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ORIGINAL STUDY:
Extremely high lipoprotein(a) and early atherosclerosis

SYSTEMATIC REVIEW:
ChatGPT in medical education

CLINICAL CASE:
Late-onset myelopathy after Torkildsen shunt

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Extremely high lipoprotein (a) as a marker of early atherosclerosis: analysis of a large real-world cohort

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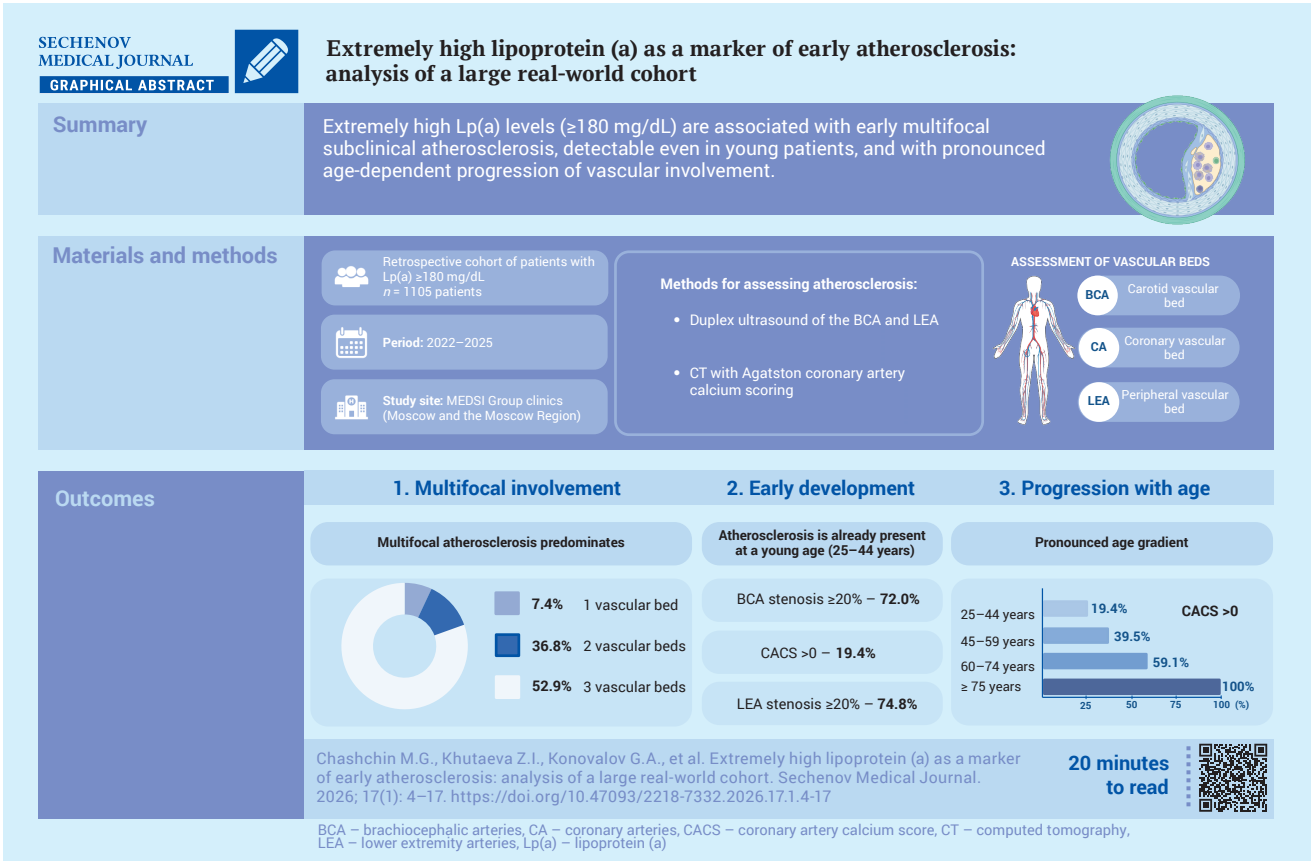

Abstract

Lipoprotein (a) (Lp(a)) is a genetically determined risk factor for atherosclerosis, with extremely high levels associated with very high cardiovascular risk. Despite this, in routine clinical practice these patients often remain insufficiently identified.

Aim. To characterize the prevalence and severity of subclinical atherosclerosis in various vascular beds in patients with Lp(a) ≥ 180 mg/dL, including younger age groups.

Materials and methods. We performed a retrospective analysis of a database comprising 101,078 outpatients, from which 1105 (1.09%) individuals with Lp(a) ≥ 180 mg/dL and available lipid profile data were selected; women

accounted for 67.2%, and the mean age was 52.74 ± 14.59 years. The presence of atherosclerotic cardiovascular disease (ASCVD) was ascertained from medical records, and atherosclerosis was assessed by duplex ultrasound of the brachiocephalic arteries (BCA) and lower extremity arteries (LEA), as well as by the Agatston coronary artery calcium score (CACS). At least one vascular bed was evaluated in 69.8% of patients, and all three were evaluated in 6.2%.

Results. Most patients showed elevated levels of total cholesterol and low-density lipoprotein cholesterol. From the age of 25–44 years onward, a substantial proportion of patients already showed atherosclerotic involvement of the BCA and LEA with stenosis ≥20% and pronounced coronary calcification (CACS > 100 units), with a shift toward more severe lesions in older age groups. In the subgroup that underwent imaging of all three vascular beds, 60.0% of patients aged 25–44 years had two or three beds that were affected; the proportion of patients with involvement of all three vascular beds increased to 40.0% in those aged 45–59 years, 76.9% in those aged 60–74 years, and reached 100% in patients aged ≥ 75 years ($p < 0.001$). The prevalence of clinically documented ASCVD increased from 10.3% in the 25–44 age group to 67.1% in patients aged ≥ 75 years. Even among patients without documented ASCVD, atherosclerotic involvement of the BCA, LEA and coronary calcification was detected in 85.9%, 82.6% and 37.1% of cases, respectively.

Conclusion. Patients with Lp(a) ≥ 180 mg/dL are characterized by a high prevalence and early onset of subclinical, frequently multifocal atherosclerosis, with a pronounced age-related gradient of progression. These findings support the case for designating this cohort as a priority group for in-depth evaluation, risk re-stratification and more intensive preventive management.

Keywords: lipoprotein (a); cardiovascular risk; multifocal atherosclerosis; coronary artery calcium score; cardiovascular diseases

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Compliance with ethical standards. The study was conducted in accordance with the principles of the Declaration of Helsinki. The retrospective design using anonymized data did not require additional approval from the local ethics committee. At the initial visit, all patients signed informed consent for the processing of personal data.
Data availability. The data confirming the findings of this study are available from the authors upon reasonable request. Data and statistical methods used in the article were examined by a professional biostatistician on the Sechenov Medical Journal editorial staff.
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Экстремально высокий липопротеин (а) как маркер раннего атеросклероза: анализ крупной когорты реальной практики

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Аннотация

Липопротеин (а) [Лп(а)] – генетически обусловленный фактор атеросклероза, при этом его экстремальные значения ассоциированы с крайне высоким сердечно-сосудистым риском. Однако в реальной клинической практике такие пациенты выявляются и характеризуются недостаточно.

Цель. Охарактеризовать распространенность и выраженность субклинического атеросклероза в различных сосудистых бассейнах у пациентов с уровнем Лп(а) ≥ 180 мг/дл, включая молодые возрастные группы.

Материалы и методы. Проведен ретроспективный анализ базы данных 101 078 амбулаторных пациентов, из которой выделено 1105 (1,09%) с Лп(а) ≥ 180 мг/дл и доступными данными липидного профиля; женщины составили 67,2%, средний возраст – 52,74 ± 14,59 года. По данным медицинских карт оценивали частоту атеросклеротических сердечно-сосудистых заболеваний (АССЗ), атеросклероз – по дуплексному сканированию брахиоцефальных артерий (БЦА) и артерий нижних конечностей (АНК), а также по индексу коронарного кальция (ИКК) по Агатстону; хотя бы один сосудистый бассейн был обследован у 69,8% пациентов, все три – у 6,2%.

Результаты. У большинства пациентов отмечались повышенные значения общего холестерина и холестерина липопротеинов низкой плотности. Начиная с возраста 25–44 лет у значительной части пациентов выявлялись атеросклеротические изменения БЦА и АНК со стенозом ≥ 20% и выраженный коронарный кальциноз (ИКК > 100 ед.), причем с возрастом структура поражения смещалась в сторону более тяжелых форм. В подгруппе с обследованием трех сосудистых бассейнов поражение двух или трех бассейнов имели 60,0% пациентов 25–44 лет; доля пациентов с вовлечением всех трех бассейнов составила 40,0% в группе 45–59 лет, 76,9% – в группе 60–74 года и достигала 100% у пациентов 75 лет и старше ($p < 0,001$). Частота верифицированных АССЗ увеличивалась с 10,3% в группе 25–44 года до 67,1% у пациентов 75 лет и старше. Даже среди пациентов без АССЗ атеросклеротическое поражение БЦА, АНК и коронарный кальциноз выявлялись в 85,9, 82,6 и 37,1% случаев соответственно.

Заключение. Пациенты с Лп(а) ≥ 180 мг/дл характеризуются высокой распространенностью и ранней реализацией субклинического, часто мультифокального атеросклероза с выраженным возрастным градиентом прогрессирования. Полученные данные поддерживают целесообразность выделения данной когорты в приоритетный контур углубленного обследования, рестратификации риска и более интенсивной профилактической тактики.

Ключевые слова: липопротеин (а); сердечно-сосудистый риск; мультифокальный атеросклероз; индекс коронарного кальция; сердечно-сосудистые заболевания

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Соответствие принципам этики. Исследование выполнено в соответствии с принципами Хельсинкской декларации. Ретроспективный характер исследования с использованием анонимизированных данных не требовал дополнительного одобрения локального этического комитета. При первичном обращении все пациенты подписали информированное согласие на обработку персональных данных.
Доступ к данным исследования. Данные, подтверждающие выводы этого исследования, можно получить у авторов по обоснованному запросу. Данные и статистические методы, представленные в статье, прошли статистическое рецензирование редактором журнала – сертифицированным специалистом по биостатистике.
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Abbreviations:

ASCVD – atherosclerotic cardiovascular disease
BCA – brachiocephalic arteries
CACS – coronary artery calcium score
CAD – coronary artery disease
HDL-C – high-density lipoprotein cholesterol
LDL-C – low-density lipoprotein cholesterol
LEA – lower extremity arteries
Lp(a) – lipoprotein (a)
TC – total cholesterol
TG – triglycerides

HIGHLIGHTS

- In routine clinical practice, the prevalence of extremely high lipoprotein (a) ≥ 180 mg/dL among more than 100,000 outpatients is 1.09%.
- As early as the 25–44 age range, a notable proportion of patients with lipoprotein (a) ≥ 180 mg/dL have documented atherosclerotic cardiovascular disease, with the prevalence rising substantially in older age groups.
- Among patients without clinically documented atherosclerotic cardiovascular disease, a high frequency of subclinical and often multifocal atherosclerosis is observed, with onset already in young adulthood and a pronounced age-related gradient of severity.
- Extremely high lipoprotein (a) levels are associated with an atherogenic lipid profile, underscoring the very high lifetime risk of atherosclerotic cardiovascular disease in this patient population.
- These findings support the use of a lipoprotein (a) cut-off of ≥ 180 mg/dL as a practical criterion for identifying a priority group of patients warranting comprehensive multi-bed vascular assessment, risk re-stratification, and intensification of preventive measures.

Lipoprotein (a) (Lp(a)) is a genetically determined risk factor for atherosclerotic cardiovascular disease (ASCVD). Plasma Lp(a) concentration is largely genetically determined, reaches stable values in early childhood, and remains essentially constant throughout life.

Elevated Lp(a) is detected in approximately 20% of the general population and represents one of the most common inherited dyslipidemias [1]. Current clinical guidelines and consensus statements recommend a one-time measurement of Lp(a) in every adult. In real-world practice, however, the testing rate remains very low (less than 1%) and does not reflect the epidemiological importance of this risk factor [2–5].

Particular clinical interest is drawn to patients with Lp(a) ⩾ 180 mg/dL (⩾430 nmol/L), which

corresponds to approximately the 99th percentile of the population distribution and affects roughly 1% of the population (about 1 in 100 individuals) – nearly three times more frequently than heterozygous familial hypercholesterolemia (around 1:313) [6, 7]. In terms of prognostic significance for cardiovascular outcomes, extremely high Lp(a) is comparable to classical forms of inherited dyslipidemia, primarily familial hypercholesterolemia. Despite this, patients with extremely high Lp(a) remain underrepresented in clinical research and, in particular, poorly characterized in routine clinical settings, including with respect to detection rates, clinical and demographic profile, ASCVD burden, and the specifics of preventive and therapeutic strategies.

Epidemiological and genetic studies show that as Lp(a) levels rise, the risk of ASCVD progressively increases, the spectrum of associated vascular lesions broadens, and a pan-vascular pattern of involvement emerges. In a large population-based study, Lp(a) above the 95th percentile (⩾120 mg/dL) was associated with an almost 4-fold increase in the risk of a first myocardial infarction [8]. In another large prospective study, Lp(a) values above the 99th percentile (⩾143 mg/dL) were associated with a 2- to 3-fold increase in the risk of peripheral artery disease and abdominal aortic aneurysm [9].

A pooled analysis of Danish cohorts demonstrated that Lp(a) above the 95th percentile (>90 mg/dL) was associated with an almost 3-fold increase in the risk of degenerative aortic stenosis [10], and a 30-year follow-up of initially healthy women revealed significant associations between high Lp(a) concentrations and the risk of ischemic stroke and cardiovascular mortality [11].

Together, these data emphasize that early identification of elevated Lp(a) is critically important not only in the context of coronary risk, but also with respect to a broader spectrum of vascular outcomes. Despite this, the real-world healthcare system still lacks a unified approach to the identification, evaluation and management of patients with extremely high Lp(a): testing is performed sporadically, referral pathways and the scope of additional work-up remain heterogeneous, and subclinical stages of atherosclerosis often go unrecognized despite their high prevalence. At the same time, this very category of patients is potentially highly amenable to proactive management through earlier and more intensive correction of modifiable risk factors and, in the longer term, the introduction of Lp(a)-targeted therapy.

In this context, organized screening programs become particularly important. Beginning in 2026, the Russian Federation's medical examination (dispanserization) program includes a one-time laboratory measurement of Lp(a) in individuals aged 18–40 years[1]. Indications for testing include a family history of cardiovascular disease, early-onset myocardial infarction or stroke, and a high cardiovascular risk despite normal low-density lipoprotein cholesterol (LDL-C). Patients with elevated Lp(a), particularly those with extreme values, require subsequent follow-up and the application of personalized diagnostic and preventive algorithms.

The aim of the study was to provide a comprehensive evaluation of the lipid profile and the prevalence and pattern of clinical and subclinical atherosclerosis across several vascular beds in patients with extremely high Lp(a) ⩾ 180 mg/dL, and to determine its relevance for cardiovascular risk stratification.

MATERIALS AND METHODS

A retrospective analysis of real-world clinical data was performed. Electronic medical records of patients undergoing outpatient evaluation at the MEDSI Group clinics (Moscow and the Moscow Region) between January 5, 2022, and May 29, 2025 were reviewed. Prior to analysis, all personal data were anonymized in accordance with current legislation and internal regulations on the protection of medical information.

The source database comprised 101,078 patients in whom Lp(a) had been measured as part of routine clinical practice. From this sample, patients with Lp(a) ⩾ 180 mg/dL and available lipid profile parameters – total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) – were selected. The final study cohort consisted of 1105 patients (1.09% of the total database) who were not receiving therapeutic apheresis.

Demographic variables included age and sex. Patients were stratified by age according to the following categories: under 18 years – children and adolescents; 18–24 years – young adults; 25–44 years – early adulthood; 45–59 years – middle age; 60–74 years – older age; and 75 years and over – advanced age.

History of myocardial infarction or ischemic stroke, coronary interventions (coronary stenting, coronary artery bypass grafting), the presence of coronary artery disease (CAD), as well as ASCVD risk factors (arterial hypertension, type 2 diabetes mellitus, smoking) were recorded on the basis of the documented diagnosis in the medical record.

A positive family history was recorded when there was documentation of CAD, stroke or hypercholesterolemia in first-degree relatives.

Laboratory analyses were performed in the certified laboratory of the MEDSI Group network in accordance with internal quality control standards and participation in an external quality assessment scheme (EQAS). Venous blood was collected after an overnight fast. Lp(a)

[1] Decree of the Government of the Russian Federation No. 2188 of 29 December 2025 "On the Program of State Guarantees of Free Provision of Medical Care for 2026 and the planning period of 2027 and 2028". https://dgp69.mos.ru/public/docs/legaldoc/pprf-29-12-2025-2188.pdf (access date: 09.02.2026).

was measured by an immunoturbidimetric method with latex enhancement using monospecific antibodies to apolipoprotein (a) on a Beckman Coulter DxC 700 AU automated biochemistry analyzer (Beckman Coulter, USA). Lipid profile parameters were measured on the same analyzer using standard enzymatic-colorimetric and immunonephelometric methods.

Atherosclerotic involvement of three vascular beds was assessed by duplex ultrasound of the brachiocephalic arteries (BCA) and lower extremity arteries (LEA), as well as by non-contrast computed tomography with calculation of the coronary artery calcium score (CACS) by the Agatston method on a SOMATOM Definition AS scanner (Siemens Healthineers, Germany). For the BCA and LEA, the presence of atherosclerotic plaques and the maximum degree of stenosis according to the European Carotid Surgery Trial (ECST) criteria were recorded. CACS values were classified as 0, 1–10, 11–100, 101–399 and ⩾ 400 units [3].

Data on the assessment of vascular beds (BCA, LEA, CACS) were available for 69.8% of patients (n = 771). One vascular bed had been imaged in 30.8% of patients (n = 340), two in 32.9% (n = 363), whereas evaluation of all three vascular beds had been performed in only 6.2% of patients (n = 68).

Statistical analysis

Normality of continuous variables was assessed using the Kolmogorov–Smirnov test with Lilliefors correction. Normally distributed continuous variables were summarized as mean and standard deviation (M ± SD), and non-normally distributed variables as median and interquartile range (Me [Q25; Q75]).

Categorical variables were presented as absolute (n) and relative (%) frequencies. Comparisons of continuous variables among three or more groups were performed using the non-parametric Kruskal–Wallis test (H-statistic), with post-hoc pairwise comparisons performed using the Dunn test with Bonferroni correction. Comparisons of categorical variables among groups were performed using the Pearson χ^2 test. A two-sided p-value of < 0.05 was considered statistically significant.

Statistical analysis was performed using MedStat.Pro, version 0.8.1 (School of Medical Statistics, Moscow, Russia)[2].

RESULTS

Baseline patient characteristics

Women predominated in the study cohort: 67.2% (n = 743) versus 32.8% men (n = 362), corresponding to a sex ratio of approximately 2:1.

Patient age ranged from 6 to 94 years, with a mean of 52.74 ± 14.59 years. The bulk of the cohort consisted of patients of working age and early older age.

The age and sex distribution is presented in Figure 1. In the under-18 group, women accounted for 58.3%, and in the 18–24 age group, all eight patients were women. Among patients aged 25–44 years, women accounted for 53.3%, rising to 68.5% in the 45–59 age group and to 74.6% in the 60–74 age group. The highest proportion of women was observed in patients aged 75 years and over, where it reached 88.6%.

History of cardiovascular events

The cohort was heterogeneous: 779 patients (70.5%) had no history of documented ASCVD, whereas 326 (29.5%) had documented ASCVD. The proportion of patients with such events was 10.3% in those aged 25–44 years and rose progressively in older age groups, reaching 67.1% in patients aged 75 years and over (Fig. 2).

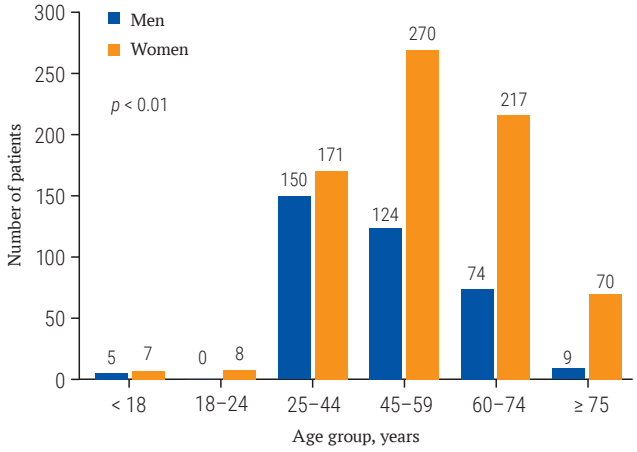

FIG. 1. Age and sex distribution of patients with extremely high lipoprotein (a) (n = 1105).

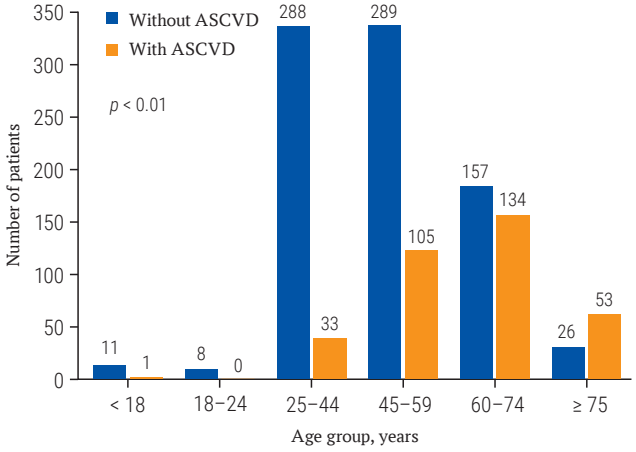

FIG. 2. Distribution of patients with extremely high lipoprotein (a) by history of atherosclerotic cardiovascular disease (n = 1105).

Note: ASCVD – atherosclerotic cardiovascular disease.

[2] MedStat.Pro: web application for statistical analysis of medical data [computer software]. Version 0.8.1. Russian software registration certificate No. 2025688091 dated 16 October 2025. Moscow; 2026. https://app.medstat.pro (access date: 15.02.2026).

Of the documented ASCVD events, myocardial infarction was the most frequent: its prevalence increased approximately 10-fold when comparing patients aged 25–44 years with those aged 75 years and over. With increasing age, statistically significant increases were also observed for CAD, prior coronary interventions, type 2 diabetes mellitus and arterial hypertension. Already in the youngest adult group (25–44 years), CAD was present in 7.2% of patients, type 2 diabetes mellitus in 6.5%, arterial hypertension in 44.2%, and smoking in 38.9%; coronary artery bypass grafting had been performed in one patient. With advancing age, the frequency of CAD and myocardial revascularization rose further. The trajectory of ischemic stroke was similar: its prevalence increased approximately seven-fold in the oldest as compared with the youngest patients (Table 1).

A family history of CAD, stroke and hypercholesterolemia, by contrast, was more frequently reported by patients in younger and middle-aged groups, with a downward trend in older age groups.

Lipid profile

Lp(a) concentration remained relatively stable across age groups, although between-group differences were statistically significant ($p < 0.001$). A modest increase in mean values was observed in the 45–59 and 60–74 age groups, but it did not give rise to clinically distinct subgroups. In patients aged 75 years and over, Lp(a) levels remained comparable to those in younger age groups (Table 2).

Analysis of the distribution of Lp(a) values showed that older age groups were characterized not by a shift in central tendency, but by greater variability driven by the appearance of isolated extreme values (Supplementary materials on the journal's website https://doi.org/10.47093/2218-7332.2026.17.1.4-17-annex). At the same time, baseline Lp(a) levels remained consistently high regardless of age, in keeping with the genetically determined nature of this trait.

Most patients had elevated TC and LDL-C levels, reflecting a markedly atherogenic background in the study cohort (Table 2). The highest TC and LDL-C levels were observed in patients aged 25–59 years, with an upward trend already apparent from the 18–24 age group. In older age groups (⩾60 years), TC and LDL-C tended to decline relative to the 25–59-year peak, although values remained elevated.

TG concentrations showed a moderate increase predominantly in the 25–59 age range, followed by a decline in older age groups. HDL-C remained relatively stable across age subgroups, with only modest differences that were not statistically significant in pairwise comparisons.

Prevalence and severity of atherosclerotic involvement across vascular beds

Brachiocephalic artery involvement

Duplex ultrasound of the BCA was available for 66.2% ($n = 731$) of patients. Moderate stenoses (20–34%) predominated and were identified in 67.9% of patients. Mild stenoses (< 20%) were much less common

Table 1. **History of atherosclerotic cardiovascular disease in patients with extremely high lipoprotein (a) by age groups**

History	Age group						*p*-value
	<18 (*n* = 12)	18–24 (*n* = 8)	25–44 (*n* = 321)	45–59 (*n* = 394)	60–74 (*n* = 291)	≥75 (*n* = 79)	
Diseases:							
myocardial infarction	0 (0)	0 (0)	11 (3.4)	65 (16.5)	75 (25.8)	27 (34.2)	<0.001
ischemic stroke	1 (8.3)	0 (0)	6 (1.9)	18 (4.6)	18 (6.2)	12 (15.2)	<0.001
CAD	0 (0)	0 (0)	23 (7.2)	87 (22.1)	115 (39.5)	47 (59.5)	<0.001
Interventions:							
coronary stenting	0 (0)	0 (0)	0 (0)	14 (3.6)	19 (6.6)	9 (11.4)	<0.001
CABG	0 (0)	0 (0)	1 (0.3)	5 (1.3)	11 (3.8)	2 (2.5)	0.032
Risk factors:							
type 2 diabetes mellitus	0 (0)	0 (0)	21 (6.5)	63 (16.0)	50 (17.2)	29 (36.7)	<0.001
arterial hypertension	1 (8.3)	0 (0)	142 (44.2)	281 (71.5)	220 (75.6)	65 (82.3)	<0.001
smoking	0 (0)	0 (0)	125 (38.9)	162 (41.4)	107 (36.9)	15 (19.0)	<0.001
Conditions in FDR:							
CAD	0 (0)	1 (12.5)	50 (15.6)	80 (20.3)	28 (9.6)	4 (5.1)	<0.001
ischemic stroke	0 (0)	0 (0)	37 (11.5)	61 (15.5)	25 (8.6)	3 (3.8)	<0.001
hypercholesterolemia	0 (0)	1 (12.5)	23 (7.2)	22 (5.6)	6 (2.1)	1 (1.3)	0.023

Notes: data are presented as the absolute number of patients with the characteristic and the proportion within the group, expressed as a percentage (in parentheses).
CABG – coronary artery bypass grafting; CAD – coronary artery disease; FDR – first-degree relatives.

Table 2. **Lipid profile in patients with extremely high lipoprotein (a) by age groups**

Parameter	Age group						*p*-value
	<18 (*n* = 12)	18–24 (*n* = 8)	25–44 (*n* = 321)	45–59 (*n* = 394)	60–74 (*n* = 291)	≥75 (*n* = 79)	
Lp(a), mg/dL	198.92 ± 18.98	205.38 ± 40.17	204.45 ± 29.92[b,c]	214.71 ± 45.65	219.07 ± 48.74	210.91 ± 37.74	<0.001
TC, mmol/L	5.52 ± 0.85[a,c]	6.31 ± 1.26	6.91 ± 1.28[d]	7.02 ± 1.49[d]	6.75 ± 2.01[d]	5.59 ± 1.48	<0.001
TG, mmol/L	0.96 ± 0.31[b]	0.87 ± 0.32	1.48 ± 0.76[b]	1.72 ± 0.97	1.66 ± 0.83	1.45 ± 0.48	<0.001
HDL-C, mmol/L	1.50 ± 0.52	1.78 ± 0.27	1.61 ± 0.38	1.68 ± 0.40	1.68 ± 0.45	1.55 ± 0.34	0.022
LDL-C, mmol/L	3.38 ± 0.60[a,b]	3.93 ± 0.94	4.42 ± 0.95[d]	4.46 ± 1.10[d]	4.29 ± 1.39[d]	3.39 ± 1.16	<0.001

Notes: superscript letters indicate statistically significant differences in post-hoc pairwise comparisons (Dunn test with Bonferroni correction): [a] $p < 0.05$ vs. 25–44 group; [b] $p < 0.05$ vs. 45–59 group; [c] $p < 0.05$ vs. 60–74 group; [d] $p < 0.01$ vs. ≥ 75 group.
HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; Lp(a) – lipoprotein (a); TC – total cholesterol; TG – triglycerides.

Table 3. **Distribution of patients with extremely high lipoprotein (a) by the degree of brachiocephalic artery stenosis across age groups (*n* = 731)**

BCA stenosis	Age group					*p*-value
	18–24 (*n* = 2)	25–44 (*n* = 175)	45–59 (*n* = 295)	60–74 (*n* = 205)	≥75 (*n* = 54)	
<20%	2 (100)	49 (28.0)	26 (8.8)	8 (3.9)	0 (0)	<0.001
20–25%	0 (0)	91 (52.0)	160 (54.2)	63 (30.7)	11 (20.4)	
26–34%	0 (0)	26 (14.9)	72 (24.4)	63 (30.7)	11 (20.4)	
35–49%	0 (0)	5 (2.9)	26 (8.8)	33 (16.1)	10 (18.5)	
50–55%	0 (0)	0 (0)	5 (1.7)	16 (7.8)	12 (22.2)	
>55%	0 (0)	4 (2.3)	6 (2.0)	22 (10.7)	10 (18.5)	

Notes: data are presented as the absolute number of patients with the characteristic and the proportion within the group, expressed as a percentage (in parentheses). Pearson χ^2 test was used for comparisons.
BCA – brachiocephalic arteries.

(11.6%), whereas hemodynamically significant stenoses (>55%) were detected in 5.7% (Table 3).

Already in the 25–44 age group, atherosclerotic involvement of the BCA (stenosis ⩾ 20%) was present in the majority of evaluated patients (72.0%). In the 45–59 age group the prevalence of stenosis rose to 91.2%, in patients aged 60–74 years it reached 96.1%, and among patients aged ⩾75 years atherosclerotic involvement of the BCA was detected in 100% of those evaluated (Table 3).

In the 25–59 age groups, mild and moderate forms of atherosclerosis (predominantly BCA stenoses of up to 35%) predominated, whereas more advanced lesions were relatively uncommon. With increasing age, the distribution shifted progressively toward more severe stenoses. The proportion of stenoses of ⩾35% rose substantially in the 60–74 age group, and patients aged ⩾ 75 years showed an accumulation of hemodynamically significant stenoses (>55%) together with a reduction in minimal lesions ($p < 0.001$).

Lower extremity artery involvement

Duplex ultrasound of the LEA was available for 36.8% (n = 407) of patients. In the 25–44 age group, atherosclerotic involvement of the LEA (stenosis ⩾ 20%) was present in 74.8% of those evaluated. In the 45–59 age group the prevalence of LEA stenosis was 87.2%, in patients aged 60–74 years it reached 96.5%, and among patients aged ⩾ 75 years atherosclerotic changes were detected in 100% of those evaluated (Table 4).

The age-related progression of atherosclerotic LEA involvement mirrored that observed in the BCA, with mild and moderate stenoses predominating in the 25–59 age groups and a rising proportion of hemodynamically significant stenoses in patients aged ⩾ 60 years.

Coronary artery involvement

CACS was assessed in 11.9% (n = 132) of patients. Coronary calcification (CACS > 0) was detected in 50.0% (n = 66) of those examined, with its prevalence increasing with age. In the 25–44 age group, CACS > 0 was identified in 19.4% of patients; in the 45–59 age group, in 39.5%; in patients aged 60–74 years, in 59.1%; and among those aged ⩾75 years, coronary calcification was present in 100% of those evaluated (Table 5).

In the 25–44 age group, only isolated cases of moderate or severe coronary calcification were observed. In the 45–59 age group, the proportion of patients with CACS values of 11–100 and 101–399 rose substantially, and in older age groups the distribution shifted markedly toward an increased frequency of severe and very severe coronary calcification.

Table 4. **Distribution of patients with extremely high lipoprotein (a) by the degree of lower extremity artery stenosis across age groups (*n* = 407)**

LEA stenosis	Age group					*p*-value
	18–24 (*n* = 1)	25–44 (*n* = 103)	45–59 (*n* = 156)	60–74 (*n* = 114)	≥75 (*n* = 33)	
<20%	1 (100)	26 (25.2)	20 (12.8)	4 (3.5)	0 (0)	<0.001
20–25%	0 (0)	54 (52.4)	88 (56.4)	48 (42.1)	7 (21.2)	
26–34%	0 (0)	20 (19.4)	35 (22.4)	29 (25.4)	6 (18.2)	
35–49%	0 (0)	3 (2.9)	8 (5.1)	13 (11.4)	8 (24.2)	
50–55%	0 (0)	0 (0)	0 (0)	10 (8.8)	4 (12.1)	
>55%	0 (0)	0 (0)	5 (3.2)	10 (8.8)	8 (24.2)	

Notes: data are presented as the absolute number of patients with the characteristic and the proportion within the group, expressed as a percentage (in parentheses). Pearson χ^2 test was used for comparisons.
LEA – lower extremity arteries.

Table 5. **Distribution of patients with extremely high lipoprotein (a) by coronary artery calcium score across age groups (*n* = 132)**

CACS	Age group				p-value
	25–44 (*n* = 36)	45–59 (*n* = 43)	60–74 (*n* = 44)	≥75 (*n* = 9)	
0 units	27 (75.0)	24 (55.8)	15 (34.1)	0 (0)	<0.001
1–10 units	4 (11.1)	7 (16.3)	7 (15.9)	0 (0)	
11–100 units	2 (5.6)	8 (18.6)	8 (18.2)	4 (44.4)	
101–399 units	3 (8.3)	3 (7.0)	8 (18.2)	4 (44.4)	
≥400 units	0 (0)	1 (2.3)	6 (13.6)	1 (11.1)	

Notes: data are presented as the absolute number of patients with the characteristic and the proportion within the group, expressed as a percentage (in parentheses). Pearson χ^2 test was used for comparisons.
CACS – coronary artery calcium score.

Three-vessel-bed involvement

Data on the assessment of all three vascular beds were available in 6.2% of patients (*n* = 68) from the age groups 25 years and older. Analysis of this subgroup showed that no signs of atherosclerosis were detected in only 2.9% (*n* = 2) of patients. Single-bed involvement was observed in 7.4% (*n* = 5) and two-bed involvement in 36.8% (*n* = 25), whereas more than half of the patients (52.9%, *n* = 36) had atherosclerotic involvement of all three evaluated vascular beds. The distribution of patients by the number of affected vascular beds across age groups is shown in Figure 3.

Combined involvement of multiple vascular beds showed a clear age-dependent pattern. In the 25–44 age group, the majority of patients evaluated (60.0%) had two- or three-bed involvement, and only 13.3% had no affected beds. In the 45–59 and 60–74 age groups, the proportion of patients with three-bed involvement increased progressively (40.0% and 76.9%, respectively), and by the age of ⩾75 years, combined involvement of all three vascular beds was observed in 100% of patients ($p < 0.001$).

Vascular involvement according to the presence or absence of atherosclerotic cardiovascular disease

Among the 731 patients for whom vascular bed imaging data were available, 65.0% (*n* = 475) had no history of ASCVD, whereas 35.0% (*n* = 256) had documented ASCVD.

Among patients without ASCVD, atherosclerotic involvement of the BCA was detected in 85.9% of cases (408 of 475 patients evaluated), LEA involvement in 82.6% (209 of 253), and coronary calcification in 37.1% (33 of 89).

By comparison, the frequency of imaging-detected vascular involvement was predictably higher among patients with documented ASCVD: BCA stenosis – 98.1%, LEA stenosis – 98.1%, and coronary calcification – 76.7% ($p < 0.001$ for all comparisons) (Fig. 4).

DISCUSSION

The present study characterizes one of the least well-described categories of patients in routine clinical practice – individuals with extremely high Lp(a) (⩾180 mg/dL).

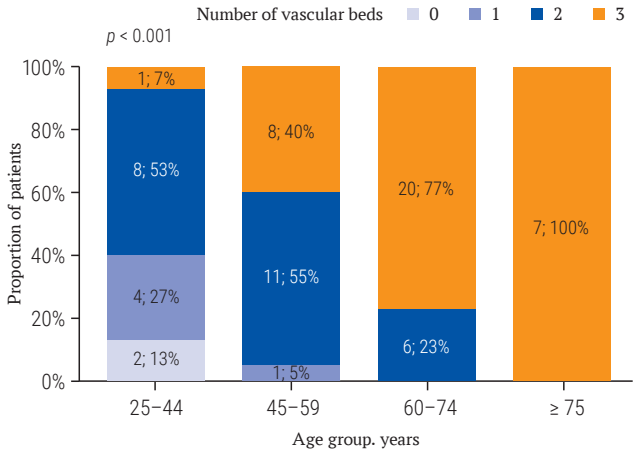

FIG. 3. Distribution of patients with extremely high lipoprotein (a) by the number of affected vascular beds (n = 68).

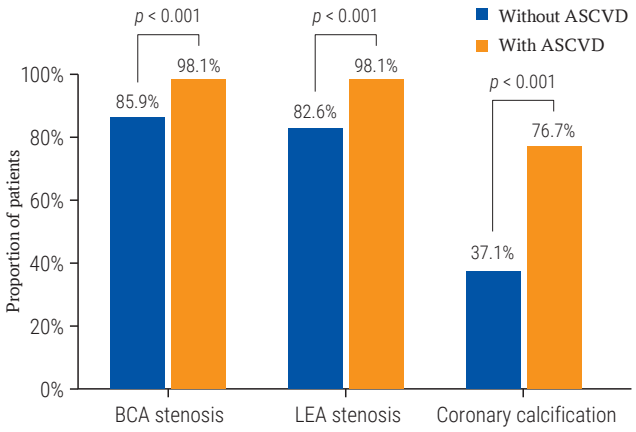

FIG. 4. Frequency of atherosclerotic vascular bed involvement in patients with and without documented atherosclerotic cardiovascular disease.

Notes: Pearson χ^2 test was used for comparisons.
ASCVD – atherosclerotic cardiovascular disease; BCA – brachiocephalic arteries; LEA – lower extremity arteries.

The study cohort comprised 1105 patients, accounting for 1.09% of the source database, which is consistent with international population estimates: in a large US registry of more than 500,000 individuals, an Lp(a) level of ⩾180 mg/dL corresponded to the 99th percentile of the distribution [12]. In an Israeli study of approximately 4000 patients, the prevalence of extremely high Lp(a) was 1.3% [13].

Notably, 29.5% of patients in our cohort had a history of ASCVD. By comparison, in the ESSE-RF study the prevalence of CAD among Russian adults aged 25–64 years was 5.7% [14], and the general population prevalence of CAD in the Russian Federation did not exceed 13.5% [15]. Thus, the frequency of ASCVD in the study cohort substantially exceeds population estimates, indirectly supporting an independent contribution of extremely high Lp(a) to an unfavorable cardiovascular prognosis.

At the national level, data from ESSE-RF show a pronounced right-skewed distribution of Lp(a) and a substantial proportion of individuals with elevated values, with an increase in ASCVD risk already apparent at Lp(a) > 9 mg/dL [6]. Within this context, the Lp(a) ⩾ 180 mg/dL group represents the most extreme segment of the population, with a very high lifetime risk. The clinical importance of this range is underscored by Russian registry data: in the REGION-MI study, Lp(a) > 180 mg/dL was detected in approximately 1 in 10 patients with myocardial infarction [16]. This emphasizes that extreme Lp(a) values are not a rarity but a practical concern for timely prevention and onward referral.

The lipid profile in our cohort was characterized by a combination of severe hypercholesterolemia and age-related changes in atherogenic lipid fractions. This phenotype is consistent with Russian population observations, in which Lp(a) showed positive associations with TC, LDL-C, and the apoB/apoA-I ratio [17]. This in part implies the presence of a modifiable risk layer (LDL-C/apoB) overlying the non-modifiable Lp(a) component, making this population potentially manageable when treatment is intensified in a timely manner.

Interpretation of LDL-C in individuals with very high Lp(a) requires caution: a portion of measured or calculated LDL-C may reflect cholesterol carried by Lp(a) particles, while approaches to correcting LDL-C for Lp(a)-cholesterol are not yet standardized [2]. In practical terms, this means that even with only moderately elevated LDL-C, a patient with Lp(a) ⩾ 180 mg/dL may retain a very high lifetime risk and may require more aggressive correction of risk factors than predicted by traditional risk scores.

It is worth noting that in real-world practice, even in patients with extremely high Lp(a), lipid-lowering therapy is often suboptimally intensified, and LDL-C targets are achieved in only a fraction of patients.

In the cross-sectional study by B. Zafrir et al. [13], only 33% of patients with Lp(a) > 430 nmol/L and CAD were receiving combination therapy with a statin and ezetimibe, and only 36% of those achieved an LDL-C target of < 55 mg/dL. At the same time, the prevalence of myocardial infarction (47.2% vs. 18.9%), CAD (62.3% vs. 28.3%), and peripheral artery disease and stroke (22.6% vs. 11.3%) was substantially higher in patients with Lp(a) > 430 nmol/L compared with those with values < 72 nmol/L [13].

Against this background, patients with extremely high Lp(a) represent a priority population both for classical LDL-C-lowering interventions and for the prospective introduction of Lp(a)-targeted therapy, which has demonstrated pronounced reductions in Lp(a) in early-phase clinical trials [18]. At present, the only available method of substantially lowering elevated Lp(a) levels is Lp(a) apheresis, used for secondary prevention when

maximally tolerated lipid-lowering therapy proves insufficient [19].

Our data show relative age-related stability of Lp(a) within the extreme range, consistent with the concept of early detection – including a one-time, lifetime measurement – followed by risk-based referral and follow-up [4].

A high prevalence of multifocal atherosclerosis was observed in the study cohort. This finding is consistent with data from the largest contemporary population-based analysis from China by S. Man et al. [20], which included approximately 2.9 million adults and showed that elevated Lp(a) was associated with subclinical atherosclerosis, with the effect being more pronounced for severe and multi-site involvement; the authors explicitly emphasize the need for comprehensive assessment of subclinical atherosclerosis in individuals with elevated Lp(a).

It should be emphasized that, in our study, full assessment of all three vascular beds was performed in only a limited number of patients, reflecting the systematic real-world under-evaluation of multifocal involvement. This in itself is an argument in favor of a standardized management algorithm for patients with extreme Lp(a) values, as an essential prerequisite for accurate risk re-stratification.

Our findings indicate an early onset, high prevalence and age-dependent nature of the atherosclerotic process in the study cohort. Additional support comes from the ESSE-RF sub-study ATEROGEN-Ivanovo [21], in which the prevalence of at least one atherosclerotic plaque in the carotid or femoral arteries among individuals aged 40–67 years was 73.6%, with plaques being detected as early as the age of 40 years. Comparable findings have been reported in the PESA study [22]: among more than 4000 asymptomatic individuals aged 40–54 years, subclinical atherosclerosis was identified in 63% of participants. Although Lp(a) was not assessed in those studies, they demonstrate a high prevalence of subclinical atherosclerosis in the working-age population and indirectly support the hypothesis of an earlier and more severe multifocal atherosclerotic phenotype in individuals with Lp(a) ⩾ 180 mg/dL.

In our cohort, coronary artery calcium screening in patients with extremely high Lp(a) reveals a clear age-related gradient not only in the frequency but also in the severity of coronary atherosclerosis. This supports the clinical value of CACS as a tool for refining individual cardiovascular risk assessment in this patient population. Further support for this approach comes from a pooled analysis of a multi-ethnic cohort, in which Lp(a) and CACS showed independent and additive effects on ASCVD risk, with the combination of CACS > 100 units and the top Lp(a) quintile being associated with an almost 5-fold increase in risk [23]. Thus, the combined assessment of these two markers identifies the highest-risk subgroups and helps to refine strategic decisions in primary prevention.

These findings, consistent with international observations, support the need for a standardized approach to identifying patients with extremely high Lp(a), with subsequent implementation of preventive programs and a system of follow-up. In particular, the Brussels International Declaration on Lp(a) Testing and Management calls for the integration of Lp(a) screening and patient referral into national cardiovascular health strategies, including a one-time, lifetime measurement in every adult [24]. In the United States, systemic initiatives are being implemented to improve detection of high-risk groups – for example, the FIND-Lp(a) project, which is developing a machine-learning model to analyze electronic medical records, identify individuals with a high likelihood of elevated Lp(a), and refer them for confirmatory laboratory testing[3].

Limitations and directions for future research

Our study is a single-center retrospective analysis, which limits the generalizability of the findings and precludes strict causal inferences. In addition, only patients with extremely high Lp(a) were included, and a complete assessment of all three vascular beds was performed only in a subset of patients, which may lead to an underestimation of the prevalence of multifocal atherosclerosis and complicate the extrapolation of these findings to patients with less marked Lp(a) elevations.

Promising directions for future research include large prospective studies with long-term follow-up of clinical outcomes in patients with extremely high Lp(a) and multifocal subclinical atherosclerosis, as well as the comparison of different screening and risk re-stratification algorithms incorporating Lp(a), CACS and vascular imaging. In addition, interventional trials of Lp(a)-targeted therapy with assessment of effects on subclinical atherosclerosis and cardiovascular events are warranted, as are efforts to standardize Lp(a) measurement and refine risk thresholds.

CONCLUSION

Patients with extremely high Lp(a) (⩾180 mg/dL) constitute a phenotype with very high lifetime cardiovascular risk and are characterized by early development of subclinical atherosclerosis. Even in young adulthood, the majority of these patients show signs of multifocal atherosclerosis, highlighting the limitations of traditional risk stratification approaches, which rely primarily on age and classical risk factors. These findings support the use of an Lp(a) threshold of ⩾180 mg/dL as a simple and reproducible criterion for

[3] The Family Heart Foundation. FIND Lp(a). https://familyheart.org/find/find-lpa (access date: 09.02.2026).

identifying a priority group warranting in-depth multibed vascular assessment, early risk re-stratification, and more intensive correction of modifiable risk factors, as well as a promising platform for the development of systemic atherosclerotic cardiovascular disease prevention.

AUTHOR CONTRIBUTIONS

Mikhail G. Chashchin developed the research idea and study design, participated in concept discussion, data analysis and verification, interpretation of results, critical revision, and manuscript writing. Zalina I. Khutaeva developed the study protocol, performed cohort selection and data verification, and participated in data analysis and interpretation, manuscript writing, and article editing. Maxim B. Mukhtarov extracted data from electronic medical records, developed the database, and participated in statistical analysis, preparation of graphical materials, and article editing. Zubaidat M. Musaeva and Khava A. Khashieva performed clinical data verification and participated in the interpretation of results and article editing. Vadim L. Averkiev reviewed clinical data and exclusion criteria and participated in the interpretation of results and article editing. Venera S. Rabicheva collected and processed the data and participated in the interpretation of results and article editing. Gennady A. Konovalov and Alexander Yu. Gorshkov participated in discussion of the study concept and methodology, critical revision of the manuscript, and article editing. Gennady A. Konovalov also participated in the interpretation of results. Oksana M. Drapkina provided overall scientific supervision and critically revised the manuscript for important intellectual content. All authors approved the final version of the article.

ВКЛАД АВТОРОВ

М.Г. Чащин разработал идею и дизайн исследования, участвовал в обсуждении концепции, анализе и верификации данных, интерпретации результатов, критическом пересмотре и написании текста рукописи. З.И. Хутаева разработала протокол исследования, проводила отбор выборки и верификацию данных, участвовала в анализе и интерпретации результатов, написании и редактировании статьи. М.Б. Мухтаров извлекал данные из электронных медицинских карт, формировал базу данных, участвовал в статистическом анализе, подготовке графических материалов и редактировании статьи. З.М. Мусаева и Х.А. Хашиева проводили клиническую верификацию данных, участвовали в интерпретации результатов и редактировании статьи. В.Л. Аверкиев оценивал клинические данные и критерии исключения, участвовал в интерпретации результатов и редактировании статьи. В.С. Рабичева проводила сбор и обработку данных, участвовала в интерпретации результатов и редактировании статьи. Г.А. Коновалов и А.Ю. Горшков участвовали в обсуждении концепции и методологии исследования, критическом пересмотре рукописи и редактировании статьи. Г.А. Коновалов также участвовал в интерпретации результатов. О.М. Драпкина осуществляла общее научное руководство и критический пересмотр рукописи с внесением значимого интеллектуального содержания. Все авторы утвердили окончательную версию статьи.

REFERENCES / ЛИТЕРАТУРА

1. *Афанасьева О.И., Покровский С.Н.* Липопротеид(а) – недооцененный в России фактор риска сердечно-сосудистых заболеваний. Время внедрять в клиническую практику. Российский кардиологический журнал. 2024; 29(8): 6035. https://doi.org/10.15829/1560-4071-2024-6035. EDN: ABZKLD / *Afanasyeva O.I., Pokrovsky S.N.* Lipoprotein (a) as underestimated cardiovascular risk factor in Russia. Time to introduce into clinical practice. Russian Journal of Cardiology. 2024; 29(8): 6035. (In Russian). https://doi.org/10.15829/1560-4071-2024-6035. EDN: ABZKLD
2. *Koschinsky M.L., Bajaj A., Boffa M.B., et al.* A focused update to the 2019 NLA scientific statement on use of lipoprotein (a) in clinical practice. J Clin Lipidol. 2024 May-Jun; 18(3): e308–e319. https://doi.org/10.1016/j.jacl.2024.03.001. Epub 2024 Apr 1. PMID: 38565461
3. *Ежов М.В., Кухарчук В.В., Балахонова Т.В. и др.* Клинические рекомендации Евразийской ассоциации кардиологии / Российского национального общества по изучению атеросклероза по диагностике и коррекции дислипидемий для профилактики и лечения атеросклероза (2025). Евразийский кардиологический журнал. 2025; 26(1): 6–34. https://doi.org/10.38109/2225-1685-2025-2-6-34. EDN: MACELC / *Ezhov M.V., Kukharchuk V.V., Balakhonova T.V., et al.* Eurasian Association of Cardiology / Russian National Atherosclerosis Society Guidelines for the diagnosis and correction of dyslipidemia for the prevention and treatment of atherosclerosis (2025). Eurasian Heart Journal. 2025; 26(1): 6–34 (In Russian). https://doi.org/10.38109/2225-1685-2025-2-6-34. EDN: MACELC
4. *Воевода М.И., Ежов М.В., Коновалов Г.А. и др.* Новые возможности применения исследования крови на липопротеин(а) в реальной клинической практике. Резолюция экспертного совета. Русский медицинский журнал. 2024; 9(2): 40–44. https://doi.org/10.32364/2225-2282-2024-9-7. EDN: WFHYUT / *Voevoda M.I., Ezhov M.V., Konovalov G.A., et al.* New opportunities to use a lipoprotein (a) blood test in real-life clinical practice. Resolution of the expert council. Russian Medical Journal. 2024; 9(2): 40–44 (In Russian). https://doi.org/10.32364/2225-2282-2024-9-7. EDN: WFHYUT
5. *Kronenberg F., Mora S., Stroes E.S.G., et al.* Lipoprotein (a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. Eur Heart J. 2022 Oct; 43(39): 3925–3946. https://doi.org/10.1093/eurheartj/ehac361. PMID: 36036785
6. *Ezhov M.V., Shalnova S.A., Yarovaya E.B., et al.* Lipoprotein (a) in an adult sample from the Russian population: distribution and association with atherosclerotic cardiovascular diseases. Arch Med Sci. 2021 Mar; 19(4): 995–1002. https://doi.org/10.5114/aoms/131089. PMID: 37560742
7. *Хутаева З.И., Коновалов Г.А.* Липопротеид(а): новые подходы в оценке риска и его управления. Атеросклероз и дислипидемии. 2025; 1(58): 5–12. https://doi.org/10.34687/2219-8202.JAD.2025.01.0001. EDN: SWYSZT / *Khutaeva Z.I., Konovalov G.A.* Lipoprotein (a): new approaches in risk assessment and management. Atherosclerosis and Dyslipidemias. 2025; 1(58): 5–12 (In Russian). https://doi.org/10.34687/2219-8202.JAD.2025.01.0001. EDN: SWYSZT
8. *Kamstrup P.R., Benn M., Tybjærg-Hansen A., Nordestgaard B.G.* Extreme lipoprotein (a) levels and risk of myocardial infarction in the general population. Circulation. 2008 Jan; 117(2): 176–184. https://doi.org/10.1161/CIRCULATIONAHA.107.715698. Epub 2007 Dec 17. PMID: 18086931
9. *Thomas P.E., Vedel-Krogh S., Nielsen S.F., et al.* Lipoprotein (a) and risks of peripheral artery disease, abdominal aortic aneurysm, and major adverse limb events. J Am Coll Cardiol. 2023 Dec;

82(24): 2265–2276. https://doi.org/10.1016/j.jacc.2023.10.009. PMID: 38057068
10. *Kamstrup P.R., Tybjærg-Hansen A., Nordestgaard B.G.* Elevated lipoprotein (a) and risk of aortic valve stenosis in the general population. J Am Coll Cardiol. 2014 Feb; 63(5): 470–477. https://doi.org/10.1016/j.jacc.2013.09.038. Epub 2013 Oct 23. PMID: 24161338
11. *Nordestgaard A.T., Chasman D.I., Moorthy V., et al.* Thirty-year risk of cardiovascular disease among healthy women according to clinical thresholds of lipoprotein (a). JAMA Cardiol. 2026 Feb; 11(2): 175–185. https://doi.org/10.1001/jamacardio.2025.5043. PMID: 41499112
12. *Varvel S., McConnell J.P., Tsimikas S.* Prevalence of elevated Lp(a) mass levels and patient thresholds in 532 359 patients in the United States. Arterioscler Thromb Vasc Biol. 2016 Nov; 36(11): 2239–2245. https://doi.org/10.1161/atvbaha.116.308011. Epub 2016 Sep 22. PMID: 27659098
13. *Zafrir B., Aker A., Saliba W.* Extreme lipoprotein (a) in clinical practice: a cross sectional study. Int J Cardiol Cardiovasc Risk Prev. 2023 Jan; 16: 200173. https://doi.org/10.1016/j.ijcrp.2023.200173. PMID: 36874038
14. *Муромцева Г.А., Вилков В.Г., Константинов В.В. и др.* Распространенность электрокардиографических нарушений в российской популяции в начале XXI века (по данным исследования ЭССЕ-РФ). Российский кардиологический журнал. 2018; 23(12): 7–17. https://doi.org/10.15829/1560-4071-2018-12-7-17. EDN: YPPAWL / *Muromtseva G.A., Vilkov V.G., Konstantinov V.V., et al.* The prevalence of electrocardiographic abnormalities in the Russian population in the early 21st century (the ESSE-RF study). Russian Journal of Cardiology. 2018; 23(12): 7–17 (In Russian). https://doi.org/10.15829/1560-4071-2018-12-7-17. EDN: YPPAWL
15. *Шальнова С.А., Деев А.Д.* Ишемическая болезнь сердца в России: распространенность и лечение (по данным клинико-эпидемиологических исследований). Терапевтический архив. 2011; 83(1): 7–12. / *Shalnova S.A., Deev A.D.* Coronary heart disease in Russia: incidence rate and treatment according to epidemiological data. Therapeutic Archive. 2011; 83(1): 7–12 (In Russian)
16. *Ежов М.В., Шахнович Р.М., Алексеева И.А. и др.* Распространенность и значение повышенного уровня липопротеина(а) у пациентов с инфарктом миокарда по данным российского регистра острого инфаркта миокарда РЕГИОН-ИМ. Кардиологический вестник. 2025; 20(1): 39–48. https://doi.org/10.17116/Cardiobulletin20252001139. EDN: WADXRV / *Ezhov M.V., Shakhnovich R.M., Alekseeva I.A., et al.* Prevalence and role of elevated serum lipoprotein (a) in patients with myocardial infarction according to the Russian register of acute myocardial infarction REGION-MI. Cardiological Bulletin. 2025; 20(1): 39–48 (In Russian). https://doi.org/10.17116/Cardiobulletin20252001139. EDN: WADXRV
17. *Шальнова С.А., Ежов М.В., Метельская В.А. и др.* Ассоциация липопротеина(а) и факторов риска атеросклероза в российской популяции (данные наблюдательного исследования ЭССЕ-РФ). Рациональная фармакотерапия в кардиологии. 2019; 15(5): 612–621. https://doi.org/10.20996/1819-6446-2019-15-5-612-621. EDN: KBMFPI / *Shalnova S.A., Ezhov M.V., Metelskaya V.A., et al.* Association between lipoprotein (a) and risk factors of atherosclerosis in Russian population (data of observational ESSE-RF study). Rational Pharmacotherapy in Cardiology. 2019; 15(5): 612–621 (In Russian). https://doi.org/10.20996/1819-6446-2019-15-5-612-621. EDN: KBMFPI
18. *O'Donoghue M.L., Rosenson R.S., Gencer B., et al.* Small interfering RNA to reduce lipoprotein (a) in cardiovascular disease. N Engl J Med. 2022 Nov; 387(20): 1855–1864. https://doi.org/10.1056/NEJMoa2211023. Epub 2022 Nov 6. PMID: 36342163
19. *Pokrovsky S.N., Afanasieva O.I., Safarova M.S., et al.* Specific Lp(a) apheresis: A tool to prove lipoprotein (a) atherogenicity. Atheroscler Suppl. 2017 Nov; 30: 166–173. https://doi.org/10.1016/j.atherosclerosissup.2017.05.004. Epub 2017 May 31. PMID: 29096833
20. *Man S., Zu Y., Yang X., et al.* Prevalence of elevated lipoprotein (a) and its association with subclinical atherosclerosis in 2.9 million Chinese adults. J Am Coll Cardiol. 2025 Jun; 85(21): 1979–1992. https://doi.org/10.1016/j.jacc.2025.02.032. Epub 2025 Apr 23. PMID: 40266173
21. *Ершова А.И., Балахонова Т.В., Мешков А.Н. и др.* Распространенность атеросклероза сонных и бедренных артерий среди населения Ивановской области: данные исследования АТЕРОГЕН-Иваново. Кардиоваскулярная терапия и профилактика. 2021; 20(5): 2994. https://doi.org/10.15829/1728-8800-2021-2994. EDN: BFATEF / *Ershova A.I., Balakhonova T.V., Meshkov A.N., et al.* Prevalence of carotid and femoral artery atherosclerosis among the Ivanovo Oblast population: data from the ATEROGEN-Ivanovo study. Cardiovascular Therapy and Prevention. 2021; 20(5): 2994 (In Russian). https://doi.org/10.15829/1728-8800-2021-2994. EDN: BFATEF
22. *Fernández-Friera L., Peñalvo J.L., Fernández-Ortiz A., et al.* Prevalence, vascular distribution, and multiterritorial extent of subclinical atherosclerosis in a middle-aged cohort. Circulation. 2015 Jun; 131(24): 2104–2113. https://doi.org/10.1161/CIRCULATIONAHA.114.014310. Epub 2015 Apr 16. PMID: 25882487
23. *Mehta A., Vasquez N., Ayers C.R., et al.* Independent association of lipoprotein (a) and coronary artery calcification with atherosclerotic cardiovascular risk. J Am Coll Cardiol. 2022 Mar; 79(8): 757–768. https://doi.org/10.1016/j.jacc.2021.11.058. PMID: 35210030
24. *Kronenberg F., Bedlington N., Ademi Z., et al.* The Brussels International declaration on lipoprotein (a) testing and management. Atherosclerosis. 2025; 406: 119218. https://doi.org/10.1016/j.atherosclerosis.2025.119218. Epub 2025 May 5. PMID: 40340180

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Immune-related thyroid dysfunction and survival in patients treated with immune checkpoint inhibitors: a multicenter prospective cohort study

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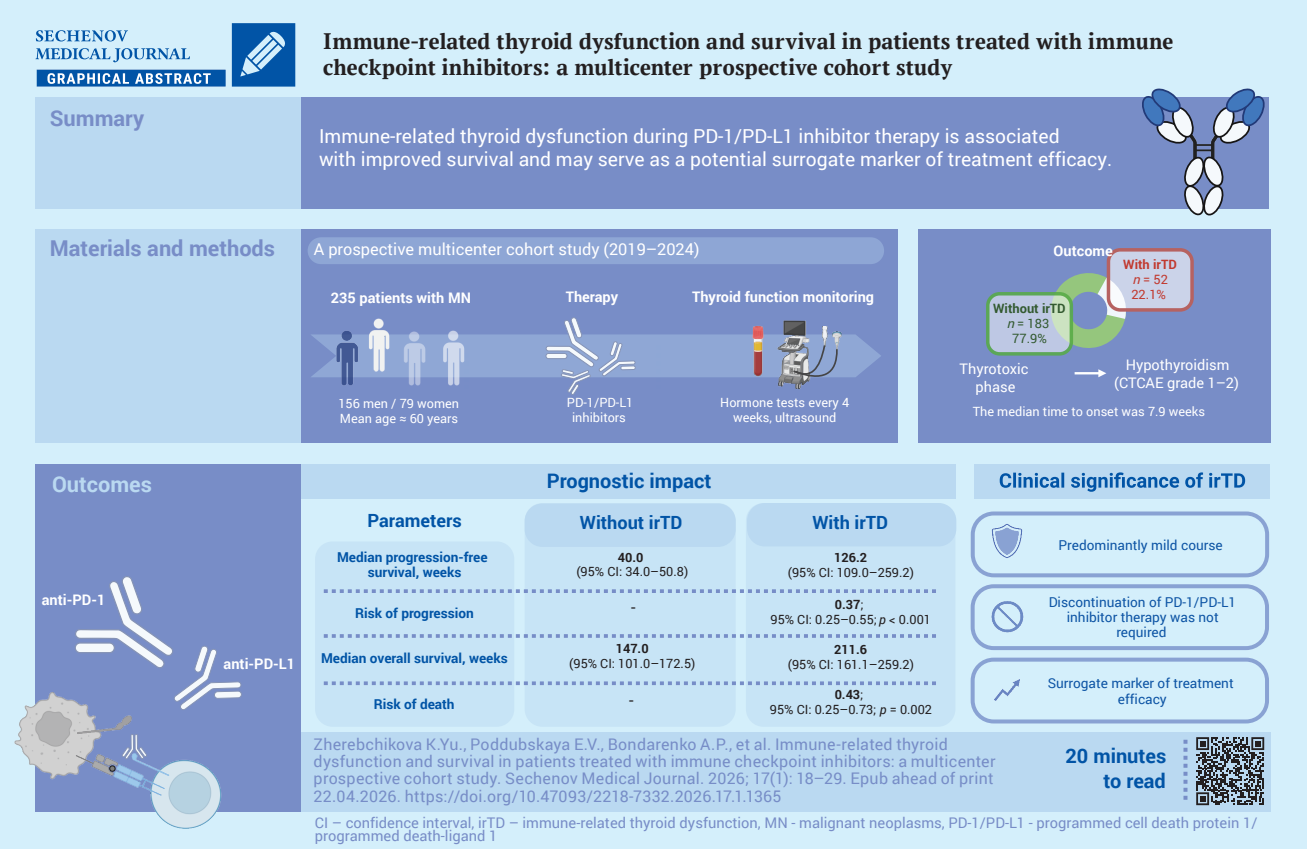

Abstract

Aim. To assess the association between immune-related thyroid dysfunction (irTD) and overall survival or progression-free survival in patients with malignant neoplasms receiving immune checkpoint inhibitor therapy.

Materials and methods. This multicenter prospective cohort study comprised 235 patients (156 men; mean age approximately 60 years) with histologically or cytologically confirmed malignancies of various localizations who were treated with programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) inhibitors. Thyroid function was assessed before the treatment and every 4 weeks thereafter. irTD was diagnosed based on standardized biochemical and ultrasound criteria. Adverse events were graded according to CTCAE (Common Terminology Criteria for Adverse Events). Survival was analyzed using the Kaplan–Meier method, with comparisons performed using

the log-rank test, and univariable Cox proportional hazards models, with hazard ratios (HRs) and 95% confidence intervals (CIs), were applied.
Results. irTD occurred in 52 patients (22.1%). In all cases, destructive thyroiditis with a transient thyrotoxic phase followed by hypothyroidism (CTCAE grade 1–2) was observed and did not require discontinuation of immune checkpoint inhibitors. The median time to irTD onset was 7.9 weeks. Patients with and without irTD were comparable in terms of sex, age, disease stage, previous cancer therapy, and type of PD-1/PD-L1 inhibitors. The development of irTD was associated with better progression-free survival (median 126.2 vs 40.0 weeks; HR 0.37; 95% CI: 0.25–0.55; $p < 0.001$) and better overall survival (211.6 vs 147.0 weeks; HR 0.43; 95% CI: 0.25–0.73; $p = 0.002$).
Conclusion. In this prospective multicenter cohort study, irTD occurred in approximately one-fifth of patients treated with PD-1/PD-L1 inhibitors, mainly during the first weeks of therapy, was generally mild, and was associated with improved survival. These findings suggest that irTD may be considered as a potential surrogate marker of treatment efficacy and support the need for regular monitoring of thyroid function during immunotherapy.

Keywords: thyroid gland; thyroiditis; adverse events; immune toxicity; PD-1/PD-L1 inhibitors
MeSH terms:
NEOPLASMS – DRUG THERAPY
IMMUNE CHECKPOINT INHIBITORS – IMMUNOLOGY
IMMUNE CHECKPOINT INHIBITORS – THERAPEUTIC USE
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THYROIDITIS – CHEMICALLY INDUCED
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Ethics statements. The study protocol was reviewed and approved by the Local Ethics Committee of Sechenov First Moscow State Medical University (Sechenov University) (protocol No. 03-19 dated February 13, 2019). In accordance with existing cooperation agreements between the institutions, the conduct of the study at the Clinical Hospital of JSC "MEDSI Group of Companies", the Department of Antitumor Drug Therapy of the Lomonosov Moscow State University Medical Research and Educational Center, and the multidisciplinary medical center "VitaMed" was carried out on the basis of this ethical approval. All patients provided written informed consent to participate in the study.
Data availability. The data that support the findings of this study are available from the corresponding authors on reasonable request. Data and statistical methods used in the article were examined by a professional biostatistician on the Sechenov Medical Journal editorial staff.
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Иммуноопосредованные тиреопатии и выживаемость пациентов, получающих терапию ингибиторами контрольных точек иммунного ответа: многоцентровое проспективное когортное исследование

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Аннотация

Цель. Оценить ассоциацию между развитием иммуноопосредованной тиреопатии (ИТ) и показателями общей выживаемости и выживаемости без прогрессирования у пациентов со злокачественными новообразованиями, получающих терапию ингибиторами контрольных точек иммунного ответа.

Материалы и методы. В многоцентровое проспективное когортное наблюдательное исследование включены 235 пациентов (156 мужчин, средний возраст около 60 лет) с гистологически или цитологически подтвержденными злокачественными новообразованиями различной локализации, впервые начинавших терапию ингибиторами рецептора программируемой клеточной гибели 1 и его лиганда (programmed cell death protein 1/programmed death-ligand 1, PD-1/PD-L1). Функцию щитовидной железы оценивали исходно и далее каждые 4 недели; ИТ диагностировали по стандартизированным биохимическим и ультразвуковым критериям. Степень тяжести нежелательных явлений определяли по шкале общих терминологических критериев оценки нежелательных явлений (Common Terminology Criteria for Adverse Events, CTCAE). Показатели выживаемости анализировали методом Каплана–Мейера с использованием лог-рангового теста и однофакторных моделей Кокса с расчетом отношения рисков (hazard ratio, HR) и 95% доверительных интервалов (ДИ).

Результаты. ИТ развилась у 52 пациентов (22,1%); во всех случаях отмечен деструктивный тиреоидит с транзиторной тиреотоксической фазой и последующим гипотиреозом 1–2-й степени по шкале CTCAE, не потребовавший отмены ингибиторов контрольных точек иммунного ответа. Медиана времени до манифестации ИТ составила 7,9 недели. Группы пациентов с ИТ и без ИТ были сопоставимы по полу, возрасту, стадии заболевания, предшествующему лечению и применяемым ингибиторам PD-1/PD-L1. Развитие ИТ ассоциировалось со значимым увеличением выживаемости без прогрессирования (медиана 126,2 против 40,0 недели; HR 0,37; 95% ДИ 0,25–0,55; $p < 0,001$) и общей выживаемости (211,6 против 147,0 недели; HR 0,43; 95% ДИ 0,25–0,73; $p = 0,002$).

Заключение. В проспективной многоцентровой когорте ИТ выявлялась примерно у пятой части пациентов, преимущественно в первые недели терапии, протекала в виде легких иммуноопосредованных нежелательных явлений и сопровождалась улучшением выживаемости. Эти данные позволяют рассматривать ИТ как потенциальный суррогатный маркер эффективности терапии ингибиторами PD-1/PD-L1 и подчеркивают необходимость регулярного мониторинга функции щитовидной железы при иммунотерапии.

Ключевые слова: щитовидная железа; тиреоидит; нежелательные явления; иммунная токсичность; ингибиторы PD-1/PD-L1

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КОНТАКТНАЯ ИНФОРМАЦИЯ:
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Доступ к данным исследования. Данные, подтверждающие выводы этого исследования, можно получить у авторов по обоснованному запросу. Данные и статистические методы, представленные в статье, прошли статистическое рецензирование редактором журнала – сертифицированным специалистом по биостатистике.
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Abbreviations:

CI – confidence interval
fT3 – free triiodothyronine
fT4 – free thyroxine
ICIs – immune checkpoint inhibitors
irAEs – immune-related adverse events
irTD – immune-related thyroid dysfunction
MN – malignant neoplasms
PD-1/PD-L1 – programmed cell death protein 1/programmed death-ligand 1
TSH – thyroid-stimulating hormone

HIGHLIGHTS

In a prospective multicenter cohort receiving programmed cell death protein 1/programmed death-ligand 1 inhibitors, immune-related thyroid dysfunction is common and rarely requires treatment discontinuation.

The most typical clinical course is thyroiditis with a transient thyrotoxic phase followed by persistent hypothyroidism; no cases of Graves' disease are observed.

The development of thyroid dysfunction is associated with improved overall survival and progression-free survival in the overall cohort.

Malignant neoplasms remain one of the leading medical and social challenges worldwide, ranking among the top causes of morbidity, disability, and mortality. According to the International Agency for Research on Cancer (IARC), approximately 20 million new cases of malignant neoplasms (MN) and more than 9.7 million cancer-related deaths were recorded globally in 2022 [1]. It is projected that by 2050, the number of newly diagnosed cases may exceed 35 million, largely due to population aging, lifestyle changes, and exposure to environmental carcinogens [2].

A breakthrough in the systemic treatment of malignant neoplasms has been achieved with the introduction of immune checkpoint inhibitors (ICIs). Unlike cytotoxic and targeted therapies, these agents do not directly affect tumor cells but instead restore the

ability of the immune system to recognize and eliminate them. Monoclonal antibodies targeting programmed cell death protein 1 (PD-1) and its ligand, programmed death-ligand 1 (PD-L1), have demonstrated substantial efficacy across a wide range of MN, including both localized and metastatic disease, significantly improving patient survival outcomes [1, 3–5].

However, by enhancing immune activation, ICIs may also induce immune-related adverse events (irAEs) affecting various organs and systems. Thyroid dysfunction represents one of the most common irAEs associated with cancer immunotherapy [6]. The most frequent immune-related thyroid dysfunction (irTD) is destructive thyroiditis, typically characterized by an initial thyrotoxic phase followed by the development of persistent hypothyroidism requiring long-term hormone replacement therapy [7–9]. The pathogenesis of this complication remains incompletely understood; proposed mechanisms include immune-mediated destruction of thyroid follicular cells, activation of thyroid-specific autoantibodies, and cross-reactivity between tumor antigens and thyroid tissue [10, 11].

Recent studies suggest that the development of irAEs, including thyroid dysfunction, may be associated with improved clinical outcomes in patients receiving ICI therapy [12–14].

The objective of this study was to evaluate the association between the development of irTD and overall survival as well as progression-free survival in patients with malignant neoplasms of various localizations treated with ICIs.

MATERIALS AND METHODS

Study design

A multicenter prospective cohort observational study was conducted. Consecutive patients referred for scheduled systemic anticancer therapy for solid MN were enrolled at the following institutions: Sechenov First Moscow State Medical University (Sechenov University), Clinical Hospital of MEDSI Group JSC, University Clinic of Lomonosov Moscow State University, and multidisciplinary medical center VitaMed LLC. Patient recruitment was carried out between October 7, 2019, and December 27, 2024.

Sample size calculation

The sample size (n = 235) was determined at the study planning stage. It was based on the expected incidence of irTD of approximately 20–25%, according to published data on PD-1/PD-L1 inhibitor therapy, with an acceptable precision of the estimate (95% margin of error of approximately ± (5–6) percentage points). In addition, the planned sample provided a sufficient number of events for survival analysis: with 91 events, the study had 80% power to detect a moderate effect size (hazard ratio of approximately 0.5) at a two-sided significance level of 0.05.

Patient enrollment

The patient inclusion flowchart is presented in Figure 1. A total of 258 patients were screened for eligibility.

Inclusion criteria:

- age ⩾ 18 years;
- histologically or cytologically confirmed solid malignant tumor requiring ICI therapy according to clinical guidelines applicable during the study period;
- euthyroid status at baseline;
- signed informed consent for study participation.

A total of 254 patients met the inclusion criteria.

Non-inclusion criteria:

- prior treatment with ICIs (n = 4);
- history of thyroid dysfunction (n = 10);
- estimated glomerular filtration rate < 30 mL/min/1.73 m^2 calculated using the CKD-EPI 2021 equation (n = 0);
- Child–Pugh class B or C liver cirrhosis (n = 0);
- psychiatric disorders (n = 0);
- amiodarone therapy (n = 0);
- pregnancy or lactation (n = 0).

Exclusion criteria:

- withdrawal of informed consent / refusal to continue participation (n = 0);
- loss to follow-up (n = 4);
- absence of laboratory data required for analysis (n = 1).

Non-inclusion criteria were identified in 14 patients. Five patients were excluded from the final analysis: four due to loss to follow-up and one because of missing laboratory data. A total of 235 patients (156 men and 79 women) who received PD-1/PD-L1 inhibitor therapy for the first time were included in the study.

Primary disease characteristics

MN staging was performed according to the 8th edition of the TNM Classification of the American Joint Committee on Cancer (AJCC), applicable during the study period [15].

Diagnosis of ICI-associated thyroid dysfunction

Thyroid hormone levels were assessed at baseline, as part of mandatory toxicity screening every 4 weeks after initiation of ICI therapy, and additionally whenever clinical symptoms suggestive of thyroid dysfunction occurred. Laboratory testing was centralized and performed at the independent laboratory INVITRO LLC. Serum thyroid-stimulating hormone (TSH), free thyroxine (fT4), and free triiodothyronine (fT3) concentrations were measured using a chemiluminescent immunoassay on the automated Alinity i analyzer (Abbott, USA) with manufacturer-provided reagents. Reference ranges were as follows: TSH, 0.4–4.0 μIU/mL; fT4, 9.0–19.05 pmol/L; fT3, 3.0–5.6 pmol/L.

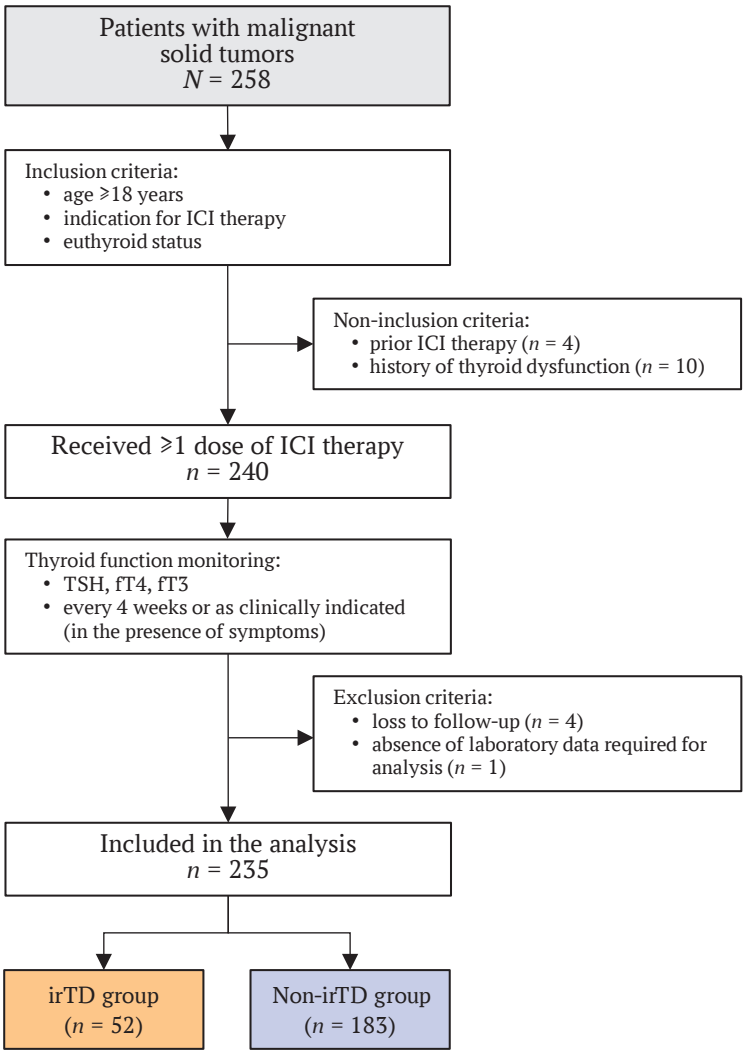

FIG. 1. Patient enrollment flowchart.

Note: fT3 – free triiodothyronine; fT4 – free thyroxine; ICI – immune checkpoint inhibitor; irTD – immune-related thyroid dysfunction; TSH – thyroid-stimulating hormone.

Thyroid ultrasound was performed centrally at University Clinical Hospital No. 2 of I.M. Sechenov First Moscow State Medical University (Sechenov University) using a Voluson-i ultrasound system (General Electric, USA) with a 12-MHz linear transducer.

Hypothyroidism was diagnosed when TSH exceeded 4.0 μIU/mL in combination with normal or decreased fT4 levels.

Thyroiditis was diagnosed in the thyrotoxic phase when TSH was decreased with elevated or normal fT4 and/or fT3 levels, and in the hypothyroid phase when TSH was elevated with decreased or normal fT4 and/or fT3 levels[1].

According to the recommendations of the National Comprehensive Cancer Network, destructive thyrotoxicosis was presumed when transient thyrotoxicosis spontaneously progressed to hypothyroidism during follow-up thyroid function assessment [16]. To exclude Graves' disease, the absence of a characteristic clinical presentation (including orbitopathy), the absence of increased intrathyroidal vascularity on color Doppler ultrasonography, and the absence of increased blood flow velocity in the inferior thyroid artery >40 cm/s were additionally taken into account.

Outcome assessment

Progression-free survival was defined as the interval from initiation of ICI therapy to disease progression according to RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1 criteria [17] or death

[1] Ministry of Health of the Russian Federation. Hypothyroidism: clinical guidelines. 2024. https://cr.minzdrav.gov.ru/view-cr/531_4 (access date: 05.08.2025).

from any cause, whichever occurred first. Overall survival was defined as the interval from initiation of ICI therapy to death from any cause or the date of last patient contact (censored observation). Tumor response assessment using computed tomography (CT) was performed every 12 weeks.

The severity of irAEs was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) [18]. Follow-up was terminated upon progression of MN, death, or patient withdrawal from the study.

Statistical analysis

Continuous variables were assessed for normality using the Kolmogorov–Smirnov test. Variables with a normal distribution are presented as mean and standard deviation, whereas non-normally distributed variables are presented as median and interquartile range (25th–75th percentiles).

Categorical variables are reported as absolute counts and percentages. Comparisons between two groups for continuous variables with normal distribution and homogeneity of variances were performed using Student's *t*-test. When the distribution deviated from normality, the nonparametric Mann–Whitney *U* test was applied.

Categorical variables were compared using Pearson's chi-square test when expected frequencies exceeded 10; otherwise, the two-sided Fisher's exact test was used. Survival analysis was performed using the Kaplan–Meier method. Differences between groups in time to death and disease progression were assessed using the log-rank test. Event risk was evaluated using univariable Cox proportional hazards models with calculation of hazard ratios (HRs) and 95% confidence intervals (CIs). A two-sided p value <0.05 was considered statistically significant.

Statistical analyses were performed using R software version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria) and StatTech version 4.6.1 (StatTech LLC, Russia).

RESULTS

Incidence of immune-related thyroid dysfunction

During the entire follow-up period, irTD was identified in 52 patients (22.1%). At initial presentation, thyrotoxicosis and hypothyroidism occurred with equal frequency (26 cases each). Graves' disease was excluded in all cases of thyrotoxicosis.

In all cases, thyrotoxicosis was transient and attributable to destructive thyroiditis. In one patient, hypothyroidism developed as part of autoimmune polyglandular syndrome, in combination with primary adrenal insufficiency and diabetes mellitus. The median time to onset of immune-related thyroid dysfunction from initiation of ICI therapy was 7.9 (6.0–9.1) weeks.

All patients with hypothyroidism received levothyroxine replacement therapy at doses of 75–150 µg/day, resulting in achievement and maintenance of TSH levels within the reference range. During the thyrotoxic phase of destructive thyroiditis, nine patients received beta-blockers for tachycardia control.

All thyroid dysfunction events were classified as grade 1 or 2 adverse events according to CTCAE and did not require treatment discontinuation or dose modification of ICI therapy.

Baseline characteristics of patients with and without immune-related thyroid dysfunction

In both groups, the majority of patients were men, with a mean age of approximately 60 years, and no significant differences were observed in these parameters. In nearly half of the patients in both groups, the primary tumor site was the lung (42–50%). Gastrointestinal malignancies (esophageal, gastric, and hepatic cancers) were observed in approximately 19–25% of patients, while cutaneous melanoma accounted for 12–19%. More than half of the patients had stage IV MN (Table).

No between-group differences were found regarding prior treatment history. A substantial proportion of patients in both groups had previously received systemic anticancer therapy (54–66%). Prior surgery had been performed in half of the patients in the first group and in 40% of those in the second group. Previous radiotherapy was reported in approximately one quarter of patients in both groups.

Most patients in both groups received PD-1 inhibitors. The most frequently prescribed agent was nivolumab, followed by pembrolizumab, whereas tislelizumab was used less often. The proportion of patients treated with PD-L1 inhibitors (atezolizumab or avelumab) was considerably lower, accounting for approximately 9–10% in each group.

Progression-free survival

Comparative analysis demonstrated that the development of irTD was significantly associated with a lower risk of disease progression compared with patients without thyroid dysfunction. The median progression-free survival in patients without thyroid dysfunction was 40.0 weeks from treatment initiation (95% CI: 34.0–50.8), whereas in patients who developed thyroid dysfunction it was 126.2 weeks (95% CI: 109.0–259.2).

In the univariable Cox proportional hazards model, the presence of irTD was associated with a statistically significant reduction in the risk of disease progression (HR 0.37; 95% CI: 0.25–0.55; $p < 0.001$), corresponding

Table. **Baseline characteristics of patients with and without immune-related thyroid dysfunction**

Variable	irTD group (*n* = 52)	Non-irTD group (*n* = 183)	*p* value
Male / female	30 / 22 (57.7 / 42.3)	126 / 57 (68.9 / 31.1)	0.181
Age, years	60.1 ± 12.0	60.5 ± 11.5	0.886
Primary tumor site			
lung	22 (42.3)	92 (50.3)	0.220
gastrointestinal tract	13 (25.0)	34 (18.6)	
melanoma	10 (19.3)	22 (12.0)	
other	7 (13.5)	35 (19.1)	
Tumor stage			
I	1 (1.9)	7 (3.8)	0.722
II	9 (17.3)	25 (13.7)	
III	13 (25.0)	35 (19.1)	
IV	29 (55.8)	116 (63.4)	
Previous treatment			
systemic anticancer therapy	28 (53.9)	120 (65.6)	0.055
surgery	26 (50.0)	73 (39.9)	0.253
radiotherapy	15 (28.9)	46 (25.1)	0.719
PD-1/PD-L1 inhibitors			
nivolumab	27 (51.9)	98 (53.4)	0.901
pembrolizumab	17 (32.7)	52 (28.4)	
tislelizumab	3 (5.8)	17 (9.3)	
atezolizumab	3 (5.8)	8 (4.4)	
avelumab	2 (3.9)	8 (4.4)	

Notes: quantitative variables are presented as mean with standard deviation (*M* ± SD), categorical variables are presented as the absolute number of patients with the characteristic and the proportion within the group, expressed as a percentage (in parentheses).
irTD – immune-related thyroid dysfunction; PD-1/PD-L1 – programmed cell death protein 1/programmed death-ligand 1.

to an approximately 2.7-fold lower relative risk of the event (Fig. 2).

Overall survival

By the end of follow-up, 91 deaths (38.7%) had been recorded. Comparative analysis demonstrated a statistically significant association between the development of irTD and a lower risk of death.

The median overall survival in patients without thyroid dysfunction was 147.0 weeks from treatment initiation (95% CI: 101.0–172.5), whereas in patients who developed thyroid dysfunction it was 211.6 weeks (95% CI: 161.1–259.2).

In the univariable Cox proportional hazards model, the development of irTD was associated with a statistically significant reduction in the risk of death (HR 0.43; 95% CI: 0.25–0.73; $p = 0.002$), corresponding to an approximately 2.3-fold lower relative risk of the event.

The 1-year and 3-year overall survival rates in the irTD group were 91.9% (95% CI: 79.9–96.9) and 69.9% (95% CI: 52.4–82.0), respectively, whereas in patients without thyroid dysfunction they were 69.0% (95% CI: 60.6–76.0) and 43.9% (95% CI: 33.3–53.9), respectively (log-rank test, $p = 0.002$; Fig. 3).

DISCUSSION

The present study, which is the first prospective multicenter study conducted in the Russian

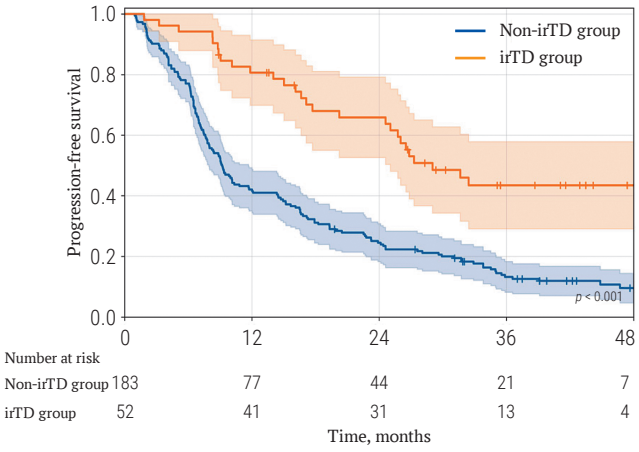

FIG. 2. Kaplan–Meier curve for progression-free survival.

Note: irTD – immune-related thyroid dysfunction.

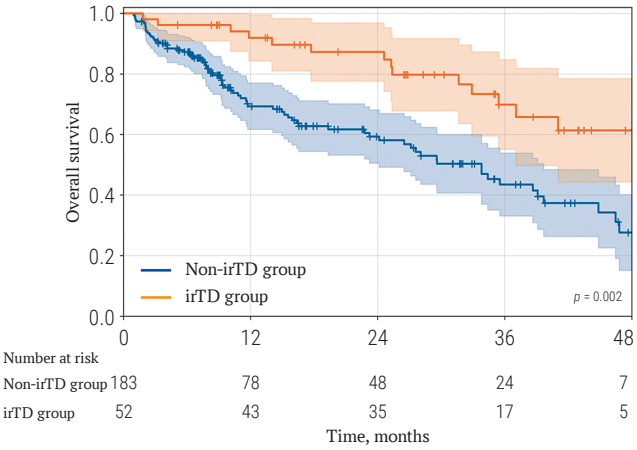

FIG. 3. Kaplan–Meier curve for overall survival.

Note: irTD – immune-related thyroid dysfunction.

Federation, demonstrated an association between the development of irTD and improved overall survival as well as progression-free survival in patients with various MN receiving PD-1/PD-L1 inhibitor therapy.

Our findings are consistent with the meta-analysis by Y.M. Cheung et al. [19], in which thyroid irAEs during ICI therapy were associated with an approximately 48% lower risk of death and a 42% lower risk of disease progression. In our cohort, the association with progression-free survival was even more pronounced: the presence of irTD was associated with a threefold increase in median progression-free survival and a 63% reduction in the risk of progression in the univariable Cox model. In addition, 1-year and 3-year overall survival in patients with thyroid dysfunction exceeded the corresponding values in patients without thyroid dysfunction by 22.9 and 26 percentage points, respectively.

It should be emphasized that our study included a heterogeneous population with different MN. In both groups, the lung was the most common primary tumor site, accounting for nearly half of all cases, followed by gastrointestinal malignancies (gastric, esophageal, and hepatic cancers), and cutaneous melanoma. Studies by Š. Cerić et al. [13], M. Xiao et al. [20], and A. Dawidowska et al. [14] in separate cohorts of patients with non-small cell lung cancer, gastric cancer, and melanoma, as well as several studies including mixed cancer populations [21, 22], have shown that the development of irAEs, including thyroid events, is associated with improved efficacy of ICI therapy and better survival outcomes. In several studies, Cox models with time-dependent covariates treating thyroid dysfunction as an event occurring during follow-up were used to minimize immortal time bias and confirmed the robustness of this association [13, 23].

Taken together, these findings support the notion that the association observed in the present study is reproducible across different patient populations, including both homogeneous disease-specific cohorts and heterogeneous cancer populations. Collectively, these data suggest that thyroid irAEs may serve as a potential surrogate marker of PD-1/PD-L1 inhibitor efficacy in patients with different MN. Although the exact biological mechanisms underlying this association remain under discussion, it has been proposed that the development of thyroid dysfunction reflects systemic immune activation induced by ICI therapy. In this context, thyroid dysfunction should not be viewed as an independent factor improving survival, but rather as a clinical marker of a more pronounced antitumor immune response, which may explain its association with more favorable oncologic outcomes [24, 25].

Immune checkpoint inhibitors are believed to disrupt mechanisms of peripheral immune tolerance, leading to activation of autoreactive T-cell clones, T-cell-mediated injury of thyroid follicular epithelium, and the development of destructive thyroiditis. The serological profile of ICI-associated thyroid dysfunction differs from that of classical Hashimoto thyroiditis: thyroid autoantibodies are detected less frequently and usually at lower titers, suggesting only partial overlap of the immunopathogenesis with spontaneous autoimmune thyroid disease [24, 26].

In our cohort, the overall incidence of irTD was 22.1%, which is comparable to the meta-analysis by J. de Filette et al. [10], where thyroid dysfunction was reported in approximately 20–30% of patients receiving PD-1/PD-L1 inhibitors. Thyroiditis most commonly developed within the first 8 weeks after initiation of ICI therapy, in agreement with previous studies by E.M. Presotto et al. [27] and R.M. Ruggeri et al. [28], in which the mean time to onset of thyroid adverse events was approximately 6–10 weeks.

In our cohort, the frequencies of thyrotoxic and hypothyroid phases were comparable, reflecting the heterogeneous clinical course of ICI-related thyroiditis described by C.A. Muir et al. [26]. All cases of thyrotoxicosis were transient and did not require antithyroid drug therapy. The absence of Graves' disease is consistent with observations by H.J. Lee et al. [29], and J.C. Osorio et al. [11], who reported this condition to be a very rare complication of PD-1/PD-L1 inhibitor therapy. All thyroid dysfunction events were classified as grade 1–2 according to CTCAE and required neither treatment discontinuation nor dose modification. This is in line with international data showing that thyroid irAEs are usually mild to moderate and rarely necessitate cessation of ICI therapy.

Study limitations and future directions

Survival analysis was performed in the pooled cohort without detailed stratification by individual tumor types; therefore, our findings do not reflect potential differences across specific malignancies. In addition, we deliberately did not apply more complex time-bias adjustment methods because, given the available number of events, such approaches could have resulted in unstable and difficult-to-interpret estimates.

Future studies should focus on individual MN types, include longer follow-up periods, and formally account for time-related biases. Another promising development is the integration of clinical, immunological, and molecular-genetic markers to develop prognostic models in which irTD is considered within the broader context of the overall immune response to therapy.

CONCLUSION

This prospective multicenter study demonstrated that the development of irTD in patients with MN of various localizations receiving ICI therapy is associated with improved progression-free survival and overall survival. irTD occurred in approximately one fifth of patients, predominantly during the first weeks of treatment, was generally mild in severity, and did not require discontinuation or modification of immunotherapy.

These findings support the concept of thyroid dysfunction as a potential clinical marker of a more pronounced antitumor immune response and underscore the importance of regular thyroid function monitoring during ICI therapy.

AUTHOR CONTRIBUTIONS

Kristina Yu. Zherebchikova conceived and designed the study. Kristina Yu. Zherebchikova, Alexey A. Vilenskiy, Alexey P. Bondarenko, and Elena V. Poddubskaya collected and processed the data. Kristina Yu. Zherebchikova compiled the electronic database, performed the statistical analysis and interpretation of the results, and drafted the manuscript. Yulia P. Sych and Valentin V. Fadeev supervised the study and critically revised the manuscript. All authors read and approved the final version of the manuscript.

ВКЛАД АВТОРОВ

К.Ю. Жеребчикова разработала концепцию и дизайн исследования. К.Ю. Жеребчикова, А.А. Виленский, А.П. Бондаренко, Е.В. Поддубская проводили сбор и обработку материала. К.Ю. Жеребчикова формировала электронную базу данных, проводила статистическую обработку, анализ полученных результатов, написание основного текста рукописи. Ю.П. Сыч и В.В. Фадеев осуществляли научное руководство проводимого исследования и редактирование рукописи. Все авторы утвердили окончательную версию публикации.

REFERENCES / ЛИТЕРАТУРА

1. *Bray F., Laversanne M., Sung H., et al.* Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024 May-Jun; 74(3): 229–263. https://doi.org/10.3322/caac.21834. Epub 2024 Apr 4. PMID: 38572751
2. *Filho A.M., Laversanne M., Ferlay J., et al.* The GLOBOCAN 2022 cancer estimates: data sources, methods, and a snapshot of the cancer burden worldwide. Int J Cancer. 2025 Apr; 156(7): 1336–1346. https://doi.org/10.1002/ijc.35278. Epub 2024 Dec 17. PMID: 39688499
3. *Wolchok J.D., Chiarion-Sileni V., Gonzalez R., et al.* Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med. 2017 Oct; 377(14): 1345–1356. https://doi.org/10.1056/NEJMoa1709684. Epub 2017 Sep 11. Erratum in: N Engl J Med. 2018 Nov; 379(22): 2185. PMID: 28889792
4. *Borghaei H., Paz-Ares L., Horn L., et al.* Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med. 2015 Oct; 373(17): 1627–1639. https://doi.org/10.1056/NEJMoa1507643. Epub 2015 Sep 27. PMID: 26412456
5. *Overman M.J., McDermott R., Leach J.L., et al.* Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. Lancet Oncol. 2017 Sep; 18(9): 1182–1191. https://doi.org/10.1016/S1470-2045(17)30422-9. Epub 2017 Jul 19. Erratum in: Lancet Oncol. 2017 Sep; 18(9): 510. PMID: 28734759
6. *Higham C.E., Olsson-Brown A., Carroll P., et al.* Society for endocrinology endocrine emergency guidance: Acute management of the endocrine complications of checkpoint inhibitor therapy. Endocr Connect. 2018 Jul; 7(7): G1–G7. https://doi.org/10.1530/EC-18-0068. PMID: 29930025
7. *Жеребчикова К.Ю., Солтаханова М.О., Сыч Ю.П. и др.* Распространенность, факторы риска и особенности течения дисфункции щитовидной железы, индуцированной иммунотерапией по поводу онкологических заболеваний. Фарматека. 2025; 32(2): 109–115. https://doi.org/10.18565/pharmateca.2025.2.109-115. EDN: NLMGAB / *Zherebchikova K.Yu., Soltakhanova M.O., Sych Yu.P., et al.* Prevalence, risk factors and features of the course of thyroid dysfunction induced by immunotherapy for cancer. Farmateka. 2025; 32(2): 109–115. (In Russian). https://doi.org/10.18565/pharmateca.2025.2.109-115. EDN: NLMGAB
8. *Mao X., Mao C., Liu J., et al.* Immune checkpoint inhibitor-induced thyroiditis and its potential mechanisms. Front Endocrinol (Lausanne). 2025 Jun; 16: 1584675. https://doi.org/10.3389/fendo.2025.1584675. PMID: 40535343
9. *Gong W., Zheng E., Liu M., et al.* Risk factors and outcomes of thyroid immune-related adverse events following PD-1/PD-L1 inhibitors treatment in a large tertiary Chinese center. BMC Endocr Disord. 2025 Jul; 25(1): 171. https://doi.org/10.1186/s12902-025-01986-1. PMID: 40660166
10. *de Filette J., Andreescu C.E., Cools F., et al.* A Systematic Review and Meta-Analysis of Endocrine-Related Adverse Events Associated with Immune Checkpoint Inhibitors. Horm Metab Res. 2019 Mar; 51(3): 145–156. https://doi.org/10.1055/a-0843-3366. Epub 2019 Mar 12. PMID: 30861560
11. *Osorio J.C., Ni A., Chaft J.E., et al.* Antibody-mediated thyroid dysfunction during T-cell checkpoint blockade in patients with non-small-cell lung cancer. Ann Oncol. 2017 Mar; 28(3): 583–589. https://doi.org/10.1093/annonc/mdw640. PMID: 27998967

12. *Das S., Johnson D.B.* Immune-related adverse events and anti-tumor efficacy of immune checkpoint inhibitors. J Immunother Cancer. 2019 Nov; 7(1): 306. https://doi.org/10.1186/s40425-019-0805-8. PMID: 31730012
13. *Cerić Š., Cerić T., Sokolović E., et al.* Impact of thyroid immune-related adverse events on clinical outcomes in non-small cell lung cancer (NSCLC) patients treated with checkpoint inhibitor therapy: A single center study. Biomol Biomed. 2025 Mar; 26(1): 144–149. https://doi.org/10.17305/bb.2025.12321. PMID: 40154981
14. *Dawidowska A., Jagodzinska-Mucha P., Koseła-Paterczyk H., et al.* Immune-Related Thyroid Adverse Events Predict Response to PD-1 Blockade in Patients with Melanoma. Cancers (Basel). 2022 Feb; 14(5): 1248. https://doi.org/10.3390/cancers14051248. PMID: 35267557
15. *Amin M.B., Greene F.L., Edge S.B., et al.* The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 2017 Mar; 67(2): 93–99. https://doi.org/10.3322/caac.21388. Epub 2017 Jan 17. PMID: 28094848
16. *Thompson J.A., Schneider B.J., Brahmer J., et al.* NCCN Guidelines® Insights: Management of Immunotherapy-Related Toxicities, Version 2.2024. J Natl Compr Canc Netw. 2024 Nov; 22(9): 582–592. https://doi.org/10.6004/jnccn.2024.0057. PMID: 39536465
17. *Eisenhauer E.A., Therasse P., Bogaerts J., et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan; 45(2): 228–247. https://doi.org/10.1016/j.ejca.2008.10.026. PMID: 19097774
18. *Freites-Martinez A., Santana N., Arias-Santiago S., Viera A.* Using the Common Terminology Criteria for Adverse Events (CTCAE – Version 5.0) to Evaluate the Severity of Adverse Events of Anticancer Therapies. Actas Dermosifiliogr (Engl Ed). 2021 Jan; 112(1): 90–92. English, Spanish. https://doi.org/10.1016/j.ad.2019.05.009. Epub 2020 Sep 3. PMID: 32891586
19. *Cheung Y.M., Wang W., McGregor B., Hamnvik O.R.* Associations between immune-related thyroid dysfunction and efficacy of immune checkpoint inhibitors: a systematic review and meta-analysis. Cancer Immunol Immunother. 2022 Aug; 71(8): 1795–1812. https://doi.org/10.1007/s00262-021-03128-7. Epub 2022 Jan 13. PMID: 35022907
20. *Xiao M., Qian L.L., Zhao Q., et al.* Changes in thyroid hormone levels indicate immunotherapy efficacy in gastric cancer. Oncol Lett. 2025 May; 30(1): 364. https://doi.org/10.3892/ol.2025.15110. PMID: 40469917
21. *Petrelli F., Grizzi G., Ghidini M., et al.* Immune-related Adverse Events and Survival in Solid Tumors Treated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-Analysis. J Immunother. 2020 Jan; 43(1): 1–7. https://doi.org/10.1097/CJI.0000000000000300. PMID: 31574022
22. *Maillet D., Corbaux P., Stelmes J.J., et al.* Association between immune-related adverse events and long-term survival outcomes in patients treated with immune checkpoint inhibitors. Eur J Cancer. 2020 Jun; 132: 61–70. https://doi.org/10.1016/j.ejca.2020.03.017. Epub 2020 Apr 22. PMID: 32334337
23. *Ishidoya M., Makiguchi T., Tanaka H., et al.* Endocrine immune-related adverse event is a prognostic biomarker independent of lead-time bias. Lung Cancer. 2024 Jun; 192: 107790. https://doi.org/10.1016/j.lungcan.2024.107790. Epub 2024 Apr 9. PMID: 38696920
24. *Singh N., Hocking A.M., Buckner J.H.* Immune-related adverse events after immune check point inhibitors: Understanding the intersection with autoimmunity. Immunol Rev. 2023 Sep; 318(1): 81–88. https://doi.org/10.1111/imr.13247. Epub 2023 Jul 26. PMID: 37493210
25. *Karaviti D., Kani E.R., Karaviti E., et al.* Thyroid disorders induced by immune checkpoint inhibitors. Endocrine. 2024 Jul; 85(1): 67–79. https://doi.org/10.1007/s12020-024-03718-2. Epub 2024 Feb 12. PMID: 38345684
26. *Muir C.A., Clifton-Bligh R.J., Long G.V., et al.* Thyroid Immune-related Adverse Events Following Immune Checkpoint Inhibitor Treatment. J Clin Endocrinol Metab. 2021 Aug; 106(9): e3704–e3713. https://doi.org/10.1210/clinem/dgab263. PMID: 33878162
27. *Presotto E.M., Rastrelli G., Desideri I., et al.* Endocrine toxicity in cancer patients treated with nivolumab or pembrolizumab: results of a large multicentre study. J Endocrinol Invest. 2020 Mar; 43(3): 337–345. https://doi.org/10.1007/s40618-019-01112-8. Epub 2019 Sep 21. PMID: 31542865
28. *Ruggeri R.M., Spagnolo C.C., Alibrandi A., et al.* Predictors of thyroid adverse events during cancer immunotherapy: a real-life experience at a single center. J Endocrinol Invest. 2023 Nov; 46(11): 2399–2409. https://doi.org/10.1007/s40618-023-02096-2. Epub 2023 Apr 20. PMID: 37076759
29. *Lee H.J., Manavalan A., Stefan-Lifshitz M., et al.* Permanent hypothyroidism following immune checkpoint inhibitors induced thyroiditis may be associated with improved survival: results of an exploratory study. Front Endocrinol (Lausanne). 2023 Apr; 14: 1169173. https://doi.org/10.3389/fendo.2023.1169173. PMID: 37168978

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The influence of ChatGPT on medical student learning: a systematic review of educational outcomes and cognitive impact

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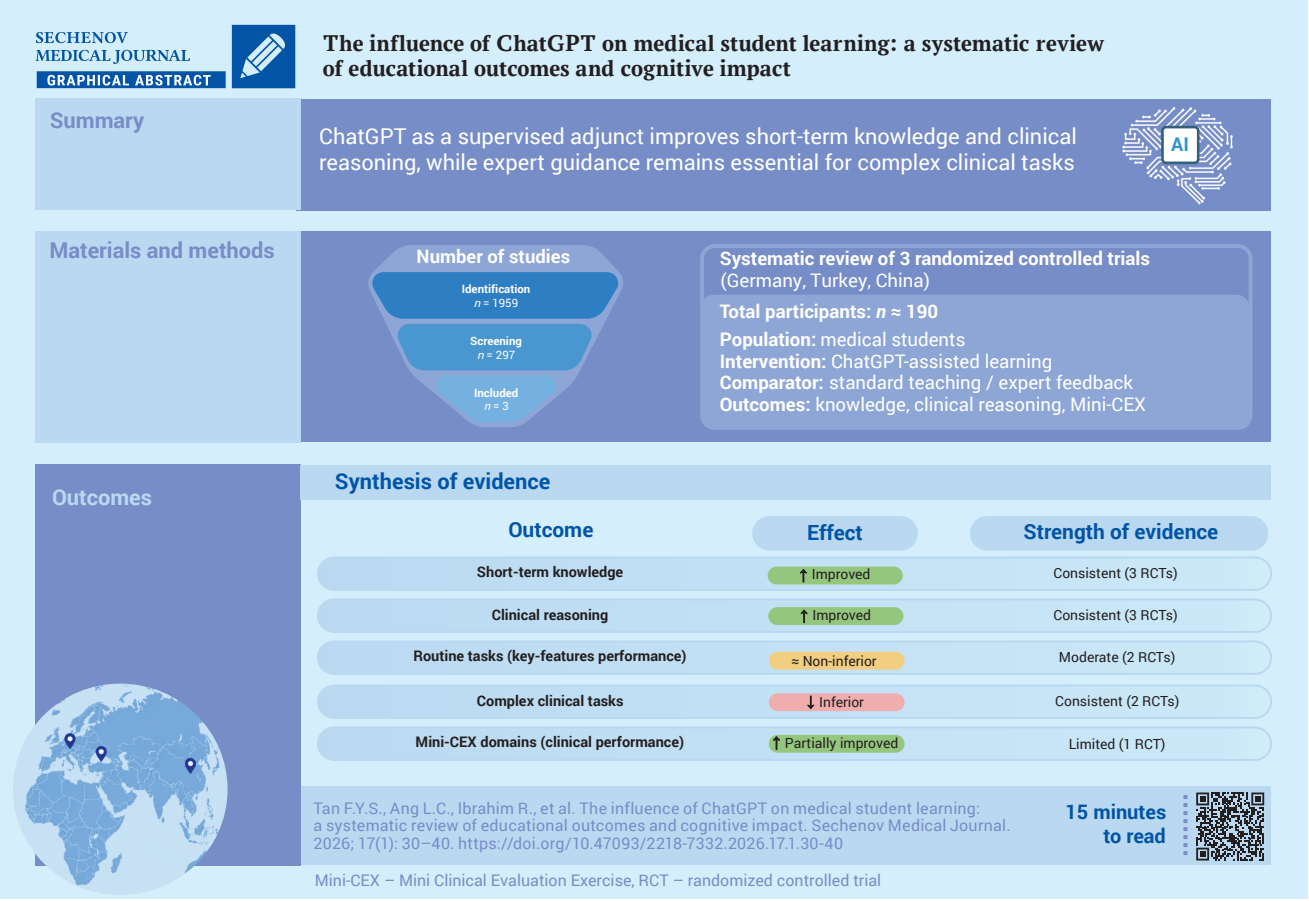

Abstract

Aim. To evaluate whether the use of ChatGPT as a supplement to usual teaching improves medical students' short-term knowledge, clinical reasoning, and near-term performance.

Materials and methods. We systematically searched PubMed, Scopus, ScienceDirect, SpringerLink, and Web of Science on 25 June 2025, for studies involving medical students that evaluated ChatGPT as a supplement to teaching and reported objective educational outcomes. Two independent reviewers screened records, extracted data, and assessed the risk of bias. A narrative synthesis was then conducted due to the level of heterogeneity in interventions and outcome measures across the studies.

Results. Three randomized trials conducted in Germany, Turkey, and China met the inclusion criteria. ChatGPT-supported interventions improved or at least maintained short-term educational outcomes over the control groups for knowledge tests, clinical reasoning, and some of the Mini-Clinical Evaluation Exercise (Mini-CEX) domains.

Structured and immediate ChatGPT feedback improved Clinical Reasoning Indicator-History Taking Inventory scores after a simulated patient encounter, and ChatGPT-generated explanations were not inferior to expert feedback in overall key-features question performance but were less effective for more complex items, where expert feedback remained superior. Overall, the risk of bias was judged to be low to some concerns, with likely unblinded Mini-CEX assessment noted as a significant limitation.
Conclusion. ChatGPT used as a supervised adjunct to teaching showed value for short-term knowledge acquisition and clinical reasoning development.

Keywords: artificial intelligence; undergraduate medical training; medical education; clinical reasoning; problem-based learning; educational innovation
MeSH terms:
EDUCATION, MEDICAL – METHODS
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Влияние ChatGPT на обучение студентов медицинских вузов: систематический обзор образовательных результатов и когнитивного воздействия

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Аннотация

Цель. Оценить, способствует ли использование ChatGPT в качестве дополнения к традиционному обучению улучшению краткосрочного уровня знаний студентов-медиков, клинического мышления и ближайших учебных результатов.
Материалы и методы. 25 июня 2025 г. был проведен систематический поиск исследований в базах данных PubMed, Scopus, ScienceDirect, SpringerLink и Web of Science. В обзор включались работы с участием студентов-медиков, в которых ChatGPT использовался как дополнение к обучению и оценивались объективные образовательные результаты. Два независимых рецензента осуществляли отбор публикаций, извлечение данных и оценку риска систематической ошибки. В связи с неоднородностью вмешательств и показателей исходов был выполнен нарративный синтез данных.

Результаты. Критериям включения соответствовали три рандомизированных исследования, проведенных в Германии, Турции и Китае. Использование ChatGPT в образовательных вмешательствах способствовало улучшению либо по меньшей мере сохранению краткосрочных учебных результатов по сравнению с контрольными группами в отношении тестов знаний, клинического мышления и ряда доменов Mini-Clinical Evaluation Exercise (Mini-CEX). Структурированная и немедленная обратная связь с использованием ChatGPT улучшала показатели Clinical Reasoning Indicator–History Taking Inventory после взаимодействия с симулированным пациентом. Объяснения ответов, сгенерированные ChatGPT, не уступали экспертной обратной связи по общему результату выполнения заданий формата key-features, однако были менее эффективны при решении более сложных вопросов, где экспертная обратная связь имела преимущество. Общий риск систематической ошибки был оценен как низкий или вызывающий некоторые опасения; существенным ограничением являлась вероятная неослепленная оценка Mini-CEX.
Заключение. Использование ChatGPT в качестве контролируемого дополнительного инструмента обучения продемонстрировало эффективность в отношении краткосрочного усвоения знаний и формирования клинического мышления.

Ключевые слова: искусственный интеллект; додипломная подготовка врачей; медицинское образование; клиническое мышление; проблемно-ориентированное обучение; образовательные инновации
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Использование искусственного интеллекта. Инструменты искусственного интеллекта не использовались при подготовке данной рукописи.

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Abbreviations:
AI – artificial intelligence
CRI-HTI – Clinical Reasoning Indicator-History Taking Inventory
KFQ – key-features questions
LLM – large language model
Mini-CEX – Mini-Clinical Evaluation Exercise
PBL – problem-based learning
RCT – randomized controlled trial

HIGHLIGHTS	КЛЮЧЕВЫЕ ПОЛОЖЕНИЯ
Controlled trial evidence suggests that ChatGPT can improve or at least maintain short-term learning outcomes in medical students when used as a supervised adjunct.	Данные контролируемых исследований свидетельствуют о том, что ChatGPT при использовании в качестве контролируемого вспомогательного инструмента обучения способен улучшать или как минимум поддерживать краткосрочные результаты обучения студентов-медиков.
Structured, immediate ChatGPT feedback after simulated histories improves observable clinical reasoning behaviours on CRI-HTI scoring.	Структурированная и немедленная обратная связь от ChatGPT после моделируемого сбора анамнеза улучшает наблюдаемые показатели клинического мышления при оценке по шкале CRI-HTI.
ChatGPT-generated explanations are non-inferior to expert feedback for overall key-features performance on routine clinical reasoning tasks.	Объяснения, сгенерированные ChatGPT, не уступают экспертной обратной связи по общим результатам выполнения заданий формата key-feature questions при решении стандартных задач клинического мышления.
Expert feedback remains superior for more complicated items, supporting human oversight for high-complexity reasoning.	При выполнении более сложных заданий экспертная обратная связь остается более эффективной, что подтверждает необходимость участия преподавателя при решении клинических задач высокой сложности.
ChatGPT-assisted problem-based learning improves short-term knowledge and selected Mini-CEX domains during a clinical rotation.	Проблемно-ориентированное обучение с использованием ChatGPT улучшает краткосрочное усвоение знаний и отдельные оцениваемые домены Mini-CEX во время клинической ротации.

The advent of artificial intelligence (AI) applications, such as ChatGPT, has had a major impact on many industries, including medical education. As medical schools advance to include innovative technologies, the literature on how AI can be employed to enhance the learning outcomes of medical trainees continues to grow. OpenAI's sophisticated large language model (LLM), ChatGPT, has demonstrated competence in various domains of medical education. It has been reported to be useful in creating experiences for individuals who learn, developing critical thinking skills, and supporting problem-based learning (PBL) interventions among medical students [1, 2]. In addition to providing tailored learning experiences, ChatGPT enables the consistent delivery of quality learning across contexts.

Despite these benefits, empirical evidence of the effectiveness of ChatGPT in medical education remains limited. Surapaneni [3] reported a performance gap between medical students and responses produced by ChatGPT for certain tests, which raises questions regarding accuracy and applicability. Moreover, the use of AI-based clinical reasoning and skills assessment raises important ethical and pedagogical issues, a theme that is further illustrated by the duality in perceptions of AI technology in clinical learning settings [4].

This review aims to synthesize controlled evidence on whether ChatGPT, used as a supplement to usual instruction, improves medical students' knowledge, clinical reasoning, and near-term performance, with the goal of identifying educational effects, boundary conditions, and implications for safe curricular use.

MATERIALS AND METHODS

Protocol and reporting framework

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. The review question was framed using the PICO structure: What is the impact of ChatGPT on the educational outcomes and cognitive development of medical students? The protocol specified the inclusion/exclusion criteria, information sources, screening methods, data extraction fields, risk-of-bias assessment by study design, and a data synthesis plan. This review was not prospectively registered with PROSPERO. Registration was not completed at inception due to resource and time constraints during the initial protocol development phase. We will prospectively register any future update or extension of this review to strengthen transparency. Nevertheless, the eligibility criteria, outcomes of interest, and synthesis approach were finalised before screening commenced and were applied consistently throughout the review process.

Eligibility criteria

We included original empirical studies published in English from 2022 onwards that enrolled medical students and evaluated ChatGPT as part of an educational intervention with measurable results. Eligible designs included randomized controlled trials (RCT) or nonrandomized controlled trials, controlled cohort studies, and mixed-methods evaluations with quantitative endpoints. We excluded editorials, letters, opinion pieces, reviews, purely technical descriptions

without analysable educational data, studies not involving medical students (unless a distinct medical-student subgroup could be extracted), non-learning uses of ChatGPT (e.g., administrative tasks), and non-English publications.

Information sources and search strategy

A comprehensive search was performed in five bibliographic databases with pre-specified Boolean logic adapted to each platform: PubMed, Scopus, ScienceDirect, SpringerLink, and Web of Science. Search strings combined terms for the technology (e.g., "ChatGPT," "large language model," "artificial intelligence") with medical education terms ("medical students," "medical education") and outcome terms ("learning outcomes," "performance," "clinical reasoning," "critical thinking", Table 1). The literature search was conducted on 25 June 2025. Searches were limited to English-language records and publication years from 2022 onwards, where database filters permitted. No study design filter was applied during the search stage. The results were exported on the same search wave, merged in a reference manager, and de-duplicated prior to screening.

Study selection

The screening was conducted in two stages by two independent reviewers (L.A.C. and R.I.). Titles/abstracts were screened against the eligibility criteria, followed by full-text assessment of potentially relevant reports. Disagreements were resolved through discussion or, if required, by a third reviewer (M.A.M.). The screening workflow was supported by Rayyan[1], a web-based platform used to facilitate blinded title/abstract screening [5]. The citation-checking workflow was supported by scite.ai[2], a web-based citation analysis platform used as a supplementary tool for verification, including checking citation contexts. The PRISMA flow diagram documents the process and counts: 1481 unique records were screened after the removal of 478 duplicates; 297 full texts were retrieved and assessed; 294 were excluded based on eligibility (review articles, n = 74; no analyzable data, n = 132; wrong study design, n = 87; non-English, n = 1). Three studies met all the criteria and were included in the narrative synthesis (Fig. 1).

Data extraction and management

A structured data-extraction form, piloted on a subset of studies, captured the following: study setting and design; participant characteristics (stage of training, sample size); description of the ChatGPT/LLM intervention (role in the learning activity, prompt structure, timing relative to instruction, presence/absence of human oversight); comparator condition(s); outcome measures and instruments (e.g., written knowledge tests, Key-Features Questions, Clinical Reasoning Indicator–History Taking Inventory (CRI-HTI), Mini-Clinical Evaluation Exercise (Mini-CEX)); follow-up interval(s); statistical results (effect estimates, measures of variability, p-values); and author-reported implementation details (e.g., disclosure of AI use, debriefing, verification steps). Two reviewers independently extracted the data; inconsistencies were reconciled by consensus with reference to the source report.

Outcomes

The primary outcomes were objective educational measures aligned with the intervention's learning aims, including near-term written knowledge performance and validated indices of clinical reasoning and skills (e.g., CRI-HTI subdomains and Mini-CEX ratings). Secondary outcomes included learner-reported indicators relevant to cognitive impact (e.g., perceived learning effectiveness, breadth of clinical exposure, and critical stance toward AI following disclosure and debriefing). Where available, immediate and short-delay (⩽10 days) post-intervention results were collected to gauge the early retention.

Risk of bias and study quality assessment

Risk-of-bias judgements were performed at the study level by design category using validated tools. RCTs were appraised using Version 2 of the Cochrane tool for assessing the risk of bias in randomized trials (RoB 2) (domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported

Table 1. **Search strategy across databases**

Database	Search string
ScienceDirect	"ChatGPT" AND "medical students" AND ("learning" OR "education" OR "academic performance" OR "critical thinking")
PubMed	((ChatGPT) OR (artificial intelligence)) AND ((medical students[Title/Abstract]) OR (medical education[Title/Abstract])) AND ((performance) OR (academic) OR (clinical reasoning)) AND (2022/1/1:2025/6/25[pdat])
SpringerLink	"ChatGPT" AND "medical education" AND ("student performance" OR "reasoning skills" OR "AI-assisted learning")
Web of Science	TS=("ChatGPT" OR "language models") AND TS=("medical students" OR "medical education") AND TS=("learning outcomes" OR "academic performance" OR "cognitive skills")
Scopus	TITLE-ABS-KEY("ChatGPT" OR "large language model") AND TITLE-ABS-KEY("medical education" OR "medical students") AND TITLE-ABS-KEY("performance" OR "critical thinking" OR "learning outcomes")

[1] Rayyan – Intelligent Systematic Review. https://www.rayyan.ai (access date: 25.06.2025).
[2] scite.ai – Smart Citations. https://scite.ai (access date: 25.06.2025).

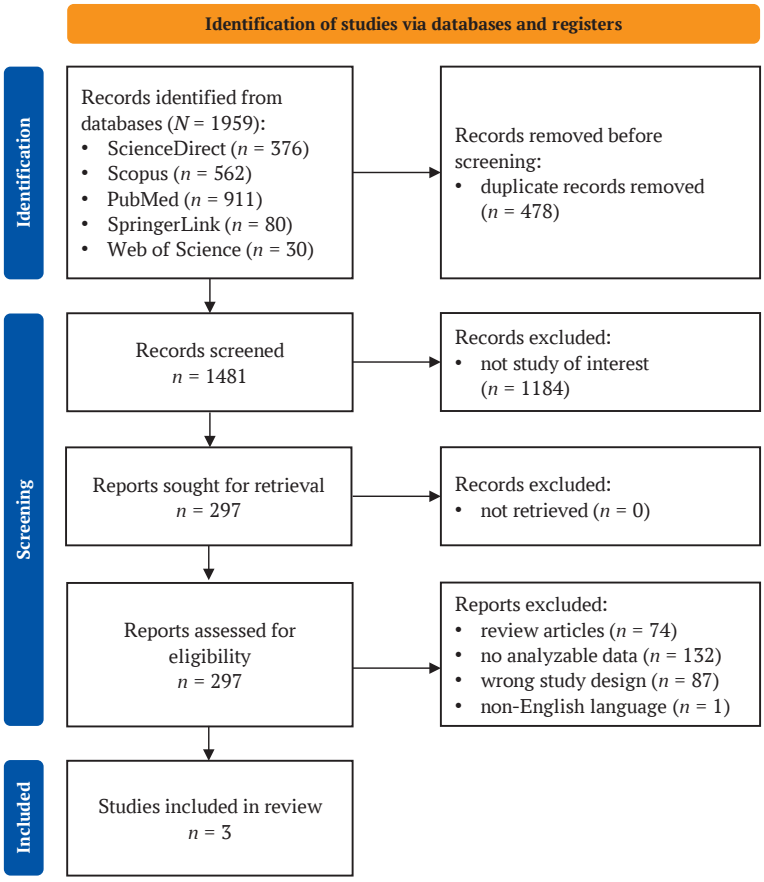

FIG. 1. PRISMA flow diagram of study selection.

result). ROBINS-I (Risk Of Bias In Non-randomized Studies-of Interventions) and MMAT (Mixed Methods Appraisal Tool) were pre-specified for non-randomized and mixed-methods studies but were not applied because all included studies were randomized. Disagreements were resolved by discussion; where reporting limited firm judgements, domains were rated "some concerns" with justification.

Data synthesis and analysis

Given the small number of eligible studies and heterogeneity in interventions (LLM role, presence of structured feedback, task complexity), comparators, and outcome instruments, a narrative synthesis was specified as the primary approach. Planned quantitative synthesis required ⩾ 5 trials with commensurate outcome measures; this threshold was not met because of non-overlapping instruments (CRI-HTI, Key-Features Questions (KFQ), Mini-CEX) across studies. If conditions permitted, continuous outcomes would have been summarized as mean differences or standardized mean differences with 95% confidence intervals using random-effects models, with heterogeneity quantified by I^2 and explored via subgroup analyses (e.g., pre-clinical vs. clinical stage, routine vs. complex case tasks, human oversight vs. AI-only feedback). Instead, we synthesized findings by mapping interventions to learning mechanisms (e.g., immediate task-specific feedback, rehearsal of history-taking, PBL scaffolding), outcome family (knowledge, clinical reasoning, clinical performance), and task complexity, noting consistencies and divergences across settings. Where immediate and short-delay outcomes were both reported, we qualitatively described patterns to indicate early retention.

RESULTS

Study selection and characteristics

Of the 1481 unique records screened, three RCTs met the inclusion criteria and were included in the review of educational outcomes in medical students. The studies were conducted in Germany, Turkey, and China, and each evaluated ChatGPT as a supplement to established teaching formats rather than as a replacement. The validated indices included CRI-HTI, KFQ, and Mini-CEX. The interventions fell into three pedagogic roles: (i) simulated patient encounters with LLM-delivered formative feedback, (ii) AI-generated written feedback on text-based clinical reasoning problems, compared directly with expert feedback, and (iii) ChatGPT-assisted PBL integrated into a brief clinical rotation. Outcomes comprised validated indices of clinical reasoning (CRI-HTI; KFQ), theory examinations, and Mini-CEX

domains, with short-delay assessments reported. The sample sizes ranged from 21 to 129 randomized participants, with follow-up completion reported in all trials. Reporting of model version, prompting and output verification was limited across trials.

Interventions and comparators

In the German trial, pre-clinical students completed four six-minute LLM-simulated history-taking encounters; only the intervention arm received structured ChatGPT feedback after each case, generated against CRI-HTI rubric [6]. Two blinded human raters scored the transcripts (intraclass correlation coefficient was 0.924). The comparator was an identical simulation without feedback.

In Turkey, first-year students undertook five days of spaced ContExtended Question practice for urinary tract infections; arms differed only in the source of explanations provided after each step (expert-written vs. ChatGPT-generated) [7]. Clinical reasoning was measured using the KFQs immediately and 10 days later.

In China, fifth-year interns on a two-week urology rotation were randomized to PBL+ChatGPT (pre-class exploration and in-class discussion with AI support, with instructor oversight) versus traditional teaching [8]. The primary outcomes were a 100-point theory exam (pre-and three days post-lecture) and Mini-CEX ratings across seven domains; student satisfaction was secondary (Table 2).

Primary outcomes

Across the two reasoning-focused trials, ChatGPT improved or matched outcomes when deployed as a feedback engine, with caveats for complex cases.

In the German simulation RCT (n = 21 analyzed), after four sessions, LLM feedback improved final CRI-HTI scores versus simulation without feedback (3.60 ± 0.13 vs. 3.02 ± 0.12; F(1,18) = 4.44, p = 0.049; partial η^2 = 0.198), with gains concentrated in 'creating context' (p = 0.046) and 'securing information' (p = 0.018), but not focusing questions (p = 0.265). The rater agreement for transcript scoring was excellent (intraclass correlation coefficient was 0.924). These findings indicate that immediate task-specific LLM feedback can shift observable reasoning behaviors over a short training period.

In the Turkish RCT (n = 129 randomized; ⩾115 tested), ChatGPT feedback vs. expert feedback produced no difference in overall KFQ scores at immediate testing (ChatGPT 74.7 ± 15.1 vs. Expert 78.5 ± 20.6; p = 0.26) or at 10 days (ChatGPT 76.0 ± 14.5 vs. Expert 78.0 ± 21.2; p = 0.57). For complicated urinary tract infection items in delayed testing, expert feedback outperformed ChatGPT (p < 0.001). Notably, the disclosure of AI use increased students' critical approach to AI, with medium to significant effects. Together, these data suggest that ChatGPT can provide non-inferior formative explanations for routine problems, while expert oversight remains advisable for nuanced scenarios.

In the Chinese rotation RCT (n = 42), both groups improved from baseline, but PBL+ChatGPT achieved a higher post-course theory score at three days (93.90 ± 3.65) than traditional teaching (90.33 ± 4.08; p < 0.01). This short-term knowledge advantage was accompanied by higher Mini-CEX ratings in medical interviewing, clinical judgement, and overall competence, with no differences in other domains. Mini-CEX gains favouring PBL+ChatGPT were concentrated in interviewing, judgement, and overall competence. These domain-specific improvements may reflect the intervention's emphasis on structured question framing and synthesis, however, this interpretation remains hypothetical. All assessments were completed within standardized time windows and by a single assessor, which supports procedural consistency but may limit blinding. Because a single, likely unblinded assessor completed the Mini-CEX, these skill domain gains warrant cautious interpretation.

Secondary outcomes (acceptability and perceived learning)

Medical students rated the LLM-supported activities favorably. In the German study, participants described the simulated encounters as realistic and feasible, mirroring the observed behavioral gains when feedback was present [6]. In Turkey, students in the ChatGPT feedback group developed a notably more critical outlook [7]. As a result, they became more skeptical about the accuracy and reliability of AI-generated information and more cautious in accepting AI content without question. In the Chinese trial, satisfaction was uniformly high after PBL+ChatGPT, with no reports of dissatisfaction [8].

Synthesis of effects and certainty

Because interventions and instruments differed across trials, meta-analysis was not appropriate; instead,

Table 2. **Characteristics of the included randomized studies**

Study	Country	Intervention/comparator	Outcome(s)
Brügge et al., 2024 [6]	Germany	LLM-simulated patient interviews ± ChatGPT feedback	CRI-HTI
Çiçek et al., 2025 [7]	Turkey	ChatGPT-generated vs. expert-written feedback on KFQs	Immediate and 10-day scores
Hui et al., 2025 [8]	China	ChatGPT-assisted PBL vs. traditional teaching	Theory test and Mini-CEX

Note: CRI-HTI – Clinical Reasoning Indicator-History Taking Inventory; KFQ – key-features questions; LLM – large language model; Mini-CEX – Mini-Clinical Evaluation Exercise; PBL – problem-based learning.

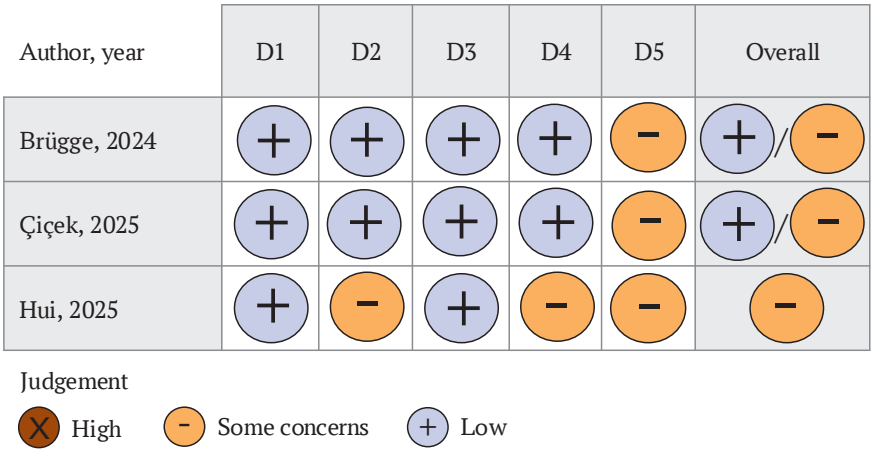

FIG. 2. Risk-of-bias assessment of randomized controlled trials.

Note: D1 – randomization process; D2 – deviations from intended interventions; D3 – missing outcome data; D4 – measurement of the outcome; D5 – selection of the reported result.

narrative synthesis showed consistent benefits of immediate, task-specific feedback, parity with expert feedback for routine problems, and short-term knowledge and Mini-CEX gains with ChatGPT-assisted PBL under supervision.

Risk of bias

We appraised the risk of bias using RoB 2 across five domains (Fig. 2). Overall, the included trials showed a generally acceptable methodological profile for short-term educational outcomes. The randomization process was judged to be at low risk of bias in all three studies: Brügge et al. used a two-group randomized design with balanced baseline characteristics, Çiçek et al. applied computer-generated randomization with comparable groups, and Hui et al. used randomized allocation with equal group sizes.

Deviations from intended interventions were unlikely to materially affect the results in the German and Turkish trials, where training procedures, exposure, and assessment conditions were standardized across arms. In the Turkish trial, participants were blinded to the feedback source, and the only intended difference between groups was whether the explanations were expert-written or ChatGPT-generated. By contrast, the Chinese trial raised some concerns because intervention delivery was unblinded, which may have influenced performance-related outcomes.

Missing outcome data were judged to be at low risk of bias across the three studies, with minimal exclusions or complete post-course assessment reported and no evidence of differential attrition. Measurement of outcomes was also robust in two trials: the German study used two independent blinded raters and the validated CRI-HTI instrument, with excellent inter-rater agreement, whereas the Turkish study relied on objective standardized key-features scoring. In the Chinese trial, the theory test was objective; however, Mini-CEX was assessed by a single likely unblinded evaluator, raising concerns about detection bias. Therefore, Mini-CEX findings, although directionally favorable, should be interpreted with caution.

The domain “selection of the reported result” was conservatively rated as “some concerns” in all three studies because none reported prospective registration or a pre-specified analysis plan. Taken together, the overall risk of bias was judged as low to some concerns for the German and Turkish trials and as some concerns for the Chinese trial. The evidence base is therefore methodologically acceptable for evaluating short-term educational outcomes, but conclusions regarding clinical skills should remain cautious when based on unblinded performance ratings.

Summary of main findings

Taken together, the best available randomized evidence supports an optimistic but circumspect conclusion: when used to augment existing teaching, it provides immediate, structured feedback; by scaffolding PBL or streamlining explanations, ChatGPT improves or maintains near-term educational outcomes for medical students, with clear added value in efficiency and reach. The signal is strongest for short-cycle learning targets (history-taking behaviors, script refinement, and theory recall), while complex clinical problems still benefit from human calibration. Across trials, disclosure and supervision varied. In the Turkish trial, disclosure of AI use was reported to increase students’ critical stance toward AI. Contrastingly, other trials provided supervision and structured feedback but did not quantify disclosure-related effects.

DISCUSSION

Principal findings and interpretation

Across three RCTs, ChatGPT used alongside usual teaching equaled or improved the learning outcomes.

The small number of eligible trials reflects the early stage of controlled research on ChatGPT in medical education rather than selective inclusion. Effects were observed in written knowledge, clinical reasoning during history taking, and selected Mini-CEX domains. Two themes recur. These findings are consistent with established learning theory. Feedback is one of the strongest influences on learning, but its effects depend on timing, specificity, and whether it directs attention to the task and process rather than to the learner alone [9]. These findings are educationally plausible because the included interventions emphasized repeated practice, timely feedback, and structured support. In the reviewed trials, ChatGPT appeared most useful when it was embedded within clearly defined learning activities rather than used as an unrestricted answer-generating tool.

First, feedback is the engine of the learning process. For example, ChatGPT provided prompt, task-based feedback after simulated patient encounters, resulting in improved clinical reasoning (measured on a validated instrument) compared to a no-feedback control group of students. When used to replace experts as the source of feedback on clinical key-features problems, ChatGPT was found to be as effective as expert-written feedback overall at immediate and 10-day testing, demonstrating scalable parity for routine problems. This pattern suggests that ChatGPT may be better suited to routine, structured tasks than to complex, ambiguity-rich clinical reasoning. In such settings, expert feedback still appears to provide a meaningful advantage. This pattern is also compatible with retrieval practice theory, which predicts that repeated testing and corrective explanation can strengthen learning more effectively than passive review alone [10].

Second, there is the question of context and complexity. In the same RCT, expert feedback outperformed ChatGPT for more complex items at late testing, indicating that cognitive scaffolding for complex multi-step reasoning is still better provided by experienced clinicians or by blended human-AI feedback calibrated to the task [7]. Beyond test scores, the Chinese controlled cohort suggests the spillover into the performance domain: ChatGPT-assisted PBL not only improved near-term theory scores but also enhanced Mini-CEX ratings for interviewing and clinical judgment, outcomes that may be relevant to supervised clinical performance [8]. In addition, ChatGPT increases the pace of formative feedback and expands case exposure. When integrated into formalized activities, it enhances knowledge and chosen performance indicators. Where issues require subtlety, the insight of an expert provides an edge [7]. The discovered limits are informative and represent design choices rather than intrinsic constraints.

Strengths, limitations, and implications

This synthesis is based on the use of validated tools (e.g., CRI-HTI, Mini-CEX) and authentic assessment tasks (key features, observed encounters). Positive results were observed across three settings (Germany, Turkey, and China), supporting further study across diverse curricula, however, they do not establish generalizability.

However, there are conditions under which highlighting is necessary for the reader. First, most outcomes were short-term, and we have limited information on longer-term retention, transfer to authentic clerkship performance, or downstream patient-centered outcomes. One plausible risk of AI-supported learning is over-reliance on the tool, whereby improved immediate task performance may not translate into durable competence if students defer reasoning rather than internalize it. This concern is particularly relevant when outcomes are measured over short intervals. Second, the learning tasks studied on history taking, key features reasoning in one topic, and short-horizon PBL represent important but narrow sections of the early curriculum [6]. Third, the primacy of expert feedback on challenging cases at late testing is a salutary reminder that blind use of LLM results to "replace" faculty is unwise; complexity calibration and human oversight seem to be essential for safety and quality [7]. LLM outputs can be fluent yet incorrect, and learners may inadvertently internalise inaccuracies or biased reasoning if responses are accepted uncritically [11]. Accordingly, educational use should be paired with explicit verification practices, particularly for safety-critical or high-complexity content. Lastly, our approach to mixed-population studies may introduce selection bias if medical-student subgroup data were selectively reported or not extractable.

Methodologically, future studies could pre-register protocols, determine power for non-inferiority or superiority prespecified outcomes, report adherence to intervention protocols (e.g., prompt templates, versioning), and disclose guardrails (instructional hints, verification steps), which may modulate both efficacy and safety. In parallel, curricular integration should acknowledge the “black box” features of LLMs and the risk of plausible-sounding inaccuracies or biased outputs.

Implementation also occurs within a pre-existing landscape of academic integrity challenges in medical training. Generative AI may amplify familiar risks (e.g., unacknowledged assistance, plagiarism, and inappropriate collaboration), particularly where institutional policies are unclear or inconsistently applied [12, 13]. In controlled, supervised interventions, the educational signal is clearer. However, in unsupervised settings, it becomes harder to distinguish AI-supported learning from AI-facilitated misconduct. Therefore, for this reason, clear permissible-use guidance, assessment design that samples unaided reasoning, and teaching students how to document and justify AI use are therefore essential complements to any educational deployment of ChatGPT [12, 13].

Three design choices appear to be important. First, feedback should be structured, timely, and task-focused; in the simulation trial, ChatGPT’s outputs were mapped

to CRI-HTI behaviors and delivered immediately after the task was completed [6]. Second, align support to task complexity: routine problems tolerate automated feedback, whereas complex or safety-critical scenarios merit clinician oversight or blended experts, which is the AI commentary [7]. Third, LLMs should be used to widen exposure and rehearsal opportunities, but they should be treated as adjuncts to live bedside teaching, not substitutes for patient contact and mentorship [7, 8].

Generative AI also raises academic and assessment integrity concerns, as unsupervised use may blur the boundary between supported learning and unpermitted assistance. Assessment policy should evolve with time. Where ChatGPT is available, assessment for learning can plausibly include AI-mediated practice (e.g., formative key features with ChatGPT feedback), while assessment of learning must ensure that summative tasks adequately sample unaided reasoning and performance. Explicit instruction on when to use AI (e.g., when setting up for PBL but not while responding to objective structured clinical examination) will allow students to benefit from AI while maintaining academic integrity and skill building.

Key questions now are the durability of gains at 3–6 months, transfer to objective structured clinical examinations and workplace-based assessments, the complexity thresholds at which AI-generated feedback underperforms expert guidance, and whether blended expert, the AI feedback narrows that gap. Adequately powered multicenter randomized trials should compare ChatGPT-only, expert-only, and blended models stratified by case complexity and accompanied by cost-effectiveness analyses. Reproducibility requires clear reporting of the model version, prompt templates, guardrails, and protocol adherence.

CONCLUSION

Across three randomized studies on medical students, ChatGPT used as a supplement to usual instruction matched or improved short-term outcomes in knowledge, clinical reasoning, and selected workplace-based domains. Benefits were clearest when the model delivered immediate, structured feedback or scaffolded PBL; by contrast, complex, nuanced problems continued to favor expert guidance. On balance, the evidence favors an adjunctive role for ChatGPT, which is expanding practice and feedback at a low marginal cost while preserving human oversight for complex reasoning and high-stakes competencies.

AUTHOR CONTRIBUTIONS

Felix Y.S. Tan conceived and designed the study, developed the methodology, performed the formal analysis, and prepared the original draft of the manuscript. Lydia C. Ang and Rahima Ibrahim participated in the investigation and screening process and contributed to the review and editing of the manuscript. Munawwarah Abdul Majeed participated in the investigation, curated the data, performed adjudication, and contributed to the review and editing of the manuscript. Mohd Aliff H. Mohd Aris performed validation procedures and contributed to the review and editing of the manuscript. Sherly D. George conceived and designed the study, developed the methodology, supervised the project, performed validation procedures, and contributed to the review and editing of the manuscript. All authors approved the final version of the article.

ВКЛАД АВТОРОВ

Ф.И.Ш. Тан разработал концепцию и дизайн исследования, сформировал методологию, выполнил формальный анализ и подготовил первоначальный вариант рукописи. Л.Ч. Анг и Р. Ибрахим участвовали в проведении исследования и скрининге публикаций, а также внесли вклад в редактирование и доработку рукописи. М. Абдул Маджид участвовала в проведении исследования, осуществляла курирование данных, выполняла экспертную оценку материалов и внесла вклад в редактирование и доработку рукописи. М.А.Х. Мохд Арис выполнял процедуры валидации и участвовал в редактировании и доработке рукописи. Ш.Д. Джордж разработала концепцию и дизайн исследования, сформировала методологию, осуществляла общее руководство проектом, выполняла процедуры валидации и внесла вклад в редактирование и доработку рукописи. Все авторы одобрили окончательную версию статьи.

REFERENCES / ЛИТЕРАТУРА

1. *Abouammoh N., Alhasan K., Aljamaan F., et al.* Perceptions and earliest experiences of medical students and faculty with chatgpt in medical education: qualitative study. JMIR Med Educ. 2025; 11: e63400. https://doi.org/10.2196/63400. PMID: 39977012
2. *Sallam M.* ChatGPT utility in healthcare education, research, and practice: systematic review on the promising perspectives and valid concerns. Healthcare (Basel). 2023; 11(6): 887. https://doi.org/10.3390/healthcare11060887. PMID: 36981544
3. *Surapaneni K.M.* Assessing the Performance of ChatGPT in medical biochemistry using clinical case vignettes: observational study. JMIR Med Educ. 2023; 9: e47191. https://doi.org/10.2196/47191. PMID: 37934568
4. *Hisan U.K., Amri M.M.* ChatGPT and medical education: a double-edged sword. Journal of Pedagogy and Education Science. 2023; 2(01): 71–89. https://doi.org/10.56741/jpes.v2i01.302
5. *Ouzzani M., Hammady H., Fedorowicz Z., Elmagarmid A.* Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016 Dec; 5(1): 210. https://doi.org/10.1186/s13643-016-0384-4. PMID: 27919275
6. *Brügge E., Ricchizzi S., Arenbeck M., et al.* Large language models improve clinical decision making of medical students through patient simulation and structured feedback: a randomized controlled trial. BMC Med Educ. 2024; 24(1): 1391. https://doi.org/10.1186/s12909-024-06399-7. PMID: 39609823
7. *Çiçek F., Ülker M., Özer M., Kıyak Y.S.* ChatGPT versus expert feedback on clinical reasoning questions and their effect on learning: a randomized controlled trial. Postgrad Med J. 2025; 101(1195): 458–463. https://doi.org/10.1093/postmj/qgae170. PMID: 39656920
8. *Hui Z., Zewu Z., Jiao H., Yu C.* Application of ChatGPT-assisted problem-based learning teaching method in clinical

medical education. BMC Med Educ. 2025; 25(1): 50. https://doi.org/10.1186/s12909-024-06321-1. PMID: 39799356
9. *Hattie J., Timperley H.* The Power of feedback. Review of Educational Research. 2007; 77(1): 81–112. https://doi.org/10.3102/003465430298487
10. *Roediger H.L., Karpicke J.D.* Test-enhanced learning: taking memory tests improves long-term retention. Psychol Sci. 2006; 17(3): 249–255. https://doi.org/10.1111/j.1467-9280.2006.01693.x. PMID: 16507066
11. *Farquhar S., Kossen J., Kuhn L., et al.* Detecting hallucinations in large language models using semantic entropy. Nature. 2024; 630(8017): 625–630. https://doi.org/10.1038/s41586-024-07421-0
12. *Kasneci E., Sessler K., Küchemann S., et al.* ChatGPT for good? On opportunities and challenges of large language models for education. Learning and Individual Differences. 2023; 103: 102274. https://doi.org/10.1016/j.lindif.2023.102274
13. *Bittle K., El-Gayar O.* Generative AI and academic integrity in higher education: a systematic review and research agenda. Information. 2025; 16(4): 296. https://doi.org/10.3390/info16040296

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Superficial temporal artery to middle cerebral artery bypass in patient with atherosclerotic right internal carotid artery occlusive disease and impaired cerebral hemodynamics: a clinical case

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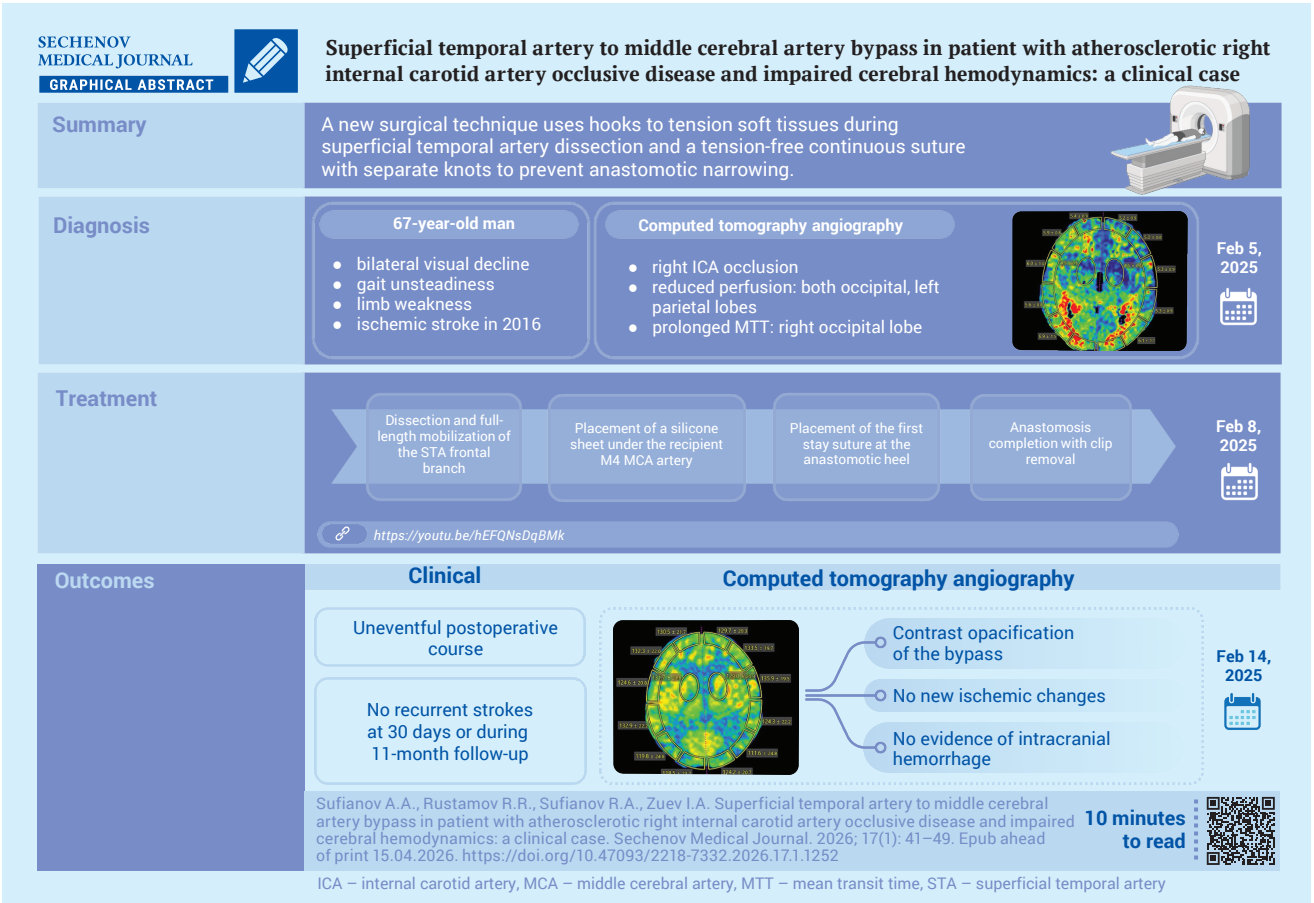

Abstract

Cerebral revascularization by superficial temporal artery (STA) to middle cerebral artery (MCA) bypass is performed in patients with moyamoya disease, complex aneurysms, and selected extra- and intracranial occlusive lesions to augment cerebral perfusion and potentially reduce the risk of ischemic complications and death.

Case report. A 67-year-old patient presented with severe visual impairment (mainly on the right), gait unsteadiness, episodic subjective limb weakness, and marked fatigue. He had a significant medical history, having suffered an

ischemic stroke in 2016 in the territory of the right MCA. A computed tomography angiography demonstrated occlusion of the right internal carotid artery and reduced cerebral blood flow in both occipital lobes and the left parietal lobe. An STA-MCA bypass anastomosis was performed. The postoperative course was uneventful; follow-up computed tomography angiography confirmed bypass patency without intracranial hemorrhage or new ischemic lesions, and a 10–15% increase in the cerebral blood volume index (up to 8.6 mL/100 g). No recurrent strokes were observed within 30 days and during 11 months of follow-up.

Discussion. Creation of an STA-MCA anastomosis may offer prospects for improving quality of life after ischemic stroke, including potential amelioration of post-stroke depression and other associated emotional disturbances.

Keywords: cerebral revascularization; extracranial-intracranial bypass; ischemic stroke; low flow bypass; cerebral blood volume

MeSH terms:

BRAIN ISCHEMIA – PHYSIOPATHOLOGY
BRAIN ISCHEMIA – SURGERY
TEMPORAL ARTERIES – SURGERY
CAROTID ARTERY, INTERNAL – SURGERY
MIDDLE CEREBRAL ARTERY – SURGERY
CEREBRAL REVASCULARIZATION – METHODS
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Обходной анастомоз поверхностной височной артерии к средней мозговой артерии при атеросклеротической окклюзии правой внутренней сонной артерии с нарушением церебральной гемодинамики: клинический случай

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Аннотация

Хирургическая реваскуляризация головного мозга посредством шунтирования поверхностной височной артерией (ПВА) и средней мозговой артерией (СМА) выполняется пациентам с болезнью моямоя, сложными аневризмами, окклюзионными заболеваниями экстра- и интракраниальных артерий с целью усиления церебральной перфузии и потенциального снижения риска ишемических осложнений и летального исхода.

Описание случая. Пациент 67 лет поступил с жалобами на выраженное снижение зрения (преимущественно справа), неустойчивость походки, эпизодическую слабость в конечностях и выраженную утомляемость. В 2016 году перенес острое нарушение мозгового кровообращения по ишемическому типу в бассейне правой СМА. По данным компьютерной томографической ангиографии выявлена окклюзия правой внутренней сонной артерии и снижение церебрального кровотока в обеих затылочных долях и левой теменной доле. Выполнен обходной анастомоз ПВА к СМА. Послеоперационный период протекал без осложнений; контрольная компьютерная томографическая ангиография подтвердила проходимость шунта при отсутствии внутричерепного кровоизлияния и новых ишемических очагов, а также отмечено увеличение индекса объема циркулирующей крови на 10–15% (до 8,6 мл/100 г). В течение 11 месяцев наблюдения рецидивов инсульта не зарегистрировано.

Обсуждение. Наложение анастомоза ПВА к СМА открывает перспективы для улучшения качества жизни пациентов после перенесенного ишемического инсульта, в том числе для коррекции постинсультной депрессии и других сопутствующих эмоциональных расстройств.

Ключевые слова: церебральная реваскуляризация; экстракраниально-интракраниальный шунт; острое нарушение мозгового кровообращения по ишемическому типу; низкопоточный анастомоз; объем мозгового кровотока

Рубрики MeSH:

МОЗГА ГОЛОВНОГО ИШЕМИЯ – ПАТОФИЗИОЛОГИЯ
МОЗГА ГОЛОВНОГО ИШЕМИЯ – ХИРУРГИЯ
ВИСОЧНЫЕ АРТЕРИИ – ХИРУРГИЯ
СОННАЯ АРТЕРИЯ ВНУТРЕННЯЯ – ХИРУРГИЯ
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Abbreviations:

CT – computed tomography
ICA – internal carotid artery
MCA – middle cerebral artery
STA – superficial temporal artery

HIGHLIGHTS	КЛЮЧЕВЫЕ ПОЛОЖЕНИЯ
Superficial temporal artery-middle cerebral artery bypass is technically feasible in patients with ischemic stroke, with potential to improve post-stroke quality of life.	Экстра-интракраниальный микроанастомоз между поверхностной височной артерией и средней мозговой артерией технически выполним у пациентов с ишемическим инсультом и потенциально может способствовать улучшению качества жизни в постинсультном периоде.
A modified superficial temporal artery dissection using hooks helps to achieve adequate soft-tissue tension and facilitate vessel mobilization.	Модифицированная диссекция поверхностной височной артерии с использованием крючков позволяет создать адекватное натяжение мягких тканей и облегчить мобилизацию сосуда.
Applying a continuous suture to one edge of the vessel without tension and tying individual knots prevents the anastomosis from narrowing.	Наложение непрерывного шва по одному краю сосуда без натяжения с последующим завязыванием отдельных узлов предотвращает сужение анастомоза.

Internal carotid artery (ICA) occlusion accounts for 15-20% of ischemic strokes and carries substantial risk of recurrent cerebrovascular events despite optimal medical management. Atherosclerotic ICA occlusion causes approximately 10% of transient ischemic attacks and 15% to 25% of ischemic strokes in the carotid territory [1–3]. The 2-year risk of subsequent ipsilateral ischemic stroke while a patient receives medical therapy is 10% to 15% [4]. While endovascular techniques address acute occlusions, chronic ICA occlusion remains resistant to recanalization, necessitating alternative revascularization approaches.

Extracranial-intracranial arterial bypass surgery was developed to prevent subsequent strokes by improving hemodynamics distal to the occluded artery [5, 6]. In 1985, a randomized trial demonstrated no benefit of this surgery in 808 patients with symptomatic carotid artery occlusion [6–8]. This trial was criticized for failing to identify the subgroup of patients with hemodynamic cerebral ischemia due to poor collateral circulation for whom surgical revascularization might be of greatest benefit [3, 5, 9]. Contemporary neuroimaging, e.g. positron emission tomography, single photon emission computed tomography, computed tomography (CT) / magnetic resonance perfusion, enables precise identification of patients with hemodynamic cerebral ischemia. The Japanese extracranial-intracranial Bypass Trial and Carotid Occlusion Surgery Study demonstrated potential benefit in highly selected patients with severe hemodynamic compromise and increased oxygen extraction fraction, underscoring the importance of rigorous assessment and technical expertise [10, 11].

The aim of this case report is to demonstrate the experience of superficial temporal artery (STA) to

middle cerebral artery (MCA) bypass in a patient with atherosclerotic right ICA occlusive disease and impaired cerebral hemodynamics.

CASE REPORT

A 67-year-old man was admitted to the Cerebrovascular Pathology Department of Federal Center of Neurosurgery (Tyumen, Russia) on February 5, 2025, for evaluation of progressive bilateral visual loss (more on the right) and gait unsteadiness with staggering. He also reported intermittent subjective weakness in the arms and legs, generalized asthenia, and easy fatigability for a prolonged period. His medical history included an ischemic stroke in 2016 in the territory of the right MCA. Cardiovascular comorbidities comprised ischemic heart disease and atherosclerotic heart disease, post-infarction cardiosclerosis (since 2012), status post percutaneous transluminal coronary angioplasty with stent implantation, and stage III arterial hypertension.

On neurologic examination, consciousness was clear; memory was mildly reduced. Meningeal signs were absent. Cranial nerve assessment demonstrated marked bilateral visual impairment, more pronounced on the right. The range of motion in the limbs and trunk was preserved; muscle strength was symmetric (Medical Research Council grade 5/5 in both upper and lower extremities), despite episodic hand clumsiness (difficulty holding cutlery) and transient leg "weakness" by history. Sensory modalities were intact. Muscle tone was normal and symmetric (D=S). Deep tendon reflexes were brisk and symmetric in the upper and lower limbs; pathological reflexes were absent. He was unstable in the Romberg position. No clinically relevant abnormalities were detected on autonomic nervous system assessment;

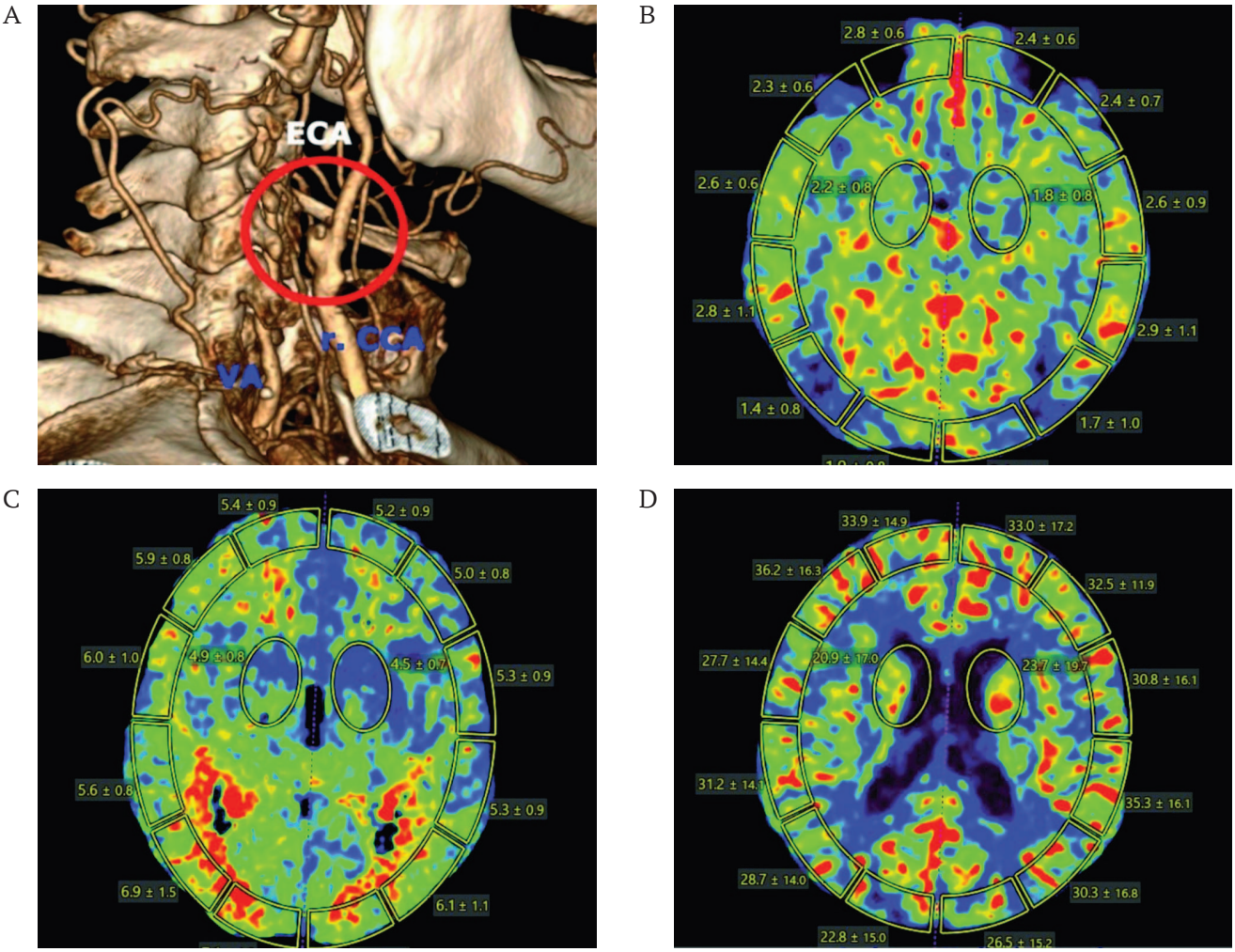

FIG. 1. Computed tomography angiography of the brachiocephalic and cerebral arteries, February 5, 2025 (A), brain computed tomography perfusion, February 6, 2025 (B, C, D) before surgery.
A. Occlusion of the right internal carotid artery.
B. Decreased cerebral blood flow in the right occipital lobe.
C. Decreased cerebral blood volume in the right occipital lobe.
D. Increase mean transit time in the right occipital lobe.
Note: CCA – common carotid artery; ECA – external carotid artery; VA – vertebral artery.

the somatic status was notable for generalized weakness and fatigue.

CT angiography of the brachiocephalic and cerebral arteries revealed occlusion of the right ICA (Fig. 1A). Brain CT perfusion demonstrated decreased cerebral blood flow and cerebral blood volume in both occipital lobes and in the left parietal lobe, together with prolonged mean transit time in the right occipital lobe (Fig. 1B–D).

The diagnosis was atherosclerosis of the brachiocephalic and cerebral arteries with occlusion of the right ICA; stenosis of the right common carotid artery up to 60% according to European Carotid Surgery Trial (ECST) criteria [11]; stenosis of the left ICA up to 30%; and 70% stenosis of the intracranial segment of the left ICA, complicated by vestibulo-ataxic syndrome.

Surgical technique

The STA was marked preoperatively with Doppler ultrasonography. With the patient in the supine position, the head was rotated to the left and rigidly fixed in a Mayfield clamp. A skin incision was made along the course of the STA. The wound edges were retracted with skin hooks to optimize exposure. Layer-by-layer dissection of the subcutaneous tissue was performed over the course of the STA. The frontal branch was dissected and mobilized along its accessible length. Both frontal and parietal branches of the STA were isolated (Fig. 2A). A frontotemporal (dermofascial) flap was then elevated over the temporalis muscle. The temporalis fascia was incised, and the temporalis muscle was split and retracted to expose the calvarium.

A standard craniotomy was performed, and the dura mater was opened in a curvilinear fashion. Under the operating microscope, a cortical recipient vessel corresponding to the M4 segment of the right MCA was identified and sharply dissected from the arachnoid adhesions. The recipient artery was mobilized sufficiently to allow microsurgical manipulation, and a silicone background sheet was placed beneath the vessel (Fig. 2B).

The donor STA branch was prepared by gentle adventitial dissection and irrigation with heparinized saline. The distal end was trimmed in a fish-mouth configuration to match the arteriotomy. After systemic heparinization according to institutional protocol, temporary microvascular clips were applied proximally and distally on the recipient artery. The intended

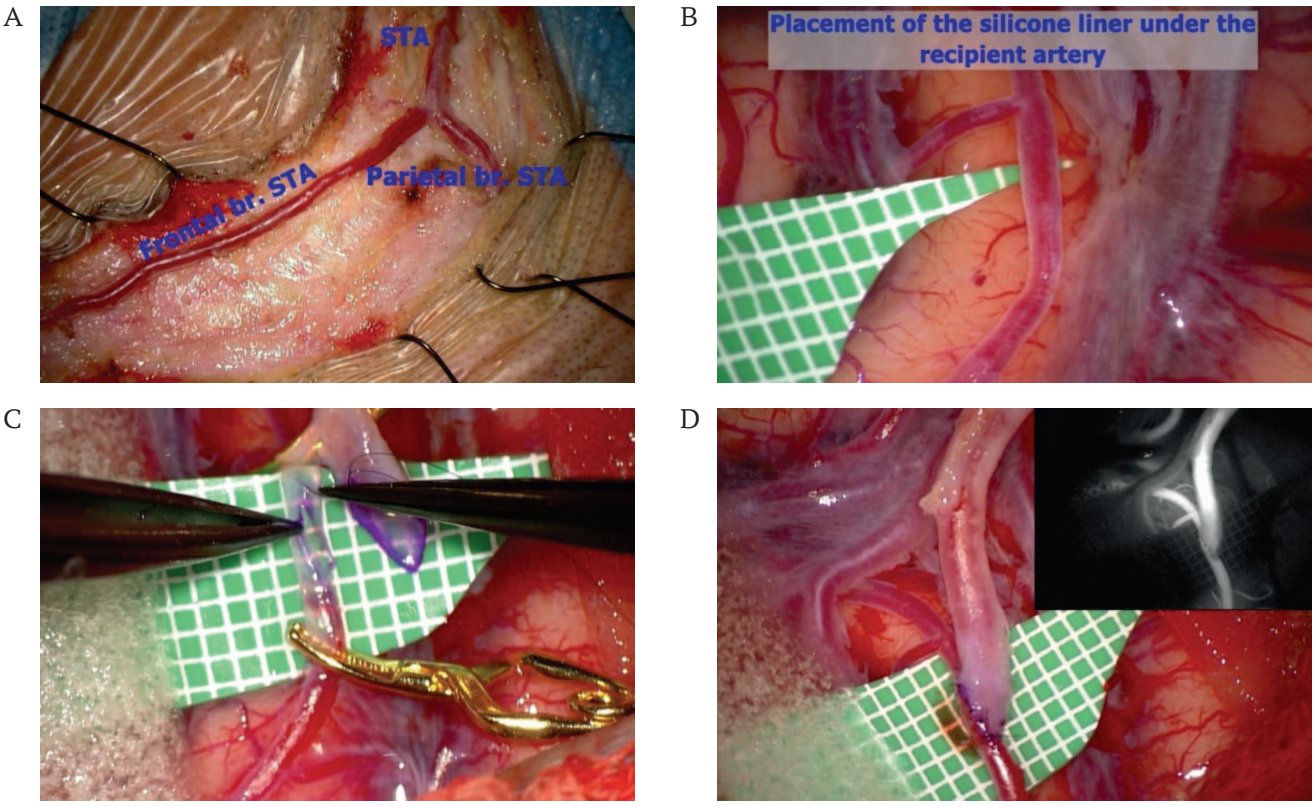

FIG. 2. Bypass anastomosis of the superficial temporal artery to the middle cerebral artery.
A. Frontal branch of the superficial temporal artery was dissected and mobilized along its entire length.
B. A silicone background sheet was positioned beneath the recipient cortical artery.
C. Placement of the first stay suture at the heel of the anastomosis.
D. Completion of the anastomosis: final sutures placed, and temporary clips removed; intraoperative indocyanine green video-angiography confirmed bypass patency and flow.
Note: STA – superficial temporal artery.

arteriotomy margins were marked, and a linear arteriotomy was performed.

An end-to-side STA–MCA anastomosis was constructed using standard microsurgical technique (Fig. 2C). Stay sutures were placed at the heel and tip to secure alignment and prevent torsion. The anastomosis was completed with sequential suturing along both vessel walls; in this case, a running technique with intermittent knot tying after division of the suture line was employed. Throughout the anastomosis, the field was continuously irrigated with heparinized saline to prevent desiccation of the intima and reduce the risk of thrombosis. The opposite wall was closed in a similar fashion, and the suture line was inspected for gaps and intimal inversion. A video of the operation is available at the link: https://youtu.be/hEFQNsDqBMk

Following completion, the temporary clips were removed to re-establish flow in the donor and recipient vessels. Intraoperative indocyanine green video-angiography confirmed immediate patency and antegrade flow through the bypass (Fig. 2D). Doppler ultrasonography further verified graft flow and anastomotic integrity (Fig. 3A–B). Postoperative CT angiography demonstrated contrast opacification of the bypass without evidence of intracranial hemorrhage or new ischemic changes. On follow-up imaging, perfusion assessment showed a moderate increase in the cerebral blood volume index by approximately 10–15%, reaching 8.6 mL/100 g (Fig. 3C–D).

DISCUSSION

In this case, the surgery was followed by an uneventful postoperative course with radiological confirmation of bypass patency on CT angiography and no evidence of intracranial hemorrhage or new ischemic lesions. Perfusion imaging performed on postoperative day 6

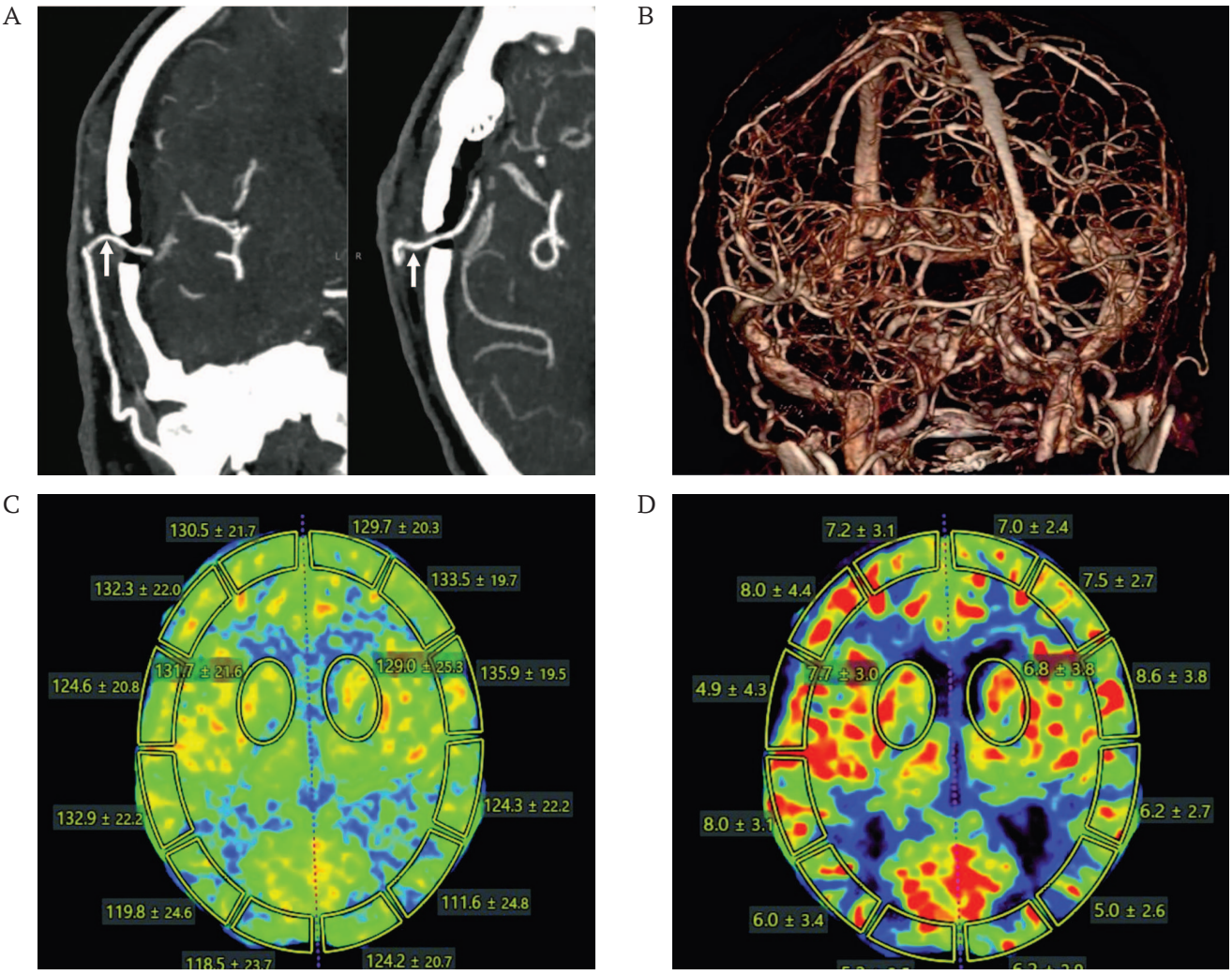

FIG. 3. Postoperative computed tomography angiography (A, B) and computed tomography perfusion (C, D) obtained 6 days after surgery.
A. Coronal and axial reconstructions demonstrating contrast opacification of the superficial temporal artery–middle cerebral artery bypass microanastomosis (white arrows).
B. 3D reconstruction of the cerebral arteries without radiologic evidence of intracranial hematoma or acute ischemic changes.
C, D. Increased cerebral blood volume in the right occipital lobe.

demonstrated a moderate increase in the cerebral blood volume index in the right occipital lobe. Although cerebral blood volume is an indirect surrogate of hemodynamic improvement and should be interpreted together with additional perfusion parameters, the observed direction of change is consistent with improved collateral supply after flow augmentation. Clinically, no recurrent strokes were observed within 30 days and during 11 months of follow-up which supports technical feasibility and short- to mid-term safety of the procedure in this highly selected patient with documented preoperative hemodynamic impairment.

The STA-MCA bypass technique developed by M.G. Yaşargil and R.M.P. Donaghy in the 1960s was rapidly adopted throughout the world as a procedure for surgical flow augmentation for ischemic cerebrovascular disease. The initial enthusiasm for revascularization in atherosclerotic cerebrovascular disease was substantially tempered by the landmark 1985 Extracranial-intracranial Bypass Study Group trial demonstrating failure to reduce stroke risk in 1377 patients with symptomatic disease [4]. Despite high graft patency and improved hemodynamic metrics, perioperative stroke and death rates in early trials were substantial, limiting net clinical benefit. Subsequently, the Carotid Occlusion Surgery Study reported by Powers et al. in 2011 attempted to identify patients with hemodynamic compromise through elevated oxygen extraction fraction on positron emission tomography imaging, but demonstrated no benefit of bypass over medical therapy with a 21% stroke rate at 2 years in the surgical group compared to 23% in medical therapy, complicated by 15% perioperative stroke rate [8–10].

In contrast, moyamoya disease has emerged as a clear indication for revascularization, with the Japan Adult Moyamoya Trial demonstrating that direct bypass prevents ischemic strokes and may reduce hemorrhagic risk by offloading hemodynamic stress from fragile moyamoya vessels [12]. Another established indication is flow preservation when planned vessel sacrifice is necessary for complex aneurysms or skull base tumors, though balloon test occlusion has limitations with approximately 3.7% ischemic events occurring despite passing BTO [2, 4, 10, 11, 13].

Technical approaches of bypass surgery are divided into low-flow and high-flow constructs. STA-MCA anastomosis remains the most widely employed low-flow technique, providing flows of 30–50 mL/min through end-to-side anastomosis using 10-0 or 11-0 microsutures with temporary recipient vessel occlusion for 25–40 minutes [3, 6]. The number of research articles reassessing bypass surgery with appropriate indications and high quality of care has recently increased, and carotid artery and MCA occlusion surgery studies designed with careful consideration for several criticisms against Carotid Occlusion Surgery Study are now being conducted in many countries [10, 13].

CONCLUSION

This case illustrates the technical feasibility of an STA-MCA bypass in a patient with chronic carotid occlusion and documented hemodynamic impairment. This procedure may offer potential quality-of-life benefits after stroke, including improvement of post-stroke depressive symptoms and other emotional disturbances, although such outcomes require systematic assessment. We demonstrate a modified technique for STA dissection using hooks to achieve adequate soft-tissue tension. In addition, a continuous suturing along one edge without tension combined with individually tied knots may help prevent anastomotic narrowing. Collectively, these technical nuances may facilitate STA–MCA bypass construction, enhance surgeon confidence, and potentially reduce procedure-related complications.

AUTHOR CONTRIBUTIONS

Albert A. Sufianov performed the surgical procedure described in the submitted publication, made a major contribution to its conception and design, and supervised the writing and editing of the scientific article. Rakhmonzhon R. Rustamov, Rinat A. Sufianov and Ilya A. Zuev contributed to the conception and design of the publication, prepared materials, wrote and edited the text, and created the illustrations and video. All authors approved the final version of the article and take responsibility for all aspects of the submitted work.

ВКЛАД АВТОРОВ

А.А. Суфианов выполнил хирургическую операцию, описанную в представленном клиническом случае, внес основной вклад в концепцию и дизайн, а также руководил процессом написания и редактирования статьи. Р.Р. Рустамов, Р.А. Суфианов и И.А. Зуев участвовали в разработке концепции и дизайна статьи, подготовке материалов, написании и редактировании текста, а также подготовке иллюстраций и видео. Все авторы одобрили окончательный вариант статьи и готовы взять на себя ответственность за все аспекты представленной публикации.

REFERENCES / ЛИТЕРАТУРА

1. *Lukyanchikov V.A., Orlov E.A., Oganesyan M.V., et al.* Anatomical bases of brain revascularization: choosing an extra-intracranial bypass option. Zh Vopr Neirokhir im. N. N. Burdenko. 2021; 85(6): 120–126 (In Russ.) https://doi.org/10.17116/neiro202185061120. PMID: 34951769
2. *Wessels L., Hecht N., Vajkoczy P.* Bypass in neurosurgery-indications and techniques. Neurosurg Rev. 2019 Jun; 42(2): 389–393. https://doi.org/10.1007/s10143-018-0966-9. Epub 2018 Mar 13. PMID: 29536207
3. *Takizawa K.* [Kamiyama-style STA-MCA bypass surgery]. No Shinkei Geka. 2022 Jul; 50(4): 759–766. Japanese. https://doi.org/10.11477/mf.1436204618. PMID: 35946364
4. *Powers W.J., Clarke W.R., Grubb R.L. Jr., et al.* Extracranial-intracranial bypass surgery for stroke prevention in hemodynamic

cerebral ischemia: the Carotid Occlusion Surgery Study randomized trial. JAMA. 2011; 306(18): 1983–1992. https://doi.org/10.1001/jama.2011.1610. Erratum in: JAMA. 2011 Dec; 306(24): 2672. Obviagele, Bruce [corrected to Ovbiagele, Bruce]. PMID: 22068990
5. *Rodríguez-Hernández A., Josephson S.A., Lawton M.T.* Bypass surgery for the prevention of ischemic stroke: current indications and techniques. Neurocirugia (Astur). 2012 Feb; 23(1): 5–14. https://doi.org/10.1016/j.neucir.2011.11.001. PMID: 22520098
6. *Yoshida K.* [Evidence of STA-MCA Bypass-History and Overseas Articles]. No Shinkei Geka. 2022; 50(4): 735–744. https://doi.org/10.11477/mf.1436204615. PMID: 35946361
7. *Sekhar L.N., Natarajan S.K., Ellenbogen R.G., Ghodke B.* Cerebral revascularization for ischemia, aneurysms, and cranial base tumors. Neurosurgery. 2008; 62(6 Suppl 3): 1373–1408. https://doi.org/10.1227/01.neu.0000333803.97703.c6. PMID: 18695558
8. *Thines L., Durand A., Penchet G., et al.* Microsurgical neurovascular anastomosis: the example of superficial temporal artery to middle cerebral artery bypass. Technical principles. Neurochirurgie. 2014; 60(4): 158–164. https://doi.org/10.1016/j.neuchi.2014.03.004. Epub 2014 May 21. PMID: 24856046
9. *Nomura M., Tamase A., Kamide T., et al.* Superficial temporal artery-middle cerebral artery bypass using a thick STA after endarterectomy: a rescue technique. J Neurol Surg A Cent Eur Neurosurg. 2017; 78(6): 595–600. https://doi.org/10.1055/s-0037-1598050. Epub 2017 Jun 6. PMID: 28586938
10. *Fischer G., Senger S., Sharif S., Oertel J.* Superficial temporal artery to middle cerebral artery bypass via a minimized approach: operative nuances and problem-solving aspects. World Neurosurg. 2016 Apr; 88: 97–103. https://doi.org/10.1016/j.wneu.2015.12.029. Epub 2015 Dec 28. PMID: 26732960
11. *Bonati L.H., Kakkos S., Berkefeld J., et al.* European Stroke Organisation guideline on endarterectomy and stenting for carotid artery stenosis. Eur Stroke J. 2021 Jun; 6(2): I–XLVII. https://doi.org/10.1177/23969873211012121. Epub 2021 May 11. PMID: 34414302
12. *Miyamoto S., Yoshimoto T., Hashimoto N., et al.* Effects of extracranial-intracranial bypass for patients with hemorrhagic moyamoya disease: results of the Japan Adult Moyamoya Trial. Stroke. 2014 May; 45(5): 1415–1421. https://doi.org/10.1161/STROKEAHA.113.004386. Epub 2014 Mar 25. PMID: 24668203
13. *The EC/IC Bypass Study Group.* Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke: results of an international randomized trial. N Engl J Med. 1985; 313(19): 1191–1200. https://doi.org/10.1056/NEJM198511073131904. PMID: 2865674

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Late-onset myelopathy following Torkildsen shunt placement for a midbrain cystic tumor: a case report

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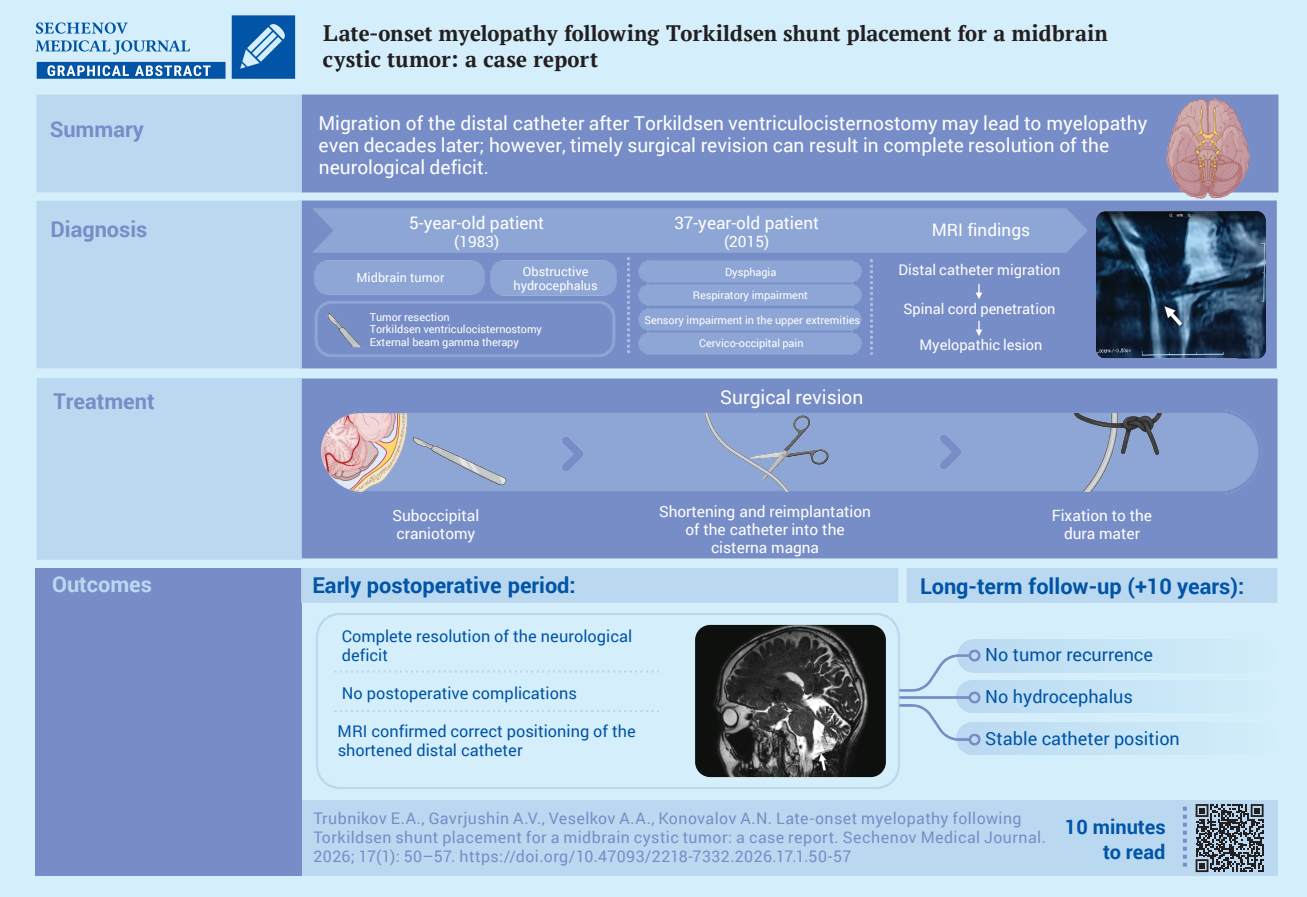

Abstract

Torkildsen ventriculocisternostomy was historically one of the principal surgical treatments for obstructive hydrocephalus. However, nowadays it tends to be regarded mainly as a salvage procedure when standard shunting or endoscopic ventriculostomy is not feasible.

Case report. A 5-year-old boy with obstructive hydrocephalus secondary to a cystic midbrain tumor underwent tumor resection combined with Torkildsen ventriculocisternostomy. Postoperatively, adjuvant radiotherapy was administered, resulting in long-term disease stabilization. At the age of 37 years, 32–33 years after surgery, he developed dysphagia, respiratory disturbances, cervico-occipital pain, and sensory impairment in the upper limbs. Magnetic resonance imaging demonstrated migration of the distal catheter tip with penetration into the upper cervical spinal cord segments and formation of a focal myelopathic lesion. A suboccipital craniotomy was performed; the migrated catheter segment was removed, the system was shortened, and the distal end was reimplanted into the cisterna magna with fixation to the dura mater. Complete regression of neurological deficits was achieved, with a favorable 10-year follow-up.

Discussion. We report a rare delayed case of myelopathy caused by migration of the cisternal catheter tip more than 30 years after Torkildsen ventriculocisternostomy. This observation highlights the need for lifelong surveillance of patients who have undergone such procedures, strict adherence to surgical technique (appropriate catheter length selection and secure fixation), and timely surgical revision at the earliest signs of brainstem dysfunction or involvement of the upper cervical spinal cord.

Keywords: brainstem tumors; occlusive hydrocephalus; Torkildsen ventriculocisternostomy; reimplantation; long-term follow-up
MeSH terms:
CASE REPORTS
BRAIN STEM NEOPLASMS – COMPLICATIONS
BRAIN STEM NEOPLASMS – SURGERY
HYDROCEPHALUS – SURGERY
HYDROCEPHALUS – ETIOLOGY
NEUROSURGICAL PROCEDURES
POSTOPERATIVE COMPLICATIONS – DIAGNOSIS
SPINAL CORD DISEASES – DIAGNOSIS
SPINAL CORD DISEASES – ETIOLOGY
FOLLOW-UP STUDIES
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Compliance with ethical standards. Consent statement. The patient consented to the publication of the article “Late-onset myelopathy following Torkildsen shunt placement for a midbrain cystic tumor: a case report” in the “Sechenov Medical Journal”.
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Миелопатия как отдаленное осложнение операции Торкильдсена у больного с кистозной опухолью среднего мозга: клиническое наблюдение

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Аннотация

Вентрикулоцистерностомия по Торкильдсену исторически была одним из основных методов лечения окклюзионной гидроцефалии, но сейчас рассматривается преимущественно как резервная процедура при ограниченных возможностях для стандартного шунтирования или эндоскопической вентрикулостомии.

Описание случая. У мальчика 5 лет с окклюзионной гидроцефалией на фоне кистозной опухоли среднего мозга выполнено ее удаление с дополнением вентрикулоцистерностомией по Торкильдсену. После операции проведена дистанционная гамма-терапия, достигнута длительная стабилизация. Через 32–33 года, в возрасте 37 лет, возникли дисфагия, дыхательные нарушения, боли в шейно-затылочной области и расстройства чувствительности в руках. Магнитно-резонансная томография выявила миграцию дистального конца катетера с инвазией в верхние шейные сегменты спинного мозга и формированием очага миелопатии. Выполнена субокципитальная краниотомия, мигрировавший сегмент катетера удален, система укорочена, дистальный конец реимплантирован в большую затылочную цистерну с фиксацией к твердой мозговой оболочке. Отмечен полный регресс дефицита и благоприятный 10-летний катамнез.

Обсуждение. Представлен редкий отсроченный случай миелопатии, обусловленной миграцией цистернального конца катетера более чем через 30 лет после вентрикулоцистерностомии по Торкильдсену. Наблюдение подчеркивает необходимость пожизненного мониторинга пациентов с такими вмешательствами, строгого соблюдения техники (подбор длины катетера, надежная фиксация) и своевременной хирургической коррекции при первых признаках стволовой симптоматики и поражения верхних шейных сегментов спинного мозга.

Ключевые слова: опухоли ствола головного мозга; окклюзионная гидроцефалия; вентрикулоцистерностомия по Торкильдсену; реимплантация; катамнестическое наблюдение

Рубрики MeSH:
ОПИСАНИЕ СЛУЧАЕВ
СТВОЛА МОЗГА НОВООБРАЗОВАНИЯ – ОСЛОЖНЕНИЯ
СТВОЛА МОЗГА НОВООБРАЗОВАНИЯ – ХИРУРГИЯ
ГИДРОЦЕФАЛИЯ – ХИРУРГИЯ
ГИДРОЦЕФАЛИЯ – ЭТИОЛОГИЯ
НЕЙРОХИРУРГИЧЕСКИЕ МЕТОДЫ
ПОСЛЕОПЕРАЦИОННЫЕ ОСЛОЖНЕНИЯ – ДИАГНОСТИКА
МОЗГА СПИННОГО БОЛЕЗНИ – ДИАГНОСТИКА
МОЗГА СПИННОГО БОЛЕЗНИ – ЭТИОЛОГИЯ
КАТАМНЕСТИЧЕСКИЕ ИССЛЕДОВАНИЯ

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Соблюдение этических норм. Заявление о согласии. Пациент дал согласие на публикацию представленной статьи «Миелопатия как отдаленное осложнение операции Торкильдсена у больного с кистозной опухолью среднего мозга: клиническое наблюдение» в журнале «Сеченовский вестник».
Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.
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Abbreviations:
MRI – magnetic resonance imaging

HIGHLIGHTS

Early revision surgery with ventricular catheter reimplantation may result in complete recovery from neurological deficits caused by myelopathy secondary to catheter migration.

This case supports lifelong neurosurgical follow-up after Torkildsen ventriculocisternostomy because delayed complications may occur decades later.

These findings support a more selective and judicious approach to the use of the Torkildsen procedure. In contemporary clinical practice, ventriculocisternostomy appears justified only in patients with absolute indications.

Torkildsen ventriculocisternostomy was historically one of the earliest and most widely used surgical procedures for the treatment of obstructive hydrocephalus. However, in contemporary neurosurgical practice it is regarded mainly as a rescue procedure [1]. Nevertheless, patients with functioning or modified Torkildsen shunt systems continue to be encountered in clinical practice, which underscores the importance of assessing long-term complications of these interventions [2].

Clinically significant late complications include migration of the distal catheter tip with penetration into surrounding structures, including the cervical spinal cord, resulting in myelopathy. Such cases are considered extremely rare but potentially disabling and often require revision surgery at the craniovertebral junction [3].

Despite various technical modifications and catheter fixation techniques, the risk of distal catheter dislocation and penetration into adjacent tissues cannot be completely eliminated [4]. In this context, isolated clinical observations with a very long interval after the primary operation are of particular interest for understanding the pathogenesis of these complications, refining revision strategies, and assessing long-term prognosis.

The aim of this report is to present a rare case of distal ventricular catheter migration into the upper cervical spinal cord occurring 33 years after surgery for a cystic midbrain tumor, and to analyze the results of catheter reimplantation together with long-term (10-year) follow-up outcomes.

CASE REPORT

Hydrocephalus first manifested in a 5-year-old boy as diplopia caused by alternating strabismus. His general somatic condition at admission was as expected for his age. A neurological examination revealed brainstem signs, including fine horizontal nystagmus on extreme gaze and static ataxia. Computed tomography demonstrated a midbrain mass with evidence of aqueductal obstruction at the level of the cerebral aqueduct.

The patient underwent surgery. Intraoperatively, a lesion with a predominantly cystic component was identified and resected. The limited amount of biopsy material did not permit histological verification of the lesion. To prevent recurrent hydrocephalus in the event of possible tumor regrowth, the procedure was supplemented with Torkildsen ventriculocisternostomy. The ventricular catheter length was selected according to the patient's anthropometric characteristics. The catheter was secured to the dura mater with interrupted sutures at two points to ensure stable positioning.

Following treatment, the patient's condition was satisfactory. Neurological examination demonstrated persistent mild brainstem signs at the level of the pontine tegmentum, including diplopia and fine horizontal nystagmus. In the postoperative period, a course of adjuvant external beam gamma therapy was administered (20 sessions), with a total focal dose of 40 Gy delivered to the operative field. During subsequent follow-up, the patient remained clinically stable, with no evidence of deterioration.

Clinical deterioration occurred at the age of 37 years. In September 2015, the patient presented with dysphagia, respiratory disturbances, and sensory loss in the upper extremities. These symptoms had been present for one month before admission and had progressively worsened.

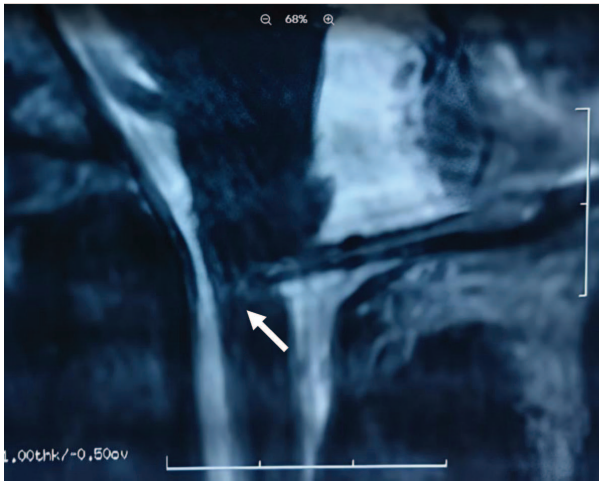
General condition on admission was satisfactory. The patient was alert and oriented, with a Glasgow Coma Scale score of 15; respiratory rate was 17 breaths per minute, heart rate 75 beats per minute, and blood pressure 125/80 mmHg. Neurological examination, in addition to persistent brainstem signs (horizontal nystagmus), revealed impaired proprioceptive and kinesthetic sensation in the upper extremities, accompanied by localized pain in the cervico-occipital region.

Magnetic resonance imaging (MRI) showed no evidence of tumor recurrence but demonstrated migration of the distal ventricular catheter tip with penetration into the spinal cord at the spinomedullary junction (Fig. 1A, B).

The development of neurological deficits associated with migration of the distal catheter tip into the upper cervical spinal cord and the presence of myelopathic lesions on MRI constituted an indication for revision surgery.

The operation was performed on September 30, 2015. A midline suboccipital craniotomy with bone flap replacement was carried out. In the region of the

A



B

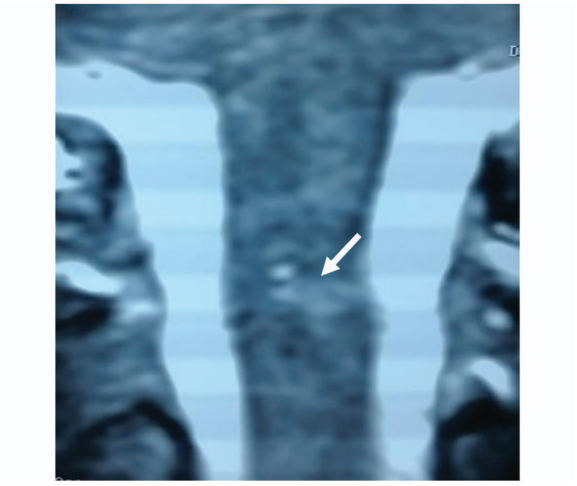
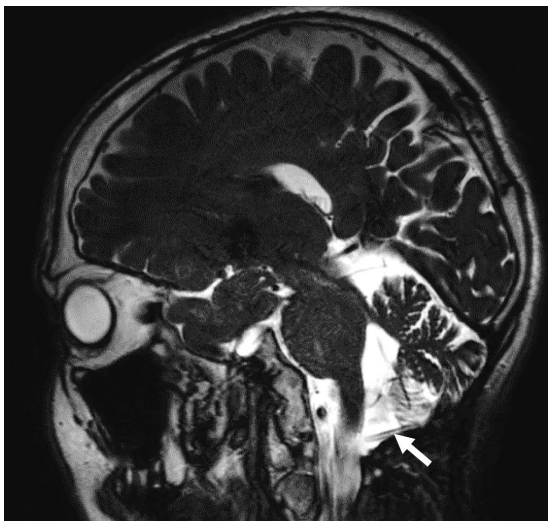


FIG. 1. Preoperative magnetic resonance imaging data of a 37-year-old patient with dislocation of the distal ventricular catheter tip (September 23, 2015).
A. T2-weighted sagittal image demonstrating penetration of the distal shunt catheter tip into the spinal cord at the level of the upper cervical segments (arrow).
B. T2-FLAIR coronal image demonstrating a hyperintense lesion with ill-defined margins corresponding to focal myelopathy (arrow).

A



B

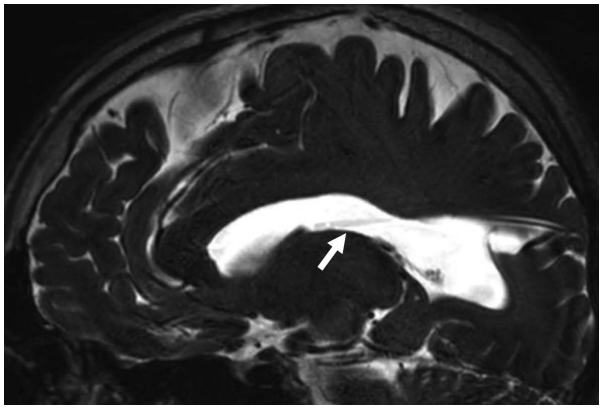


FIG. 2. Magnetic resonance imaging of the brain performed 1 month after surgery (October 29, 2015).
A. T2-weighted sagittal image showing the shortened distal ventricular catheter tip reimplanted into the cisterna magna (arrow).
B. T2-weighted sagittal image showing the proximal ventricular catheter segment in correct position (arrow); the middle third of the catheter courses through the occipital subgaleal space. No evidence of tumor recurrence is seen.

posterior median sulcus of the upper cervical spinal cord, the migrated catheter tip was identified embedded within the spinal cord parenchyma. After removal, the distal catheter segment was shortened and reimplanted into the cisterna magna; the distal end of the ventricular catheter was additionally secured to the dura mater. The postoperative course was uneventful, and the patient was discharged in satisfactory condition on postoperative day 5. At discharge, complete resolution of the neurological deficit was observed, with no new focal neurological signs.

One month after surgery, follow-up MRI confirmed correct positioning of the shortened distal ventricular catheter tip within the cisterna magna, with no evidence of tumor recurrence (Fig. 2A, B).

At the 10-year follow-up after ventricular catheter reimplantation, the patient reported only occasional cervico-occipital pain, with no focal neurological deficits. Annual follow-up MRI demonstrated no significant interval changes: there was no evidence of tumor progression or hydrocephalus, and the ventricular catheter remained in proper position.

DISCUSSION

In the present case, the total follow-up duration was 43 years, representing a rare and virtually unique experience in the management of a patient after Torkildsen ventriculocisternostomy. This highlights the fact that the long-term consequences of this procedure remain clinically relevant because despite the emergence of alternative extra- and intracranial shunting techniques, ventriculocisternostomy and its modifications continue to be used, albeit rarely, in modern neurosurgery [2, 5].

During the first decades of Torkildsen ventriculocisternostomy use, a pooled analysis of 136 published cases by J.E. Scarff [6] showed that arrest of hydrocephalus progression over a two-year period was achieved in 58% of patients, with an operative mortality of approximately 30%. According to N. Morota et al. [7], these unfavorable outcomes in historical series largely reflect the level of neuroimaging, anesthetic, and neurosurgical care available in the mid-20th century, when the procedure was performed as a palliative intervention in severely ill, often terminal patients with advanced obstructive hydrocephalus. Nevertheless, the long-term effectiveness of the technique is supported by isolated case reports with follow-up periods of up to 30 and 50 years, demonstrating durable shunt function and satisfactory neurological outcomes [1, 8].

Complications of Torkildsen ventriculocisternostomy include infectious and nonspecific surgical complications (wound infection, meningitis), mechanical shunt dysfunction (migration, kinking, axial rotation, and catheter obstruction), as well as neurological complications such as myelopathy, tetraparesis, and facial pain caused by penetration of the cisternal catheter tip into the brainstem or upper cervical spinal cord [3, 7, 9].

Myelopathy is considered one of the most serious, although rare, long-term complications of Torkildsen ventriculocisternostomy. It results from migration or progressive intraparenchymal advancement of the distal catheter tip, causing compression of the cervical spinal cord and craniocervical junction. Such cases have been reported both 8–15 years after surgery and as late as 25–30 years or more thereafter. Clinically, patients may present with progressive spastic tetraparesis, sensory disturbances, and signs of medullary involvement, whereas MRI can demonstrate the catheter penetrating the brainstem parenchyma or upper cervical spinal cord. Treatment usually consists of catheter removal, shortening, or repositioning with fixation to the dura mater; however, because of prolonged compression, neurological deficits often resolve only partially, underscoring the importance of early diagnosis and prevention of catheter migration [3, 4, 10, 11].

In the present case, myelopathy developed 32 years after Torkildsen ventriculocisternostomy and was most likely related to inappropriate selection of ventricular catheter length and insufficient fixation to the dura mater, resulting in gradual distal catheter migration with penetration into the brainstem. Surgical correction consisted of revision of the shunt system, removal of the migrated catheter segment, shortening and reimplantation of the cisternal end, and additional fixation to the dura mater.

To prevent myelopathy caused by migration or excessive advancement of the cisternal catheter tip, G. Ehni et al. [3] emphasized the need for careful selection of catheter length according to the patient's age, so that the catheter lies closely along the bone and enters the subarachnoid space of the cisterna magna only minimally. They additionally recommended positioning the distal tip strictly in the midline and securing it firmly to the dura and arachnoid mater with non-absorbable sutures, splitting the catheter tip into two thin "arms" to improve fixation. N. Morota et al. [7], based on their experience in pediatric patients, also highlighted the importance of thorough preoperative MRI assessment of the craniovertebral junction, partial resection of the posterior arch of the first cervical vertebra when necessary, and careful insertion of the catheter through a midline dural opening while limiting its intradural length to approximately 2 cm, thereby reducing the risk of compression of the brainstem and upper cervical spinal cord.

In the present case, the most likely cause of myelopathy was insufficient fixation of the ventricular catheter to the dura mater, which contributed to gradual distal catheter displacement with penetration into the brainstem. Timely diagnosis and surgical correction resulted in rapid and complete resolution of the neurological deficit.

Thus, the role of Torkildsen ventriculocisternostomy in contemporary neurosurgical practice remains debatable in the era of widespread use of endoscopic third ventriculostomy and various ventriculoperitoneal shunting techniques. In most patients, these methods are considered first-line treatment options, whereas the Torkildsen procedure and its modifications may serve as a salvage option in carefully selected cases of obstructive hydrocephalus where anatomical constraints or prior surgery limit the use of standard techniques. In such rare situations, strict adherence to technical principles – including optimal catheter length selection, secure fixation, and thoughtful revision of previously implanted shunt systems – may reduce the risk of severe complications and improve long-term clinical outcomes.

CONCLUSION

The present case demonstrates that Torkildsen ventriculocisternostomy may provide durable long-term control of obstructive hydrocephalus. However, sustained shunt function is associated with a risk of severe delayed complications related to the position of the cisternal catheter. The occurrence of myelopathy decades after surgery underscores the need for lifelong surveillance of patients who have undergone this type of cerebrospinal fluid shunting procedure, as well as timely system revision at the earliest signs of brainstem or cervical spinal cord involvement. Taken together, the available literature and the present case suggest that, in contemporary neurosurgery, the Torkildsen procedure should be regarded primarily as a reserve option for a limited subset of patients with obstructive hydrocephalus, whereas endoscopic third ventriculostomy and ventriculoperitoneal shunting remain the standard first-line treatments. In the rare situations in which ventriculocisternostomy is selected, meticulous surgical technique–including precise catheter length selection and secure fixation–is essential to reduce the risk of late complications and achieve favorable long-term outcomes.

AUTHOR CONTRIBUTIONS

Alexander N. Konovalov developed the concept. Elisey A. Trubnikov prepared the draft of the manuscript. Andrey V. Gavrjushin and Aleksei A. Veselkov contributed to the reviewing and editing of the text. Aleksei A. Veselkov and Elisey A. Trubnikov participated in data collection and patient examination. Andrey V. Gavrjushin performed the formal analysis. Alexander N. Konovalov was responsible for the methodology and provided scientific supervision throughout the study. All authors have approved the final version of the article.

ВКЛАД АВТОРОВ

А.Н. Коновалов разработал концепцию рукописи. Е.А. Трубников подготовил черновик рукописи. А.В. Гаврюшин и А.А. Веселков внесли вклад в рецензирование и редактирование текста. А.А. Веселков и Е.А. Трубников участвовали в сборе данных и обследовании пациента. А.В. Гаврюшин выполнил формальный анализ. А.Н. Коновалов отвечал за методологию и осуществлял научное руководство на протяжении всего исследования. Все авторы одобрили окончательную версию статьи.

REFERENCES / ЛИТЕРАТУРА

1. *Zinn P.O., Bozinov O., Burkhardt J.K., et al.* Failure of a Torkildsen shunt after functioning for 50 years. J Neurosurg. 2010 Apr; 112(4): 796–799. https://doi.org/10.3171/2009.7.JNS09729. PMID: 19715420
2. *Florian I.Ş., Aldea C.C.* Ventriculocisternal shunt redivivus: third ventricle-cisterna magna intradural shunt: a technical note and case report. World Neurosurg. 2018 Aug; 116: 56–59. https://doi.org/10.1016/j.wneu.2018.05.034. Epub 2018 May 14. PMID: 29772362
3. *Ehni G., Moiel R.H., Bragg T.G.* Torkildsen's ventriculocisternostomy: some complications and their prevention. Clin Neurol Neurosurg. 1976; 79(2): 119–132. https://doi.org/10.1016/0303-8467(76)90004-4. PMID: 1029636
4. *Crotty G.F., McKee K.E., Klufas R., et al.* Progressive cervical myelopathy due to intramedullary migration of forgotten Torkildsen shunt. Neurology. 2019 Sep; 93(12): 555–556. https://doi.org/10.1212/WNL.0000000000008136. PMID: 31527098
5. *Tang M., Richard S.A., Ren Y., et al.* Aqueduct-fourth ventricle-cisterna magna shunting as a prophylactic procedure for postoperative hydrocephalus in selective fourth ventricular tumors: A retrospective study. Medicine (Baltimore). 2025 Aug; 104(34): e43697. https://doi.org/10.1097/MD.0000000000043697. PMID: 40859526
6. *Scarff J.E.* Treatment of hydrocephalus: an historical and critical review of methods and results. J Neurol Neurosurg Psychiatry. 1963 Feb; 26(1): 1–26. https://doi.org/10.1136/jnnp.26.1.1. PMID: 13976518
7. *Morota N., Ihara S., Araki T.* Torkildsen shunt: re-evaluation of the historical procedure. Childs Nerv Syst. 2010 Dec; 26(12): 1705–1710. https://doi.org/10.1007/s00381-010-1182-2. Epub 2010 May 26. PMID: 20502902
8. *Eide P.K., Lundar T.* Arne Torkildsen and the ventriculocisternal shunt: the first clinically successful shunt for hydrocephalus. J Neurosurg. 2016 May; 124(5): 1421–1428. https://doi.org/10.3171/2015.1.JNS142659. Epub 2015 Sep 4. PMID: 26339852
9. *Бервицкий А.В., Мойсак Г.И., Дмитриев А.Б., Рзаев Д.А.* Лицевая боль вследствие миграции шунта, установленного по методу Торкильдсена. Нейрохирургия. 2020; 22(1): 71–76. https://doi.org/10.17650/1683-3295-2020-22-1-71-76. EDN: FPSECW / *Bervitskiy A.V., Moysak G.I., Dmitriev A.B., Rzaev D.A.* Facial pain, caused by Torkildsen shunt migration. Russian journal of neurosurgery. 2020; 22(1): 71–76. (In Russian). https://doi.org/10.17650/1683-3295-2020-22-1-71-76. EDN: FPSECW
10. *Schulder M., Maniker A.H., Lee H.J.* Cervical myelopathy due to migration of Torkildsen's shunt: case report. Surg Neurol. 1999 Jan; 51(1): 27–30. https://doi.org/10.1016/s0090-3019(97)00433-3. PMID: 9952120
11. *Pascual-Leone A., Dhuna A., Castillo R., Ala T.* Displaced Torkildsen's shunt: an unusual cause of cervical myelopathy. J Neurol Neurosurg Psychiatry. 1991 Jul; 54(7): 654. https://doi.org/10.1136/jnnp.54.7.654. PMID: 1895134

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