



Effect of Prehospital Pause on the Outcomes of Emergency Decompression and Stabilization Procedures in Patients with Tumor and Infectious Spine Diseases

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Purpose – to assess the relationship between duration of pathological symptoms developed due to tumor or infectious destruction of the spine, and the medium-term outcomes of urgent surgeries.

Methods: 84 patients with tumor (group 1, n = 43) and infectious (group 2, n = 41) lesions of the spine underwent decompression and stabilization procedures according to urgent indications in the period from 2016 to 2018. Neurological status (Frankel scale), pain intensity (VAS) and functional independence of patients (Karnofsky scale) were assessed before surgery, 3 months and 1 year after. Statistical relationship between outcomes and duration of the prehospital and hospital delay has been studied.

Results: 23 patients in each group had neurological deficit (53.5% and 56.1%), while the average duration of the prehospital period in those patients in both groups (Me) was 14.0 days. 11 out of 84 patients (13.1%), were hospitalized in the first 72 hours from the onset of vertebral syndrome; 6 (7.1%) of them had neurological disorders. An inverse correlation of high strength between the duration of neurological deterioration and the possibility of their improvement by 3 months after surgery was revealed in both groups ($r_{s1} = -0.793$ and $r_{s2} = -0.828$; $p < 0.001$) and there was no relationship between outcomes and the duration of the hospital period (surgery urgency) ($r_{s1} = -0.257$; $p = 0.283$ and $r_{s2} = -0.218$; $p = 0.330$). The possibility of neurological improvement after surgery ceases to be statistically significant after 14 days from the onset of pathological symptoms ($p_1 = 0.083$, $p_2 = 0.157$ for both groups, respectively), while the likelihood of a decrease in pain syndrome and functional dependence on others remains independent of the duration of the prehospital period.

Conclusions: In case of tumor or infectious spine lesions, urgent decompression and stabilization procedures reduce pain and improve the functional independence regardless of the duration of the prehospital period, while extension of prehospital period of more than 2 weeks is crucial for a reliable prognosis of neurological status improvement.

Keywords: destructive lesions of the spine, spondylitis, spondylodiscitis, metastatic spinal cord compression, decompression and stabilization surgeries.

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Влияние догоспитальной паузы на исходы неотложных декомпрессивно-стабилизирующих операций у пациентов с опухолевым и инфекционным поражением позвоночника

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Реферат

Цель исследования — оценить связь между длительностью вертеброгенной симптоматики, развившейся на фоне опухолевой или инфекционной деструкции позвоночника, и среднесрочными и отдаленными исходами операций, проведенных по неотложным показаниям. **Материал и методы.** 84 пациентам с опухолевым (группа 1, $n = 43$) и инфекционным (группа 2, $n = 41$) поражением позвонков по неотложным показаниям выполнены декомпрессивно-стабилизирующие операции. Неврологический статус (шкала Frankel), интенсивность болевого синдрома (визуально-аналоговая шкала, ВАШ) и функциональная независимость пациентов (шкала Карновского) оценены перед операцией, спустя 3 мес. и 1 год. Изучена статистическая связь исходов лечения с длительностью догоспитальной и госпитальной пауз.

Результаты. Неврологические нарушения на момент операции имели 23 пациента в каждой группе (53,5% и 56,1%); средняя длительность догоспитального периода у них (Me) составила 14,0 сут. Лишь 11 из 84 пациентов (13,1%) госпитализированы в первые 72 ч. после возникновения вертебрального синдрома, в т.ч. 6 (7,1%) с неврологическими расстройствами. Выявлена обратная корреляционная зависимость высокой силы между длительностью неврологических нарушений и возможностью их улучшения к 3 мес. после операции в обеих группах ($r_{s1} = -0,793$ и $r_{s2} = -0,828$; $p < 0,001$), а также отсутствие связи таких исходов с длительностью госпитального периода (экстренностью проведения операции) ($r_{s1} = -0,257$; $p = 0,283$ и $r_{s2} = -0,218$; $p = 0,330$). При госпитализации в сроки более 14 сут. от возникновения симптоматики возможность неврологического улучшения после операции перестает быть статистически значимой для обеих групп ($p_1 = 0,083$, $p_2 = 0,157$ соответственно), в то время как вероятность уменьшения болевого синдрома и функциональной зависимости от окружающих сохраняется независимо от длительности догоспитального периода. **Заключение.** При опухолевой и инфекционной деструкции позвонков неотложные декомпрессивно-стабилизирующие операции приводят к значительному уменьшению болевого синдрома и улучшению функциональной независимости пациентов в сроки 3 и 12 мес. после операции независимо от длительности догоспитального периода. Длительность догоспитального периода более 2 нед. является критической для прогнозирования улучшения неврологических расстройств после таких вмешательств.

Ключевые слова: деструктивные поражения позвоночника, спондилит, спондилодисцит, метастатическая компрессия спинного мозга, декомпрессивно-стабилизирующие операции.

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Background

In 2019, the incidence rate of malignant neoplasms in Russia was 436.0 per 100,000 population [1]. Metastatic spinal lesions are registered in >20% of these patients and 5%–10% of cases are accompanied by metastatic spinal cord compression syndrome (MSCC) and neurological disorders [2, 3]. An acute vertebral syndrome is quite often the first manifestation of a tumor lesion, as >40% of patients in primary hospitalization in the spinal departments do not have an oncological history [4, 5]. As an interdisciplinary problem that requires a comprehensive oncological and neurosurgical, as well as traumatological and orthopedic approach, the adoption of decisions on approach is often delayed for a long time, increasing the risk of an unfavorable treatment outcome of this pathology in general [6].

The incidence of acute infectious lesions of the spine (spondylitis/spondylodiscitis) is 1.0–2.5 cases per 100,000 population, of which 5.8%–14.6% are complicated by sepsis and 1.2%–8.0% of cases lead to lethal outcomes [7, 8, 9]. The incidence of neurological disorders, in this case, ranges from 27.0% to 46.2% [10, 11]

Some patients with spinal tumor or infectious lesions in the presence of a high risk of a significant deterioration in the general condition and quality of life require emergency care. These conditions include the following [12, 13, 14, 15, 16]:

- the occurrence and/or increase in neurological symptoms due to compression myelo-, caudo-, or radiculopathy (spinal compression syndrome);
- instability of the spine, accompanied by an intense pain syndrome and the risk of compression of the spinal structures (instability syndrome).

The development of emergencies in vertebrology often implies the absence of a confirmed etiological diagnosis in a patient; therefore, emergency care mainly targets spinal cord decompression and spinal stabilization, i.e., medical care is provided not according to the etiological but according to the syndromic principle.

The surgery performed within the first 72 h after the onset of acute, primarily neurological disorders, is believed to provide the best outcomes for spinal metastatic lesions treatment [17]. However, in a real situation, patients are extremely rarely hospitalized within the indicated periods, which are due to both their low awareness of the need for early examination by a vertebrologist with minimal complaints and insufficient alertness of doctors at the initial pathologic manifestations. Concurrently, the duration of clinical complaints preceding hospitalization in specialized departments (the so-called prehospital pause) can af-

fect not only the well-being and quality of life of patients but also the treatment outcomes. Assuming a certain relationship between these parameters is logical: however, this has not been previously studied.

This study aimed to evaluate the relationship between the duration of vertebrogenic symptoms that developed in the presence of a spinal tumor or infectious destruction and the medium- and long-term surgical outcomes performed for urgent indications.

Methods

Study design

Figure 1 presents a block diagram of the selection of patients for the study. The primary sample was retrospectively formed based on a two-center cohort of patients aged 18 years and older with acute pathology of the thoracic and lumbar spine, who received emergency treatment in the departments of traumatology and orthopedics, neurosurgery of I.I. Dzhanelidze Research Institute of Emergency Medicine and the Pavlov State Medical University of Saint Petersburg (total base 841 patients). Both hospitals work 24/7 according to a unified system for providing emergency care to patients with spinal pathology in St. Petersburg. The period for collecting material was related to the direct work of the main authors of the publication (authors 1, 3) in these institutions during the period specified.

When forming the analyzed sample, 649 patients were excluded from the general database based on the nature of the disease, 91 patients due to the nature of the surgical intervention (non-decompressive-stabilizing surgeries), and 17 patients due to unsuitable medical documentation or archive of X-ray data for analysis. Thus, the final analyzed sample was retrospectively formed, including 84 patients who, in presence of tumor (group 1, $n = 43$) or infectious (group 2, $n = 41$) lesions of the vertebrae, underwent decompressive-stabilizing surgeries for emergency indications.

The study subject was the assessment of the dynamics of the parameters that are most reproducible in the condition analysis of patients with spinal pathology in need of urgent surgical treatment. Neurological status was assessed using the Frankel scale (types A-E), included in the AIS/ASIA standard for the study of patients with spinal cord injury/lesion [17, 18, 19]. The pain syndrome severity was assessed subjectively using a visual analog scale from 0 to 10 points. The functional independence of patients was assessed using the Karnofsky scale from 10 to 100 points, where 100 points means complete independence in the absence of any functional restrictions for self-service and movement [20].

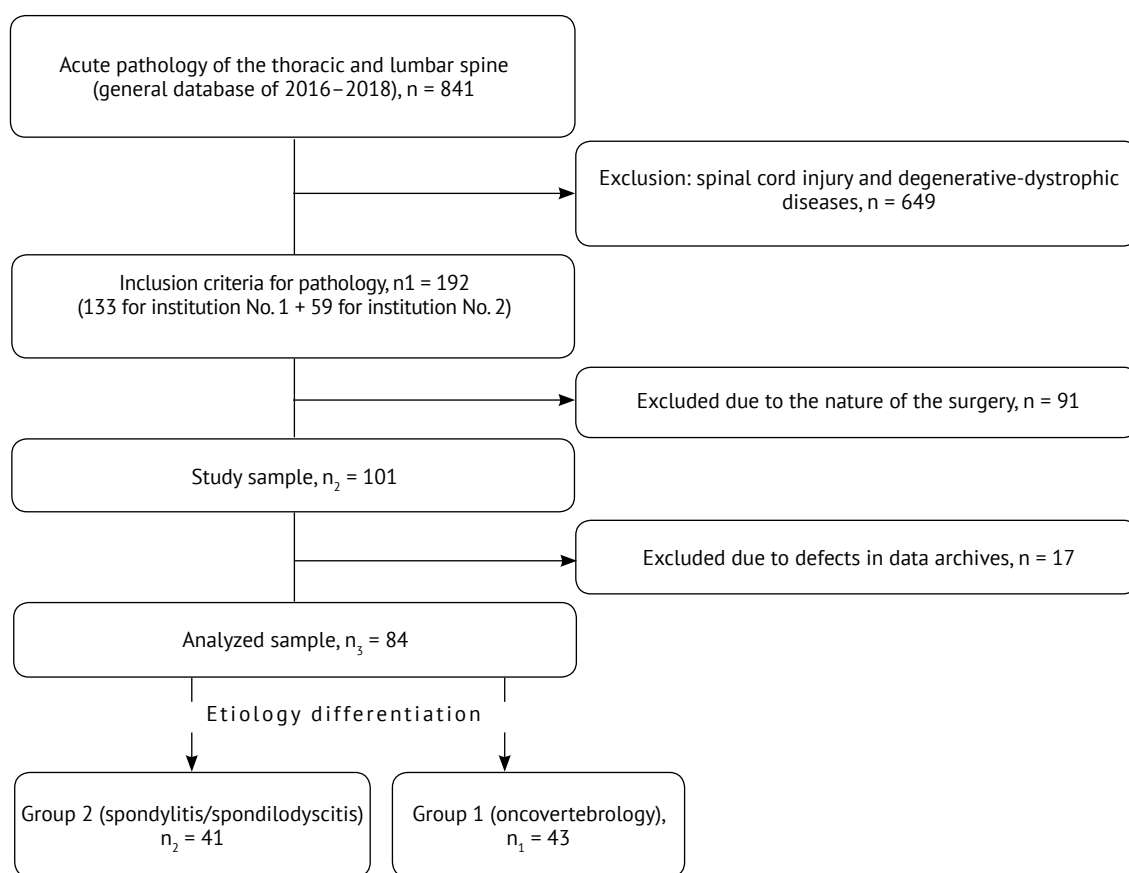


Fig. 1. Patient selection flowchart

These parameters were entered into the medical documentation during hospitalization and clinical control at 3 and 12 months after emergency surgery. The most convenient time for evaluating the so-called medium-term results of treatment is at 3 months postoperatively, since such period of predicted survival is considered as a criterion for the possibility of performing “major” spinal surgeries for tumor lesions [21], and L. Lenke et al. believe that a stable level of somatic nutritional recovery of the patient is formed after any of spinal reconstructions in this period [22].

The statistical relationship of treatment outcomes with the prehospital pause duration was studied, i.e., with the timing of the development of the condition that led to the hospitalization of the patient; the term “pause” seems to us more convenient than the concept of “delay” adopted in the English literature [23].

Statistical analysis

The statistical processing of the material was performed in the International Business Machines Statistical Package for the Social Sciences (IBM SPSS) Statistics 22 program. The nature of the distribution of quantitative parameters in groups was assessed using the nonparametric Kolmogorov–Smirnov test. The significant changes in the indicator within the

groups were tested using the Wilcoxon test and that of intergroup differences was tested using the Mann–Whitney U-test with an abnormal distribution or the t-test (after assessment of the Levene test for homogeneity of variances [$p > 0.05$]) and in the case of normal quantitative data distribution (age of patients). The correlation between the parameters and the duration of the prehospital and hospital pauses primarily changes in the neurological status of patients who had such disorders during admission was studied. The influence of factors on treatment outcomes in each group was assessed using a two-sided Spearman correlation analysis r_s with correlation strength determination (<0.3 indicated as weak, 0.3–0.7 meant medium, and 0.7 and more indicated strong) and its orientation due to the abnormal distribution of the analyzed parameters.

The analyzed factors using the Spearman correlation include 1) the number of days from the moment of manifestation of urgent vertebral syndrome to the hospitalization or the moment of hospitalization to surgery and 2) change in the neurological status over time.

The types of the Frankel scale were assigned numerical values (points) (A was 1, B was 2, C was 3, D was 4, and E was 5) in statistical analysis, and changes in the indicator were assessed at 3 and 12

months after the surgery, both in comparison with the baseline and among themselves. A multiple regression model was used to test the results (dependent variable was Frankel dynamics; and the independent variable was days from the moment of hospitalization to surgery, days from the moment of deterioration to hospitalization) using the logarithmic transformation function of independent variables SPSS (Ln). Given the two independent analyzed variables, the backward stepwise method was chosen. The data of the standard β -coefficient of the regression model with the construction of scatterplots is presented to determine the strength and type of relationship. Changes were considered statistically significant at $p < 0.05$.

The mean values of the parameters in the groups were calculated using the descriptive statistics method (the results are presented for normal distribution as $M \pm \sigma$ [where M is the mean value, σ is the standard deviation], as well as Me [Q25; Q75] (Me is the median, the first and third quartiles)) for non-normal distribution of data. Thus, within the retrospective two-center cohort study, the methodologies of factorial (PPO) and comparative analysis were used.

Detailing the options for surgical interventions is not the subject of analysis, and their clarification is not given in this work. We consider it fundamental that patients with MSCC syndrome complicated by neurological disorders underwent decompressive-stabilizing interventions stabilizing or reconstructive-stabilizing surgeries in case of instability without neurological disorders; radical sanitizing, if possible, including decompressive and stabilizing surgeries in infectious processes.

Results

The distribution of patients by gender, age, and nature of urgent vertebrogenic syndrome, which caused emergency hospitalization, is presented in Table 1.

From 3 to 12 months, 8 patients died after the surgery due to disease progression or other causes, including 7 patients from group 1 (during hospitalization 6 of them had neurological disorders of varying severity, namely Frankel A–D) and 1 patient from group 2 who had baseline paraplegia, type Frankel A.

In group 1, during the emergency hospitalization, only 22 (51%) patients had a known oncological history (Fig. 2).

Table 1

Distribution of patients by gender, age, and nature of urgent vertebrogenic syndrome

Etiology	Mean age ($M \pm \sigma$)	Gender, n (%)	Major clinical symptom	
			Neurological disorders	Pain syndrome
Tumor lesion	58.91±12.63	male – 25 (58%); female – 18 (42%)	23 (53%)	20 (47%)
Nonspecific spondylitis/ spondylodiscitis	58.05±15.45	25 (61%); 16 (39%)	23 (56%)	18 (44%)
p-value	0.781*	0.792**	0.811**	
Total			46 (55%)	38 (45%)

* – t-test; ** – Mann–Whitney U-test.

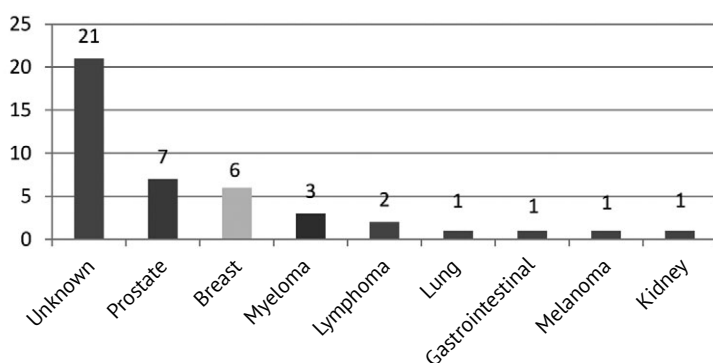


Fig. 2. Distribution of patients with metastatic vertebral fractures by types of primary tumors (localization) at the time of emergency admission

Our data analysis drew attention to the real situation with early hospitalization of patients with urgent vertebral pathology, which is extremely far from ideal. Initially, the chronometric ranking of the prehospital stage was performed considering the criterion recommended for urgent care at 72 h from the onset/increase of neurological deficit [15] (Table 2).

During hospitalization, 23 out of 43 patients in group 1 had neurological disorders of varying severity, while only 10 of them were hospitalized in emergency spinal surgery centers at week 1 after the onset of vertebral syndrome and only 6 in the first 72 h. During hospitalization, of the 41 patients with infectious spondylitis, 23 also had neurological disorders, of which 11 were hospitalized in the first 7 days and 5 in the first 72 h.

Therefore, in the first 3 days, only 11 (13.1%) of 84 patients in both groups were hospitalized. Only 6 (7.1%) of them had neurological disorders (types A-D according to Frankel), and recommendations for early decompressive surgery aimed at achieving regression of severe neurological disorders (lower paraplegia) could potentially be used in 3 (3.6%) patients [15].

The main chronometric indicators of patients in both groups, differentiated according to the presence or absence of neurological disorders in the patient, are presented in Table 3.

Comparison of indicators of neurological disorder severity, pain syndrome severity, and functional dependence on others are presented in Tables 4 and 5.

The results of neurological status changes are presented only 3 months after the surgery due to the absence of significant differences after 3 and 12 months,

which was statistically confirmed with $p = 0.317$ for group 1 and $p = 0.083$ for group 2.

Thus, significant positive neurological status changes were noted in patients with metastatic lesions both in severe plegia (type B according to Frankel) and mild paresis (type D), whereas in infectious spondylitis group only in patients with mild paresis. Concurrently, significant positive changes were noted by the end of the follow-up in both the pain syndrome severity and the Karnofsky score in both nosological groups.

The correlation analysis revealed a strong inverse relationship between the duration of neurological disorders before hospitalization and a possible improved neurological status after surgery in both groups ($r_s = -0.828$ and $r_s = -0.822$; $p < 0.001$), which was quite expected. Unexpectedly, no relationship was found between such outcomes and hospital period duration before the surgery, i.e., with surgical urgency ($r_s = -0.082$; $p = 0.711$ and $r_s = -0.223$; $p = 0.306$). The data were confirmed by the regression analysis results (Table 6, Figs. 3, 4).

The duration of the prehospital period was ranked by 7-day intervals for statistical analysis due to the small number of hospitalized patients within the first 72 h after the onset of symptoms. The distribution of patients is presented in Table 7.

The subsequent analysis revealed that for both clinical groups with a hospitalization period of >14 days from the appearance of complaints, the possibility of improving the neurological deficit ceases to be statistically significant ($p = 0.083$ for tumor lesions and $p = 0.157$ for infectious ones), while the probability of their improvement remains for any prehospital period duration for pain syndrome and the Karnofsky scale (Table 8).

Table 2

The distribution of patients with spinal tumor and infectious lesions, according to the nature of neurological disorders, hospitalized within the first 72 h after the onset of complaints

Severity of neurological disorders according to Frankel	Group 1	Group 2
A	–	–
B	3	–
C	1	–
D	–	2
E	2	3
Total	6	5

Table 3

Main chronometric indicators of the prehospital stage

Chronometric indicator	Values of the indicator, days		p-value, Mann-Whitney test
	Me (Q25; Q75)	(min; max)	
For patients with neurological deficit			
from the moment of deterioration to hospitalization group 1 (n = 23) group 2 (n = 23)	14.0 (6.0; 19.0) 14.0 (7.0; 24.0)	(2; 26) (3; 71)	0.230
from hospitalization to surgery group 1 (n = 23) group 2 (n = 23)	2.0 (1.0; 3.0) 2.0 (1.0; 3.0)	(0; 9) (1; 4)	0.422
from the moment of deterioration to the surgery group 1 (n = 23) group 2 (n = 23)	16.0 (8.0; 23.0) 17.0 (10.75; 26.25)	(3; 29) (5; 75)	0.642
For patients without neurological impairment			
from the moment of deterioration to hospitalization group 1 (n = 20) group 2 (n = 18)	22.5 (14.25; 40.0) 14.5 (6.25; 30.0)	(2; 80) (3; 45)	0.048
from hospitalization to surgery group 1 (n = 20) group 2 (n = 18)	3.0 (2.0; 7.5) 5.0 (3.75; 6.0)	(1; 14) (1; 14)	0.126
from the moment of deterioration to the surgery group 1 (n = 20) group 2 (n = 18)	33.5 (16.0; 45.75) 20.0 (13.50; 33.25)	(6; 84) (5; 50)	0.077

Table 4

The distribution of patients according to the nature of neurological disorders

Severity of neurological disorders according to Frankel	Group 1 (n = 43)			Group 2 (n = 41)		
	Admission	After 3 months	p	Admission	After 3 months	p
A	1	1		1	1	
B	6	1	0.034	3	2	0.317
C	4	1	0.063	3	1	0.083
D	12	10	0.005	16	8	0.001
E	20	30	1.0	18	29	1.0

Table 5

The distribution of patients according to the pain syndrome severity and functional dependence on others with the Wilcoxon test significant assessment

Assessed criterion of quality of life	Group 1 (n = 43)				Group 2 (n = 41)			
	Admission (t1)	3 months (t2)	12 months (n = 36) (t3)	p (t1,2) p (t2,3)	Admission (t1)	3 months (t2)	12 months (n = 40) (t3)	p (t1,2) p (t2,3)
Pain intensity (Mean ± SD)	7.56±1.24	2.37±1.12	1.67±1.28	<0.001 0.002	6.80±1.36	2.20±0.98	1.88±1.06	<0.001 0.005
Karnofsky score (Mean ± SD)	56.74±17.83	80.23±14.56	83.61±13.12	<0.001 0.346	54.15±13.41	76.10±16.41	79.00±15.15	<0.001 0.046

Table 6

Assessment of linear regression scores

Model	Independent variables	Standardized β coefficients (groups 1; 2)	Significance (groups 1; 2)
1	Days from deterioration to hospitalization (Ln) Days from hospitalization to surgery (Ln)	-0.803; -0.723 0.223; -0.107	<0.001; <0.001 0.149; 0.484
2	Days from deterioration to hospitalization (Ln)	-0.749; -0.741	<0.001; <0.001

Dependent variable: Frankel dynamics.

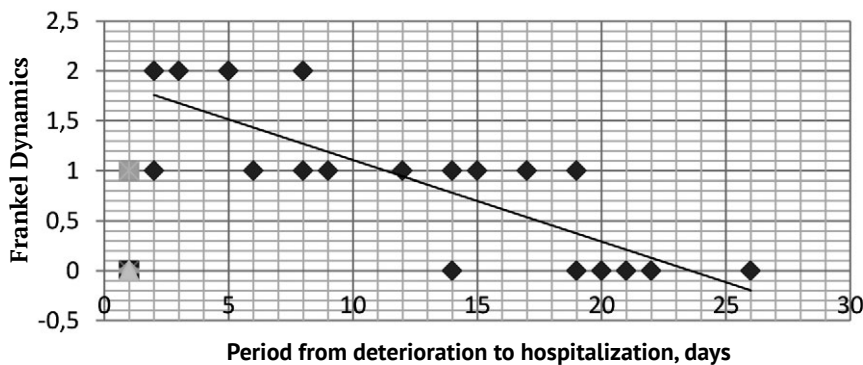


Fig. 3. Scatter plot for the analyzed factors of group 1

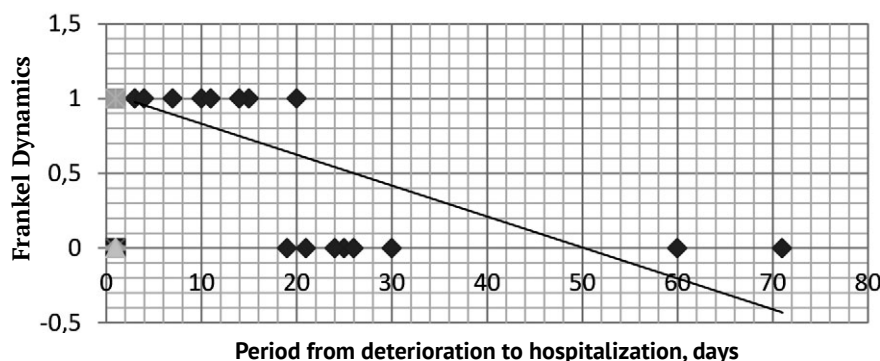


Fig. 4. Scatter plot for the analyzed factors of group 2

Table 7

The distribution of patients of groups 1 and 2 over the 7-day intervals

Duration of the prehospital period	Group 1		Group 2	
	n	%	n	%
≤7 days	10	24	11	26
>7, но ≤ 14 days	9	20	11	29
> 14 days	24	56	19	45
Total	43	100	41	100

Table 8

Changes in neurological state, pain syndrome severity, and functional dependence on others depending on the duration of prehospital complaints

Prehospital duration of vertebral syndrome	Wilcoxon test value (months 3/12)					
	Group 1			Group 2		
	Frankel	VAS	Karnofsky scale	Frankel	VAS	Karnofsky scale
≤7 days	0.014/0.083*	0.005/0.027	0.005/0.026	0.014/0.020	0.003/0.003	0.003/0.003
7–14 days	0.011/0.011	0.008/0.007	0.007/0.011	0.008/0.011	0.003/0.003	0.003/0.003
>14 days	0.083/0.083	<0.001/<0.001	<0.001/<0.001	0.157/0.083	<0.001/<0.001	<0.001/<0.001

* The Wilcoxon test value was $p = 0.083$ in group 1 for patients hospitalized in week 1 from the onset of vertebral syndrome, probably associated with the death of 4 out of 10 patients who had positive ranks when assessed after 3 months.

Discussion

In the context of planned surgical care for patients with spinal destructive lesions, verification of the tumor or infectious etiology of the process is of fundamental importance, and the doctor has a certain amount of time for diagnostic procedures and the choice of etiologically justified treatment. Contrarily, under urgent conditions, verification is usually simultaneously performed with the elimination of spinal

cord compression syndromes and spinal instability, which, in the case of a retrospectively established tumor process, becomes the subject of discussion about the priority of one or another component of the neurological, oncological, or mechanical strategy in the choice of approach [24].

In the medical literature, the issues of postoperative regression of neurological complications in the presence of a vertebral tumor and infectious lesions

are usually analyzed depending on the hospital pause duration, i.e., from the patient's admission to the hospital. Moreover, if most authors promptly recommend assisting such patients [5, 8, 12, 15] then the results of such assistance are assessed extremely ambiguously. Both the benefit of early surgical treatment [25] and the lack of fundamental advantages of early (relative to the time of hospitalization) spinal cord surgical decompression have been indicated [26, 27]. The characteristic of the prehospital pause duration in such patients is not discussed i.e., initially, an ideal clinical situation is considered, which involves patient hospitalization when the first signs of vertebral pathology appear, primarily neurological disorders, which is extremely far from reality according to our study.

Problems of adequate routing of such patients exist not only in Russia but researchers from the Netherlands and Canada are now paying attention to this [23]. Patients from risk groups, primarily oncological (primary and secondary immunodeficiency can also be included) with complaints of spinal pathology characteristics are monitored for days and sometimes weeks by neurologists, traumatologists, and oncologists against the increasing symptoms. Our data revealed that under conditions of such a metropolis as St. Petersburg, almost half of patients are admitted to spinal centers later than 2 weeks after the onset of vertebral, including neurological symptoms, and only 13.6% of patients are admitted within the first 3 days. This disables the statistical confirmation or refutes the thesis about the early decompression efficiency in the analyzed category of patients. However, if the duration of neurological disorders is >14 days, the possibility of their regression after surgery becomes statistically insignificant (i.e., unpredictable). This does not exclude the possibility of regression of disorders during surgeries performed at a later date but considers 2 weeks as an additional critical criterion for an objective treatment outcomes prognosis of this pathology.

The shorter duration of the prehospital pause that we noted in group 2 without neurological disorders may be associated with greater pain intensity in presence of a local inflammatory process (the task of testing this hypothesis was not set in this study).

Regardless of the prehospital period duration, emergency treatment significantly reduces pain and improves the functional independence of patients, while the positive dynamics of these indicators are noted throughout the year after surgery. An important and unexpected study result was not the confirmation of a strong inverse correlation between the duration of neurological disorders and the possibility of their regression after surgery, but the absence of such relationship with the hospital preoperative duration, i.e., with surgical urgency.

Conclusions

The analysis of the influence of specialized medical care timing on such criteria as functional dependence revealed that the severity of pain syndrome and the possibility of regression of neurological disorders is important not only for an objective prognosis of treatment outcomes of patients with spinal tumor and infectious pathology but also for optimizing the system to provide them with specialized care. Firstly, informing the patients from risk groups (a cohort of oncological dispensaries, patients with immunodeficiency conditions) about the possibility of a secondary spinal lesion in them and the possibility/necessity of early contact with specialized spinal clinics is necessary. Reducing the hospitalization time of patients in such hospitals requires the development of regional recommendations on routing, primarily for neurologists and trauma orthopaedists.

In our opinion, information and organizational solutions can provide a more significant medical and social effect for such patients than the improved certain urgent surgical interventions. Timely referral of patients to specialized clinics before the development of an emergency condition will provide a sufficient reserve of time for a comprehensive diagnostics of spinal destructive lesions (including before the onset of severe neurological disorders that have the least potential for recovery) and the choice of not only syndromic but also etiologically justified treatment.

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Mushkin A.Yu. — developed the concept and design of the article, reviewed the literature, wrote and edited the text.

All authors read and approved the final version of the manuscript. All authors agree to be responsible for all aspects of the work to ensure proper consideration and resolution of all possible issues related to the correctness and significance of any part of the work.

Conflict of interest:

The authors declare no conflict of interest.