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POTENTIAL "EFFICIENT" COVARIATES FOR TREATMENT RESULTS PREDICTION IN SEVERE TRAUMA POPULATION

Grabovschi I.[1], Trofimov C., Mogildea V., Baltaga R.[2], Sandru S.[2], Cobiletchi S.[2], Arnaut O.[1,2]

[1]Department of Human Physiology and Biophysics, Nicolae Testemitanu State University of Medicine and Pharmacy, Chisinau, the Republic of Moldova

[2]Valeriu Ghereg Department of Anesthesiology and Intensive Care Nicolae Testemitanu State University of Medicine and Pharmacy, Chisinau, the Republic of Moldova

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ПОТЕНЦІАЛЬНІ "ЕФЕКТИВНІ" КОВАРІАТИ ДЛЯ ПРОГНОЗУВАННЯ РЕЗУЛЬТАТІВ ЛІКУВАННЯ У КОГОРТИ ПАЦІЄНТІВ З ВАЖКОЮ ТРАВМОЮ

Грабовський І., Трофимов К., Могилдеа В., Балтага Р., Шандру С., Кобилецький С., Арнаут О.

Вступ: Незважаючи на основну добре відому епідеміологічну проблему за останній період, травматизм є однією з основних причин смерті у всіх країнах Європейського регіону ВООЗ, незалежно від економічного статусу. Як ми всі можемо зрозуміти, смертельні травми – це лише незначна частина всіх травм, які в основному складаються з нелетальних, але іноді надзвичайно важких травм. Є деякі фактори ризику та захисні фактори травми, які роблять передбачуваними та запобіжними багато аспектів травми. Починаючи з цього моменту, було розроблено кілька прогностичних шкал, але вони не є універсальними через поліморфні особливості пацієнтів, які отримували лікування в різних медичних системах. Це є причиною того, що існуючі шкали слід постійно переоцінювати та коригувати.

У цій статті дані біохімії, дані йонограми та гемолейкограми, стать, вік та супутні захворювання були розглянуті як провісники та проаналізовані без анатомічного компонента травми, що продемонструвало здатність прогнозувати в попередніх дослідженнях. Ці змінні не були вибрані випадковим чином. По-перше, ці показники відображають стан різних систем органів. По-друге, ця інформація є доступною для кожного пацієнта з важкою травмою, який потрапляє до реанімації. На основі отриманих результатів будуть запропоновані потенційні моделі з урахуванням біологічної статі та віку.

Мета та завдання: Тестувати рутинні клінічні/параклінічні параметри, як провісники виживання важкої травми, щоб позначити потенційно «ефективні» змінні для заповнення загальних балів травми.

Методи: Аналітичне когортне клінічне дослідження (ретро проспективне) було розроблене для аналізу даних 2651 пацієнта з важкою травмою, послідовно госпіталізованих до травматологічного центру з Республіки Молдова у період з січня 2013 року по листопад 2018 року. база даних без персональних даних. Були розглянуті спеціальні критерії включення та виключення. Ефективні біомаркери/фактори ризику були виявлені та вивчені із використанням статистичної обробки даних з метою розробки альтернативних прогнозних моделей результатів лікування (виживання / смерті).

Результати: Майже всі параметри, включені в дослідження, показали прогностичні здібності при одновимірному аналізі. Використовуючи клініко-параклінічні дані, включаючи супутні захворювання, була розроблена багатоваріантна модель прогнозування важкої травми.

Висновок: Біохімічні параметри, показники йонограми та гемолейкограми, що відображають реакцію при травматичному ушкодженні, є потенційним джерелом для прогнозування відповіді на лікування коваріатами результатів лікування у важких випадках травматизму. Більше того, разом із супутніми захворюваннями при багатовимірному аналізі ці рутинні параметри показали прогнозуючий потенціал.

Ключові слова: травма, модель прогнозування виживання

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Introduction: Despite main well-known epidemiological problem in the last period, injuries are among leading causes of death in all countries of the WHO European Region, regardless of economic status. As we all can understand, the fatal injuries are only a small part of all traumas that are mainly consisted by nonlethal, but sometimes extremely severe injuries. There are some risk and protective determinants of the trauma that make predictable and preventable many injury aspects. Starting from this point, were developed several predictive scores, but they are not universal ones, because of polymorphic aspects of different patients treated within different medical systems. This is the reason why existing scores should be continuously reevaluated and adjusted.

In this article, biochemistry data, ionogram and hemoleukogram data, sex, age and comorbidities were considered as predictors and analyzed without anatomical trauma component, which demonstrated the ability to predict in previous studies. These variables were not randomly selected. First, these indicators reflect the state of different organ systems. Second, being "routine" parameters, this information is available for each severe trauma patient admitted to the ICU. Based on the obtained results, potential predictive models adjusted to biological gender and age will be proposed.

Purpose and task: To test the routine clinical/paraclinical parameters as severe trauma survival predictors in order to mark potentially "efficient" variables for common trauma scores completion.

Methods: An analytical cohort clinical study (retro prospective) was designed to analyze the data of 2651 severe trauma patients consecutively admitted to a trauma center from Republic of Moldova in period between January 2013 – November 2018. The information was extracted from the trauma center electronic database with no personal information. Special inclusion and exclusion criteria were considered. Effective variables / biomarkers / risk factors were identified and studied using statistical data processing in order to develop alternative predictive models of treatment outcomes (survival / death).

Results: Almost all parameters included in the study has shown predictive abilities in univariate analysis. Using clinical-paraclinical data including comorbidities, Multivariate predictive model for severe trauma was developed.

Conclusion: The biochemical parameters, ionogram and hemoleucogram indicators, reflecting the host response in traumatic injury, represent a potential source for treatment result prediction covariates in severe trauma scores. Moreover, together with comorbidities in multivariate analysis these routine parameters have showed predictive potential.

Key words: trauma, survival predictive model

Relevance and problem statement. Despite main well known epidemiological problem in the last period, a new report from WHO highlights that violence and injuries are a leading cause of death in all countries of the WHO European Region, regardless of economic status, causing almost 500 000 deaths each year from causes including falls, road traffic injuries, drowning, burns, poisoning, interpersonal violence and suicide [1]. As we all can understand, the fatal injuries are only a small part of all traumas that are mainly consisted by nonlethal, but sometimes extremely severe injuries. Thus, trauma still remains the main cause of death among 1-46 years aged population [2].

There are some risk and protective determinants of the trauma that make predictable and preventable many injury aspects. Starting from this point, they were developed several predictive scores in order to predict some aspects of trauma patient's treatment. They are not universal ones, being imperfect instruments because of polymorphic aspects of different patients treated within different medical systems. This is the reason why existing scores should be continuously reevaluated and adjusted to concrete populations [3][4][5][6].

Modeling the treatment results (survival / death) of a patient with severe trauma, like any other modeling, requires a preparation of potential variables / covariates by univariate analysis preliminary estimation of their predictive power for the interest variable. It is also important to highlight the interactions between different variables in order to avoid multicollinearity, when two covariates, being closely associated, reduce the predictive ability of the eventual model. A suitable method in this case – determining the form of relationships between covariates and the dependent binary variable (survival / death) by univariate regression analysis, followed by multivariate one. This onset will allow to find the variables with maximal potential and put the bases for the alternative predictive model's elaboration with ability to predict the treatment results in severe trauma.

In this article, biochemistry data, ionogram and hemoleukogram data, sex, age, comorbidities (chronic diseases, such as and the occurrence of pneumonia during hospitalization in the ICU of the Emergency Medicine Institute (EMI)) were considered as predictors and analyzed without anatomical trauma component, which demonstrated the ability to predict in previous studies [7]. These variables were not randomly selected. First, these indicators reflect the state of different organ systems. Second, being "routine" parameters, this information is available for each severe trauma patient admitted to the ICU. Based on the obtained results, potential predictive models adjusted to biological gender and age will be proposed.

Goals and objectives. The purpose of this study is to test the routine clinical/paraclinical patient data as severe trauma survival predictors. Especially, the article has the aim to highlight the potentially "efficient" variables in order to complete the existing commonly used trauma scores. Also, the results presented tend to attract attention and motivate specialists from other medical centers to follow the same strategy for the institutions in which they operate.

Materials and methods. Current analytical cohort clinical study (retro prospective) had the aim to identify some unrevealed efficient variables able to give us some information regarding severe trauma patients treatment results. "Nicolae Testemiţanu" State University of Medicine and Pharmacy (Chisinau, Republic of Moldova) Ethical Committee approved the design of study (Protocol 33/46 from 16.12.2016). Totally 2651 severe trauma patients consecutively ICU admitted in EMI, Chisinau, Republic of Moldova were considered (period January 2013 – November 2018). The information source was the electronic archive of EMI for the years 2009-2019 with no personal data consideration, inclusion criteria being: age over 18, blunt trauma, traumatic injuries appreciated on admission with NISS (New Injury Severity Score)>15 [8], acute trauma period, direct admission in EMI and survive first 24 hours, complete data

The following parameters, collected at the hospitalization, were used as potential predictors for severe trauma treatment result:

- age, gender;
- systolic blood pressure (SBP), respiratory rate (RR) and Glasgow Coma Scale (GCS);
- comorbidities according to the codes of the International Classification of Diseases and Related Health Problems, Edition 10 (Hypertensive diseases, Ischemic Heart diseases, Cerebral Palsy and other paralytic syndromes, Respiratory diseases affecting especially interstitial tissue (Pulmonary fibrosis), chronic lower respiratory diseases , Viral hepatitis, Chronic hepatitis, Atrial fibrillation / flutter, Chronic respiratory failure, Hemoperitoneum, Pneumonia, Mental and behavioral disorders due to alcohol use, Tuberculosis, diseases of arteries, arterioles and capillaries (atherosclerosis), mental disorders, including organic mental disorders, Hemorrhagic gastroduodenal ulcer, Type I and II diabetes, diseases of veins, lymph vessels and lymph nodes, other forms of heart disease, Osteoporosis, Chronic pyelonephritis, Chronic rheumatic heart disease);
- biochemistry data (General protein, g / l; Urea, mmol / l; Creatinine, umol / l; ALT, U / l; AST, U / l; AST / ALT; Bilirubin, μmol / l; Bilirubin conjugate, μmol / l; Glucose, mmol / l; Fibrinogen, g / l; Prothrombin, %; INR);
- ionogram (Na +, mmol / l; K +, mmol / l; Cl-, mmol / l);
- hemoleukogram indicators (Hb, g / l; Platelets, thousand / μL; Leukocytes, 109 / l; Metamyelocytes, %; Myelocytes, %; Segmented, %; Non-segmented, %; Juvenile neutrophils, %; Juvenile neutrophils,> 10%; Lymphocytes, %; Monocytes, %; Eosinophilia, %; Basophilia, %).

Results and Discussions.

A. Univariate analysis for treatment result prediction

Total number of eligible patients constituted 2651 subjects. Descriptive statistics and the univariate analysis of potential covariates are reflected in Table 1. Based on these data, the intrahospital lethality for the studied severe trauma population patients was 29.95% (95% CI 28.24, 31.72), which is considerably higher than 19.1% – German trauma register data for the lethality at the institutional level [9]. Of course, it's about preliminary data and it's not excluded that the data standardization will show other relationships. At the same time, the obtained figures could not be neglected and once again confirms the relevance of the studied topic.

The majority of the studied cohort were men – 2036 cases, which is 76.8% (95% CI 75.2, 78.4) of all the analyzed cases. Gender as a variable, despite expectations, did

not show even a tendency to be a predictor of lethality, the univariate analysis having a negative result in this sense (OR= 0.920, 95% IC 0.754, 1.122). This parameter will probably show the ability to predict treatment results in the context of multivariate analysis, being adjusted to the covariates in the potential model.

Age, considering a far from normal distribution, was estimated median (Mn) at the level of 48 years (95% CI 47, 50), the interquartile range (IR) being 29. The deceased patients presented a higher age (Mn = 54 (95% CI 54, 57), IR = 26) compared to those who survived (Mn= 43 (95% CI 42, 46), IR = 30), age covariate being a predictor for treatment results (OR = 0.975 95% IC 0.971, 0.980). This means that survival probability was reduced by about 2.5% by every life year..

The Glasgow Coma Scale value (GCS) tends to 13 points (Mn value, 95% CI 13, 14), IR = 5. Obviously, the absolute value of GCS was higher in survivors (Mn = 14) (95% CI

Table 1

Descriptive statistics and univariate analysis for treatment outcomes modelling

		Death, n=794		Survival, n=1857		Total, n=2651	
	OR (95% CI), univariate analysis	**n**	**Mn (95% CI), IR/ % (95% CI)**	**n**	**Mn (95% CI), IR/ % (95% CI)**	**n**	**Mn (95% CI), IR/ % (95% CI)**
Age, years	0.975 (0.971, 0.980)	794	56 (54, 57), 26	1857	43 (42, 46), 30	2651	48 (47, 50), 29
Gender, males	0.920 (0.754, 1.122)	618	77.8 (74.8, 80.6)	1418	76.4 (74.4, 78.3)	2036	76.8 (75.2, 78.4)
GCS, pts	1.360 (1.320, 1.401)	794	10 (10, 11), 7	1857	14 (14, 15), 3	2651	13 (13, 14), 5
RR, /min	1.037 (1.013, 1.061)	794	18 (18, 19), 4	1857	18 (18, 19), 3	2651	18 (18, 19), 4
SPB, mmHg	1.004 (1.001, 1.007)	794	120 (120, 130), 40	1857	120 (120, 125), 20	2651	120 (120, 125), 30
GCS_{rank}, 3	0.022 (0.008, 0.063)	794	4.7 (3.3, 6.5)	1857	0.2 (0.1, 0.6)	2651	1.5 (1.1, 2.1)
GCS_{rank}, 4-5	0.026 (0.014, 0.051)		10.9 (8.7, 13.4)		0.7 (0.4, 1.1)		3.6 (2.9, 4.4)
GCS_{rank}, 6-8	0.132 (0.102, 0.171)		28.5 (25.2, 32.0)		8.7 (7.4, 10.1)		14.4 (13.0, 15.9)
GCS_{rank}, 9-12	0.308 (0.242, 0.391)		24.1 (21.0, 27.4)		17.1 (15.3, 18.9)		19.1 (17.6, 20.7)
GCS_{rank}, 13-15	1		31.9 (28.4 -35.4)		73.4 (71.2, 75.5)		61.3 (59.3, 63.3)
RR_{rank}, 0	2.236 * 10^-10	794	1.4 (0.7, 2.5)	1857	0 (-)	2651	0.4 (0.2, 0.7)
RR_{rank}, 1-5	0.151 (0.053, 0.429)		1.8 (1.0, 3.1)		0.3 (0.1, 0.7)		0.7 (0.4, 1.2)
RR_{rank}, 6-9	0.205 (0.119, 0.353)		5.7 (4.1, 7.7)		1.3 (0.8, 1.9)		2.5 (1.9, 3.2)
RR_{rank}, >30	0.135 (0.036, 0.512)		1.2 (0.6, 2.3)		0.2 (0.1, 0.5)		0.5 (0.3, 0.8)
RR_{rank}, 10-29	1		89.8 (87.3, 92.0)		98.2 (97.5, 98.8)		95.9 (95.0, 96.6)

Continuation of the Table 1

SPB_{rank}, 0	2,2923* 10^-10		0.7 (0.3, 1.6)		0 (-)		0.2 (0.1, 0.5)
SPB_{rank}, 1-49	0.023 (0.003, 0.175)		2.3 (1.4, 3.6)		0.1 (0, 0.3)		0.7 (0.4, 1.1)
SPB_{rank}, 50-75	0.378 (0.252, 0.567)	794	7.1 (5.4, 9.2)	1857	3.0 (2.3, 3.9)	2651	4.2 (3.4, 5.1)
SPB_{rank}, 76-89	0.552 (0.376, 0.808)		6.8 (5.1, 8.9)		4.2 (3.3, 5.2)		5.0 (4.1, 5.9)
SPB_{rank}, >90	1		83.1 (80.1, 85.7)		92.8 (91.4, 93.9)		89.9 (88.7, 91.1)
ICU	5.089 (3.504, 7.392)	762 32	96.0 (94.4, 97.2) 4.0 (2.8, 5.6)	1530 327	82.4 (80.6, 84.1) 17.6 (15.9, 19.4)	2292 359	86.5 (85.1, 87.7) 13.5 (12.3, 14.9)
Total protein, g/l	1.048 (1.037, 1.058)	794	55 (55, 56), 12	1857	60 (60, 61), 12	2651	58 (58, 59), 13
Urea, mmol/l	0.917 (0.899, 0.936)	794	6.8 (6.5, 7.2), 5.7	1857	5.5 (5.4, 5.7), 3.3	2651	5.8 (5.7, 6), 3.9
Creatinine, μmol/l	0.990 (0.988, 0.993)	794	98 (96, 102), 51	1857	87 (86, 89), 30	2651	90 (89, 92), 35
ALT, U/l	0.998 (0.997, 0.999)	794	33 (31, 36), 39	1857	29 (28, 31), 35	2651	31 (30, 33), 37
AST, U/l	0.998 (0.997, 0.999)	794	51 (47, 57), 68.5	1857	39 (38,42), 43	2651	42 (41, 44), 51
AST/ALT	0.873 (0.805, 0.946)	794	1.56 (1.48, 1,65), 0.99	1875	1.35 (1.31, 1.40), 0.9	2651	1.41 (1.38, 1.44), 0.99
Bilirubin, μmol/l	0.984 (0.977, 0.991)	794	12 (12, 14), 12	1857	12 (12, 13), 8	2651	12 (12, 13), 9
$Bilirubin_{conjugated}$, μmol/l	0.952 (0.935, 0.968)	794	3 (3, 4), 3	1857	2 (2, 3), 2	2651	2 (2, 3), 3
Na^+, mmol/l	0.938 (0.915, 0.953)	794	146 (146,147.6), 9	1857	144 (144, 145), 6	2651	144 (144, 145), 7
K^+, mmol/l	1.398 (1.157, 1.688)	794	4.1 (4.1, 4.3), 0.9	1857	4.3 (4.3, 4.4), 0.8	2651	4.2 (4.2, 4.3), 0.81
Cl^-, mmol/l	0.951 (0.938, 0.966)	794	114 (113, 116), 11	1857	110 (110, 111), 9	2651	111 (111, 112), 10
Glucose, mmol/l	0.873 (0.847, 0.899)	794	7 (6.8, 7.3), 4.2	1857	6.1 (6, 6.3), 2.5	2651	6.3 (6.2, 6.4), 2.9
Fibrinogen, g/l	0.945 (0.896, 0.997)	794	3.1 (3.1, 3.3), 1.9	1857	3.1 (3.1, 3.3), 1.5	2651	3.1 (3.1, 3.3), 1.5
Prothrombin, %	1.030 (1.023, 1.038)	794	82 (82, 84), 16	1857	87 (87, 88), 15	2651	85 (85, 86), 15
INR	0.414 (0.272, 0.629)	794	1.24 (1.23, 1.27), 0.25	1857	1.18 (1.17, 1.19), 0.21	2651	1.19 (1.19, 1.2), 0.22
Hb, g/l	1.014 (1.011, 1.018)	794	122 (120, 124), 33	1857	129 (128, 131), 29	2651	127 (126, 129), 32
Trombocytes, n	1.000 (0.999, 1.001)	794	200 (192, 209),102	1857	198 (194, 204), 100	2651	198 (194, 203), 100
Leucocytes, 10^9/l	0.994 (0.978, 1.009)	794	12.2 (11.7, 12.7), 7	1857	11.7 (11.5, 12), 5.8	2651	11.8 (11.6, 12.2), 6.1

Continuation of the Table 1

Metamielocytes, %	0.726 (0.676, 0.780)	794	1 (1, 2), 2	1857	0 (-), 1	2651	0 (-), 1
Mielocytes, %	0.829 (0.766, 0.898)	794	0 (-), 1	1857	0 (-), 1	2651	0 (-), 0
Segmented, %	1.018 (1.010, 1.026)	794	67 (66, 68), 16	1857	69 (69, 70), 15	2651	68 (68, 69), 15
Unsegmented, %	0.968 (0.959, 0.977)	794	13 (12, 15), 12	1857	10 (10, 11), 10	2651	11 (11, 12), 11
Young Neutrophiles, %	0.960 (0.952, 0.969)	794	15 (14, 16), 13	1857	11 (11, 12), 11	2651	12 (12, 13), 12
Juvenile neutrophiles, >10%	0.434 (0.357, 0.528)	435	67.7 (64.0, 71.2)	674	47.6 (45.0, 50.2)	1109	53.9 (51.7, 56.0)
Limfocytes, %	1.015 (1.002, 1.028)	794	10 (10, 11), 9	1857	12 (12, 13), 11	2651	11 (11, 12), 10
Monocytes, %	1.022 (0.995, 1.049)	794	5 (5, 6), 5	1857	5 (5, 6), 5	2651	5 (5, 6), 5
Eosinophiles, %	0.990 (0.943, 1.040)	794	1 (1, 2), 1	1857	1 (1, 2), 2	2651	1 (1, 2), 2
Basophiles, %	1.020 (0.945, 1.101)	794	0 (-), 0	1857	0 (-), 0	2651	0 (-), 0

Note: OR – odds ratio,95% CI – 95% confidence interval, Mn – median, IR – interquartile range

14, 15), IR= 3) compared to the deceased (Mn = 10 (95% CI 10, 11), IR = 7. The form of these relationships was quantitatively estimated at OR = 1.360 (95% CI 1.320, 1.401) – GCS one-point variations will change survival probability by 36% (95% CI 32.0, 40.1). At the same time, the analysis of GCS-survival rate relations shows that there is a risk for irregular relationships, i.e., the coefficient describes well the current situation for high values of GCS, but information on low GCS values consists an uncertain area of lethality. This is a sign that eventual alternative models will not reflect the reality and there is a high probability to induce prediction errors. To correct these possible problems, the transformation of the GCS variable in a rank variable (categorization being proposed by the authors of the RTS score) was parallelly performed which improved predictive value of GCS. Having a total of five categories, the last most valuable category was considered as a reference point (GCS_{rank} between 13 and 15 points). Consecutive passing from a higher category to a lower category significantly reduces the OR value. For GCS_{rank} these values constituted 1, 0.308 (95% IC 0.242, 0.391), 0.132 (95% IC 0.102, 0.171), 0.026 (95% IC 0.014, 0.051), 0.022 (0.008, 0.063) for GCS_{rank} 13-15, GCS_{rank} 9-12, GCS_{rank} 6-8, GCS_{rank} 4-5 and GCS_{rank} 3, respectively. As it can be seen, the hypothesis exposed above was correct and GCS_{rank} relations are not constant, but instead, after considering GCS as a rank variable, the relationships are described and the coefficients are estimated for each category. Apart from this, it is important to consider the practical aspects -- when sometimes is difficult to determine the absolute values of the GCS. The described procedure is excluding these problems. GCS_{rank} 4-5 and GCS_{rank} 3 do not clinically differ a lot and reduce the probability of survival by about 40 times compared to the chances of a

patient in the GCS_{rank} category 13-15, GCS_{rank} 6-8 (7.6 times) and GCS_{rank} 9-12 (3.2 times) with 7.6 and 3.2 survival chances smaller, respectively.

Respiratory rate values (RR) at admission tend to Mn =18 breaths per minute (95% CI 18, 19), IR = 4. Interestingly, the difference between deceased patients (Mn = 18, (95% IC 18, 19), IR = 4) and survivors is practically insensitive (Mn = 18, (95% IC 18, 19), IR = 3), OR being estimated at 1,037 (95% CI 1,013, 1,061). The problem of irregular relationships is more acute than GCS variable because normal values are placed in the middle of the amplitude of the possible values. Data transformation (categorization) showed the following results. RR_{rank} value 10-29 was considered as a reference value (OR = 1) and was significantly different according to the effects on the survival rate compared to all categories formed, the same for RR_{rank} 0. At the same time, the remaining three categories do not differ from each other, being different compared to RR_{rank} 10-29 and RR_{rank} 0, reducing the probability of survival 5 – 6 times (RR_{rank} 1-5 OR = 0.151 (95% CI 0.053, 0.429), RR_{rank} 6-9 OR = 0.205 (95% IC 0.119, 0.353) and RR_{rank} > 30 OR = 0.135 (95% CI 0.036, 0.512) from the reference category, with large confidence intervals. This, in perspective, may be a cause for excluding this variable from the equation for treatment outcomes prediction of severe trauma patients.

Systolic blood pressure (SPB) values at hospital admission of a severe trauma patient were estimated at 120 mmHg (Mn) (95% CI 120, 125), IR = 30, the absolute level being equal for survivors, the difference is highlighted only for the spread indicator (Mn=120 (95% IC 120, 125), IR = 20) and deceased (Mn = 120 (95% IC 120, 125), IR = 40). The effect SBP was estimated at OR = 1.004 (95% CI 1.001, 1.007) – SBP fluctuations with 1mmHg are associated with survival rate fluctuations of 0.4%, these results being clinically insignificant. Similar to GCS and RR, categorization was performed, SPB> 90 mmHg being a reference value (OR = 1). The odds ratio was 0.552 (95% CI 0.376, 0.808), 0.378 (95% IC 0.252, 0.567), 0.023 (95% IC 0.003, 0.175), 2.2923 * 10 ^ -10 for SPB_{rank} 76-89 mmHg, SPB_{rank} 50-75 mmHg, SPB_{rank} 1-49 mmHg and SPB_{rank} 0 mmHg, respectively, compared to SPB_{rank} SPB_{rank} > 90 mmHg (OR = 1). Its important to mention about the categories SPB_{rank} 76-89 mmHg and SPBrank 50-75 mmHg, which, being different from the standard category, does not differ significantly one from another, the other categories having significant differences, 95% confidence intervals being narrower compared to RR categories.

Hemoleucogram, standard biochemical analysis and ionogram performed at hospital admission complete the table described above. It is important to mention some trends determined in the present article, characteristic to severe trauma. Hyperglycemia was found (Mn = 6.3 (95% CI 6.2, 6.4) IR = 2.9), the values in deceased patients being significantly higher (Mn = 7.0 (95% CI 6.8, 7.3), IR = 4.2 compared to Mn = 6.1 (95% CI 6.0, 6.3) IR = 2.5), estimated effect OR = 0.873 (95% IC 0.847, 0.899). The prothrombin value for the studied population was estimated at the level of 85% (Mn, 95% CI 85, 86), IR = 15), being less than 80% in 30% of the respondents. The comparative assessment of prothrombin values showed a low level for the deceased (Mn = 82 (95% IC 82, 84) IR = 16 compared to Mn = 87 (95% IC 87, 88) IR = 15), parameter change with 1% being associated with the 3% survival probability oscillations (OR = 1,030 (95% CI 1.023, 1.038). Also, the increase of INR was found (Mn = 1.19, 95% CI (1.19, 1.2), IR = 0.22), the value being lower in survivors (Mn = 1.18 (95% CI 1.17, 1.19), IR = 0.21 compared with Mn = 1.24 (95% IC 1.23, 1.27), IR = 0.25), OR = 0.414 (95% IC 0.272, 0.629). In addition, increase in the number of leukocytes was noted – a sign of aseptic inflammation in se-

vere trauma Mn = 11.8 (95% CI 11.6, 12.2), IR = 6.1, neutrophilia with lymphopenia and left deviation of the leukocyte formula. The occurrence of juvenile forms could affect the prediction results. The increase in metamyelocytes or myelocytes was negatively associated with the rate of survival (OR = 0.726 (95% CI 0.676, 0.780) and OR = 0.829 (95% CI 0.766, 0.898), respectively). In 53.9% (95% CI 51.7, 56.0) of the studied population, juvenile neutrophils were more than 10%. Platelets showed no significance (OR = 1,000 (95% CI 0.999, 1.001)), Hb concentration being lower in patients with negative outcome (Mn = 122 (95% CI 120, 124), IR = 33 compared to Mn = 129 (95% IC128, 131), IR = 29) with effect size OR = 1,014 (95% IC 1.011, 1.018) – decrease in Hb by 1 g / l reduces the survival probability by 1.4%.

Standard biochemistry parameters, as well as ionogram indicators, as shown by univariate analysis, presents a potential source for treatment outcomes biomarkers/predictors, all parameters showing significance. Urea (OR = 0.917 (95% CI 0.899, 0.936)), creatinine (OR = 0.990 (95% IC 0.988, 0.993)), ALT (OR = 0.998 (95% IC 0.997, 0.999)), AST (OR = 0.998 (95% CI 0.997, 0.999), bilirubin (OR = 0.984 (95% CI 0.977, 0.991)), conjugated bilirubin (OR = 0.952 (95% CI 0.935, 0.968)), general protein (OR = 1.048 (95% CI 1.037, 1.058)), prothrombin (OR = 1,030 (95% CI 1,023, 1,038)), fibrinogen (OR = 0.945 (95% CI 0.896, 0.997)), Na+ concentration (OR = 0.938 (95% CI 0.915, 0.953) and Cl^- concentration (OR = 0.951 (95% CI) 0.938, 0.966)) showed less than 10% changes in survival probability and can be considered as low potential predictors. At the same time, INR value, concentration glucose and K + concentration were above mentioned value (OR = 0.414 (95% CI 0.272, 0.629), OR = 0.873 (95% CI 0.847, 0.899) and OR = 1.398 (95% CI 1.157, 1.688)), respectively, being potential biomarkers for the variable of interest.

Also, it is important to mention that within multivariate analysis, when all parameters will be evaluated simultaneously, the coefficients can be modified. For these reasons, the obtained results guidance value.

B. Predictive model based on the correlation of clinical-paraclinical data.

Potential effects of biochemical parameters, ionogram, hemoleucogram indicators, clinical signs and comorbidities were analyzed together in a predictive model, the purpose being the treatment results prediction (survival / death), adjusted for age and male sex. Null hypothesis – covariates included in the model (biochemistry and ionogram parameters, indicators, clinical signs and comorbidities, sex, age) cannot predict the probability of survival at patients with severe trauma better than a model that is based only on a single constant. Alternative hypothesis – at least one of the mentioned variables can predict the probability of survival at patients with severe trauma better than a model that is based only on a single constant. Null hypothesis was rejected (Omnibus Test of Model Coefficients ($\chi 2 = 264{,}792$, df = 13, $p < 0.001$). Further analysis found the following characteristics of the developed model. Determination indicator, Nagelkerke R Squared, showed the value 0.394 (39.4%), which means that almost 40% of the interest variable dispersion was explained by the parameters in the developed model.

The calibration indicator (Hosmer – Lemeshow test) demonstrated an appropriate value, $\chi 2 = 11{,}592$, df = 8, p = 0.170, the model being well calibrated and can be further evaluated, the data being accurate on the whole predicted scores amplitude divided by 10 deciles.

Discrimination indicators resulting from the classification table, namely specificity and sensitivity, were equal to 69.8% and 75.4%, respectively, the summary (overall)

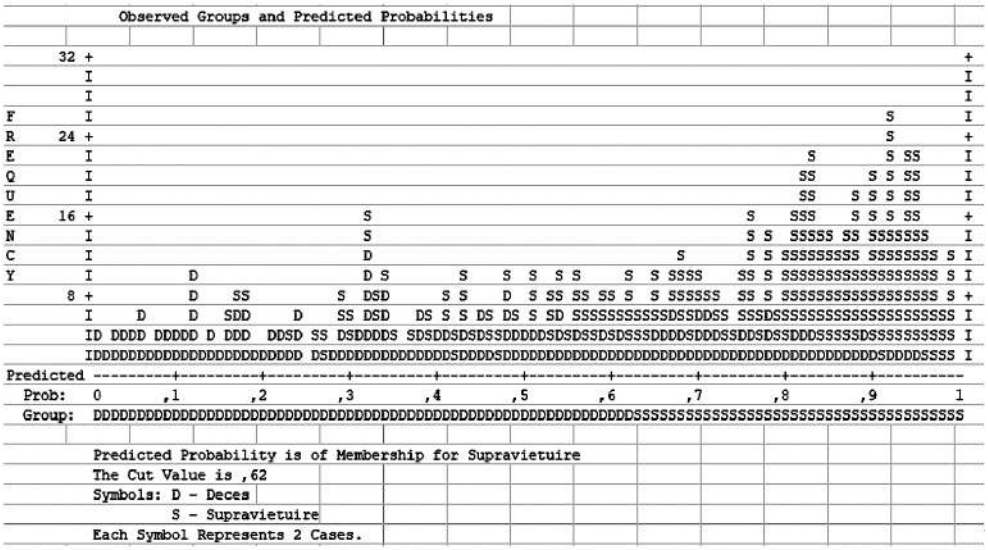

Figure 1. Classification chart for the predictive model of survival probability in severe trauma patients based on the correlation of clinical-paraclinical data

percentage being estimated at 73.3%. The results were obtained after optimization by changing the cut-off value from 0.5 at 0.61 (Figure 1).

The area under the ROC Curve, for the proposed model, was 0.823, with 95% confidence interval (0.794, 0.851) and with a significant difference from 0.5 value ($p < 0.001$) (Fig. 3.6). The model included constant (B = 9,824), age, years (B = -0,040), male sex (B = -0,877), supplemented by the urea (B = -0.042), creatinine (B = -0.004), conjugated bilirubin (B = -0.048), K + (B = 0.406), Cl- (B = -0.057), respiratory diseases mainly affecting the interstitial tissue (lung fibrosis) (B = -1,599), % myelocytes (B = -0,235),

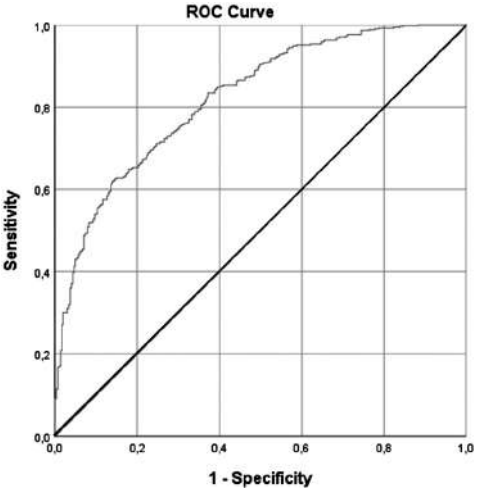

Figure 2. ROC curve for the predictive model of the probability of survival in patients with severe trauma based on the correlation of clinical-paraclinical data

GCSrank, 3 = -2,921, GCSrank, 4-5 = -2,654, GCSrank, 6-8 = – 1,866, GCSrank, 9-12 = – 0.965. The other parameters did not show significant effect and did not enter in the final model (Table 2, section a). Stability analysis by resampling, bootstrapping method (1000 samples) of the model developed for the probability of survival in severe trauma, despite the large number of predictors, showed that the coefficients are stable, significant, without inversions of the signs in front of the coefficients (Table 2, section b). It is important to note that the variables in the model are not strongly associated, which is nothing but the criterion of absence collinearity – an important condition to consider the model developed below.

Taking into account the mentioned coefficients, the developed model has the following mathematical expression:

$p = \frac{1}{1+e^{-b}}$ (formula 3.3), where

p – the probability of survival in severe traumas;

b = constant x 9.824 – age x 0.040 – male x 0.877 – urea x 0.042 – creatinine x 0.004 – conjugated bilirubin x 0.048 + K^+ x 0.406 – Cl^- x 0.057 – respiratory diseases mainly affecting interstitial tissue (fibrosis) x 1.599 – myelocytes x 0.235 – coefficient x GCSrank (if GCS_{rank} 3 coefficient = 2.921, GCS_{rank} 4-5 = 2.654, GCS_{rank} 6-8 = 1.866, GCS_{rank} 9-12 = 0.965), e (exponent) – constant equal to 2.71828.

All predictors except potassium concentration showed a negative association with the survival rate of a patient with severe trauma. The male effect was estimated at OR = 0.416 (95% CI 0.268, 0.646). This assumes that in that model the information included

Table 2

Equation variables in survival prediction models for severe trauma patients based on clinical–paraclinical data correlation. SPSS Output 23

a. Model's coefficients

							95% C.I. for EXP(B)	
	B	S.E.	Wald	df	Sig.	Exp(B)	Lower	Upper
Gender (male)	–.877	.224	15.282	1	.000	.416	.268	.646
Age, years	–.040	.006	50.591	1	.000	.961	.951	.972
GCS_{rank}, 13–15			84.964	4	.000			
GCS_{rank}, 3	–2.921	.835	12.230	1	.000	.054	.010	.277
GCS_{rank}, 4–5	–2.654	.451	34.675	1	.000	.070	.029	.170
GCS_{rank}, 6–8	–1.866	.237	61.798	1	.000	.155	.097	.246
GCS_{rank}, 9–12	–.965	.223	18.634	1	.000	.381	.246	.591
Urea	–.042	.018	5.267	1	.022	.959	.926	.994
Creatinine	–.004	.001	6.368	1	.012	.996	.993	.999
$Bilirubin_{conjugated}$	–.048	.017	8.271	1	.004	.953	.923	.985
K^+	.406	.130	9.690	1	.002	1.501	1.162	1.938
Cl^-	–.057	.010	31.045	1	.000	.945	.926	.964
%Mielocytes	–.235	.066	12.631	1	.000	.791	.695	.900

Continuation of the Table 2

respiratory diseases especially affecting tissue interstitial (fibrosis)	−1.599	.463	11.955	1	.001	.202	.082	.500
Constant	9.824	1.368	51.564	1	.000	18468.013		

b. Bootstrap resampling results for variables included in the model

					95% Confidence Interval for B	
	B	**Bias**	**S.E.**	**Sig.**	**Lower**	**Upper**
Gender (male)	−.877	−.036	.234	.001	−1.392	−.456
Age, years	−.040	.000	.006	.001	−.051	−.029
GCS_{rank}, 13–15	−2.921	−2.433	6.465	.001	−22.593	−1.781
GCS_{rank}, 3	−2.654	−.077	.476	.001	−3.687	−1.829
GCS_{rank}, 4–5	−1.866	−.022	.236	.001	−2.365	−1.425
GCS_{rank}, 6–8	−.965	−.017	.244	.001	−1.479	−.492
GCS_{rank}, 9–12	−.042	−.011	.031	.100	−.126	−.010
Urea	−.004	.000	.002	.016	−.007	.000
Creatinine	−.048	−.003	.016	.002	−.087	−.024
$Bilirubin_{conjugated}$	.406	.010	.139	.003	.150	.690
K^+	−.057	.000	.010	.001	−.077	−.037
Cl^-	−.235	−.022	.086	.004	−.459	−.127
%Mielocytes	−1.599	−.036	.491	.001	−2.751	−.737
respiratory diseases especially affecting tissue interstitial (fibrosis)	9.824	.111	1.310	.001	7.427	12.672
Constant	−.877	−.036	.234	.001	−1.392	−.456

in the variable reduces the probability of survival more than twice. Age, measured in years, showed a greater effect compared to the univariate analysis, increasing the age by one year reduces the probability of a positive result by 3.9%. If the effect of age can be explained by the reduction of physiological reserves and the occurrence of concomitant chronic diseases, the effect of male biological gender is most likely related to diagnosis, another explanation being the physiological peculiarities.

The effects of GCS_{rank} were not different from the univariate analysis for all categories because the estimated OR value is included in the range of confidence intervals. Next GCS_{rank} 3 and GCS_{rank}4-5 not differ and patients in these categories are likely close identical for survival after severe trauma, being different from $GCS_{rank,}$ 6-8, GCS_{rank}9-12 and GCS_{rank}13-15 (OR = 0.155 (95% CI 0.097, 0.246; OR = 0.381 (95% CI 0.246.0.591)) and 1, respectively). Of all the potential predictors that are part of concomitant pathologies, within of the proposed model showed significance only the presence of pulmonary fibrosis (respiratory diseases reaching especially interstitial tissue) the estimated effect (OR = 0.202 (95% CI 0.082, 0.500)) being similar univariate analysis (OR = 0.266 (95% CI 0.171, 0.413)). Hemoleukogram parameters also were presented by a single

significant indicator -% myelocytes (OR = 0.791 (95% CI 0.695, 0.900)) – an increase in myelocytes to 1% reduces the probability of survival by about 20%, effect similar to the results of univariate analysis (OR = 0.829 (95% CI 0.766, 0.898)). The growth K^+ and Cl^- concentrations included in this model showed a positive prediction (OR = 1.501 (95% CI 1.162, 1.938)) and, respectively, negative (OR = 0.945 (95% IC 0.926, 0.964)). Biochemical parameters, such as urea, creatinine and conjugated bilirubin showed negative effects in terms of prediction, ie their consecutive increase was associated with a reduction in the probability of survival (OR =0.959 (95% CI 0.926, 0.994), OR = 0.996 (95% CI 0.993, 0.999) and OR = 0.953 (95% CI 0.923, 0.985). It is important to note that the impact of urea growth on the treatment outcome was significantly lower than the univariate analysis, which shows a sign of its weak association with others covariates in the equation, as well as discussing the meanings found for biochemical parameters, because when adding other predictors (anatomical component for example) with very high probability great, these meanings will disappear from the equation.

Conclusions. The biochemical parameters, ionogram and hemoleucogram indicators, reflecting the host response in traumatic injury, represent a potential source for treatment result prediction covariates in severe trauma scores. Moreover, together with comorbidities in multivariate analysis these routine parameters have showed predictive potential. At the same time, having low indicators for determination coefficient, the elaborated model needs to be supplemented and validated.

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