Analysis of the Early Posttraumatic Period Pathophysiology in Case of the Severe Combined Thoracic Trauma Using Multivariate Logistic Regression

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Abstract. Severely injured patients are always challenging, even more so when they have suffered critical trauma to the chest. The aim of this study is to create a prognostic tool for outcome prediction for patients with combined thoracic trauma based on the determination of main homeostasis parameters on the 1st and 2nd day after injury. Multivariate logistic regression analysis with forward elimination of the variables was used for modeling the dependence of outcome on clinical and laboratory parameters that reflects main pathophysiological mechanisms developed on the 1st and 2nd day after combined thoracic trauma. 73 Male patients with combined thoracic trauma were included in the study. The results of fitting a logistic regression model show the relationship between mortality and six independent variables: transferrin saturation, percentage of eosinophils, TNF-a concentration, total iron binding capacity, inspiratory fraction of oxygen and albumin concentration. Besides that, forward elimination of the variables into the logistic regression equation helps to recognize relatively independent pathophysiological mechanisms involved to progression of wound dystrophy. The likelihood ratio tests can reflect the contribution degree of each pathogenesis rout responsible for the negative outcomes of the severe combined thoracic trauma. The study contributes to our understanding of interaction between pathophysiological mechanisms that make harmful effects and are involved in the progression of wound dystrophy and compensatory reactions directed on stabilization of vital function disturbances and maintenance of homeostasis during this type of wound dystrophy.

Keywords: Combined thoracic trauma, Multivariate logistic regression, Outcome prediction, Pathophysiologic mechanisms of polytrauma.

1 Introduction

Logistic regression provides a useful means for modeling the dependence of a binary response variable on one or more explanatory variables, where the latter can be either categorical or continuous. The fit of the resulting model can be assessed using a number of methods [1–3].

Polytrauma has great social and economic value as 80% polytrauma victims are able-bodied aged [4, 5]. Thoracic trauma is the leading cause of death nearly 25% of polytrauma patients and, when especially associated with other injuries, it may causes death in additional 50% of polytrauma patients [6]. Severely injured patients are always challenging, even more so when they have suffered critical trauma to the chest [7]. Blunt chest trauma is understood to be an injury to the thoracic cage affecting the rib cage itself, the lung parenchyma, the heart, great vessels and/or mediastinal structures, although the bony structures are the ones that are usually the most damaged. Such trauma is potentially life threatening, with a direct mortality rate of around 25% and it is related indirectly to mortality in polytrauma patients in another 25% of cases [8]. Management of chest injuries requires multidisciplinary approach [9] and involves different specialists: emergency physicians both out of hospital and in hospital settings, anesthesiologists, intensivists, radiologists, and surgeons [10].

The pathophysiology of polytrauma is complex, involves mostly all systems and organs and is still being elucidated [11, 12]. The injury rapidly activates the immune defense, which includes some protease cascades (coagulation and complement) and the cellular innate and adaptive immune response. Central part of the pathophysiological changes is the trauma-induced coagulopathy, hypothermia, and acidosis. The complex pathophysiological interactions of damaged and dysfunctional molecules, cells, and organs with the defense systems result in a systemic inflammatory response and severe complications such as sepsis, multi-organ dysfunction, and multi-organ failure [11, 13]. The comprehensive knowledge of the underlying pathophysiological mechanisms and the corresponding principles of clinical management are indispensable for the successful treatment of multiple injured patients [13].

Characterization of the severity of injury is crucial for the scientific study of trauma, triage, classification of patients, quality management and the assessment of prognosis (prediction of mortality of an individual patient) [14]. Various scoring systems have been created for prognostic value in patients with thoracic trauma (Thoracic trauma score, Injury severity score, Abbreviated injury score thoracic, and pulmonary contusion score). However, existing data stay dubious about the final risk in terms of morbidity and mortality [15]. The search for the best marker or set of markers for the diagnosis, prognosis and treatment quality of “at risk” trauma patients is ongoing.

2 Aim

The aim of this study is to create a prognostic tool for outcome prediction for patients with combined thoracic trauma based on the determination of main homeostasis parameters on the 1st and 2nd day after injury.

3 Materials and methods

3.1 Patients.

73 Male patients with combined thoracic trauma were included in the study. They were treated in anesthesiology and intensive care department for patients with combined trauma of Kharkiv Municipal Clinical Emergency Hospital named by prof. O.I. Meshchaninov. As inclusion criteria were chosen ISS > 16, two or more injured body regions, presence of severe blunt thoracic injuries (AIS 3 and more). Excluding criteria was a concomitant chronic disease in subcompensation or decompensation phase. Survival / nonsurvival ratio was 42 / 31. The examination was performed on the 1st and 2nd day after trauma (10.75 – 33.5 hours). Table 1 gives some of the main characteristics of the patients' groups. It can be seen that there were no significant differences according to age, admission time and the anatomical classification between patients groups.

Table 1. Patient Characteristics (Median, 95% confidence interval).

	Survivors	Nonsurvivors	P
Number of patients	42	31	
Age, years	41 (38.21-44.89)	42 (36.7-46.46)	1
ISS score	24.5 (22.73-28.22)	34 (30.38-38.53)	0.0006
RTS score	7.84 (7.051-7.684)	6.17 (5.356-6.464)	<0.0001
TRISS probability	0.964 (0.871-0.961)	0.717 (0.556-0.766)	<0.0001
Admission time, hours	1 (0.854-1.97)	1 (0.435-3.297)	0.8434
Craniothoracic	6	3	
Thoracoabdominal	3	1	
Thoracoscelethal	7	1	
Craniothoracoabdominal	5	5	0.0901
Craniothoracoscelethal	7	7	
Thoracoabdominoscelethal	5	2	
Craniothoracoabdominoscelethal	9	12	

3.2 Laboratory methods.

In general, 89 clinical and laboratory parameters, as well as their relationships were used for the regression analysis as explanatory variables. The patients' plasma was assayed for biochemical markers using spectrophotometric methods in the Biochemistry department of Kharkiv National Medical University. White blood cell count was performed according to the standard method in the clinical laboratory of Kharkiv Municipal Clinical Emergency Hospital. The level of eosinophils was expressed as

percentages to the total white blood cells. Albumin concentration was estimated through the turbidimetric method and was expressed in g/L. Plasmatic Iron concentration and total iron-binding capacity (TIBC) were estimated spectrophotometrically and both were expressed in μmol/L. These biochemical markers were estimated with the help of "Filisit-Diagnostica" diagnostic kits. Transferrin saturation was calculated as Iron/TIPS ratio and was expressed in percentages. ELISA kit "Vector-Best" was used for the determination of Tumor necrosis factor-α (TNF-α) concentration and was expressed in pg/mL.

3.3 Data analysis.

Data were collected in a Microsoft Excel spreadsheet. STATGRAPHICS Plus 5.0 was used for multivariate logistic regression analyses with forward elimination of the variables [1, 3]. Analysis of deviance was used to measure the usefulness of the model and the goodness of fit of the model was assessed according to Chi-square goodness of fit test. The presence of serious multicollinearity was checked by the correlation matrix for coefficient estimates of the regression equation. Mann-Whitney test was used to assess differences between groups. Chi-square test for trends was performed to consider differences in nominal data. The significance level was specified as $p < 0.05$.

4 Results.

4.1 Logistic regression.

Table 2 shows the results of the estimated regression model. The results of fitting a logistic regression model show the relationship between mortality and six independent variables.

Table 2. Estimated Regression Model (Maximum Likelihood).

Parameter	Estimate	Standard Error	Estimated Odds Ratio
Constant	-4.38337	6.0877	
Transferrin saturation	0.268732	0.0907964	1.3083
Eosinophils	6.88929	2.39064	981.706
TNF-α	0.153333	0.0655899	1.16571
TIBC	-0.102003	0.0635617	0.903027
FiO2	32.7435	9.29733	1.66089×10^{14}
Albumin	-0.825942	0.209276	0.437822

The equation of the fitted model is:

$$Probability\ of\ lethal\ outcome\ = \frac{e^k}{1+e^k} \quad (1)$$

Where k is calculated from the formula:

$$k = -4.38337 + 0.268732 \times Tranferrin\ Saturation + 6.88929 \times Percentage\ of\ eosinophils + 0.153333 \times TNF\text{-}a - 0.102003 \times TIBC + 32.7435 \times FiO_2 - 0.825942 \times Albumin \quad (2)$$

Table 3 shows the results of the analysis of deviance. Because the p-value for the model in the Analysis of Deviance table is less than 0.01, there is a statistically significant relationship between the variables at the 99% confidence level. Furthermore, the p-value for the residuals is greater than 0.10, indicating that the model is not significantly worse than the best possible model for this data at the higher than 90% confidence level.

Table 3. Analysis of deviance.

Source	Deviance	Df	p-Value
Model	86.4843	6	0.0000
Residual	5.6549	61	1.0000
Total (corr.)	92.1392	67	

The analysis also shows that the percentage of deviance in lethal outcome explained by the model equals 93.8627%. This statistic is similar to the usual R-Squared statistic. The adjusted percentage, which is more suitable for comparing models with different numbers of independent variables, is 78.6683%.

The results of Likelihood ratio tests are described in Table 4. In determining whether the model can be simplified, notice that the highest p-value for the likelihood ratio tests is 0.0246, belonging to Transferrin saturation.

Table 4. Likelihood Ratio Tests.

Factor	Chi-square	Df	p-Value
Transferrin saturation	5.05213	1	0.0246
Eosinophils	10.5325	1	0.0012
TNF-α	10.2318	1	0.0014
TIBC	15.9856	1	0.0001
FiO_2	15.4042	1	0.0001
Albumin	22.3353	1	0.0000

Because the p-value is less than 0.05, that term is statistically significant at the 95% confidence level. Consequently, there is no need to remove any variables from the model.

The results of Chi-square goodness of fit test are illustrated in Table 5. This test determines whether the logistic function adequately fits the observed data.

Table 5. Chi-Square Goodness of Fit Test

Class	Logit interval	N	True		False	
			Observed	Expected	Observed	Expected
1	less than -10.2567	17	0.0		17.0	17.0
2	-10.2567 to 0.734184	24	1.0	1.69911	23.0	22.3009
3	0.734184 to 16.7516	26	26.0	25.2774	0.0	0.72258
4	16.7516 or greater	68	28.0	27.9766	40.0	40.0234
	Total	135	55.0		80.0	

Chi-squared was calculated as 1.05286 with 2 d.f. and p-value = 0.590709. Because the p-value is greater than 0.10, there is no reason to reject the adequacy of the fitted model at the higher than 90% confidence level.

Table 6 shows the estimated correlations between the coefficients in the fitted model.

Table 6. Correlation matrix for coefficient estimates

	Constant	SatTrans	Eosinoph	TNF-α	TIBC	FiO_2	Albumin
Constant	1.0	-0.536	-0.078	-0.302	-0.484	-0.634	-0.298
SatTrans	-0.536	1.0	0.283	0.251	0.261	0.564	-0.447
Eosinoph	-0.078	0.283	1.0	0.362	-0.467	0.482	-0.438
TNF-α	-0.302	0.251	0.362	1.0	-0.319	0.422	-0.338
TIBC	-0.484	0.261	-0.467	-0.319	1.0	-0.1	0.348
FiO_2	-0.634	0.564	0.482	0.422	-0.1	1.0	-0.357
Albumin	-0.298	-0.447	-0.438	-0.338	0.348	-0.357	1.0

SatTrans – Transferrin saturation; Eosinoph – percentage of eosinophils.

These correlations can be used to detect the presence of serious multicollinearity. In our case, there is 1 correlation with the absolute value greater than 0.5 – in the case of FiO_2 with Transferrin saturation.

5 Discussion

In the present study, we proposed a useful tool for mortality risk stratification on the 1^{st} and 2^{nd} day after trauma for patients with combined thoracic injuries based on six available variables. Once the probability of mortality after emergency surgery due to trauma is established, the provided supportive care of vital function management can be revised according to the risk degree. Frequently reoperations can be necessary for definitive correction of the injured organs' impaired functions. Adequate risk assess-

ment before the such second-stage surgery can be useful for planning the amount and duration of operative treatment. The use of this score offers an effective clinical tool for decision making in case of massive patients' admission when intensive care must be provided according to injury severity, patients' survival ability and hospital facilities.

Forward elimination of the variables into the logistic regression equation allows increasing the quality of the regression model. On the other hand, it removes variables that duplicate information as a part of redundant features [3]. So, we can hypothesize that pathophysiological mechanisms, responsible for wound dystrophy progression, which activity markers were defined most significant for outcome prediction, are independent of each other. Besides, this independence is relative to how much it can be in biological systems. These results can be interpreted as that there are several relatively independent pathophysiological mechanisms involved in the progression of the wound dystrophy in case of the severe combined thoracic trauma on the 1st and 2nd day after injury. These findings are supported by data from the correlation matrix for coefficient estimates (Table 6).

Logistic regression parameters with positive sides mean that pathophysiological mechanisms that they reflect make harmful effects and are involved in the progression of wound dystrophy and parameters with negative sides reflect the capacity of compensatory mechanisms directed on stabilization of vital function disturbances and maintenance of homeostasis in case of the severe combined thoracic trauma.

The likelihood ratio tests may help to understand the contribution degree of each pathogenesis routs involved in the progression of wound dystrophy in case of the severe combined thoracic trauma. It can be done according to chi-square values of the logistic regression factors (Table 4). Mechanisms associated with blood loss, and most of all, with a decrease of plasma albumin concentration are the most responsible for the progression of the wound dystrophy on the 1st and 2nd day of the early post-traumatic period. The multifunctionality of this class of protein molecules (maintenance of oncotic pressure, transport of hormones, drugs and inorganic ions, etc.), obviously, determines the need for stable albumin concentration for aerobic metabolism providing in case of traumatic shock.

Total iron binding capacity has the second importance degree according to chi-square value. Sufficient transferrin concentration is necessary for binding and subsequent disposal of toxic iron released into the bloodstream after significant tissue damage and parenchymal hemorrhages [16, 17]. The presence of the transferrin saturation in the logistic regression equation underlines the importance of the damaging and compensatory mechanisms counterbalance, involved in the pathogenesis of the shock period in case of the severe combined thoracic trauma. On the one hand, hemolysis of erythrocytes in hematomas occurs after closed traumatic injuries and increasing of free toxic iron concentration in the blood produces a disturbance of antioxidant homeostasis [18, 19]. At the same time, on the other hand, the compensatory mechanisms involved in the processes of transport, deactivation and absorption of the iron from the blood are depleted due to decrease of transferrin concentration in the blood plasma as the result of blood loss, which always accompanies severe trauma [17, 20]. The current data highlight the importance of the critical loss of such valuable plasma

proteins as albumin and transferrin with bleeding that determines the body's future ability of the damaging factors compensation associated with traumatic shock due to combined thoracic trauma.

The respiratory failure is the third most important pathophysiological mechanism involved in the progression of the severe combined thoracic injury wound dystrophy on the 1st and 2nd day after trauma, determined by logistic regression. This finding can be postulated according to the presence of FiO_2 parameter in the logistic regression equation with chi-square value 15.4 in Likelihood ratio test (Table 4). This parameter reflects patients' oxygen dependence occurring due to both ventilatory disorders (damage to the rib cage, mechanical lung ventilation, presence of intrathoracic volumes) and direct damage to the alveolocapillary membrane as the result of direct lung contusion [21].

Furthermore, early activation of the immune system with the development of systemic inflammatory response syndrome occurs [11, 22]. This pathophysiology mechanism was defined as the fourth degree importance of contributing to the progression of wound dystrophy of this type of polytrauma. The presence in the equation of logistic regression the percentage of eosinophils, as well as the plasma concentration of TNF-α suggests that disturbations of host defense processes are the next most important pathophysiological mechanisms of the shock period of the severe combined thoracic trauma. In accordance with previous studies, the present results have demonstrates that the release of proinflammatory cytokines, including TNF-α, occurs proportionally to the volume of damaged tissues and cells of the body which leads to the activation of nonspecific mechanisms of immune defense [11, 22], including the increase in the number of blood eosinophils involved in the pathophysiological mechanisms of systemic inflammatory response. Prior studies have noted that maximum activation of hyperinflammation occurs within 3-4 days after trauma insult [11, 23–25]. These accords with our observations, which showed less influence of immune parameters in the regression equation on outcome prediction on the 1st and 2nd day after trauma.

Conclusions

The main goal of the current study was to create a prognostic tool for outcome prediction for patients with combined thoracic trauma based on determination of main homeostasis parameters on the 1st and 2nd day after injury. Multiple regression analysis revealed that the outcome prediction can be fulfilled according to transferrin saturation, percentage of eosinophils, TNF-a concentration, total iron binding capacity, inspiratory fraction of oxygen and albumin concentration on the 1st and 2nd of the posttraumatic period in case of the severe combined thoracic trauma. The study contributes to our understanding of the interaction between pathophysiological mechanisms that make harmful effects and are involved in the progression of wound dystrophy and compensatory reactions directed on stabilization of vital function disturbances and maintenance of homeostasis during this type of wound dystrophy. Multi-

variate logistic regression analysis with forward elimination of the variables allows finding and analyzing detailed features of pathophysiological mechanisms.

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