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PECULIARITIES OF THE SEVERE BURN DISEASE COURSE LEADING TO SEPSIS AND MOD IN CHILDREN

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Abstract

Burns in children is a serious international problem. In the structure of child traumatism in Ukraine, burns are ranked third in frequency and represent not only a medical but also a socio-economic problem.

A late and formidable complication in patients with a severe burn injury is the development of liver failure. The sepsis-induced liver dysfunction is mainly caused by systemic or microcirculatory disorders, bacteremia, and endotoxicosis, following inflammatory cellular cytokines and mediators' activation. Implementation of the phlogogenic potential of reactivated NG in the liver enhances its acute damage. Liver damage in septic patients grows in two main directions: hepatitis and hepatosis. Hypoxic hepatitis developing as a result of hypovolemia and hypoperfusion is accompanied by the increase of transaminases level in the blood serum on the background of acute cells and mitochondria damage in the liver. Sepsis-associated acute hepatic failure is followed by coagulopathy, which aggravates the cascade of disorders throughout the body (cardiovascular, renal, and respiratory failure, cerebral edema) and leads to MODS development.

Until now, there has been insufficient attention to the development of an algorithm for the burn sepsis diagnosis and MODS in children having severe and significantly severe burns. It vastly complicates the treatment and often leads to unfavorable outcomes.

The aim: to analyze the retrospective data on the sepsis incidence and MODS in children with severe and extremely severe burn injuries, as well as to determine their prognostic value.

Materials and methods. A retrospective analysis has been conducted on the treatment results and frequency of complications in children having mild and moderate burn injuries with boiling water (the most common etiological factor). They were hospitalized in the period from 2007 to 2017, in the intensive care unit of the Burn Department, the Communal Nonprofit Enterprise "Odessa Regional Clinical Medical Center" of the Odessa Regional Council. The inclusion criteria were: the age of 0 to 5 years and the modified index of injuries severity (MISI) from 60 to 91 and above. The data were exported to Microsoft Excel and were analyzed using Statistica 6.0. The descriptive statistics were calculated to determine the frequency, mean, and median of clinical characteristics. The statistical analysis was carried out using the Student, Fisher, and Mann-Whitney test depending on the indicators, $p < 0.001$ was taken as statistically significant.

As a result of the data analysis in children with severe and significantly severe burn injury, there were prognostic criteria of MODS and sepsis development determined as complications of burn disease and reasons of deaths.

All human studies were conducted in compliance with the rules of the Helsinki Declaration of the World Medical Association "Ethical principles of medical research with human participation as an object of study". Informed consent was obtained from all participants

Key words: *Children, burn, liver failure, renal failure, hyperglycemia, multiple organ dysfunction*

Introduction

Burns in children is a serious international problem. In the structure of child traumatism in Ukraine, burns are ranked third in frequency and represent not only a medical but also a socio-economic problem [1].

Severe and extremely severe burns lead to the development of cosmetic and functional disorders requiring long-term medical, psychological and social rehabilitation to reduce the degree of disability, and 20% of their cases are recorded as lethal outcomes [2].

The development of sepsis and multiple organ dysfunction syndromes (MODS) cause several severe complications even in cases when deep burns from 5% of the total body surface (TBS) take place in the younger age group. It happens due to the immaturity of children's retention systems and organs in the conditions of concomitant pathology. Reactivation of protective antimicrobial and antitoxic mechanisms leads to the systemic inflammatory response growth, which is a basis for the sepsis development on the background of the microbial infection attachment, the further MODS progression, and an unfavorable prognosis [3].

The early anti-inflammatory response occurring immediately after the severe burn injury acts as a counterbalance to the systemic inflammatory response syndrome and restores immune homeostasis, and is called the compensatory anti-inflammatory response syndrome (CARS) [4]. In some patients, CARS is pathologically enhanced and lasts longer than 48 hours. This stable condition is called immune paralysis, which increases the frequency of nosocomial sepsis, multiple organ dysfunction syndromes, and death in critically ill patients [5, 6]. The main reason for mortality among patients with severe and extremely severe burns on the background of the development of sepsis remains MODS. Thus, the American Burn Association found that 50% of deaths from burn injuries are caused by MODS, but only a few studies have shown MODS as a burn complication [7].

Significant shifts in erythropoiesis consist of stem pool depletion due to emergent granulopoiesis in the acute stage of burn disease. It is a part of the mechanisms' triad for anemia and lymphopenia growth accompanied by a decrease of the myelopoiesis cells differentiation level, it causes further ineffectiveness of nonspecific cell resistance, the imperfection of immune response, and the development of sepsis. [7, 8, 9].

Gore et al. found a connection between the development of sepsis, children's hospital stay length with severe burns, and insulin resistance; a statistically higher incidence of fungemia in patients with hyperglycemia. Since hyperglycemia enhances protein glycosylation, IgG inactivation is accompanied by weakened suppression of IL-2 and IL-10, which disrupts the function of macrophages and neutrophilic granulocytes (NG) and provokes the development of a general inflammatory reaction [10, 11]. Also, in patients with burns and hyperglycemia, the process of wound healing slows down and the graft engraftment rate decreases, the frequency of pulmonary complications, such as pneumonia, increases in the early stages. On the first day of burn disease, the blood glucose level is considered as a predictive criterion of mortality: the higher hyperglycemia is, the higher is the risk of an unfavorable outcome. [12, 13].

A late and formidable complication in patients with a severe burn injury is the development of liver failure. The sepsis-induced liver dysfunction is mainly caused by systemic or microcirculatory disorders, bacteremia, and endotoxicosis, following inflammatory cellular cytokines and mediators' activation. Implementation of the phlogogenic potential of reactivated NG in the liver enhances its acute damage. Liver damage in septic patients grows in two main directions: hepatitis and hepatosis. Hypoxic hepatitis developing as a result of hypovolemia and hypoperfusion is accompanied by the increase of transaminases level in the blood serum on the background of acute cells and mitochondria damage in the liver. Sepsis-associated acute hepatic failure is followed by coagulopathy, which aggravates the cascade of disorders throughout the body (cardiovascular, renal, and respiratory failure, cerebral edema) and leads to MODS development [14, 15].

Until now, there has been insufficient attention to the development of an algorithm for the burn sepsis diagnosis and MODS in children having severe and significantly severe burns. It vastly complicates the treatment and often leads to unfavorable outcomes.

Aim of the study to analyze the retrospective data on the sepsis incidence and MODS in children with severe and extremely severe burn injuries, as well as to determine their prognostic value.

Methods

A retrospective analysis has been conducted on the treatment results and frequency of complications in children having mild and moderate burn injuries with boiling water (the most common etiological factor). They were hospitalized in the period from 2007 to 2017, in the intensive care unit of the Burn Department, the Communal Nonprofit Enterprise "Odessa Regional Clinical Medical Center" of the Odessa Regional Council. The inclusion criteria were: the age of 0 to 5 years and the modified index of injuries severity (MISI) from 60 to 91 and above. The data were exported to Microsoft Excel and were analyzed using Statistica 6.0. The descriptive statistics were calculated to determine the frequency, mean, and median of clinical characteristics. The statistical analysis was carried out using the Student, Fisher, and Mann-Whitney test depending on the indicators, $p < 0.001$ was taken as statistically significant.

The following indicators were analyzed to assess the peculiarities of burn disease course in children:

- an average length of hospital stay, bed-day (BD);
- the incidence of sepsis;
- the frequency of MODS development;
- existing concomitant pathology;
- the frequency of deaths;
- of clinical and laboratory studies indicators on the 1st, 3rd, 7th, 14th, 21st days, such as the number of leukocytes (10^9/L), and the level of glucose in the blood (mmol / L), level of creatinine (mmol / l), urea (mmol / l), ALT, AST units per liter in serum.

Results

The studied children (n = 66) were divided according to MISI into 2 main groups.

Group 1 consisted of (n = 43) children aged 2.7 ± 0.3 years, 59% of which were boys (n = 25) and 41% were girls (n = 18), MISI 72.1 ± 1.3 U. In group I, the average total burn surface area was 35.1 ± 1.1% of the total body surface area (TBSA), the average deep burns area was 12.7 ± 1.3% of the TBSA. The average duration of inpatient treatment was 28.7 ± 1.7 BD. Among complications from the respiratory system (pneumonia) was observed in 6.9% (n = 3); late complications of severe burn disease were impaired renal function 4.7% (n = 2) and hepatobiliary system 2.3% (n = 1). In group 1, the development of sepsis was seen in 83.7% (n = 36) of patients, MODS developed in 2.3% (n = 1) of the patient and was fatal.

Group 2 consisted of (n = 23) children aged 2.1 ± 0.3 years, of which 65% were boys (n = 15) and 35% were girls (n = 8), MISI 123.0 ± 7.7 units. In group 2, the average total burn surface area was 1.5 times higher than in group 1 and amounted to 53.0 ± 2.7% of TBSA, and the deep burns area was 22.2 ± 4.8% of the TBSA. In group 2, the average duration of hospitalization for treatment was 25.1 ± 3.0 BD. Among complications from the respiratory system (pneumonia) in 50% (n = 12) patients, complications that appeared later of renal function 56.5% (n = 13) and hepatobiliary system complications in 25% (n = 6). In this group, the mortality rate was 25% (n = 6), and sepsis developed in 87.5% of children (n = 21), and in 25% (n = 6) of cases led to the further development of MODS.

The control group consisted of somatically healthy children (n = 208), where 55% (n = 114) were boys, and 45% (n = 94) girls. All of them were examined when applying for preschool institutions in the city of Yuzhny, the Odessa region.

We analyzed leukocyte and glucose levels in the peripheral blood according to the Sepsis-3 criteria to verify the timing of the infectious complications' development [16]. In both groups, the number of leukocytes was maximum on the 1st day (in group 1, 15.2 ± 0.7 10^9/L, in group 2, 15.4 ± 1.0 10^9/L, $p = 0.837$) and remained higher than average indicators of the control group even on the 21st day of the analysis (in group 1, 9.6 ± 0.6 10^9/L, in group 2, 8.9 ± 0.7 10^9/L, $p = 0.348$). A shift in the leukocyte formula towards immature forms combined with an increase of leukocytes level on the 7th day was noted equally in groups 1 and 2 and amounted to 13.8 ± 0.8 10^9/L, $p = 0.021$, and 14.9 ± 1 2 10^9/L, $p = 0.006$. It, together with other indicators, showed the development of septic complications of severe burn disease (fig. 1).

The analysis of glucose level indexes confirmed a direct connection between the glucose level on the first day after injury and the frequency of pulmonary complications in both studied groups. Thus, the

glucose level was 6.1 ± 0.2 mmol / l, and pneumonia appeared in 6.9% (n = 3) of patients in group 1 on day 1. In group 2, the level of glucose in blood serum was 7.3 ± 0.2 mmol / l on day 1, which was 17.3% higher than in group 1 (p <0.001), and the incidence of pneumonia was 50% (n = 12). It is 4 times higher than in group 1 (fig. 2).

The results of the analysis of both patient groups medical records showed that in group 1 on day 1, the average urea levels (5.2 ± 0.3 mmol / l) remained within the average range and did not exceed the regional norm (4.2 ± 1.1 mmol / L) during following days too. In group 1, the serum creatinine level exceeded the average indicators of the regional norm (50.2 ± 2.8 μmol / L) and, on the first day of severe burn disease, was (55.9 ± 1.7 μmol / L). By the 21st day of burn disease (50.1 ± 2.3 μmol / l, p = 0.887) it reached normal indexes and the frequency of acute renal failure was 6.5% (n = 4). In group 2, the urea level increased from the 1st day of burn disease (7.3 ± 0.6 mmol / l) to its maximum level on the 14th day. It was 8.6 ± 2.2 mmol / l (p = 0.305). Here, the maximum creatinine level on the 3rd day was 85.8 ± 4.2 μmol / L (p = 0.032) and remained high on the 21st day of burn disease (59.9 ± 3.6 μmol / L, p = 0.003). The incidence of acute renal failure was 56.4% (n = 22) in group 2 (fig. 3, 4).

On the first day of the burn disease course, the level of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increased due to the background hypovolemia and hypoperfusion (95.5 ± 15.3 U/L and 228.1 ± 35.3 U/L, p = 0.001) in groups 1 and 2. The maximum ALT levels (103.6 ± 19.5 U/L, p = 0.230) were observed on the 3rd day of the acute burn disease phase, in group 1. The AST level indicators gradually decreased in the blood serum of groups 1 and 2 on the 21st day, but they still exceeded the regional norm (47.9 ± 3.7 U/L, and 72.9 ± 21.9 U/L, p <0.001) (fig. 5).

On the first day, AST level indicators were 80.8 ± 11.8 U/L and 172.4 ± 16.7 U/L (p = 0.364) in both groups respectively, with the maximum increase of indicators on the 3rd day (80, 4 ± 11.4 μmol / L and 178.7 ± 30.2 μmol / L, p <0.001), and following gradual decrease in the level of indicators. On day 21, AST indices exceeded the average ranges of the regional norm by 43.9% in group 1 (47.9 ± 3.7 U/L, p = 0.130) and by 69.7% (72.9 ± 21.9 U/L, p = 0.277) in the 2nd group.

Hepatic failure was diagnosed in 2.3% (n = 1) in patient group 1 and 47.8% (n = 11) in group 2, which directly correlated with deaths in both groups (fig. 6).

We noted, there were no clinical and laboratory signs of hepatosis and a significant increase of the bilirubin level in patients of group 1 observed. In group 2, on the 3rd day of the burn disease course, there was an increase of bilirubin in the blood serum by 30.1% from the average indexes of the regional norm (10.2 μmol / L) and amounted to 14.6 ± 0.8 μmol / L (p = 0.021). A complication such as hepatosis was recorded in pathological and anatomical diagnoses in 2.3% (n = 1) of patients who died in group 1, and 26.1% (n = 6) of patients with a fatal outcome in group 2. It indicates that morphological development may outpace the increase of laboratory parameters (fig. 7).

Conclusions

As a result of the data analysis in children with severe and significantly severe burn injury, there were prognostic criteria of MODS and sepsis development determined as complications of burn disease and reasons of deaths.

1. A significant increase in the number of leukocytes in the children blood is associated with the development of systemic inflammatory response, on the 1st day of the severe burn injury in groups 1 and 2, but these indicators increase on the 7th day is associated with the development of burn toxemia.

2. An increase in glucose levels on the 1st day is an early predictor of the pulmonary complication's development.

3. The increase in creatinine indexes on the 3rd day, and urea on the 3rd and 14th days reflects the likelihood of developing renal failure in the children's blood with severe and extremely severe burn injury.

4. Liver failure, which is one of the earliest and the most frequent, unfavorable complications in children with severe burn injury, was diagnosed in all children with a fatal outcome in the patient's group 2.

5. Depending on the severity of the burn injury, on the 1st day of trauma, the development of liver failure shows itself with an increase of the transaminases level developing further in hepatitis.

More severe morphological changes in the liver are not reliably displayed by laboratory parameters and are detected later.

Acknowledgments

The authors declare that there are no conflicts of interest.

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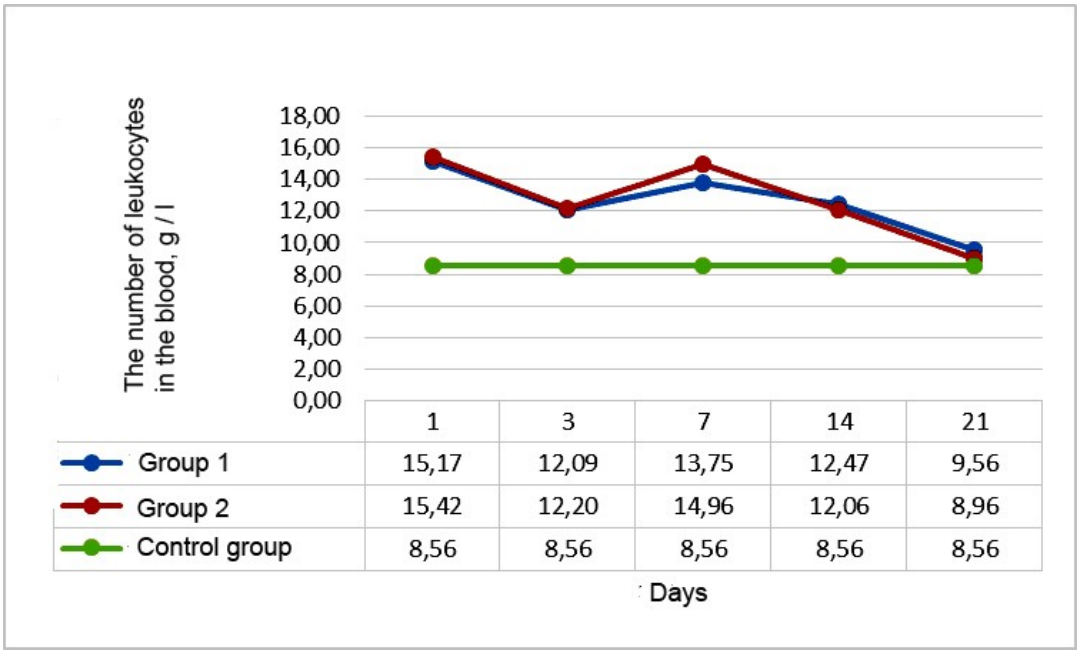
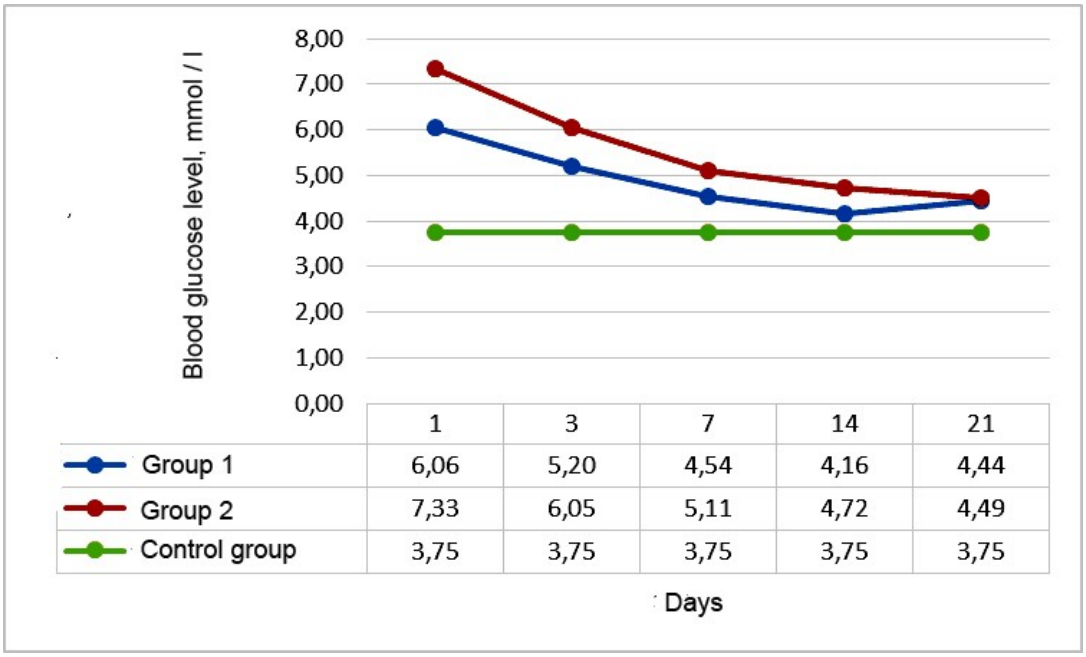
Figure 1. Dynamics of leukocytes number in the blood



	1	3	7	14	21
Group 1	15,17	12,09	13,75	12,47	9,56
Group 2	15,42	12,20	14,96	12,06	8,96
Control group	8,56	8,56	8,56	8,56	8,56

Figure 2. Dynamics of serum glucose levels



	1	3	7	14	21
Group 1	6,06	5,20	4,54	4,16	4,44
Group 2	7,33	6,05	5,11	4,72	4,49
Control group	3,75	3,75	3,75	3,75	3,75

Figure 3. Dynamics of urea indicators in blood serum

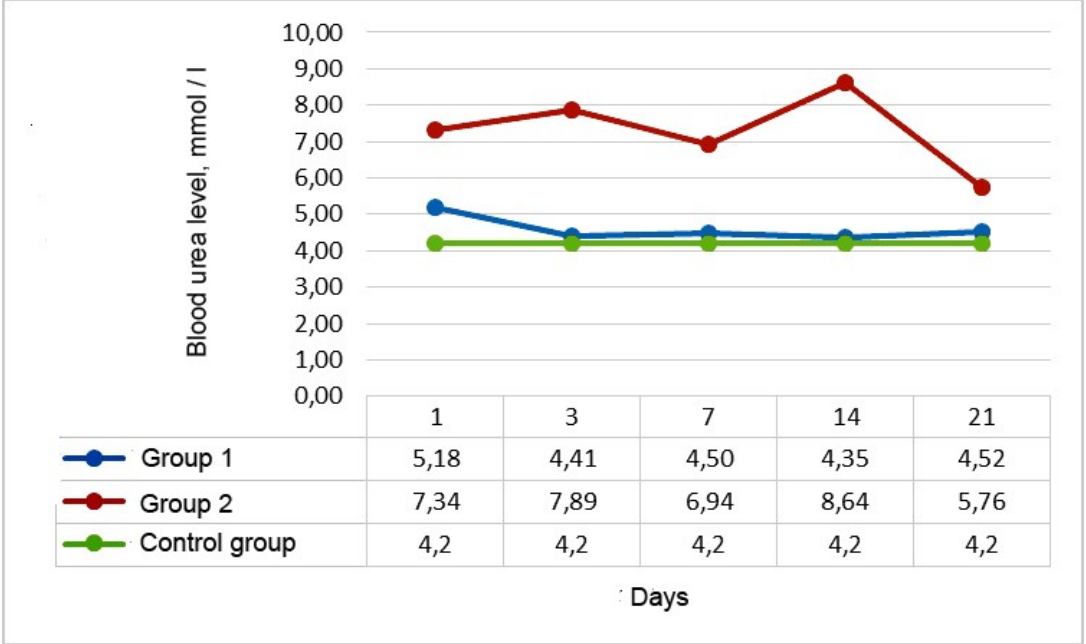


Figure 4. Dynamics of serum creatinine parameters

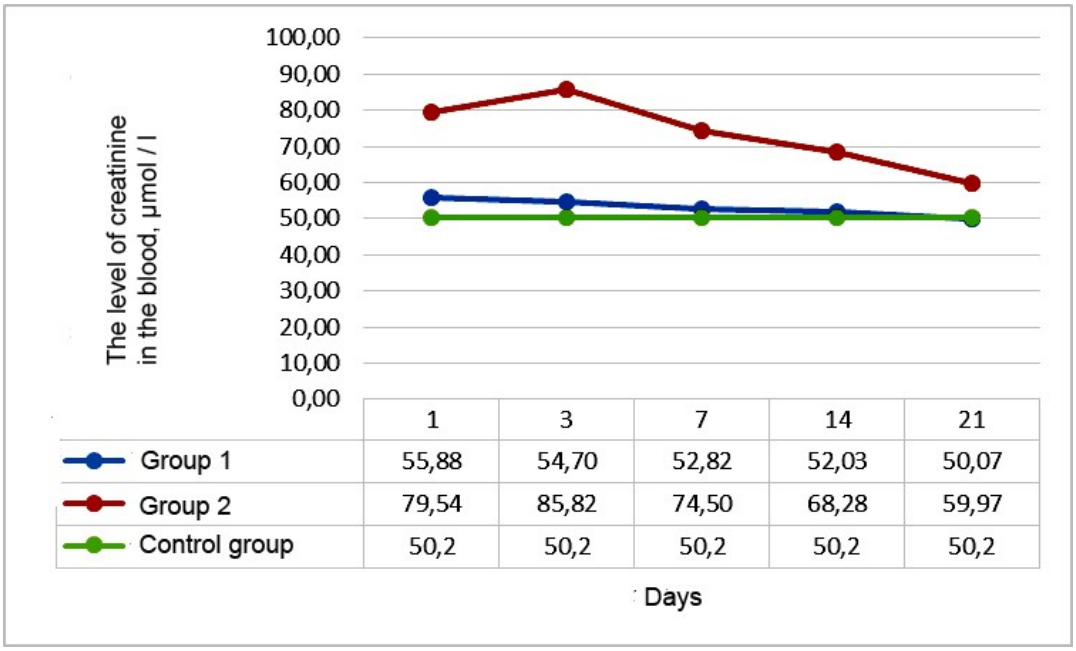
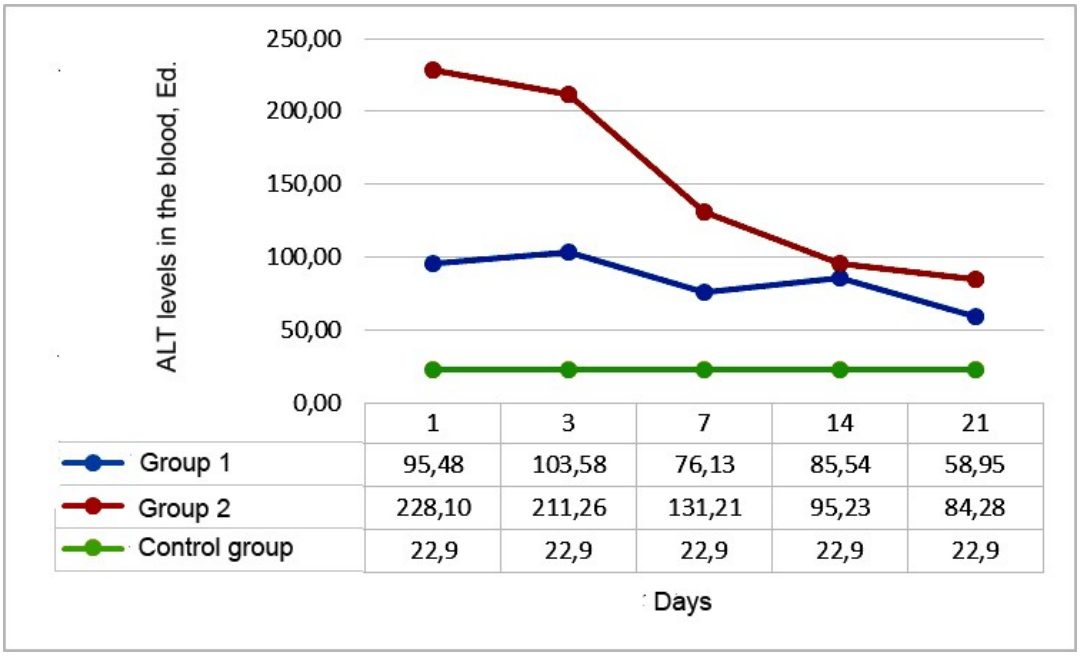
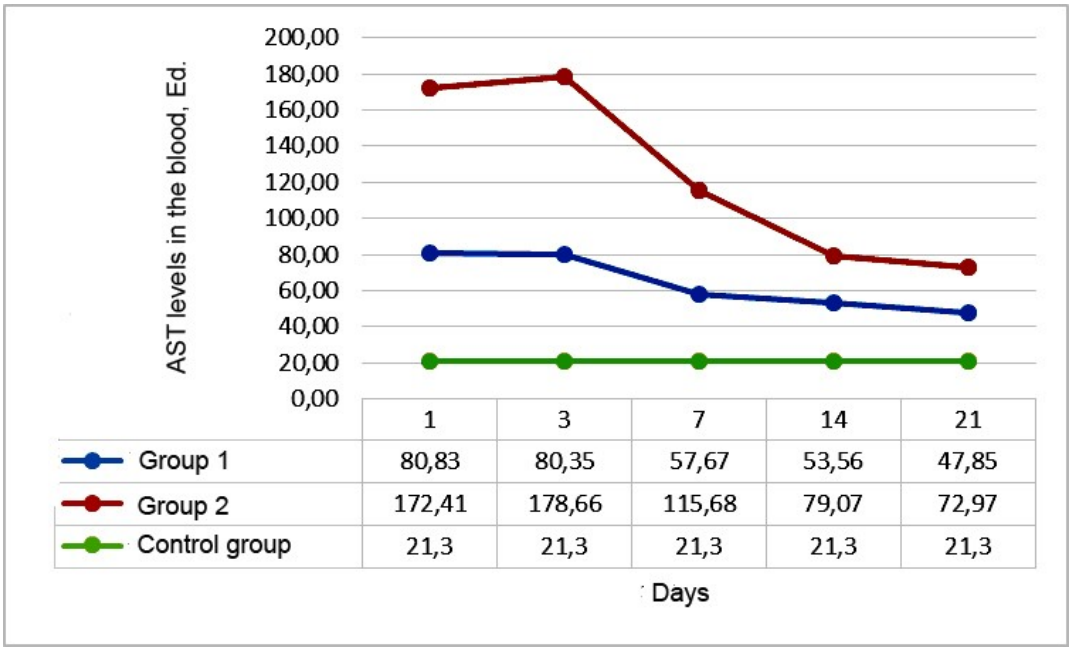


Figure 5. Dynamics of ALT indicators in blood serum



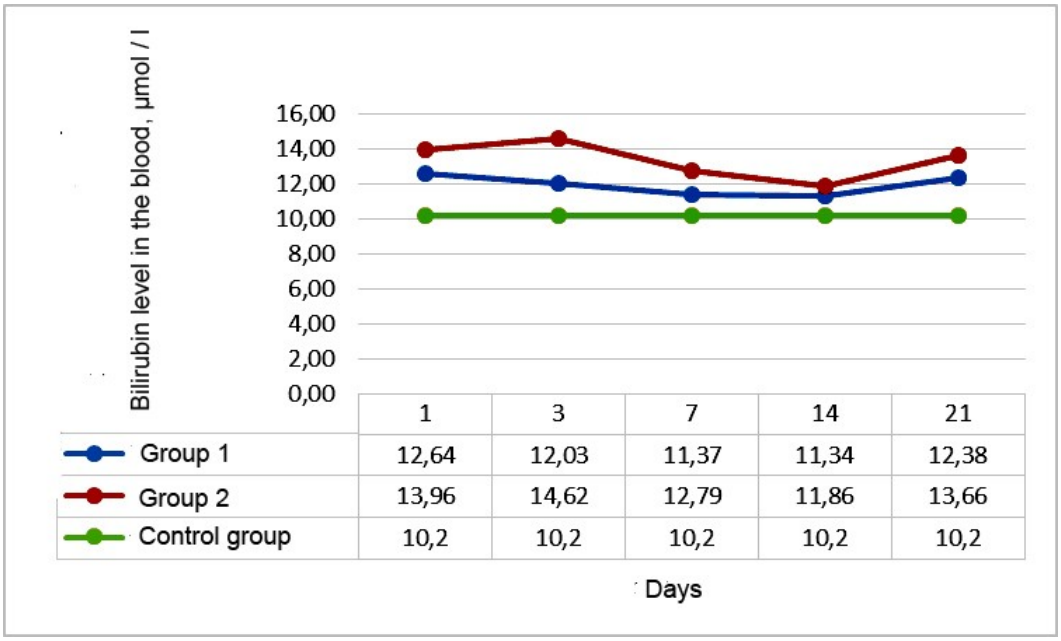
	1	3	7	14	21
Group 1	95,48	103,58	76,13	85,54	58,95
Group 2	228,10	211,26	131,21	95,23	84,28
Control group	22,9	22,9	22,9	22,9	22,9

Figure 6. Dynamics of AST indicators in blood serum



	1	3	7	14	21
Group 1	80,83	80,35	57,67	53,56	47,85
Group 2	172,41	178,66	115,68	79,07	72,97
Control group	21,3	21,3	21,3	21,3	21,3

Figure 7. Dynamics of total bilirubin indicators in blood serum



	1	3	7	14	21
Group 1	12,64	12,03	11,37	11,34	12,38
Group 2	13,96	14,62	12,79	11,86	13,66
Control group	10,2	10,2	10,2	10,2	10,2