VENOUS THROMBOEMBOLISM IN COMPLICATED CERVICAL SPINE INJURY

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Objective. To determine incidence rate and risk factors for the development of venous thromboembolism in complicated cervical spine injury.
Material and Methods. The study included 34 patients with acute complicated cervical spine injury. Inclusion criteria were newly diagnosed venous thromboembolic complications, and application of low-frequency piezothromboelastography to study the hemostasis system. All patients received standard drug thromboprophylaxis. Patients were divided into two study groups: Group I included 21 patients with venous thromboembolic complications, and Group II — 13 patients without thromboembolic complications.
Results. The incidence of venous thromboembolism in the total sample was 61.8 %. Pulmonary artery embolism developed in 4.7 % of cases. In 91,0 % of cases, thrombosis was asymptomatic. The state of the hemostatic system in Group I before the start of thromboprophylaxis was characterized by chronometric hypocoagulation, and structural hypercoagulation with a 2.6-fold increase in the intensity of clot retraction and lysis. In Group II, there was chronometric and structural hypercoagulation with a 14.4-fold increase in the intensity of clot retraction and lysis. The main significant predictors of the development of venous thromboembolism were identified as intestinal paresis ($p = 0.004$), absence of changes in neurological status ($p = 0.012$), length of stay in the ICU ($p = 0.025$), and length of hospital stay ($p = 0.039$). The building of a multivariate logistic regression model revealed multiplicative significant predictors of the development of thromboembolism. It has been shown that the presence of intestinal paresis is associated with a 25.07-fold increase in the chances of developing DVT of lower extremities.
Conclusion. Considering the high incidence of venous thromboembolic complications in patients with complicated cervical spine injury, further research is required to study the effectiveness and safety of correction of drug thromboprophylaxis regimens in the form of increasing doses of anticoagulants or the frequency of their administration.
Key Words: complicated cervical spine injury, spinal cord injury, venous thromboembolic complications, thromboprophylaxis, logistic regression models.
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Despite the implementation of conventional thromboprophylaxis management, 12 to 64 % of patients with spinal cord injury (SCI) at the cervical spine experience acute venous thromboembolism, which includes pulmonary embolism (PE) and deep vein thrombosis of the lower extremities, and mortality rate exceeds 9.7 % [1–3]. Large population studies have shown that the incidence of PE after spinal cord injury is 4–5 % [4].

While the specific mechanism of venous thromboembolism in patients with SCI is uncertain, it is significantly associated with immobility, which is the main feature of patients with complicated cervical spine injuries. There is the highest chance of acquiring these complications during the first three months following an injury [5–7].

Because hypercoagulable disorders contribute to the clotting mechanism and that standard hemostatic screening tests do not provide sufficient diagnostic information, it is pertinent to look for informative techniques that can quickly diagnose hemostasis system disorders and possibly predict thromboembolic episodes.

Nowadays, techniques based on the evaluation of the viscoelasticity of blood are known and have been accepted as global coagulation tests designed to analyze the mechanisms of blood clotting from thrombin activation to fibrinolysis. In particular, the study of the viscoelasticity of blood by thromboelastography (TEG) or using rotational thromboelastometry (ROTEM) provides for the detection of both hypocoagulable and hypercoagulable states. It is also possible to monitor the efficiency of anticoagulation therapy and assess the function of platelets at that moment [8–10].

The importance of such studies in various areas of medicine and intensive care has increased considerably over the past 20 years and remains relevant. But, there are only a few articles concerning the diagnostic efficacy of the TEG technique in intensive care for patients with cervical SCI. Both the issues of incidence and of possibilities of predicting the development of venous thromboembolism in this category of patients require clarification.

The objective is to determine the incidence rate and risk factors for the development of venous thromboembolism in complicated cervical spine injuries.

Material and Methods

A retrospective single center study included 34 patients with cervical SCI who underwent treatment in Novosibirsk

Research Institute of Traumatology and Orthopaedics n.a. Ya.L. Tsivyan in 2019–2022.

Inclusion criteria: acute isolated cervical SCI, newly diagnosed venous thromboembolism, and the use of low-frequency piezothromboelastography for the study of the hemostasis system.

Exclusion criteria: concomitant injury, polytrauma, absence of neurological disorders, blood diseases. There were no withdrawal criteria.

The study was approved by the ethics committee of the institution (extract 020/23 from the minutes of the meeting 007/23 as of November 20, 2023). The primary endpoint of the study was the diagnosis of deep vein thrombosis of the lower extremities and PE.

Two study groups were formed to identify predictors of venous thromboembolism: Group I – 21 patients with diagnosed deep vein thrombosis of the lower extremities and any form of PE; Group II – 13 patients without venous thromboembolism.

The absolute majority of patients in both groups underwent decompression and stabilization surgeries as an emergency. Postoperative follow-up and treatment were performed in the intensive care unit (ICU).

The severity of spinal cord injury was assessed according to the classification of the American Spinal Injury Association, IMSOP-ASIA: type A – no sensory or motor function is preserved; B – sensory is preserved below the injury level, no motor function; C – paresis below the injury level of less than 3 points; D – paresis below the injury level of more than 3 points; E –motor and sensory functions are preserved [11].

All patients underwent standard drug thromboprophylaxis: nadroparin calcium at a dose of 38 anti-Xa IU/kg once a day subcutaneously in Group I in 52 % of cases; in Group II – in 54 % ($p > 0.999$); enoxaparin sodium at a dose of 40 mg once a day subcutaneously in Group I in 29 % of patients, in Group II – in 23% ($p > 0.999$); fondaparinux sodium at a dose of 2.5 mg once a day subcutaneously in Group I in 19 % of cases; in Group II – in 23 % ($p > 0.999$). Anticoagulant doses were raised to therapeutic levels in case of the registration of the occurrence of venous thromboembolism.

After decompression and stabilization surgeries, according to the current protocol of the institution for acute spinal cord injury, drug thromboprophylaxis was prescribed 12 hours after the completion of the surgical stage of treatment; for non-operated patients, it was prescribed from the moment of admission to the hospital. Non-drug thromboprophylaxis measures in the postoperative period in the absence of contraindications included compression stockings, intermittent pneumatic compression, remedial gymnastics and massage.

A computer-assisted coagulation analyzer was used (thromboelastograph's model: "NPTEG MED-NORD", Russia; registration certificate of the Federal Registration Service No. P3H 2020/12855) to study the hemostasis system. The study was performed in compliance with the existing guidelines for the procedures of low-frequency piezothromboelastography [12–13].

The main stages of fibrinogenesis, from platelet aggregation to fibrinolysis, were displayed on the computer screen as an integrated curved line. The most significant indicators analyzed during the study were: the maximum amplitude (density) of the clot per relative units (MA, relative unit), the time to reach the maximum amplitude in minutes (t5, min), and the intensity of retraction and lysis of the clot as a percentage (IRLC, %). Comparison of the parameters of the recorded piezothromboelastogram with known reference ranges established for the normal coagulation state in different genders and age groups (starting from 18 years old) promoted the identification of shifts in the hemostasis system at the stages of intensive care in patients with cervical SCI in the ICU.

Low-frequency piezothromboelastography was combined with laboratory tests. The platelet count, fibrinogen level, prothrombin time (PT), activated partial thromboplastin time (APTT) and D-dimer level were defined.

Studies of the hemostasis system were conducted throughout the entire period of the patients' stay in the ICU with several control points: the 1st, 3rd, 7th and 10th days of the injury course.

The lower extremity ultrasound was performed using the General Electric Logiq E system (General Electric, USA) in the first three days and then every 7–10 days to identify the thrombosis development. CT scan of the lungs using an iodine-containing contrast media (CT angiography) was performed only in the presence of a PE clinical picture.

The following factors were analyzed for intergroup comparison and identification of possible predictors of venous thromboembolism: gender, age, mechanism of injury, occurrence and origin of comorbidity, severity of spinal cord injury, type of surgery, complications, findings of laboratory tests of the hemostasis system and results of low-frequency piezothromboelastography, number of days in the ICU, duration of hospital stay, mortality.

Statistical data processing was performed for the general sample of patients and for the formed study groups. Continuous indicators were tested for compliance with the normal distribution law (the Shapiro – Wilk test), and the uniformity of deviations of indicators in the compared groups was tested by the Fisher's F-test. Due to the small number of indicators fulfilling the applicability condition of the Student's t-test, continuous indicators were compared using nonparametric rank criteria: the Mann – Whitney U test between groups at one time point and the Wilcoxon signed-rank test between time points within groups.

The continuous data are given as the median [first quartile; third quartile] of binary data, described as the number (frequency) of events; the number of patients at the level (percentage of the total number of patients in the group) is given for each level of the categorical data. Binary and categorical indicators were compared between groups using the Fisher's F-test.

The determination of predictors of the development of deep vein thrombosis of the lower extremities was performed by the construction of logistics regression models. Numerical associations (predictors) between individual indicators and the development of deep vein thrombosis of the lower extremities were revealed using univariate models. Multivariate logistic regression models were used to study the correlation between factors and to build more accurate predictive models.

Multivariate models were also calibrated using ROC analysis; prognostic features were calculated with the construction of a 95 % CI: AUC, sensitivity, specificity, and positive and negative prognostic significance. The Hosmer-Lemeshow test was used to evaluate the compliance of the multivariate model.

All the tests used were two-sided. Statistical hypotheses were tested at a critical significance value of 0.05, i.e., the difference was considered statistically significant at the reached value of $p < 0.05$.

All statistical calculations were performed in RStudio software (version 1.3.959, © 2009-2020 RStudio, Inc., USA, URL: https://www.rstudio.com) in the R language (version 4.0.2, URL: https://www.R-project.org).

Results

All patients included in the study suffered a lower cervical spinal cord injury. The largest part of the total sample consisted of men of working age (88.2 %). The absolute majority of the patients belonged to the category with the most severe spinal cord injury according to the ASIA classification: type A – 22 (64.7 %) patients, type B – 6 (17.7 %) patients. Decompression and stabilization surgeries were associated with spinal cord compression and performed in 28 (82.3 %) patients.

Deep vein thrombosis of the lower extremities in the total sample developed in 21 (61.8 %) patients. 4 (66.7 %) of 6 patients who did not undergo surgery were diagnosed with thrombosis. In 91.0 % of cases, thrombosis was asymptomatic and was detected by screening ultrasound of the lower extremity veins. The largest number of thrombosis appeared in the first ten days after the admission of patients to the hospital. Thrombosis was detected in 2 (9.5 %) patients on the first day after injury.

Nonfatal PE developed in one patient (4.7 %) with a complicated fracture of the ankylosed spine at the C6–C7 level (type A according to ASIA). This complication was associated with occlusive thrombosis of the deep veins of the lower extremities on the 10th day of the injury.

Positive changes in neurological status in the form of a transition from one grade to another according to the ASIA classification were observed in 12 patients: in five patients with the initial ASIA grade A, in three patients with the initial ASIA grade B and in four patients with the initial ASIA grade C. Among 12 patients with positive changes in neurological status, deep vein thrombosis of the lower extremities developed in 4 (33.0 %).

The changes in the indicators of laboratory tests of hemostasis and indicators of low-frequency piezothromboelastography for a general sample of patients are given in Table 1.

According to the mean values defining the main stages of fibrinogenesis detected by low-frequency piezothromboelastography, the hemostatic system on the first day following injury was characterized by chronometric and structural hypercoagulation with a significant increase in the blood lytic value. Meanwhile, the laboratory test values were within the reference ranges. Later, despite statistically significant differences in hemostasis indicators at the follow-up stages, they did not exceed the conditional norm, with the exception of fibrinogen level. The condition of increasing hyperfibrinogenemia was registered on the third day in the ICU.

The following was found in an intergroup comparison: the mean age of patients in Group I was 40 [35; 59] years, in Group II – 35 [22; 47] years; p = 0.329. Decompression and stabilization surgeries as an emergency treatment were performed in 17 (81 %) patients in Group I and in 11 (8 5%) patients in Group II (p > 0.999). The distribution of patients in groups by gender, mechanism of injury, severity of spinal cord injury, neurological deficit and comorbidity is shown in Table 2.

As can be seen from the data given in Table 2, the study groups are comparable in terms of the main studied characteristics.

From the moment of admission to the hospital, all patients underwent urgent intensive treatment aimed at stabilizing and maintaining appropriate perfusion pressure with target values of mean arterial pressure (APm) of at least 85–90 mm Hg. The intergroup comparison by number of patients requiring long-term hemodynamic support only tended to show significant differences: 18 (86 %) patients in Group I, and 7 (54 %) in Group II (p = 0.057).

Cases of complications have been reported in both groups: cardiac rhythm disorder, pneumonia, gastrointestinal bleeding, acute renal failure, liver failure, multiple organ dysfunction syndrome and sepsis. Nevertheless, there were no statistically insignificant differences in the frequency of these complications in the intergroup comparison. Pulmonary sepsis was the cause of mortality in 3 (14 %) patients in Group I; there were no mortality in Group II (p = 0.270).

Statistically significant differences in the incidence of intestinal paresis were found in 19 (90 %) and 5 (38 %) patients of groups I and II, respectively (p = 0.002). Other statistically significant intergroup differences are given in Table 3.

The changes in the parameters of the studied laboratory tests and low-frequency piezothromboelastography in the studied groups are shown in Table 4.

The hemostatic system before the beginning of thromboprophylaxis in patients in Group I was characterized by the following: chronometric hypocoagulation, structural hypercoagulation with 2.6-fold increase in the intensity of retraction and lysis of the clot when compared with the reference range. Meanwhile, chronometric and structural hypercoagulation with pronounced activation of fibrinolysis was observed in Group II – 14.4-fold increase in the intensity of clot retraction and lysis. These indicators of low-frequency piezothromboelastography can be viewed in Table 4. At the same time, APTT indicators only in Group I had a trend towards hypercoagulation at normal values of other hemostasis indicators.

Due to thromboprophylaxis, it was possible to maintain the initial state of chronometric hypocoagulation in patients in Group I. Meanwhile, structural hypercoagulation and a considerable increase in the intensity of retraction and lysis of the clot remained. Despite thromboprophylaxis, chronometric and structural hypercoagulation, as well as activation of fibrinolysis with a peak on the 10th day of follow-up, remained in patients in Group II. According to laboratory tests, stable hyperfibrinogenemia was registered in both groups on the 3rd day.

D-dimer concentration in the blood in both groups was above the upper normal level and was 1,575.50 ng/l [956.00; 2,700.00] and 960.00 ng/l [769.25; 1,042.50] on the 10th day in groups I and II, respectively ($p = 0.188$).

Logistic regression was used to identify predictors of the development of deep vein thrombosis of the lower extremities. By building univariate models of logistic regression, some relevant predictors of the development of venous thromboembolism was identified: intestinal paresis ($p = 0.004$); absence of changes in neurological status ($p = 0.012$); oxygenation index ($p = 0.034$); number of days in the ICU ($p = 0.025$); number of days of hospital stay ($p = 0.039$); APTT index on the 7th day of follow-up ($p = 0.048$); and cardiovascular failure ($p = 0.050$).

It was found that the presence of intestinal paresis raises the chances of thrombosis by 15.20 [2.81; 125.53] times; the absence of positive changes in the neurological status – by 7.20 [1.64; 37.87] times; an increase in the length of stay in the ICU by k days – by 1.06^k [1.01^k; 1.12^k] times; increase in hospital stay by k days – by 1.04^k [1.01^k; 1.08^k] times; cardiovascular failure – by 5.14 [1.06; 30.31] times. In turn, an increase in the oxygenation index by k is associated with a reduced chance of thrombosis by 0.98k [0.96^k; 0.99^k] times, and an increase in the values of the APTT index on the 7th day of follow-up by k is associated with a decrease in the chances of thrombosis by 0.7^k [0.46^k; 0.95^k] times.

The building of a multivariate logistic regression model revealed a significant predictor of the development of thrombosis. It turned out that the presence of intestinal paresis was associated with an increased chance of developing deep vein thrombosis of the lower extremities by 25.07 [3.55; 523.50] times with the same indicators of chronic diseases of the respiratory system in patients in a multivariate model (Table 5).

Using ROC analysis, the best sensitivity indicators were determined for the multivariate model as 100.0 % and specificity as 53.8 % with the threshold value of the probability of developing deep vein thrombosis of the lower extremities at 27.0 % (Fig.).

A table of correspondence has been compiled (Table. 6), and the prognostic indicators of the model are calculated (Table 7) to study the prognostic features of a multivariate model of deep vein thrombosis of the lower extremities. The total number of patients in the multivariate model is 34.

To define the prognostic features of low-frequency piezothromboelastography, ROC analysis defined a threshold value of 2.85 min with the maximum amount of sensitivity and specificity for the difference of t5 values between the first and the third days. Deep vein thrombosis of the lower extremities was predicted in patients with a t5 difference of more than 2.85 minutes between the first and the third days. Indeed, deep vein thrombosis of the lower extremities developed in all the patients with a t5 difference of more than 2.85 minutes between the first and the third days. In patients with the difference of the indicator of less than 2.85 minutes, deep vein thrombosis of the lower extremities was absent in 64 % of cases and developed in 36 % of cases. The sensitivity of the prognosis was 67 %, the specificity and positive predictive value (ppv) were 100 %, and the negative prognostic value (npv) was 64 %.

Discussion

Patients with complicated injuries to the cervical spine are often exposed to prolonged circulatory failure affected by venous stasis in the lower extremities, associated with both disrupted innervation of the vascular wall and a decrease in the pumping ability of the muscles due to their paralysis. These factors, together with endothelial injury and hypercoagulation, are the main etiopathogenetic components defining the affinity of this category of patients to the group with the highest risk of venous thromboembolism [14–16].

Data on the venous thromboembolism rate in complicated spinal injuries vary significantly, from 1.6 to 80.0 %. This is due to the heterogeneity of studies that considered isolated spinal injury or combined injuries and polytrauma, injury to the cervical or thoracic spine, management of patients with or without pneumatic compression, and other clinical situations [16]. Most cases of venous thromboembolism occur during the first three months after injury. However, 21.2 % of patients with acute SCI already suffered from venous thrombosis at the stage of admission to specialized clinics [17, 18]. The incidence of venous thrombosis determined by us was 61.7 %, which, along with the timing of its occurrence, fully corresponds to the published data and does not contradict the data presented by us earlier [3, 19, 20].

ICU patients with injuries have hypercoagulation shifts in the hemostatic system that are recorded even during the convalescence period. Despite ongoing thromboprophylaxis, venous thromboembolism is recorded in more than 25 % of cases [21, 22]. The state of hypercoagulation in terms of low-frequency piezothromboelastography in the current study was found at admission in 18 (52.9 %) patients, with subsequent development of deep vein thrombosis of the lower extremities in 59 % of cases. Almost the same rate of detection of hypercoagulation shifts in the hemostatic system is provided by Kashuk et al. [23]. They studied the possibilities of the thromboelastography technique for diag-

Table 1

Changes of values of hemostasis laboratory tests and low-frequency piezothromboelastography in the general sample of patients

Value (normal)	the 1st day	the 3rd day	the 7th day	the 10th day	Wilcoxon test, p
	MED [Q1; Q3]	MED [Q1; Q3]	MED [Q1; Q3]	MED [Q1; Q3]	
Laboratory tests					
Activated partial thromboplastin time (25.4–36.9 sec)	25.30 [23.10; 27.00]	29.50 [26.30; 31.50]	28.30 [27.00; 30.40]	28.80 [26.90; 30.00]	1–3: <0.001* 1–7: 0.004* 1–10: <0.001* 3–7: 0.468 3–10: 0.979 7–10: 0.443
Prothrombin time (11–16 sec)	12.00 [11.20; 13.00]	12.10 [11.60; 13.10]	13.70 [12.80; 14.30]	14.50 [13.60; 15.60]	1–3: 0.339 1–7: <0.001* 1–10: <0.001* 3–7: <0.001* 3–10: <0.001* 7–10: 0.050
Fibrinogen (2–4 g/L)	3.10 [2.90; 3.70]	4.65 [3.80; 5.80]	6.11 [5.40; 6.80]	5.70 [5.40; 6.10]	1–3: <0.001* 1–7: <0.001* 1–10: <0.001* 3–7: 0.005* 3–10: 0.021* 7–10: 0.648
Platelets (150–350*10^9/L)	179.00 [143.50; 19.50]	136.00 [110.00; 174.50]	178.00 [139.00; 201.50]	217.00 [186.00; 262.00]	1–3: <0.001* 1–7: 0.980 1–10: <0.001* 3–7: <0.001* 3–10: <0.001* 7–10: <0.001*
Low-frequency piezothromboelastography values					
t5 (34 min)	30.30 [25.80; 45.80]	25.50 [21.40; 33.40]	32.10 [26.40; 45.00]	48.50 [18.40; 60.10]	1–3: 0.033* 1–7: 0.685 1–10: 0.839 3–7: 0.666 3–10: 0.191 7–10: 0.916
Maximum amplitude (510 relative units)	543.00 [446.00; 585.00]	536.00 [444.00; 610.00]	549.00 [470.00; 605.00]	592.00 [537.00; 691.00]	1–3: 0.588 1–7: 0.735 1–10: 0.093 3–7: 0.675 3–10: 0.294 7–10: 0.588
Intensity of retraction and lysis of the clot (0.29 %)	2.37 [-0.26; 4.14]	1.89 [0.21; 7.44]	3.04 [0.82; 7.98]	1.76 [0.92; 10.38]	1–3: 0.313 1–7: 0.641 1–10: 0.195 3–7: 0.945 3–10: 0.383 7–10: 0.945

* Statistically significant differences.

Table 2

Comparison of patients in the study groups according to the main studied features

Characteristics	Group I (n = 21)	Group II (n = 13)	Fisher's exact test, p
Gender, n (%)			
Male	19 (90.5)	11 (84.6)	0.627
Female	2 (9.5)	2 (15.4)	0.627
Injury reasons, n (%)			
Road traffic accident	5 (23.8)	4 (30.8)	0.704
Diving injuries of the cervical spine	10 (47.6)	5 (38.5)	0.728
Catatrauma	3 (14.3)	1 (7.7)	>0.999
Other	3 (14.3)	3 (23.1)	0.653
ASIA, n (%)			
A	14 (66.7)	8 (61.5)	>0.999
B	5 (23.8)	1 (7.7)	0.370
C	2 (9.5)	3 (23.1)	0.348
D	0 (0.0)	1 (7.7)	0.382
Neurological status, n (%)			
Quadriplegia	5 (23.8)	0 (0.0)	0.132
Triplegia	1 (4.8)	1 (7.7)	>0.999
Paraplegia	12 (57.1)	6 (46.2)	0.725
Monoplegia	0 (0.0)	1 (7.7)	0.382
Quadraparesis	3 (14.3)	5 (38.5)	0.211
Comorbidity, n (%)			
Cardiovascular system	6 (29)	4 (31)	>0.999
Respiratory system	8 (38)	2 (15)	0.251
Endocrine system	3 (14)	1 (8)	>0.999
Urinary track system	3 (14)	1 (8)	>0.999
Other	9 (43)	3 (23)	0.292

only a part of the total sample of patients, while in the study presented by us, all participants suffered spinal cord injury.

The increased lytic activity recorded in both groups indicates, in our opinion, the appropriate functioning of the hemostatic self-regulation system in response to the presence of structural and chronometric hypercoagulation. It should be noted that in the study group, which included patients without venous thromboembolism, the increase of lytic activity was by 5.5 times more pronounced. Such an increase in fibrinolysis system seems more typical for the studied category of patients. According to the data from previously performed experimental and clinical studies, stagnant blood has increased thrombolytic activity [24, 25].

There is data to show that the severity of the neurological deficit (paraplegia, quadriplegia) did not affect the incidence of venous thromboembolism [4]. Other academic sources report that venous thromboembolism is more common in the development of quadriplegia [17]. There is data indicating that decreased muscle strength in the lower extremities results in a 5-fold increase of the risk of deep vein thrombosis [1]. And the absence of a spastic increase in muscle tone is described as a risk factor for the development of venous thromboembolism [26]. In our study, all patients suffering from neurological deficit in the form of quadriplegia were included in Group I; patients with paraplegia were in both groups. During an intergroup comparison, no statistically significant difference in the severity of neurological disorders between the groups was

nosing hypercoagulation and predicting thromboembolism in surgical patients, including those with spinal cord injuries. According to TEG data, hypercoagulation was detected in 67 % of 152 surgical patients in critical condition. Subsequently, thromboembolic events were detected in 19 % of patients in the group with hypercoagulation. According to these findings, the authors concluded that the presence of hypercoagulation revealed by the TEG technique is a predictor of thromboembolism in surgical patients [23]. The lower incidence of thrombosis in comparison with the data collected by us can be explained by the fact that patients with spinal cord injury in the described study accounted for

Table 3

Statistically significant differences in the studied characteristics in the study groups

Values	Group I	Group II	Comparison	
	MED [Q1; Q3]	MED [Q1; Q3]	Pseudomedian [95 % CI]	Mann – Whitney U test, p
Mechanical ventilation, days	20.0 [10; 30]	1.0 [0; 10]	14.0 [2; 23]	0.006*
Duration of treatment in the ICU, days	40.0 [18; 45]	13.0 [5; 23]	19.1 [4; 35]	0.010*
Total length of hospital stay, days	63.5 [26.75; 70.00]	23.5 [15.75; 6.25]	19.0 [4.00; 49.00]	0.022*

The difference is represented by the median of pairwise differences with 95 % CI of the median.

* Statistically significant differences.

Table 4

Changes of values of laboratory tests and low-frequency piezothromboelastography in the study groups

Measured parameters	The 1st day MED [Q1; Q3]	The 3rd day MED [Q1; Q3]	The 7th day MED [Q1; Q3]	The 10th day MED [Q1; Q3]	Wilcoxon test, p
Activated partial thromboplastin time (normal 25.4–36.9 sec)					
Group I	25.00 [23.00; 27.90]	30.40 [26.30; 31.50]	27.40 [26.40; 29.80]	28.80 [27.00; 32.43]	1–3: 0.002* 1–7: 0.093 1–10: 0.009* 3–7: 0.080 3–10: 0.570 7–10: 0.102
Group II	25.70 [24.15; 6.62]	27.75 [25.98; 30.15]	29.25 [28.25; 33.15]	27.70 [26.65; 29.40]	1–3: 0.106 1–7: 0.008* 1–10: 0.030* 3–7: 0.055 3–10: 0.383 7–10: 0.461
Fibrinogen (normal 2–4 g/L)					
Group I	2.98 [2.88; 3.47]	4.40 [3.76; 5.54]	6.11 [5.50; 7.05]	5.60 [4.90; 6.36]	1–3: 0.002* 1–7: <0.001* 1–10: <0.001* 3–7: 0.012* 3–10: 0.032* 7–10: 0.551
Group II	3.52 [3.32; 3.90]	5.54 [3.85; 6.24]	5.95 [5.15; 6.58]	5.90 [5.70; 5.93]	1–3: 0.055 1–7: 0.014* 1–10: 0.008* 3–7: 0.195 3–10: 0.400 7–10: 0.888
Prothrombin time (normal 11–16 sec)					
Group I	11.80 [11.20; 12.30]	12.10 [11.60; 13.40]	13.70 [12.60; 14.30]	14.50 [13.50; 15.30]	1–3: 0.026* 1–7: <0.001* 1–10: 0.003* 3–7: 0.004* 3–10: 0.007* 7–10: 0.127
Group II	12.15 [11.78; 14.20]	12.05 [11.73; 12.27]	13.75 [12.88; 14.45]	14.5 [13.75;15.72]	1–3: 0.207 1–7: 0.461 1–10: 0.025* 3–7: 0.021* 3–10: 0.014* 7–10: 0.313
*Platelets (normal 150–35*10^9/L)*					
Group I	160.00 [127.75; 224.00]	124.50 [103.50; 62.25]	162.00 [130.50; 101.75]	199.00 [161.00; 254.25]	1–3: 0.002* 1–7: 0.616 1–10: 0.004* 3–7: 0.004* 3–10: <0.001* 7–10: 0.006*

The end of the Table 4

Changes of values of laboratory tests and low-frequency piezothromboelastography in the study groups

Measured parameters	The 1st day MED [Q1; Q3]	The 3rd day MED [Q1; Q3]	The 7th day MED [Q1; Q3]	The 10th day MED [Q1; Q3]	Wilcoxon test, p
Group II	188.00 [166.00; 201.00]	144.00 [136.00; 184.00]	180.00 [166.00; 201.00]	235.00 [217.00; 268.00]	1–3: 0.008* 1–7: 0.483 1–10: 0.008* 3–7: 0.009* 3–10: 0.009* 7–10: 0.004*
t5 (normal 34 min)					
Group I	38.20 [30.20; 57.10]	22.30 [21.10; 42.90]	37.20 [27.30; 65.00]	49.20 [31.40; 60.10]	1–3: 0.129 1–7: 0.820 1–10: 0.734 3–7: 0.734 3–10: 0.129 7–10: 0.859
Group II	26.05 [24.53; 28.58]	25.55 [24.50; 27.15]	28.15 [22.30; 35.10]	16.80 [15.15; 29.02]	1–3: 0.250 1–7: 0.875 1–10: 0.875 3–7: >0.999 3–10: 0.875 7–10: 0.875
Maximum amplitude (normal 510 relative units)					
Group I	544.00 [438.00; 593.00]	536.00 [444.00; 585.00]	551.00 [470.00; 605.00]	681.00 [570.00; 693.00]	1–3: 0.652 1–7: 0.734 1–10: 0.013* 3–7: 0.678 3–10: 0.044* 7–10: 0.250
Group II	542.00 [517.25; 553.50]	571.00 [488.25; 615.00]	507.50 [470.00; 571.00]	466.00 [429.25; 498.25]	1–3: 0.875 1–7: >0.999 1–10: 0.625 3–7: 0.875 3–10: 0.625 7–10: 0.375
Intensity of retraction and lysis of the clot (normal 0.29 %)					
Group I	0.76 [-0.33; 2.03]	1.89 [1.07; 6.14]	5.16 [0.67; 10.38]	1.24 [0.92; 3.12]	1–3: 0.375 1–7: 0.375 1–10: 0.625 3–7: >0.999 3–10: 0.875 7–10: 0.375
Group II	4.18 [2.94; 5.77]	1.97 [-0.29; 7.47]	3.04 [1.60; 5.03]	9.22 [1.67; 18.87]	1–3: 0.625 1–7: 0.875 1–10: 0.375 3–7: 0.875 3–10: 0.125 7–10: 0.625

* Statistically significant differences.

Table 5

Logistic regression model of deep vein thrombosis of the lower extremities for all patients

Covariat	Univariate models		Multivariate models	
	OR [95 % CI]	p	OR [95 % CI]	p
Intestinal paresis	15.20 [2.81; 125.53]	0.004*	25.07 [3.55; 523.5]	0.006*
Chronic diseases of the respiratory system	3.38 [0.67; 25.67]	0.171	7.58 [0.89; 184.78]	0.110

OR — odds ratio.

* Statistically significant differences.

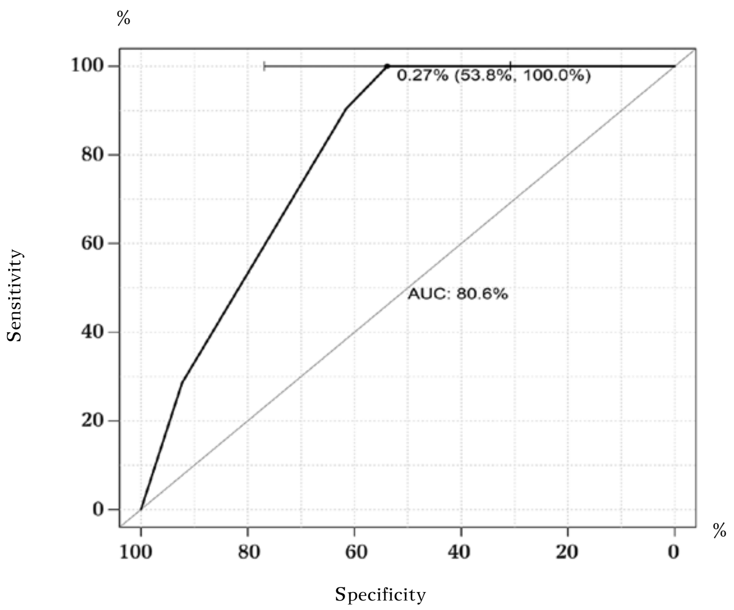

Fig.
ROC curve for a multivariate model of deep vein thrombosis of the lower extremities in all patients

revealed. In this regard, we cannot draw similar conclusions.

Although venous thromboembolism is typical for acute SCI, its incidence and contributing factors remain understudied and, in some cases, contradictory [4]. For example, when determining risk factors for venous thromboembolism in patients with cervical spinal cord injury, Lv et al. [1] found that the incidence of deep vein thrombosis was 21.71 %. According to multivariate regression analysis, the main risk factors for the development of venous thrombosis were a decrease in muscle strength in the lower extremities to less than three points at admission to the hospital, time from injury to admission, and D-dimer level. Meanwhile, the diagnostic consideration of the D-dimer turned out to be the highest [1]. According to our study, the concentration of D-dimer, which is formed during fibrin degradation in the process of fibrinolysis, was increased in both groups. Nevertheless, the informative value of this indicator in the studied category of patients, as we noted earlier, is limited due to the fact that the reason for the increased concentration of D-dimer is often severe infectious complications associated with acute and subacute courses of complicated cervical spine injury [19]. This is confirmed by the absence of statistically significant differences in the level of D-dimer between the study groups of patients at all stages of the study. Thus, lower extremity ultrasound, especially when detecting elevated level of D-dimer, is considered to be the most objective technique to diagnose thrombosis.

A number of researchers provide other highly relevant factors associated with postoperative thromboembolism: the length of stay in the intensive care unit ($p < 0.001$), the number of days on mechanical ventilation ($p < 0.001$) and the length of hospital stay ($p < 0.001$) [23]. Delayed admission of patients to a specialized clinic was found to have a negative impact on the incidence of venous thromboembolism [17].

There are reports that the following factors are closely associated with the risk of venous thromboembolism: age, male gender, type and severity of injury, presence of paraplegia, history of thrombosis, smoking, including the use of smokeless tobacco and prohibited substances, serum homocysteine level, D-dimer level and Leiden mutation, the gene responsible for the synthesis of blood coagulation (Factor V) [18]. Even the patients' low socioeconomic background is linked to a higher risk of developing venous thromboembolism following spinal cord injury, as a result of an increase in comorbidities or the presence of diseases undetected before the injury. Also, the body mass index had a strong tendency to significance [4].

The authors of the meta-analysis [18], performed in 2023 and including 25 research papers, showed that the risk of

Table 6

Contingency table of the multivariate model of deep vein thrombosis of the lower extremities in all patients

Prognosis	Real data		Total
	«+»	«-»	
«+»	21	6	27
«-»	0	7	7
Total	21	13	34

Table 7

Prognostic values of a multivariate model of deep vein thrombosis of the lower extremities

Characteristics	Value [95 % CI], %
Frequency of cases of the method	79.4 [62.1; 91.3]
Actual frequency of cases	61.8 [43.6; 77.8]
Sensitivity	100.0 [83.9; 100.0]
Specificity	53.8 [25.1; 80.8]

venous thromboembolism in patients with spinal cord injury is considerably associated with middle and old age (OR = 2.08; 95 % CI [1.47; 2.95]); male gender (OR = 1.41; 95 % CI [1.26; 1.59]); complete paralysis (OR = 3.69; 95 % CI [2.60; 5.24]); personal/family history of venous thrombosis (OR = 1.95; 95 % CI [1.35; 2.81]); smoking (OR = 2.67; 95 % CI [1.79; 3.98]); lack of compression therapy (OR = 2.44; 95 % CI [1.59; 3.73]); the presence of a fracture of the lower extremity/pelvis (OR = 3.47; 95 % CI [1.79; 6.75]); paraplegia (OR = 1.81; 95 % CI [1.49; 2.19]) and diabetes (OR = 4.24; 95 % CI [2.75; 6.52]).

We have not found most of the prognostic factors identified by building of univariate models of logistic regression in the analyzed academic papers. These were intestinal paresis (p = 0.004), absence of positive changes in neurological status (p = 0.012), oxygenation index (p = 0.034), APTT index on the 7th day of follow-up (p = 0.048) and cardiovascular failure (p = 0.050). As for the “intestinal paresis” predictor, it was also included into the multivariate model of deep vein thrombosis of the lower extremities. It has been shown that the presence of intestinal paresis is associated with a 25.07-fold increase in the risk of developing deep vein thrombosis of the lower extremities. The established negative clinical significance of intestinal paresis can be explained by an increased intra-abdominal pressure with blood circulatory disturbance in the inferior vena cava, which with the lack of function of the musculoskeletal pump of the shins even more worsens the phenomenon of blood stasis in the veins of the lower extremities [24, 25].

The hemostatic system is a complex physiological process involving the interaction between blood cells, dissolved in the plasma by coagulation and anticoagulation factors, and endothelial cells [27]. Standard coagulation tests are not always informative. However, thromboelastography provides data on the status of the coagulation system in a particular patient at a specific time. In our study, it was demonstrated that the analysis of the indicators of low-frequency piezothromboelastography can detect the state of hypercoagulation. In terms of the time to reach the maximum amplitude of the clot (t5) associated with the risk of venous thrombosis, the ROC analysis selected a threshold value with the highest sensitivity and specificity.

Undoubtedly, the performed research has certain limitations. First of all, this is a single-center retrospective study with a small sample size. Secondly, some significant patients’ features were not included in the study. Thirdly, the study had a time frame limited only by the period of follow-up in the ICU. From this point of view, the application of the findings of the study to other specialized clinics may be inaccurate.

Conclusion

Considering the high incidence of venous thromboembolism in patients with complicated cervical spine injuries despite ongoing thromboprophylaxis measures, established prognostic factors for the development of venous thrombosis and the diagnostic capabilities of low-frequency piezothromboelastography, which indicates the presence of hypercogulation disorders in the hemostatic system, further prospective cohort studies are required aimed at study the effectiveness and safety of correction of drug thromboprophylaxis regimens in the form of increasing doses of anticoagulants or the frequency of their administration.

The study had no sponsors. The authors declare that they have no conflict of interest.
The study was approved by the local ethics committee of the institution. All authors contributed significantly to the research and preparation of the article, read and approved the final version before publication.

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