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Casual Relationship between the GUT Microbiota Dysbiosis, Intestinal Motility, and Development of Protein-Energy Malnutrition in Patients in a Chronic Critical State after Severe Brain Damage

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Summary

Protein-energy malnutrition (PEM) remains one of the most pressing issues in patients with severe traumatic brain injury in intensive care units (ICUs), as it is highly prevalent, difficult to manage, and its causes are not fully understood.

The aim of the study was to assess the influence of gut microbial imbalance and gastrointestinal motility on the development of malnutrition in patients in a chronic critical state and severe brain damage.

Materials and methods. A single-center prospective observational study included 31 patients (median age 52 years; 68% males) aged 18–74 years with traumatic brain injury or stroke requiring ICU stay for more than 5 days and enteral tube feeding. Patients with diabetes mellitus, acute multiple organ failure (MOF), shock, implanted devices, or tracheoesophageal fistula were excluded. Nutritional status was assessed at baseline and on Day 20 using the Russian malnutrition scale and the Global Leadership Initiative on Malnutrition (GLIM) criteria. Additionally, clinical outcomes, anthropometric data, gastrointestinal biomarkers, gut microbiota composition, electrogastroenterography (EGEG) and functional scales parameters were recorded.

Results. Moderate and severe malnutrition according to the GLIM criteria was found at baseline in 29.1% of patients, and in 27.7% of patients on Day 20 ($P=0.9$), while according to the Russian scale these numbers were 61.3% and 78.6%, respectively ($P=0.8$). Dynamics of clinical scales, functional indicators, and gastrointestinal biomarkers during the follow-up revealed no clinically significant changes. Significant and persistent deviations 2 from reference values in gut microbiota composition (decrease in the content of *E. coli*, $P=0.026$; increase in *Enterobacter* spp., $P=0.020$) and EGEG parameters were recorded at both evaluation time-points. Identified PEM was also associated with impaired gastrointestinal motility.

Conclusion. The data indicate a statistically significant relationship between PEM, changes in the gut microbiota and gastrointestinal motility, which confirms the important role of these factors in PEM pathogenesis in patients with severe brain damage in a chronic critical state.

Keywords: protein-energy malnutrition; ICU; microbiota; electrogastography; stroke; traumatic brain injury

Conflict of interest. The authors declare no conflict of interest.

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Introduction

Severe brain damage, whether it is traumatic brain injury (TBI) or acute cerebrovascular accident (CVA), is a serious pathology that can cause severe neurological deficits and prolonged/chronic critical conditions, requiring long-term neurorehabilitation [1–3]. Protein-energy deficiency (or nutritional deficiency, or malnutrition — PEM) is a widespread and clinically significant complication in patients with severe TBI, associated with adverse outcomes and increased mortality [4, 5]. This is a multifactorial condition resulting from interaction of various pathogenetic factors that disrupt the regulation of metabolic processes [6]. Gut dysfunction in critical conditions is characterized by a series of pathological responses, including increased gut permeability syndrome, gut microbiota dysbiosis, and altered gastrointestinal tract (GIT) motility [7, 8].

The severity of the disease, high energy consumption, intense catabolism, and gastrointestinal dysfunction make enteral nutrition insufficient to achieve energy and substrate balance in such patients [9]. There is growing evidence that disruption of gut microbiota balance affects other organs and contributes to progression of critical diseases [10, 11]. We have earlier established the association between the neurological status of patients with severe brain damage and considerable alterations in the composition and metabolic activity of gut microbiota [12]. It has been shown that a disruption in the intestinal barrier function, manifested in increased intestinal permeability, is associated with a high risk of developing sepsis and multiple organ failure [13].

Gastrointestinal motility disorders are a common and significant complication in critically ill patients, leading to various adverse consequences interfering with recovery of vital functions [14]. Gastrointestinal motility dysfunction contributes to establishing PEM, therefore can be considered as a promising therapeutic target in patients with disrupted gut-brain axis, which is common in severe brain injuries [15]. Electrogastroenterography (EGEG) is a modern non-invasive diagnostic modality based on registration of gastrointestinal tract myoelectric activity. This modality allows for quantification of electrical activity, and demonstrates high efficiency in assessing neurological dysfunction [16–19]. Despite the available data, the relationship between various manifestations of intestinal failure syndrome and nutritional status requires further study. The aim of the study was to comprehensively assess gastrointestinal dysfunction and its relationship with the degree of malnutrition in patients in a chronic critical condition after severe brain damage.

Materials and Methods

The study outline. A single-center prospective observational clinical study was conducted. The study protocol was approved by the local ethics committee of the Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitation (No. 2/24/6 dated June 18, 2024) and registered on the ClinicalTrials.gov platform (NCT06545825). The study was initiated on September 9, 2024 as a pilot, exploratory, and observational, therefore no formal calculation of sample size or power was performed. The study was planned and designed in accordance with the principles of the Declaration of Helsinki [20]. The protocol was developed in accordance with the recommendations of SPIRIT 2013 [21]. The manuscript was prepared in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for reporting observational studies [20]. The STROBE checklist is presented in the supplementary table A1 (the supplementary materials for the article are published in Mendeley Data, doi: 10.17632/76hzzg54t7.1; https://data.mendeley.com/datasets/76hzzg54t7/1).

Selection criteria and study population. In the period from September to November 2024, all patients admitted to the Federal Scientific and Clinical Center for Resuscitation and Rehabilitation (FSCC RR) were screened for eligibility criteria. The inclusion criteria were: age between 18 and 74 years; presence of a traumatic brain injury or stroke; duration of stay in the intensive care unit exceeding 5 days at the time of screening (prolonged or chronic critical condition) [22]; and optionality of enteral nutrition.

All patients were transferred from other medical facilities and had previously received treatment in the ICU, including antibiotic therapy with one or more antimicrobial drugs.

The exclusion criteria included the following conditions: diabetes mellitus, acute kidney injury, acute liver failure or shock of any etiology; the presence of cardiac implantable electronic devices (CIEDs) or a neurostimulator, or a tracheoesophageal fistula. Patients who needed to maintain a positive end-expiratory pressure of more than 12 mBar were also excluded.

If all the eligibility criteria were met, a voluntary written informed consent was obtained from the participants, or, if this was not possible, the decision to include the patient was made by a medical council of the institution in accordance with regulatory requirements.

Data collection and outcomes. For each patient included in the study, an electronic individual registration form was completed based on a comprehensive clinical assessment. The collected data included demographic characteristics (age, gender, height, and body weight), medical history, informa-

tion about concomitant pathology and concomitant therapy, as well as hospital outcomes: mortality, need for mechanical ventilation (MV), duration of MV, use of vasoactive drugs, duration of enteral nutrition, and presence of specified complications.

Nutritional status was assessed on Day 0 (at inclusion), and on Day 20 according to the Global Leadership Initiative on Malnutrition (GLIM) criteria [23] and the national Russian malnutrition assessment scale (Supplementary Table A2). The risk of malnutrition was assessed using the Prognostic Nutritional Index (PNI), calculated as follows: [10 × serum albumin (g/dL)] + [0.005 × absolute lymphocyte count (in mm³)] [24].

On Days 0 and 20, vital signs and anthropometric data were recorded. The neurological and functional status was assessed using the modified Rankin Scale (mRS), the Barthel Index, and the Functional Independence Measure (FIM). Evaluated gut excretion biomarkers included nitrogen excretion, fecal zonulin concentration, and fecal α-1-antitrypsin. Also gut microbiota composition and electrogastroenterography (EGEG) parameters were examined.

Microbiota assessment. Fecal samples were collected in disposable sterile containers. The containers were immediately transported to the laboratory and frozen. Gut microbiota composition was analyzed using the real time PCR (qPCR) and the Kolonoflor-16 test systems (AlfaLab LLC, St. Petersburg, Russia) in accordance with the manufacturer's instructions. Composition of gut microflora was evaluated using the DT-prime amplifier (DNA Technology LLC, Moscow, Russia).

Electrogastroenterography. EGEG was performed on an empty stomach using the Gastroscan-GEM system (Istock-System JSC, Russia) with the Gastro-Scan software version 20.8. Spectral analysis included the coefficient of rhythm calculation (rate rhythm Kritm = peak frequency / dominant power), relative segmental power (P (i) / PS), and intersegmental propagation coefficient (P (i) / P (i+1)) [19, 25].

Statistical analysis. The data were processed statistically using the IBM SPSS Statistics program for Windows, version 29.0 (IBM Corp., Armonk, NY, USA). Quantitative (continuous) variables were summarized as the median and interquartile range (IQR), and categorical variables were presented as absolute values and percentages. The data distribution type was assessed using the Shapiro–Wilk test and histogram analysis.

Quantitative variables whose distribution did not follow a normal distribution were compared using the Mann–Whitney test. For paired quantitative data, the Wilcoxon paired rank test was used. Categorical variables were compared using the χ^2 test or the Fisher exact test (depending on the applicability conditions); for paired binary data, the McNemar test was used. The Spearman rank correlation coefficient was used for correlation analysis. All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

The Python programming language (version 3.10) and the Matplotlib (version 3.10) and Pandas (version 2.2.3) libraries were used for data visualization.

Results

Patients' characteristics. Between September and November 2024, 39 patients admitted to the ICU were examined for compliance with the inclusion criteria. Eight patients were excluded based on the exclusion criteria, therefore 31 patients (21 men) with a median age of 52 years (IQR 40; 68) were included into final analysis. The flowchart of patient selection is presented in Fig. 1.

The baseline demographic and clinical characteristics, including information on comorbidities, concomitant therapy, and outcomes related to ICU stay, are presented in Table 1. Nine patients were diagnosed with TBI, 21 patients presented with ischemic or hemorrhagic stroke, and 1 patient had a combination of TBI and stroke. Arterial hypertension was found in 22 patients (71%).

All patients required respiratory support (low- or high-flow oxygenation, or mechanical ventilation in various modes). All patients also continued on antimicrobial therapy, either prescribed earlier or modified. Patients' neurological status was characterized by varying degrees of impaired consciousness, cognitive and speech disorders, and severe dysphagia, which necessitated feeding through a nasogastric tube or gastrostomy.

During the follow-up period, one patient died, another was transferred to another medical facility before the study was completed. Twenty patients (65%) required mechanical ventilation, with a median duration of 17 days. Six patients (19%) received

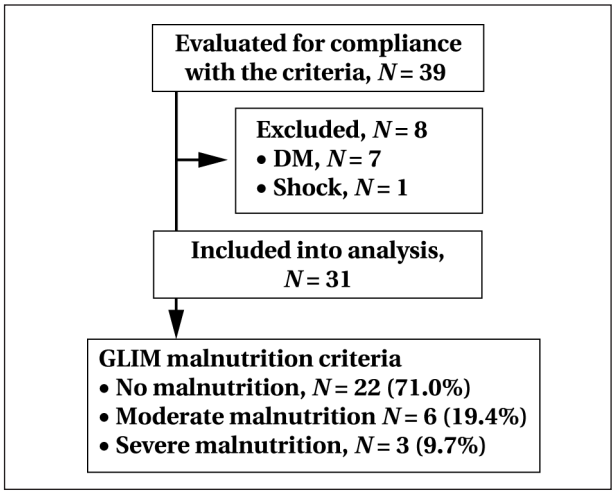

Fig. 1. The flowchart of patient selection for the study.

vasopressor or inotropic support. Seven patients (22.6%) developed sepsis according to the Sepsis-3 criteria, and eight patients (25.8%) developed multiple organ failure.

PEM characteristics within the follow-up. At baseline, the Russian scale of malnutrition assessment showed moderate and severe degree PEM in 19 patients (61.3%), and by Day 20, the proportion of such patients tended to increase (78.6%, $P=0.8$; Table 2).

Baseline assessment by the GLIM criteria identified moderate and severe malnutrition in 9 patients (29.1%). By Day 20, the overall proportion of patients with moderate and severe malnutrition did not significantly change (27.7%; $P=0.9$; Table 2).

Changes in anthropometric and clinical parameters. Anthropometric data did not change over time, except for a decrease in the mid-upper arm circumference (median: 24.5 cm vs. 23.3 cm; $P=0.004$, Table 2).

Clinical scales, including the mRS, Barthel Index, and FIM, also did not show any differences (Table 2). No statistically significant changes in nitrogen excretion and fecal α-1-antitrypsin concentration were observed during the observation period ($P=0.4$ and $P=0.9$, respectively). Despite the statistically significant deviation in fecal zonulin concentration to 11.5 ng/mL from a median value of 7,5 ng/ml ($P=0.028$), it remained within the reference range.

No statistically significant changes in colonic microbiota composition were detected (Fig. 2, Additional Table A3). However, there were significant deviations from the reference values in both assessments. More than 50% of patients had an increased titer of pathogenic bacteria, including *Klebsiella pneumoniae, Proteus vulgaris / mirabilis, Enterobacter* spp., and *Acinetobacter* spp. and an increase in the ratio of *Bacteroides* spp. / *Faecalibacterium prausnitzii*. A decrease in the content of «beneficial» bacteria, including *Lactobacillus* spp., *Bifidobacterium* spp., *Faecalibacterium prausnitzii, Blautia* spp., *Eubacterium rectale*, and *Roseburia inulinivorans* was documented in greater part of the cohort.

A significant proportion (more than 70% for some parameters) of patients showed significant deviations from the physiological reference values of the EGEG parameters in both assessments (Fig. 2, Additional Table A3). Most of them had gastrointestinal dyscoordination: increased absolute rhythmic activity in the upper parts (stomach, duodenum) against decreased activity in the lower parts (jejunum, ileum, colon). Simultaneously, noticeable changes in the stomach and duodenum, ileum, and colon contractile patterns were revealed. Over time, these parameters tended to normalize.

PEM associated changes. A comparative analysis of patients with normal nutritional status and patients with moderate and severe protein-energy malnutrition according to the GLIM criteria showed statistically significantly lower values of anthropometric parameters in patients with PEM, including BMI and the triceps skinfold thickness on Day 20 ($P=0.006$ and $P=0.015$, respectively). In ad-

Table 1. Patients' baseline characteristics, clinical features, concomitant therapies and clinical outcomes.

Parameter	Values
Total number of patients	$N=31$
Gender	
M	21 (68%)
F	10 (32%)
Age, years	52 (IQR 40; 68)
BMI, kg/m²	26.0 (IQR 21.6; 29.4)
Occurrence rates of various pathologies on admission	
Stroke	22 (71.0%)
Arterial hypertension	22 (71.0%)
Traumatic brain injury	10 (32.3%)
Pleural effusion	5 (16.1%)
Sepsis	4 (12.9%)
Congestive heart failure (NYHA II, III, IV)	3 (9.7%)
Atrial fibrillation	2 (6.5%)
Myocardial infarction	2 (6.5%)
Chronic kidney disease (stage C3b)	1 (3.2%)
Renal replacement therapy	1 (3.2%)
Drug use for concomitant therapy	
Anticoagulants	27 (87.1%)
Antibacterial drugs	22 (71.0%)
Beta blockers	18 (58.0%)
ACE inhibitors/ARBs	16 (51.6%)
Diuretics	13 (41.9%)
Statins	11 (35.5%)
Calcium channel blockers	7 (22.6%)
Antiplatelet agents	5 (16.1%)
Antiemetics	3 (9.7%)
Alpha blockers	2 (6.5%)
Antiarrhythmic drugs	1 (3.2%)
Antifungal agents	1 (3.2%)
Outcomes	
Mortality	1 (3.2%)
Use of mechanical ventilation	20 (64.5%)
Duration of mechanical ventilation, days	17.0 (IQR 5.5; 18.0), $N=20$ (64.5%)
Use of vasopressors / inotropes	6 (19.4%)
Duration of use of vasopressors / inotropes, days	3.5 (IQR 2.0; 12.0), $N=6$ (19.4%)
Duration of enteral nutrition, days	18 (IQR 17; 20), $N=31$ (100%)
MOF syndrome	8 (25.8%)
Sepsis	7 (22.6%)
Arrythmia	2 (6.5%)
Acute kidney injury	2 (6.5%)
Renal replacement therapy	2 (6.5%)
Bleeding	1 (3.2%)
Respiratory failure	1 (3.2%)
DVT	1 (3.2%)
Nonfatal cardiac arrest	1 (3.2%)
Seizures	1 (3.2%)
Stroke	0
MI	0

Note. ACE — angiotensin-converting enzyme; ARB — angiotensin II receptor blocker; BMI — body mass index; ICU — intensive care unit; IQR — interquartile range; MOF- multiple organ failure; DVT — deep vein thrombosis; MI — myocardial infarction; MV — mechanic ventilation; NYHA — New York Heart Association.

Table 2. Dynamics of clinical, nutritional indicators, and biomarkers of the gastrointestinal tract.

Parameters	Parameter values		*P**
	Day 0, *N*=31	Day 20, *N*=29	
PEM degree			
GLIM	No: 22 (71.0%) Moderate: 6 (19.4%) Severe: 3 (9.7%)	No: 21 (72.4%) Moderate: 5 (17.4%) Severe: 3 (10.3%)	0.9
Russian PEM Scale	Mild: 12 (38.7%) Moderate: 16 (51.6%) Severe: 3 (9.7%)	Mild: 6 (21.4%) Moderate: 21 (75.0%) Severe: 1 (3.6%)	0.8
PNI	37.8 (30.6; 42.0)	36.0 (28.2; 40.4)	0.4
Clinical and anthropometric parameters			
Heart rate (beats/min)	83 (75; 94)	80 (74; 90)	
Body temperature (°C)	36.6 (36.5; 36.8)	36.6 (36.5; 36.8)	0.6
Height (cm)	171 (170; 178)	171 (170; 176)	0.9
Body weight (kg)	75.0 (67.5; 87.0)	75.0 (63.5; 80.0)	0.3
BMI, kg/m²	26.0 (21.6; 29.4)	25.1 (21.3; 27.5)	0.3
Mid-upper arm circumference (cm)	27.5 (25.4; 29.3)	26.5 (23.7; 28.6)	0.07
Triceps skinfold thickness (mm)	9.0 (7.0; 12.0)	10.0 (8.0; 11.5)	0.7
Upper arm muscle circumference (cm)	24.5 (22.6; 25.6)	23.2 (20.3; 24.6)	0.004
Scale scores			
Modified Rankine scale	5 (5; 5)	5 (5; 5)	0.9
The Bartel Index	0 (0; 0) from 0 to 20	0 (0; 0) from 0 to75	0.3
FIM	19 (19; 19)	19 (19; 19)	0.1
Nitrogen excretion rate and gastrointestinal biomarkers			
Nitrogen excretion (g/day)	*N*=27, 8.8 (4.6; 12.3)	*N*=27, 8.7 (3.9; 12.8)	0.4
Fecal zonulin (ng/ml) reference: 0–83.15	*N*=23, 7.5 (4.5; 13.3)	*N*=23, 11.5 (6.5; 36.2)	0.028
Fecal α-1-antitrypsin (mg/L) reference: < 250 (neg.)	*N*=23, 17.3 (8.6; 80.9)	*N*=23, 25.1 (15.1; 74.4)	0.9

Note. PEM — protein-energy malnutrition; GLIM — Global Leadership Initiative on Malnutrition; PNI — prognostic nutritional index; BMI — body mass index; FIM — Functional Independence Measure; ICU — intensive care unit. * — McNemar test, Wilcoxon paired rank test.

dition, patients with PEM had lower mid-upper arm circumference and upper arm muscle circumference at the follow-up (Supplementary Table A4).

There were also no significant differences in clinical scale scores, biomarkers of gut excretion, or hospital outcomes. However, the presence of PEM was associated with significant changes in the composition of the colonic microbiota by Day 20. In particular, patients with PEM had lower *Escherichia coli* titers (P=0.026) and higher *Enterobacter* spp. titers (P=0.020).

By Day 20, patients with moderate and severe protein-energy malnutrition had higher motor activity in the duodenum and jejunum relative to overall motor activity (P (i) / PS (%) for the duodenum — P=0.003, for the jejunum — P=0.006), than patients without PEM. An increase in the P (i) / P (i+1) ratio for the jejunum and ileum (P=0.019) and a decrease in the P (i)/P (i+1) ratio for the stomach and duodenum (P=0.011) were also documented (Supplementary Table A4, Fig. 3).

By means of correlation analysis, several statistically significant relationships between PNI, gut microbiota composition and EGEG parameters were revealed. On Day 0, a moderate inverse correlation between PNI and *Klebsiella pneumoniae* titer (Spearman coefficient R=–0.50, P<0.001) was established, as well as PNI and *Acinetobacter* spp. titer (R=–0.40, P=0.001). Additionally, a moderate inverse correlation was established between individual EGEG parameters and the titer of several microorganisms (additional Figures A1–A2).

Discussion

Moderate or severe nutritional status disorders were detected in approximately one-third of patients with severe TBI/ischemic stroke. During the follow-up, marked deviations in the gut microbiota composition and EGEG parameters from reference microbiome profile were defined, while biochemical markers of intestinal permeability (zonulin and alpha-1-antitrypsin) remained within the normal range. It can be reasoned that PEM was associated with significant dyscoordination in GIT function and substantial changes in gut microbiota composition (decreased *E. coli* titer, P=0.026; increased *Enterobacter* spp., P=0.020).

The results of previous studies indicate that the incidence of PEM in patients with severe brain damage ranges from 6.1% to 62% [26]. PEM etiology is influenced by a variety of factors, but its underlying causes remain poorly understood [27]. It has been established that protein metabolism is the most vulnerable component of nutritional status in patients in chronic critical conditions [9]. Some reports indicate that the fact of brain damage is a sta-

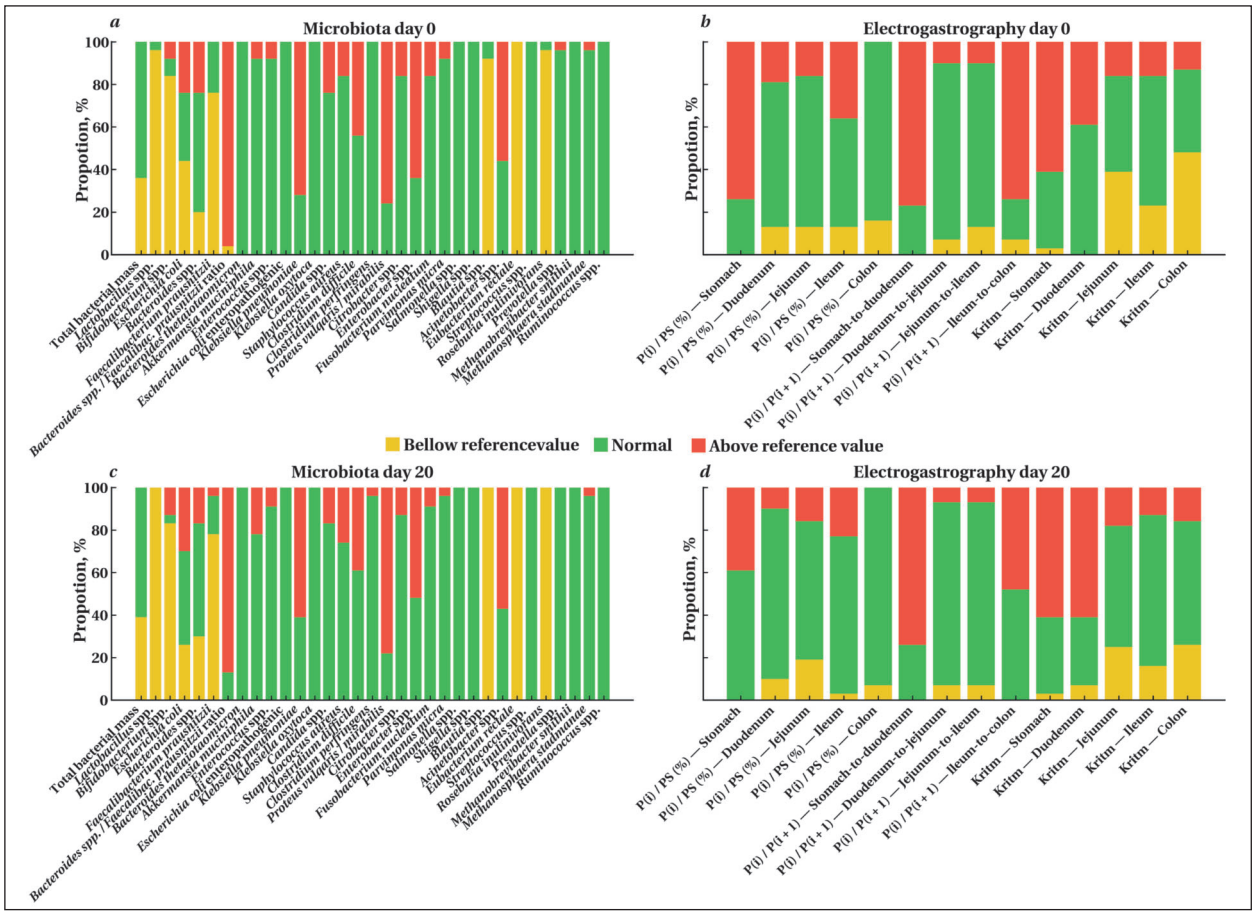

Fig. 2. Composition of gut microbiota determined by qPCR and parameters of electrogastroenterography at baseline — Day 0 (*a, b*), and on Day 20 (*c, d*), presented in comparison with reference values.

tistically significant factor of increased risk of sarcopenia and malnutrition [28, 29]. An increase of small intestine permeability persisting for up to 28 days was reported in mice with modelled TBI, in contrast to controls [30]. In this study, no increase in intestinal permeability was found among examined patients: the concentrations of fecal zonulin and alpha-1-antitrypsin remained within the reference values. There were some reports indicating an increase in zonulin concentration in patients in critical conditions developing sepsis [31, 32]. However, extreme reduction of zonulin activity may signify an attempt to compensate for the loss of intestinal barrier integrity, as shown, for example, in children in the postoperative period [33].

Abnormal chyme transit could be another cause of malnutrition. We suggest that PEM in patients in chronic critical condition may also be associated with uncoordinated gastrointestinal motility. The gut microbiota plays the key role in maintaining homeostasis [34], and severe brain damage may critically affect this principal function leading to inevitable complications.

Intestinal dysbiosis can be a consequence of poor nutrition in the ICU. In particular, K. Shimizu et al. demonstrated a significant decrease in the total titer of obligate anaerobes, including *Bacteroidaceae* and *Bifidobacterium*, and increase in the titer of staphylococci in patients having challenges with enteral nutrition [35]. Eventually this study demonstrated improvement in GIT function, reducing diarrhea episodes after replacement of enteral mixture with natural food through a gastrostomy. Logical to suggest, that this improvement could be associated with modification in gut microbiota composition [36].

A PCR-based testing was used in this study for rapid assessment of the amount of clinically relevant microorganisms in gut microbiota. The results obtained are consistent with findings in patients with severe TBI [37–39], including an increase in the titer of *Enterobacteraceae* and a decrease in saprophytes. Patients with PEM had a lower titer of *Escherichia coli* and a higher titer of *Enterobacter* spp. A decrease in the titer of *E. coli* (a typical representative of healthy microbiota) and an increase in the titer of opportunistic *Enterobacter* spp. indicate an imbalance in the microbiota, supporting the hypothesis that PEM is associated with severe dysbiosis. *E. coli* plays an important role in synthesis of vitamins (K, B12) and fermentation of fiber [40]. A deficiency of these bacteria can exacerbate mal-

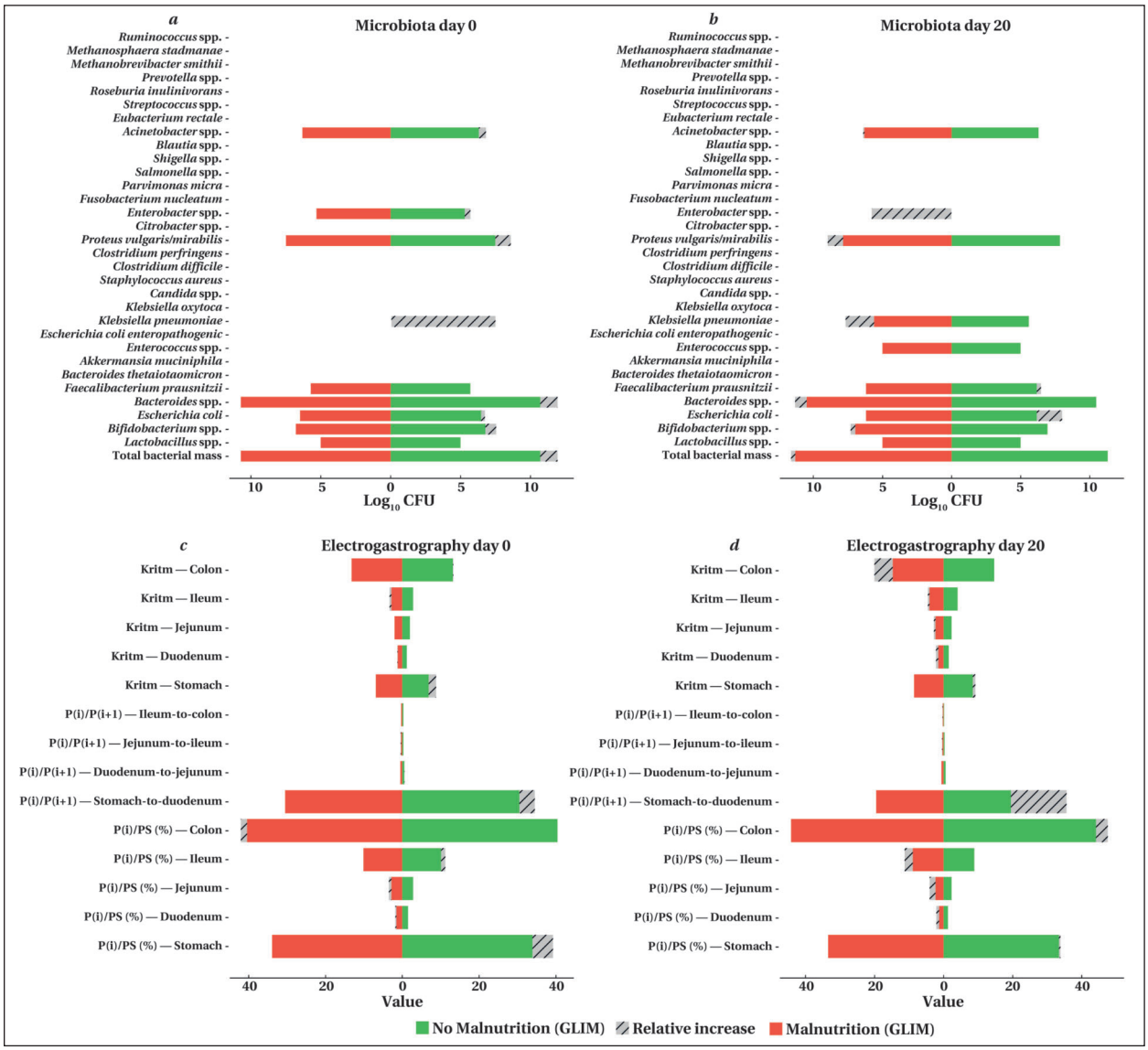

Fig. 3. Comparative analysis of gut microbiota composition (q PCR) and the parameters of electrogastroenterography at baseline, Day 0 (*a, c*) and on Day 20 (*b, d*) in patients stratified by nutritional status according to the GLIM criteria. Median values are presented.

absorption disorders, forming a vicious circle in PEM. This necessitates personalized treatment, including correction of microbiota (probiotics, prebiotics) and simultaneous nutritional support to restore metabolic and immune processes.

Of particular interest are the identified correlations between the titers of individual microorganisms and EGEG parameters. Modified GIT transit time — through the entire length and through individual segments, has a major impact on gut microbiota composition [41]. Reciprocally, the gut microbiota acts co-dependently and regulates microbial colonization of the gut ecosystem by influencing GIT motility [42]. We have identified not only a decrease in peristaltic activity, but also a significant imbalance in intestinal motility, which can also disrupt the growth of the intestinal microflora. However, the detailed mechanisms of this complex regulatory system remain insufficiently studied, especially in critically ill patients, which requires additional research.

We have identified a statistically significant association between PEM development and gut microbiota dysbiosis in combination with GIT motor dysfunction in patients in a chronic critical condition after traumatic brain injury and stroke. A comprehensive therapy in accordance with the approved treatment protocols aimed at improving patients' nutritional status did not bring statistically significant improvement of variables characterizing gut microbiota and intestinal motility. Proven high prognostic significance of PEM in development of adverse clinical outcomes [5] stimulates the search for and implementation of innovative technologies for correcting intestinal dysfunction in clinical practice.

Study limitations. As the sample size was not calculated, it may limit the statistical power to detect clinically significant differences. The single-center observational design does not allow for the generalization of the results to other patient populations and clinical conditions, nor does it establish the nature of causal relationship between GIT dysfunction and development of PEM. Additionally, the incomplete assessment of metabolic processes and gut microbiota composition due to the lack of metagenomic sequencing should be considered. Addressing this methodological gap and conducting multicenter clinical trials will complement the interpretation of results and expand our understanding of the processes been studied.

Conclusion

Development of malnutrition in patients with severe brain damage is associated with both severe gut microbiota dysbiosis and impaired gastrointestinal motility. Specific identifiable changes in gut microbiota included a decrease in *E. coli* and other beneficial microorganisms titers (*Lactobacillus, Bifidobacterium*), an increase in the titer of opportunistic pathogens (*Enterobacter* spp., *Klebsiella*, *Proteus, Acinetobacter*), as well as untoward shifts in the ratio of *Bacteroides* spp. / *Faecalibacterium prausnitzi*. These results emphasize the relevance of considering the state of gut microbiota and GIT motor function when providing nutritional support in intensive care.

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