

# LONG-TERM RESULTS OF TREATMENT OF PATIENTS WITH MONOSEGMENTAL STENOSIS OF THE SPINAL CANAL IN THE LUMBAR SPINE

Sh.A. Akhmetyanov, A.A. Azizkhonov, E.A. Mushkachev, A.J. Sanginov, I.D. Isakov, A.V. Peleganchuk Novosibirsk Research Institute of Traumatology and Orthopaedics n.a. Ya.L. Tsivyan, Novosibirsk, Russia

**Objective.** To evaluate the long-term results of surgical treatment of patients with monosegmental stenosis of the lumbar spine after using minimally invasive and standard open techniques.

Material and Methods. The open cohort randomized prospective study included 132 patients. Long-term results were assessed in 110 patients, some patients discontinued participation in the study for natural reasons. Patients were operated on in 2009—2011 in the volume of minimally invasive decompression and stabilization surgery (Group 1) and decompression and stabilization surgery through conventional posteromedial approach (Group 2). The following parameters were analyzed: Oswestry Disability Index and VAS pain intensity. Formation of an interbody block was assessed using the Tan scale, and the fatty degeneration of the paravertebral muscles — according to the Goutallier scale. Development or aggravation of the course of degeneration of the adjacent segment was also evaluated. Statistical analysis was performed using the R packages for data processing and plotting.

Results. At long-term follow-up (144 months), when assessing back pain according to VAS and ODI, a statistically significant difference p < 0.001 in favor of minimally invasive interventions was revealed. Both surgical methods resulted in high rates of fusion and low reoperation rates. In the group of minimally invasive surgical interventions, there is a lower incidence of fatty degeneration of the paravertebral muscles and damage to the adjacent segment.

Conclusions. Open and minimally invasive surgical interventions have comparable long-term clinical and morphological results. Open surgical interventions in the long term are fraught with aggravation of fatty degeneration of the paravertebral muscles and more frequent development of the adjacent level syndrome. Minimally invasive techniques are an effective and safe alternative to traditional open surgery and can reduce trauma, preserve the intact posterior support complex of the spine at adjacent levels, while performing adequate decompression and stabilization, followed by the formation of a bone block.

**Key Words:** spinal stenosis, minimally invasive surgery, over-the-top contralateral decompression, fatty degeneration of paravetebral muscles, adjacent disc syndrome.

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Due to developing technological advances and innovations a minimally invasive spine surgery (MISS) is becoming more popular, especially in recent years [1-5]. The main purpose of MISS is to reduce approach-associated injury to soft tissues, the muscular-ligamentous apparatus of the spinal motion segments, while preserving the clinical benefits and radiological findings of open techniques [4-7]. MISS is aimed at reducing intraoperative blood loss, the rate of surgical site infections, postoperative hematomas and stabilization of normal muscle function by preserving the innervation of the paravertebral muscles [8–11].

Other expected benefits are faster wound healing, reduced postoperative pain and analgesic consumption, a shorter time to full mobilization and a shorter length of hospital stay. An option for such MISS techniques is minimally invasive transforaminal interbody fusion, contralateral decompression (over-the-top), transcutaneous transpedicular fixation. One of the disadvantages of MISS is the higher intraoperative irradiation due to the more frequent and prolonged use of fluoroscopy [12].

The objective of the study is to evaluate the long-term outcomes of surgical treatment of patients with monosegmental stenosis of the lumbar spine after

using minimally invasive and standard open techniques.

Design: a randomized prospective cohort study.

# **Material and Methods**

Compliance criteria Inclusion criteria:

- syndrome of mono- or polyradicular compression of the spinal nerve roots with a possible combination with reflex pain syndromes, neurogenic intermittent claudication caused by stenosis of one lumbar spinal motion segment;
- instability or degenerative spondylolisthesis requiring instrumental stabili-

zation at only one lumbar spinal motion segment.

Exclusion criteria:

- bilateral foraminal stenosis;
- polysegmental spinal canal stenosis;
- spondylolisthesis of grade II and higher;
  - the need to correct sagittal balance;
- recurrence of pain syndrome after previous spinal surgery;
- severe concomitant somatic condition;
  - age under 20 and over 75 years;
- other diseases of the spine or large joints of the lower extremities, including congenital stenosis of spinal canal, injuries, tumors and inflammatory disorders of the lumbar spine, etc.

**Patients** 

The above-mentioned criteria were met by 132 patients operated on at the neurosurgical clinic between 2009 and 2011. The main indications for surgery were reflex and radicular pain syndromes that were resistant to non-surgical treatment and caused by monosegmental stenosis of the lumbar spine. The patients were divided into 2 groups by simple randomization using a software application:

- Group 1 (the main group), 64 patients underwent minimally invasive decompression and stabilization surgery for monosegmental spinal stenosis in the lumbosacral spine;
- Group 2 (comparison), decompression and stabilization surgeries were performed in 68 patients through a conventional posteromedial approach with skeletonization of the posterior spine.

The outcomes were assessed in the long term (144 months) in 110 patients: 53 patients in Group 1 and 57 patients in Group 2. 22 patients discontinued participation in the study due to natural causes.

The study was approved by the local Ethics Committee of Novosibirsk Research Institute of Traumatology and Orthopaedics n.a. Ya.L. Tsivyan.

Description of medical treatment

Patients in Group 1 underwent minimally invasive procedures. An approach to the spine was done in a parasagittal way by blunt muscle dissection in the intermuscular sulcus and between the muscle fibers through skin incisions of

about 3–4 cm. An interlaminar approach to the spinal canal was performed. The dural sac was completely exposed in the direction of the contralateral side of the spinal canal. The placement points of the pedicular screws in the angle between the transverse and articular processes are clearly visualized through this approach. On the opposite side, the screw fixation was performed using transcutaneous technology along guide pins, which were placed in the vertebral bodies under image intensifier control with a Jamshidi needle. Interbody fusion was performed using the TLIF technique with total foraminotomy. In Group 2, all decompression and stabilization surgeries were performed through a conventional posteromedian approach with skeletonization of the posterior parts of the vertebral structures. Patients underwent adequate conventional decompression of intracanal neurovascular formations (decompression laminectomy with obligatory removal of compressing substrates), transpedicular fixation and posterior lumbar interbody fusion (PLIF).

Data on injury rate and clinical efficacy in the compared groups in the early postoperative period and in follow-up periods up to 24 months have been published in previous articles and studies [12, 13].

Examination techniques

Patients in the study groups underwent MRI, MSCT of the lumbar spine, and full-length standing spine radiography with capture of the femoral heads in two views during the follow-up period of 144 months. The changes in neurological status and pain syndrome were assessed according to a ten-point VAS scale and the changes in functional activity were assessed according to the Oswestry Disability Index (ODI) [14].

According to the radiological examination findings, the indicators of global (SVA, SSA) and local (Cobb angle of LL, L4–S1) sagittal balances were assessed [15]. The assessment of the indicators of the proper lordosis (LL) was calculated using the formula: LL = PI  $\times$  0.54 + 27.6°, then the proper angle L4–S1 according

to the formula is  $0.66 \times LL$  [16]. According to the radiological findings the possible development of proximal (PJK) and distal (DJK) junctional kyphosis was also assessed.

According to CT findings the formation of a bone block was assessed on the Tan scale: the bone block was considered completed at Grade 1 and 2; and was bone block malformation at Grade 3 and 4 [17]. MSCT was used to detect the formation of the posterior block, the migration and subsidence of the interbody cage and the integrity of the transpedicular instrumentation. MRI was used to define the condition of adjacent segments: disc degeneration according to Pfirrmann [18], lumbar spinal canal stenosis according to Schizas [19] and fatty degeneration of paravertebral muscles according to Goutallier [20].

Statistical analysis

Descriptive statistics for continuous indicators were calculated in the form of median [first quartile; third quartile] (MED [Q1; Q3]), arithmetic mean  $\pm$  standard deviation (M  $\pm$  SD) and minimum-maximum (MIN-MAX) values. The number of patients (frequency) for each category was defined for categorical indicators; the number of patients, frequency and 95 % confidence interval (95 % CI) of frequency were determined using the Wilson formula for binary indicators.

The Shapiro – Wilk test did not reveal normally distributed indicators. Thus, comparisons of continuous indicators between groups were performed using the Mann – Whitney U test. Categorical and binary indicators were compared using two-tailed Fisher's exact test. Correction of the error of multiple testing when comparing categories was performed by the Benjamini – Hochberg Method.

Statistical hypotheses were tested at a critical significance value of p = 0.05, i.e., the difference was considered statistically significant if p < 0.05.

Statistical calculations were performed in the RStudio software (version 2022.02.1 Build 461 – © 2009–2022 RStudio, Inc., USA) in the R language (version 4.1.3 (2022-03-10), Austria, URL: https://www.R-project.org).

### Results

According to the main controlled parameters, apart from the age of patients (which is not an indicator defining the treatment outcome), there were no differences between the patient groups; the mean age was  $48.47 \pm 10.86$  years in Group 1 and  $54.7 \pm 10.64$  years in Group 2; p = 0.002. There were 18 (34%) male patients in Group 1 and 30 (53%) in Group 2; p = 0.056. The dominant localization of injuries in patients of both groups was the L4–L5 level. According to the localization of the injury, the patient groups differed statistically regarding the level of L3–L4 (p = 0.047; Fig. 1).

A statistically significant difference was found (p < 0.001; Fig. 2), while assessing back pain according to VAS. It was found that the pain syndrome is not of a radicular origin but a reflex one, while assessing the lower extremity pain by VAS. There was no statistically significant difference in the groups (Fig. 2).

During the comparison of functional activity according to the Oswestry Disability Index, a statistically significant difference (p = 0.001) was noted among the groups: in the group of minimally invasive surgical procedures patients noted a significantly better quality of daily life (Fig. 2).

There was no statistically significant difference in the number of repeated surgeries in the groups (p > 0.999). The development of PJK was recorded in 2 (4 %) patients (95 % CI [1 %; 13 %]) in Group 1; in 3 (5 %) patients (95 % CI [2 %; 14 %]) in Group 2; p > 0.999. There were no cases of DJK in the groups. Subsidence of the interbody cage was observed in 7 (13 %) cases (95% CI [7 %; 25 %]) in Group 1; in 4 (7 %; 95 % CI [3 %; 17 %]) in Group 2; p = 0.352 (Table 1).

There was no statistically significant difference between the indicators of global and local sagittal balances in the groups before surgery and in the long-term postoperative period. All patients did not have a local segmental imbalance. The values of SVA and SSA did not exceed the determining value of the global imbalance indicator (Table 1).

According to the MSCT findings, the lack of a bone block according to the Tan scale was found in 4 patients in the group of open surgeries. The indicators of the examined patients in the group of minimally invasive surgical procedures corresponded to Grades 1 and 2 (Fig. 3). There is a statistically significant difference in the formation of the posterior block of the operated segment in favor of open surgeries.

This is probably associated with skeletonization of the spine on both sides and possible partial resection of the medial sections of the facet joints that in combination with rigid fixation of the spinal motion segment results in the formation of a posterior block (Fig. 4).

In the group of open surgeries, the MRI findings revealed a statistically significant difference in terms of formation of adjacent segment disease with a predominance of adjacent disc degeneration according to Pfirrmann. There were no statistically significant differences according to the results of the assessment of spinal stenosis of the adjacent segment on the Schizas grading system (Table 2).

A statistically significant difference between the groups was revealed during the assessment of fatty degeneration of paravertebral muscles according to the Goutallier scale. The onset and progression of the course are less severe in the group of minimally invasive surgical procedures. The reason for this is that the paravertebral muscles become injured and ischemic from further compression with wound retractors when performing a median approach with skeletonization of the spine. If the Wiltse approach is used, the structures of the spine are accessed in the intermuscular sulcus between the fasciculus lateralis and fasciculus gracilis (Table 2).

Adverse events

During control examinations in the groups in the postoperative period, early complications were identified, that were reversed for up to two years. Within the period from 24 to 144 months, one (1.7 %) case of pseudoarthrosis was recorded in the group of open surgeries, and the instrumentation was re-installed. In 3 (5.6 %) cases in the group of mini-

mally invasive surgical procedures, the extension of the instrumentation to the superjacent segment was associated with the development of adjacent disc disease. In the group of open surgeries the extension of the instrumentation was required in 10 (17.5 %) cases.

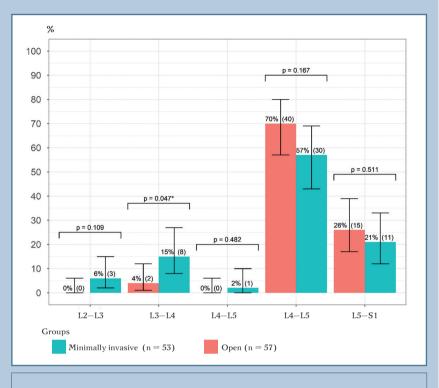
### Discussion

The long-term clinical outcomes of surgical treatment of single-level stenosis in patients suffering from lumbar degenerative disease show that both approaches (minimally invasive and open) provided a significant improvement in clinical outcomes immediately after surgery; the outcomes remained significant in the long-term follow-up.

According to the results of our study, there was a statistically significant difference in back pain and quality of life indicators in favor of a minimally invasive approach when followed up to 144 months. Probably, it is associated with significant injury to the paravertebral muscles during skeletonization and impaired attachment of aponeurosis to spinous processes in the group of open surgeries, which in the long-term followup results in damaging adjacent segments and changes in the muscular system of the spine. Many authors have revealed significant differences in the immediate postoperative outcomes [21–26].

In a systematic review by Li et al. [26], there was no significant difference in the postoperative indicators of VAS and ODI between the techniques. There were also no statistically significant differences in secondary outcomes, although the follow-up period was much shorter than in our study.

The symptoms of adjacent disc disease are more often found in the group of open surgeries and statistically significantly differ in upper segment injury. Only 5 of the studies included in the meta-analysis contained reports of adjacent disc disease [27]. It is doubtful if there was an assessment of this disease in other studies or if this outcome was simply not mentioned. Its prevalence has not been reported in other systematic reviews.



**Fig. 1**Distribution of study group patients by lesion level

An adequate rate of bone block formation was found in both groups. Pseudoarthrosis was found in 4 patients in the group of open surgeries, which required repeated surgery. The observed rate of

bone block formation was lower than reported in previously published systematic reviews on this issue [21, 23]. According to Sun et al. [23], there was a 97.2 % incidence of bone block formation in

the cohort of minimally invasive surgical procedures and a 98.5 % incidence in the cohort of open surgical procedures; and Xie et al. [21] reported a 95.9 % incidence of bone block formation in cases involving minimally invasive procedures and a 97.7 % incidence in cases involving open surgical interventions.

Sun et al. [23] reported a large number of repeat surgeries in the MISS group (5.0 % vs 2.9 %), while Xie et al. [21] found the same rate of repeat surgeries using both approaches (0.4 % vs 0.5 %). There was no statistically significant difference in the rate of repeated surgeries in our study. Repeated surgical interventions were associated with the formation of pseudoarthrosis and adjacent disc disease.

A statistically significant difference is observed in the assessment of fatty degeneration of the paravertebral muscles; this difference is substantially more frequent in the group of open surgeries performed over a long period of time. During the assessment of the initial MRI findings, the degree of fatty degeneration in both groups was comparable. In our study, the fatty degeneration of muscles was evaluated on the Goutallier scale, which is an imaging system for the qualitative assessment of fatty infiltration [20, 28]. The Goutallier classification, originally proposed for the assessment of fatty

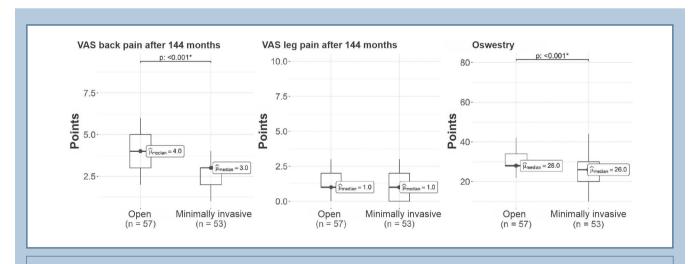


Fig. 2
Comparison of pain according to VAS and Oswestry index in study groups

Table1 Indicators of sagittal balance and development of PJK and DJK in the study groups

Indicators	Group 1 (n=57)  MED [Q1; Q3] $M \pm SD$ (MIN-MAX)		Group 2 (n=53)		Comparison of groups	
			MED [	Q1; Q3]		
			$egin{aligned} \mathtt{M} \pm \mathtt{SD} \ & (\mathtt{MIN-MAX}) \end{aligned}$			
	before surgery	after surgery	before surgery	after surgery	before surgery	after surgery
PI, degrees	56 [46; 61]	56 [46; 61]	52 [45; 61]	52 [45; 61]	0.711	0.711
	$53.86\pm11.64$	$53.86 \pm 11.64$	$52.96 \pm 10.57$	$52.96 \pm 10.57$		
	(20-79)	(20-79)	(26-76)	(26-76)		
PT, degrees	56 [46; 61]	16 [12; 22]	19 [12; 21]	15 [12; 19]	0.326	0.352
	$53.86 \pm 11.64$	$16.88 \pm 6.41$	$18.38 \pm 8.72$	$15.91\pm7.16$		
	(20-79)	(2-38)	(-4-40)	(1-33)		
SS, degrees	36 [27; 43]	37 [31; 43]	35 [28; 43]	36 [29; 43]	0.827	0.765
	$34.61 \pm 10.59$	$36.12 \pm 9.77$	$35.75\pm10.74$	$35.79 \pm 10.21$		
	(5-56)	(12-55)	(18-62)	(14-65)		
LL, degrees	52 [38; 60]	52 [41; 59]	51 [35; 56]	49 [40; 57]	0.660	0.317
	$48.30 \pm 15.83$	$49.23 \pm 13.44$	$47.17 \pm 16.32$	$46.58 \pm 14.75$		
	(1-80)	(9-76)	(-7-80)	(-14-76)		
L4-S1,	27 [21; 35]	30 [25; 38]	32 [23; 38]	31 [23; 37]	0.405	0.445
degrees	$28.28\pm10.96$	$31.28 \pm 8.51$	$29.75 \pm 11.29$	$29.72 \pm 10.55$		
	(1-47)	(6-51)	(-4-56)	(-11-58)		
SVA,	28 [18; 34]	21 [13; 32]	21 [12; 31]	16 [6; 24]	0.016*	0.014*
degrees	$28.79 \pm 14.86$	$23.00 \pm 17.26$	$21.71 \pm 10.58$	$15.43 \pm 12.38$		
	(2-74)	(от -28.3 до -86.0)	(2-45)	(от -30 до -36)		
SSA,	122 [113; 128]	124 [116; 129]	122 [112; 128]	126 [117; 130]	0.933	0.519
degrees	$120.59 \pm 8.72$	$122.07 \pm 8.72$	$120.50 \pm 8.38$	$123.25 \pm 7.86$		
	(102-132)	(95-132)	(102-132)	(100-132)		
YJK, n	3		2		>0.999	
% [95 % CI]	5 [2	; 14]	4 [1; 13]			
OJK. n	0		0		>0.999	
% [95 % CI]	0 [0	0; 6]	0 [0; 7]			

Statistically significantly different indicators. Comparison of continuous indicators was performed using the Mann - Whitney U test and binary indicators using the two-tailed Fisher's exact test.

degeneration of the rotator cuff on CT, was expanded to include an MRI assessment of other muscles, including back muscles [29–31]. Fatty degeneration of the multifidus muscles and a decrease in the transection of the lumbar muscles were associated with lower functional indicators in terms of higher data on the Oswestry Disability Index [31].

In addition, there is evidence of a positive correlation between the Goutallier scale and the percentage of fat in the multifidus muscle measured in a quantitative way [32]. Similarly, Crawford et al. [33] reported a substantial or very strong correlation between Goutallier scores and mean percentage fat measured using

the same method as in our study for MR images of 25 randomly selected subjects.

Moreover, the presence of fatty degeneration of the paravertebral muscles in preoperative studies results in worse clinical outcomes after surgery for spinal canal stenosis [34].

During open surgeries, the paravertebral muscles must be dissected from the spinous processes, which can trigger muscle denervation, ischemia, and progressive muscle atrophy [35–37].

Several studies have compared postoperative degeneration of the paravertebral muscles, which occurs after open and minimally invasive surgical interventions using MRI or CT [34]. Mori et al. [38] evaluated muscle deterioration caused by open surgeries and found significant postoperative atrophy of the paravertebral musculature at the operated and caudal adjacent levels. They measured the mean transection area and fatty infiltration of the muscles at the L1–S1 level and reported less paravertebral muscle degeneration after minimally invasive surgeries rather than open ones.

Several studies demonstrated that fatty infiltration in the paravertebral muscles is more pronounced in the lower lumbar segments in asymptomatic individuals [33, 39]. Gille et al. [40] discovered that the change in the contractile component of the transection area of

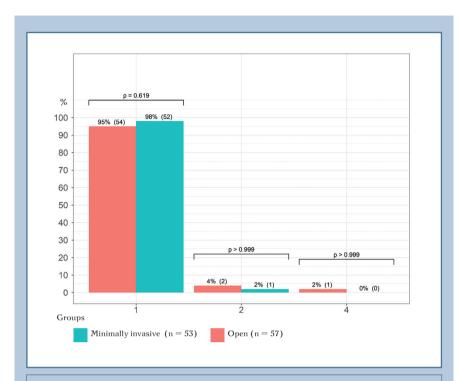


Fig. 3
Bone block formation in patients in the study groups according to the Tan scale

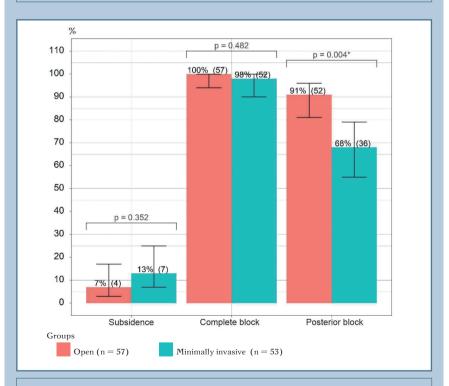


Fig. 4
Comparison of formation of the interbody and bone blocks in patients of the study groups

the erector muscle mainly occurs distal to the operated lumbar segment. In our study fatty infiltration in postoperative muscles was also more pronounced at the caudal level than at the cranial level. This observation is probably associated with the fact that fatty infiltration of skeletal muscle usually begins in more distal areas of the skeleton [41].

### Conclusion

Open and minimally invasive surgical interventions have comparable longterm clinical and morphological outcomes. Open surgeries in the long term are fraught with the aggravation of fatty degeneration of the paravertebral muscles and more frequent development of the adjacent level syndrome. Minimally invasive techniques are an effective and safe alternative to conventional open surgery. They may reduce injury rates and preserve the intact posterior support complex of the adjacent segments by performing adequate decompression and stabilization, followed by the formation of the block.

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.

 Table 2

 Indicators of development of adjacent segment syndrome and fatty degeneration of the paravertebral muscles in patients of the study groups

Indicators	Group 1 (n = 57), n (%)		Group 2 (n = 53), n (%)		Comparison of groups by two-tailed Fisher's exact test with  Benjamini — Hochberg method, p value		
	before	after	before	after	before surgery	after surgery	
	surgery	surgery	surgery	surgery			
				0 7			
Pfirrmann	1:17 (29.8)	1:2 (3.5)	1: 22 (41.5)	1: 14 (26.4)	Overall comparison: 0.050*	Overall comparison: 0.003*	
cranial	2: 28 (49.1)	2:8 (31.6)	2: 14 (26.4)	2: 19 (35.8)	category: p, p adjustment	category: p, p adjustment	
	3: 12 (21.1)	3: 28 (49.1)	3: 17 (32.1)	3: 16 (30.2)	1: 0.234; 0.234	1: <0.001*; 0.003*	
		4:9 (15.8)		4: 4 (7.5)	2: 0.019*; 0.056	2: 0.689; 0.689	
					3: 0.203; 0.234	3: 0.052; 0.105	
						4: 0.241; 0.322	
Pfirrmann	0: 18 (31.6)	0: 18 (31.6)	0: 12	0:12 (22.6)	Overall comparison: 0.741	Overall comparison: 0.257	
caudal	1:3 (5.3)	1:0 (0.0)	(22.6)	1:3 (5.7)	category: p, p adjustment	category: p, p adjustment	
	2: 20 (35.1)	2:7 (12.3)	1:5 (9.4)	2: 11 (20.8)	0: 0.392; 0.957	0: 0.392; 0.588	
	3:11 (19.3)	3: 18 (31.6)	2: 17 (32.1)	3: 17 (32.1)	1: 0.478; 0.957	1: 0.109; 0.588	
	4:4 (7.0)	4: 10 (17.5)	3: 12 (22.6)	4: 5 (9.4)	2: 0.841; >0.999	2: 0.304; 0.588	
	5:1 (1.8)	5: 4 (7.0)	4:4 (7.5)	5: 5 (9.4)	3: 0.815; >0.999	3: >0.999; >0.999	
			5:3 (5.7)		4: >0.999; >0.999	4: 0.272; 0.588	
					5: 0.350; 0.957	5: 0.736; 0.883	
Schizas cranial	A: 50 (87.7)	A: 35 (61.4)	A: 45	A: 39 (73.6)	Overall comparison: 0.783	Overall comparison: 0.253	
	B: 7 (12.3)	B: 18 (31.6)	(84.9)	B: 13 (24.5)	category: p, p adjustment	category: p, p adjustment	
		C: 4 (7.0)	B: 8 (15.1)	C: 1 (1.9)	A: 0.783; 0.783	A: 0.223; 0.525	
					B: 0.783; 0.783	B: 0.525; 0.525	
						C: 0.365; 0.525	
Schizas caudal	0: 17 (29.8)	0:17 (29.8)	0: 10	0: 10 (18.9)	Overall comparison: 0.105	Overall comparison: 0.077	
	A: 37 (64.9)	A: 22 (38.6)	(18.9)	A: 28 (52.8)	category: p, p adjustment	category: p, p adjustment	
	B: 3 (5.3)	B: 18 (31.6)	A: 33 (62.3)	B: 12 (22.6)	0: 0.193; 0.387	0: 0.193; 0.258	
	C: 0 (0.0)	C:0 (0.0)	B: 9 (17.0)	C: 3 (5.7)	A: 0.844; 0.844	A: 0.180; 0.258	
			C: 1 (1.9)		B: 0.067; 0.268	B: 0.392; 0.392	
					C: 0.482; 0.642	C: 0.109; 0.258	
Goutallier	0: 29 (50.9)	0:1 (1.8)	0: 33	0: 17 (32.1)	Overall comparison: 0.417	Overall comparison: < 0.001	
classification	1:15 (26.3)	1:0 (0.0)	(62.3)	1: 19 (35.8)	category: p, p adjustment	category: p, p adjustment	
of fatty	2: 10 (17.5)	2: 3 (5.3)	1: 15 (28.3)	2: 10 (18.9)	0: 0.253; 0.633	0: <0.001*; <0.001*	
degeneration	3: 2 (3.5)	3: 19 (33.3)	2:4 (7.5)	3: 3 (5.7)	1: 0.834; >0.999	1: <0.001*; <0.001*	
	4: 1 (1.8)	4: 34 (59.6)	3: 1 (1.9)	4: 4 (7.5)	2: 0.155; 0.633	2: 0.038*; 0.038*	
		,	4:0 (0.0)		3: >0.999; >0.999	3: <0.001*; <0.001*	
			, ,		4: >0.999; >0.999	4: <0.001*; <0.001*	

<sup>\*</sup> Statistically significantly different indicators.

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### Address correspondence to:

Akhmetyanov Shamil Alfirovich Novosibirsk Research Institute of Traumatology and Orthopaedics n.a. Ya.L. Tsivyan, 17 Frunze str., Novosibirsk, 630091, Russia, sh.ahmetyanov@yandex.ru

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Shamil Alfirovich Akhmetyanov, MD, PhD, Department of Neurosurgery No. 2, Novosibirsk Research Institute of Traumatology and Orthopaedics n.a. Ya.L. Tsivyan, 17 Frunze str., Novosibirsk, 630091, Russia, ORCID: 0000-0003-0505-8319, sh.abmetyanov@yandex.ru;

Abduvoris Abduakhadovich Azizkhonov, clinical resident, Department of Neurosurgery No. 2, Novosibirsk Research Institute of Traumatology and Orthopaedics n.a. Ya.L. Tsivyan, 17 Frunze str., Novosibirsk, 630091, Russia, ORCID: 0009-0005-1471-3989, voris28.09.97@mail.ru;

Evgeny Andreyevich Mushkachev, junior researcher, Research Department of Neurovertebrology, Novosibirsk Research Institute of Traumatology and Orthopaedics n.a. Ya.L. Tsivyan, 17 Frunze str., Novosibirsk, 630091, Russia, ORCID: 0000-0003-0346-3898, mushkachevi@gmail.com;

Abdugafur Jabborovich Sanginov, MD, PhD, Department of Neurosurgery No. 2, Novosibirsk Research Institute of Traumatology and Orthopaedics n.a. Ya.L. Tsivyan, 17 Frunze str., Novosibirsk, 630091, Russia, ORCID: 0000-0002-4744-4077, Dr.sanginov@gmail.com;

Ilya Dmitrievich Isakov, junior researcher, Research Department of Neurovertebrology, Novosibirsk Research Institute of Traumatology and Orthopaedics n.a. Ya.L. Tsivyan, 17 Frunze str., Novosibirsk, 630091, Russia, ORCID: 0000-0002-9228-3241, doctorisakov@mail.ru;

Aleksey Vladimirovich Peleganchuk, MD, PhD, researcher, Research Department of Neurovertebrology, Head of the Department of Neurosurgery No. 2, Novosibirsk Research Institute of Traumatology and Orthopaedics n.a. Ya.L. Tsivyan, 17 Frunze str., Novosibirsk, 630091, Russia, ORCID: 0000-0002-4588-428X, apeleganchuk@mail.ru.

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