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CHRONIC LIMB THREATENING ISCHEMIA — EPIDEMIOLOGY, PATHOGENESIS, DIAGNOSTICS AND TREATMENT STRATEGIES

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Abstract. Chronic limb threatening ischemia (CLTI) is a syndrome of chronic obliterating diseases of peripheral arteries, different in etiology and pathogenesis. Diseases caused by degenerative damage to the arterial bed can lead to CLTI, causing aneurysm and long chronic occlusions. Such diseases include: Marfan syndrome, Ehlers–Danlos, Erdheim tumor, neurofibromatosis, fibrotic dysplasia. Multiple vasculitis are found in systemic vasculitis and connective tissue diseases. The most common cause of CLTI is atherosclerosis and vascular complications associated with diabetes mellitus. In the vast majority of cases (75–80%), atherosclerosis is the pathogenetic mechanism leading to the development of chronic obliterating diseases of the lower limb arteries. All these diseases lead to a significant reduction of perfusion blood flow at the level of microcirculation, causing severe metabolic disorders. Over time, the rheological properties of the blood are impaired, contributing to the progression of tissue ischemia. With CLTI, many of the body’s compensatory capabilities have been exhausted, but conducting revascularization of the lower limb is still possible.

Keywords: atherosclerosis, chronic limb threatening ischemia, revascularization, hybrid approach, epidemiology, diagnostics

ХРОНИЧЕСКАЯ ИШЕМИЯ, УГРОЖАЮЩАЯ ПОТЕРЕЙ КОНЕЧНОСТИ, — ЭПИДЕМИОЛОГИЯ, ПАТОГЕНЕЗ, ДИАГНОСТИКА И СТРАТЕГИИ ЛЕЧЕНИЯ

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Резюме. Хроническая ишемия, угрожающая потерей конечности (ХИУПК), — это синдром хронических облитерирующих заболеваний периферических артерий, различных по этиологии и патогенезу. Заболевания, вызванные дегенеративным поражением артериального русла, могут приводить к ХИУПК, вызывая аневризмы и длительные хронические окклюзии. К таким заболеваниям относятся: Синдром Марфана, Элерса–Данло, опухоль Эрдгейма, нейрофиброматоз, фиброзная дисплазия. Множественные васкулиты встречаются при системных васкулитах и заболеваниях соединительной ткани. В подавляющем большинстве случаев (75–80%) патогенетическим механизмом, приводящим к развитию хронических облитерирующих заболеваний артерий нижних конечностей и ХИУПК, являются атеросклероз и сосудистые осложнения, связанные с сахарным диабетом. Все эти заболевания приводят к значительному снижению перфузионного кровотока на уровне микроциркуляции, вызывая тяжелые метаболические нарушения. Со временем нарушаются реологические свойства крови, способствуя прогрессированию ишемии тканей. При ХИУПК многие компенсаторные возможности организма уже исчерпаны, но проведение реваскуляризации нижней конечности все еще возможно.

Ключевые слова: атеросклероз, хроническая ишемия, угрожающая потерей конечности, реваскуляризация, гибридный подход, эпидемиология, диагностика

CONCEPT OF THE TERM “CHRONIC LIMB THREATENING ISCHEMIA”

The famous scientist P.R. Bell first introduced the concept of the word combination “critical lower limb ischemia or chronic limb threatening ischemia” into medical terminology in 1982. It was intended to designate patients with occlusive lesions of lower limb arteries, which are manifested by: pain at rest, trophic defects and the threat of lower limb gangrene [8]. In 1992, at the Second European Consensus on Chronic Critical Ischemia of the Lower Extremities, the definition of critical ischemia includes such concepts as: the presence of constant or recurrent pain in the lower extremities at rest, requiring analgesia with narcotic analgesics and existing for more than two weeks [26].

The syndrome of decompensated chronic arterial insufficiency of the limb, occurs against the background of reduced hemodynamic indices:

- ankle blood pressure indices 50–70 mm Hg;
- indexes of finger arterial pressure 30–50 mm Hg;
- transcutaneous oxygen tension values 30–50 mm Hg.

In recent decades, the term “CLTI” has become more widely used, which, in addition to focusing on hemodynamic parameters of the distal part of the lower extremity, includes other factors that negatively affect the healing of the trophic defect. Such factors include indicators as: the depth of the trophic defect, the presence and degree of its infection, the general morbid background of the patient. With the increasing incidence of diabetes mellitus and the impossibility to focus solely on hemodynamic parameters of the distal limb channel, it became necessary to develop a new classification of CLTI [4]. The new WIFI classification of lower extremity critical conditions meeting these criteria has been proposed for use in patients with and without diabetes mellitus. This classification takes into account the degree of ischemia, wound depth, peripheral blood supply, presence and severity of the infectious process in the trophic defect. Using this classification, it is possible to analyze the condition of the limb, estimate the expected benefit from the proposed revascularization of the lower limb, and predict the risk of major amputation [42]. Lack of CLTI treatment leads to the disability of patients due to the high risk of lower limb amputation. To date, the treatment of CLTI still remains one of the main problems in modern vascular surgery, as there is still a high risk of lower limb amputation and high mortality of patients after it. CLTI is a terminal stage of chronic arterial insufficiency of the lower extremities, in which the combined state of microcirculation of the lower extremities, namely, reduced perfusion of the foot tissues, will not allow to achieve adequate repair of the trophic defect without limb revascularization.

EPIDEMIOLOGY OF CHRONIC LIMB THREATENING ISCHEMIA

The incidence of chronic limb threatening ischemia or critical lower limb ischemia varies from 50 to 100 cases per 100,000 population in European and US populations [69]. The prognosis in CLTI patients remains extremely unfavorable. According to the TASC document when comparing the results of treatment of patients with CLTI are comparable to the results of treatment of patients with severe oncologic diseases. Only in half of cases patients diagnosed with CLTI undergo limb revascularization, 25% undergo a course of conservative therapy, and the remaining 25% undergo primary amputation.

In the absence of adequate treatment within 5 years, only 30% of patients with CLTI manage to preserve the limb, 52% of patients undergo amputation, and the remaining 18% of patients die from complications associated with CLTI progression. Publications in domestic and foreign literature indicate that the percentage of amputations in patients with CLTI is still quite high [1, 70, 71, 79]. With the advent of high-tech methods of endovascular reconstruction, the overall amputation rate is significantly decreasing due to the possibility of successful revascularization of the tibial segment [31]. Despite the active development of reconstructive vascular surgery, up to 500 lower limb amputations per 1 million population are performed annually. The share of all performed amputations on CLTI reaches 90%. In Russia about 300 amputations per 1 million population are performed annually due to the presence of CLTI in a patient. In Finland and the USA this figure is 120 and 280 respectively [1, 2, 25]. According to different literature data, 25% of patients die within one month after high amputation of the lower limb. In 2 years after high amputation the mortality rate varies from 25 to 60%. The mortality rate within 5 years after high lower extremity amputation ranges from 50 to 70%. After 10 years, this figure reaches 90% [7, 40, 70]. Such high figures of mortality after high amputation are associated with the presence of concomitant pathology, as well as caused by: advanced age, multifocal character of atherosclerosis lesion with involvement of coronary and carotid basins and manifestation of its complications in the form of metabolic disorders and nutritional status, due to decompensated limb ischemia and endogenous intoxication, as well as the traumatic nature of the operation. Among the main causes of death after amputation: acute cardiovascular insufficiency (50–66.4%), purulent and septic complications (11–34.1%), and acute cerebral circulatory failure (3.6%) are in the first place [32, 79].

PATHOGENESIS OF CHRONIC LIMB THREATENING ISCHEMIA

CLTI is a syndrome of chronic obliterative diseases of peripheral arteries, different in etiology and pathogenesis [72]. Diseases caused by degenerative lesions of the arterial bed can lead to CLTI, being the cause of aneurysms and dissections. Such diseases include Marfan syndrome, Ehlers–Danlos syndrome, Erdheim's tumor, neurofibromatosis, fibromuscular dysplasia. Multiple vascular lesions are noted in systemic vasculitis and connective tissue diseases [73]. The most frequent cause of CLTI development is atherosclerosis and vascular complications associated with the presence of diabetes mellitus. In the vast majority of cases (75–80%), atherosclerosis is the pathogenetic mechanism leading to the development of chronic obliterative diseases of lower limb arteries [73]. All these diseases lead to a significant decrease in perfusion blood flow at the level of microcirculation, causing severe metabolic disorders. Over time, the rheological properties of blood are disturbed, contributing to the progression of tissue ischemia [73]. In CLTI, many compensatory capabilities of the organism are exhausted, but revascularization of the lower limb is still possible [74].

DIAGNOSTIC METHODS OF CHRONIC LIMB THREATENING ISCHEMIA

Ankle-brachial index

Ankle brachial index (ABI) is a non-invasive and simple method for the diagnosis of peripheral arterial disease. The sensitivity of the ABI in the presence of CLTI ranges from 80% to 95% in patients without DM. In patients with DM this indicator varies between 50–71%. The specificity of ABI in detecting CLTI in patients without diabetes ranges from 95 to 100%. In the presence of DM, the specificity of ABI is 30–96% [34]. The value of ABI up to 0.7 indicates circulatory compensation, the range of ABI from 0.7 to 0.4 indicates circulatory sub compensation. In the presence of ABI less than 0.4 blood circulation of the lower leg in the decompensation stage (CLTI). The correlation of the degree of severity of chronic limb ischemia depending on the index of ABI according to the national recommendations for the management of patients with vascular arterial pathology was used. CLTI I — ankle brachial index ≥0.9; IIa — resting ABI 0.7–0.9; II b — resting ABI less than 0.7–0.9; III — resting ankle pressure <50 mm Hg; IV — resting ankle pressure <50 mm Hg. False-positive result of ABI is observed in patients suffering from long-term diabetes mellitus, terminal stage of renal failure due to pronounced development of media calcinosis of arterial wall [13, 62]. In case of elevated ABI (more than 1.4) and ABI is considered uninformative, other non-invasive methods of measuring peripheral hemodynamics are used. Finger-brachial index (FBI) is an informative method of diagnosing CLTI in patients with the presence of DM or terminal renal failure. Normally, the FBI is greater than 0.75. FBI less than 0.25 corresponds to severe CLTI [15, 62].

Duplex or Triplex scanning of vessels

Duplex or Triplex scanning is one of the highly accurate, noninvasive methods of diagnostics of vascular pathology, both in venous and arterial basins. Triplex vascular scanning includes 3 main ultrasound modes [63]:

- Normal mode is carried out to assess the structure of vessels, vascular walls and the degree of their tortuosity, which is especially important to consider for making the correct diagnosis and in preparation for various operations.

- Dopplerography — the study of the speed and direction of blood flow in the vessels, as well as its basic digital characteristics.
- Color Doppler mapping — helps to assess the patency of vessels, to detect the presence of thrombosis and atherosclerotic plaques, narrowing the vessel lumen, due to the sensitivity to slow flows improves differentiation between severe stenosis and occlusion, and also allows visualizing small vessels not distinguishable in B-mode [75].

The limitation in the use of duplex scanning is the difficulty of visualization and assessment of the lumen of calcified arteries. Difficulty in visualization of iliac arteries, provided there is gas in the intestine. Difficulty in visualization of collateral blood flow and reduced visualization of the affected arteries of the lower leg, especially the peroneal artery [21, 76].

Laser Doppler flowmetry

The leading link in the pathogenesis of CLTI is microcirculatory disorders. Laser Doppler flowmetry (LDF) allows to evaluate the state of microcirculatory channel [9]. The LDF method is based on optical noninvasive probing of tissues with laser radiation and analysis of scattered and reflected radiation from erythrocytes moving in tissues. The use of LDF provides a deeper understanding of the pathogenesis of microcirculation disorders and allows, along with early diagnosis, to conduct objective control over therapeutic measures by analyzing the results in dynamics [24]. The absence of absolute contraindications to LDF and a wide range of indications for its use to assess both systemic and local state of microcirculation allows using this noninvasive diagnostic method in patients with severe somatic diseases [9].

Spiral computed tomography

Good visualization of the localization level and extent of the pathological process in the arteries of the lower limbs is necessary to determine the nature and scope of surgical treatment. Modern CT scanners in diagnostics of the aortoiliac segment have high sensitivity — 96% and specificity — 98%. When assessing the femoral-popliteal, femoral-tibial segments, these indicators are 97 and 94%, respectively. In assessing the state of the more distal channel, the sensitivity of the method is 95%, specificity 91% [67]. The sensitivity and specificity of this method are comparable to the invasive diagnostic method — selective angiography of lower limb arteries [3].

Application of multidetector CT angiography technique, has a number of advantages over traditional contrast angiography. One of the significant advantages of this method is the possibility to perform it at the outpatient stage. Spiral CT angiography allows visualization of arteries in several planes, creating volumetric images [49]. SCT angiography can be performed in patients who have had a pacemaker installed. CT angiography clearly visualizes calcium and implanted stents within the artery. With CT angiography, it is possible to visualize the tissues around the vessel, which allows the detection of arterial compression from the outside by a tumor, lymph nodes, cyst, or aneurysm [52]. Allergic reaction to iodine-containing contrast agents and renal insufficiency of the patient are the limitations of CT angiography.

Magnetic resonance imaging

Magnetic resonance angiography (MRA), being a noninvasive study with absence of nephrotoxic effects of magnetic resonance contrast agents and radiation exposure, provides an opportunity for objective assessment of peripheral vessels [48]. However, in case of multilevel atherosclerotic lesions of lower limb arteries, adequate visualization of the affected segment is performed using special contrast agents - paramagnetic [48, 55]. The advantage of this method is simultaneous visualization of soft tissues, which is necessary in assessing the prevalence of necrotic lesion in the presence of trophic defect [75]. Despite the fact that MRA has high specificity and sensitivity (93–100%), being a promising technique, it also has a number of disadvantages. In the presence of hemodynamic disturbances and turbulent blood flows, the degree of stenosis may be overestimated. Limitation of MRA use in the presence of stented arteries of the lower limbs, as stents may be accompanied by artifacts, simulating vessel occlusion. It is impossible to perform MRA in patients with pacemakers, as well as in patients with clipped cerebral aneurysms, presence of metal structures. In patients with elevated creatinine, magnetic resonance angiography with gadolinium contrast in rare cases may cause toxic effects on the kidneys. MRA poorly visualizes arterial calcinosis, which may significantly limit its use in planning for vascular anastomosis [48, 57, 64].

Peripheral arteriography of the lower limbs

Peripheral angiography of lower limb arteries belongs to the invasive method of investigation and is a necessary method of investigation in case a patient is planned to undergo revascularization of lower limb arteries [5, 18]. Due to the intensive development and increasing informativity of noninvasive methods of investigation, peripheral arteriography is no longer the “gold standard” in the diagnosis of lower limb peripheral arterial diseases and is performed as a diagnostic procedure less and less frequently [5, 19]. Angiography allows to determine the localization and extent of the pathological process, assess the state of the arterial or venous channel, visualize and evaluate the state of collateral circulation. Angiography of lower limb arteries is of-

ten used to visualize congenital vascular anomalies. Angiography allows visualization of stented arteries of the lower extremities without artifacts or image distortion.

There are no absolute contraindications to angiography of the lower limb arteries; relative contraindications include: acute renal or hepatic insufficiency, allergy to iodine preparations, acute stages of specific diseases (tuberculosis, viral hepatitis B and C) [20, 73].

Transcutaneous oximetry

Transcutaneous oximetry ($TcPO_2$) is a simple and non-invasive way to assess the microcirculation. Transcutaneous oximetry is monitored using a Clark electrode placed on the skin and heated. It determines the level of tissue oxygen saturation, thereby reflecting the state of microcirculation [77]. Although there are some known drawbacks, this method is the "gold standard" in assessing tissue perfusion in the presence of CLTI [70]. $TcPO_2$ is used for amputation risk stratification, and assessment of distal perfusion with $TcPO_2$ is recommended for use in patients with CLTI and DM. Some conditions limit the use of $TcPO_2$. Indications are distorted in the presence of: elevated body temperature, peripheral edema, widespread inflammation, cutaneous hyperkeratosis, and obesity [3].

TREATMENT METHODS FOR CHRONIC LOWER LIMB ISCHEMIA

Treatment of chronic critical lower limb ischemia is currently one of the unsolved problems in vascular surgery. Quite often the use of surgical method of treatment in the presence of severe concomitant pathology is not possible. Despite the achievements of modern pharmacotherapy, many existing drugs in the treatment of critical ischemia of the lower limbs are ineffective. In this regard, the search for new approaches to the solution of this problem is underway. The latest pharmacological breakthrough was the introduction of methods of angiogenesis stimulation in the affected limbs based on the possibilities of genetically engineered technology. The mechanism of action of the drug is aimed at stimulation of capillary growth and development of microcirculatory channel in ischemic tissues [29, 30, 46]. When determining the possibility of using genetically engineered method of angiogenesis stimulation in clinical practice, it turned out that the most effective use of this technology was noted in patients with CLTI of IIb–III stages according to Fonteyn-Pokrovsky classification. Taking into account the low efficacy of conservative therapy, when determining the therapeutic tactics in patients with CLTI, it is necessary, first of all, to decide on the possibility of reconstructive surgery on vessels. Surgical treatment aimed at revascularization of the lower limb is the optimal method of treatment of ischemic syndrome caused by severe morpho-functional changes in the arterial bed. Surgical treatment can be performed in all patients with CLTI in the presence of appropriate indications and absence of contraindications to intervention. Maximum restoration of blood circulation in the lower extremities is possible only by using direct revascularization: endovascular revascularization, open surgery, hybrid reconstruction [45, 47, 74].

Endovascular surgery — remains a young direction in modern vascular surgery and is increasingly used in the treatment of obliterative diseases of the arteries of the lower extremities. Balloon angioplasty and stenting of lower limb arteries are the most common endovascular interventions for pathology of lower limb arteries, allowing to restore blood flow through vessels without open surgery. Over the last decade, endovascular methods of revascularization of lower limb arteries have been rapidly improved, so in a significant number of patients they are used as a less invasive treatment for lower limb arterial disease [39, 51, 74].

For many years, open surgery was considered the "gold standard" treatment for patients with clinical presentation of CLTI. With the advent of endovascular surgery, these two methods were constantly opposed to each other [59].

Recently, however, there have been more and more reports about the desire to find the best treatment options for patients with CLTI, which has led to the merging of these areas [74].

In case of multilevel lesions of lower limb arteries, combined operations consisting in the simultaneous use of open arterial reconstructive surgeries with endovascular procedures (stenting, balloon angioplasty, etc.) have been performed more often [33, 78–80].

The first data on the use of open and endovascular surgery in a patient with critical lower limb ischemia were published in 1973 by J. Porter, who reported on balloon angioplasty of the iliac artery with simultaneous femoral-femoral cross-over bypass [54].

At present, hybrid surgery is a rather promising direction in the treatment of CLTI and accounts for 5 to 21% of lower extremity arterial vessel surgeries in foreign clinics [16, 22, 23].

Some authors mean hybrid surgery as a combined one-stage intervention combining open and endovascular stages within one operating room, while others suggest that these interventions can be separated in time by minutes, hours, or even days [6, 12, 50, 66, 74, 78–80].

There is an opinion that when endovascular and "open" techniques are combined in a single patient, the risk of restenosis and reconstruction occlusions in the distant postoperative period, is much higher than after performing standard open surgery [74, 80].

Hybrid surgery should be used for patients with high surgical risk, with severe concomitant pathology in multilevel

atherosclerotic lesions, but it should be taken into account that in the presence of stage IV limb ischemia, diabetes mellitus, and chronic renal failure, it can negatively affect the remote patency of the reconstruction zones [37, 68, 78].

Considering the fact that the development of critical ischemia in one third of cases is associated with multilevel atherosclerotic lesions of the arterial channel of the lower extremities and the lack of randomized clinical trials in this area is of scientific interest [17, 74, 78, 80]. The accumulated experience of open bypass surgeries, hybrid reconstructions, and endovascular techniques for the treatment of patients with critical ischemia over many years demonstrate positive results. The existing studies comparing the advantages and disadvantages of open, endovascular and hybrid operations in critical ischemia do not consider separately patients with previously performed stenting of lower limb arteries in the clinical picture of critical lower limb ischemia due to disease progression.

CURRENT RANDOMIZED TRIALS INVESTIGATING THE TREATMENT OF PATIENTS WITH CLTI

BASIL is the only randomized controlled trial to date comparing the results of surgical lower extremity arterial reconstruction with those of endovascular revascularization of the lower extremity arteries, in patients with critical lower extremity ischemia. In their original 2005 publication, the BASIL investigators reported that the main clinical outcomes (overall survival and amputation-free survival) at 2 years did not differ between groups. However, after 2 years, open bypass surgery appeared to be advantageous, prompting the continuation of the study [10]. The final analysis of the BASIL results now suggests that patients who initially underwent endovascular interventions have a much worse outcome in the late postoperative period than patients initially treated surgically. Quality of life scores and costs were not significantly different overall. There are many controversies surrounding the BASIL trial and its interpretation. These include the choice of study population, the endpoints considered, and the nature of the procedures performed. The BASIL trial confirms the primacy of open surgical bypass with autovenous for the majority of patients with critical lower extremity ischemia and raises questions about the consequences of failed endovascular interventions. Complications during hybrid operations range from 2–6.5% and are typical complications for endovascular and open interventions [44]. Further multicenter studies are needed to address the large evidence gap for treatment selection in this patient population [14].

BASIL-2 is a multicenter prospective randomized study including patients with critical lower extremity ischemia. The aim of the study was to evaluate the economic and clinical efficacy of treatment of endovascular and femoral-popliteal bypass below the knee joint target with autovenous in patients with critical lower limb ischemia with localization of the lesion at the level and below the popliteal artery. Official recruitment of centers included in the study has been started since July 2014. In total, 600 patients are planned to be included in the study, with a follow-up time of 3 years. As of November 01, 2017, a total of 40 clinical centers are open for participation in the Basil-2 study; 29 in England, 5 in Scotland, 2 in Wales, 3 in Denmark and 1 in Sweden. Thirty-nine of the 40 clinical centers have cumulatively recruited 249 participants [11, 53].

BASIL-3 is a multicenter randomized controlled trial. Comparing the clinical and cost-effectiveness of simple balloon angioplasty with or without metallic stenting, drug-coated balloon angioplasty with or without bare metal stenting, and primary stenting with drug-coated stents secondary to the femoral-popliteal segment. Patients with multilevel atherosclerotic lesions of the lower extremity arteries may receive aorto-iliac and/or popliteal-tibial revascularization at the same time as their randomized femoral-popliteal intervention. The primary clinical outcome is amputation-free survival. The primary outcome in the economic analysis is cost per year. Secondary outcome measures include overall survival, major adverse limb events, major adverse cardiac events, ischemic pain relief, trophic defect healing, and quality of life. The required sample size was calculated for 861 participants (287 at each shoulder). These patients will be recruited over 3 years and followed up for 2 to 5 years [11, 35].

BEST-CLI is a prospective, multicenter, randomized, open comparative study. The primary objective of the study is to compare the efficacy, functional outcomes, and cost of treatment in patients with infrainguinal lesions of lower extremity arteries and the presence of critical lower extremity ischemia who underwent open surgical treatment or endovascular revascularization [27]. The study includes 2100 patients at 140 medical sites in the United States and Canada who are candidates for both revascularization options. This is a 4-year study, ongoing from 2014–2017, with each patient being followed for a minimum of 2 years after treatment [56, 58].

Critical lower extremity ischemia continues to represent a huge public health problem in the developed world. The BEST-CLI study is a timely and necessary study to help identify best practices and provide a framework for thoughtful application of current and future treatment options for critical lower extremity ischemia [28, 41, 43].

Currently, there is no consensus on the prioritized method of surgical treatment for patients with critical lower extremity ischemia. For a long time, open arterial operations remained the “gold standard” in the treatment of CLTI. Since

the advent of endovascular surgery, many positions in the treatment of CLTI began to be reconsidered. Despite the variety of existing methods of surgical treatment, none of them is without disadvantages.

Recently, there has been a rapid increase in the use of minimally invasive technology in revascularization of lower limb arteries in patients with CLTI [38, 74, 78, 80–87]. Repeated surgical interventions on arterial segments are usually technically much more difficult and traumatic [36, 60, 61, 65].

It follows that the problem of choosing the optimal and hybrid surgical tactics for treatment of patients with critical lower limb ischemia or chronic limb threatening ischemia in the presence of extended occlusion of the SFA and lesions of the lower leg arteries is relevant and of scientific and practical interest.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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