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The von Willebrand factor as a marker of partially controlled asthma severity in children

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Asthma is one of the most common chronic non-communicable diseases among adults and children. Recent studies have paid special attention to endothelial dysfunction in the mechanism of development and progression of asthma, on the one hand, and the occurrence of long-term consequences of endothelial damage, on the other hand. Endothelial dysfunction in the modern sense is not only a pathology of the vascular wall but also a deep, complexly organized system of disorders and compensatory and adaptive reactions that originates at the molecular genetic level.

Purpose — to improve the knowledge of assessing the levels of von Willebrand factor (VWF) as a marker of endothelial dysfunction in the blood of children with partially controlled asthma.

Materials and methods. 94 children participated in the study. Patients were divided into 4 groups: the Group 1 — children with mild persistent asthma (n=59), the Group 2 — moderately severe persistent asthma (n=10), the Group 3 — severe persistent asthma (n=12), and the Group 4 — control group (n=13).

The study of VWF was carried out by a standard enzyme-linked immunosorbent assay (ELISA) using the Human VWF ELISA Kit. Data were analyzed using Statsoft Statistica version 8 (Tulsa, OK) and MedCalc statistical software version 17.2.

Results. It was found that children with asthma had significantly increased levels of VWF in the blood serum compared to the control group. The highest levels of serum VWF were found in patients with severe asthma.

Conclusions. Elevated levels of VWF indicate the presence of endothelial dysfunction. Increased levels of VWF depending on the severity of asthma indicate more severe endothelial damage in children with severe asthma.

The research was carried out in accordance with the principles of the Declaration of Helsinki. The research protocol was approved by the Local Ethics Committee of the institution mentioned in the work. Informed consent of parents or their guardians was obtained for conducting research. No conflict of interests was declared by the authors.

Keywords: asthma, children, endothelial dysfunction, von Willebrand factor.

Фактор Віллебранда як маркер тяжкості частково контрольованої бронхіальної астми в дітей

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Бронхіальна астма (БА) — це одне з найпоширеніших хронічних неінфекційних захворювань серед дорослих та дітей. Дослідження останніх років приділяють особливу увагу ендотеліальній дисфункції в механізмі розвитку та прогресування БА, з одного боку, та виникненню віддалених наслідків пошкодження ендотелію, з іншого. Ендотеліальна дисфункція в сучасному розумінні — це не тільки патологія стінки судин, але й глибока, складно організована система порушень і компенсаторно-пристосувальних реакцій, що бере початок на молекулярно-генетичному рівні.

Мета — поглибити знання з оцінки рівнів фактора Віллебранда як маркера ендотеліальної дисфункції в крові дітей з частково контрольованою БА.

Матеріали та методи. У дослідженні взяли участь 94 дитини. Пацієнтів поділено на 4 групи: 1-ша група — діти з легкою персистуючою БА (n=59); 2-га група — із середньотяжкою персистуючою БА (n=10); 3-тя група — із тяжкою персистуючою БА (n=12); 4-та група — група контролю (n=13).

Дослідження фактора Віллебранда виконано стандартним імуноферментним методом із використанням набору «Human VWF (Von Willebrand Factor) ELISA Kit». Проведено аналіз даних за допомогою «Statsoft Statistica» версії 8 («Tulsa», OK) і статистичної програми «MedCalc» версії 17.2.

Результати. Встановлено, що в дітей з БА вірогідно підвищені рівні фактора Віллебранда у сироватці крові порівняно з групою контролю. Найвищі показники фактора Віллебранда сироватки крові виявлено в пацієнтів із тяжкою БА.

Висновки. Підвищений рівень фактора Віллебранда свідчить про наявність ендотеліальної дисфункції. Збільшення рівня фактора Віллебранда залежно від ступеня тяжкості БА вказує на більш тяжке пошкодження ендотелію в дітей з тяжкою БА.

Дослідження виконано відповідно до принципів Гельсінської декларації. Протокол дослідження ухвалено Локальним етичним комітетом зазначеної в роботі установи. На проведення досліджень отримано інформовану згоду дітей, батьків.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: бронхіальна астма, діти, ендотеліальна дисфункція, фактор Віллебранда.

Introduction

The WHO Regional Office for Europe, within the framework of the Health for All strategy, has classified allergic diseases as markers of public health.

The increasing prevalence of asthma, which is one of the most common and severe allergic diseases, including among children, necessitates further research into the mechanisms of pathogenesis and, on their basis, the development of new treatment and prevention programs to control the disease [8,18].

Asthma is a chronic inflammatory airway disease that leads to airway obstruction, which can be partially irreversible, which defines the concept of airway remodeling [8].

Chronic inflammation affects the vascular endothelium, blood coagulation system, complement system, and others [6].

The endothelium is more than a physical barrier between air, blood and connective tissue. The endothelium is actively involved in metabolic processes and plays a key role in gas and nutrient metabolism, haemostasis, angiogenesis, and in the processes that control inflammation, leukocyte transport, vascular tone, and endocrine signalling [2,16].

At the present stage, scientists pay special attention not only to endothelial dysfunction in the mechanism of development and progression of chronic diseases, including asthma, but also to the occurrence of long-term consequences of endothelial damage.

In the event of various pathological conditions (damage/inflammation), the endothelium reacts quickly, promoting thrombus formation, proliferation and remodelling of the vascular wall, which in turn has a significant impact on the progression of cardiovascular disease.

Endothelial dysfunction has been proven in various diseases, including atherosclerosis, arterial hypertension, hypercholesterolemia, chronic heart failure, diabetes mellitus, rheumatic diseases, and infective endocarditis, which is one of the main causes of cardiovascular complications.

Endothelial cells (ECs) play an important role in the bronchopulmonary system. The pulmonary vascular bed is the largest vascular bed in the human body, and pulmonary ECs are an important component of the gas exchange apparatus of the alveoli [14].

It is well known that patients with moderate and severe asthma with uncontrolled asthma are accompanied by chronic hypoxia, which becomes progressive over time [4,23]. Chronic hypoxia leads not only to airway remodeling and damage to the lung endothelium, but also to dysfunction of other organs and systems [19,26]. Hypoxia is not the only mechanism of damage, of course, dysfunction of the immune system also plays an important role, which is the primary factor in the exacerbation of asthma, but the dynamic progression of the deterioration of the bronchopulmonary system can eventually lead to pathology in other body systems.

Taking into account all of the above, it is crucial to continue the search for indicators of endothelial damage.

According to the literature, pro-inflammatory and anti-inflammatory cytokines can serve as markers of endothelial dysfunction [17,22].

One such marker is von Willebrand factor (VWF) [12,29]. The plasma glycoprotein VWF is synthesized only in ECs or megakaryocytes, and its main function is hemostasis. That is why any changes in the state of the vascular endothelium are manifested by an instantaneous change in the concentration of VWF in the blood plasma [13].

The ***purpose*** of the study — to measure VWF to find evidence of endothelial activation in children with different degrees of uncontrolled asthma.

Materials and methods of the research

This was a cohort study. The study included children aged 5 to 17 years with an already established diagnosis of allergic asthma (IgE-dependent or IgE-independent), persistent mild, moderate, severe (2–4 severity), partially controlled, in the period of exacerbation. Exacerbations were mild to moderate in severity.

Patients were recruited at the pulmonology department of the children's hospital.

Out of 130 children admitted to the hospital during this period, 81 children were selected. The main condition for participation in this study was compliance with the inclusion and exclusion criteria.

Inclusion criteria: children aged 5 to 17 years with a diagnosis of persistent mild, moderate, severe (2–4 severity) asthma, partially controlled, in the period of exacerbation; 1–2 days of exacerbation; children with signed consent from both parents, and at the age of 14 years, from the patients themselves.

Exclusion criteria: children under 5 years of age or over 17 years of age; children under 17 years of age whose parents (or one of the parents) did not give written consent to the study; patients aged 14 years and older without written consent to the study; patients with acute bronchitis simple, acute obstructive bronchitis, intermittent asthma, pneumonia; patients diagnosed with asthma in remission and controlled asthma; patients with congenital and chronic cardiopulmonary or neurological diseases; hereditary diseases leading to changes in the functioning of the respiratory tract, including cystic fibrosis; proven immune deficiency; patients with severe somatic conditions and decompensation of vital functions; suspected or confirmed gastrointestinal diseases; patients with neoplasms of any location.

Patient's parents received comprehensive information about the methods and scope of the study.

The study was performed with minimal psychological distress on the part of the patients.

The control group consisted of 13 healthy children (of similar age/sex) without any signs of chronic or acute illnesses during the previous three months, who were referred for age-related control or vaccination. Parents of the control group children were informed about the objectives of the study and signed a written informed consent before enrolment.

All patients with asthma were diagnosed by a pediatric respiratory specialist (pulmonologist or allergist). The diagnoses and examinations were by the protocols for the treatment of children with asthma No. 868 of 08.10.2013 «On Approval and Implementation of Medical and Technological Documents for Standardisation of Medical Care in Bronchial Asthma». The Global Initiative for Asthma (GINA) 2020 recommendations were also taken into account.

The examination was carried out in the first days of asthma exacerbation, namely in the presence of dyspnea, cough, and wheezing and before correction of basic therapy.

Patients received basic asthma treatment by the accepted GINA 2020 guidelines [18].

To assess control, we used diagnostic tests, taking into account the age of the children. The test is for children aged 4–11 years and 12 years and adolescents [18,24,28]. According to the results and GINA criteria, partially controlled asthma was present (2 criteria were positive).

All patients underwent physical and laboratory examinations. A thorough study of anamnestic data was carried out, namely: age at diagnosis of asthma, duration of asthma, and burdened family history of allergic conditions (any and specifically asthma).

Patients were divided into groups depending on the degree of asthma. The Group 1 included children with mild persistent asthma (n=59), the Group 2 — had moderate persistent asthma (n=10), the Group 3 — had severe persistent asthma (n=12) and the Group 4 was the control group (n=13).

Methods for assessing the state of the endothelial component. Serum samples were taken during routine examination of children before therapy correction. Blood samples were drawn by a trained pediatric phlebotomist nurse. Blood was collected in the morning, on an empty stomach, by venipuncture. Blood sampling was preceded by 20 minutes of physical and emotional rest. The material was collected in special tubes. For serum collection, tubes without fillers were used. Centrifugation to obtain serum was performed at 2000–2500 rpm for 15–20 minutes. After centrifugation, the materials were distributed into disposable tubes using a sterile pipette and stored at -70°C. Aliquots of samples were analyzed once without a repeated freeze-thaw cycle.

The study of VWF was carried out by a standard enzyme-linked immunosorbent assay (ELISA) using the Human VWF ELISA Kit.

The assessment of the external respiratory function of children was performed using the SpiroCom AINC.941311.005 I spirographic complex. It was manufactured by the National Aerospace University «Kharkiv Aerospace Institute» («KhAI»), Science and Technology Centre of Electronic Medical Devices and Technologies «KhAI–Medica», Kharkiv, Ukraine (TU U-33.1–02076 005–2002). The study was conducted according to the standard method of spirography. The patients and their parents were given the most accurate instructions on how to prepare for the study and the medication of spirography was explained. The patients did not eat for 2 hours before the study, the intensity of physical activity was reduced 1 hour before the study (risk of bronchospasm), the patients' clothes were loose and did not restrict chest and abdominal movements, and inhaled medications were discontinued 12 hours before spirometry.

The planned clinical trial was conducted after obtaining the approval of the Ethics and Bioethics Commission of Kharkiv National Medical University on 2 October 2019, protocol No. 6, and was conducted by the principles of the Declaration of Helsinki as amended in October 2013.

Methods of statistical analysis. The statistical processing of the study results was performed using the statistical packages EXCELL FOR WINDOWS, StatSoft STATISTICA Version 7 (Tulsa, OK) and MedCalc Statistical Software (version 17.2). The Shapiro–Wilk test and histogram and q-q plots were used to assess normality. Since the sample distribution differed from the normal one, the median (Me) and interquartile range (Lq — lower quartile; Uq — upper quartile) were determined. For multiple comparisons (the study included 4 groups), the non-parametric Kruskal–Wallis test was used. Differences were considered significant with the Bonferroni correction. The nonparametric Mann–Whitney test was used to determine the difference between groups. The difference between two parameters was considered statistically significant at $p<0.05$. The cor-

Table

Clinical and laboratory data

Sign	Group 1 (Mild asthma)	Group 2 (Moderate asthma)	Group 3 (Severe asthma)	Group 4 (Control)	p
Number	59	10	12	13	
Gender, M/F	23/36	4/6	6/6	7/6	$P_1<0.05$ $P_{2,3,C}>0.05$
Age, years Me (Lq; Uq)	11.0 (7.0;15.0)	10.0 (10.0;11.0)	12.5 (11.0;14.0)	8.0 (6.0;10.0)	p_{1-2} – 0.798 p_{1-3} – 0.253 p_{2-3} – 0.129
Disease duration Me (Lq; Uq)	2.0 (1.0;6.0)	3.0 (2.0;4.0)	6.5 (3.5;10.0)		p_{1-2} – 0.213 p_{1-3} – 0.002 p_{2-3} – 0.075
Allergic diseases in the family	52.5% (31/59)	60% (6/10)	66.7% (8/12)		p_{1-2} – 0.707 p_{1-3} – 0.442 p_{2-3} – 0.791
Asthma in the family	39.0% (23/59)	30.0% (3/10)	58.3 (7/12)		p_{1-2} – 0.651 p_{1-3} – 0.293 p_{2-3} – 0.262
Ig E increase, IU/ml (more than 50 IU/ml)	74.5% (44/59)	100.0% (10/10)	91.6% (11/12)		p_{1-2} – 0.034 p_{1-3} – 0.003 p_{2-3} – 0.391
CRP, mg/l	16.9% (10/59)	40.0% (4/10)	66.7% (8/12)		p_{1-2} – 0.246 p_{1-3} – 0.007 p_{2-3} – 0.291
FEV1	105.0 (102.0; 126.0)	99.0 (90.0; 103.0)	77.5 (74.0; 79.0)		$p_{1-2}<0.001$ $p_{1-3}<0.001$ $p_{2-3}<0.001$
FEV1/FVC	107.0 (105.0; 108.0)	101.0 (95.0; 103.0)	94.0 (89.0; 97.0)		$p_{1-2}<0.001$ $p_{1-3}<0.001$ p_{2-3} – 0.010
PEF	107.0 (105.0; 120.0)	101.5 (89.0; 108.0)	63.5 (58.5; 68.0)		$p_{1-2}=0.036$ $p_{1-3}<0.001$ $p_{2-3}<0.001$

relation between the parameters was determined by Spearman's rank correlation analysis (r); $p<0.05$ was considered a statistically significant difference.

The rank biserial correlation coefficient (r rb) has been used for dichotomous nominal data versus rankings (ordinal). The pointwise biserial correlation coefficient measures the strength of the relationship between two variables in the range from -1 to +1, where -1 indicates a perfect negative relationship and +1 indicates a perfect positive relationship. Receiver operating characteristic (ROC) curves were constructed for the variables to determine the optimal cut-off values for predicting the endpoint. The endpoint of this study is the formation of endothelial dysfunction in children with partially controlled asthma. The cut-off point of each variable and the sensitivity, specificity, positive likelihood ratio (+LR), and negative likelihood ratio (LR) of this cut-off point were obtained using the Juden index. To determine the most reliable screening tool among these four variables, a pairwise comparison of these variables was performed by determining the difference between the areas under the curve using the Hanley and McNeil method.

Results of the research and discussion

The study involved 81 children with asthma. No significant statistical difference was found between the groups when taking a medical history. This concerned the age of the children and the presence of atopy in close relatives (first-degree relatives) (atopic dermatitis, allergic rhinitis, allergic diseases in the family, asthma in the family). Differences were found in two anamnestic indicators: boys statistically predominated in mild asthma, other groups had no significant differences, and the duration of the disease in patients with severe asthma was statistically significant. In the laboratory examination, statistically significant increases in IgE and C-reactive protein (CRP) levels were found in patients with severe asthma compared with mild asthma. Results, lung function tests: FEV1 (Forced Expiratory Volume in one second), Tiffno test — FEV1/FVC (Forced Vital Capacity), PEF (Peak Expiratory Flow), were processed using the Kruskal–Wallis test. This criterion was significantly high: H FEV1 = 39.087; $p<0.001$, H FEV1/FVC = 41.766; $p<0.001$,

H PEF = 33.420; p<0.001. There was also a statistically significant decrease in lung function in patients with severe asthma compared with mild asthma (Table).

The level of VWF in the blood serum of children with asthma

Statistical processing using the Kruskal–Wallis test revealed the presence of a highly significant H-criterion, which allowed us to conclude that the levels of VWF have a significant difference in the groups, and given that the distribution into groups was carried out depending on the severity of asthma, it can be assumed that the levels of VWF depend on the severity. When calculating the differences between groups using the Mann–Whitney test, increased levels of VWF were found in children with asthma in all groups, with the highest levels in children with severe asthma (Figure 1).

A negative correlation was found between the level of VWF in children's serum and FEV1 r=-0.603, p<0.05; FEV1/FVC r=-0.582, p<0.05; PEF r=-0.537, p<0.05.

The biserial correlation was used to assess the relationship between the level of VWF and the presence of allergic diseases in the family history. The existence of a strong relationship was determined: r rb=0.79, p<0.05, T=4.16.

The biserial correlation was also used to assess the relationship between VWF levels and CRP elevation in the blood. The existence of a strong relationship was determined: r rb=0.81, p<0.01, T=4.16.

The vascular endothelium at rest plays an important protective role in the body, but in the event of damage or inflammation, the endothelium reacts quickly, releasing a variety of biologically active substances [13,25]. The occurrence of endothelial dysfunction is a reaction to its damage.

Scientists are constantly searching for markers of endothelial dysfunction, and one of the already identified ones is VWF, which is stored in the Weibel–Palade bodies of the pulmonary vascular endothelium and released from ECs in response to damage [1,22,27].

In our study, we found elevated levels of VWF in all children with different degrees of partially controlled asthma at the height of clinical manifestations. These data indicate the presence of endothelial dysfunction.

Similar data were reflected in scientific papers where the object of study was childhood asthma in exacerbation and remission. Both conditions were accompanied by an increase in VWF levels, but

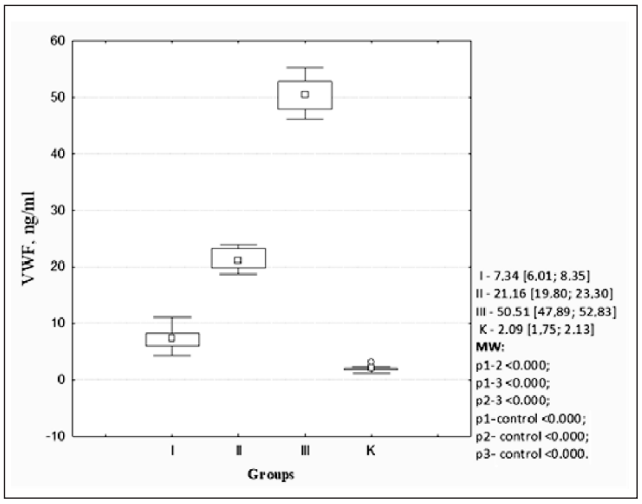

Fig. 1. Statistical indices of the Von Willebrand Factor, (Me (Lq; Uq))

the highest levels were observed in patients with extensive clinical manifestations [11]. Increased levels of VWF have also been reported by researchers studying asthma in adults in remission [15].

It is not known for certain whether the presence of an increased amount of VWF indicates the cause or consequences of endothelial dysfunction, but changes in its levels are directly or indirectly related to the onset of the pathological process [1].

Statistical processing of VWF levels using the Kruskal–Wallis test revealed a significant difference in the groups, and given that the groups were divided according to the severity of asthma, it can be assumed that VWF levels depend on the severity of asthma. The highest values of VWF in our study correspond to severe asthma.

Scientists studying the risk of venous thromboembolism in adult patients with stable asthma (mild, severe and prednisone) found that VWF levels increase with increasing asthma severity [20].

Our study revealed a negative correlation between VWF and indicators of external respiratory function. The highest levels of VWF were associated with reduced lung function.

This fact is confirmed in scientific practice, given that one of the factors of damage in uncontrolled or poorly controlled asthma is chronic hypoxia. Taking into account that lung ECs are an important component of the alveolar gas exchange apparatus, their damage occurs with a constant lack of oxygen [4,23].

A group of researchers who studied asthma in adults aged 18–70 years with stable asthma found a negative correlation between endothelial damage and external breathing function, which is consis-

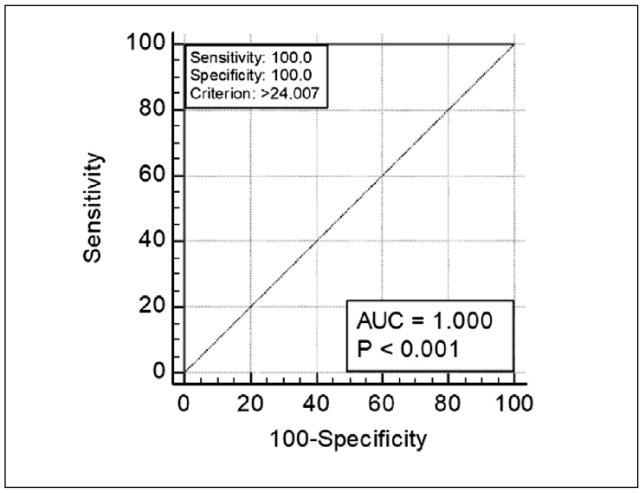

Fig. 2. ROC curves for von Willebrand factor as a biomarker of the severity asthma in children

tent with our data, but they used brachial artery dilatation and common carotid intima-media thickness as markers of endothelial damage [9]. They claim that this negative correlation between external breathing functioned indicators of external respiratory function was found by them for the first time [15].

Scientists conducting research in children with periodic and recurrent wheezing found that in the latter, lung function decreases over time (5–7 years), indicating not only the negative impact of the number of obstructions, but also the chronic nature of the process [21].

The presence of an inflammatory process in our study is supported by the data on elevated CRP levels in children with severe asthma. A positive relationship between VWF and CRP in patients with severe asthma was observed in the biserial correlation calculation.

Scientists call CRP one of the markers of systemic inflammation [15]. Scientists study the informativeness of CRP as an indicator of inflammation in various diseases, including pathologies of the bronchopulmonary system [7]. The data indicate that it is more informative at the peak of the inflammatory process, but may also have elevated levels when clinical manifestations subside.

In favor of the chronic nature of inflammation, our study obtained the following data: a link was found between the duration of the disease and the severity of asthma, and a positive correlation was found between the level of VWF and the duration of the disease.

Modern studies show a link between elevated levels of VWF and the formation of chronic inflammation in children with diagnosed asthma and at the stage of its formation [10]. These studies have made it possible to see dynamic changes in VWF levels at the height of clinical manifestations of asthma and multiple bronchial obstruction in children, and in the period outside of exacerbations.

The non-hemostatic role of VWF is still not fully understood, but the occurrence of disorders in the coagulation and anticoagulation system, where the role of VWF is well known, in various inflammatory processes of the respiratory tract has been proven by modern scientists. Such data were obtained in studies of children and adults with acute respiratory distress syndrome, chronic obstructive pulmonary disease, pulmonary fibrosis, and pneumonia [3,5,25].

This suggests that both acute and chronic pathological conditions can lead to endothelial dysfunction.

The ROC analysis made it possible to determine the cut-off values of VWF in the blood serum that were prognostically significant in terms of asthma severity. It was found that VWF>24.007 ng/ml had prognostic significance for severity among children with asthma (Figure 2).

The limitation of this study is the presence of concomitant allergic pathology in patients: atopic dermatitis (45%), allergic rhinitis (72%) or their combination (29%). These comorbidities can also affect serum VWF levels [11].

Conclusions

In all patients with asthma during the period of clinical manifestations, the levels of VWF are elevated, indicating endothelial dysfunction.

The highest levels of VWF in the blood serum are associated with severe asthma, indicating an increase in the intensity of endothelial damage.

The presence of a significant negative correlation between the VWF and indicators of external respiratory function confirms its dependence on the severity of the disease.

The positive correlation between the VWF and the duration of asthma and the presence of increased CRP levels confirms the thesis that the VWF is involved in chronic inflammation.

The concentration of VWF in the blood serum of children with asthma above VWF>24.007 ng/ml can be considered as an additional marker of its severity.

The results of our study will probably be able to influence the further tactics of examination and treatment of patients with asthma.

Gratitude. We thank all patients and their families for agreeing to participate in our study. He also expresses his sincere gratitude to all the participants who spent their time for their contribution to this study.

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No conflict of interests was declared by the authors.

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