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Evaluation of severe rhabdomyolysis on day 30 mortality in trauma patients admitted to intensive care: a propensity score analysis of the Traumabase registry

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Abstract

Background Traumatic rhabdomyolysis (RM) is common and associated with the development of acute kidney injury and potentially with other organ dysfunctions. Thus, RM may increase the risk of death. The primary objective was to assess the effect of severe RM (Creatine Kinase [CK] > 5000 U/L) on 30-day mortality in trauma patients using a causal inference approach.

Methods In this multicenter cohort study conducted in France using a national major trauma registry (Traumabase) between January 1, 2012, and July 1, 2023, all patients admitted to a participating major trauma center hospitalized in intensive care unit (ICU) and with CK measurement were included. Confounding variables for both 30-day mortality and exposure were used to establish a propensity score. A doubly robust approach with inverse treatment weighting enabled the calculation of the average treatment effect on the treated (ATT). Analyses were performed in the overall cohort as well as in two subgroups: hemorrhagic shock subgroup (HS) and traumatic brain injury subgroup (TBI). Sensitivity analyses were conducted.

Results Among the 8592 patients included, 1544 (18.0%) had severe RM. They were predominantly males (78.6%) with median [IQR] age of 41 [27–58] years and severely injured (ISS 20 [13 – 29]) mainly from blunt trauma (90.8%). In the entire cohort, the ATT, expressed as a risk difference, was 0.073 [-0.054 to 0.200]. Considering the 1311 patients in the HS subgroup, the ATT was 0.039 [0.014 to 0.063]. As in the overall cohort, there was no effect on mortality in the TBI subgroup. Severe RM was associated with greater severity of trauma and more complications (whether related to renal function or not) during the ICU stay. Mortality due to multiorgan failure (39.9% vs 12.4%) or septic shock (2.6% vs 0.8%) was more frequent among patients with severe RM.

Conclusions Severe RM was not associated with 30-day mortality considering the overall cohort. However, it was associated with a 4.0% increase in 30-day mortality among patients with concurrent hemorrhagic shock. Severe RM plays a significant role in ICU morbidity.

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Keywords Rhabdomyolysis, Crush syndrome, Severe trauma, Hemorrhage, Intensive care unit, Trauma related death, Multiple organ failure

Background

Trauma is the leading cause of death in young adults (aged 15–49) [1]. Approximately 25% of trauma-related deaths are deemed preventable, primarily attributable to hemorrhage, traumatic brain injury, and infections [2, 3]. Morbidities emerging during hospitalization, notably in the intensive care unit (ICU), significantly contribute to this mortality rate. Among these, rhabdomyolysis (RM) is a frequent trauma-related morbidity.

Trauma-related RM can be caused by several factors, including direct injury such as crush syndrome, major limb trauma, and surgical repair, as well as indirect muscular injury due to massive hemorrhage or vascular damage. Elevated creatine kinase (CK) levels are reported in up to 85% of trauma patients, although the precise frequency of traumatic RM remains uncertain.

Acute kidney injury (AKI) is the most common complication of RM, occurring in 10% to 55% of patients presenting with RM [4]. The current understanding of RM pathophysiology focuses on the myoglobin release axis and its degradation pathways, known as the heme/iron axis [5]. Experimental studies have suggested an association between rhabdomyolysis and the development of multi-organ injuries, particularly extra-renal injuries [6, 7]. In the pathophysiology of these injuries, inflammation and iron toxicity play significant roles and potentiate each other [8, 9]. Considering these factors, rhabdomyolysis may contribute to the development of multiple organ failure beyond renal damage alone, thereby worsening the prognosis of severely injured trauma patients.

The primary objective of this study was to examine the association between severe traumatic RM and 30-day mortality following severe trauma. We focused secondarily on two specific subgroups relevant to trauma-related mortality: patients with hemorrhagic shock (HS) and traumatic brain injury (TBI). Other objectives included describing the incidence of traumatic RM and evaluating its associated morbidity.

Methods

Patients

This retrospective multicenter observational study used prospectively collected data from the TraumaBase® registry encompassing 26 level 1 trauma centers in France. Briefly, clinical, paraclinical, and anamnestic data were prospectively recorded in the registry [10–12]. Patients admitted directly to 21 participating centers between January 2012 and July 2023 for severe trauma and initially admitted to the ICU were included. Patients aged under 18, those without serum CK measurements, or those with missing 30-day mortality data were excluded from the analysis.

The following definitions were used:

- A blood CK peak exceeding 1000 U/L defined RM, and exceeding 5000 U/L defined severe RM [13].
- HS was determined if patients met at least one of the following criteria: receiving four or more pRBC transfusions within the first 6 h of management, association of base excess ≤ -5 mEq/L and shock index > 1 on arrival, or requiring immediate hemostatic surgery or interventional radiology before completion of full lesion assessment by whole-body CT scan [12, 14, 15].
- The primary endpoint was 30-day mortality. Patients discharged from ICU to a "regular" department (e.g., surgery ward or rehabilitation ward) or home before day 30 were considered alive at day 30.
- Massive transfusion was defined as the transfusion of at least 10 pRBCs over the first 24 h.
- TBI was defined as head abbreviated injury scale > 3.
- The definition of AKI was based on the kidney disease improving global outcomes (KDIGO) stage, determined using the maximum creatinine during the ICU stay. Since baseline creatinine was unavailable for trauma patients, it was back-calculated according to the KDIGO guidelines using the modification of diet in renal disease formula with a glomerular filtration rate of 75 ml/min per 1.73 $m.^2$ [16, 17].
- To define shock severity, patients were categorized into four groups based on the Shock Index (SI): *no shock* defined by SI < 0.6, *mild shock* by SI ≥ 0.6 to < 1.0, *moderate shock* by SI ≥ 1.0 to < 1.4, and *severe shock* by SI ≥ 1.4 [18]. Because norepinephrine is used early in cases of shock following trauma in France, this may bias the interpretation of the shock index at admission. Therefore, patients receiving norepinephrine in the trauma bay, with a heart rate > 120 bpm at admission and who were transfused in the first few hours, were categorized into *severe shock* [19].

Statistical analysis

Data were summarized as median (interquartile range [IQR]) for quantitative variables and count (percentage) for qualitative variables. For the univariate analysis,

the tests used depended on the type of variable, its distribution, and the number of patients. Specifically, we employed Fisher's exact test, the chi-square test, Student's t-test, or the Mann–Whitney test, with significance set at $p < 0.05$. Statistical analysis was conducted using R software version 4.3.2 for Macintosh (R Foundation for Statistical Computing, Vienna, Austria). Missing data were imputed using a factorial analysis method only for variables used to estimate propensity scores (PSs) (Additional file 1–Table S1). Imputed values were used solely for constructing PSs, while unimputed data were utilized for descriptive analyses.

According to Hsieh's formula, with a 30-day mortality prevalence of 20% among the non-exposed, a non-exposed/exposed ratio for severe rhabdomyolysis (RM) of 4.5, and a power of 90%, a total sample size of approximately 4653 subjects would be required. This sample would consist of 846 exposed individuals and 3807 non-exposed individuals to detect a 5% difference with an alpha level of 0.05 (post-hoc calculation).[20].

Doubly robust analysis was performed to study the impact of severe RM on mortality within the overall cohort and two subgroups: HS without TBI (defined as HS subgroup) and TBI without HS (defined as TBI subgroup). In each group, propensity scores (PSs) models were calculated and included confounding factors linked to severe RM and 30-day mortality, as well as prognostic factors only linked to mortality, such as age, sex, trauma type, injury severity score (ISS), and different ICU morbidities (Details are provide in the Additional file 2).

PSs were estimated using logistic regression, and kernel density graphs were used to assess the overlap between exposed and unexposed groups. The inverse probability of treatment weights (IPTW) was calculated to balance covariates. The average treatment effect on the treated (ATT) criterion was used to measure the effect of severe RM on mortality and was estimated using augmented inverse propensity weighting (AIPW). Results are expressed as ATT [95% confidence interval].

To address bias due to the statistical method, sensitivity analyses were performed. Three additional methods were employed: random forest PSs estimations with doubly robust estimation using AIPW or targeted maximum likelihood estimates, and adjustments based on PSs estimated by logistic regression, expressed as odds ratios (OR) with 95% confidence intervals. Furthermore, we considered different patient categories: those with ICU stays exceeding 2 days and patients with severe RM, defined by serum myoglobin levels exceeding 5000 µg/L. Finally, to address potential biases associated with the date of hospital admission, the admission period was considered as a clustering factor in the calculation of the ATT.

Furthermore, 30-day mortality was analyzed using Kaplan–Meier estimates for both the unweighted and PS-weighted datasets. P-values were calculated using the log-rank test.

Results

Between January 2012 and July 2023, a total of 42,970 patients were included in the TraumaBase® registry, of whom 12137 had CK peak values available. Among them, 8592 patients were admitted to the ICU and included in the analysis (Fig. 1). Of these, 4606 (53.6%) presented with RM, and 1544 (18.0%) were classified as having severe RM. The majority of patients were male (78.6%), with a median age of 41 [27–58]. The median ISS was 20 [12–28], and the predominant trauma mechanism was blunt (90.8%). Patients with severe RM were younger and had more severe injuries (median ISS 26 [12, 17–35] in the severe RM group vs. 19 [11–26] in the group without severe RM, $p < 0.001$). In the severe RM group, 18.7% patients had TBI (vs. 31.6% in the other group, $p < 0.001$) and 48.3% had HS (vs. 16.5%, $p < 0.001$). Table 1 details the cohort characteristics.

PSs were calculated using the 17 variables detailed in the Additional file 2. IPTW was employed to effectively balance the major differences between the two groups (Additional file 3 – Figure S1).

Study of the primary outcome

Analysis of the overall cohort

Univariate analysis showed no difference in 30-day mortality between the severe RM group and the group without RM (21.2% vs. 21.8%; $p = 0.7$; Table 2). Following a doubly robust estimation of causal effect, no significant difference remained in the overall cohort, with the ATT expressed as a difference in 30-day mortality risk measured at 0.073 [−0.054–0.200] (Table 3). These results were consistent regardless of the sensitivity analyses except for doubly robust estimation of causal effect using random forests (Additional file 1–Table S2).

Analysis of the HS subgroup

Univariate analysis showed a difference in 30-day mortality in the HS subgroup (24.9% in the group with severe RM vs. 19.1% in the group without, $p = 0.012$; Table 2). Following a doubly robust estimation of causal effect, the risk of mortality was significantly elevated in the HS subgroup, with an ATT measured at 0.039 [0.014 to 0.063] (Table 3). These results were consistent regardless of the doubly robust statistical method used. The OR for mortality in this subgroup was 2.14 (1.41 to 3.23), $p < 0.001$. Similar results were observed in patients with an ICU length of stay exceeding 2 days, and the magnitude of the effect was greater (ATT 0.046 [0.020 to 0.072]; OR 3.37

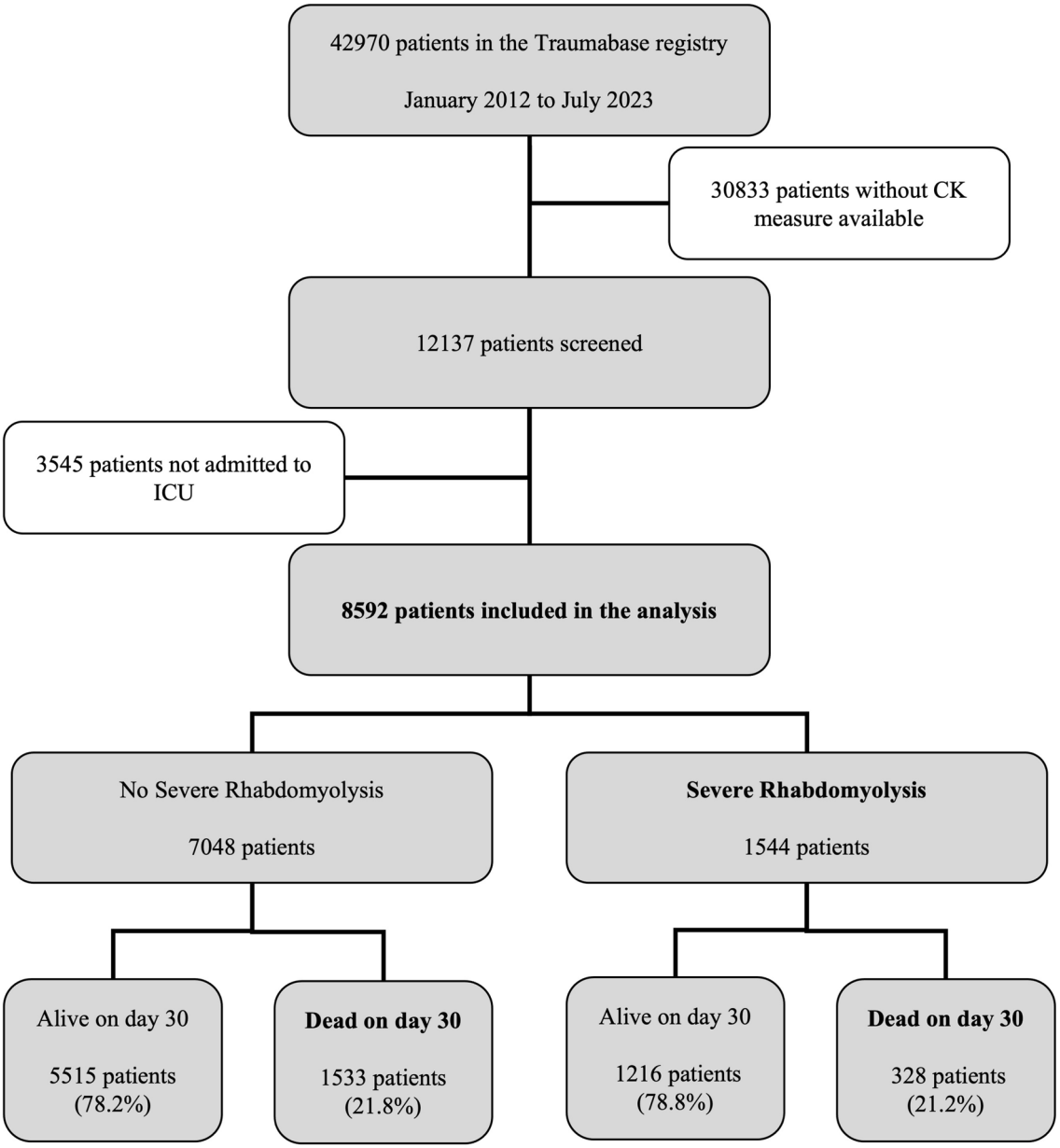

Fig. 1 Study flow chart

(2.05 to 5.67), $p < 0.001$). However, when defining severe RM by peak myoglobin levels, no difference was found between groups (Additional file 1 – Table S2).

Analysis of the TBI subgroup

Univariate analysis showed no difference in 30-day mortality (42.1% in the group with severe RM vs. 48.7% in the group without, $p = 0.14$). After a doubly robust estimation of causal effect, no significant differences were found in mortality, with an ATT measured at 0.001 [−0.015 to 0.018] (Table 3). These results were consistent regardless of the sensitivity analyses performed (Additional file 1–Table S2).

Unadjusted and adjusted Kaplan–Meier curves for each patient category are provided in the Fig. 2.

Analysis of the mortality causes

Without adjustment, mortality due to exsanguination, septic shock, and multiple organ failure was more frequent in the group with severe RM compared to those without severe RM. These differences were more pronounced in the HS subgroup. (Table 2).

Table 1 Patients characteristics

Severe rhabdomyolysis (CK > 5000U/L)					
Characteristic	**Overall cohort**[1]	**No, N = 7048**[1]	**Yes, N = 1544**[1]	**Missing values, n (%)**	***p*-value**[2]
Age (years)	41 [27–58]	42 [28–59]	35 [26–49]	0	< 0.001
Men	6749 (78.6)	5474 (77.7)	1275 (82.7)	9 (0.1)	< 0.001
ASA status > 2	977 (11.6)	862 (12.5)	115 (7.6)	161 (1.9)	< 0.001
SOFA	5 [1–9]	4 [1–9]	8 [3–11]	92 (1.1)	< 0.001
SAPSII	33 [19–52]	31 [18–51]	40 [25–59]	44 (0.5)	< 0.001
ISS	20 [12–28]	19 [11–26]	26 [12, 17–35]	174 (2.0)	< 0.001
AIS Head	2 [0–4]	2 [0–4]	0 [0–3]	212 (2.5)	< 0.001
AIS Face	0 [0–1]	0 [0–1]	0 [0–1]	212 (2.5)	0.13
AIS Thorax	2 [0–3]	2 [0–3]	3 [0–4]	212 (2.5)	< 0.001
AIS Abdomen	0 [0–2]	0 [0–2]	2 [0–3]	212 (2.5)	< 0.001
AIS extremity	2 [0–3]	1 [0–2]	3 [2, 3]	212 (2.5)	< 0.001
AIS Skin	0 [0–0]	0 [0–0]	0 [0–0]	212 (2.5)	0.7
Blunt trauma	7751 (90.8)	6279 (89.8)	1472 (95.8)	60 (0.7)	< 0.001
Trauma mechanism				60 (0.7)	< 0.001
Traffic accident	4029 (47.2)	3161 (45.2)	868 (56.5)		
Fall	2461 (28.8)	2035 (29.1)	426 (27.7)		
Pedestrian hit by vehicle	792 (9.3)	676 (9.7)	116 (7.5)		
Other	469 (5.5)	407 (5.8)	62 (4.0)		
Stab wound	429 (5.0)	406 (5.8)	23 (1.5)		
Firearm	352 (4.1)	310 (4.4)	42 (2.7)		
Hospital admission					
Total prehospital time (min)	78 [57–105]	77 [56–105]	80 [59–110]	2510 (29)	0.002
Shock index	0.7 [0.6–0.9]	0.7 [0.6–0.9]	0.9 [0.7–1.2]	149 (1.7)	**< 0.001**
Blood lactate (mmol/L)	2.0 [1.0–3.0]	2.0 [1.0–3.0]	3.0 [2.0–5.0]	870 (10)	**< 0.001**
Hemoglobin (g/dL)	12.7 [11.0–14.0]	12.9 [11.3–14.1]	11.7 [9.9–13.3]	63 (0.7)	**< 0.001**
Platelets count (G/L)	222 [180–266]	222 [182–266]	218 [171–266]	108 (1.3)	**0.003**
Quick time ratio (%)	79 [64–91]	81 [68–93]	67 [52–81]	271 (3.2)	**< 0.001**
Blood fibrinogen (g/L)	2.3 [1.8–2.8]	2.3 [1.9–2.9]	1.9 [1.4–2.4]	368 (4.3)	**< 0.001**
Mechanical ventilation use	3992 (47.2)	3139 (45.3)	853 (55.9)	130 (1.5)	**< 0.001**
Norepinephrine infusion	2,834 (34.1)	2,006 (29.5)	828 (54.3)	276 (3.2)	**< 0.001**
Shock severity				145 (1.7)	**< 0.001**
No shock	2,288 (27.1)	2,103 (30.3)	185 (12.2)		
Mild shock	4,351 (51.5)	3,692 (53.2)	659 (43.6)		
Moderate shock	1,084 (12.8)	753 (10.9)	331 (21.9)		
Severe shock	724 (8.6)	386 (5.6)	338 (22.3)		
Groups characteristics					
Hemorrhagic shock	1,909 (22.2)	1,163 (16.5)	746 (48.3)	0 (0)	**< 0.001**
Traumatic brain injury	2455 (29.3)	2174 (31.6)	281 (18.7)	212 (2.5)	**< 0.001**
Rhabdomyolysis	4607 (53.6)	3063 (43.5)	1544 (100)	0	**< 0.001**
Highest CK level (U/L)	1143.0 [389.0–3248.0]	808.5 [311.8–1849.0]	8037.0 [5963.0–12,716.8]	0	**< 0.001**
Highest myoglobin level (µg/L)	758.5 [256.0–2162.3]	516.5 [196.3–1164.0]	5667.5 [3168.5–9217.5]	5694 (66)	**< 0.001**

[1] Median [IQR]; n (%), [2]Wilcoxon rank sum test; Pearson's Chi-squared test, *AIS* Abbreviated Injury Scale*; ASA* American Society of Anesthesiology*; CK* Creatine kinase*; GCS* Glasgow coma scale*; HR* Heart rate*; ISS* Injury Severity Score*; SAP* Systolic arterial pressure*; SAPSII* Simplified Acute Physiology Score II*; SOFA* Sequential Organ Failure Assessment

Table 2 Mortality and ICU morbidity in the overall cohort and in the HS subgroup

Characteristic	Overall cohort			HS subgroup		
	No severe RM N = 7,048[1]	Severe RM N = 1,544[1]	*p*-value[2]	No severe RM N = 737[1]	Severe RM N = 574[1]	p-value[2]
Massive transfusion	146 (2.1)	249 (16.3)	**< 0.001**	102 (13.9)	196 (34.7)	**< 0.001**
pRBC in the first 24 h (units)	0.0 [0.0–0.0]	0.0 [0.0–6.0]	**< 0.001**	4.0 [1.0–7.0]	6.0 [2.0–12.0]	**< 0.001**
Plasma in the first 24 h (units)	0.0 [0.0–0.0]	0.0 [0.0–5.0]	**< 0.001**	2.0 [0.0–6.0]	5.0 [0.0–10.0]	**< 0.001**
Platelets concentrates in the first 24 h (units)	0.0 [0.0–0.0]	0.0 [0.0–0.0]	**< 0.001**	0.0 [0.0–1.0]	0.0 [0.0–2.0]	**< 0.001**
Acute kidney injury	785 (13.5)	421 (34.2)	**< 0.001**	179 (29.3)	213 (46.7)	**< 0.001**
KDIGO			**< 0.001**			**< 0.001**
0	5,047 (86.5)	809 (65.8)		432 (70.7)	243 (53.3)	
1	399 (6.8)	171 (13.9)		99 (16.2)	81 (17.8)	
2	229 (3.9)	116 (9.4)		48 (7.9)	67 (14.7)	
3	157 (2.7)	134 (10.9)		32 (5.2)	65 (14.3)	
Renal replacement therapy	115 (1.7)	185 (12.1)	**< 0.001**	36 (4.9)	123 (21.7)	**< 0.001**
Day 30 ventilator free days	29.0 [3.0–30.0]	25.0 [2.0–29.0]	**< 0.001**	26.0 [8.0–29.0]	21.0 [2.0–28.0]	**< 0.001**
ARDS	656 (9.4)	313 (20.6)	**< 0.001**	104 (14.3)	142 (25.3)	**< 0.001**
Infection	1,499 (21.3)	547 (35.4)	**< 0.001**	236 (32.0)	253 (44.1)	**< 0.001**
Septic shock	263 (3.7)	168 (10.9)	**< 0.001**	58 (7.9)	96 (16.7)	**< 0.001**
Surgery during hospital stay	3,831 (54.4)	1,301 (84.4)	**< 0.001**	627 (85.2)	540 (94.2)	**< 0.001**
ICU LOS	5.0 [2.0–11.0]	9.0 [4.0–20.0]	**< 0.001**	7.0 [3.0–15.5]	11.0 [5.0–24.0]	**< 0.001**
Hospital LOS	11.0 [5.0–23.0]	24.0 [11.0–45.0]	**< 0.001**	17.0 [8.0–36.0]	30.0 [13.0–58.0]	**< 0.001**
Dead on day 1	126 (1.8)	26 (1.7)	0.8	25 (3.4)	14 (2.4)	0.3
Dead on day 30	1,533 (21.8)	328 (21.2)	0.7	141 (19.1)	143 (24.9)	**0.012**
In hospital death	1,661 (23.6)	354 (23.0)	0.6	157 (21.4)	150 (26.2)	**0.041**
Death cause			**< 0.001**			0.12
CNS	959 (63.0)	104 (34.0)		20 (14.7)	12 (9.3)	
Exsanguination	45 (3.0)	27 (8.8)		30 (22.1)	22 (17.1)	
MOF	189 (12.4)	122 (39.9)		57 (41.9)	75 (58.1)	
Other	12 (0.8)	3 (1.0)		2 (1.5)	2 (1.6)	
Septic shock	12 (0.8)	8 (2.6)		4 (2.9)	5 (3.9)	
Withdrawal of care	305 (20.0)	42 (13.7)		23 (16.9)	13 (10.1)	

[1] n (%); Median [Q1—Q3], [2]Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test

In the overall cohort, after PS-matching, the causes of mortality differed between patients with and without severe RM (Table 4; $p = 0.040$). Mortality from central neurological causes was predominantly observed in the group without severe RM (40.1% with severe RM vs. 46.9% without severe RM), while mortality from multiple organ failure or septic shock was more frequent in the group with severe RM (31.7% with severe RM vs. 22.4% without severe RM and 2.7% with severe RM vs. 1.0% without severe RM, respectively). The prevalence of deaths due to exsanguination or related to withdrawal of care was lower in the group with severe RM (8.6% with severe RM vs. 7.9% without severe RM and 17.6% with severe RM vs. 21.1% without severe RM, respectively).

RM-related morbidity

The prevalence of RM was 41.2% for patients with an ISS ≤ 14, 58.2% for patients with an ISS between 15 and 24, and 60.3% for those with an ISS ≥ 25. Severe RM followed this increasing severity distribution, with rates of 10.4%, 17.9%, and 24.0%, respectively (Fig. 3). Table 2 details morbidity in the ICU. Patients with severe RM exhibited greater morbidity, with an increased prevalence of AKI and requirement for renal replacement therapy (RRT). They experienced longer durations of mechanical ventilation and were more prone to developing ARDS, infections, or septic shock. Patients with severe RM were also more frequently transfused and had prolonged ICU and hospital stays.

Table 3 Doubly robust estimation of causal effect: main evaluation

Statistical method	Propensity Score	Odd ratio	ATT	Mean SE
Overall Cohort, n = 8592 (RM severe = 1544; No RM severe = 7048)				
Double robust, AIPW	LR	–	0.073[– 0.054,0.2]	0.065
Double robust, AIPW	Random forest	–	**0.011[0.004,0.018]**	**0.003**
Double robust, TMLE	Random forest	–	**0.013[0.006,0.019]**	**0.003**
Adjustment on PS	LR	1.16 (1.05,1.28) [ns]	–	–
Hemorrhagic shock subgroup, n = 1311 (RM severe = 574; No RM severe = 737)				
Double robust, AIPW	LR	**–**	**0.039[0.014,0.063]**	**0.012**
Double robust, AIPW	Random forest	**–**	**0.029[0.012,0.046]**	**0.009**
Double robust, TMLE	Random forest	**–**	**0.031[0.015,0.048]**	**0.009**
Adjustment on PS	LR	**2.14(1.41,3.23)** [‡]	**–**	**–**
Traumatic brain injury subgroup, n = 1916 (RM severe = 133; No RM severe = 1783)				
Double robust, AIPW	LR	–	0.001[–0.015,0.018]	0.008
Double robust, AIPW	Random forest	–	–0.007[–0.024,0.009]	0.008
Double robust, TMLE	Random forest	–	–0.005[–0.022,0.011]	0.008
Adjustment on PS	LR	1.68(0.54,5.55)[ns]	–	–

ns: *p*-value > 0.05/‡: *p*-value = < 0.001, *AIPW* augmented inverse propensity weighting; *ATT* Average treatment effect on the treated; *HS* Hemorrhagic shock; *ICU* intensive care unit; *LOS* length of stay; *LR* Logistic regression; *SE* Standard error; *TBI* Traumatic brain injury; *TMLE* targeted maximum likelihood estimates

Discussion

In this cohort of severe trauma patients admitted to the ICU, RM was frequent, affecting more than half of patients, with almost one in five experiencing severe RM. Thirty-day mortality did not show significant modification by the presence of severe RM in the overall cohort or the TBI subgroup. However, a significant increase in mortality was observed in the HS subgroup, with a 3.9% increase in mortality in patients with HS and severe RM. Severe RM was associated with increased mortality from multiple organ failure and septic shock. Additionally, severe RM correlated with increased morbidity during the ICU stay in the entire cohort, particularly evident in the HS subgroup.

Few studies have examined the mortality associated with rhabdomyolysis other than by univariate analysis, and, as in our study, they have shown no difference in mortality (Additional file 1–Table S3). TBI and HS patients represent two specific populations in traumatology, with these conditions often responsible for most of mortality cases. Unlike the overall cohort, mortality increased notably in HS subgroup. It is consistent with a recent animal study analyzing the effects of this double insult on renal function. In this porcine model with RM and HS, the double insult was responsible for greater renal failure, but also an increase in mortality and extra-renal organ failure [21]. From a pathophysiological perspective, an overlap exists between the mechanisms of RM toxicity and those of HS. In HS, hypovolemia, ischemia–reperfusion injury, and the severity of trauma trigger an inflammatory cascade leading to organ failure and mortality [22–24]. RM toxicity includes hypovolemia and consequent vasoconstriction, myoglobin precipitation, and direct myoglobin toxicity. Notably, the iron ion in heme is central in local toxicity through lipid peroxidation, ultimately resulting in cell death by ferroptosis [25–27]. Additionally, a significant systemic inflammatory response is associated with RM toxicity [28, 29]. While traumatic RM is predominantly associated with renal injury in the literature, it is notable that this toxicity may extend to other organs, such as the liver [6, 13, 30–32]. Furthermore, among medical causes of RM, its contribution to increased mortality and the development of multiple organ failure has been established.[33, 34] RM may act as a "second hit" following HS, potentially worsening organ failure and contributing to mortality. The observed effect, though significant, was relatively modest, with mortality increasing by approximately 3–5%. Limited sample sizes in previous studies may have constrained their ability to draw definitive conclusions regarding mortality [35]. The mortality patterns in the overall cohort (Table 2) indicated differences in causes of death, with central nervous system-related mortality primarily in the group without severe RM and exsanguination predominantly in the severe RM group. This variation in the distribution of neurological lesions may account for the lack of significant mortality differences between groups in univariate analysis, despite the more severe clinical presentation and higher severity scores in patients with severe RM. This study highlights significantly higher morbidity and the highest consumption of healthcare resources in the ICU among patients with severe RM

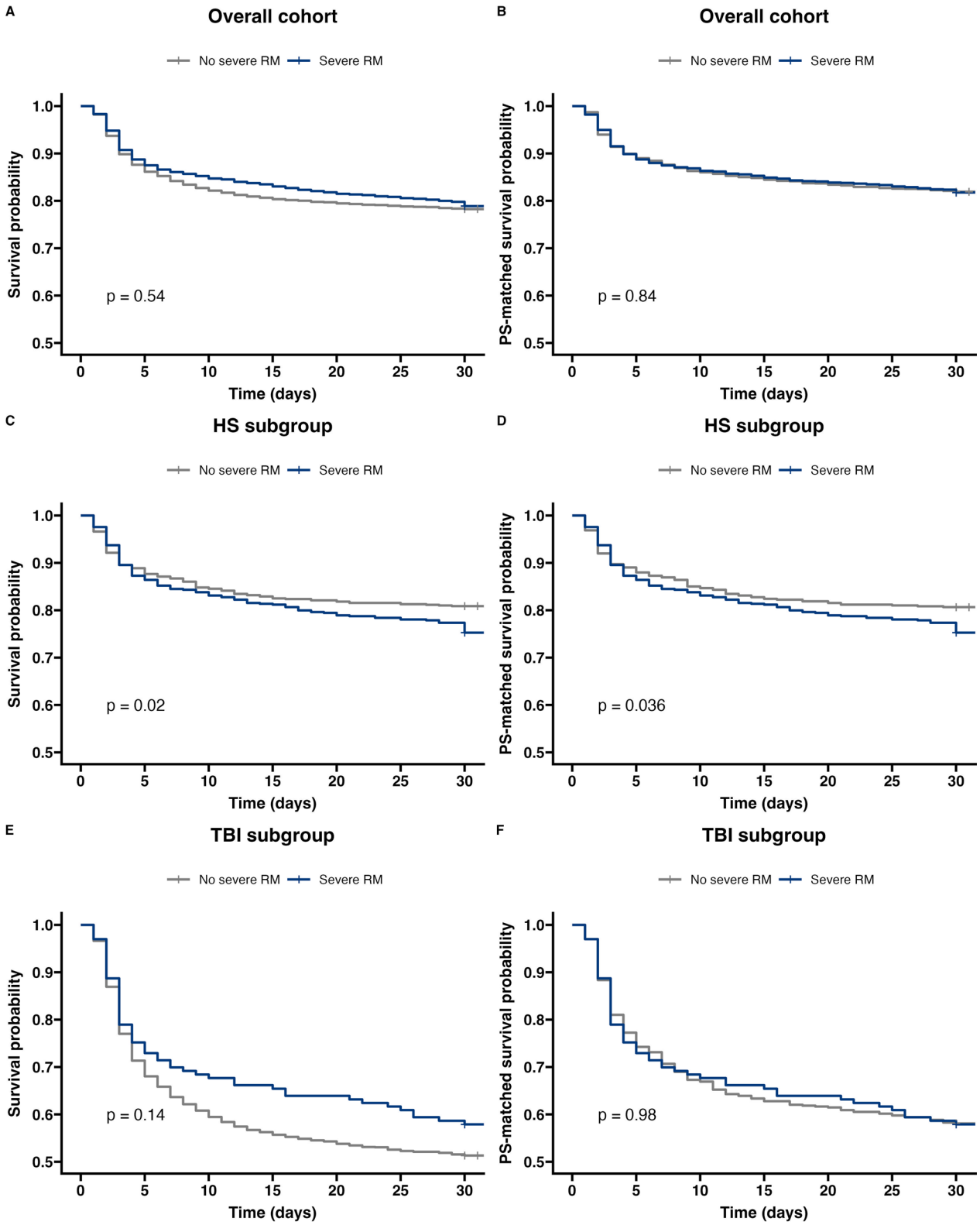

Fig. 2 Kaplan–Meier survival curve of patients with or without severe rhabdomyolysis (RM). **A** Unweighted Kaplan–Meier survival curves in the overall cohort. **B** Propensity score-weighted Kaplan–Meier survival curves in the overall cohort. **C.** Unweighted Kaplan–Meier survival curves in the hemorrhagic shock (HS) subgroup. **D** Propensity score-weighted Kaplan–Meier survival curves in the HS subgroup. **E** Unweighted Kaplan–Meier survival curves in the traumatic brain injury (TBI) subgroup. **F** Propensity score-weighted Kaplan–Meier survival curves in the TBI subgroup

Table 4 Death causes after 2:1 matching after PS estimation in the overall cohort

Severe rhabdomyolysis (CK > 5000U/L)			
Characteristic	**No N = 2174[1]**	**Yes N = 1332[1]**	***p*-value**
Death causes			**0.040**
CNS	191 (46.9)	91 (40.1)	
Exsanguination	35 (8.6)	18 (7.9)	
MOF	91 (22.4)	72 (31.7)	
Septic shock	4 (1.0)	6 (2.7)	
Withdrawal of care	86 (21.1)	40 (17.6)	

[1] n (%), [2]Fisher's exact test, *CNS* central nervous system; *MOF* multiple organ failure

compared to those without, regardless of HS status. While the causal relationship between RM and acute AKI requiring RRT is established, the specific contribution of severe RM to other complications, such as infections and prolonged ventilation, remains inconclusive. As noted by Stewart et al., RM may exacerbate these comorbidities [16]. Additionally, patients with severe RM tended to have more severe trauma and a higher incidence of HS, both linked to greater morbidity. Therefore, assessing the severity of RM seems crucial for evaluating the prognosis of trauma patients.

From a clinical perspective, the results of this study highlight the potential role of rhabdomyolysis in the development of organ failure in intensive care. The diagnosis of rhabdomyolysis is likely to be regularly underestimated, as evidenced by the number of patients in the database lacking CK measurements (Fig. 1). Implementing measures to diagnose rhabdomyolysis and assess its severity can help evaluate patient prognosis from the early days of treatment. Currently, there is no specific therapy; only preventive measures are suggested to mitigate renal impairment due to rhabdomyolysis [13]. Our results suggest a harmful association between hemorrhage and rhabdomyolysis. In this context, tourniquets can contribute to the development of rhabdomyolysis. While the benefits of tourniquets are well established, it is essential to adhere strictly to the indications for their use and to consider alternatives, such as hemostatic

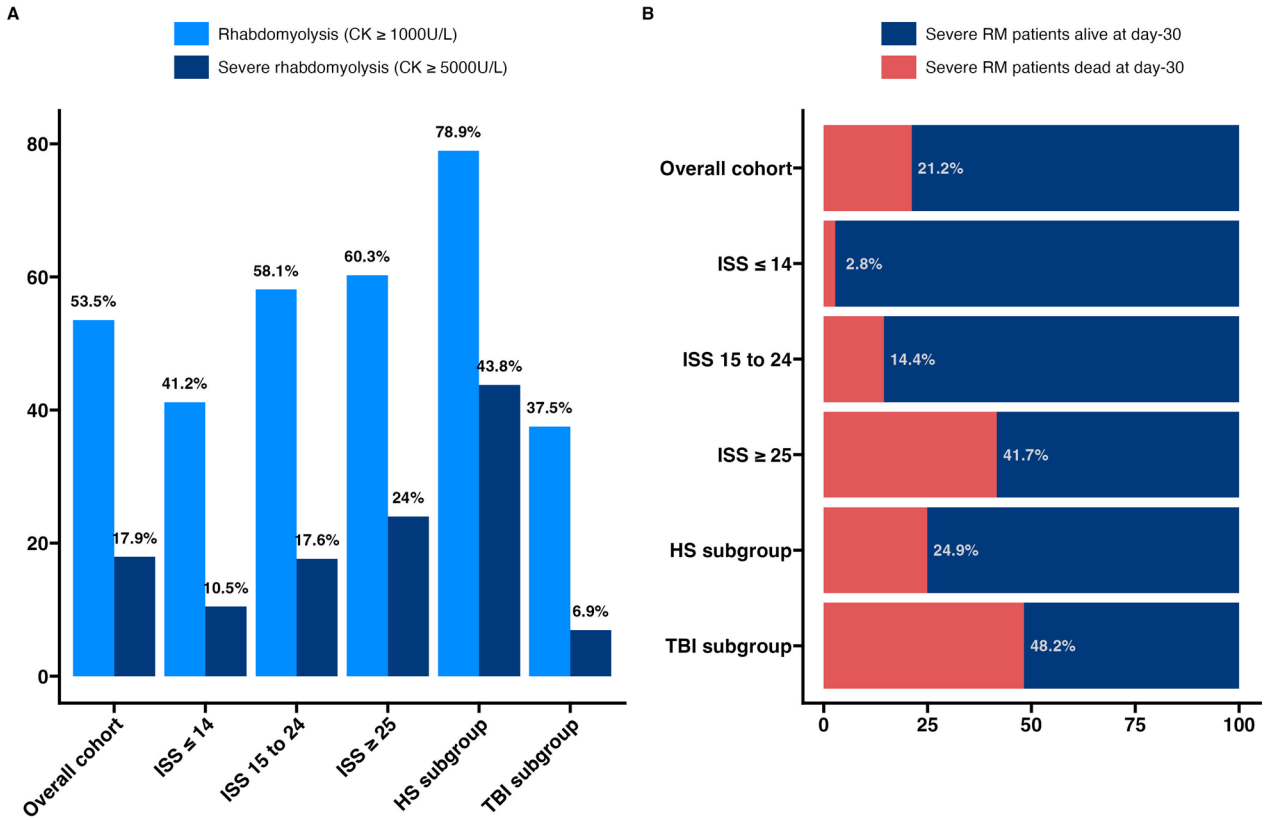

Fig. 3 **A** Distribution of the prevalence of rhabdomyolysis and severe rhabdomyolysis across different severity classes: overall cohort, ISS ≤ 14, ISS 15 to 24, ISS ≥ 25, HS subgroup, and TBI subgroup.**B** Mortality rates among patients with severe RM across different severity classes: overall cohort, ISS ≤ 14, ISS 15 to 24, ISS ≥ 25, HS subgroup, and TBI subgroup. *RM* Rhabdomyolysis; *ISS* injury severity score; *HS* Hemorrhagic shock; *TBI* Traumatic Brain Injury

pressure bandages, from the pre-hospital phase onward. Additionally, limiting the duration of tourniquet use appears to be a crucial measure to reduce rhabdomyolysis resulting from prolonged ischemia. Re-evaluation of the tourniquet should occur as early as possible, ideally in the pre-hospital phase, to convert it to hemostatic pressure bandage [36]. The demographic characteristics of our cohort align with previous studies on trauma patients: predominantly young males, severely injured, and primarily with blunt trauma [16, 17, 30, 37, 38]. The prevalence of severe RM was similar to that reported in research focusing on patients admitted to the ICU [16, 37–39]. Moreover, the incidence of AKI and the need for RRT align with findings from previous studies [16, 17, 37, 38, 40]. We relied on the peak CK value to conduct our analysis. Numerous studies have elucidated CK kinetics following trauma, with the peak typically occurring within the first 3 days post-admission [17, 30, 31, 37, 41]. To ensure the inclusion of patients within this critical time frame, we conducted a sensitivity analysis limited to those with a hospital stay exceeding 2 days. The results from this analysis corroborated the results of our primary investigation. Both CK and myoglobin levels are commonly used biomarkers for diagnosing RM [4, 13]. While CK has been the traditional biomarker, some studies suggest that myoglobin may offer advantages enabling earlier RM detection [17, 31, 37]. In the study cohort, peak myoglobin was measured in only 2898 patients (33.7%), including 576 with severe RM. Considering only these patients, no statistically significant difference in 30-day mortality was observed, even among patients with HS. However, the very small number of patients with HS (Additional file 1–Table S2) probably limited the statistical power, precluding definitive conclusions in this subgroup.

This study has several strengths. Beyond being the largest study of traumatic RM, it is the only one to employ a statistical method of causal inference by adjusting for a wide range of cofactors to analyze the association between RM and mortality, thereby reinforcing the robustness of the results. In particular, it is the first study to consider RM by focusing the analysis on patients with hemorrhage or head trauma, despite the acknowledged importance of these populations in traumatology.

Several limitations should be acknowledged. Firstly, the retrospective nature of the study may introduce inherent biases, despite the prospective data collection in a research database. Additionally, the database format limited access to detailed patient background information beyond ASA status. Only peak CK and myoglobin values were available, with timing and duration not recorded, restricting our analysis of their temporal evolution and impact on outcomes, particularly for severely injured patients who died before the myoglobin peak. To mitigate bias, we performed a sensitivity analysis focusing on patients who remained hospitalized for at least 3 days, which confirmed the main results. Secondly, the study was conducted exclusively in French trauma centers that primarily treat blunt trauma, potentially limiting generalizability due to differing transport and resuscitation practices. However, the inclusion of multiple centers enhances the representation of diverse cases. Thirdly, pre-hospital management time, a known prognostic factor, could not be analyzed due to significant missing data (> 20%), as imputation could introduce bias. Finally, the study's external validity may be affected by the one-third of patients with measured CK levels, as the decision for bedside investigations was left to clinicians, indicating a high pre-test probability of rhabdomyolysis. This may suggest an underestimation of rhabdomyolysis' significance in morbidity during hospital stays, especially in intensive care. Consequently, while the observed prevalence of rhabdomyolysis aligns with other trauma populations, it may represent an upper limit in this context.

Conclusions

In this retrospective multicenter study of trauma patients admitted to the ICU, RM was present in half of the patients, while severe RM was observed in 1 in 5 patients. Through doubly robust analysis, severe RM was associated with a significant 3.9% increase in 30-day mortality in patients with concurrent HS, while no such association was found in the remainder of the cohort. RM appears to significantly contribute to ICU morbidity, potentially leading to multiple organ failure. Further research is warranted to elucidate the underlying mechanisms, particularly in cases of combined hemorrhage and RM.

Abbreviations

AIPW	Augmented inverse propensity weighting
AIS	Abbreviated injury scale
AKI	Acute kidney injury
ARDS	Acute respiratory distress syndrome
ASA	American society of anesthesiology
ATT	Average treatment effect on the treated
CK	Creatine kinase
CNS	Central nervous system
GCS	Glasgow coma scale
HR	Heart rate
HS	Hemorrhagic shock
ICU	Intensive care unit
IPTW	Inverse of the probability of being treated weight
IQR	Interquartile range
ISS	Injury severity score
KDIGO	Kidney disease improving global outcomes
LOS	Length of stay
LR	Logistic regression
MT	Massive transfusion
pRBC	Packed red blood cells
PS	Propensity score
RM	Rhabdomyolysis
RRT	Renal replacement therapy

SAP	Systolic arterial pressure
SAPSII	Simplified acute physiology score II
SE	Standard error
SOFA	Sequential organ failure assessment
TBI	Traumatic brain injury
TMLE	Targeted maximum likelihood estimates
VFD	Ventilator free days

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-024-05158-w.

Additional file 1.

Additional file 2.

Additional file 3.

Additional file 4.

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Author contributions
TM, NL performed conception of the work, data collection, data analysis and interpretation, drafting the article, critical revision of the article, final approval of the version to be published. TM and EV performed statistical analysis. AC, NM, ML, BP, BC, JP, VR, NG, JLH, VD, ND, QL, MP, AH and MB done data collection, critical revision of the article, final approval of the version to be published. All authors read and approved the final manuscript.

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Availability of data and materials
Data are from the Traumabase, a collaborative project that consists of trauma practitioners, from different centres all over the country, sharing the registry for research and public health issues. Even though datasets are de-identified, the National Commission for data protection (CNIL) has imposed restrictions on data sharing since they contain sensitive informations. Conventions are signed for researcher before any access to the data. For data access, interested researchers can contact the Traumabase scientific committee on reasonable request with the following email address: contact@traumabase. eu.

Declarations

Ethics approval and consent to participate
This study complies with the STROBE and RECORD (Additional file 4) recommendations for the conduct of retrospective observational studies [41]. It has received the approval of the Paris Nord Research Ethics Committee (IRB number 00006477) and has been declared to the French National Commission on Computing and Liberty (Commission nationale de l'informatique et des libertés, CNIL, N° 2233446).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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