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## **MARKER PROFILE OF DIGESTIVE SYSTEM ORGANS COMORBID PATHOLOGY IN CHILDREN**

**Snizhana Vasylivna Sokolnyk, Tamila Vasylivna Sorokman, Ganna Borysivna Bodnar,  
Pavlo Mykhailovych Moldovan, Iryna Yaroslavivna Loziuk,  
Nadiia Yaroslavivna Vaskul**

**Bukovinian State Medical University, Chernivtsi, Ukraine**

Sokolnyk Snizhana Vasylivna, head of the department of Pediatrics and Medical Genetics, DMS, MD, professor; e-mail: [Sokolnyk.Snizhana@bsmu.edu.ua](mailto:Sokolnyk.Snizhana@bsmu.edu.ua)  
<https://orcid.org/0000-0002-9399-4010>

### **Abstract**

The article highlights the current state of the comorbid pathology of the digestive system problem in children. Attention is paid to the most significant trigger factors of comorbid pathology of the digestive system organs in children and they are given a prognostic assessment with the development of a mathematical model of developmental risk.

**Aim.** To identify predictors of comorbid pathology of the digestive system in children and to determine their prognostic value.

**Material and methods.** 115 children with comorbid pathology of the digestive system organs and 80 healthy children aged 7-18 years were examined. The state of biological, social and genealogical well-being was determined by means of questionnaires. Laboratory and instrumental studies were conducted in accordance to the Ministry of Health of Ukraine orders in the specialty "Pediatric Gastroenterology" with the informed consent of patients to participate in the study.

Results. Etiologically determining risk factors for the development of comorbid pathology of the digestive system organs in children are unfavorable genealogical history with hereditary burden by both pedigrees, age and sex of the child, *H. pylori* infection, stress, vitamin D3 and iodine deficiency, endothelial dysfunction, disruptions of regional blood flow in the abdominal trunk, premorbid background.

Conclusion. It is established that the risk of comorbid pathology of the digestive system in children will increase by 4.27 times if the child has identified by us non-modifying factors, and by 2.62 times under the influence of modifying factors.

**Key words: comorbid pathology; digestive system organs; children; risk factors.**

**Introduction.** Recently, the issue of comorbidity in pediatric practice has been raised more frequently, researches are being conducted to study the peculiarities of comorbid pathology, the required range of diagnostic tests and treatment tactics, because in everyday practice pediatricians often face the presence of several diseases in children, most of which have multifactorial nature [1, 2].

According to statistics, the pathology of the digestive system ranks second among childhood morbidity [6]. On the background of increasing prevalence and morbidity of the digestive system among children, the frequency of comorbid pathology is increasing, which is associated with the modern way of life of children (inactivity, fast-food, etc.) and the influence of numerous adverse environmental factors [4, 5]. The multifactorial nature of comorbid pathology, the systemic nature of affection makes it difficult for primary care physicians to make a diagnostic search aimed at isolating the underlying disease and the subsequent choice of treatment tactics [7-9].

Therefore, it is important to study the comorbid pathology, in particular, of the digestive system organs, with the analysis of factors and mechanisms of development, highlighting the main clinical and diagnostic characteristics among children of different ages to determine the optimal algorithm for choosing appropriate treatment tactics.

**Aim.** To identify predictors of comorbid pathology of the digestive system organs in children and to determine their prognostic value.

**Material and methods.** The study was conducted on the basis of the gastroenterology department of the Chernivtsi Regional Children's Clinical Hospital. 115 children with comorbid pathology of the digestive system aged 7 to 18 years and 80 healthy ones of the appropriate age were examined after signing the patient's informed consent to participate in

the study. The average age of the examined children was  $12.4 \pm 2.5$  years. Research groups are representative by age, sex, place of residence ( $p > 0.05$ ). Criteria for patients inclusion in the study: the presence of comorbid diseases of the digestive system, established in accordance to the order of the Ministry of Health of Ukraine №53 from 29.01.2013; age of children from 7 to 18 years; signed information consent of parents / guardians and children to conduct the planned survey as part of the research. Criteria for patients exclusion from the study: refusal of parents / guardians and children to participate in the study; age of the child up to 6 years; concomitant pathology of other systems and organs. Criteria for the patient's withdrawal from the study: the decision of parents / guardians and the patient to terminate their participation in research; lack of compliance in the process of examination and treatment; appearance of exclusion criteria in the patient during the scientific study.

To establish the determining etiological predictors of comorbid pathology using sociometric and genealogical research methods, a thorough survey of children and their parents / guardians was conducted in accordance with the questionnaires, developed by the Department of Pediatrics and Medical Genetics of Bukovinian State Medical University. The questionnaire paid special attention to the data on the nature of heredity in three generations of kinship, the course of the ante- and postnatal periods, the neonatal period, the nature of the mother's nutrition before, during pregnancy and breastfeeding, the organization and nature of breastfeeding and nutrition until inclusion in research, the presence of early diseases of the digestive system and other systems and organs with subsequent assessment of biological, social and genealogical well-being.

Assessment of the child's physical development was performed by the centile method with the calculation of its age accordance.

Assessment of psycho-emotional status of children was performed after acquaintance with the state of their health, exclusion of mental disorders and neurological pathology.

According to conventional methods, children underwent paraclinical examination, which included a general blood test, biochemical blood indicators, blood sugar test, general urine test, fecal analysis for helminth eggs, coprogram, fecal occult blood analysis. Additionally, the concentration of vitamin D3, indicators of endothelial dysfunction and the level of thyroid hormones, the level of pancreatic elastase in the stool, the level of calprotectin in the stool were determined.

In order to verify the diagnosis of ICD-10 patients, endoscopic examination was performed according to standard methods using fibrogastrosopes "Pentax FG-24P" and "Fuginon FG-12P" with the interpretation of changes in the mucous membrane of the

gastrointestinal tract according to the "Sydney system" (1990) with taking into account the peculiarities in children (Doletsky S.Ya., 1984) and targeted biopsy for morphological examination to determine the variant and activity of the inflammatory process, contamination of the mucous membrane by *H. pylori*.

Identification of *H. pylori* was performed by several methods: semi-quantitative assessment of seeding of the mucous membrane by *H. pylori* by the method of Aruin L.I. (1998); determination of CagA *H. pylori* antigen in feces by enzyme-linked immunosorbent assay; determination of specific immunoglobulins of M, A and G classes to CagA *H. pylori* antigen in blood serum.

The assessment of the risk of the event was carried out taking into account the probability of the values of relative risk (RR) and odds ratio of the event (OR) with the determination of their confidence intervals (95% CI). Clinically significant protective effect was considered an indicator at OR less than 0.8. Clinically significant risk factor was the value of the indicator with OR greater than 1.2. The strength of the associations was assessed by etiological (EF,  $RR \geq 1$ ) or preventive (PF,  $RR < 1$ ) fractions. Assessment of the diagnostic value of tests, risk indicators of events was carried out from the standpoint of clinical epidemiology [3].

**Research results and discussion.** Epidemiological studies of the structure of comorbid pathology of the digestive system in children have shown that the leading position belongs to functional dyspepsia with a predominance of changes in the intestine (irritable bowel syndrome) and biliary system (functional disorder of the sphincter of Oddi, biliary dyskinesia); second place is occupied by organic lesions of the gastroduodenal area (gastroduodenitis, ulcer disease); third - chronic diseases of the pancreas and liver.

On the basis of conducted researches with use of multifactor analysis and calculation of epidemiological indicators, the risk of development of comorbid pathology of digestive system organs in children was established.

Multifactor analysis of the risk of comorbid pathology of the digestive system is shown in table 1, the results of which can be displayed as a mathematical model of the risk of disease development:

$$\text{risk of comorbid pathology} = 0.27F1 + 0.43F2.$$

It is established that the first factor (73.7% of information) is caused by both non-modifying and modifying predictors: sex, age, burdened heredity in diseases of the gastrointestinal tract, especially in two pedigrees, unfavorable biological (peculiarities of antenatal and postnatal development of the child, analysis the nature of the mother's nutrition

during pregnancy and lactation, peculiarities in nutrition of the child under one year, the time of complementary foods introduction, the presence of acute infectious and non-infectious diseases, the nature of the child's nutrition (food composition, regularity and diet)) and positive genealogical history, nature and personality traits; the second factor (56.8% of information) was determined by modification predictors: the presence of *H. pylori* and premorbid pathology in the anamnesis, stress, vitamin D3 deficiency, iodine, endothelial dysfunction, disruptions of regional blood flow in the abdominal trunk.

**Table 1**

**Multifactor analysis of risk predictors of comorbid pathology of the digestive system organs in children**

Traits	Factor 1	p <sub>1</sub>	Factor 2	p <sub>2</sub>
Sex	0,512384	<0,05	-0,217634	>0,05
Age	-0,442123	<0,05	0,343546	>0,05
Conditionally favorable social history	0,234111	>0,05	0,354213	<0,05
Unfavorable social history	0,126735	>0,05	0,432181	<0,05
Conditionally favorable biological history	0,242178	>0,05	0,265436	>0,05
Unfavorable biological history	0,653217	<0,05	0,312274	>0,05
Conditionally favorable genealogical history	0,432155	<0,05	0,221243	>0,05
Unfavorable genealogical history	0,587322	<0,05	0,243322	>0,05
Burdened heredity of diseases of the gastrointestinal tract by one pedigree	0,445638	<0,05	0,272545	>0,05
Burdened heredity for diseases of the gastrointestinal tract by both pedigrees	0,743566	<0,05	0,298744	>0,05
Character and personality traits	0,445769	<0,05	0,287644	>0,05
Stress	0,112764	>0,05	0,612342	<0,05
Emotional lability	0,123329	>0,05	0,543288	<0,05
Disorders of regional blood flow in the abdominal trunk	0,142654	>0,05	0,532432	<0,05
Vitamin D3 deficiency	0,165438	>0,05	0,632544	<0,05
Endothelial dysfunction	0,123156	>0,05	0,587996	<0,05
Iodine deficiency	0,221432	>0,05	0,411273	<0,05
The presence of <i>H. pylori</i>	0,213456	>0,05	0,692234	<0,05
Premorbid background	0,111651	>0,05	0,697845	<0,05

The calculation of epidemiological indicators showed that the most etiologically determining risk factors for the development of comorbid pathology of the digestive system organs in children is an unfavorable genealogical history (OR=4.32 [2.42-7.68]) with hereditary burden on both maternal and paternal lines (OR=6.48 [[3,51-11,72]), *H. pylori* infection (OR=4,23 [0,18-11,32]), the presence of stressful situations (OR = 3,20 [1,01-10 , 28]), vitamin D3 deficiency (OR=3.21 [0.15-10.12]), age (OR=3.12 [1.08-6.14]) (Table 2).

It is established that the risk of developing comorbid pathology of the digestive system organs in children will increase by 4.27 ([0.31-10.49],  $\chi^2 = 13.24$ ,  $p < 0.01$ ) times in the presence of the child's determining non-modifying factors, by 2.62 ([0.52-6.36],  $\chi^2 = 8.46$ ,  $p < 0.01$ ) times under the influence of modification factors, which allows us to assess the non-modification component as a basis for further development of diseases under the influence of external factors.

**Table 2**

**Prognostic assessment of statistically significant predictors of risk of comorbid pathology of the digestive system organs in children**

Traits	RR, 95 % CI	OR, 95 % CI	df=1; $\chi^2$ / p
<i>Non-modifying predictors</i>			
Age	2,46 [1,12-5,84]	3,12[1,08-6,14]	8,97/0,0151
Sex	2,37 [0,18-6,39]	2,50 [0,20-7,97]	9,25/0,0121
Unfavorable genealogical history	1,73 [1,40-2,19]	4,32 [2,42-7,68]	28,98/0,0001
Burdened heredity of diseases of the gastrointestinal tract by one pedigree	1,94 [1,56-2,34]	4,93 [2,23-10,66]	11,99/0,0022
Burdened heredity for diseases of the gastrointestinal tract by both pedigrees	3,15 [0,34-7,28]	6,48 [3,51-11,72]	40,54/0,0001
<i>Modification predictors</i>			
Alimentary factor	1,34 [0,08-3,69]	1,56 [0,20-5,32]	4,78/0,024
Disruptions of regional blood flow in the abdominal trunk	1,26 [1,02-1,54]	1,89 [1,10-3,22]	5,80/0,0333
Stress	2,19 [0,08-5,17]	3,20 [1,01-10,28]	8,22/0,0192
The presence of <i>H. pylori</i>	2,58 [0,11-6,48]	4,23 [0,18-11,32]	11,86/0,0016
Vitamin D3 deficiency	2,31 [0,13-5,28]	3,21 [0,15-10,12]	8,93/0,0163
Endothelial dysfunction	1,56 [0,12-4,26]	2,75 [0,75-4,28]	4,25/0,041
Iodine deficiency	1,57 [0,13-4,28]	2,35 [1,03-6,19]	5,67/0,018
Premorbid background	1,28 [0,04-3,22]	1,74 [0,26-4,72]	4,35/0,038

Using the results of multifactor risk analysis as a mathematical model of comorbid pathology of the digestive system and indicators of epidemiological risks will allow us to form risk groups more accurately, identifying the most significant factors in the formation of disease in a particular child and to develop measures of individual primary prevention.

**Conclusion.** Determining the marker profile of comorbid pathology of the digestive system in children allows to establish a share of individual influence of each of the adverse

factors with the subsequent selection of leading predictors in a particular child and calculate the risk of comorbid pathology of the digestive system development.

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