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# Focal Segmental Glomerulosclerosis: Current State of the Problem

## Abstract

One of the most prognostically unfavorable variants of glomerulopathy is focal segmental glomerulosclerosis (FSGS), which is detected by nephrobiopsy in 5-20% of patients with nephrotic syndrome (NS) and in 15% of adult patients with chronic glomerulonephritis. FSGS recurs in a transplanted kidney in 30-50% of patients. Among adult patients with FSGS, men predominate. A poor prognosis of FSGS is explained by the heterogeneity of the disease and is exacerbated by a poor response to treatment. According to current data, FSGS is characterized by sclerosis of the mesangial matrix, hyalinosis, damage to capillaries, an increase in foam cells and their adhesion between the glomerular bundle and the Bowman capsule. In 2004, the following histological variants of FSGS were proposed: tip, perihilar, collapsing, cellular and classical. Each histological variant of FSGS differs in etiology, response to treatment, and prognosis. The clinical diagnosis of primary FSGS should be based on the exclusion of secondary causes of the disease. Focal sclerotic changes in the glomeruli can be caused by various factors and occur in various conditions, including the existing kidney pathology. According to international recommendations for the treatment of FSGS, one should focus on the amount of daily proteinuria. For patients with FSGS without pronounced proteinuria, the use of angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) is recommended. In FSGS and NS, immunosuppressive therapy is used along with ACE inhibitors or ARB. For adult patients, glucocorticoids (GC) are prescribed daily in a single dose at a dose of 1 mg/kg per day, the maximum dose is 80 mg with a daily intake and 120 mg with an alternating regimen. Resistance to GC is detected in the absence of effect after 16 weeks. In the presence of contraindications or intolerance to GC, calcineurin inhibitors are used. The recommended initial dose of cyclosporine is 2 mg/kg/day, taken twice a day with a gradual increase to 3.5-4 mg/kg/day. The duration of therapy with satisfactory tolerance to cyclosporine is more than six months. After achieving complete remission, the dose of cyclosporin is gradually reduced by 0.5 mg/kg/day to the minimum effective dose (1.5-2 mg/kg/day) and such maintenance therapy is carried out for 1-2 years. A treatment option is possible using lower doses of GC and cyclosporine, or a combination of mycophenolate mofetil with a high dose of dexamethasone.

**Key words:** *focal segmental glomerulosclerosis, glomerulonephritis, nephrotic syndrome, immunosuppressants, monoclonal antibodies*

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ACE inhibitors — angiotensin converting enzyme inhibitors, ARBs — angiotensin II receptor blockers, CI — calcineurin inhibitors, CPF — circulating permeability factors, FSGS — focal segmental glomerulosclerosis, GBM — glomerular basement membrane, GC — glucocorticoids, SSNR — Scientific Society of Nephrologists of Russia, RAAS — renin-angiotensin-aldosterone system, RF — renal failure, RRT — renal replacement therapy

Currently, significant progress has been made in understanding the complex molecular mechanisms and pathways responsible for maintaining the healthy state of podocytes with the structural and functional integrity of the glomerular filtration barrier. Structural abnormalities of podocytes, changes in actin cytoskeleton, smoothing of pedicles, and fusion of filtration gaps lead to the development of proteinuria, which is typical for most proteinuric forms of glomerulopathy [4, 2]. Proteinuria directly damages the tubule epithelium, which, in turn, stimulates the synthesis of vasoactive molecules, such as monocyte chemoattractant protein-1 (MCP-1), endothelin-1 and osteopontin [3]. The development of nephrosclerosis is based on the remodeling of tubulointerstitial tissue. Changes in the tubulointerstitial component of nephron are the most important element in the progression of chronic kidney disease. Excessive amounts of vasoactive molecules produced by renal tubules, MCP-1 and endothelin-1 are secreted through the basal parts of cells in the interstitium, which leads to the development of inflammatory reaction which, in most forms of nephritis, precedes the development of nephrosclerosis [3, 5]. In the structure of morphological variants of the glomerular lesion, focal segmental glomerulosclerosis (FSGS), which is based on podocytopathy [4, 5], plays a special role. According to current data, FSGS is characterized by sclerosis of the mesangial matrix, hyalinosis, capillary damage, enlargement of foam cells and their adhesion between the glomerular bundle and Bowman's capsule [6, 7]. According to the clinical recommendations of the Scientific Society of Nephrologists of Russia (SSNR), FSGS is characterized by sclerosis of separate segments (foci) in the part of glomeruli, with the remaining glomeruli having no changes at the start of this disease, i. e. only a part of a separate glomerulus is damaged [5]. FSGS is believed to be the most common type of glomerular lesion leading to terminal stage of renal failure (RF) when renal replacement therapy (RRT) is required.

It is important to note that the problem of FSGS involves the fact that it recurs in a transplanted kidney in 30-50% of patients. FSGS is found in 15% of adult patients with chronic glomerulonephritis; men dominate among adult patients with FSGS. FSGS is the most common cause of steroid-resistant nephrotic syndrome (NS) in children [5]. However, in previous analytical studies, it was noted that FSGS is also the most common cause of NS in adults [8]. Currently, FSGS is divided into primary (idiopathic) and secondary types [5]. Causes for primary FSGS are shown in Table No. 4; moreover, multiple factors play the etiological role in the formation of secondary FSGS.

Podocytes are highly differentiated, specialized cells with a complex structure. Podocytes wrap around glomerular capillaries and are the main component of glomerular filtration barrier. As stated above, the most important aspects of FSGS pathogenesis are structural and functional changes in podocytes [9, 10]. This fact is confirmed by the results of experimental studies where the severity of damage to podocytes and the grade of podocytopenia are closely correlated with the histological model of the damage [11]. Pathogenic mechanisms of FSGS are still not fully established. However, it was noted that gene mutations (ACTN4, INF2, COQ6, NPHS2, CD2AP, CD2AP, PDSS2, Glepp1, LMBX1, COL4A3/COL4A4, LAMB2, A3243G) that encode the state of the proteins of the podocyte gap membrane underlie the development of hereditary forms of this disease [12, 13]. In several families, different mutations of genetic factors related to FSGS were detected and described [14]. In the publication by A. A. Melnik (2019), the role of podocytic dysfunction in the formation of proteinuria during FSGS was definitely stated [8]. In particular, it was noted that the loss of less than 20% of podocytes can be regenerated by resident glomerular epithelial cells that migrate from a niche adjacent to Bowman's capsule to the glomerulus and replace podocytes damaged during necrosis or apoptosis [8]. As early

**Table 1.** Factors for the secondary focal segmental glomerulosclerosis development

1	<b>Genetically determined</b>
1.1.	Familial mutations (NPHS1, ACTN4, CD2AP, INF2, NPHS2, TRPC6, WT-1, LIMP2, mitochondrial cytopathies, etc.)
1.2.	Sporadic mutations (NPHS1-nephrine, NPHS2-podocin, ACTN4, CD2AP, etc.)
2	<b>Virus-induced</b>
	HIV, parvovirus B19, cytomegalovirus, Epstein-Barr virus, Coxsackievirus, etc.
3	<b>Drug-induced</b>
	Heroin, Interferon- $\alpha$ , adriamycin, doxorubicin, lithium, anabolic steroids, tacrolimus, pamidronate, valproic acid, etc.
4	<b>Structural and functional changes of glomeruli</b>
4.1.	With a decrease in the mass of renal tissue (oligomeganephronia, unilateral agenesis, renal dysplasia, cortical necrosis, reflux-nephropathy, nephrectomy, chronic transplant nephropathy, low birth weight, late stage of any kidney disease with a decrease in the mass of active nephrons, etc.)
4.2.	With initially normal number of nephrons (hypertension, diabetes, obesity, congenital cyanotic heart defects, sickle cell anemia, etc.)
5	<b>Malignant tumors (lymphoma, etc.)</b>
6	<b>Non-specific FSGS-like changes caused by nephrosclerosis in glomerular diseases</b>
	Focal proliferative GN, hereditary nephritis (Alport syndrome), membrane nephropathy, thrombotic microangiopathy, etc.

**Note:** HIV — human immunodeficiency virus; FSGS — focal segmental glomerulosclerosis; GN — glomerulonephritis

as 1974, R. J. Shalhoub suggested the existence of a “permeability factor” circulating in blood, produced by T cells and causing podocyte dysfunction with subsequent development of proteinuria, as well as having an effect on the glomerular basement membrane (GBM) or activated mesangial cells [15]. In FSGS, damage to podocytes also occurs with exposure to circulating permeability factors (CPFs) or external damaging agents. CPFs are a group of proteins that change glomerular permeability [15]. Cardiotrophin-like cytokine-1 (from interleukin-6 family) and a soluble urokinase receptor are considered as CPFs [5]. In FSGS and other non-proliferative glomerulopathies, the activity of CPFs depends on the balance between the production of these factors (as a result of T-cell dysregulation) and the loss of their inhibitors with urine (presumably, high density lipoproteins). Proteins of slit diaphragm of podocytes which are involved in maintaining the integrity of the structure and selectivity of the glomerular filter can be the target of CPFs [5]. So, with prolonged and/or significant effect of CPF, apoptosis mechanisms are activated, podocytes die, their connection with GBM is lost, and they are then desquamated in the urinary space, exposing areas of GBM in these parts [5]. As a rule, foci of fibrosis in glomeruli develop at the foci of podocyte fusion with GBM. In parts of segmental

(focal) sclerosis, filtration changes its direction towards the interstitium that surrounds glomerulus [5]. As a result, global glomerular sclerosis and interstitial fibrosis are formed [16]. Subsequently, in the course of damage, podocytes undergo transdifferentiation, acquiring the properties of fibroblasts, and participate in the synthesis of the extracellular matrix, accelerating the formation of fibrosis foci [2, 5, 17]. According to D. Yu et al. (2005), podocytes can be found in the urine of patients with proteinuric types of glomerulopathy, which indicates the severity of glomerular damage [18]. It is possible that in the presence of primary FSGS, a special role at all stages of disease progression is played by pro-inflammatory cytokines; damaged podocytes are also the source of their production. When discussing details of the formation of secondary FSGS, it should be noted that the following hemodynamic mechanisms play an important role in the damage to podocytes: adaptive intraglomerular hypertension and hyperfiltration with increased glomerular volume, which leads to increased mechanical load on podocytes [19]. Hyperproduction of angiotensin II and increased synthesis of transforming growth factor beta-1 cause activation of apoptosis, reorganization of cytoskeleton and dedifferentiation of podocytes [5]. In cases of both primary and secondary FSGS, if the loss of podocytes is in the range

of 20-40%, then damage that is typical for FSGS appears, whereas loss of more than 40% of podocytes leads to global sclerosis [5, 8, 20]. Nevertheless, it was noted that the number of podocytes in the classic variant of FSGS was reduced and, on the contrary, increased in the case of a collapsing and cellular variant of this disease [21].

In 2004, five histological variants of FSGS were proposed, which are completely based on light microscopy [22]. Although this classification includes most of the primary and some secondary forms of FSGS [23], it will be appropriate to mention that histological variants of FSGS differ in etiology, response to treatment, and prognosis [5, 8]. As can be seen in Table No. 2, five-year renal survival with the tip variant is 76%, and three-year renal survival with the classic variant is 65% [5, 8]. Rare spontaneous remissions of primary FSGS justify the need to achieve drug remission, although spontaneous remissions are also possible with the tip variant of FSGS or with unexpressed proteinuria [5]. There is data that perihilar FSGS is often detected in patients with obesity, as well as with decreased proportion of functioning nephrons and hyperfiltration [24]. Clinically, the perihilar variant is most often manifested by incomplete NS [20]. In case of nephrobiopsy, perihilar FSGS requires preliminary exclusion of cellular, tip and collapsing variants [23]. According to several authors, one of the rare types (up to 5%) of primary FSGS is the cellular variant [25]. The cellular variant is diagnosed only when if tip and collapsing variants of FSGS are excluded [23]. With multiple glomerular damage, the process becomes similar to proliferative glomerulonephritis [26]. The

cellular variant of FSGS is histologically characterized by the fusion of podocyte processes and is clinically manifested by nephrotic proteinuria [23].

M. A. Weiss et al. first described collapsing glomerulopathy in 1986, when they studied the clinical and morphological complex of severe NS and rapidly progressing RF in black patients [27]. The same researchers reported the detection of FSGS in some patients with viral infections, parvovirus B19, as well as in elderly subjects. Glomerular collapse is accompanied by severe hypertrophy and podocyte hyperplasia [23]. An important component of this histological subtype is tubulointerstitial damage, the development of which usually positively correlates with the grade of glomerular sclerosis. According to some authors, the concept of collapsing FSGS is used in cases where there is segmental or total obliteration of the lumen of glomerular capillaries, as well as GBM wrinkling and collapse, and these changes are associated with hypertrophy and hyperplasia of podocytes [28, 29]. It is worth noting that histological examination of collapsed lobes revealed wrinkling and a slight thickening of GBM, and underlying podocytes are characterized by noticeable hypertrophy and significant fusion of their processes. In addition, cells with empty cytoplasm were found during FSGS due to the disruption of actin cytoskeleton integrity. Significant fusion of the processes of podocytes was also found in intact capillaries. In other studies, it was reported that the collapsing variant of FSGS is rarely detected among the European population, whereas the incidence of collapsing FSGS among African Americans is quite high [23, 30].

**Table 2.** Morphological classification of FSGS [5]

Variant	Incidence	Description
Tip	17%	In most cases, serious proteinuria, NS, a positive response to GC therapy. Complete remissions of NS occur in 50% of patients. The prognosis is favorable; five-year renal survival is 76%.
Perihilar	26%	Rarely developed NS, mostly detected AH.
Collapsing	11%	High proteinuria, severe NS, rapid decline in renal function. Only 25% of patients have a positive response to GC.
Cellular	3%	Responding to therapy and the rate of progression of CKD occupies an intermediate position between tip variant and collapsing nephropathy.
Classic	42%	67% of patients develop NS, 80% — hypertension, complete remission is achieved in 13% of patients. The prognosis is favorable; three-year renal survival is 65%.

**Note:** FSGS — focal segmental glomerulosclerosis; GC — glucocorticoids; NS — nephrotic syndrome; CKD — chronic kidney disease

## Diagnosis of FSGS

FSGS is a group of disorders united not by a specific etiological factor, but by the nature of histological changes. Clinical diagnostics of primary FSGS should be based on the exclusion of secondary causes of disease. Segmental (focal) sclerotic changes in glomeruli can be caused by various factors and occur with various underlying conditions, including an existing kidney pathology, in particular, semilunar glomerulonephritis, immunoglobulin-A nephropathy, Alport syndrome, etc. This fact reflects the endpoint in the histopathological evolution of different biological processes. Therefore, it is very important to exclude the secondary nature of FSGS development [5].

## Drug Treatment of FSGS

The goal of pharmacological therapy of FSGS is to achieve complete or partial remission, and therefore, to prolong the pre-dialysis period of the disease. According to the recommendations of SSNR, during FSGS therapy, the daily proteinuria level should be considered [5].

In the case of FSGS without significant proteinuria (daily proteinuria below 500 mg), it is recommended to use angiotensin converting enzyme inhibitors (ACE inhibitors) or angiotensin II receptor blockers (ARBs). Prescribing statins, or the continuation of statin therapy (if previously prescribed) is also possible [5]. The antiproteinuric effect of ACE inhibitors / ARBs as the blockers of renin-angiotensin-aldosterone system (RAAS) can be explained by decreased apoptosis and hypertrophy, inhibition of podocyte actin cytoskeleton rearrangement, retained nephrin expression, decreased synthesis of IV type collagen  $\alpha$ -3 chain, decreased endothelial permeability, and decreased synthesis of the extracellular matrix [31, 32].

In FSGS with severe proteinuria or NS, using RAAS blockers is indicated (when there are no contraindications for ACE inhibitors or ARBs). If daily proteinuria is more than 3.5 g or if it is not possible to reduce its level by the methods of maximum conservative therapy, then immunosuppressive therapy should be started [5]. High doses for at least 4 weeks are recommended as an initial therapy. If there is a tendency to a decrease in daily urinary

protein excretion, high doses of GC should be continued, with satisfactory tolerance of up to maximum 16 weeks, or until complete remission if it develops earlier than 16 weeks [5]. Short-acting GC, i. e. prednisolone, is preferred. GCs stabilize cell membranes, reduce capillary permeability, inhibit the migration of monocytes, neutrophils, and macrophages to the inflammation focus and their phagocytic activity, and also restore the charge selectivity of podocytes. Long-term administration of GCs is accompanied by inhibition of the apoptosis process, increased stability of actin cytoskeleton, and decreased smoothing of podocyte pedicles [5]. Prednisolone for adult patients is prescribed once daily, at the dose of 1 mg/kg (maximum 80 mg/day), or in alternating mode, once every other day at the dose of 2 mg/kg (maximum 120 mg/day) [5, 33]. It is worth noting that refractoriness to GCs is detected if there is no decrease in proteinuria level after 16 weeks (4 months). In the cases of complete and incomplete remission, supporting therapy with GCs lasts about 24 months; it can be extended to 5 years, if necessary [5]. Patients with FSGS are considered steroid-dependent if they had two episodes of relapse within two weeks after completion of GC therapy [5]. The development of temporary resistance to GC with relapses of NS is often due to simultaneous viral, bacterial, or mycotic infections requiring targeted therapy [34]. In such cases, an examination is indicated to identify active infections and immunodeficiency [35]. Calcineurin inhibitors (CI) are proposed as first-line drugs in patients with relative contraindications or intolerance to high doses of GCs (gastric ulcer, steroid-induced osteoporosis, uncontrolled hyperglycemia, psychoses, cataract, hirsutism, etc.) [5, 33]. According to the recommendation of SSNR, the initial dose of cyclosporine is 2 mg/kg/day, in two intakes with a 12-hour break. Daily dosage should be gradually increased to 3.5-4 mg/kg/day for more than six months. It is important to note that the daily dose of cyclosporine should not exceed 5 mg/kg. During cyclosporine therapy, it is necessary to control hemodynamic parameters (with long-term intake), activity of hepatic transaminases and serum creatinine concentration. After achieving complete remission, the cyclosporine dose is gradually reduced by 0.5 mg/kg/day to the minimum effective dose (1.5-2 mg/kg/day),



and such supportive therapy should be carried out for 1-2 years [5].

After penetrating a cell, cyclosporin binds to cyclophilin protein, then the resulting complexes competitively inhibit phosphatase activity of calcineurin, which, in turn, inhibits dephosphorylation and nuclear translocation of the nuclear factor of activated T-lymphocytes [36]. This is accompanied by suppressed transcription of proinflammatory cytokine genes and disrupts the proliferation and differentiation of T-lymphocytes [36]. Therapy with cyclosporine provides remission of FSGS in a large portion of patients [5, 8, 37, 38]. Most of these patients are generally steroid-resistant; steroid-sensitive patients have better response to CI therapy. According to the recommendations, CI (cyclosporin A) is prescribed when daily proteinuria retains at the level of more than 3 g, in spite of GC therapy, as well as in cases where adult patients have not achieved at least partial remission after 8 weeks of daily use of prednisolone [5]. There are isolated reports where prescribing CI for patients with FSGS that are resistant to GCs reduced disease recurrence to 60-80%, [39, 40]. It should be remembered that KDIGO (Kidney Disease Improving Global Outcomes) recommends GC and immunosuppressive therapy for the initial treatment of FSGS only for the primary form of FSGS [44]. Recent molecular studies made it possible to better understand the nephroprotective potential of CIs. Cyclosporin has an effect on podocytes unrelated to T and B cells [42]. In particular, CI — cyclosporin inhibits calcineurin-mediated dephosphorylation of synaptopodin (protects it from hydrolysis) and thus stabilizes actin cytoskeleton of podocytes [43]. Accumulated results of numerous clinical studies have shown that using cyclosporine in patients with FSGS is currently considered fully justified [44, 45]. When partial or complete remission is achieved, it is proposed to continue treatment with CI (cyclosporine) for at least 12 months, followed by gradual dose tapering [5, 45]. Using cyclosporine is possible both in the form of monotherapy (when there are contraindications for GCs), and in combination with GCs (in small doses). If subjects taking cyclosporine for six months demonstrated no response to the therapy, then the question of replacing cyclosporin with another drug should be considered [5]. In particular, for patients who have resistance to

GCs and cyclosporine intolerance, a combination of mycophenolate mofetil with a high dose of dexamethasone, or treatment only with mycophenolate mofetil can be proposed [5]. There are reports of the advisability of transferring patients with developed nephrotoxicity from CI (cyclosporine) to mycophenolate mofetil, which leads to the improvement of renal function [46]. According to M. S. Ignatova et al. (2017), simultaneous use of mycophenolate mofetil with cyclosporine for the treatment of NS is possible; it can apparently enhance the effect of both drugs and also reduce the nephrotoxic effect of CI [13]. Regarding the pathogenic therapy of primary FSGS, we should mention the possibility of using cytostatics. If patients with FSGS demonstrated resistance to GCs, treatment with cyclophosphamide is an optional variant [5, 8]. The recommended dose is 500 mg/m<sup>2</sup>. The possibility of using azathioprine for primary FSGS is not considered, since it has a large number of undesirable effects. Although up to 2000, alkylating agents (cyclophosphamide and chlorobutine) were considered an alternative to cyclosporine; they caused long-term steady remission in patients with FSGS (30% steroid-resistant and 70% steroid-dependent). It should be remembered that patients with FSGS, as well as with membranous nephropathy, are at risk of systemic thromboembolic complications [5]. In this connection, it is preferable to use small doses of anticoagulants (rivaroxaban or warfarin), especially for severe proteinuria, hypoalbuminemia, hyperlipidemia, taking large doses of GCs and loop diuretics.

A controversial issue in the treatment of FSGS is the use of rituximab, which is a complex of chimeric monoclonal antibodies that act selectively on the B-lymphocyte surface antigen CD20. In addition, rituximab has a direct protective effect on podocytes [47]. Rituximab is administered in 2 or 4 injections at the dose of 375 mg/m<sup>2</sup> per week, or once every two weeks. T. Nakagawa et al. in their study (2016) demonstrated that using rituximab in three patients with steroid-resistant NS resulted in complete remission: in two patients after one treatment course; in one — after two courses [48]. Another study showed the effectiveness of treatment with rituximab in combination with pulse therapy with methylprednisolone and immunosuppressive drugs in eight out of ten patients with

steroid-resistant NS: complete long-term remission was achieved in seven patients, partial remission — in one [49]. In this study, there was no effect of therapy in two patients; they developed the terminal stage of chronic RF [49]. In a prospective study performed by C. S. Wang et al. (2017), a humanized anti-CD20 monoclonal antibody — ofatumumab — was used in five patients with steroid-resistant NS [50]. Ofatumumab was found to be effective in four patients; one patient could not complete the treatment course due to reactions that developed during drug infusion [50]. The possibility of achieving and maintaining the remission of NS with the help of ofatumumab was obtained in the course of a randomized controlled trial, where ofatumumab was compared with rituximab [51, 52]. It should be noted that the use of rituximab for primary FSGS is an additional method of therapy, and the question of the risk-benefit ratio concerning clinical nephrology is still open, although practical experience of using rituximab for membranous nephropathy is accumulating. A number of researchers report about the effectiveness of plasmapheresis for removing antibodies, immune complexes, cytokines, fibrinogen, and other biologically active substances [43]. This improves the function of the mononuclear phagocytic system, rheological properties of blood, and also increases sensitivity to immunosuppressive therapy. Usually, no more than 3-4 sessions of plasmapheresis are performed, with intervals of 1-2 days with the total volume of the removed plasma — 1 volume of circulating plasma with replacement of the removed volume with 10-20% albumin and rheopolyglukin [43]. Summarizing all these data, we would like to note that nephrologists and clinicians will have at their disposal such drugs as mizoribine, adalimumab, fresolimumab, etc. for the management of FSGS in the near future [8, 43].

## Conclusion

Despite certain success achieved concerning diagnostics and management of FSGS, the prognosis for this type of glomerulopathy remains unfavorable. FSGS is the outcome of many glomerular pathological processes. In the routine clinical practice of nephrologists, the management of FSGS creates certain challenges, and the management

of secondary forms of this disease of any origin requires establishing the nature of morphological changes in the kidneys, although it is not always possible to establish primary or secondary FSGS on the basis of the morphological form only. Studying genetic markers in patients with FSGS is impossible in real clinical practice. A more detailed analysis of the structural and functional conditions of podocytes and the results of controlled prospective studies in the near future will influence the outcomes of FSGS.

## Author Contribution:

**I. T. Murkamilov (ORCID ID: <https://orcid.org/0000-0001-8513-9279>):** interpretation and critical analysis of the results, formulation of conclusions

**I. S. Sabirov (ORCID ID: <https://orcid.org/0000-0002-8387-5800>):** concept and design development

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