MINISTERY OF HEALTH, LABOUR AND SOCIAL PROTECTION OF THE REPUBLIC OF MOLDOVA

PI *NICOLAE TESTEMITANU* STATE UNIVERSITY OF MEDICINE AND PHARMACY OF THE REPUBLIC OF MOLDOVA

Manuscript title:

C.Z.U: 616-001-037(043.2)

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SEVERE TRAUMA: EVOLUTION AND OUTCOME PREDICTIVE MODELS

312.01. Physiology and pathophysiology

321.19. Anesthesiology and intensive care

Summary of habilitated doctor thesis in medical sciences

CHIŞINĂU, 2021

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The doctoral thesis and the summary can be consulted at the PI *Nicolae Testemitanu* State University of Medicine and Pharmacy of the Republic of Moldova library and on the website of ANACEC (www.cnaa.md).

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LIST OF ABBREVIATION

AEE – elastase enzymatic activity

AET – trypsin enzymatic activity

AECG – cathepsin G enzymatic activity

AECD – cathepsin D enzymatic activity

AECH – cathepsin H enzymatic activity

AECL – cathepsin L enzymatic activity

AEADA – adenosindesaminase enzymatic activity

AEAMP – adenilatdesaminase enzymatic activity

M – α_2-macroglobulin

AT – α_1-antitrypsin

M – mean

Mn – median

AS – standard deviation

AI – interquartile range

EMI – Emergency Medicine Institute

MODS – Multiple organ dysfunction syndrome

95% CI – 95% confidence interval

AST – aspartate aminotransferase

ALT – alanine aminotransferase

OR – odds ratio

VAP – mechanical lung ventilation

UTIR – Intensive Care Unit/Reanimatology Department

CONCEPTUAL LANDMARKS OF THE RESEARCH

The actuality of the subject and the importance of the problem. According to the World Health Organization, tens of millions of people are traumatized each year, of whom 5 million die (9% of all recorded deaths) and the prognosis is negative [1]. Moreover, trauma remains the leading cause of death for children, adolescents and adults between the ages of 1 and 44 years [2]. The Republic of Moldova, having some peculiarities of socio-economic development, is no exception. According to the data of the Statistical Database of the Republic of Moldova, in the period 2009-2018, a resident person with a certain age has the same probability of death due to traumatic injuries as 10 years ago [3].

One of the tools to reduce the increased mortality rate in a trauma is to identify patients at increased risk of adverse events and/or death, using two strategies. The first - the identification of patients with „severe trauma", „major trauma" or „polytrauma". Another approach used is the application of traumatic scores (models) to estimate the primary outcomes of treatment (probability of death or survival), the most common scores used to be Revised Trauma Score (RTS), Injury Severity Score (ISS), New Injury Severity Score (NISS), Trauma Score – Injury Severity Score (TRISS) and A Severity Characterization Of Trauma (ASCOT). These models consider anatomical criteria (severity of lesions according to the Abbreviated Injury Scale (AIS)) and/or some physiological parameters (systolic blood pressure, respiratory rate, Glasgow coma scale), age, etc. Their use has the potential to improve the prognosis of trauma patient by optimizing their management. Studies show that implementing traumatic scores could optimize triage and trauma treatment outcomes [4].

At the same time, the usual models (scores), having in some researchs optimal values of the discrimination indicator (area under the ROC curve) close to 0.9, usually have a low sensitivity. Moreover, the confidence intervals (95% CI) for the odds ratio (OR) have a high amplitude and the coefficient of determination - an important feature of the model, which reflects how fully the model explains the dependent variable (survival or death rate in in case of trauma), the optimal value being ≥ 0.8, is not estimated/mentioned. For example, the sensitivity for TRISS varies around 0.7, in some studies being lower than the sensitivity for ISS and NISS. A 2016 meta-analysis that included 11 studies (11866 patients) demonstrated sensitivity of 0.64 and 0.71 for ISS and NISS, respectively, OR was rated at 27.75 (95% CI 9.93, 77.53) for ISS and 24.74 (95% IC 10.19, 60.07) for NISS [5].

Moreover, all attempts to find an universal score with optimal characteristics for all existing populations/medical systems failed, as shown by the systematic analysis of the literature in the PubMed/Medline, Web of Science and EBSCO databases from 2016, the same model having the predictive power depending on the studied population and/or the examined medical system. Currently, there is no consensus among the main trauma registries regarding the estimation of the probability of death/survival in trauma patients. Each trauma register is based on its own scores (models) or validated scores, developed for another population, the coefficients being corrected for the current situation and implemented especially for the given population. The German Trauma Registry proposes the second edition of the Revised Injury Severity Classification

(RISC II), the English medical system is based on the Probability of Survival model 14 (PS 14), the American system - The Trauma and Injury Severity Score (TRISS). In conclusion, the authors emphasize that the probability of survival or death should be assessed in patients with severe trauma with a score derived from a population that reproduces current demographic data [6].

Based on literature data, industrially developed countries usually use their own national trauma registers and scores, which are developed, validated and used for the given population. Scores (models) are reviewed periodically (usually every five years) or in real time, and each patient has its contribution to the correction of the coefficients within that model and is considered when estimating the probability of survival/death in subsequent patients. Instead, countries with medium or low economic development use the usual traumatic predictive scores or their adapted variants, the coefficients in the equation describing the relationship between covariates and the variable of interest, being corrected for one institution population or whole medical system. In both cases, an institution can use a predictive traumatic model only after an internal validation - a procedure demonstrating that the model is well predicting the observed outcome on the cohort of patients who did not participate in the development of the given model in the given institution [4,6,7].

Also, the question remains about the predictors/risk factors/effective variables that have the ability to predict treatment outcomes. Their identification can open perspectives for the elaboration of alternative predictive models with better characteristics than the existing/accepted ones. One potential direction is the use as predictors of various components of the protease/antiprotease system - active participants in the immune response to trauma. Proteases are aggressive factors, released by immunocompetent cells even in intact tissues, producing here „indirect" lesions, antiproteases being the protective factors that counterbalance the negative effects of proteases. It is important to note that the problem of developing predictive models for „indirect" injuries, which are an important source for the occurrence of MODS and as a result, increased lethality in trauma, presents some perspectives for reducing their negative effects on treatment outcomes and is not moment [8,9].

Thus, from the above, it is attested that the problem of predicting the results of treatment and injuries at a „distance" in trauma, including severe trauma, remains open. Only an overall analysis, using statistical analytical methods of data processing, with adjustment to the current demographic situation for the Republic of Moldova, will allow to develop/validate optimal predictive models (scores) for analyzing the results of treatment of a patient with severe trauma local medial system. For the moment, such a complex interdisciplinary study has not been conducted at either the institutional or national level. Also, the application of analytical methods in an experimental study has the potential to be the foundations for predicting „indirect" lesions in terms of the effects of the protease/antiprotease system. All these are the arguments for the initiation of this study.

Aim of the study: Elaboration and validation of evolution and outcome predictive models in severe traumas and/or polytraumas for the optimal risk estimation unfavorable evolution within the local medical system.

Research objectives:

1. Analysis of the common traumatic scores used to predict survival/death in a patient with trauma in order to determine the potential score for implementation in the local medical system.
2. Effective variables/biomarkers/risk factors identification in order to develop alternative predictive models for treatment outcomes (survival/death) in severe trauma.
3. Common predictive trauma models validation for the severe trauma population within the Emergency Medicine Institute (EMI) from Chișinău, Republic of Moldova.
4. Development and validation of alternative survival predictive models in severe trauma within the EMI.
5. Comparative evaluation of the developed/validated predictive model/models with the common traumatic scores.
6. Elaboration of predictive models for prolonged artificial pulmonary ventilation (VAP) risk estimation and the effect of pneumonia in UTIR, both being based on the developed/validated alternative predictive scores.
7. Complex analysis of the protease/antiprotease system components in order to predict the „indirect" lesions occurrence in experimental model of severe trauma.
8. „Indirect" injuries intensity predictive scores elaboration for severe trauma experimental model.
9. Protease/antiprotease system destructive/protective potential estimation in polytrauma patients. Elaboration and comparative evaluation of newly developed scores.
10. Principles formulation for creating the National Trauma Register in the Republic of Moldova.

Methodology. To achieve the goal and objectives, a complex, interdisciplinary study was planned, which was conducted within the Department of human physiology and biophysics (experimental part) and the Department of anesthesiology and reanimation no. 1 „Valeriu Ghereg" (clinical part) of PI SUMPh „Nicolae Testemitanu" as follows:

1. Retro-perspectivesive cohort clinical study (objectives 2-6 and 10) that included patients with severe trauma (NISS > 15) hospitalized in the UTIR during the acute period of trauma. The validation of the usual predictive models was performed by applying multivariate logistic regression, the univariate technique being used to identify potential predictors of survival rate. The elaboration of alternative models for treatment outcome required data processing by multivariate analysis of 70% of randomly selected patients, completed by the procedure of validation of new models on the rest of 30% of patients, whose data were not included in the alternative score's elaboration. As potential predictors were considered the clinical signs at admission, the data of standard biochemical analyzes with ionogram, hemoleucogram, comorbidities, all adjusted to the anatomical component. The comparative evaluation of the elaborated models with the usual ones was performed according to

the discriminative capacity, calibration, as well as the determination coefficients of the models.

2. The prospective pilot clinical study (objective 9) included patients with polytrauma, the predictive models for treatment outcomes being developed based on the components of the protease/antiprotease system, collected at 3, 6, 12 and 24 hours after the traumatic impact. Potential predictors were included in the logistic regression equation in traditional form (absolute values of different components) or in the form of „latent" factors, extracted in the factorial analysis. The indicators of determination, calibration and discrimination, similar to the retro-perspectivesive cohort clinical study were used for the comparative evaluation of the developed models with highlighting of the optimal model for predicting the survival rate.
3. The fundamental study for solving objectives 7 and 8 was performed using the experimental model of severe trauma developed previously, the components of the protease/antiprotease system as well as arterial pO_2, all measured before trauma, at 2, 5 and 24 hours after impact. These data were supplemented by information from histological analysis performed after animal sacrification, estimated by the Semicantitatively Reflected Calitative Changes Assesment Scale (SRCCAS). Similar to the pilot clinical study, the predictors were included in two forms, traditional and alternative after factorial analysis, the basic statistical method being linear regression, because the variable of interest is interpreted as a continuous one.

Scientific novelty. For the first time, for the population of patients with severe traumas within the local medical system, the usual traumatic scores were validated. Potential predictors for the survival rate of a severely traumatized patient were also identified. Considering the routine biochemical parameters, as well as the data of the hemoleucogram, completed with ionogram, comorbidities and anatomical component adjusted to the injured topographic region, a series of alternative predictive models were created, some being validated on a group of patients who did not have participated in the elaboration of the models. The characteristics of the alternative scores were superior to the usual validated models. In the alternative scores, the effects of pneumonia and prolonged VAP risk estimated. In addition, for the first time, predictive models were proposed for „indirect" lesions in severe experimental trauma, the predictors being the values of the components of the protease/antiprotease system or the „latent" factors estimated from these components by factorial analysis. In addition, predictive models for survival rate in polytraumas were improved after estimating the protective/destructive potential at different time intervals after the traumatic impact. Based on the obtained results, the principles of creating the Trauma Register in the Republic of Moldova were formulated.

The applied scientific problem of major importance solved: The scientific base of the predictive scores evaluation/elaboration for the evolution or treatment outcome in severe trauma, which led to prognostic models for survival rate and „indirect" lesions development. This allowed the patients stratification according to the risk of unfavorable evolution and the determination of research directions for the prediction/prophylaxis/treatment of „indirect" lesions in severe trauma.

Theoretical importance and applicative value of the paper. This study will allow to complete the contemporary views on the interpretation of the „routine" physiological parameters collected at the hospitalization of a patient with severe trauma in order to predict the results of treatment; validation of the usual predictive models for the population in the national medical system; elaboration and validation of alternative predictive models with superior characteristics compared with the usual models; the effects of pneumonia and prolonged VAP; identification of predictors for „indirect" lesions in experimental trauma with complex analysis of protease/antiprostatic system components with extraction of "latent" factors that represent the quantification of pathophysiological mechanisms involved in severe trauma with the ability to predict the expression of these lesions, to monitor and in the future, to influence complex processes instead of separate elements; estimation of the protective/destructive potential of the protease/antiprotease system in polytraumas; development of screening models to identify patients at risk of dying or requiring prolonged VAP. It is also important to note that the developed/validated scores have the potential to improve the quality of trauma studies because they have the ability to estimate the severity of injuries with high accuracy. Moreover, the results obtained will be used to reduce the occurrence of „undesirable" events in the evolution of severe trauma and to formulate the principles of creating the Trauma Register in the Republic of Moldova.

The complex analysis of the routine physiological parameters obtained at hospitalization will provide useful information for optimizing the process of collecting relevant data in sense of association with the results of treatment in a traumatized patient. The validation of the usual traumatic scores will be of practical interest because it will allow to use these tools more efficiently for the patients from the studied population, considering the correction of the coefficients that will be performed in the given study. Alternative predictive models, with better characteristics than usual scores, will provide the possibility to stratify the risks for death and prolonged VAP with maxEMIm accuracy, at least until other more accurate models are proposed. The inclusion of the components of the protease/antiprotease system as predictors for the severity of „indirect" lesions will open the perspectives of reducing their expression by generating new strategies, such as the use of antiprotease inhibitors at the right time. Also, the components of this system, being involved in the immune response and having the ability to predict treatment outcomes, will be a potential source of predictors/variables that are effective from a prognostic point of view and probably from a prophylactic or therapeutic point of view. Eventually developed screening models will be applied at the time of admission and will make it possible to identify patients at high risk of dying or requiring prolonged VAP, which is beneficial in determining the optimal treatment strategy for the traumatized patient.

Implementation of scientific results. The results of the study and the methodical recommendations were implemented in the daily activity of the Clinic of Anesthesiology and Reanimatology at Institute of Emergency Medicine, in the teaching process at the Department of human physiology and biophysics and the Department of anesthesiology and reanimatology no.1 "Valeriu Ghereg", SUMPh "Nicolae Testemitanu".

Approval of results. The scientific results obtained during the research were presented and discussed in the communications at the scientific forums: The VIth International Congress „Black Sea Pearl" (Odessa, Ukraine, 2020); The 46th Congress of the Romanian Society of Anesthesia and Intensive Care (Sinaia, Romania, 2020); The XIIIth National Congress of Romanian Society of Physiology (Târgu-Mureș, Romania, 2020); Congress dedicated to the 75th anniversary of the founding of SUMPh „Nicolae Testemitanu" (Chisinau, Republic of Moldova, 2020); International Scientific Conference for Researchers in the Field of Anesthesiology and Intensive Care „In memoriam, Professor Valeriu Ghereg" (Chisinau, Republic of Moldova, 2020); The IIIrd International Symposium „ New horizons for anesthesiology, critical care and pain management", Dnepr; The XIIIth Congress of the Association of Surgeons „Nicolae Anestiadi" and IIIrd Congress of the Society of Endoscopy, Minimally Invasive Surgery and Ultrasonography „V. M. Guțu „(Chisinau, Republic of Moldova, 2019); The 4th International Conference on Nanotechnologies and Biomedical Engineering (Chisinau, Republic of Moldova, 2019); The 31th National Conference of Physiology. Physiology Today: Innovation, Integration, Translation (Timișoara, Romania, 2019); National scientific conference with international participation. Integration through research and innovation. Natural and exact sciences (Chisinau, Republic of Moldova, 2019); The 20th European Society for Trauma & Emergency Surgery Congress (Prague, Czech Republic, 2019); The 5th International Congress „Black Sea Pearl" (Odessa, Ukraine, 2018); The 30th National Conference of Physiology. Integrative Physiology, from Fundamental Mechanisms to Biomedical Application (Cluj-Napoca, Romania, 2018); The 19th European Society for Trauma & Emergency Surgery Congress (Valencia, Spain, 2018); The IIIrd International Conference on Anesthesiology and Intensive Care „Autumn meeting in Odessa" (Odessa, Ukraine, 2017); The 12th National Congress of the Romanian Society of Physiology (Craiova, Romania, 2016); The 27th National Conference of Physiology of the Romanian Physiological Society (Bucharest, Romania, 2014).

Also, the results were presented at the following invention fairs, the works being mentioned with distinctions (medals): Proinvent International Exhibition of Research, Innovation and Invention (Cluj-Napoca, Romania 2020 - gold medal); The 12th edition of European Exhibition of Creativity and Innovation (Iași, Romania; 2020 - silver medal); Infoinvent International Specialized Exhibition (Chisinau, 2019 - gold medal); Proinvent International Exhibition of Research, Innovation and Invention (Cluj-Napoca, Romania 2019 - gold medal); The 11th edition of European Exhibition of Creativity and Innovation (Iași, Romania; 2019 - gold medal); The 23rd International Salon & Exhibition of Inventics Inventica (Iași, Romania; 2019– gold medal); The 7th edition of European Exhibition of Creativity and Innovation (Iași, Romania; 2015– bronze medal); Proinvent International Exhibition of Research, Innovation and Invention (Cluj-Napoca, Romania; 2015 - gold medal); The 19th International Exhibition of Inventics, Research and Technological Transfer Inventica (Cluj-Napoca, Romania; 2015 - gold medal); The 18th International Exhibition of Inventics, Research and Technological Transfer Inventica (Cluj-Napoca, Romania; 2014 - gold medal);

The 6th edition of European Exhibition of Creativity and Innovation (Iași, Romania; 2014 - gold medal).

The results of the thesis were discussed and approved during the united meeting of the Department of human physiology and biophysics and the Department of Anesthesiology and Reanimatology nr.1 „Valeriu Ghereg" (protocol nr.7 from 12.10.2020) and at the meeting of the Profile Scientific Seminar 312. Physiology, 315. Biochemistry and molecular biology, specialties 312.01. Physiology and pathophysiology, 315.01. Medical Biochemistry, 315.02. Molecular biology and medical genetics (protocol nr. 2 from 20.11.2020).

Topic publications. 77 papers were published on the topic of the thesis, including a single-author monograph "Complex polytrauma with acute respiratory distress syndrome. Experimental and predictive modeling" (277 pages), 8 articles in various recognized scientific journals abroad, 14 articles in scientific journals from the National Register of Specialized Journals, in the materials of congresses, national scientific conferences, 32 abstracts in collections of papers within conferences, international congresses, as well as intellectual property exhibitions, 22 patents were registered with copyright.

Thesis structure: introduction, seven chapters, conclusions and recommendations, bibliography (189 titles), 249 pages of basic text, 83 figures, 89 tables, 41 formulas and 13 annexes.

Keywords: Severe trauma, predictive models, „indirect" lesions, protease/antiprotease system.

THESIS CONTENT

1. SEVERE TRAUMA. PREDICTION MODELS

The literature examination allowed the highlighting the predictive scores for trauma patients evolution, which, after validation, can be implemented in the local medical system [4]. At the same time, the development of alternative models with superior characteristics to the existing ones (usual, „routine") requires the identification of new predictors for primary outcome or other variables of interest, a perspective is the use of different biological indicators [10], mainly to those involved in the pathophysiological processes characteristic for severe traumas or polytraumas, such as the components of the protease/antiprotease system [11,12]. In addition, the immune mechanisms involved in the pathophysiology of severe trauma and the occurrence of „indirect" lesions were discussed [9,13–17]. Moreover, a number of predictive models for treatment outcomes in polytrauma were also presented, as well as perspectives in this area.

2. RESEARCH METHODOLOGY

In order to achieve the goal and objectives, an interdisciplinary study at the Department of human physiology and biophysics and the Department of anesthesiology and reanimatology nr.1 „Valeriu Ghereg" EMI clinical base of PI SUMPh „Nicolae Testemitanu" was planned.

The research is divided into clinical trials and experimental study. In clinical trials, patients with severe trauma/polytrauma hospitalized in the Anesthesiology and Reanimatology Clinic of EMI were included. In the experimental study, the experimental model of severe trauma developed previously was used. In clinical trials, objectives 2-6 and 9 were solved, the experimental model of trauma (rabbits) served as a basis for studying the associations between the components of the protease/antiprotease system or the factors extracted from the factorial analysis (destructive/protective potential) with the appearance of "indirect" injuries in severe trauma (targets 7 and 8). The design of the research as well as the ethical aspects were discussed and approved at the meeting of the Research Ethics Committee of PI SUMPh „Nicolae Testemitanu" (protocol nr. 46 of 16.12.2016).

2.1. Evolution and outcome predictive models elaboration in clinical trials

2.1.1. Analytical cohort clinical study (retro-prospective)

The source for information, according to the pre-established questionnaire, was the electronic archive of EMI for the years 2009-2019. At the request of the work team, the data required for the study were extracted by employees of the IT and Communication Service in Medicine and presented as a file in DBF format (the advantage being data stability compared to EXCEL) without including personal data such as: first and last names, adress, IDPN, telephone number, etc. The members of the research team did not have direct access to the EMI electronic archive.

According to the data obtained, during the research period, 8677 trauma patients were hospitalized in the UTIR for various reasons. This constitutes 10.07% (95% CI 9.87, 10.27) of the total number of traumatized patients discharged during that period. According to the inclusion and exclusion criteria mentioned below, 2651 patients with severe traumas remained eligible for analysis, for which the lethality was estimated at 30% compared to 2-3% of the general trauma population hospitalized in EMI.

Inclusion criteria: Patients ≥ 18 years old; patients with non-penetrating trauma; patients with traumatic injuries assessed at admission with NISS (New Injury Severity Score) > 15 [18]; patients who were hospitalized during the acute period of trauma (the first 72 hours after the traumatic impact) directly to EMI; patients with traumatic injuries assessed at hospitalization with NISS ≤ 15 with high risk of unfavorable evolution, including death (hospitalized in UTIR); traumatized patients who survived the first 24 hours after the traumatic impact and were in the UTIR for more than one day.

Exclusion criteria: patients < 18 years; patients with penetrating trauma; patients transferred via the AVIASAN line; patients transferred to the UTIR due to senile or alcoholic psychosis; burn patients; patients transferred to other institutions of the Republic of Moldova or abroad; hospitalized patients repeatedly with severe trauma; patients who required transfer to the UTIR for postoperative recovery; patients with incomplete data (eg: RISC II score has only 25% complete data available) [19]; patients who arrived at the hospital without signs of life or died in the stabilization ward.

As potential predictors, the following parameters were used:

• age, sex;

• systolic blood pressure (SBP), respiratory rate (RR) and GCS;

• comorbidities according to the codes of the International Classification of Diseases and Related Health Problems, Edition 10 (Hypertensive diseases, Ischemic Heart disease, Cerebral Paralysis and other Paralytic Syndromes, Respiratory diseases affecting especially interstitial tissue (Pulmonary Fibrosis), Chronic Lower Respiratory Airways 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), Disorders of mental state, including organic mental disorders, Hemorrhagic gastroduodenal ulcer, Type I and II diabetes mellitus, Diseases of veins, lymph vessels and lymph nodes, other forms of heart disease, Osteoporosis, Chronic pyelonephritis, Chronic rheumatic heart disease);

- biochemistry data (Total protein, g/l; Urea, mmol/l; Creatinine, μmol/l; ALT, U/l; AST, U/l; AST/ALT; Total bilirubin, μmol/l; Conjugated bilirubin, μmol/l l; Glucose, mmol/l; Fibrinogen, g/l; Prothrombin, %; INR);
- ionogram (Na +, mmol/l; K +, mmol/l; Cl-, mmol/l)
- hemoleucogram indicators (Hb, g/l; Platelets, n; Leukocytes, 109/l; Metamyelocytes, %; Myelocytes, %; Segmented, %; Unsegmented, %; Juvenile Neutrophils, %; Juvenile Neutrophils,> 10%; Lymphocytes, %; Monocytes, %; Eosinophilia, %; Basophilia, %).

2.1.2. Estimating the proteases/antiprotease system destructive/protective potential in polytrauma patients. Comparative evaluation

Prospective analytical study (Objective 9), which included 65 patients with polytrauma, the criteria being included in the Berlin definition stipulating the criteria mentioned in Chapter 1 (lesions of at least two regions of the body, assessed by AIS ≥ 3 and the presence of at least one of the 5 altered physiological parameters (systolic pressure ≤ 90 mmHg, GCS ≤ 8, acidosis, coagulopathy and age ≥ 70 years [20]).

Totally 10 components of the protease/antiprotease system were analyzed at different time intervals (3, 6, 12 and 24 hours after the traumatic impact), with caution in the criteria for considering the obtained models. The parameters followed, in addition to the components of the protease/antiprotease system, were the treatment outcome, the variable survival/death, age and sex.

Initially, predictors (covariates, effective variables) were determined for potential models. The minimum volume of the sample, as well as the strategy for their identification were obtained similarly to the experimental study in subchapter 2.3 by two parallel methods (correlational analysis or factorial analysis). The elaboration of the models (logistic regression) as well as their comparative evaluation (determination, calibration, discrimination) was performed according to the principles formulated in subchapter 2.1.1.

2.2. Methods for the determination of protease activity, associated enzymes and antiprotease concentration

The functional status of the protease/antiprotease system in the experimental and clinical studies was assessed by enzymatic activity meseament of elastase, trypsin, catepsins L, H, D, G, AT and M concentration, being supplemented by serum activity

of adenosine and adenylate deaminases. The biochemical analyzes were performed according to the methodological elaboration created by V. Gudumac et al. [21].

2.3. Predictive models development for „indirect" injuries after severe trauma (experimental study)

2.3.1. Reproduction the severe trauma conditions in the experiment

The experimental research solves objectives 7 and 8 of the current study. As previously mentioned, severe experimental trauma was reproduced according to the method developed by O. Arnaut et al. in 2013 [22].

Before the trauma and at the 2^{nd}, 5^{th} and 24^{th} hours after the impact, blood samples were collected. The arterial sample was taken using 2 ml heparinized syringes with the application of the heparin plug to measure pO_2. These instantly obtained results reflect the primary lung function (gas exchange), the effectiveness of the respiratory support and the acid-base status of the examined object. The rabbits breathed during the experiment with atmospheric air without an additional flow of oxygen, the inspired fraction (FiO_2) of oxygen being 0.21.

The venous sample was collected in a volume of 5 ml before the trauma, immediately before the trauma and 2, 5 and 24 hours after the traumatic impact (four samples for each subject) - a total of 19 cases. After that, the blood samples were centrifuged for 10 minutes at a speed of 3000 rpm. The obtained serum was frozen and stored at -40 °C. At 24 hours after the trauma, the rabbits were sacrificed, taking two fragments of tissue from the same location of each organ complex (lung, heart, spleen, liver and kidneys). The samples taken had 10x10x5 mm each.

2.3.2. Monitored indices (parameters)

1. The components of the protease/antiprotease system in the research were used as predictors/biomarkers for „indirect" lesions as well as the functional condition of the lungs 24 hours after trauma (pO_2 in the arterial sample). From the collected and frozen samples, subsequently, the following indicators were measured (n = 10): enzymatic activity of elastase, cathepsins G, D, L, H, trypsin, adenosine and adenylate deaminases, M and AT concentration.

2. The partial pressure of oxygen (arterial pO_2, an indicator of the functional state of the lungs), measured during the gas analysis, was determined in the arterial blood sample in 5-7 minutes, being analysed using the RADIOMETER ABL 555 Blood Gas Analyzer.

For each subject, totally four samples were collected, immediately before trauma and 2, 5 and 24 hours after it, the dorsal artery of the ear was catheterized before, being the optimal access „path" for repeated collections. In all cases, the arterial PaO_2/FiO_2 ratio $\leq$ 300 mm Hg at 24 hours (a criterion met for the definition of ARDS), which means that the „indirect" acute lung lesion was found.

3. The estimation of the histological changes was performed according to the SRCCAS [22]. The analysis of tissue samples taken was used as a tool to quantify „indirect" lesions outside the primary traumatic site. Initially, the tissue taken was subjected to the technical staining procedures with hematoxylin and eosin: fixing, washing, dehydration, paraffin embedding, sectioning, display, deparaffining, rehydration, clarification, staining and mounting. The examination of the

morphological pieces was performed under an optical microscope with artificial light („Micros", Austria), the histological picture being evaluated by the semiquantitative method. The objectives necessary to obtain an optimal amplification (x100 and/or x200 each time) were used to examine the structures of interest. The evaluation of histological specimens used SRCCAS with values between 0 and 3 for the degree of variation of the investigated changes, assigned as follows: 0 - "no noticeable" changes, 1 - "poorly pronounced" changes, 2 - "moderately pronounced" changes, 3 - "excessively pronounced" changes. For each tissue, the specific features of the systemic inflammatory response syndrome (SIRS) were studied. At 24 hours after trauma, totally five tissue types were taken for each statistical unit. In parentheses, the parameters that constitute the elements of the SRCCAS score are presented:

- ✓ Cardiac tissue (cardiomyocyte hypertrophy, interstitial edema, venous congestion, interstitial granulocyte infiltrates, fiber ondulation);
- ✓ Lung tissue (interstitial pulmonary edema, venous congestion, interstitial granulocytic infiltration, hemorrhagic imbibition, hemosiderosis, lymph node hyperplasia);
- ✓ Liver tissue (hypertrophy of liver cells, protein dystrophy, hydropic dystrophy, portal and perilobular venous congestion, infiltration by the immunocompetent cells of the portal and perilobular area);
- ✓ Spleen tissue (follicular hyperplasia, decomplexation (reorganization) of the follicular structure, venous congestion, hyalinosis, hemorrhagic inhibition);
- ✓ Renal tissue (interstitial edema, glomerular edema, venous congestion, protein dystrophy of the tubular epithelium, necrosis of the tubular epithelium and interstitial hemorrhage).

The SRCCAS score was calculated by summing all the scores within the separate tissues, resulting in $SRCCAS_{heart}$, $SRCCAS_{lungs}$, $SRCCAS_{liver}$, $SRCCAS_{spleen}$ and $SRCCAS_{kidneys}$. Their summ, in turn, being the basis for the overall score of „indirect" lesions ($SRCCAS_{total}$).

3. „EFFICIENT" VARIABLES IDENTIFICATION FOR SEVERE TRAUMA OUTCOME MODELING

Modeling the primary outcomes (survival/death) for a patient with severe trauma, like any other modeling, requires a preparation of potential variables/covariates by preliminary estimation of their predictive power for the variable of interest by univariate analysis. 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 capacity of the eventual model.

A suitable method in this case - determining the form of the relationships between covariates and the binary dependent variable (survival/death) by univariate regression analysis, followed by multivariate analysis. This approach will allow to find the variables with maximal potential and to consist the foundations for the alternative predictive models development with the ability to predict treatment outcomes in severe trauma.

In this chapter, as predictors, were considered the data of biochemistry, ionogram, heumoleucogram indicators, sex, age, comorbidities (chronic diseases, as well as the occurrence of pneumonia during hospitalization in UTIR of EMI) analyzed without the anatomical component, which demonstrated predictive ability in previous studies [23].

Univariate analysis of potential predictors for modeling treatment outcomes

As mentioned in Chapter 2, according to the inclusion/exclusion criteria for the current research, the total number of eligible sevare trauma patients was 2651. Descriptive statistics as well as the univariate analysis of potential covariates are concentrated in Table 3.1.

Based on these data, the majority of patients with severe trauma were hospitalized in Reanimatology Department (86.5% (95% CI 85.1, 87.7)). The in-hospital lethality for the population of patients with severe trauma studied was 29.95% (95% CI 28.24, 31.72), which is considerably higher than 19.1% - the lethality of those with ISS higher than 15 at the institutional level as shown by the German trauma registry [19]. Of course, this is raw data and it is possible that standardization will show other relationships. At the same time, the figures obtained cannot be neglected and once again confirm the relevance of the studied topic. The vast majority of the cohort were men - 2036 cases, which is 76.8% (95% CI 75.2, 78.4) of all cases analyzed. Gender as a variable, despite expectations, did not even show a tendency to be a predictor of lethality, the univariate analysis having a negative result in this sense (OR = 0.920, 95% CI 0.754, 1.122). This parameter will probably show the ability to predict treatment outcomes in the context of multivariate analysis, being adjusted to the covariates in the potential model.

Age, considering a distribution far from normal, was estimated by Mn = 48 years (95% CI 47, 50), the interquartile range (AI) being 29. The deceased patients presented an older age (Mn = 54 (95% CI 54, 57), AI = 26) compared to those who survived (Mn = 43 (95% CI 42, 46), AI = 30), covariate Age being a predictor for treatment outcome (OR = 0.975 95% IC 0.971, 0.980). This means that the probability of surviving is reduced by about 2.5% for every one year of age increases. In the present study, Age, being an effective variable for treatment outcome, will be used as an absolute value as well as a transformed variable according to the applied traumatic scores or the optimal predictive power of the variable in the equation.

Also, the clinical signs evaluated at the time of the first contact of the anesthesiologist with the patient and included in several predictive traumatic models (RTS, TRISS, ASCOT, NTRISS, etc.) were considered as follows. The Glasgow Coma Scale value (GCS) of patients with severe trauma tends to 13 points (Mn value, 95% CI 13, 14), AI = 5. Obviously, the absolute value of GCS was higher in survivors (Mn = 14 (95% CI 14, 15), AI = 3) than in the nonsurvivors (Mn = 10 (95% CI 10, 11), AI = 7. The shape of these relationships was estimated quantitatively at the level of OR = 1.360 (95% CI 1.320, 1.401) - the difference in GCS by one-point changes and the probability of surviving by 36% (95% CI 32.0, 40.1). The GCS value and survival relashionship analysis shows that there is a risk for nonlinear associations, that means that the coefficient describes well for high values of GCS, but on low values lethality

Table 3.1. Descriptive statistics and univariate analysis results for potential predictors for treatment outcomes modelling

			Deces, n=794		Supraviețuire, n=1857		Total, n=2651
	OR (95% IC), analiza univariată	**n**	**Mn (95% IC), AI/ % (95% IC)**	**n**	**Mn (95% IC), AI/ % (95% IC)**	**n**	**Mn (95% IC), AI/ % (95% IC)**
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, points	1.360 (1.320, 1.401)	794	10 (10, 11), 7	1857	14 (14, 15), 3	2651	13 (13, 14), 5
RR, min^{-1}	1.037 (1.013, 1.061)	794	18 (18, 19), 4	1857	18 (18, 19), 3	2651	18 (18, 19), 4
SBP, mmHg	1.004 (1.001, 1.007)	794	120 (120, 130), 40	1857	120 (120, 125), 20	2651	120 (120, 125), 30
GCS_{rang}, 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_{rang}, 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_{rang}, 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_{rang}, 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_{rang}, 13-15	1		31.9 (28.4 -35.4)		73.4 (71.2, 75.5)		61.3 (59.3, 63.3)
RR_{rang}, 0	2.236 * 10^-10	794	1.4 (0.7, 2.5)	1857	0 (-)	2651	0.4 (0.2, 0.7)
RR_{rang}, 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_{rang}, 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_{rang}, >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_{rang}, 10-29	1		89.8 (87.3, 92.0)		98.2 (97.5, 98.8)		95.9 (95.0, 96.6)
SPB_{rang}, 0	2,2923* 10^-10	794	0.7 (0.3, 1.6)	1857	0 (-)	2651	0.2 (0.1, 0.5)
SPB_{rang}, 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_{rang}, 50-75	0.378 (0.252, 0.567)		7.1 (5.4, 9.2)		3.0 (2.3, 3.9)		4.2 (3.4, 5.1)
SPB_{rang}, 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_{rang}, >90	1		83.1 (80.1, 85.7)		92.8 (91.4, 93.9)		89.9 (88.7, 91.1)
Department, Reanimatology/ Intensive Care Unit	5.089 (3.504, 7.392)	762	96.0 (94.4, 97.2)	1530	82.4 (80.6, 84.1)	2292	86.5 (85.1, 87.7)
		32	4.0 (2.8, 5.6)	327	17.6 (15.9, 19.4)	359	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

Table 3.1. Descriptive statistics and univariate analysis results for potential predictors for treatment outcomes modelling (continuation)

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
Bilirubine, µmol/l	0.984 (0.977, 0.991)	794	12 (12, 14), 12	1857	12 (12, 13), 8	2651	12 (12, 13), 9
Bilirubine$_{conjugated}$, 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
Prothrombine, %	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
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
JN, %	0.960 (0.952, 0.969)	794	15 (14, 16), 13	1857	11 (11, 12), 11	2651	12 (12, 13), 12
JN, >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
Eosinophils, %	0.990 (0.943, 1.040)	794	1 (1, 2), 1	1857	1 (1, 2), 2	2651	1 (1, 2), 2
Basophils, %	1.020 (0.945, 1.101)	794	0 (-), 0	1857	0 (-), 0	2651	0 (-), 0

OR – odds ratio,95% CI - 95% confidence interval, Mn – median value, AI – interquartile range, GCS - Glasgow coma scale, RR – respiratory rate, SBP – systolic blood pressure, AST – aspartataminotransferase, ALT – alaninaminotransferase, ALT/AST – AST/ALT ratio, JN – juvenile neutrophiles

being undetailed. This is a sign that reality will not be reflected in possible alternative models and with very high probability, prediction errors will be attested. In order to correct these possible problems, in parallel, the transformation of the GCS variable into a rank variable was performed (the categorization being proposed by the authors of the RTS), which finally improved the predictive value of GCS. With a total of five categories, the last category with the maximal value was considered as a reference point (GCSrang between 13 and 15 points). Consecutive switching from a higher to a lower category significantly reduces the OR value. For GCS_{rang}, these values were 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_{rang} 13-15, GCS_{rang} 9-12, GCS_{rang} 6-8, GCS_{rang} 4-5 and GCS_{rang} 3, respectively. As it can be seen, the hypothesis set out above was correct and the GCS_{rang} relationships are not uniform, but instead, after interpreting GCS as a rank variable, the relationships are described and the coefficients for each category are estimated. In addition, it is important to mention the practical aspect which is that there are sometimes difficulties in determining the absolute values of the GCS, the procedure described partially solves these problems. GCS_{rang} 4-5 and GCS_{rang} 3 do not differ in quantitative terms and reduce the probability of survival by around 40 times compared to the chances of a patient in the category GCS_{rang} 13-15, GCS_{rang} 6-8 and GCS_{rang} 9-12 having decreased chances to survive by 7.6 and 3.2 times respectively.

Respiratory rate (RR) values at admission tend to the value of 18 (Mn) breaths per minute (95% CI 18, 19), AI = 4. Interestingly, the difference between nonsurvivors (Mn = 18, (95% CI 18), 19), AI = 4) and survivors (Mn = 18, (95% CI 18, 19), AI = 3) is practically insensitive, OR being estimated at 1.037 (95% CI 1.013, 1.061). The problem of non-uniform relations is even more acute compared to GCS, because measured values are placed in the middle of the amplitude of possible values. Data transformation (categorization) showed the following results. The value of RR_{rang} 10-29 was considered as the reference value (OR = 1) and was significantly different in terms of effects on the survival rate compared to all categories formed, the same is true for RR_{rang} 0. At the same time, three remaining categories do not differ from each other, being different from RR_{rang} 10-29 and RR_{rang} 0, decreasing the probability of survival 5-6 times (RR_{rang} 1-5 OR = 0.151 (95% IC 0.053, 0.429), RR_{rang} 6-9 OR = 0.205 (95% CI 0.119, 0.353) and RR_{rang} > 30 OR = 0.135 (95% CI 0.036, 0.512) compared to the reference category, the confidence intervals having large amplitudes. This, in perspective, may be a cause for excluding this variable from the equation for predicting treatment outcomes in patients with severe trauma.

Systolic blood pressure (SBP) values at the hospitalization of a patient with severe trauma were estimated at 120 mmHg (Mn) (95% CI 120, 125), AI = 30, the absolute level being equal for the survivors (Mn = 120 (95% IC 120, 125), AI = 20) and those nonsurvivors (Mn = 120 (95% IC 120, 125), AI = 40), the difference is highlighted only for the interquartile range. The effect of SBP was estimated at OR = 1.004 (95% CI 1.001, 1.007) - SBP fluctuations with 1mmHg are associated with survival rate fluctuations by 0.4%, the results are probably insignificant from a clinical point of view. Similar to GCS and RR, the categorization was performed, SPB > 90 mmHg, being a reference value (OR = 1). The OR was 0.552 (95% CI 0.376, 0.808), 0.378 (95% CI 0.252, 0.567), 0.023 (95% CI 0.003, 0.175), 2.2923 * 10 ^-10 for

SPB_{rang} 76-89 mmHg, SPB_{rang} 50-75 mmHg, SPB_{rang} 1-49 mmHg and SPB_{rang} 0 mmHg, respectively, compared to SPB_{rang} > 90 mmHg (OR = 1). It is important to mention the categories SPB_{rang} 76-89 mmHg and SPB_{rang} 50-75 mmHg, which, being different from the standard category, do not differ significantly from each other, the other categories having significant differences, 95% confidence intervals being narrower compared to the categories RR.

The hemoleucogram, standard biochemical analysis and ionogram performed at hospitalization complete the picture described above. It is important to mention some tendencies characteristic for severe trauma determined in the present study. Hyperglycemia was found (Mn = 6.3 (95% CI 6.2, 6.4) AI = 2.9), the values in deceased patients being significantly higher (Mn = 7.0 (95% CI 6.8, 7.3), AI = 4.2 compared to Mn = 6.1 (95% CI 6.0, 6.3) AI = 2.5), estimated effect OR = 0.873 (95% CI 0.847, 0.899). The prothrombin value for the studied population was estimated at 85 (Mn, 95% CI 85, 86), AI = 15), being less than 80% in 30% of respondents. The comparative evaluation of prothrombin values showed a low level for the nonsurvivors (Mn = 82 (95% CI 82, 84) AI = 16 compared to Mn = 87 (95% CI 87, 88) AI = 15), the change of the parameter by 1% being associated with 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), AI = 0.22), the value being lower in survivors (Mn = 1.18 (95% CI 1.17, 1.19), AI = 0.21 compared with Mn = 1.24 (95% IC 1.23, 1.27), AI = 0.25), OR = 0.414 (95% IC 0.272, 0.629). In addition, an increase in the number of leukocytes was found - a sign of aseptic inflammation in severe trauma Mn = 11.8 (95% CI 11.6, 12.2), AI = 6.1, neutrophilia with lymphopenia and leukocyte formula left shift. The juvenile forms appearence presents interest in terms of prediction. The increase in metamyelocytes or myelocytes was negatively associated with the survival rate (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)), the Hb concentration (g/l) being lower in patients with negative outcome (Mn = 122 (95% CI 120, 124), AI = 33 compared to Mn = 129 (95% IC 128, 131), AI = 29) with effect OR = 1.014 (95% IC 1.011, 1.018) - decreasing Hb by 1 g/l reduces the probability of survival by 1.4%.

The parameters of standard biochemistry, as well as ionogram indicators, as shown by the univariate analysis, present a potential source for biomarkers/predictors of treatment outcome, all parameters showing significance. Urea (OR = 0.917 (95% CI 0.899, 0.936)), creatinine (OR = 0.990 (95% CI 0.988, 0.993)), ALT (OR = 0.998 (95% CI 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)), total 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^+ (OR = 0.938 (95% CI 0.915, 0.953)) and Cl^- concentration (OR = 0.951 (95% CI 0.938, 0.966)) showed changes in the survival probability less than 10% and can be considered predictors with low potential. At the same time, this value for INR, glucose and K^+ concentration were above the 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% IC 1,157, 1,688)) respectively, being potential

biomarkers for the variable of interest. At the same time, it is important to mention that in the multivariate analysis, when all the parameters will be evaluated simultaneously, the coefficients can be modified, for these reasons the obtained results have only orientative value.

4. VALIDATION OF COMMON SURVIVAL PREDICTIVE SCORES FOR SEVERE TRAUMA PATIENTS

Validation of common traumatic scores (models) is a mandatory condition for their application to a specific population or within a specific medical system. This has the advantage of correcting the coefficients in the regression equation based on the current situation and considerably increases the accuracy of the prognosis. As previously mentioned, such a procedure was not performed for the population of patients in the Moldovan medical system for the usual traumatic scores, which induces some problems regarding their application by medical staff at different stages, including UTIR conditions.

This chapter contains information on the validation of routine predictive models for the severe trauma patients population within the Clinic of Anesthesiology and Reanimatology of EMI - trauma center in the Republic of Moldova. For validation, the most popular traumatic scores were chosen from the category of physiological (RTS, GAP, qSOFA), anatomical (ISS, NISS) and mixed (TRISS, NTRISS, ASCOT). Also, a comparative evaluation of the validated models was performed in order to highlight the most suitable model for the studied population, the criteria being determination, calibration and discrimination. The best score will be recommended for use in the UTIR clinical practice of EMI and will be compared with other possible alternative models, proposed in the future to assess the condition of a patient with severe trauma.

4.3. Validation of mixed predictive scores for patients with severe trauma

For validation, three scores−TRISS, NTRISS and ASCOT were selected from the variety of mixed predictive models. Null hypotheses have been formulated that these scores do not have the ability to predict the probability of survival in patients with severe trauma better than a model that is based only on a constant, with alternative hypotheses arguing that scores may predict treatment outcome better than a model which is based on only one constant.

The NTRISS, which uses NISS instead of ISS, similar to TRISS, showed the ability to predict the treatment outcome of a severe trauma patient, the null hypothesis being rejected (Omnibus Test of Model Coefficients ($\chi2 = 965,427$, $df = 3$, $p < 0001$)). Subsequent analysis showed the following features of the validated model.

The Nagelkerke R Square determination coeffitient showed a higher value compared to TRISS − 0.496 (49.6%), which means that almost half of the dispersion of the variable of interest (survival/death) was explained by the covariates from the validated NTRISS model.

The calibration indicator (Hosmer-Lemeshow test) showed a significant value, $\chi2 = 61,793$, $df = 8$, $p <0.001$ − the calibration indicator that requires optimization, i.e. the score does not effectively predict the results over the full range of possible scores − it is not possible to stratify the risk of death. At the same time, the model predicts quite

accurately whether the patient will die or not, compared to other models presented before.

The discrimination indicators in the classification table, namely specificity and sensitivity, were equal to 74.4% and 89.1% respectively, the summary percentage (global) being estimated at 85.0%. The results were obtained after optimization by changing the critical point to 0.6 compared to 0.5 standard.

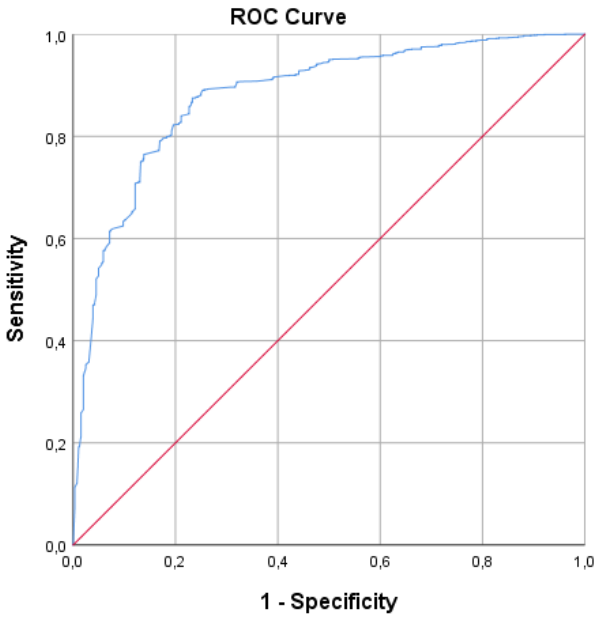

Fig. 4.1. ROC curve for survival predicticting in patients with severe trauma based on the NTRISS score

Table 4.1. Variables in the equation of the survival predictive model for severe trauma patients based on the NTRISS score. SPSS 23 output

a. Model coefficients

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
							Lower	Upper
Age, ≥ 55 years	-1.496	.128	135.845	1	.000	.224	.174	.288
RTS	.869	.064	187.026	1	.000	2.384	2.105	2.700
NISS, points	-.138	.008	308.408	1	.000	.871	.858	.885
Constant	-1.543	.479	10.387	1	.001	.214		

b. Bootstrepping resampling results

	B	Bias	S.E.	Sig.	95% Confidence Interval for B	
					Lower	Upper
Age, ≥ 55 years	-1.496	-.006	.126	.001	-1.770	-1.259
RTS	.869	.006	.070	.001	.742	1.012
NISS, points	-.138	.000	.009	.001	-.157	-.122
Constant	-1.543	-.034	.531	.007	-2.674	-.487

Note: B - B coefficients, SE - standard errors, Wald - Wald statistics, df - degrees of freedom, Sig.- statistical significance, Exp (B) - odds ratio (OR) values, 95% C.I.for EXP (B) - confidence interval for odds ratio

The area under the ROC curve, for the predictive model based on the NTRISS score, was 0.881, with 95% confidence interval (0.865, 0.896) and with a significant difference from the value 0.5 (p <0.001) (Fig. 4.1). The model included the constant (B = -1.496), the NISS value (B = -0.138), the age, similar to TRISS (B = -1.496) and the RTS value (B = 0.869), the coefficients having the appropriate sign in front (Table 4.1, section a). Stability analysis by resampling the model developed for the probability of survival in severe trauma, the bootstrapping method (1000 samples), showed that the coefficients are stable, the argument being their significance, the small amplitude of the confidence intervals and keeping the signs in front of the logistic coefficients. (Table 4.1, section b).

Considering the mentioned coefficients, the elaborated model has the following mathematical expression:

$$p = \frac{1}{1+e^{-(-1.496-0.138*\text{valoarea NISS}-1.496*\text{Age}\geq 55+0.869*\text{RTS})}}$$, where

p - the probability of survival in severe trauma, e (exponent) - constant equal to 2.71828

The components of the NTRISS score showed the following effects. The RTS value, as for TRISS, showed a positive association with the probability of survival (OR = 2.384 (95% CI 2.105, 2.700)), adjustment to NISS and age showed a tendency to reduce the impact of RTS. The difference with one point changes the prognosis more than 2 times, the confidence interval being narrower than the odds ratio within the TRISS score. At the same time, age used as a predictor in binary form (under or over 55 years) showed a negative association (OR = 0.224 (95% CI 0.174, 0.288)) - is associated with reduced survival by about five times. The values of the NISS score, obviously, were negatively correlated with the treatment outcome (OR = 0.871 (95% CI 0.858, 0.885)), the odds ratio being similar to the value from the univariate analysis performed during the validation.

4.4. Comparative evaluation of validated models

The comparative evaluation of the determination, calibration and discrimination indicators of the validated physiological models showed GAP score superiority over RTS and qSOFA. It demonstrated an estimated maximum coefficient of determination of 30.5% compared to 24.3 and 19.1% for RTS and qSOFA, respectively. GAP also showed the optimal calibration value ($\chi 2$ = 5,651, df = 7, p = 0.581), compared to the other physiological scores analyzed ($\chi 2$ = 10,046, df = 4, p = 0.040 for RTS and $\chi 2$ = 3,806, df = 3, p = 0.283 for qSOFA). Also, the comparative evaluation of the areas under the ROC curve showed the higher value of GAP compared to RTS and qSOFA, the differences being significant (z = 6.259, p <0.001 and z = 7.767, p <0.001, respectively).

Such an analysis of anatomical scores highlighted the superiority of the NISS score compared to the ISS score, the arguments being the higher *Nagelkerke R Square* indicator (32.7% versus 12.0%) and the much better discriminatory abilities (area under the ROC curve) (z = 20,854, p < 0001). In contrast, both scores showed a significant calibration test.

The comparison of the mixed scores included in the research showed that the NTRISS score showed an optimal coefficient of determination (49.6%) compared to

TRISS (37.1%) and ASCOT (30.2%), all models having calibration indicators that need improvement, the criterion being the significance of the Hosmer-Lemeshow test ($\chi2$ = 16,864, df = 8, p = 0.032, $\chi2$ = 61,793, df = 8, p <0.001 and $\chi2$ = 22,353, df = 8, p <0.004 respectively). Comparisons of surface values under the ROC curve showed the superiority of the NTRISS score (z = 13,345, p <0.001 versus TRISS and z = 14,505, p <0.001 ASCOT score). All this allows to consider NTRISS the optimal score from the category of mixed predictive models, at least from those included in the analysis.

At the same time, the analysis of the indicators of all traumatic scores in the current research evidenced the NTRISS score as a predictive model with the best dependent variable (survival) dispersion covering, the GAP score having an optimal calibration. The discriminative capacity was also was also the highest for the NTRISS score compared to GAP (z = 10.385, p <0.001) and NISS (z = 6.809, p <0.001), NISS having better discrimination than GAP (z = 3.766, p <0.001).

5. ALTERNATIVE PREDICTIVE MODELS DEVELOPMENT FOR SEVERE TRAUMA PATIENTS

In the previous chapters, it was prepared a field for the alternative survival predictive models elaboration for severe trauma patient. First, potential „effective" variables for treatment outcome were identified (Chapter 3). They made possible to obtain valuable information on the impact of covariates and their usefulness for prediction, inclusively through complex analysis. Also, the ways of inclusion and possible interactions in the potential models were analyzed, thing what increases their predictive power. In the same time, the validation of the usual predictive models for trauma (Chapter 4) allowed to identify their shortcomings in application conditions for severe trauma patients from EMI and to highlight a standard model with optimal characteristics (NTRISS) for the studied population. In the currents chapter, the elaborated alternative prediction models will be compared among them and with the common optimal model (NTRISS). Moreover will be estimated the effect of having pneumonia in UTIR and will be developed a model for prolonged VAP risk.

5.1. Alternative predictive models elaboration for treatment outcome prediction in severe trauma patients

Alternative model 5 included lnNISS and absolute values of age, GSS_{rang}, SBP_{rang}, maximal AIS score (AIS_{max}) for head and neck injuries ($AIS_{head\ and\ neck}$), abdomen ($AIS_{abdomen}$), thorax (AIS_{thorax}), extremities ($AIS_{extremities}$), supplemented by the absolute value of the total protein concentration (g/l). The inclusion of this variable has the advantage of estimating a biochemical indicator associated with the survival rate, the characteristics of the model being better.

Alternative model 5 showed the ability to predict the treatment outcome (survival/death) in severe trauma patient, the null hypothesis being rejected (*Omnibus Test of Model Coefficients* (χ^2 = 1381.553, df = 8, p <0.001)). Subsequent analysis showed the listed below features of the developed alternative model.

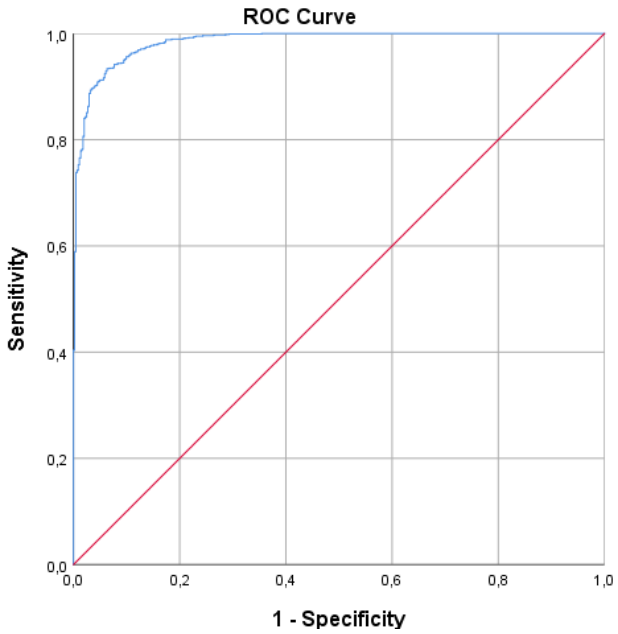

Fig. 5.1. ROC curve for survival predictiction in patients with severe trauma based on the *5 alternative model*

The *Nagelkerke R Square* determination indicator showed the value 0.863 (86.3%), which means that more than 86% of the interest variable dispersion was explained/covered by the covariates from the *alternative model* 5.

The calibration indicator (Hosmer-Lemeshow test) showed an insignificant value, χ^2 = 9,667, df = 8, p = 0.289, the results having fidelity in the sense of the obtained results accuracy throughout the range of predicted scores, these being close to the real ones.

The discrimination indicators in the classification table, namely specificity and sensitivity, were equal to 91.6% and 94.4% respectively, the summary (global) percentage was estimated at 93.5%. These results were obtained at the cut-off point 0.70 after balancing the sensitivity/specificity relationships.

The area under the ROC curve, for the *alternative model 5*, was 0.984 (95% CI (0.979, 0.990)) and with a significant difference compared to value 0.5 (p <0.001) (Fig. 5.1).

The model included constant (B = 31,619), lnNISS value (B = -17,968), age (B = -0.031), total protein (B = 0.065), GCS_{rang} (B = 1.070), SBP_{rang} (B = 0.876), $AIS_{head\ and\ neck}$ (B = 3.049), $AIS_{abdomen}$ (B = 1.044), AIS_{thorax} (B = 2.745) and $AIS_{extremities}$ (B = 2.129), the arguments regarding the coefficients signs for the alternative model 4 being valid also for the current model except for the total protein concentration. The total protein showed the positive sign in front, being positively associated with the survival rate (Table 5.1, section a). Possible explanation − insignificant changes in the liquid compartments. Stability analysis by resampling of the alternative model developed for the probability of survival in severe trauma, bootstrapping method (1000 samples), showed that the coefficients are stable, the arguments being the covariates significance, confidence intervals small amplitude and coefficient signs stability (Table 5.1, section b).

Considering the mentioned coefficients, the developed model has the following mathematical expression:

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

p - survival probability in severe trauma, e (exponent) - constant equal to 2.71828
*b = 31.619 – 17.968 * lnNISS - 0.031 * Age + 0.065 * total protein + 1.044 * $AIS_{abdomen}$ + 2.745 * AIS_{thorax} + 2.129 * $AIS_{extremities}$ + 3.049 * $AIS_{head\ and\ neck}$ + 1.07 * GCS_{rang} + 0.876 * SBP_{rang}*

Table 5.1. Variables in the equation of the survival predictive model for severe trauma patients with based on the 5 alternativ model. SPSS 23 output

a. Model coefficients

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
							Lower	Upper
lnNISS	-17.698	1.182	224.247	1	.000	2.06*10^-8	2.03*10^-9	2.09*10^-7
Vârsta, ani	-.031	.008	15.549	1	.000	.969	.954	.984
GSS_{rang}	1.070	.152	49.295	1	.000	2.915	2.162	3.930
SBP_{rang}	.867	.249	12.147	1	.000	2.380	1.461	3.875
$AIS_{abdomen}$	1.044	.180	33.805	1	.000	2.840	1.998	4.038
AIS_{thorax}	2.745	.197	193.957	1	.000	15.569	10.580	22.912
$AIS_{extremities}$	2.129	.173	151.936	1	.000	8.405	5.991	11.791
$AIS_{head\ and\ neck}$	3.049	.224	185.121	1	.000	21.087	13.592	32.715
Total protein	.065	.014	20.337	1	.000	1.067	1.038	1.098
Constant	31.619	2.623	145.355	1	.000			

b. Bootstrepping resampling results

	B	Bias	S.E.	Sig.	95% Confidence Interval for B	
					Lower	Upper
lnNISS	-17.698	-.524	1.134	.001	-20.417	-16.136
Virsta, ani	-.031	-.001	.009	.001	-.050	-.015
GSS_{rang}	1.070	.039	.162	.001	.818	1.461
SBP_{rang}	.867	.026	.296	.003	.369	1.474
$AIS_{abdomen}$	1.044	.037	.204	.001	.707	1.488
AIS_{thorax}	2.745	.083	.197	.001	2.460	3.245
$AIS_{extremities}$	2.129	.060	.178	.001	1.867	2.579
$AIS_{head\ and\ neck}$	3.049	.090	.234	.001	2.720	3.643
Total protein	.065	.002	.017	.001	.035	.101
Constant	31.619	.909	2.704	.001	27.494	38.289

Note: B - B coefficients, SE - standard errors, Wald - Wald statistics, df - degrees of freedom, Sig.- statistical significance, Exp (B) - odds ratio (OR) values, 95% C.I.for EXP (B) - confidence interval for odds ratio

The covariates included in alternative model 5 showed the following associations with the survival rate. LnNISS and Age values showed a negative association with the survival probability (OR = 2.06 * 10 ^ -8 (95% CI 2.03 * 10 ^ -9, 2.09 * 10 ^ -7) and OR = 0.969 (IC95% 0.954, 0.984). The increased impact of lnNISS for a unit can be explained as follows. First, it represents a lower amplitude score because it consists a transformed value of NISS by natural logarithm, adjusted for the

effects of anatomical components in the topographic regions. The increase in age by one year is associated with a survival probability reduction by 3.1% (95% CI 1.6, 4.6). The other variables showed positive associations. The oscillations for a category at GCS_{rang} and SBP_{rang} showed OR = 2.915 (95% CI 2.162, 3.930) and OR = 2.380 (95% CI 1.461, 3.875) respectively. The total protein positive effect, estimated at 6.7% (95% CI 3.8, 9.8) for a unit, can be explained by the fact that this parameter reflects the fluid compartments disturbances within the severe traumas. $AIS_{head\ and\ neck}$ and AIS_{thorax} presented maximum values, followed by $AIS_{extremities}$, $AIS_{abdomen}$ being minimal. The effects magnitude of anatomical components other than lnNISS did not change after inclusion in the model of the total protein value at admission.

5.3. Comparative evaluation of alternative models and standard NTRISS score

The *alternative model 1* compared to the NTRISS model showed its superiority through a higher determination coefficient (52.5% compared to 49.6%), the calibration being adequate ($\chi2 = 9.088$, df = 8, p = 0.335) compared to the NTRISS score ($\chi2 =$ 61,793, df = 8, p <0.001). Moreover, the surface values significant difference under the ROC curve was determined (z = 2,864, p = 0.004), being more extensive for the *alternative model 1* − an indicator of a better discriminating ability than the common standard score, determined in the previous chapter.

Alternative model 2 compared to *alternative model 1* and the NTRISS demonstrated a maximum determination coefficient (55%), being well calibrated ($\chi2 =$ 8,480, df = 8, p = 0.388) and significantly higher by the surface value under the ROC curve (z = 3.011, p = 0.003 compared to *alternative model 1* and z = 5.134, p <0.001 compared to the common NTRISS).

Alternative model 3, which also included comorbidities, had a determination coefficient equal to 57% (and higher), being well calibrated ($\chi^2 = 10,662$, df = 8, p = 0.222). Concerning the area under the ROC curve also the *alternative model 3* showed better characteristics compared to the first two alternative models (z = 5.134, p <0.001 and z = 3.456, p = 0.001) and NTRISS (z = 6.090, p <0.001).

Alternative model 4 showed the determination coefficient equal to 85.9%, a value over 80%, which is a standard for the elaboration of predictive models. The model shows an adequate calibration ($\chi2 = 8,986$, df = 8, p = 0.34), having superior discrimination characteristics compared to NTRISS and the first three mentioned alternative models (z = -10,937 p <0.001, z = -10,341 p <0.001, z = -10,276 p <0.001 and z = -9,662 p <0.001, respectively).

Alternative model 5, which was supplemented with the total protein concentration, compared to *alternative model 4*, showed the determination coefficient 86.3% with an appropriate calibration ($\chi^2 = 9.667$, df = 8, p = 0.289). Discriminatory ability comparative evaluation with the previos four alternative predictive models (z = 10,262 p <0.001, z = 10,188, z = 9,595 and z = 10,188, z = 2,136 p = 0.002) and NTRISS (z = 11,170 p <0.001) demonstrated this model superiority according to the respective indicator.

For the *alternative model 6*, a model without GCS_{rang} information, the determination coefficient was estimated at 84.3%. The calibration indicator showed no significance ($\chi^2 = 9.667$, df = 8, p = 0.289) − the model is well calibrated. The developed

alternative score showed the lowest discriminative power compared to the *alternative model 5* (z = 2,972 p = 0.003), without significant differences compared to the *alternative model 4* (z = -0.963 p = 0.336), being higher than the *alternative model 3* (z = 9.081 p <0.001), *alternative model 2* (z = 9.742 p <0.001), *alternative model 1* (z = 9.890 p <0.001) and NTRISS (z = 10.670 p <0.001).

6. „INDIRECT" LESIONS PREDICTION IN THE SEVERE TRAUMA EXPERIMENTAL MODEL BASED ON THE COMPONENTS OF THE PROTEASE/ANTIPROTEASE SYSTEM

The „indirect" lesions in polytrauma/severe trauma represents the damage of intact tissues by immunocompetent cells (mainly by neutrophils), which, being activated, pass through biological barriers, infiltrate organs unaffected by the traumatic agent and release proteases and/or free oxygen radicals. These, in turn, are substances with a destructive potential causing a physiological reserve decrease and/or further development of those organs' insufficiency.

The „indirect" injuries problem, often encountered in UTIR patients, including those with severe trauma, is insufficiently reflected in the literature. One of the obstacles is the lack of experimental/clinical studies in which the relationships between different aggressive factors (potential biomarkers) released by immunocompetent cells and „indirect" traumatic morphological changes were studied.

In the experimental study presented in this chapter, it was tried to partially solve the given problem by analyzing the associations between different components of the protease/antiprotease system and the morphological picture/functional state (whose changes can be visualized by direct microscopy or numerically estimated by measuring physiological indices). The potential expected outcome is the „indirect" lesions biomarkers identification and the predictive models' development for estimating their degree. Moreover, some hypotheses regarding the pathophysiological mechanisms of „indirect" lesions and their prophylaxis/treatment can be formulated. In the following pages, are presented the correlations and predictive tools for modeling lesions in the myocardium, lungs, liver, kidneys, spleen and general picture of „indirect" lesions, all expressed by the SRCCAS score 24 hours after trauma. The functional state of the lungs expressed by arterial pO_2 was also modeled.

Pulmonary morphological changes ($SRCCAS_{lungs}$) at 24 hours after traumatic impact prediction

In the first stage, before the elaboration of the $SRCCAS_{lungs}$ predictive model, the correlations and their tendencies between $SRCCAS_{lungs}$ at 24 hours after the traumatic impact and the components of the protease/antiprotease system were analyzed. $SRCCAS_{lungs}$ was associated with AET_0 (r = -0.343, p = 0.075, effect size 0.12), AET_2 (r = 0.466, p = 0.022, effect size 0.22), AET_{24} (r = -0.358, p = 0.066, effect size 0.13), $\alpha 2\text{-macroglobulin}_2$ (r = -0.401, p = 0.044, effect size 0.16), $AEAMP_{24}$ (r = 0.311, p = 0.097, effect size 0.01), $AECG_2$ (r = 0.590, p = 0.004, effect size 0.35), $AECG_{24}$ (r = -0.317, p = 0.093, effect size 0.10), $AECL_2$ (r = 0.441, p = 0.029, effect size 0.20), AEE_0 (r = -0.479, p = 0.019, effect size 0.23) and AEE_{24} (r = -0.342, p = 0.076, effect size 0.17).

Table 6.1. Linear regression coefficients and collinearity analysis for $SRCCAS_{lungs}$ prediction in experimental sever trauma. SPSS 23 output

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95,0% Confidence Interval for B		Collinearity Statistics	
	B	Std. Error	Beta			Lower Bound	Upper Bound	Tolerance	VIF
Constant	9.427	.966		9.763	.000	7.341	11.513		
α_2-macroglobulin$_0$	-4.053	1.063	-.847	-3.813	.002	-6.350	-1.757	.421	2.373
$AEAMP_0$	.002	.001	.430	1.937	.075	.000	.004	.423	2.366
$AEAMP_{24}$	-.006	.002	-1.353	-3.569	.003	-.010	-.002	.145	6.905
$AECG_2$	.081	.019	1.089	4.306	.001	.040	.122	.325	3.076
AEE_0	-.026	.007	-.698	-3.840	.002	-.040	-.011	.630	1.588

Nota: Std. Error – standard error, t – t test, Sig. – significance, VIF – variance inflation factor

The associations with the negative sign between $SRCCAS_{lungs}$ and the concentration of α2-macroglobulin$_2$ as well as the positive associations with the most proteases enzymatic activity can be explained by the protective or destructive effects, characteristic for the respective substances. In the same time, the negative correlations between $SRCCAS_{lungs}$ at 24 hours with the elastase enzymatic activity value before trauma, as well as the tendencies towards negative associations with AET_0, AET_{24}, $AECG_{24}$, AEE_{24} can be explained by the polymorphic relations within the protease/antiprotease system. Probably, signs will reverse or associations will disappear upon the multivariate analysis adjustment. Moreover, before the trauma, the balance of protection/destruction was reached.

All the associations found were considered for the predictive model elaboration that can estimate the value of the $SRCCAS_{lungs}$ score at 24 hours after the trauma, the model having following characteristics. The predicted results correlation coefficient by applying the model elaborated with the real values of $SRCCAS_{lungs}$ was 0.854, the determination coefficient (*Adjusted R Squared*) being 0.626, the squares sum was 17896 of 24526 possible, which means that the proposed model explains approximately 2/3 from the dispersion of the interest variable ($SRCCAS_{lungs}$ at 24 hours after trauma). The null hypothesis (none of the parameters included in the model can predict the $SRCCAS_{lungs}$ value at 24 hours after trauma) was rejected ($F = 7.017$, $p = 0.002$).

The Backward method was used to quantify the model. According to this method, initially, all potential variables are considered, after which, step by step, insignificant covariates are excluded until the moment when only the variables that have a meaning in the sense of predicting the studied result will remain. To predict the value of $SRCCAS_{lungs}$ at 24 hours after trauma, from the start, the following parameters were included: AET_0, AET_2, AET_{24}, α2-macroglobulin$_2$, $AEAMP_{24}$, $AECG_2$, $AECG_{24}$, $AECL_2$, AEE_0, AEE_{24}. In addition, the values of these potential biomarkers before trauma were considered, the argument being that there is probably a predisposition to develop „indirect" morphological disorders after a traumatic impact.

The final model included the following parameters (Table 6.1):

• Constant (B = 9.427; 95% IC 7.341, 11.513; p <0.001);

• α2-macroglobulin$_0$ (B = -4.053; 95% CI -6.350, -1.757; p = 0.002);

• $AEAMP_0$ (B = 0.002; 95% IC 0.000, 0.004; p = 0.075);
• $AEAMP_{24}$ (B = -0.006; 95% IC -0.010, -0.002; p = 0.003);
• $AECG_2$ (B = 0.081; 95% IC 0.040, 0.122; p = 0.001);
• AEE_0 (B = -0.026; 95% IC -0.040, -0.011; p = 0.002).

Other parameters, such as AET_0, AET_2, AET_{24}, $AECG_{24}$, $AECL_2$, AEE_{24} as well as their pre-traumatic values weren't significant, therefore they did not enter the final predicting "indirect" lung lesions model. The obtained model shows the following mathematical expression:

$$SRCCAS_{lungs}\ 24\ hours = 9.427 - \alpha_2\text{-macroglobulin}_0 * 4.053 + AEAMP_0 * 0.002 - AEAMP_{24} * 0.006 + AECG_2 * 0.081 - AEE_0 * 0.026$$

As the collinearity analysis showed that the prediction quality was not affected by the potential strong correlations between the model parameters (Tolerance and VIF being higher than 0.1 and lower than 10, respectively). From a quantitative point of view, it was demonstrated by standardizing the coefficients that the $AEAMP_{24}$ effects on $SRCCAS_{lungs}$ are the most significant (Beta = -1,353), followed by $AECG_2$ (Beta = 1,089), α2-macroglobulin$_0$ (Beta = -0,847), AEE_0 (Beta = -0.698) and $AEAMP_0$ effects (Beta = 0.430). The antiproteases protective and proteases destructive effects concept was supported by the regression coefficients signs of α2-macroglobulin$_2$, $AEAMP_0$ and $AECG_2$ that follow its logic. $AEAMP_{24}$ and AEE_0 are proteases and having negative regression coefficients signs, do not correspond to the exposed logic, the results obtained being suspicious and requiring elucidation. Possibly, this fact can be explained by the need to complete the model (1/3 of the dispersion is not explained, the constant being significant), and their adjustment to the potential effective variables will reverse their sign or will exclude them from the final model. Other possible variants −the proteases are in balance with the antiproteases before trauma or have protective effects for lung injuries.

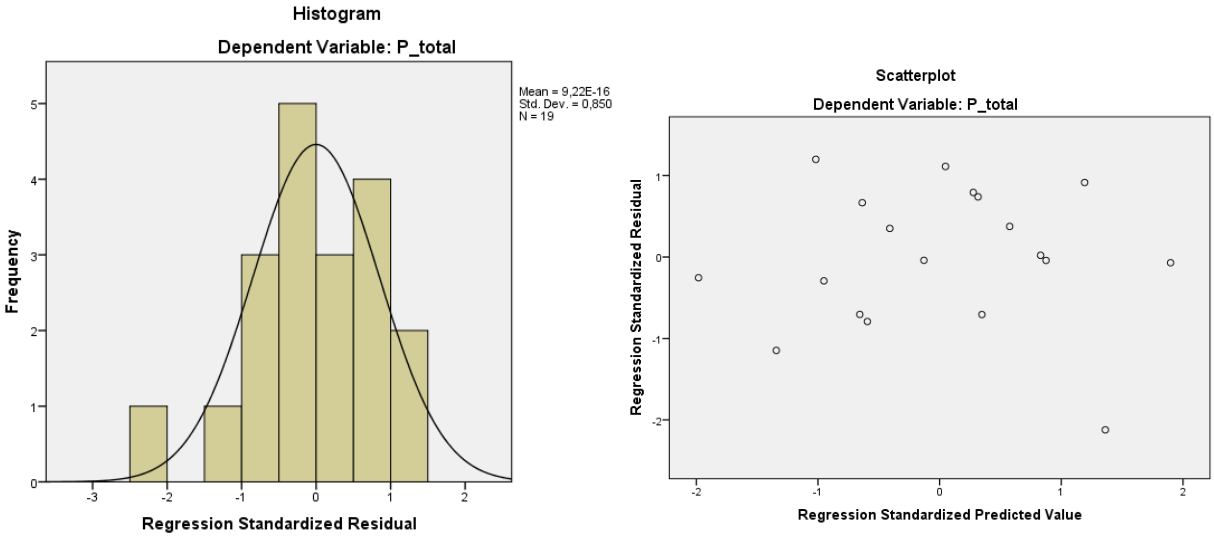

Fig. 6.1. Standardized residual distribution (left); Standardized predicted value – Standardized residual scatterpot (right)

In addition, the developed model also met the requirements for linear regression residues. Their analysis demonstrated an almost normal distribution and lack of

associations between standardized predictive values and standardized residues (Fig. 6.1). All this together allows us to consider the model as a suitable one.

Table 6.2. Bootstrapping for $SRCCAS_{lungs}$ prediction in experimental sever trauma at 24 hour after impact. SPSS 23 output

	B	Bias	Std. Error	Sig. (2-tailed)	95% Confidence Interval for B	
					Lower	Upper
Constant	9.427	.047	1.369	.001	6.683	12.193
$AECG_2$	.081	-.003	.026	.009	.022	.129
$AEAMP_0$	.002	3.004E-05	.001	.079	.000	.005
$AEAMP_{24}$	-.006	.000	.002	.016	-.011	-.002
AEE_0	-.026	.000	.008	.011	-.039	-.009
α_2-macroglobulin$_0$	-4.053	-.166	1.514	.039	-7.364	-1.264

Nota: B – regression coefficient, Std. Error – standard error, Sig. – significance

Considering that the model was developed on a relatively small participants number which increases the risk of model instability, especially since the latter five biomarkers were included in addition to the constant, resampling was performed by bootstrapping (Table 6.2). The model showed its stability, $AECG_2$, $AEAMP_0$ and α_2-macroglobulin$_0$ being potential „indirect" lung damage biomarkers. The $AEAMP_{24}$ and AEE_0 effects, even if significant and stable, require verification in further studies.

The model needs to be supplemented with effective parameters/variables at least up to 0.80 (80%) of the determination coefficient value to remove one of the research weaknesses, namely the fact that about one third of the $SRCCAS_{lungs}$ dispersion at 24 hours after trauma remained unexplained. Therefore, the predictive model for $SRCCAS_{lungs}$ at 24 hours after trauma included $AECG_2$, $AEAMP_0$, α_2-macroglobulin$_0$, $AEAMP_{24}$ and AEE_0, the latter two components needing detailed study as "indirect" lung injury biomarkers, the model requiring completion, validation and testing in clinical trials. Considering that the developed model includes two parameters that represent the values of the enzymatic activity of proteases before trauma, it is not excluded the predisposition possibility for the „indirect" lung lesions occurrence in experimental severe trauma.

7. MODELING THE SEVERE TRAUMA EVOLUTION AND TREATMENT OUTCOME BASED ON THE PROTEASE/ANTIPROTEASE SYSTEM COMPONENTS DIMENSION REDUCTION

Different protease/antiprotease system components show different effects at different times, the relationships between the parameters inside the system being complex. The correlation analysis with the morphological changes outside the traumatic site modeling in the previous chapter allowed to investigate separately each potential biomarker within the studied system as taken out of the context of their concerted action, which underlies the pathophysiological processes characteristic for severe traumas (standard approach, material and methods). All this despite the fact that statistical data processing was performed using multivariate methods that could identify complex relationships. However, this strategy has made it possible to

successfully model „indirect" lesions, to identify potential biomarkers and to sketch perspectives for further research in this field.

The possibility of improving the obtained results by applying the standard strategy imposed the need to use an alternative approach. This involves the size reducing procedure (complexity of data expressed by multicollinearity in predictive models) by factorial analysis (analysis of main components) and extraction of „latent" factors (most likely factors with protective potential and factors with destructive potential). It is also possible to treat the protease/antiprotease system components as elements within the complex pathophysiological processes characteristic of severe traumas that completes the „indirect" morphological lesions general picture known at the moment.

This chapter contains information both on the severe trauma experimental model simension reduction and on the „latent" factors' extraction and identification with subsequent modeling of „indirect" lesions. The developed models will be evaluated compared to standard strategy obtained models, the criterion being the determination, stability and the conditions for residues. Also, the results of a pilot clinical study are presented in which, after dimension reducing, the extracted factors were used as treatment outcome (survival/death) predictors/biomarkers.

Treatment outcomes (survival/death) predictive models in the pilot clinical trial based on extracted factors

Model 4 has the ability to predict the survival probability in a severe trauma patient based on the protease/antiprotease system components at 24 hours after trauma grouped (expressed) in the form of „latent" factors.

For patients who met the polytrauma criteria, the following hypotheses were formulated. *Null hypothesis* - covariates included in the model (gender, age and factors extracted after protease/antiprotease system components size reduction) cannot predict the survival probability in patients with polytrauma better than a model that is based only on a single constant. *Alternative hypothesis* - at least one of the variables mentioned can predict the survival probability in polytrauma patients better than a model that is based only on a single constant.

The null hypothesis was rejected (*Omnibus Test of Model Coefficients* (χ^2 = 51.569, df = 6, p <.001, the significance level being 0.05/4 = 0.0125)). Subsequent analysis found the following characteristics of the developed model.

The *Nagelkerke R Square* determination indicator showed the value 0.759 (70.4%), which means that more than 75% of the interest variable was explained by the parameters in the developed model - a value very close to the standard 0.8 (80%).

The calibration indicator (Hosmer-Lemeshow test) demonstrated a practically ideal value, χ^2 = 1.547, df = 7, p = 0.981. Although the model can be further evaluated, the results can be considered accurate.

The discrimination indicators in the classification table, namely, specificity and sensitivity, were equal to 81.8% (18 out of 22) and 90.7% (39 out of 43), respectively, and the summary percentage (overall) was estimated at 87.7 %. The results were obtained after optimizing the survival/death ratio after changing the cut-off value from 0.5 to 0.054.

The area under the ROC curve for the proposed model was 0.956, with a 95% confidence interval between the values of 0.912 and 1,000 and with a significant difference from the value of 0.5 (p <0.001) (Fig. 7.1).

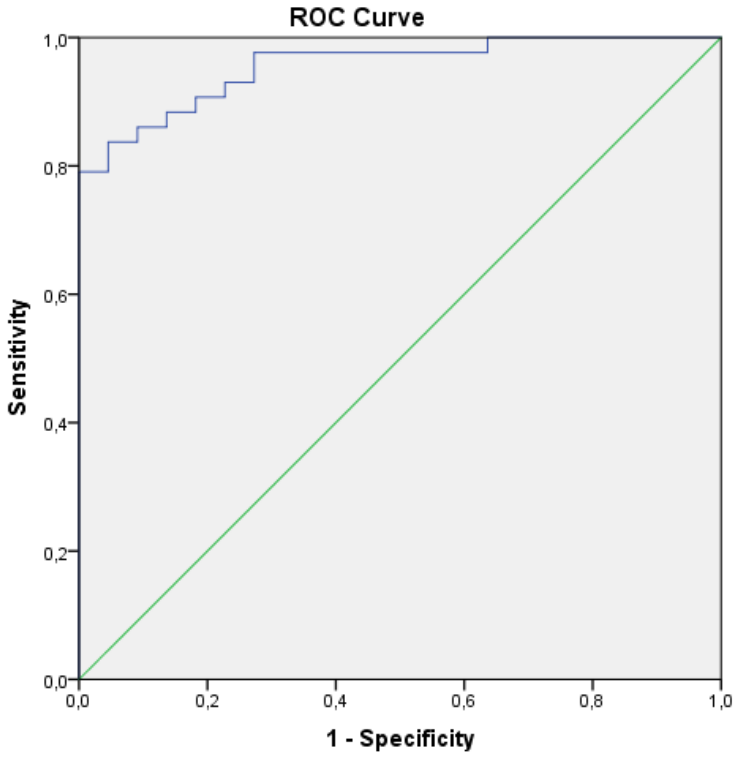

Fig. 7.1. ROC curve for survival predictiction in polytrauma patients at 24 after the impact

Considering the coefficients in table 3, the developed model has the following mathematical expression:

$$p = \frac{1}{1+e^{-b}}, \text{ where}$$

p - the polytrauma survival probability, e (exponent) - constant equal to 2.71828
*b = 7.816 + 4.038*factor2$_{model2}$ - 2.752*factor3$_{model1}$ - 2.623*factor2$_{model3}$ - 1.504*factor2$_{model4}$ - 3.333*male gender - 4.731*ARDS*

The model includes the constant (B = 7.816), the values of factor 2$_{\text{model 2}}$ (B = 4.038), factor 3$_{\text{model 1}}$ (B = -2.752), factor 2$_{\text{model 3}}$ (B = -2.623), factor 2$_{\text{model 4}}$ (B = -2.623), male gender (B = -3.333) and ARDS (B = -4.731). Age and other extracted factors at 3, 6, 12 and 24 hrs did not show a significant effect and, of course, did not enter the final model (Table 7.1, section a).

The most important factor included in the model is the factor 3$_{\text{model 1}}$, for which, the determination coefficient was equal to 0.230 (23%), after which, the factor 2$_{\text{model 2}}$ with the approximate value of 17.1%, and ARDS determining 12.7% of the interest variable dispersion (survival), followed by male gender 10.3%, factor 2$_{\text{model 3}}$ with the value of 7.3% and factor 2$_{\text{model 3}}$ with 5.5%.

Within the developed model, ARDS, factor 3$_{\text{model 1}}$, factor 2$_{\text{model 3}}$, factor 2$_{\text{model 4}}$ and male gender were the factors that decrease the survival probability (OR = 0.009, 95% CI 0.000, 0.267; OR = 0.064, 95% CI 0.011, 0.360; OR = 0.073, 95% IC 0.011,

0.468; OR = 0.222, 95% CI 0.051, 0.968 and OR = 0.036, 95% CI 0.002, 0.693, respectively). Factor $2_{\text{model 2}}$, identified as a protective factor at the development stage is a protective biomarker that increases the severe trauma surviving probability with OR = 56.693 times 95% CI being 4.506, 713.222 (Table 7.1, section a). The stability analysis by resampling (bootstrapping, 1000 samples) the developed model for the severe trauma survival probability in 24 hours after trauma showed that the coefficients are stable (Table 7.1, section b), the criterion being the significance of coefficients and lack of inversions. It is important to mention that there were no close associations between the variables in the equation (lack of collinearity).

Table 7.1. Variable coefficients for predictive survival polytrama patients model at 24 hour after impact. SPSS 23 output

a. Model coefficients

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
							Lower	Upper
ARDS	-4.731	1.739	7.397	1	.007	.009	.000	.267
factor $3_{\text{model 1}}$	-2.752	.883	9.723	1	.002	.064	.011	.360
factor $2_{\text{model 2}}$	4.038	1.292	9.767	1	.002	56.693	4.506	713.222
factor $2_{\text{model 3}}$	-2.623	.950	7.617	1	.006	.073	.011	.468
Gender	-3.333	1.513	4.851	1	.028	.036	.002	.693
factor $2_{\text{model 4}}$	-1.504	.751	4.011	1	.045	.222	.051	.968
Constant	7.816	2.555	9.362	1	.002	2480.270		

b. Bootstrepping resampling results

	B	Bias	S.E.	Sig.	95% Confidence Interval for B	
					Lower	Upper
ARDS	-4.731	-89.957	715.811	.002	-615.579	-2.512
factor $3_{\text{model 1}}$	-2.752	-45.593	305.169	.003	-389.184	-1.728
factor $2_{\text{model 2}}$	4.038	86.037	528.509	.002	2.488	671.286
factor $2_{\text{model 3}}$	-3.333	-62.414	372.735	.006	-562.397	-.793
Gender	-2.623	-53.494	413.554	.001	-381.894	-1.756
factor $2_{\text{model 4}}$	-1.504	-22.276	133.442	.004	-143.446	-.403
Constant	7.816	140.631	1045.749	.001	5.189	1136.440

Note: B - B coefficients, SE - standard errors, Wald - Wald statistics, df - degrees of freedom, Sig.- statistical significance, Exp (B) - odds ratio (OR) values, 95% C.I.for EXP (B) - confidence interval for odds ratio

In conclusion, it can be mentioned that the protease/antiprostate system components at 24 hours after the traumatic impact, being grouped by factorial analysis, showed a better prediction capacity compared to the previous data analysis, with closer calibration and determination indicators to the etalon, the discrimination being similar, the completed model representing a stable model. Nonetheless, this model needs to be further complemented by the efficient variables' inclusion.

The results can be interpreted as follows. Factor $3_{\text{model 1}}$ produces negative effects at 3 o'clock. At 6 o'clock, a protective factor appears (factor $2_{\text{model 2}}$), which most likely reduces the negative effects produced in the previous stage, after which, at 12 hours, the factor $2_{\text{model 3}}$ is involved that triggers/presents/highlights another pathogenetic link, different from factor $3_{\text{model 1}}$ (because there are no associations between the respective parameters) and the male biological gender (probable explanation - reduced

physiological reserves or some gender-related protective effects, for example estrogens). At 24 hours, another aggressive factor is added, not being associated with those mentioned.

Table 7.2. Comparative evaluation of survival predictive models for polytrauma patient

a. Survival predictive models elaborated before (standard method)				
	Model 3	**Model 4**	**Model 1**	**Model 2**
Timing (hours)	3	6	48	48
Calibration Testul Hosmer – Lemeshow	χ^2 = 13.895, df = 8, p=0.085	χ^2 = 12.415, df = 8, p = 0.134	χ^2 = 4.462, df=8, p=0.813	χ^2 = 13.401, df=8, p=0.099
Determination Nagelkerke R Square	0.257	0.437	0.648	0.425
Discrimination				
Sensibility, %	88.6	86.4	95.5	90.7
Specificity, %	26.3	78.9	68.4	73.7
Area under ROC curve (95% CI)	0.742 (0.622, 0.863)	0.850 (0.749, 0.952)	0.943 (0.889, 0.997)	0.831 (0.706, 0.956)
b. Survival predictive models elaborated in actual research (alternative method)				
	Model 1	**Model 2**	**Model 3**	**Model 4**
Timing (hours)	**3**	**6**	**12**	**24**
Calibration Testul Hosmer – Lemeshow	χ^2 = 7.587, df = 7, p = 0.370	χ2 = 4.134, df = 7, p = 0.764	χ2 = 1.112, df = 7, p = 0.993	χ^2 = 1.547, df = 7, p = 0.981
Determination Nagelkerke R Square	0.487	0.528	0.704	0.759
Discrimination				
Sensibility, %	86	88.4	90.7	90.7
Specificity, %	68.2	63.6	81.8	81.8
Area under ROC curve (95% CI)	0.866 (0.778, 0.953)	0.879 (0.790, 0.969)	0.942 (0.890, 0.994)	0.956 (0.912, 1.000)

In addition, the protective effects hypothesis of the factor $2_{\text{model 2}}$ as well as the destructive effects of factor $3_{\text{model 1}}$, factor $2_{\text{model 3}}$ and factor $2_{\text{model 4}}$ within the model obtained by dimension reduction was confirmed.

The comparative evaluation of the previously models developed by including covariates as usualy, based on the correlational analysis with the predictive models obtained by grouping covariates in the factorial analysis, is presented in table 7.2. As criteria, the determination coefficient, the calibration indicator and the discriminative ability were considered. According to the obtained data, the standard predictive models have optimal characteristics when assessing the patient with polytrauma at 48 after impact, the model having specificity problems - about a third of those who died were not identified by this model. The determination coefficient constituted only 2/3 of the dependent variable dispersion. In contrast, predictive models based on „latent" factors showed almost ideal characteristics at 12 and 24 hours after trauma.

The mentioned models had higher determination coefficient (0.704 and 0.759 compared to 0.648), the alternative models being more calibrated (χ^2 = 1.112, df = 7, p = 0.993; χ^2= 1.547, df = 7, p = 0.981 versus χ^2 = 4,462, df = 8, p = 0.813) and had

comparable discriminative capacity (area under ROC curve was 0.942, 95% CI 0.890, 0.994 and 0.956 95% CI 0.912, 1.000 compared to 0.943 95% CI 0.889, 0.997). It was possible to apply models with adequate characteristics starting from 12 hours after the traumatic impact compared to 48 hours for the optimal model from the group of previously developed models.

GENERAL CONCLUSIONS AND RECOMMENDATIONS

Conclusions

1. According to the obtained results, the severe trauma patients' population in the local medical system has an estimated lethality of 29.95% (95% CI 28.24, 31.72), even if patients who die within the first 24 hours after hospitalization are not considered. This value can be considered as a reference point for following comparative studies.
2. The univariate analysis highlighted a number of potential „effective" variables for predicting treatment outcome, which are part of the „routine" information collected at hospitalization. In particular, it was prouven the association of biochemistry parameters, ionogram and hemoleucogram values with survival rate, the age effects, the consequences of comorbidities, GCS, RR and SBP being previously demonstrated. Moreover, the complex analysis of these „routine" physiological parameters allowed the development of three severe trauma survival rate predictive models, their characteristics being comparable to those of the common accepted trauma scores.
3. The study performed an institutional validation procedure and the correction of the coefficients in the equations, adjusted to the current situation, to estimate the survival rate in eight common models, three being physiological scores (RTS, GAP, qSOFA), two - anatomical (ISS, NISS) and three - mixed (TRISS, NTRISS, ASCOT). The comparative evaluation highlighted optimal characteristics of the NTRISS, which consisted of RTS, NISS and age, compared to the other tested instruments.
4. The associations analysis of the „routine" physiological parameters, completed with the anatomical component, allowed to elaborate six alternative predictive scores for modeling the treatment outcome in patients with severe traumas. Four of the six models passed the validation procedure on a group of patients, whose data were not included in the model development – an indicator that the results are valid for the entire population of patients with severe trauma hospitalized to UTIR of EMI. All of these models present tools for stratifying patients according to risks, as well as for individualizing therapy.
5. The comparative evaluation showed superior characteristics (coefficient of determination, model calibration indicators and discriminative capacity) of the alternative developed and validated predictive models, the models being stable compared to the usual accepted trauma scores.
6. In the alternative predictive models, the effect of pneumonia in UTIR conditions (determination coefficient 1.5% of total dispersion) was estimated for the severe trauma patient's survival rate (OR = 0.216 (95% CI 0.136, 0.342)), the interrelationships of pneumonia development with the treatment outcome being insignificantly affected by the variables in the alternative model equation.

7. The predictive model for the prolonged VAP patient's identification included the anatomical component (lnNISS) adjusted according to the topographic region, GCS in the form of ranks and the total plasma protein concentration at hospitalization.
8. Experimental studies have developed predictive models for „indirect" damage to the heart, lungs, liver, spleen and kidneys based on the protease/antiprotease system components. This, on the one hand, constituted the basis for similar predictions in severe trauma patients, on the other hand, allowed elucidation of the pathophysiological mechanisms characteristics for „indirect" injuries in severe trauma and opens perspectives on their prophylaxis/therapy.
9. Predictive models for „indirect" lesions were completed by adding the latent factors obtained in dimension reduction, the developed models having a higher predictive potential compared to the models developed by the standard method. The advantage of the proposed models is the inclusion of the quantitatively estimated pathophysiological processes impact.
10. The prospective clinical study evaluated the protease/antiprotease system destructive/protective potential for polytrauma patients. Based on the results, four predictive models were developed for treatment outcomes (survival/death) that can be applied at 3, 6, 12 and 24 hours after traumatic impact, discriminatory capacity, calibration and determination indicators having values close to the standard.
11. The scientific problem solved in the thesis consists in the elaboration and evaluation of predictive scores for severe traumas evolution or treatment outcome, which led to the development of prognostic models for survival rate and occurence of „indirect" lesions. This allowed the stratification of patients according to the unfavorable evolution risk and the research directions determination for prediction/prophylaxis/treatment of „indirect" lesions.

Recommendations

1. Based on the severe trauma increased lethality values, it is reasonable to initiate research on improving their management in the context of developed alternative models or validated usual scores. This would make it possible to monitor the net effect of any proposed procedure/strategy. Having controversial results in different studies, by adjusting the effect of potential therapy to the current situation (covariates in that equation), the impact of the intervention will be estimated with much greater accuracy. For example, solving the problem of the need for tracheostomization of patients requiring prolonged VAP, as well as the appropriate time for it can be tested in the proposed models, resulting in optimizing the management of a patient with trauma requiring prolonged VAP.
2. Predictive models for treatment outcome in severe trauma based on „routine" physiological parameters are recommended for use if the common validated scores or alternative models are not available. For example, we have the case of institutions that do not meet the criteria of a trauma center and do not have computed tomography, the mandatory conditions being the institutional validation of the models. Moreover, it is welcome to supplement them by adding potential biomarkers, such as the protease/antiprotease system components investigated in the current study.

3. The usual predictive models in which the coefficients have been corrected for the current situation are recommended for application in order to predict treatment outcomes if alternative scores cannot be used. The use of scores in other institutions can be recommended only after the correction of the coefficients, using a validation sample. Regarding the perspectivess of using the usual scores, considering the characteristics of alternative models, it is optimal to validate the predictive scores based on ICD-10, which is possible only if a base of tens of thousands of respondents will be accumulated.
4. Alternative predictive models developed/validated for the survival rate in severe trauma are recommended as first-line (standard) scores under the UTIR conditions of the EMI. As for other models presented above, the validation of the model precedes the implementation in daily practice of other institutions that are part of the local medical system.
5. The implementation of the usual validated models as well as of the models elaborated and subsequently validated for the population of patients with severe traumas within UTIR of EMI is possible only by introducing the equations developed/corrected in the institutional information system, the scores being estimated automatically.
6. It is recommended to reevaluate all proposed models, the ideal option being the correction of coefficients in real time − the data of the discharged patient being taken into account to estimate the results of the hospitalized patient, the coefficients in the equations being permanently corrected.
7. The developed predictive model for prolonged VAP may be recommended for use in clinical conditions, the score needing to be supplemented.
8. Predictive scores for „indirect" lesions developed in the severe trauma experimental model based on the protease/antiprotease system components may be recommended for clinical trials testing.
9. Predictive models developed in the pilot clinical trial are recommended for validation in large clinical trials, the protease/antiprotease system components, with their predictive potential, being candidates to become part of the „routine" biochemistry set for a patient with trauma/ severe trauma/polytrauma.
10. The experimental study results as well as the pilot clinical study demand us to issue some hypotheses regarding the optimization of antiprotease treatment in severe trauma for different time intervals after trauma, the developed hypotheses will be tested in subsequent studies.
11. In the same time, the components of the protease/antiprotease system need to be supplemented with oxidative stress indicators, both being released by activated immunocompetent cells, the predictive models developed, especially in the experimental study, require improved characteristics.
12. It is appropriate to consider the alternative data preparation technique (dimension reduction) with the extraction and quantitative estimation of „latent" factors for severe trauma modeling, given the complexity of the problem and the multitude of potential covariates, multivariate analysis being the optimal elaboration tool for predictive models.

13. Considering the results of the research, to initiate the *National Trauma Register* at the clinical base EMI −the national trauma center. The common validated models as well as the alternative ones elaborated/validated within the retro-prospective study will consist the basis of the newly created register, being incorporated and calculated by default. The extension of the network will be possible only after the correspondence of the IT systems and after the proposed models validation in other medical institutions.

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1. **Monografii**
   1.1. monografii monoautor

1.1.1 ARNAUT, Oleg. *Politraumatism complicat cu sindrom de detresă respiratorie acută. Modelare experimentală şi predictivă.* Chişinău: Centrul Editorial-Poligrafic *Medicina*, 2019. 277 p. ISBN 987-9975-82-121-6.

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ADNOTARE
Arnaut Oleg
TRAUMATISMELE SEVERE: MODELE DE PREDICȚIE A EVOLUȚIEI şi REZULTATELOR TRATAMENTULUI
Teză de doctor habilitat în ştiinţe medicale. Chisinau, 2021

Structura tezei: introducere, şapte capitole, concluzii şi recomandări, bibliografia (189 titluri), 249 pagini de text de bază, 83 de figuri, 89 tabele, 41 formule. Rezultatele obținute au fost publicate în 77 de lucrări ştiinţifice.

Cuvinte cheie: Traumatisme severe, modele predictive, leziuni „la distanță", sistemul proteaze/antiproteaze.

Domeniul de studiu: Fiziologie şi fiziopatologie, Anesteziologie şi terapie intensivă.

Scopul studiului: Elaborarea şi validarea modelelor predictive a evoluţiei şi rezultatelor tratamentului în traumatismele severe şi/sau politraumatisme pentru estimarea optimă a riscului de evoluție nefavorabilă a acestuia din cadrul sistemului medical autohton.

Obiectivele cercetării: Analiza scorurilor traumatice uzuale folosite pentru predicția supraviețuirii/decesului la un pacient cu traumatism în vederea determinării scorului potențial pentru implementarea în sistemul medical autohton; Identificarea variabilelor eficiente/biomar-kerilor/factorilor de risc pentru elaborarea modelelor alternative predictive a rezultatelor tratamentului (supraviețuire/deces); Validarea modelelor traumatice predictive uzuale pentru populația pacienților cu traumatisme severe din cadrul IMSP IMU; Elaborarea şi validarea modelelor predictive alternative pentru rezultatele tratamentului în traumatisme severe din cadrul IMSP IMU; Evaluarea comparativă ale modelelor predictive elaborate/validate cu scorurile traumatice acceptate; Elaborarea modelelor predictive pentru estimarea riscului ventilației artificiale pulmonare (VAP) prelungite şi estimarea efectului pneumoniei în UTIR, ambele fiind realizate în baza scorurilor predictive alternative elaborate/validate; Analiza complexă a componentelor sistemului proteaze/antiproteaze în vederea prezicerii apariției leziunilor „la distanță" din cadrul modelului experimental al traumatismului sever; Elaborarea scorurilor predictive a intenstății leziunilor „la distanță" pentru modelul experimental de traumatism sever; Estimarea potențialului distructiv/protectiv al sistemului proteaze/antiproteze la pacienții cu politraumatisme. Elaborarea şi evaluarea comparativă a scorurilor propuse; Formularea principiilor de creare a Registrului Național de Traumă în Republica Moldova.

Noutatea şi originalitatea ştiinţifică: În baza studiului interdisciplinar au fost validate scoruri traumatice uzuale pentru populatia autohtonă, elaborate modele predictive alternative, estimat potențialul predictiv al componentelor sistemului proteaze/antiproteaze pentru rezultatele tratamentului, precum şi pentru leziunile „la distanță".

Problema ştiinţifică aplicativă de importanță majoră soluționată: Fundamentarea ştiinţifică a evaluării/elaborării scorurilor predictive pentru evoluția sau rezultatele tratamentului în traumatismele severe, ceea ce a condus la elaborarea modelelor prognostice pentru rata de supraviețuire şi dezvoltarea leziunilor „la distanță". Acest fapt a permis stratificarea pacienţiilor după riscul evolutiei nefavorabile şi determinarea direcţiilor de cercetare pentru prezicerea/profilaxia/tratamentul leziunilor „la distanță".

Semnificația teoretică şi valoarea aplicativă a lucrării: Rezultatele cercetării au completat lacunele privind fiziopatologia traumatismelor severe şi au permis de a forma un sistem de modele predictive pentru individualizarea tratamentului pacienților cu traumatisme severe, precum şi stratificarea riscului a evoluției nefavorabile a bolii traumatice.

Implementarea rezultatelor ştiinţifice: Rezultatele studiului şi recomandările metodice au fost implementate în activitatea cotidiană a Clinicii Anesteziologie şi Reanimatologie la baza ISMP Institutul de Medicină Urgentă, în procesul didactic la Catedra de fiziologie a omului şi biofizică şi Catedra de anesteziologie şi reanimatologie nr.1 „Valeriu Ghereg" ale USMF „Nicolae Testemițanu".

РЕЗЮМЕ
ТЯЖЕЛАЯ ТРАВМА: ПРЕДИКТИВНЫЕ МОДЕЛИ ТЕЧЕНИЯ И РЕЗУЛЬТАТОВ ЛЕЧЕНИЯ
Арнаут Олег
Диссертация доктора медицинских наук. Кишинев, 2021.

Структура: Диссертация представлена на 249 страницах и включает: введение, 7 глав, общие выводы и рекомендации, резюме на румынском, русском, английском языках и библиографию (189 ссылок), 89 таблиц, 83 рисунков и 41 формул. Полученные результаты отражены в 77 научных работах.

Ключевые слова: Тяжелая травма, предиктивные модели, „непрямое" повреждение, протеазы, антипротеазы.

Область исследования: нормальная и патфизиология, анестезиология и нтенсивная терапия.

Цель исследования: Разработка/валидация прогностических моделей течения/результатов лечения тяжелой травмы для оптимальной оценки риска неблагоприятного развития в рамках национальной медицинской системы.

Задачи исследования: Анализ скорринговых моделей, используемых для прогнозирования выживаемости/смерти пациентов с травмой, с целью определения отимальной шкалы для внедрения на уровне Института Экстренной Медицинской Помощи (ИЭМП); Валидация скорринговых моделей прогнозирования травм для популяции пациентов с тяжелой травмой в ИЭМП; Определение эффективных переменных/биомаркеров/факторов риска для разработки альтернативных прогностических моделей результатов лечения; Разработка и валидация прогностических моделей результатов лечения тяжелой травмы в ИЭМП; Сравнительная оценка разработанных/валидированных альтернативных прогностических моделей со стандартными; Прогностические модели для длительной искусственной вентиляции легких и оценки эффекта развития пневмонии в рамках альтернативных прогностических моделей; Комплексный анализ компонентов системы протеаз /антипростаз с целью прогнозирования возникновения „непрямых" повреждений в рамках экспериментальной модели тяжелой травмы; Разработка прогностических моделей „„непрямых" повреждений для экспериментальной модели тяжелой травмы; Оценка деструктивного/защитного потенциалов системы протеазн-антипротез для пациентов с политравмой. Разработка и сравнительная характеристика предложенных моделей; Разработка принципов создания Национального реестра травм в Республике Молдова.

Новизна и оригинальность исследования: в рамках междисциплинарного исследования были валидированы скорринговые модели для оценки тяжести травмы для местного населения, разработаны альтернативные прогностические модели, оценен прогностический потенциал компонентов системы протеаз/антипростаз для результатов лечения и для „непрямых" повреждений.

Решена важнейшая прикладная научная задача: научное обоснование оценки/разработки прогностических моделей для течения и результатов лечения тяжелой травмы, в результате были разработаны прогностические модели для выживаемости при тяжелой травме и для развития „непрямых" повреждений, что позволило стратифицировать пациентов по риску неблагоприятного развития и определить направления исследований в области прогнозирования/профилактики/лечения „непрямых" повреждений.

Теоретическая значимость и прикладное значение научной работы. Результаты исследования восполнили пробелы в патофизиологии тяжелой травмы и позволили сформировать систему прогностических моделей для индивидуализации лечения тяжелой травмы.

Результаты исследования были внедрены в дидактическую и научную деятельность Кафедры физиологии человека и биофизики и Кафедры анестезиологии и реаниматологии № 1 „Валериу Герег", ГМФУ „Николае Тестемицану", а также в научную и клиническую практику Клиники Анестезиологии и Реаниматологии Института Экстренной Медицинской Помощи, Республика Молдова.

ANNOTATION

Arnaut Oleg

SEVERE TRAUMA: EVOLUTION AND OUTCOME PREDICTIVE MODELS

Habilitated doctor thesis. Chisinau, 2021

Structure: introduction, seven chapters, conclusions, bibliography (189 entries), 249 text pages, 83 figures, 89 tables, 41 formulas. Obtained results were published in 77 scientific works.

Keywords: Severe trauma, predictive models, „distant" lesions, protease/antiprotease system

Study field: Physiology and physiopathology, Anesthesia and Intensive Care

Study aim: Elaboration and validation of evolution and outcome predictive models in severe traumas and/or polytraumas for the optimal risk estimation unfavorable evolution within the local medical system.

Study objectives: Analysis of the common traumatic scores used to predict survival/death in a patient with trauma in order to determine the potential score for implementation in the local medical system; Effective variables/biomarkers/risk factors identification in order to develop alternative predictive models for treatment outcomes (survival/death) in severe trauma; Common predictive trauma models validation for the severe trauma population within the Emergency Medicine Institute (EMI) from Chișinău, Republic of Moldova; Development and validation of alternative survival predictive models in severe trauma within the EMI; Comparative evaluation of the developed/validated predictive model/models with the common traumatic scores; Elaboration of predictive models for prolonged artificial pulmonary ventilation (VAP) risk estimation and the effect of pneumonia in UTIR, both being based on the developed/validated alternative predictive scores; Complex analysis of the protease/antiprotease system components in order to predict the „indirect" lesions occurrence in experimental model of severe trauma; „Indirect" injuries intensity predictive scores elaboration for severe trauma experimental model, Protease/antiprotease system destructive/protective potential estimation in polytrauma patients. Elaboration and comparative evaluation of newly developed scores; Principles formulation for creating the National Trauma Register in the Republic of Moldova.

Novelty and scientific originality: in an interdisciplinary study they were validated the usual traumatic scores for national healthcare system, alternative predictive models were developed, protease/antiprotease system components potential in predicting tretment otcomes and "distant" lesions was estimated.

The applied scientific problem of major importance solved: scienticical fundametation of the evaluation / elaboration of predictive scores for the evolution or treatment outcomes for severe trauma, which led to the development of predictive models for severe trauma patients survival rate and development of "distant" lesions, which allowed to stratify patients according to the risk of unfavorable evolution and determine the research directions for the prediction / prophylaxis / treatment of "distant" lesions.

Theoretical significance and applicative value of the paper: The research results filled the gaps in the pathophysiology of severe trauma and allowed to form a system of predictive models for individualizing treatment of severe trauma patients.

Implementation of scientific results: The methodical recommendations were implemented in the daily practice of the Clinic of Anesthesiology and Reanimatology no. 1 „ValeriuGhereg" of EMI, in the teaching process of training medical staff in the Discipline of Physiology and the Discipline of Anesthesiology and Intensive Care, SUMPh „Nicolae Testemitanu".

ARNAUT OLEG

SEVERE TRAUMA: EVOLUTION AND OUTCOME PREDICTIVE MODELS

312.01. Physiology and pathophysiology

321.19. Anesthesiology and intensive care

Summary of habilitated doctor thesis in medical sciences

Aprobat spre tipar: 15.12.2020 Formatul hârtiei A4
Hârtie ofset. Tipar digital. Tiraj 20 ex.
Coli de tipar.: 4,0 Comanda nr. 48

Tipografia PRINT-CARO

str. Columna, 170

tel.: 022-85-33-86