Original Article

Metabolic syndrome - ways to the development of oncopathology

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ABSTRACT

Objectives

To determine the probability of developing oncological pathology in individuals with metabolic syndrome (MS) and compare the results with the frequency of tumor development in patients without MS by conducting a retrospective cohort study.

Methods

This observational retrospective study was conducted between April 2021 and September 2023. According to outpatient charts, the incidence of oncological diseases in 994 patients with MS lasting more than 10 years, and the degree of dependence on its components: abdominal obesity (AO), arterial hypertension (AH), carbohydrate metabolism disorders, dyslipidemia were analyzed[1]. According to the same parameters, the data of 999 patients without MS who made up the comparison group were analyzed. By the method of cross-tabulation, the odds ratios (OR) of carcinogenesis and 95% confidence intervals (95% CI) were estimated. The SPSS 22.0 program is used for statistical processing of the results of the study.

Results

The study made it possible to conclude that if a patient has MS, the ten-year risk of developing oncopathology is almost three times higher than in its absence (with MS, an oncoprocess was detected in every 5th patient, in its absence in every 14th). AO, especially grade I, is a risk factor for cancer of various localization. It was revealed that hypertension is a universal risk factor for cancer and aggravates the course of oncological diseases in combination with MS. An important role in the development of cancer processes is played by the age of the patient[1]. Analysis of the data obtained indicates a decrease in the risk of cancer in people with MS with impaired tolerance to carbohydrates taking metformin.

Conclusion

MS is a risk factor for the development of oncological diseases of any localization. AO, as the main criterion of MS, is associated with an increased risk of carcinogenesis. Hypertension is the main risk factor for the development of oncological diseases, regardless of the presence or absence of MS.

Keywords

metabolic syndrome; oncological diseases; arterial hypertension; hyperglycemia; dyslipidemia.

INTRODUCTION

Despite the well-known connection between obesity and metabolic syndrome (MS), their association is still being actively studied.[1] The relevance of further research is determined by the clarification of the mechanisms underlying the association, the peculiarities of systemic inflammation in these conditions, and modern methods of treatment and prevention. The basis of MS is a large volume of visceral fat, which determines hyperinsulinemia, decreased sensitivity of peripheral tissues to insulin, metabolic disorders (lipid, purine, carbohydrate).[2] MS is prevalent throughout the world. MS is most common (up to 40%) in developing countries, both among adults and children. The reasons for the high prevalence are related to urbanization and, as a consequence, hypodynamia, frequent consumption of high-calorie food like fast food, prevalence of bad habits. According to the forecasts of experts of the World Health Organization, the number of obese people may increase 2 or more times in the next 20 years.[3] Therefore, to prevent the development of MS and, as a consequence, endocrine, cardiovascular and oncologic diseases, it is extremely important to timely detect and correct hyperglycemia, hyperlipidemia, overweight or obesity, which are the unifying criteria of the concept of MS.[4] MS has been proven to be a factor contributing to an increase in overall mortality.[1-5]

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The aim of this study was to determine the probability of developing oncological pathology in individuals with metabolic syndrome and to compare the results obtained with the frequency of tumor development in patients with normal weight by conducting a retrospective cohort study.

METHOD AND MATERIALS

An observational retrospective cohort study involving 1993 patients was conducted at the clinical base of the Department of Polyclinic Therapy of the Sechenov First Moscow State Medical University (Sechenov University). The main group consisted of 994 patients (289 men and 705 women). The average age of the participants in the main group at the time of selection for the study was 62.48±13.49 years (from 20 to 87 years). A mandatory criterion for inclusion in the study was the presence of MS in patients for 10 years or more.

The comparison group consisted of 999 patients (261 men and 738 women), whose average age corresponded to the indicators in the main group. The mandatory criterion for selecting patients in the comparison group was the absence of MS.

In both samples, there are more women than men, since women are more likely to be obese and seek medical help more often. [6]

In the study, the clinical recommendations of the Russian Society of Cardiology (RSC) 2009, 2nd revision (Table 1) were used to determine the presence of MS in a patient.[7]

When selecting patients for the comparison group, the presence of changes in one or two parameters corresponding to additional MS criteria was allowed. The study assessed the level of total cholesterol, triglycerides (TG), low-density lipoproteins (LDL), which are not MS criteria, but indicate the presence of dyslipidemia in the patient as a risk factor for various diseases.

In the comparison group, a similar assessment of the levels of laboratory parameters and the above-mentioned chronic diseases was carried out. The comparison group allowed the inclusion of patients taking hypolipidemic therapy (n=145) with a statin prescription of no more than 3-6 months. The comparison group also included 190 patients with type 2 diabetes taking hypoglycemic therapy (119 of whom took metformin).

Outpatient charts and databases of outpatient patients of medical institutions also served as a source of morphologically confirmed data on the presence and prescription of oncological diseases.

The SPSS 27.0 program was used to carry out statistical processing of the results of the study using parametric and nonparametric methods. Cross-tables were used to identify the dependencies between the components of MS and the risk of oncopathology. Proportional risk models were used to assess the OR and 95% CI of the compared relationships. Statistical significance ($p<0.005$) was determined by Kruskal–Wallis criterion and Pearson's chi-squared criterion.

The study examined the relationship of each component of MS and their combinations with the risk of carcinogenesis. Additionally, patients with MS were divided into three age groups (up to 55 years, 55-74 and 75 and older) and degrees of obesity (I st. BMI 30-34.9 kg/m2, II st. BMI 35-39.9 kg/m2, III st. BMI 40 kg/m2 and above), and in each group was determined the risk of developing oncopathology. In the comparison group, the relationship between the levels of laboratory parameters and the presence of chronic diseases with the risk of oncopathology in three age groups was studied.

RESULTS

Among the study participants (Fig. 1), the main group (70.9%) and the comparison group (73.87%) are dominated by females. The average age of participants in the main group was 62.48±13.49, in the comparison group 64.05±19.75 years. The mean value of waist circumference (WC) in the main group was 103.8±10.50 cm, BMI - 36.05±4.12 kg/m2.1 In the comparison group, the average WC value was 84.0±9.3 cm. In the main group, obesity of the I st. was determined in 49.9% of participants, obesity of the II and III st. 29.4% and 20.7%, respectively. The group of patients without MS, according to the criteria for inclusion in the study, had no signs of obesity, therefore, when comparing anthropometric data (BMI, WC), intergroup differences were established ($p<0.005$).

Abdominal obesity (AO). In our work, we sought, first of all, to assess the likelihood of developing cancer in patients with MS lasting more than 10 years. And the contribution of obesity was confirmed by the statistically significant difference in the values of the study participants of the first and second groups in an intergroup comparison (adjusted significance level $p<0.001$).

It should be noted that in the main group of patients with MS, the oncological process was detected in 18.6% of patients, while a pronounced dependence of carcinogenesis on the degree of obesity was established. The most unfavorable prognostic effect was observed in people suffering from obesity of the 1st degree, in whom the risk of developing cancer increased to 65.4% (OR – 2.188; CI – 1.568-3.053; p=0.01). And adjusted for age and gender, the probability of carcinogenesis was higher (up to 74.6%) in women over 75 years of age with a BMI of 30.0-34.9 (p = 0.001). In patients with obesity of the 2nd and 3rd degrees of the main group, conjugation with oncogenesis was revealed to a lesser extent (Table 2). The probability of carcinogenesis in the second degree of obesity was 17.8% (OR - 0.461; 95% CI 0.308—0.691; p=0.03) and in the third degree - 16.8% (OR - 0.729; 95% CI 0.479—1.11; p=0.153) In patients with normal BMI without MS, cancer developed in 7.3% of cases.

Arterial hypertension (AH). We have established that AH is a powerful risk factor for carcinogenesis. In patients with MS, AH was registered in 774 patients, while in 20.8% of cases AH was combined with oncological pathology. In patients of the comparison group in the absence of MS, AH was combined with cancer in 8.7% of cases (Table 3).

The results of the analysis showed that in patients with MS and AH, compared with patients with AH without MS, cancer developed 2 times more often (asymptotic significance <0.001 with Pearson chi-squared value = 34.117).

It should be noted that during the multivariate analysis, an associative relationship of carcinogenesis was established depending on age, the presence of AH and the degree of obesity. The risk of carcinogenesis in people with MS over 75 years of age increased, the incidence of cancer in this category of people was 89.6% (OR = 2.145; 95% CI: 1.357–3.391; p=0.001).

In other age groups of people with MS and AH, the risk of developing cancer was lower: in the group under 55, the probability of developing cancer was 1.021 (95% CI: 0.405–2.578; p=0.02) and in patients 56-74 years old – 0.970 (95% CI: 0.405–2.578; p=0.741).

Dyslipidemia. Dyslipidemia was detected in 837 patients of the main group and in 21 patients of the comparison group. Hypertriglyceridemia of more than 150 mg/dl and a decrease in HDL levels of less than 40 mg/dL at the time of the study were registered in patients with MS in 59.9% and 50.1% of all cases. In patients without MS, the incidence of these dyslipidemias was detected in 1.1% and 1% of cases. Dyslipidemia in combination with MS (main group), compared with dyslipidemia without MS (comparison group), was more often associated with carcinogenesis. In patients with MS with a TG level of ≥150 mg/dL and an LDL level of ≥ 130 mg/dL, the risk of developing cancer was 3.2 times higher compared with patients without MS, whose TG and LDL levels were lower than <120 mg/dL and 110 mg/dL, which, according to the Kruskal-Wallis criterion, had intergroup differences in the proportional risks model (Table 4). It should be noted that the use of lipid-correcting therapy did not reveal any connection with either a decrease in the likelihood of carcinogenesis or its initiation (Table 4).

Hyperglycemia. In the main group 594 patients had certain types of carbohydrate metabolism disorders, while in all age groups the probability of developing oncopathology was, on average, 22.2% (n = 119 - the total number of cases of oncopathology in the presence of hyperglycemia). It was noted that when taking metformin, the incidence of cancer decreases. The highest probability of carcinogenesis in the absence of metformin use was found in patients of the older age group (56-74 years) (OR - 2,892; 95% CI - 1,915–4,366; p <0.05).

In the comparison group, where hyperglycemia was detected in 203 cases, we also analyzed the dependence of the risk of oncological pathology on glucose values and revealed an increase in the incidence of oncopathology with elevated glucose levels. In an intergroup statistical analysis, we proved a 5-fold increase in the risk of cancer with hyperglycemia above 108 mg/dL with proven reliability of differences.

DISCUSSION

The presence of MS is associated with a 33% increased risk of death from cancer.[6, 8-11] Each criterion of MS is an established cancer risk factor, and when combined, it significantly increases.[10]

AO. Obesity is one of the leading causes of mortality today. It is associated with hormone-dependent and hormone-related cancer types in both men and women. The distribution of abdominal body fat, which varies dramatically by gender, is considered an independent risk factor.[12] Despite the high prevalence of obesity

worldwide, the number of obese individuals is very variable. The lowest percentage of obese individuals is found in Japan (about 4%) and the highest in the United States (about 40%).[3] In Russia, 20% of the population has signs of obesity. [13]

WHO experts note the expediency of increasing oncological vigilance in countries with a high prevalence of obesity and recommend assessing waist circumference in combination with BMI, which allows to identify the abdominal phenotype of obesity, most associated with a high risk of cancer and cardiovascular diseases.[3, 14] In AO low-dose and chronic systemic inflammation occurs due to long-term compensatory insulin resistance. After a persistent disorder occurs (a «vicious circle»): insulin resistance leads to the progression of AO, development of MS with a combination of several components and the onset of early endocrine, cardiac and oncologic diseases.[1, 2, 4, 10]

According to our results 65.4% of patients among those who developed cancer had AO the I st. more than 10 years, with more than 80% of them suffering from both AH and obesity for 10-15 years. The association between AO (high incidence of cancer in patients with obesity of the I st.) and the risk of cancer development is confirmed by the results of other researchers, especially in relation to colorectal cancer. A group of researchers led by prof. Zhang showed a causal relationship between obesity of the I st. and the development of colon cancer. The OR was 1.35 (95% CI: 1.08-1.69; p = 0.0096) [15]. In our study, as in other studies, a positive relationship was observed between obesity of the I st. and postmenopausal breast cancer. [6, 12, 16]

AH. The association between hypertension and cancer (as well as higher cancer mortality) was first reported in a prospective fourteen-year follow-up of 1233 men with high blood pressure.[17] But today the role of AH in the development of carcinogenesis is still undisputed. Prolonged and persistent high blood pressure (BP) is associated with an increased likelihood of developing both hormone-dependent and hormone-independent cancers. In our study there was a significant association between systolic BP levels ≥140 mm Hg and cancer risk in both groups; however, patients with a combination of MS and AH compared with patients with AH without MS, were 2 times more likely to develop cancer (asymptotic significance < 0.001). The underlying mechanism of this association is explained by the commonality of risk factors such as hypodynamia, obesity, smoking and alcohol abuse, but the detailed study of the commonality of pathogenetic processes is still ongoing. A new concept of oncohypertension has been defined experimentally and is related to the dysregulation of apoptosis due to uncontrolled increase in blood pressure and the role of angiotensin II in activation of vascular endothelial growth factor (which enhances angiogenesis associated with cancer transformation). [1, 10, 18, 19]

Dyslipidemia. As in other studies we analyzed the association of changes in lipid spectrum parameters with the risk of oncopathology. Dyslipidemia with high levels of TG (level of ≥150 mg/dL) and LDL (level of ≥ 130 mg/dL) was associated with a high risk of carcinogenesis, especially prostate cancer and colorectal cancer in men and breast cancer in women. There is speculation that the cancer-initiating role of hyperlipidemia is related to its effect on systemic inflammation and the special role of total cholesterol. Cholesterol, as one of the main components of the phospholipid membrane of the cell, plays a key role in maintaining its integrity. [20] Excess cholesterol accumulates in the membrane and combines with sphingolipids to form compartmentalized microdomains «lipid-rafts», which activate Epidermal Growth Factor Receptor (EGFR) - important signaling receptors for tumor growth factor. [21] In addition, imbalance in the system of oxidative degradation of lipids with excessive accumulation of free radicals leads to damage to nucleic acids, induction of chromosomal aberrations and impaired regulation of cell proliferation. Further lipid modification exacerbates the disruption of vital cellular functions, including genetic processes and apoptosis, leading to malignant cell transformation and tumor progression. [2, 22-24]

Hyperglycemia. Hyperglycemia (being one of the criteria of MS) creates conditions not only for rapid growth of malignant neoplasms, but also for metastasis of tumor masses. [1, 2, 12, 25] Hyperglycemia as well as dyslipidemia increases the production of free radicals, triggering systemic inflammation. [26, 27] The effects of glycation end products are directly related to damage to protein structures and modification of the extracellular matrix, oxidative damage to deoxyribonucleic acid and mutations in proto-oncogenes and tumor suppressor genes. [28] Our work has established a high probability of carcinogenesis in hyperglycemia with a particularly high incidence of breast and pancreatic cancer in individuals with grade 1 obesity and glycemic

levels greater than 126 mg/dL. AO of more than 10 years in these individuals defined long-term chronic hyperinsulinemia and insulin resistance. Elevated insulin levels are known to stimulate tumor cell growth factor and EGFR. [20, 26, 29] Subsequently, cancer cells are able to produce energy by oxidizing glucose to lactic acid (the Warburg effect), which promotes their further proliferation, tumor growth and metastasis.[28] The proliferation process is accelerated by an increase in the number of glucose transporters (GLUT 1, 3, 4), hybrid insulin receptors and insulin-like growth factor 1 on the membranes of malignant cells.[29-32]

Similar results were obtained by other scientists who showed a high association of hyperglycemia, dyslipidemia and cancer, as well as a cancer determining role of tumor-associated antigen CA19-9 in the pathogenesis of pancreatic cancer initiated by high serum total cholesterol levels, impaired insulin secretion and hyperglycemia. [33, 34] Due to the high prevalence of individuals with type 2 diabetes mellitus, no association between type 1 diabetes and cancer was established in our study.

CONCLUSIONS

MS is a risk factor for the development of oncological diseases of any localization equally. As it was proved in the first part of the study, AO, as the main criterion of MS, is associated with an increased risk of cancer. With MS, the greatest risk is associated with the I degree of AO. As an independent risk factor, the development of cancer processes is influenced by the age of patients. Hyperglycemia increases the risk of developing oncopathology, and taking metformin and controlling glycemia reduce the risk of oncogenesis. Hypertension exacerbates the risk of cancer even in the absence of metabolic disorders, and in the presence of MS significantly increases the likelihood of their development, therefore, hypertension can be considered a universal risk factor for oncogenesis.

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Conflict of interest. The authors declare that there is no potential conflict of interest.

Ethical purity: The study was approved by the local ethics committee 1-st Federal State Autonomous Educational Institution of Higher Education I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University) 15.06.2023, protocol number № 11-23.

Authors's contribution

concept and design of the study — M. Osadchuk, O. Mitrokhina, I. Vasileva;

collection and processing of material—O. Mitrokhina, I. Vasileva;

statistical data analysis—O. Mitrokhina, I. Vasileva;

writing the text — I. Vasileva, O. Mitrokhina;

editing — M. Osadchuk, O. Mitrokhina, I. Vasileva, M. Trushin.

Study design: Observational retrospective study

Data collection: between 2021 - 2023

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List of abbreviations

MS – metabolic syndrome

AH – arterial hypertension

BP – blood pressure

AO – abdominal obesity

DM – diabetes mellitus

CVD – cardiovascular diseases

BMI – body mass index

WS - waist size

HDL – high density lipoproteins

LDL – low density lipopriteins

TG – triglycerides

CI - confidence interval

OR – odds ratio

Table 1. RSC criteria for the diagnosis of metabolic syndrome

Criteria	Values
The main	
AO, WS	males > 94.0 cm, females >80.0 cm
Additional	
BP	More than 140/90 мм рт.ст. or in the presence of AH in the anamnesis
TG	>1.7 mmol/L
HDL	males < 1.0 mmol/L, females < 1.2 mmol/L
Hyperglycemia or DM type 2	In the presence

Note: the diagnosis of MS is established if there is a basic criterion in combination with two or more additional ones.

AO, WS- abdominal obesity, waist circumference

BP - blood pressure

TG - triglyceridemia

HDL - high density lipoproteins

DM - diabetes mellitus

Table 2. The frequency of oncogenesis in MS, depending on the degree of obesity patients of the main group

The degree of AO	OR, Odds Ratio
I	n = 496; OR =0.527 [95% CI: 1.568 - 3.053]; p = 0.01
II	n = 292; OR =0.461 [95% CI: 0.308 - 0.691]; p = 0.03
III	n = 292; OR =0.729 [95% CI: 0.479 – 1.111]; p = 0.153

Note: C.I, 95% confidence interval. A lower risk of carcinogenesis was observed among patients with grade 2-3 obesity (the probability of carcinogenesis in the second degree of obesity was 17.8% and in the third degree - 16.8%); in comparison, patients with grade 1 obesity had a higher risk.

Table 3. The incidence of cancer and arterial hypertension in patients of both groups

Patients of the first group; n = 994	AH, n = 774	Cancer, n = 161 (20.8 %)
		No cancer, n = 613 (79.2%)
	No AH, n = 220	Cancer, n = 24 (10.9%)
		No cancer, n = 196 (89.1%)
Patients of the second group; n =999	AH, n = 709	No cancer, n = 647 (91.3%)
		Cancer, n = 62 (8.7%)
	No AH, n = 290	No cancer, n = 279 (96.2%)
		Cancer, n = 11 (3.8%)

Note: AH – arterial hypertension

Table 4. Association of the risk of oncopathology in patients with MS with hyperlipidemia and lipid-correcting therapy

Indicator			Cancer		Total
			No	Yes	
Hyperlipidemia (LDL)	No	Number of patients	257_a	68_a	325
		oncopathology, %	33.1%	39.3%	34.2%
	Yes	Number of patients	520_a	105_a	625
		oncopathology, %	66.9%	60.7%	65.8%
	Total	Number of patients	777	173	950
		oncopathology, %	100.0%	100.0%	100.0%
Lipid-correcting therapy (HMG-CoA reductase inhibitors, other lipid-lowering medication)	No	Number of patients	417_a	91_a	508
		oncopathology, %	51.5%	49.2%	51.1%
	Yes	Number of patients	392_a	94_a	486
		oncopathology, %	48.5%	50.8%	48.9%
	Total	Number of patients	809	185	994
		oncopathology, %	100.0%	100.0%	100.0%
Chi-square criteria			Meaning	deg. of fr.	p
Pearson's Chi-square			22,981	2	0,000
Likelihood relations			23,651	2	0,000
Linear-linear connection			13,864	1	0,000
The number of allowed observations			994		

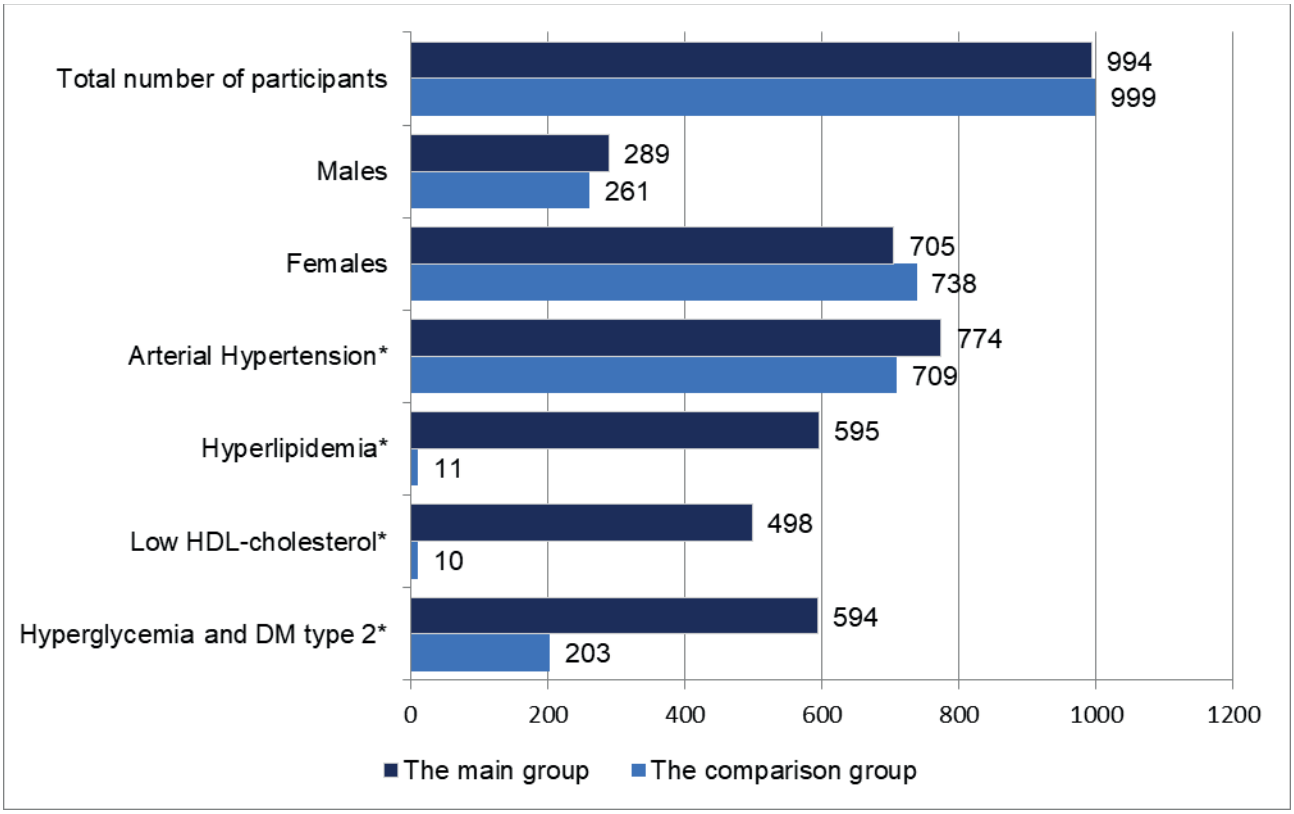

Figure 1. Common characteristics of the studied patients

Note: data on the clinical and demographic characteristics of the main group were reflected when the first part of the study was published.

* Statistically significant differences were obtained according to these parameters in the intergroup comparison ($p<0.005$, asymptotic significance<0.001)

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