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Impact and Weight of Trauma Load and Inflammation Load Variables on the Severity and Outcome of Major Trauma Patients

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Abstract

Background: Several conditions related to injury severity (trauma load) and systemic inflammatory response (SIRS) after major trauma could affect the outcome. The aim of this study was to assess the influence in the outcome of variables related to trauma and to systemic inflammation after major trauma.

Materials and Methods: Prospective cohort study involving patients admitted to the trauma room of a level 1 trauma center. Variables related to the trauma load and to the inflammation load were collected in the first six hours after trauma. IL-6 was measured on admission and at 24, 48 and 72 hours. All variables were correlated with negative outcomes, namely ICU admission, ARDS development, MODS development and death. Univariate and multivariate analysis were performed.

Results: Ninety nine patients (aged 31 years;, ISS-29) were enrolled. Regarding trauma load variables, in univariate analysis, severity scores were correlated with all the negative outcome variables, TBI severity with ICU admission and death and CT severity with development of ARDS. Regarding inflammation variables, hypothermia and lethal triad were correlated with MODS; SIRS with hypoperfusion, shock, hypothermia, hyperlactacidemia, coagulopathy and lethal triad with death. IL-6 and IL-10 also correlated with negative outcomes. In multivariate analysis, TRISS, hypothermia and shock in the first six hours and IL- 6 at 48 and 72 hours correlated either with MODS development or death.

Conclusions: TRISS, shock and hypothermia in the first six hours and IL-6 level at 48 and 72 hours were independently and significantly associated with MODS development or with death. Avoidance or swift resolution of shock and hypothermia may well be the most important goal in the first six hours after major trauma.

Keywords: Major trauma; Severity; Outcome

Introduction

Primary or immediate mortality occurs at the moment of the accident and depends on the severity of the lesions. Severe trauma brain injury (TBI) and great vascular lesions in penetrating trauma are the primary reasons for death within 24 hours after major trauma (secondary mortality). Chest trauma (CT) and, again, TBI are commonly related to later poor outcomes [1]. Anatomic and physiologic scores, such as injury severity score (ISS), revised trauma score (RTS), and trauma injury severity score (TRISS) are usually used to assess severity and also to predict outcome after trauma [2]. Complications of the primary lesions, as rhabdomyolisis and hemorrhagic shock and may be present in the resuscitation period also contribute to secondary mortality.

But development of organ dysfunction is also markedly driven by the systemic inflammatory response. Hypothermia, acidosis and coagulopathy (lethal triad, LT), although multifactorial, are closely related to this response and significantly impact on mortality [3,4]. This inflammatory response depends on the production and release of a complex network of mediators [5], both pro- and anti-inflammatory. Their level and balance regulates much of the possible development of acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS). This balance also depends on several other factors, such as age, nutritional state, co-morbidities, and genetic factors [6]. In the trauma model, interleukin-6 (IL-6) and IL-10 have crucial role and are recognized markers of the systemic inflammatory response [7-10].

The aim of this study was to assess the influence of trauma load and inflammatory load variables in the outcome of severe trauma.

Methods

Study design

This was a prospective cohort study for which ethical approval was obtained from the hospital committee. All adult patients with severe trauma (ISS > 15) admitted to the trauma room (TR) of a level 1 Trauma Centre in the North of Portugal. These patients were assessed and treated according to a specific emergency department protocol for major trauma patients, which is based on international recommendations. Demographic, clinical, and analytical parameters were obtained from the hospital clinical reports and recorded at discharge in a database sheet. IL-6 and IL-10 were measured at admission, 24, 48 and 72 hours. The exclusion criteria for this study were the following: death while in the TR, a delay between accident and admission >360 min, age <18 years, non-compliance with the inclusion criteria and hospital transference in the first 72 hours.

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This is a substudy of a previously published paper [10].

Variables, clinical parameters, and definitions

The characteristics of the participants were obtained, including their age, gender, injury mechanism, and ISS, and baseline clinical, imaging, and analytical parameters were collected. The abbreviated injury scale (AIS) was used to calculate the ISS by the same investigator for classifying the injuries. The formulae for determining RTS and TRISS were obtained from the Trauma.org website. Metabolic and hemodynamic disorders were identified. Variables related to the direct injury or first hit (trauma load) studied were: ISS, RTS, TRISS, severe TBI (AIS >2) and severe CT (AIS >2).

Variables related to the systemic inflammatory response (inflammation load) studied were: SIRS with hypoperfusion (SIRS with lactate levels >2 mmol/L or at least one organic dysfunction as a result of the trauma, without hypotension refractory to fluid therapy), shock (SIRS associated with hypotension refractory to fluid therapy and requiring vasopressor support), hyperlactacidemia (serum lactate >4mmol/L), coagulopathy (increase by 1.5 of the activated partial thromboplastin time or prothrombin time), hypothermia (body temperature <35°C), lethal triad and IL-6 and IL-10 levels at admission and after 24, 48, and 72 hours. The same investigator conducted assays for IL-6 and IL-10, using the enzyme-linked immunosorbent assay method, following Biosource, Paisley, UK technical recommendations.

Outcome variables

Negative outcomes were defined as target variables, namely admission to ICU, development of ARDS, development of MODS and death. The criteria used for SIRS, ARDS, and MODS were those proposed by the consensus conference of the American College of Chest Physicians and the Society of Critical Care Medicine [11].

Statistical analysis

The statistical analysis was conducted using IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp Categorical variables were described as absolute and relative frequencies, and continued variables were described as the median, percentiles, minimums, and maximums. To test hypotheses about independent categorical variables, a Chi-square or Fisher's exact test were applied. To test continuous variables with non-normal distribution, Mann-Whitney and Kruskal-Wallis non-parametric tests were used.

The correlation of clinical variables, scores and inflammatory mediators with the outcome variables was studied. A logistic regression was used to assess all the variables when the risk factors for the outcomes were considered. The odds ratios and their confidence intervals at 95% were determined. TRISS is derived from ISS and RTS and therefore, only TRISS was considered in the multivariate analysis (stepwise method). The sensitivity of IL-6 and IL-10 in relation to the outcomes was assessed with Receiver Operating Characteristics Curve (ROC) curves. The level of significance was set at $p<0.05$.

Results

Sample characteristics, variables, and outcomes

During the 12-month study period, 99 patients met the inclusion criteria and were enrolled; median age was 31 years (range, 18-60 years), 83% were male, and median ISS was 29 (range, 17–52). The injury mechanism included traffic accidents (81%), work accident (6%), and others (13%). Trauma load variables are presented in Table 1 and inflammation load variables in Table 2. Sixty six percent of the patients were admitted to the ICU, ARDS occurred in 19%, MODS developed in 34% and mortality was 28%. Median length of stay was 15 (range: 1-75).

Trauma load	
ISS median (P05–P95)	29 (17–529)
RTS median (P05–P95)	6.6 (3.4–7.8)
TRISS median (P05–P95)	90.8 (7.7–98.9)
TBI ais >2 (%)	62
CT ais >2 (%)	22
Abd ais >2 (%)	20
Extremity ais >2 (%)	36
Severe.fractures.ais >2 (%)	33
Musculoskeletal injuries (%)	42

Table 1: Trauma load variables.

Inflammation load			
SIRS with hypoperfusion (%)	39	Hyperlactacidemia (%)	46
Shock (%)	17	Coagulopathy (%)	26
Hypothermia (%)	13	Lethal Triad (%)	7
IL-6 (admission)	459.5 (45.4–1527)	IL-10(admission)	74,45 (1,0-601,0)
IL-6 (24 h)	343.0 (60.8–1507)	IL-10 (24 h)	5,59 (1,0-84,2)
IL-6 (48 h)	204.0 (16.8–1490)	IL-10 (48 h)	1,00 (1,0-31,6)
IL-6 (72 h)	182.5 (1.0–1488)	IL-10 (72 h)	1,16 (1,0-62,2)

Table 2: Inflammation load variables.

Effect of variables on the outcome

Older age was correlated with both ICU admission and development of ARDS. Table 3 shows the correlations between trauma load variables and outcome variables. Severity scores were correlated with all the negative outcome variables; TBI severity with ICU admission and death and CT severity with development of ARDS (Table 3).

Several inflammation load variables were correlated with the outcomes: SIRS with hypoperfusion, shock, hypothermia and hyperlactacidemia were associated with ICU admission. Hypothermia and lethal triad were correlated with MODS. Severe SIRS, shock, hypothermia, hyperlactacidemia, coagulopathy and lethal triad were correlated with death (Table 4). IL-6 at 24, 48 and 72 hours was correlated with UCI admission, IL-6 at 72 hours with ARDS development, IL- 6 at 48 and 72 hours with MODS development and IL-6 at 72 hours with death; IL-10 at 72 hours was correlated with UCI admission, IL-10 at admission, 24, 48 and 72 hours with all the outcomes, IL-10 at 24 and 72 hours with MODS development and IL-10 at 48 and 72 hours with death (Table 4).

Multivariate regression analysis to assess the variables role in the outcome

A multivariate regression analysis was performed to assess the role of the several variables (related with trauma and inflammation load) as outcome predictors. According to the multivariate analysis, high age, low TRISS, hyperlactacidemia on admission and high IL-6 at 24 hours were independent predictors of ICU admission. High age and low TRISS were predictors of ARDS development. Low TRISS, hypothermia on admission and high IL-6 at 48 hours were predictors of MODS development. Low TRISS, shock on admission and high IL-6 at 72 hours were predictors of death (Table 5).

		ICU admission (n=66)		ARDS (n=19)		MODS (n=34)		Death (n=28)	
		no	yes	no	yes	no	yes	no	yes
Age	med	22	34	29	39	30	32	31	27
	P05-P95	18-54	18-62	18-60	24-65	18-58	18-62	18-62	18-65
	p	0,019*		0,008*		0,149*		0,750*	
ISS	med	22	30	29	35	26	30	28	34
	P05-P95	15-38	19-54	17-48	17-66	17-45	21-59	17-45	25-54
	p	0,001*		0,012*		0,006*		0,002*	
RTS	med	5,96	2,62	6,90	5,88	6,90	5,92	7,10	5,03
	P05-P95	5,96-7,84	1,89-5,96	3,56-7,84	2,62-7,84	2,09-7,84	2,62-7,84	4,29-7,84	2,62-7,55
	p	0,001*		0,009*		0,001*		0,001*	
TRISS	med	97	81,2	93,3	64,7	95,1	77,8	95,1	52,6
	P05-P95	87,6-99,1	7,5-98,9	7,6-98,9	5,2-98,6	7,7-98,9	7,6-97,3	36,2-98,9	3,2-90,8
	p	0,001*		0,003*		0,001*		0,001*	
TBI ais>2	n	15	51	5	14	7	27	3	25
	%	23	77	26	74	21	79	11	89
	p	0,042**		0,728***		0,169**		0,011**	
CT ais>2	n	40	26	7	19	17	17	17	11
	%	60	40	27	73	50	50	61	39
	p	0,557**		0,011***		0,060**		0,805**	

Table 3: Relationship between age and trauma load studied variables according to outcomes.
*Mann-Whitney test, **Chi-square test (Pearson), ***Exact Fisher test.

		ICU admission (n=66)		ARDS (n=19)		MODS (n=34)		Death (n=28)	
		no (%)	yes (%)	no (%)	yes (%)	no (%)	yes (%)	no (%)	yes (%)
SIRS with hypoperfusion	no	27 (45)	6 (15)	52 (87)	27 (71)	42 (70)	23 (59)	49 (82)	22 (56)
	yes	33 (55)	33 (85)	8 (13)	11 (29)	18 (30)	16 (41)	11 (18)	17 (44)
	p	0,002*		0,057*		0,259*		0,006*	
Shock	no	33 (40)	0 (0)	69 (84)	10 (63)	57 (70)	8 (47)	68 (83)	3 (18)
	yes	49 (60)	17 (100)	13 (16)	6 (38)	25 (30)	9 (53)	14 (17)	14 (82)
	p	0,001*		0,077**		0,076*		0,001*	
Hyperlactacidemia	no	27 (51)	6 (13)	46 (87)	33 (73)	38 (72)	27 (59)	45 (85)	26 (57)
	yes	26 (49)	40 (87)	7 (13)	12 (27)	15 (28)	19 (41)	8 (15)	20 (43)
	p	0,001*		0,093*		0,174*		0,002*	
Coagulopathy	no	24 (36)	6 (23)	52 (79)	20 (80)	44 (67)	15 (58)	53 (80)	14 (54)
	yes	42 (64)	20 (77)	14 (21)	5 (20)	22 (33)	11 (42)	13 (20)	12 (46)
	p	0,221*		0,899*		0,419*		0,010*	
Hypothermia	no	33 (38)	0 (0)	72 (84)	7 (58)	62 (72)	3 (23)	66 (77)	5 (38)
	yes	53(62)	13 (100)	14 (16)	5 (42)	24 (28)	10 (77)	20 (23)	8 (62)
	p	0,004**		0,052**		0,001**		0,008**	
Lethal Triad	no	33 (36)	0 (0)	75 (82)	4 (67)	63 (68)	2 (29)	71 (77)	0 (0)
	yes	59 (64)	7 (100)	17 (18)	2 (33)	29 (32)	5 (71)	21 (23)	7 (100)
	p	0,092**		0,329**		0,045**		0,001**	

			Ad	24h	48h	72h	Ad	24h	48h	72h	Ad	24h	48h	Ad	24h	48h	72h
IL-6	**yes**	pg/mL	436,5	569	315	294,5	450	522	326	419	403	474	319	388	523	335	441
		P05	45,4	72,3	30,3	0,1	61	33,7	30,3	0,1	61	33,7	16,8	41,2	109	28,9	0,1
		P95	1527	1590	1520	1490	1520	1502	1510	1490	1523	1500	1470	1523	1510	1490	1499
	no	pg/mL	525,5	190	117	53,7	449	316	179	145	499	271	169	470	316	194	144
		P05	17	0,1	0,1	0,1	41,2	60,8	0,1	0,1	19	60,8	28,9	61	54,3	16,8	0,1
		P95	1527	1127	1165	624	1520	1502	1510	1490	1523	1500	1165	1523	1510	1490	1499
		p***	0,779	0,006	0,001	0,001	0,580	0,309	0,057	0,036	0,604	0,173	0,034	0,745	0,258	0,180	0,024
IL-10	yes	pg/mL	85,55	8,38	0,31	3,35	128	13,05	6,67	10,8	65,8	10,2	0,8	102	12,4	10,9	19,1
		P05	0,1	0,1	0,1	0,1	13,2	0,1	0,1	0,1	8,13	0,1	0,1	0,1	0,1	0,1	0,1
		P95	618	87,4	23,9	40,6	349	405	269	40,6	349	291	135	683	291	135	79,9
	no	pg/mL	72,55	2,45	0,1	0,1	51,05	3,59	0,1	0,1	74,5	1,2	0,1	72,3	4,3	0,1	0,1
		P05	0,1	0,1	0,1	0,1	0,1	0,1	0,1	0,1	0,1	0,1	0,1	5,9	0,1	0,1	0,1
		P95	527	84,2	31,6	62,2	618	37,6	14,8	67,90	618	69,4	23,9	349	84,2	23,9	18,4
		p***	0,481	0,194	0,594	0,019	0,007	0,003	0,035	0,015	0,751	0,008	0,189	0,476	0,079	0,025	0,001

Table 4: Correlation between inflammation load variables and the outcomes.*Chi-square test (Pearson), **Exact Fisher test, ***Mann-Whitney test, Ad-admission.

RISK FACTORS FOR ICU ADMISSION			
	OR	95%CI	p
Age	1.086	1.019–1.157	<0.011
TRISS	0.165	0.066–0.414	<0.001
Hyperlactacidemia	4.207	0.962–16.682	<0.008
IL-6 (24 h)	1.002	1.001–1.004	<0.008
AUC using these four variables = 0.928 [0.872–0.984]			
RISK FACTORS FOR ARDS DEVELOPMENT			
	OR	95%CI	p
Age	0.835	O.751–0.928	<0.001
TRISS	0.977	0.962–0.993	<0.006
AUC using these four variables = 0.764 [0.652–0.877]			
RISK FACTORS FOR MODS DEVELOPMENT			
	OR	95%CI	p
TRISS	0.983	0.967–1.000	<0.049
Hypothermia	4.740	1.063–21.133	<0.041
IL-6 (48 h)	1.002	1.000–1.003	<0.023
AUC using these four variables =0.842; [0.735–0.950]			
RISK FACTORS FOR MORTALITY			
	OR	95%CI	p
TRISS	0.975	0.953–0.997	<0.025
Shock	6.161	1.212–31.325	<0.028
IL-6 (72 h)	1.001	1.000–1.003	<0.013
AUC using these four variables = 0.868; [0.782–0.953]			

Table 5: Multivariable analysis of the correlation between trauma and inflammation load variables and outcome measures.

Discussion

The ability to assess severity and predict outcome is decisive for strategy and therapy improvement in severe trauma. We were able to show that both trauma load and inflammation load variables correlate with the outcome and that, among the several variables studied, low TRISS, hypothermia and shock on admission and high IL-6 at 48 or 72 hours were independently associated either with MODS development or death. Therefore, anatomic and physiological variables directly related trauma and to physiological variables associated with trauma inflammation, together with a biomarker are independently correlated with the outcome.

Regarding variables directly related to the primary lesion itself, all severity scores were correlated with all negative outcomes and severe TBI was associated with ICU admission and death, as described in the literature [12], but TRISS, an anatomic and physiological systemic score, is the only variable that shows independent significance for the prediction of all negative outcomes considered.

In addition to initial injuries, the outcomes depend on early immune-inflammatory response and its clinical consequences [13,14]. In univariate analysis, hypothermia and lethal triad were correlated with MODS development and these and also SIRS with hypoperfusion, shock, hyperlactacidemia and coagulopathy, were correlated with death. Coagulopathy in trauma may result from hypovolemic shock by activation of the C protein cascade and hemodilution. Coagulopathy has been associated with poor outcomes, including MODS [15]. Rotondo et al. formulated the lethal triad concept, as the combination of coagulopathy, acidosis and hypothermia. The early presence of the lethal triad has been proven to have a strong correlation with mortality in major trauma [5]. In our study, in multivariate analysis, only hypothermia and shock have shown independent significance for prediction of MODS development and death, respectively. In fact, hypothermia, which was present in 13% of the patients, is usually associated with massive fluid replacement for the treatment of shock.

Immunological response induced by trauma is an outcome determinant. The physiological activation of the immune system (SIRS) creates a series of processes that may evolve in the following 2 ways: (1) resolution and maintenance of homeostasis of organs and systems or (2) disruption of homeostasis evolving towards MODS and death. Systemic endothelial inflammation leading to organ failure may depend on a complex cytokine system of stimulation/restraint and adhesion of leukocytes to the endothelium, which is dependent on adhesion molecules. This facilitates transudation and edema, disturbs oxygenation, and increases cellular death and parenchymal injury with a progressive decrease in organ function, which may culminate in death [16]. We were able to confirm SIRS as a frequent event in major

trauma patients, occurring in 73% of our patients in the first 6 hours, but without correlation with the outcome. This adds to the increasing amount of literature that denies a role for SIRS in severity stratification of severe acute injuries, both conceptually [17] and epidemiologically [18]. However, in our study, IL-6, a marker of endothelial inflammation [19,20], when measured at 48 and 72 hours, was significantly and independently correlated with MODS development and with mortality, respectively. IL-6 emerges at an early stage in trauma (1–4 hours) and persists in the circulation for days [8]; increased IL-6 levels have been correlated with injury severity and negative outcomes [21-23]. A serum level >500 pg/mL has been correlated with MODS and death [24]. In this study, we found significant specificity and sensitivity with IL-6 levels >250 pg/mL at 48 hours for ICU admission and >294 pg/mL and >276 pg/mL at 72 hours for MODS and death, respectively.

The combination of low TRISS, hypothermia and high IL-6 level at 48 hours showed an AUC of 0.842 (range: 0.652–0.877) for the prediction of MODS development and low TRISS, shock and high IL-6 level at 72 hours an AUC of 0.868 (range: 0.782–0.953) for the prediction of death. The highest odds ratio is clearly that of hypothermia and of shock, respectively for MODS and death.

The small sample size and the observational nature were recognized limitations of this study.

Conclusions

In our study, both direct trauma load associated variables and inflammation load associated variables are correlated with negative outcomes. TRISS, shock and hypothermia in the first six hours and IL-6 level at 48 and 72 hours were independently and significantly associated with MODS development or with death. Avoidance or swift resolution of shock and hypothermia may well be the most important goal in the first six hours after major trauma, as these two variables showed the strongest correlation with MODS development and death.

Competing Interests

The authors declare that they have no competing interests.

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