Biochemical and Anthropometric Nutritional Assessment in Children Infected with COVID-19: A Cross-sectional Study

Hoda Atef Abdelsattar Ibrahim1*, Eatemat Helmy2, Aya Amin3, Dina Mahmoud4

1Pediatric Clinical Nutrition Unit, Department of Pediatrics, Faculty of Medicine, Cairo University, Cairo, Egypt; 2Department of Pediatrics, El-Matria Teaching Hospital, General Organization for Teaching Hospitals and Institutes, Cairo, Egypt; 3Department of Cancer Epidemiology and Biostatistics, National Cancer Institute, Cairo University, Cairo, Egypt; 4Department of Clinical Pathology, Faculty of Medicine, Cairo University, Cairo, Egypt

Abstract

BACKGROUND: Severe acute respiratory syndrome coronavirus 2019 (COVID-19) has led to a pandemic of coronavirus disease 2019 (COVID-19). Malnutrition either biochemically or anthropometrically is a well-known risk factor for COVID-19 and may be the vice versa.

AIM: The objectives of this study were to investigate the prevalence of malnutrition in children infected with COVID-19 through evaluating the nutritional biomarkers such as serum electrolytes, serum albumin, and hemoglobin together with the anthropometric assessment.

METHODS: A cross-sectional study that was conducted at El-Matria Teaching Hospital for all children admitted with confirmed COVID-19 for 6 months from February 1, 2021 to the end of July, 2021. Nutritional biochemical evaluation included serum electrolytes particularly the potassium and other nutritional biomarkers such as serum albumin and hemoglobin. Nutritional anthropometric evaluation depended on body mass index, the height/length, weight for age, weight for height, and weight for height. The prevalence of malnutrition esp. hypokalemia was the main outcome.

RESULTS: Hypokalemia was present in 21.8% of the study participants. Other nutritional biomarkers were found as hyponatremia, hypocalcemia, hypophosphatemia, and hypomagnesemia were detected in 49.1%, 38.2%, 21.8%, and 34.5% of the study subjects, respectively. Anthropometric malnutrition was present in most of the enrolled children with COVID-19 in the study (65.5 % [n = 36]) through which overweight and obese children occupied a greater percentage.

CONCLUSION: Malnutrition either biochemically or anthropometrically could be linked to COVID-19 in children. COVID-19 could have negative outcomes on the nutritional status such as electrolytes disturbances. Both malnutrition and COVID-19 are considered synergistic associations.

Introduction

The novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is resulting in a current worldwide pandemic of coronavirus disease 2019 (COVID-19). It has become a globe health problem and disturbed the main health determinants [1], [2], [3]. Nutritional status has been utilized as resilience toward the destabilization during the COVID-19 pandemic. Optimal nutrition can improve the immune system; thus, a sustainable approach to survive in the current context is to reinforce the immune system [4], [5].

Malnourished children are among the reported patients with worst outcomes and higher morbidities and mortalities during COVID-19 pandemic. Diagnosis, prevention, and treatment of malnutrition should therefore be routinely involved in the management of children with COVID-19 to improve the short and long-term prognoses [6], [7], [8], [9].

Childhood malnutrition is recognized to be a worldwide concern as it is problematical with poor growth and declined educational outcomes of children and can have undesirable effects during the adulthood [10], [11]. It is among the most serious health matters facing the developing countries especially Egypt. Malnutrition does not only affect the health status of children, but it also affects the economic growth as described by a former study, in which a robust statistically significant negative association between the economic growth and outcomes of child malnutrition, namely, underweight, wasting, and stunting in Egypt for 1992–2008 was found [12]. In children, the most serious risks resulted from COVID-19 crisis are not those of the COVID-19 itself, but its associated damages. These can include insufficient nutrition statuses with a risk of both underweight and overweight [13].

Particularly, COVID-19 can be associated with vomiting and diarrhea affecting the child’s food intake and absorption [14]; therefore, a good nutritional status is a healthy benefit for children at risks for severe COVID-19.
In a recent review about potential interventions for pandemics, authors recommended that the nutritional status of infected patients should be assessed before management with the general treatments [15].

Malnutrition states excess, deficiencies, or imbalances in a child’s intake of energy and/or nutrients. Malnutrition includes three main groups. First group is the undernutrition group that addresses wasting, stunting, and underweight. Second group is the micronutrient-related malnutrition group that addresses the micronutrient deficiencies (a lack of important minerals or vitamins) or micronutrient excess. Third group is the overweight and obesity group [16]. A deficiency of micronutrients can lead to weakened immune responses resulting in an improper cytokines release, alterations in the secretory antibody response, and the antibody affinity. Micronutrients deficiency can be treated by proper nutritional supplements, prescribed after assessing the child’ nutritional status [17].

One of the major micronutrients affected is the potassium electrolyte. Correction of hypokalemia is a challenge due to the continuous potassium loss from kidneys that results from the degradation of angiotensin-converting enzyme 2 (ACE2). The high prevalence of hypokalemia among children with COVID-19 proposes the presence of disordered activity of the rennin-angiotensin system that increases as a result of diminished counteractivity of ACE2 that is bound by SARS-CoV-2 [18].

The European Society for Clinical Nutrition and Metabolism has set recommended guidelines aiming at providing experts statements and applied recommendations for the nutritional management of COVID-19 patients. One of these recommendations states that identification of malnutrition risks should be an initial step in the general evaluation of all COVID-19 patients considering that obesity should be screened and investigated as it is a great comorbidity [6].

There are hypothesized links between obesity and the COVID-19 existence. It is well-recognized that dysbiosis has a strong association with the development of obesity and metabolic syndrome. Dysbiosis is characterized by the low diversity of microbes including a low abundance of Bifidobacterium spp., Lactobacillus spp., and Faecalibacterium prausnitzii. Consequently, children experiencing these disorders are much more prone to COVID-19 infections, primarily due to the existing disturbances within their gut microbiota [19]. An extended link is the link of dysbiosis to the malnutrition. To illustrate, altered bacterial interactions – seen in dysbiosis – can result in reduced productions of several essential amino acids with further development of malnutrition [20].

The objective of our study was to assess the pattern of malnutrition focusing on the potassium and body mass index (BMI), respectively. Besides, addressing the prevalence of malnutrition in these children was another objective.

Methods

The current study design

This study was a cross-sectional analytical study.

Criteria of the infected children in the study

Inclusion criteria

Admitted children within the first 2 days in El-Matria Teaching Hospital along a period of 6 months—both males and females—with confirmed COVID-19, and whose parents or legal guardians approved to be enrolled in the study.

Exclusion criteria

Children who were not confirmed to be COVID-19 and whose parents or caregivers did not approve to be enrolled in the study. In addition, admitted children with periods of admission which was more than 2 days were excluded to avoid bias that could be produced from the adverse outcomes of hospitalization as the child may become malnourished during the hospital stay due to a poor appetite.

Sample technique

A convenient sample of all pediatrics with COVID-19 (n = 55) who were admitted at El-Matria Teaching hospital was recruited for the current study along the study period.

Sample size estimation

The primary objective of the present study was to detect the prevalence of biochemical disturbances in COVID-19 children, especially hypokalemia which is one of the major and most serious complications of COVID-19. De Carvalho et al. reported that hypokalemia was found in 15.1% COVID-19 patients [21]. Using Epi Info™ software [22], and by setting an acceptable margin of error of ±0.10 and confidence level of 95%, the minimum required that sample size for the present study was 49 patients.
Operational definitions

1. Biochemical nutritional levels: Definitions of normal, deficiency, and excess were identified using the reference ranges that differ according to the age and sex.
2. Anthropometric nutritional assessment using the World Health Organization (WHO) charts:
   A. Overweight: When the weight for the length and the weight for the height in birth to 2 years and 2–5 years, respectively, is $>\text{the mean by two standard deviations (SDs)}$ of the WHO Child Standards for growth or BMI z score is $>1 \text{SD of the WHO Child Standards for BMI 5–19 years charts}$.
   B. Obesity: When the weight for the length and the weight for the height in birth to 2 years and 2–5 years, respectively, is $>\text{the mean by three SDs of the WHO Child Standards for growth or BMI z score is } >2 \text{SD of the WHO Child Standards for BMI 5–19 years charts}$.
   C. Wasting: When the weight for the length and the weight for the height in birth to 2 years and 2–5 years, respectively, is $<\text{the mean by two SDs of the WHO Child Standards for growth or BMI z score is } <2 \text{SD of the WHO Child Standards for BMI 5–19 years charts}$.
   D. Underweight: When the weight for age is $<\text{the mean by two SD of the WHO Child Standards for growth}$.
      • WHO recommends BMI as the best indicator or measure after the age 10 as the age of puberty is variable. Tracking the weight alone is not recommended. Underweight and wasting among the adolescents (10–19 year) are defined as a BMI-for age $\leq 2 \text{Z-scores of a reference}$.
      • Weight-for-age represents body weight relative to the child’s age. This indicator addresses whether a child is underweight or severely underweight, but it is not used to address a child as overweight or obese [23].
   E. Stunting: When the length/height for age is $<\text{the mean by two SDs of the WHO Child Standards for growth}$.
3. Confirmation of the diagnosis of COVID-19 was done by a positive reverse transcription-PCR (RT-PCR) targeting the different genes of COVID-19 on nasopharyngeal swabs.

Ethical statement

The study was revised and approved by the Scientific Ethical Research Committee of General Organization for Teaching Hospitals and Institute (GOTHI), ethical clearance number HM000139, and the study was done in accordance with the lows for the human research. An informed consent was obtained.

Statistical methods

Statistical calculations were conducted by means of SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 25. Quantitative data were tested for normality through exploring the variable histogram, Q-Q plots, mean, median, SDs, coefficient of variation, and skewness as well as performing the normality tests (Kolmogorov–Smirnov and Shapiro–Wilk tests). Normally distributed numerical variables were described in terms of mean, SD, and range. Non-normally distributed quantitative variables were statistically described as median, interquartile range, and range. Categorical variables were summarized as numbers and percentages.

Efforts to address and avoid potential sources of bias

1. This study was carried out on the admitted children in the first one or 2 days to avoid the impact of the prolonged hospital stay due to the possible malnutrition or weight loss that could occur due to the possible appetite loss.
2. Pediatrics with associated chronic illnesses were excluded as they might have additional external reasons for malnutrition due to the chronic disease effect.

Results

Fifty-five children were enrolled. Regards the demographic criteria, male patients represented 52.7 % of the study group (n=29). Female patients represented 47.3 % of the study group (n=26). Male-to-female ratio was 1.1:1 (Table 1).

| Characteristic         | Number (n = 55) | Percent |
|------------------------|-----------------|---------|
| Age groups (years)     |                 |         |
| <2                     | 28              | 50.9    |
| 2–<6                   | 13              | 23.6    |
| 6–13                   | 14              | 25.5    |
| Median (IQR)*          | 1.5 (0.5–6)     |         |
| Range                  | 0.1–13          |         |
| Gender                 |                 |         |
| Male                   | 29              | 52.7    |
| Female                 | 26              | 47.3    |
| Male: Female ratio     | 1.1             |         |

Malnutrition was evaluated in the enrolled children. Biochemical nutritional assessment was dependent on the electrolytes levels (Table 2). Moreover, other biochemical nutritional evaluations included serum albumin (Table 3) and hemoglobin (Table 4).

Hypokalemia was observed in 21.8% (n = 12), while hyperkalemia was observed in 5.5% (n = 3) of the study groups. About 72.2% of the study participants (n = 40) had normal serum potassium. Other electrolytes
observed were sodium, calcium, magnesium, and phosphorus.

| Electrolytes | Number (n = 55) | Percent | 95% CI** |
|--------------|-----------------|---------|---------|
| Na           | 27              | 49.1    | 35.4–62.9 |
| Normal Na level | 29          | 52.7    | 39.2–66.5 |
| Hypokalemia  | 12              | 21.8    | 11.5–35.0 |
| Mean ± SD    | 11.1–0.8       | 1.1–1.2 |         |
| Range        | 2.3–5.8        |         |         |
| Mg           | 19              | 34.5    | 22.2–48.3 |
| Normal Mg level | 31          | 56.4    | 48.2–65.8 |
| Hypomagnesemia | 5           | 9.1     | 3.0–20.8  |
| Mean ± SD    | 1.8±0.3        | 1.8–1.9 |         |
| Range        | 1.4–2.5        |         |         |
| PO4          | 12              | 21.8    | 11.8–35.0 |
| Normal PO4 level | 43         | 78.2    | 65.0–88.2 |
| Hypophosphatemia | 4            | 7.3     | 4.5–10.0  |
| Mean ± SD    | 4.8±0.8        | 4.5–10  |         |
| Range        | 3.6–6.8        |         |         |

*SD: Standard deviation, **95% CI: Confidence interval.

Hypokalemia was detected in 49.1% (n = 27), while hyperkalemia was observed in 3.6% (n = 2) of the study groups. About 47.3% of the children in the study (n = 26) had normal serum sodium. As regards the calcium level, most of the enrolled pediatrics with COVID-19 (61.8% of the study participants [n = 34]) had normal serum calcium. Only 38.2% (n = 21) of the study participants had hypocalcaemia.

Levels of magnesium in the serum were also noticed. Hypomagnesemia was observed in 34.5% (n = 19), while hypermagnesemia was observed in 9.1% (n = 5) of the study groups. About 56.4% of the study participants (n = 31) had normal serum magnesium.

As serum albumin is an important nutritional biomarker, it was included in the evaluation. Interestingly, it was affected in most of the cases. Hypoalbuminemia was present in 74.5 % of the study groups. (n = 41). Only 25.5 % (n = 14) of the enrolled children had normal serum albumin.

Table 4: Anemia in children with COVID-19

| HB level | Number (n = 55) | Percent | 95% CI** |
|----------|-----------------|---------|---------|
| Anemia   | 43              | 78.2    | 66.0–88.2 |
| Normal HB level | 12         | 21.8    | 11.8–35.0 |
| Mean ± SD | 11.0±1.6    | 10.6–11.4 |         |
| Range    | 6.4–15.4       |         |         |

*SD: Standard deviation, **95% CI: Confidence interval.

Another affected electrolyte in the course of COVID-19 infection was the phosphorus. To illustrate, hypophosphatemia was observed in 21.8% (n = 12) in the infected children. However, 78.2% of the study participants (n = 43) had normal serum phosphorus.

Discussion

Balanced nutritional status during the course of any illness is important for improving the health outcomes [24], [25]. Indeed, malnutrition is a great burden in Egypt with a considerable prevalence of short stature, underweight, overweight, and obesity [26]. However, our study did not only include malnourished children, but it also included the healthy ones. This helps address the role of the nutritional status in the course of COVID-19 infection. Therefore, bias that can develop from the prevalence of malnutrition in Egypt that can result in expressing the malnutrition rate in it as the malnutrition rate in our study can be slightly avoided. Moreover, the estimated prevalence of malnutrition in Egypt is much lower than the estimated prevalence of malnutrition in our study addressing the impact of COVID-19 on the nutritional state in the present study [26]. In addition, our study enrolled the biochemical nutritional assessment, not only the anthropometric one.

Male patients occupied the higher percentage in our study. This finding agrees with a previous study,
in which it was found that, of the 48 pediatrics admitted with COVID-19, 25 (52%) were male [27]. This gender factor, besides the higher incidences in males for most of the diseases, might correlate with a shorter life expectancy in males – which is a general demographic fact – compared to females in the world [28], [29]. Another hypothesis of this gender difference is that males are more vulnerable to infections, whereas females have a stronger antigenic response to infections and vaccines at the cost of the higher prevalence of autoimmune diseases [30].

Malnutrition was present in a greater percent in our study. This finding was consistent with the results of one previous study, which indicated that malnourished patients or patients at risks of malnutrition are at a risk of acquiring COVID-19 [24]. Significantly, regions with an increased burden of malnutrition have a greater risk of acquiring COVID-19 as stated in a former study. That study showed increased risks of fatal COVID-19 at populations with increased indicators of malnutrition [31]. Malnutrition can result in immunosuppression – which further enhances acquiring COVID-19 – through different means, including the contribution of leptin and the hypothalamic-pituitary-adrenal axis. Malnutrition decreases leptin concentrations and rises serum levels of stress hormones, that is, glucocorticoids. Therefore, it is likely that the hypothalamic-pituitary-adrenal axis occupies a crucial role in malnutrition-related immune deficiency [32].

Children infected with COVID-19 are at greater risks for fluid and electrolyte disturbances and complications. This was figured by a former article, in which hyponatremia, hypokalemia, and hypocalcemia were the most common electrolytes disorders detected in COVID-19 patients [33].

Hypokalemia was an electrolyte disorder in a considerable percentage of children with COVID-19 in our study. In contrast to the general people, COVID-19 children can experience three risk factors for hypokalemia. First, respiratory alkalosis due to the hypoxia-driven hyperventilation that can stimulate transcellular shifts with augmented intracellular uptakes. Second, anorexia, as a result of continuative use of face masks can result in a decrease in the potassium intake. Third, diarrhea due to the cytopathic effect of COVID-19 on the gastrointestinal cells may be a recurrent cause of potassium losses from the gastrointestinal tract [34].

Another investigated cause of hypokalemia is through the angiotensin system. To illustrate, the virus invades the cells through the ACE2 on the membrane. Angiotensin converting enzyme 2 is the main counter-regulatory mechanism for the key axis of the rennin angiotensin system (RAS) that is important in the control of the blood pressure and electrolyte balance. COVID-19 binds ACE2 and augments the degradation of ACE2 and, so, decreases the counteraction of ACE2 on RAS. This results in increasing the reabsorption of sodium and water, thus increasing blood pressure and excretion of potassium that leads to hypokalemia [18].

Interestingly, there was a considerable percentage of hyperkalemia in our study. Furin has a role in this disorder. To explain, furin is required for cleaving both COVID-19 spike protein and epithelial sodium channels (ENaC) subunits. As the furin is hijacked by COVID-19, the reduced activity of ENaC would be anticipated, that causes retention of potassium ions with subsequent hyperkalemia [35].

From the perspective that the occurrence of hypokalemia is greater than hyperkalemia in COVID-19 children in our study, it seems that mechanisms of hypokalemia predominated.

Hyponatremia occupied the higher percentage of the sodium imbalance in the present study. This result is similar to the result of another study, in which it was found that sodium imbalance disorders, particularly hyponatremia, are a common abnormality among COVID-19 patients [36]. The pathophysiological mechanisms of hyponatremia in COVID-19 patients are different, including syndrome of inappropriate antidiuretic hormone secretion, gastrointestinal loss of sodium ions, or lowered sodium ion intakes. Hyponatremia may also be a negative predictive factor in COVID-19 patients [37].

A small percentage of the study group had hypernatremia. This is probably due to the increased angiotensin II activity secondary to the SARS-CoV-2-induced downregulation of ACE2 receptors as stated by a previous study [38].

In the context of higher percentage of hyponatremia encountered in the study, it appears that the mechanisms of hyponatremia overcame those of hypernatremia in the enrolled children.

Magnesium has a strong link to the immune system and the immunological functions are disturbed in case of magnesium deficiency. It has been reported that free basal magnesium concentration has an essential role in regulating the cytotoxic immune function. By that, intracellular free magnesium concentration contributes considerably to the antiviral immunity. Therefore, decreased resistance against infection with COVID-19 in case of magnesium deficiency can be assumed [39]. This may be the cause why hypomagnesemia occupied a higher percentage among the magnesium imbalance in our study. In a preceding study, it was concluded that magnesium should be observed and, in case of the imbalanced magnesium homeostasis, an appropriate nutritional regimen or supplementation could contribute to protect against SARS-CoV-2 infection, reduce severity of COVID-19 infection, and enhance the recovery after the acute phase [40], [41].

A fewer percentage of the enrolled children was noticed to have hypermagnesemia. A link between hypermagnesemia among patients admitted with COVID-19 and the increased mortality has been identified by a prior research. Although the precise
mechanism of this relationship remains unclear, this result potentially represents increased cell turnover and the severity of illness that is frequently associated with more severe forms of acute kidney injuries [42]. In fact, hypomagnesemia could be a predisposing factor for COVID-19 infection, while hypermagnesemia could be a result found in the severe COVID-19 infection form. A detailed analysis of magnesemia and the associated factors in a cohort of 300 patients was performed. Among these, 48% had a magnesemia below 0.75 mmol/L, involving 13% of severely hypomagnesemic patients (0.65 mmol/L); on the other hand, a fewer proportion of patients (9.6%) was hypermagnesemic (>0.95 mmol/L). In this report, in moderate cases of COVID-19, serum magnesium concentrations were considerably lower and the prevalence of hypomagnesemia was significantly higher than in the critical cases, while the prevalence of hypermagnesemia was significantly increased in the ICU cases [43].

It was recommended that more care and medical attention should be provided to COVID-19 patients with hypophosphatemia at the admission as hypophosphatemia is greatly linked to increased mortalities in COVID-19 patients [44]. Hypophosphatemia observed in the children with phosphorus imbalance in our study that could be the result of malnutrition, extensive energy consumption and uncontrolled losses from the intestinal tract and kidneys, and respiratory alkalosis [45], [46], [47], [48]. Besides, hypocalcemia observed in the present study could be a direct effect of COVID-19 or could be the consequence of an imbalance in parathyroid hormone and/or 25-hydroxyvitamin D. In general, calcium is needed for the virus structure formation, its entry, its replication, and release [49].

Hypoalbuminemia can be considered as a severity indicator of epithelial–endothelial damage in COVID-19 children. There are suspicions that pulmonary capillary leak syndrome has a significant role in the pathogenesis of COVID-19 infection and could be a potential therapeutic target [50]. Our finding is very near to a recent report that pointed to reduced albumin levels in pediatrics with mild/moderate COVID-19 [51]. Importantly, hypoalbuminemia is a negative acute phase reactant that has been associated with the inflammatory response and undesirable outcomes in the infectious diseases such as COVID-19. Serum albumin concentration can address children who are at high risks of developing potential life-threatening conditions and death, improving risk stratification in COVID-19 children [52]. Another retrospective preceding research has found that hypoalbuminemia at the presentation independently increased the risks of deaths in COVID-19 patients by at least 6-fold and recommended evaluation of the potential therapeutic value of albumin in COVID-19 patients [53]. Similarly, a former study has postulated the possible value of the nutritional support therapy to patients with hypoalbuminemia in the course of COVID-19 infection as that study has yielded that hypoalbuminemia was common in COVID-19 patients and might be the result of a combination of inflammation and malnutrition in these patients. These patients with hypoalbuminemia tend to have more severe clinical courses and more abnormal results of the biochemical tests that may lead to poorer clinical outcomes. Hypoalbuminemia might indicate a poorer prognosis and the necessity for more diverse therapies [54]. Furthermore, hypoalbuminemia can guide the clinicians in the risk stratification of COVID-19 patients as concluded by a prior article, in which authors demonstrated the link between hypoalbuminemia and the severe COVID-19 infection. A low albumin serum level can potentially result in an early recognition of severe courses and assist clinicians in making informed stratifications and subsequent decisions for their patients [55].

According to the conclusion of a previous research, the BMI of patients with COVID-19 was significantly higher than those without [56]. This conclusion goes in line with the current study that yielded a high prevalence of overweight and obesity among those of malnourished children with COVID-19. Our study is further closely located to a previous report that indicated increased risks of acquiring COVID-19 infection among pediatrics with medical comorbidities and certain disorders such as obesity [57]. Obesity should be recruited as individual risk factors for higher COVID-19 severity and mortality outcomes [58]. Obesity is a well-known risk factor for acquiring COVID-19 and infections in general [59]. The regulated expression of miRNAs (microRNA) is crucial in the immunomodulation and more than 23 circulating miRNAs are deregulated in obese individuals. These miRNAs have valuable effects on the immune cell development, the T lymphocyte generation, the lipid metabolism, and the macrophage pro-inflammatory responses [60].

**Conclusion**

The present study has identified the prevalence of the biochemical and the anthropometrical malnutrition in pediatrics infected with COVID-19. Large-scale prospective studies are needed to prove further hypotheses underlying different pathophysiological mechanisms that link COVID-19 infection and the malnutrition to each other’s. Timely diagnosis and treatment of children with malnutrition or those at nutritional risks are recommended.

**Data Availability**

The datasets analyzed during the present study are available from the corresponding author on reasonable request.
Authors’ Contributions

Hoda Atef Abdelsattar Ibrahim., the main author: Conceptualization, visualization, methodology, interpretation of data, writing—original draft preparation, reviewing and editing, software and validation, supervision; Eatemad Helmy: Acquisition of data; Aya Ahmed Amin.: Formal analysis; Dina Mahmoud Nabil: Investigation; all the authors approved for the final version.

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