



# Clinical and Neurological Features with Covid-19 Associated Cavernous Sinus Thrombosis

**Yakubova Markhamat Mirakramovna**

*Doctor of Medical Sciences, Professor of the Department of Neurology and Medical Psychology, Tashkent Medical Academy, Uzbekistan*

**Rakhmatullaeva Gulnora Kutbiddinovna\***

*Doctor of Medical Sciences, Associate Professor of the Department of Neurology and Medical Psychology, Tashkent Medical Academy, Uzbekistan*

\*Corresponding author

**Said-Akhmedova Saodat Karimdzhanovna**

*Independent Applicant, Department Of Neurology and Medical Psychology, Tashkent Medical Academy, Uzbekistan*

## Abstract

In principle, cavernous sinus thrombosis is a rare disease and can occur as a complication of ear, nose and throat (ENT) infections or facial infections, as well as due to hypercoagulability, however, there is an increase in the frequency of its occurrence in patients who have had COVID -19. Purpose of the study was evaluate the characteristics of clinical and neurological symptoms and laboratory parameters with thrombosis of the cavernous sinus after suffering from COVID -19. Material and research methods. We studied 147 patients with cavernous sinus thrombosis (CS) after coronavirus. The patients were examined at the bases of the Tashkent Medical Academy. The patients were divided into 2 groups: 1) main group-patients with cavernous sinus thrombosis (CS) + type 2 diabetes mellitus (DM), n = 103, 2) control group - patients with TCS without type 2 DM, n = 44. Research results: It was revealed that thrombosis of the cavernous sinus was more common in patients aged 40–70 years (82.1%). Type 2 diabetes was especially common-in 103 (70.1%) patients. Of these, newly diagnosed type 2 diabetes was in 20 (19.4%) patients, more often detected in males-12 (18%) cases. Hypertension was detected in 38 (33.6%) patients, the least common ischemic heart disease was observed - in 10 (9%) and pyelonephritis in 7 (6.1%) patients. With COVID-19, before the appearance of TCS, the following diseases were observed in patients: purulent-necrotic manifestations of the upper respiratory tract (osteonecrosis), phlegmon (orbit, palate, and face), pneumonia, chronic renal failure (CRF), pyelonephritis, central nervous system intoxication, stroke, hyperglycemic ketoacidosis. They may be associated with an inflammatory or prothrombotic state that may cause them. Imaging remains an important part in the management of sick patients, especially when it comes to rare complications, as shown in the example of TCS with patients.

**Conclusion:** Thus, in patients with Covid-19 and a history of diabetes complicated by cavernous sinus thrombosis, a severe course was more often observed. Signs of cavernous sinus thrombosis appeared on average  $21.18 \pm 1.66$  ( $P \leq 0.05$ ) days of illness.

## Keywords

COVID -19, Cavernous sinus thrombosis, Neurological disorders

## 1. Introduction

COVID -19 is a viral infection with a severe course and extremely severe complications. Moreover, despite the fact that it is a respiratory pathogen, it can cause damage to many body systems. It has also been revealed that due to infection with the new coronavirus (COVID-19), changes occur in the functioning of the blood coagulation system, which may result in damage to both large vessels and disruption of microcirculation [1, 9].

### **Purpose of the study:**

To study the characteristics of clinical and neurological symptoms and laboratory parameters with thrombosis of the cavernous sinus after suffering from COVID-19.

## 2. Material and Research Methods

We studied 147 patients with cavernous sinus thrombosis (CS) after coronavirus. The patients were examined at the bases of the Tashkent Medical Academy. The age of the patients ranged from 22 to 81 years (mean age:  $54.97 \pm 0.93$  years), of which 88 (61%) were male (mean age:  $51.68 \pm 1.17$  years) and 59 (39%) females (average age  $60.22 \pm 1.25$  years). The patients were divided into 2 groups: 1) main group - patients with cavernous sinus thrombosis (CS) + type 2 diabetes mellitus (DM),  $n = 103$ , 2) control group - patients with TCS without type 2 DM,  $n = 44$ .

A comprehensive examination included: clinical, neurological and laboratory tests (CBC, Blood Biochemistry). Statistics of the research results were carried out using standard statistical methods.

### 2.1 Research Results

It was revealed that thrombosis of the cavernous sinus was more common in patients aged 40–70 years (82.1%) (See Fig. 1). At the same time, at the age of under 50 years (16.8%), TCS was more often observed in males. Female patients were more often ill at an older age: 50 years and above (19.4% each), but with the same frequency as males.

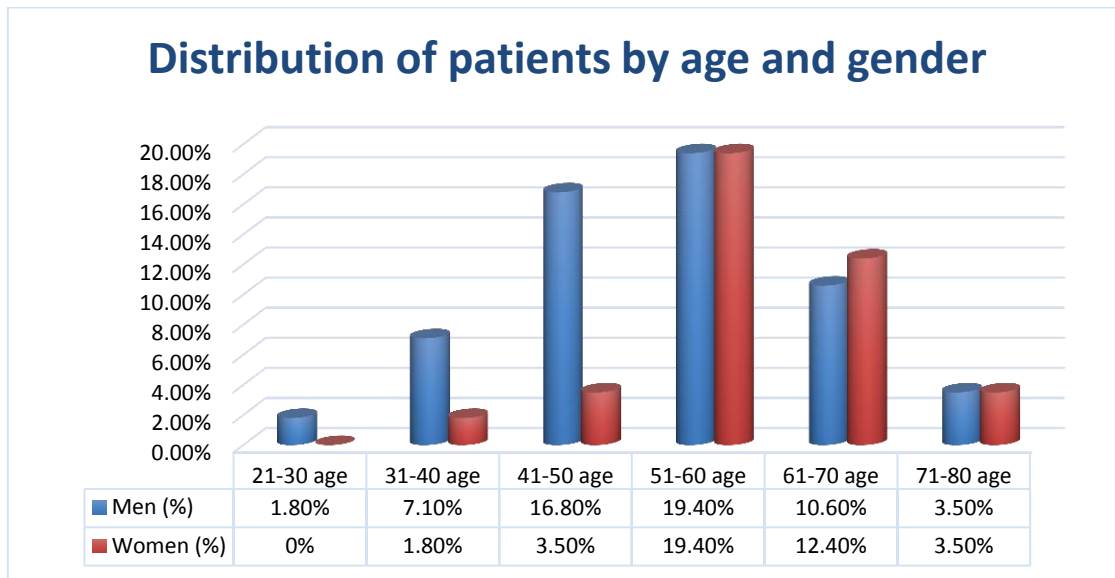


Fig. 1 Distribution of patients by age and gender

A study of the comorbidity of diseases of patients showed that 147 patients with TCS had various concomitant pathologies (see Fig. 2). Type 2 diabetes was especially common - in 103 (70.1%) patients. Of these, newly diagnosed type 2 diabetes was in 20 (19.4%) patients, more often detected in males - 12 (18%) cases. Hypertension was detected in 38 (33.6%) patients, the least common ischemic heart disease was observed - in 10 (9%) and pyelonephritis in 7 (6.1%) patients.

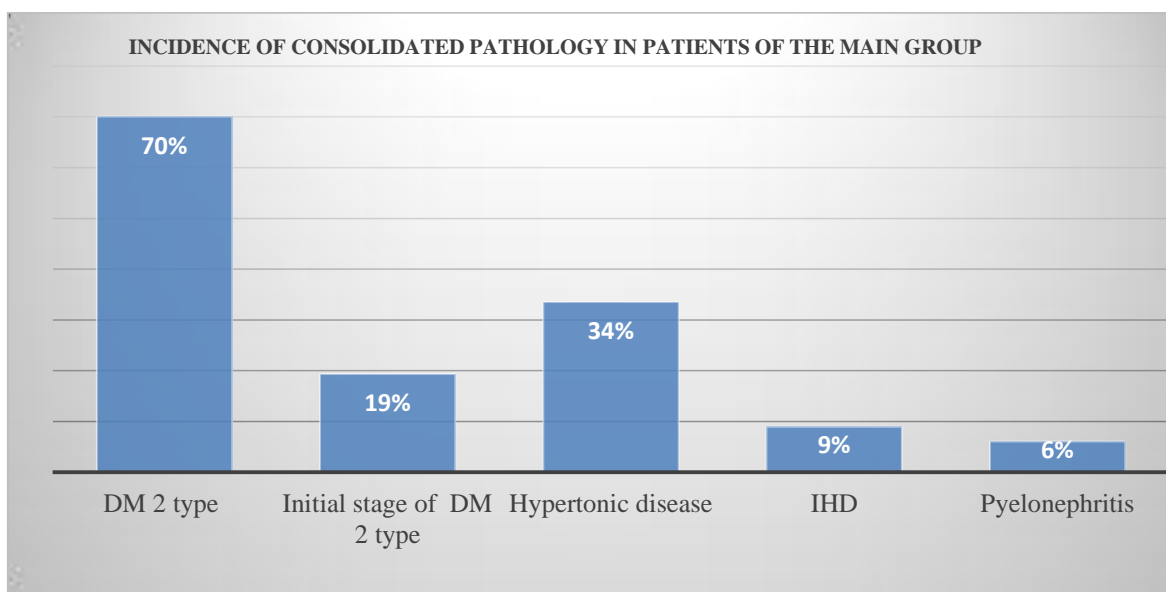


Fig. 2 Incidence of concomitant diseases in patients with cavernous thrombosis sine survivors of COVID-19

We studied the clinical picture of COVID-19 and the clinical signs of cavernous sinus thrombosis after a coronavirus infection.

The initial signs of COVID-19 and the main symptoms of TCS were studied. The most common initial signs were increased body temperature, disturbance of taste and smell (see Table 1). An increase in body temperature was observed in 134 (91%) patients, of which 81(92%) were in men and 53(90%) in women. Impaired taste and smell occurred in 131 (89%) patients (men - 79(90%) and women - 52(88%)). The next common symptoms were coughing and shortness of breath with a feeling of lack of air. Cough occurred in 58 (39%) patients and shortness of breath with a feeling of lack of air in 43 (29%), with a predominance in men - 40(45%) and 33(37%) cases, in women, respectively, 18(30%) and 10 (17%) cases. Signs such as chest pain and nasal congestion were observed less frequently, 10(7%) and 19(13%), respectively. At the same time, there were no large gender differences (respectively, in men-7(8%) and 13(15%) cases and in women-3(5%) and 6(10%) cases).

**Table 1** Initial signs of coronavirus infection in patients with cavernous sinus thrombosis

Initial manifestations of COVID-19	Men N=88	%	Women N=59	%	Total N=147	%
Increased body temperature	81	92	53	90	134	91
Shortness of breath and feeling of lack of air	33	37	10	17	43	29
Chest pain cage	7	8	3	5	10	7
Nasal congestion	13	15	6	10	19	13
Violation taste and smell	79	90	52	88	131	89
Cough	40	45	18	30	58	39

After suffering from COVID-19, signs of thrombosis of the cavernous sinuses appeared on average on the 21.18±1.66 day of illness (see Table 2). The table shows that women had an earlier manifestation of initial signs of TCS (on average 18.56±2.12 days against the background of Covid-19) compared to men (on average 23.37±2.13 days ( $P \leq 0.05$ )).

**Table 2** The timing of the development of initial manifestations of TCS after the onset Covid-19

Time frame for the development of initial signs of TCS	Average (days)	Credibility criteria
Men	23.37±2.13	$P \leq 0.05$
Women	18.56±2.12	$P \leq 0.05$
Total	21.40±1.54	$P \leq 0.05$

**Table 3** The timing of the development of the initial manifestations of TCS after the onset of Covid-19, depending on gender (by day).

Time frame for the development Of initial signs of TCS, by day	Husband	%	Women	%	Total	%
1-10 days	27	31	24	41	51	35
11-20 days	23	26	18	31	41	28
21-30 days	26	30	10	17	36	24
31-40 days	3	3.4	2	3.4	5	3.4
41-50 days	3	3.4	1	1.7	4	2.7
51-60 days	3	3.4	2	3.4	5	3.4
61-70 days	0	0	1	1.7	1	0.7
71-80 days	0	0	0	0	0	0
81-90 days	1	1.1	1	1.7	2	1.4
91-100 days	1	1.1	0	0	1	0.7
101-110 days	0	0	0	0	0	0
111-120 days	1	1.1	0	0	1	0.7
Total	88		59		147	

When studying the period of development of the initial manifestations of TCS after the onset of Covid-19, depending on gender, shows that TCS developed mainly in the first 30 days from the onset of Covid-19 (87%) (See Table 3). In women, TCS was detected earlier - in the first 20 days (71%), and in men later - in the first 30 days (86%).

With COVID-19, before the appearance of TCS, the following diseases were observed in patients: purulent-necrotic manifestations of the upper respiratory tract (osteonecrosis), phlegmon (orbit, palate, face), pneumonia, chronic renal failure (CRF), pyelonephritis, central nervous system intoxication, stroke, hyperglycemic ketoacidosis (see Table 4). The most frequently observed were pneumonia (53.7%), purulent hemi- and pansinusitis (sinusitis, sphenoiditis, frontal sinusitis, etc.) (56.5 %), stroke (16.3 %), central nervous system intoxication (12%), phlegmon (orbit, palate, face) (11.6%), rarely - respiratory failure of the 2nd degree (8.2%), chronic renal failure (2.7%), hyperglycemic ketoacidosis (3.4%), meningoencephalitis (2.7%), very rarely-systemic vasculitis (1.4%), pyelonephritis (0.68%), cerebral arachnoiditis (0.68%). In all cases, they prevailed in patients with diabetes.

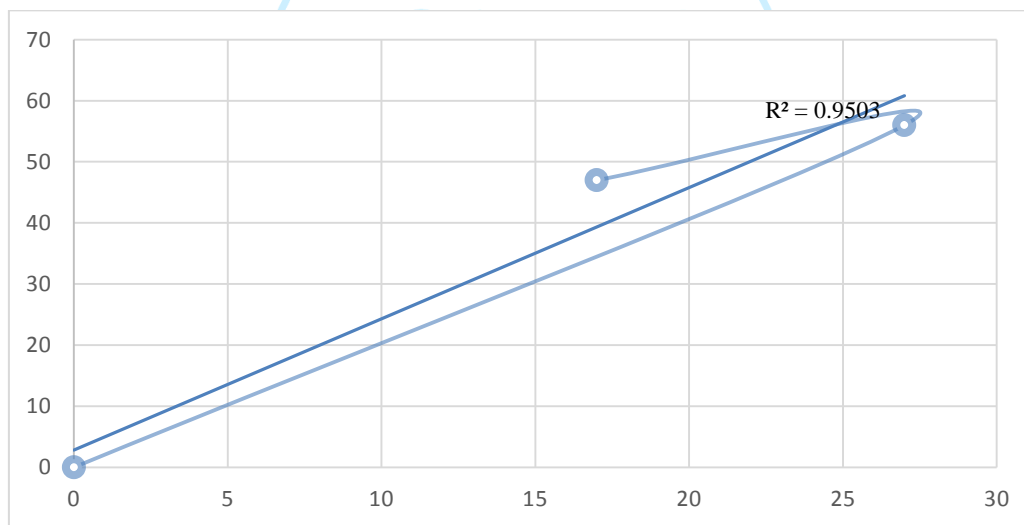
**Table 4** Distribution of diseases associated with COVID-19 before the development of TCS

Diseases	c type 2 diabetes n=103		Without type diabetes n=44		Total n=147	
	N	%	N	%	N	%
Purulent hemi, pansinusitis (purulent sinusitis, sphenoiditis, frontal sinusitis, etc.)	56	54.4	27	61.4	83	56.5
Cellulitis (orbit, palate, face)	14	13.5	3	6.8	17	11.6
Pneumonia	55	53.4	24	54.5	79	53.7
chronic renal failure	3	2.9	1	2.3	4	2.7
Pyelonephritis	1	0.97	-	-	1	0.68
CNS intoxication	15	14.6	3	6.8	18	12.2
ONMK	14	13.6	10	22.7	24	16.3
Hyperglycemic ketoacidosis	5	4.9	-	-	5	3.4
Respiratory failure stage 2	9	8.7	3	6.8	12	8.2
Meningoencephalitis	2	1.9	2	4.5	4	2.7
Cerebral arachnoiditis	-	-	1	2.3	1	0.68
Systemic vasculitis	1	0.97	1	2.3	2	1.4

I would like to draw attention to the fact that the strokes were mainly of the ischemic type, only in one case of the hemorrhagic type (in patients with type 2 diabetes).

**Table 5** Incidence of hypercoagulation in patients with COVID-19

	With type 2 diabetes		Without type 2 diabetes		Total	
	N	%	N	%	N	%
Hypercoagulation + sinusitis (purulent-necrotic in nature)	56	67%	27	33%	83	57%
Hypercoagulation (without sinusitis)	47	73%	17	27%	64	43%
<b>Total</b>	<b>103</b>		<b>44</b>		<b>147</b>	



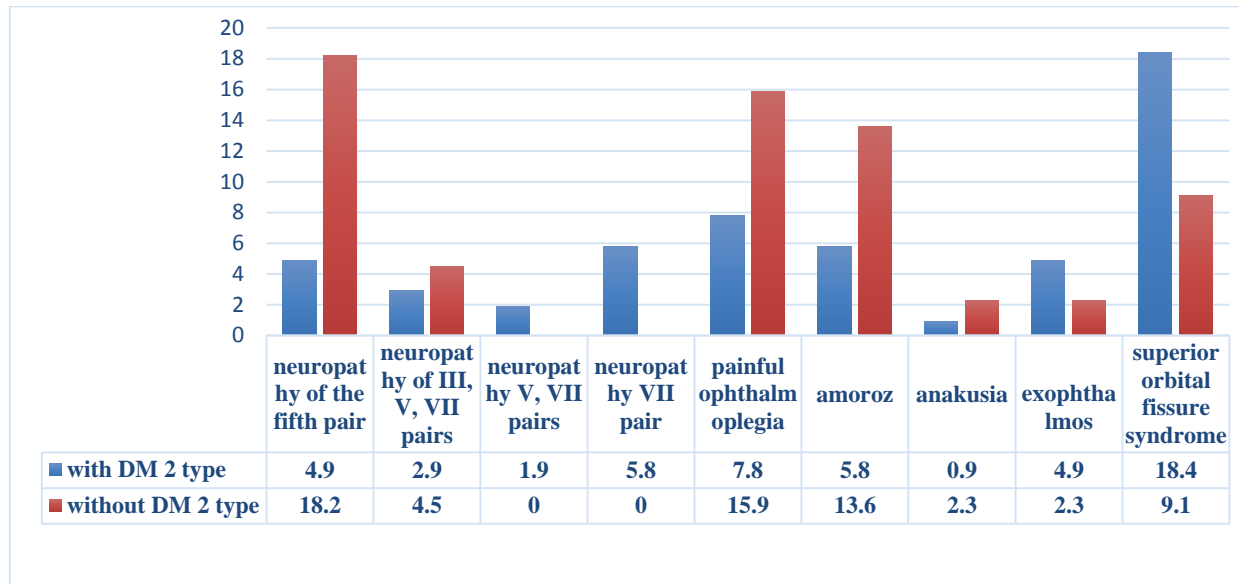
**Fig. 3** Correlation rates between hypercoagulability and TCS in patients with Covid-19.

**Note.** The connection between the studied characteristics is direct; the closeness (strength) of the connection on the Chaddock scale is very high. The correlation coefficient (r) is 0.975.

The 147 patients who had suffered COVID-19, 83 (57%) had purulent-necrotic sinusitis with hypercoagulable changes in the blood (see Table 5). The study of indicators revealed a direct strong correlation between hypercoagulation and TCS in patients with Covid-19 (see Fig. 4), with the correlation coefficient (r) equal to 0.975.

As can be seen from Table 5, hypercoagulation with purulent-necrotic changes in diabetes was a prerequisite for the development of cavernous sinus thrombosis. Of 103 patients with diabetes, 56 (67%) patients with purulent-necrotic sinusitis of varying severity due to blood hypercoagulation developed TCS (usually on the side of sinusitis), compared with patients without diabetes-27 (33%) cases. Only 64 (43%) patients with diabetes who did not have purulent-necrotic sinusitis, but with hypercoagulation, developed TCS. Here, patients with diabetes also prevailed (respectively: 47 (73%) and 17 (27%)).

In patients with TCS against the background of COVID-19, hypercoagulation manifested itself in the form of an increase in fibrinogen, PTI, TV, INR and APTT of the blood. In 88 (60%) patients, an increase in fibrinogen was detected in cases. In 40 (27.2%) patients, an increase in the thrombotest index above 5 was detected. An increase in INR and PTI was detected in 15 (10.2%) patients. An increase in aPTT was less frequently detected - in 4 (2.7) patients.



**Fig. 4** Prevalence of neurological symptoms in patients with TCS who have had Covid-19 (in %).

A study of clinical and neurological signs revealed that the first signs of TCS were headache (27.4 %) and pain in the orbital area (23.1 %) (Lesion VFMN pairs). Then the following focal symptoms were added: painful ophthalmoplegia (23.7 %), amaurosis (19.4 %), neuropathies III, V, VII (7.4%), V and VII (1.9%) And V II (5.8%) pairs of cranial nerves, exophthalmos (4.8%), superior orbital fissure syndrome (27.5%), anosmia (3.2%) (see Fig. 5). These manifestations mainly occurred on the side of cavernous sinus thrombosis.

### 3. Discussion

Due to viral infections caused by COVID-19, complications are becoming more numerous and varied. They may be associated with an inflammatory or prothrombotic state that may cause them. Imaging remains an important part in the management of sick patients, especially when it comes to rare complications, as shown in the example of TCS with patients [4, 13].

A study of the comorbidity of diseases in the studied patients showed that 147 patients with TCS had various concomitant pathologies. Type 2 diabetes was especially common-in 103 (70.1%) patients. Of these, newly diagnosed type 2 diabetes was in 20 (19.4%) patients, more often detected in males-12 (18%) cases.

Our results also show that COVID-19 often leads to upper and lower respiratory tract complications of varying severity. Especially if COVID-19 is accompanied by hypercoagulation and hyperglycemia, which further increases the risk of developing TCS. This is confirmed by literary data. COVID-19 leads to the release of inflammatory cytokines, which in turn cause endothelial cell dysfunction and in doing so causes coagulopathy, which increases the risk of stroke or thrombosis [10].

According to some literature data, the occurrence of TCS is more often observed at the age of 31–50 years [2,5] (according to our data, patients with TCS were more often encountered at the age of 40–70 years, which amounted to 82.1% of cases ). The ratio of men to women in this group of patients is 3:1, in 70–80% of cases of cerebral vein thrombosis, which more often develops in patients of reproductive age [12,14]. According to the results of our study, TCS was more often observed in males under 50 years of age (16.8%). Female patients were more often ill at an older age: 50 years and above (19.4%).

Research by the authors (Baldini s al., 2021) [8] shows different time intervals between the onset of COVID-19 symptoms and the development of TCS. The interval between clinical manifestations of COVID-19 and the development of TCS varied from 7 to 25 days. Our data coincide with the literature: signs of cavernous sinus thrombosis appeared on average  $21.18 \pm 1.66$  ( $P \leq 0.05$ ) days of illness.

According to our data, with COVID-19, before the advent of TCS, the following diseases were observed in patients: purulent-necrotic manifestations of the upper respiratory tract (osteonecrosis), phlegmon (orbit, palate, face) (% course kerak ), which coincides with the data of other authors, for example ( Maksimova M.Yu et al ., 2015) suggested that the cause of cavernous sinus thrombosis is infections of the paranasal sinuses (ethmoid and sphenoid) [3].

The study of clinical and neurological signs revealed that the first signs of TCS were headache (27.4 %) and pain in the orbital area (23.1%) (Lesion VFMN pairs). Then the following focal symptoms were added: painful ophthalmoplegia (23.7%), amaurosis (19.4 %), neuropathies III, V, VII (7.4%), V and VII (1.9%) And VII (5.8%) pairs of cranial nerves, exophthalmos (4.8%), superior orbital fissure syndrome (27.5%), anosmia (3.2%). Maybe high risk of damage to the II, III, V, VI cranial nerves due to thrombosis of the cavernous sinus [6]. Data available Sakr Y et al. 2019 and Abou-Ismael MY et al. 2020 [7,11] which also states that with thrombosis of the cavernous sinus, the III and IV pairs of cranial nerves, as well as the two branches of the V and VI pairs that pass through the anatomical structures of the cavernous sinus, are often susceptible to damage. In the world medical literature there are only a few descriptions of cases of sinus thrombosis as a complication of COVID-19.

#### 4. Conclusion

Thus, in patients with Covid -19 and a history of diabetes complicated by cavernous sinus thrombosis, a severe course was more often observed. Signs of cavernous sinus thrombosis appeared on average  $21.18 \pm 1.66$  ( $P \leq 0.05$ ) days of illness. Most often, in 82.1% of cases, it occurred between the ages of 40–70 years; in addition, 70–80% of cases occur in patients of reproductive age. Often the initial signs of cavernous sinus thrombosis were headaches and facial pain. The most frequently observed were pneumonia (53.7%), purulent hemi- and pansinusitis (sinusitis, sphenoiditis, frontal sinusitis, etc.) (52.4%) more often observed in patients with diabetes. TCS was more often observed on the side of hemi and pansinusitis of a purulent-necrotic nature. A close correlation between TCS and coagulopathies has been revealed ( $r$  is equal to 0.975).

#### Ethical Considerations

Not violated

#### Conflict of Interest

The authors declare no conflict of interest.

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