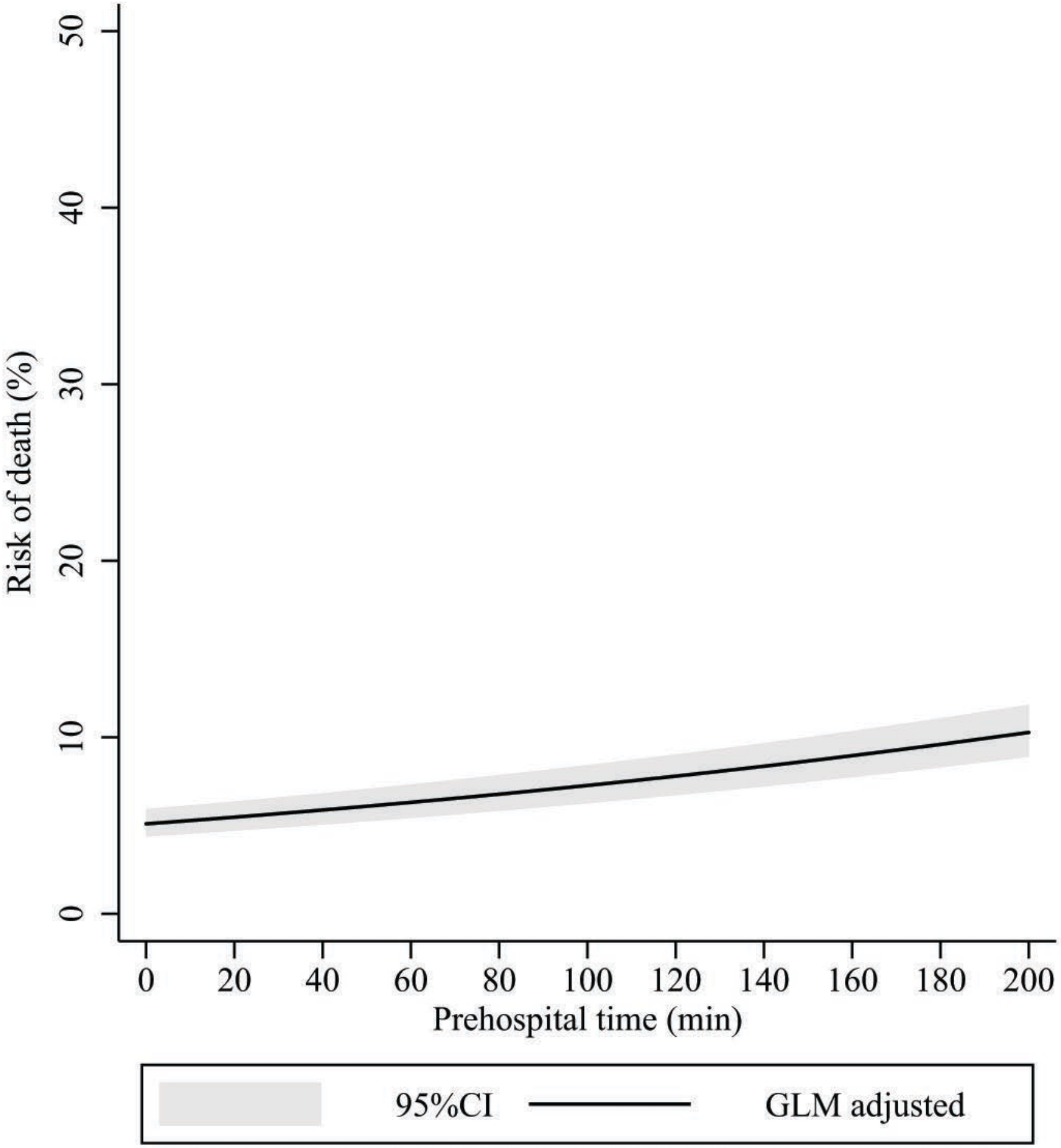


Figure 2. Adjusted relationship between death and prehospital time.

Footnote: Multivariable Generalized Linear Mixed Model representing the risk of death from all cause according to prehospital time adjusted for Age, Systolic blood pressure, GCS and Injury Severity Score. Full model is presented in eTable 5. Area Under the Curve: 0.96 (0.95-0.96), Internal overall calibration E/O: 1.00 (0.96-1.04), Calibration slope: 1.00 (0.94-1.06).


Risk of death (%)
0
10
20
30
40
50
0
20
40
60
80
100
120
140
160
180
200
Prehospital time (min)
95%CI
GAM


Risk of death (%)
0
10
20
30
40
50
0
20
40
60
80
100
120
140
160
180
200
Prehospital time (min)
95%CI
GLM


Risk of death (%)
0
10
20
30
40
50
0
20
40
60
80
100
120
140
160
180
200
Prehospital time (min)
95%CI
GLM adjusted