

Impact of the COVID-19 Era on Phenylalanine Levels and Classical Phenylketonuria Patients Follow-Up: A Retrospective Analysis

COVID-19 Döneminin Fenilalanin Düzeyleri ve Klasik Fenilketonüri Hastalarının Takibi Üzerindeki Etkisi: Retrospektif Bir Analiz

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ABSTRACT

Objective: Phenylketonuria is a metabolic disorder resulting from mutations in the *PAH* gene, causing elevated blood phenylalanine (Phe) levels which can lead to severe neurological damage if untreated. The primary treatment is a lifelong low-protein diet with amino acid substitutes and micronutrient supplements. During the COVID-19 pandemic, classical phenylketonuria (PKU) patients faced significant challenges, including restricted access to routine care like clinical visits and metabolic control monitoring. The aim of this study was to examine the disruptions in outpatient visits, the variances in pre- and post-pandemic Phe levels, and clinical severity among patients who contracted COVID-19.

Material and Methods: Starting from the pandemic date of March 11, 2020, demographic data, laboratory characteristics, and details about COVID-19 infection were retrospectively reviewed for classical PKU patients with accessible electronic records from March 2018 to March 2022.

Results: When the median blood Phe levels before and after the pandemic were compared, a significant difference was found. We observed that adult patients diagnosed with classical PKU often defaulted on their follow-up appointments.

Conclusion: The COVID-19 pandemic significantly disrupted the follow-up and management of classical PKU patients. However, no severe COVID-19 cases were reported among this population, suggesting they did not face an increased risk from the infection. This study emphasizes the critical need to develop robust strategies for patient engagement and follow-up, especially for adult classical PKU patients who are at risk of discontinuing routine care.

Keywords: Classical phenylketonuria, COVID-19, Phenylalanine levels, SARS-CoV-2

ÖZ

Amaç: Fenilketonüri, PAH genindeki mutasyonlardan kaynaklanan ve tedavi edilmediği takdirde ciddi nörolojik hasara yol açabilecek yüksek kan fenilalanin (Phe) seviyelerine neden olan bir metabolik bozukluktur. Birincil tedavi, ömür boyu düşük proteinli diyet ve amino asit ikameleri ile mikro besin takviyeleridir. COVID-19 pandemisi sırasında, klasik fenilketonüri (PKU) hastaları, klinik ziyaretler ve metabolik kontrol izlemeleri gibi rutin bakıma erişimde önemli zorluklarla karşılaştı. Bu çalışmanın amacı, ayakta hasta ziyaretlerindeki aksaklıkları, pandemi öncesi ve sonrası Phe seviyelerindeki farklılıkları ve COVID-19'a yakalanan hastalar arasındaki klinik şiddeti incelemektir.

Gereç ve Yöntemler: Pandemi başlangıç tarihi olan 11 Mart 2020'den itibaren, Mart 2018'den Mart 2022'ye kadar elektronik kayıtlara erişilebilen klasik PKU hastaları için demografik veriler, laboratuvar özellikleri ve COVID-19 enfeksiyonu ile ilgili detaylar retrospektif olarak incelendi.



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Bulgular: Pandemi öncesi ve sonrası medyan kan Phe seviyeleri karşılaştırıldığında, anlamlı bir fark bulundu. Klasik PKU tanısı alan yetişkin hastaların takip randevularını sıklıkla aksattıkları gözlemlendi.

Sonuç: COVID-19 pandemisi, klasik PKU hastalarının takibi ve yönetimini önemli ölçüde aksattı. Bununla birlikte, bu popülasyon arasında ciddi COVID-19 vakaları bildirilmemiştir, bu da enfeksiyon açısından artmış bir riskle karşı karşıya olmadıklarını düşündürmektedir. Bu çalışma, özellikle rutin bakımı aksatma riski taşıyan yetişkin klasik PKU hastaları için, hasta katılımı ve takip konusunda sağlam stratejiler geliştirilmesi gerekliliğini vurgulamaktadır.

Anahtar Sözcükler: Klasik fenilketonüri, COVID-19, Fenilalanin seviyeleri, SARS-CoV-2

INTRODUCTION

Phenylketonuria (PKU; OMIM 261600) is a metabolic disorder caused by mutations in the PAH gene, which encodes the liver enzyme phenylalanine hydroxylase (PAH). This enzyme typically converts the amino acid phenylalanine (Phe) into tyrosine. A deficiency in PAH activity leads to elevated blood Phe levels, which can reach toxic concentrations and primarily affect the central nervous system (CNS). If untreated, symptoms such as neurological impairment, psychomotor delay, seizures, autism, and behavioral disorders can develop soon after birth (1,2). The primary treatment is a lifelong dietary intervention to ensure normal growth and neurodevelopment. This diet includes low-protein foods, amino acid substitutes, and micronutrient supplements. Türkiye has the highest prevalence of PKU, partly attributed to the high incidence of consanguineous marriages (3).

In recent times, the world faced the COVID-19 pandemic, one of the most significant global health disasters of the century. The World Health Organization (WHO) proclaimed COVID-19 a pandemic on March 11, 2020. Following the first reported case, many countries declared implementing quarantine measures. Ensuring continuous care for patients with intricate health requirements, particularly those with rare diseases, has emerged as a significant challenge for healthcare providers during the COVID-19 pandemic.

During the COVID-19 pandemic, PKU patients faced unprecedented challenges, including severely restricted access to routine care such as in-person clinical visits, metabolic control monitoring, and self-sampling blood tests. Additionally, there was significant uncertainty surrounding their ability to obtain essential medical supplies and specialized low-protein food. Due to their need for special dietary products, the pandemic was a challenging period for PKU patients. In the study conducted by Akar et al. (4), it was shown that 61.2% of patients with classical PKU were more anxious.

While we have made substantial strides during the COVID-19 pandemic, there is no assurance against future pandemics. This unprecedented period has imparted critical lessons for the innovation of our healthcare system, one of the most pivotal being the integration of telemedicine. Our understanding of the ongoing pandemic remains incomplete, underscoring the need for continuous knowledge expansion to confront prospective challenges. Within this framework, we sought to analyze the implications of the pandemic on classical PKU, a prevalent inherited metabolic disorder in Türkiye. Our study examined the disruptions in outpatient visits, the variances in pre- and post-pandemic Phe levels, and clinical severity among patients who contracted COVID-19.

MATERIALS and METHODS

This study received approval from the Hacettepe University Ethics Committee for Non-Interventional Clinical Studies (GO22/176, 2022/08–23). Classical PKU was defined as untreated Phe levels above 20 mg/dL (1200 µmol/L) (5). In the two-year follow-up before and after March 11, 2020, when the pandemic was declared, the average of blood Phe values and the number of admissions were recorded and compared. Additionally, the study included patients who tested positive for SARS-CoV-2 PCR or antibodies. The patients were reached through phone calls and invited to participate in a survey that obtained demographic data and details about COVID-19 infection. Informed consent was obtained from all participants or their parents/guardians.

Inclusion and exclusion criteria

The start date of the pandemic was considered to be March 11, 2020. The patients with diagnosed disorders of Phe metabolism, for whom electronic health record data was accessible between March 2018 and March 2022, were reviewed retrospectively. Patients diagnosed with classical PKU through molecular analysis, who require dietary intervention and are under follow-up at our department (Hacettepe University, Pediatric Metabolism Unit) were included in this study. The patients with diagnosed mild hyperphenylalaninemia, pregnancy, and tetrahydrobiopterin (BH4)-responsive PKU were considered as exclusion criteria due to potential biases related to their different follow-up frequencies.

Demographic data, laboratory characteristics, and information related to COVID-19 infection were extracted retrospectively from the patients' electronic medical records. Additionally, patients who tested positive for SARS-CoV-2 via PCR or antibody tests were identified and included in the study. These patients were contacted by phone and invited to participate in a survey to obtain further details about their COVID-19 infection and overall health during the pandemic. The number of outpatient visits and blood Phe levels before and after the pandemic were recorded and compared to assess the impact of the pandemic on metabolic control and patient follow-up.

Statistical Analyses

The data were analyzed by IBM SPSS Statistics Version 25.0 (IBM Corp., Armonk, NY, USA). The normality of the variables was investigated by visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests). Descriptive statistics were presented as mean, standard deviation, median, range (minimum-maximum), interquartile range (IQR), and frequencies. Since the blood Phe level and admission number

were not normally disturbed; nonparametric tests were conducted to compare these parameters. The Wilcoxon test was used to compare the change in admission number and blood Phe level between pre-pandemic and post-pandemic period. A p value of less than 0.050 was considered to show a statistically significant result.

RESULTS

Since 2018, our department has been following up 1960 patients diagnosed with PKU, hyperphenylalaninemia, or BH4-responsive PKU. Of these, 809 patients with classic PKU were included in the study after excluding 1151 patients with HPA or BH4-responsive PKU. Among the total cohort (n=1960), we had a total of 118 patients who contracted COVID-19. Of the 118 patients, 25 classic PKU patients were ‘lost to follow-up,’ who did not have any blood Phe level measurements before or after the pandemic, and could not be contacted. These patients were excluded. Additionally, 16 patients diagnosed with BH4-responsive PKU and HPA, as well as five patients with pregnancy-classic PKU, were excluded. Patients without mild hyperphenylalaninemia or BH4-responsive PKU and those not being followed up for pregnancy with a more frequent protocol than usual were included in the study. Seventy-two patients with classical PKU who had contracted COVID-19 were included in the study. Among the 809 patients with classic PKU,

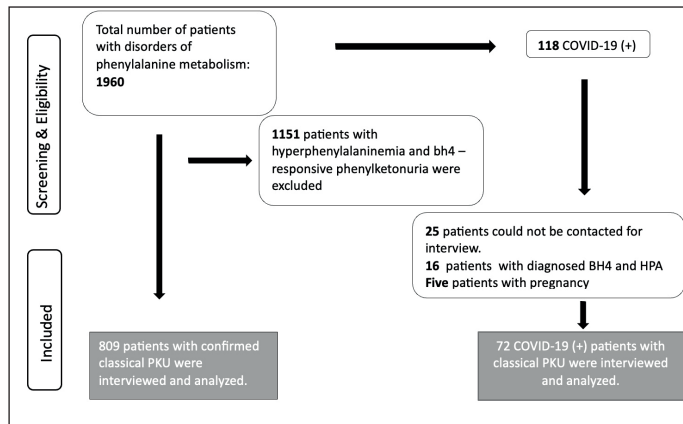


Figure 1: Flowchart of patients. **BH4:** Tetrahydrobiopterin responsive phenylketonuria, **COVID-19 (+):** Coronavirus disease 2019, **HPA:** Hyperphenylalaninemia, **PKU:** Phenylketonuria.

Table I: Characteristics of the classic phenylketonuria patients

		P
Age, years*	18 (1-49)	-
Sex, Female/Male (n)	361/448	-
Number of Phenylalanine measurements*		
Pre-Pandemic (n=809)	4 (1-41)	<0.001†
Post-Pandemic (n=707)	2 (1-59)	
Phenylalanine level*		
Pre-Pandemic (n=809)	10.4 (0.86-38.4)	<0.001†
Post-Pandemic (n=707)	9.1 (0.51-29.4)	

*: median (minimum-maximum), †: Wilcoxon test,

Table II: Characteristics of classical phenylketonuria patients with COVID-19 positive (n=72)

		P
Age, years*	21 (2-43)	-
Age group†		
Child	30 (41.7)	-
Adult	42 (58.3)	
Sex†		
Male	35 (48.6)	-
Female	37 (51.4)	
Phenylalanine level pre-pandemic (mg/dl)*	9.3 (1.7-26.7)	0.025‡
Phenylalanine level post-pandemic (mg/dl)*	9.0 (2-24.8)	
Number of Phenylalanine measurement pre-pandemic*	3 (1-27)	0.075‡
Number of Phenylalanine measurements post-pandemic*	3 (1-16)	
Clinical Spectrum of COVID-19*		
Asymptomatic:	12 (16.7)	-
Mild Illness:	56 (77.8)	
Moderate Illness:	4 (5.6)	
Hospitalization*		
Yes	3 (4.2)	-
No	69 (95.8)	
Oxygen requirement*		
Yes	2 (2.8)	-
No	70 (97.2)	
Feeding difficulties*		
Yes	20 (27.8)	-
No	52 (72.2)	

*: median (IQR), †: n(%), ‡: Wilcoxon test, **Phe:** Phenylalanine,

72 who had contracted COVID-19 were included in the study. The flowchart of participants is shown in Figure 1.

The characteristics of the patients with classical PKU are given in Table I. There were 420 patients aged 18 and over, and 389 patients under the age of 18. There was a significant difference in the number of Phe measurements before and after the pandemic. The median number of Phe measurements before the pandemic was 4 (1-41), while after the pandemic it decreased to 2 (1-59) (p<0.001). Furthermore, the median Phe levels before the pandemic were 10.4 mg/dL (0.86-38.4), and this decreased to 9.1 mg/dL (range: 0.51-29.4) after the pandemic (p<0.001). There was a 12% decrease in the number of follow-up Phe measurements of patients with classical PKU. Among 102 patients lost to follow-up, the median age was 18 years (3–36), with a female-to-male ratio of 48:54. The median number of phenylalanine measurements was 2 (1–42), and the median phenylalanine level was 15.8 mg/dL (1.4–35.9).

Among the 72 classic PKU patients who contracted COVID-19, the median age was 21 years. When the median blood Phe levels before and after the pandemic were compared, a significant difference was found (9.3 [1-27] vs. 9.0 [2.0-24.8], respectively, p=0.025). However, there was no significant difference in the number of Phe measurements before and after the pandemic (3 [1- 27] vs. 3 [1-16], respectively, p=0.750) (Table II).

The clinical features of patients with classical PKU who contracted COVID-19 are provided in Table II. None of the patients were

admitted to the intensive care unit or required invasive mechanical ventilation. No patient was deceased. Regarding the clinical spectrum of COVID-19 among these patients, 12 (16.7%) were asymptomatic, 56 (77.8%) had mild illness, and four (5.6%) experienced moderate illness. Hospitalization was required for only three patients (4.2%), and two patients (2.8%) needed oxygen therapy. Feeding difficulties were reported in 20 patients (27.8%).

DISCUSSION

In the management of PKU treatment, the aim is to keep Phe levels under control throughout life, along with adherence to the diet, to achieve positive neurocognitive outcomes. The COVID-19 pandemic posed significant challenges for the follow-up and management of patients with PKU. Studies are showing increased stress levels and treatment noncompliance among PKU patients and their parents during the pandemic (4,6). The challenges faced by patients in accessing special dietary products during the pandemic were notable, highlighting the need for robust supply chain mechanisms to ensure continuous access to necessary dietary products. Additionally, the frequency of outpatient visits, dietary assessments, and frequent biochemical monitoring requirements cause patients to be lost to follow-up even outside of the pandemic. As patients age, the likelihood of being lost to follow-up care significantly increases (7). This study highlights several critical insights from a single-center experience regarding the metabolic control and follow-up status of PKU patients.

One notable finding from our study is the difficulty in maintaining follow-up for adult PKU patients. The median age of our patients who discontinued follow-up is 18, and they were who generally already had poor metabolic control. Many adult patients discontinued their regular monitoring during the pandemic. As a reference center, we have patients from many cities across our country. We anticipated that the geographical limitations in transportation would cause some of our patients to lost-follow-up during the pandemic period. This gap in follow-up is concerning given the potential for long-term complications if metabolic control is not maintained.

Similar to the study by Walkowiak et al. (8), patients who were non-compliant with their follow-ups in the past were more likely to drop out of follow-up, while those who continued their follow-ups did not experience an increase in Phe levels. Herle et al. (9), reported that school-aged patients sent fewer samples during the COVID-19 period, and patients over the age of 16 sent significantly fewer dried blood spots samples in 2020. As patients get older, they may exhibit a tendency to miss follow-ups due to the need to manage their diet independently of their parents, and because they are more susceptible to the influences of their social environment and work life. Previous studies have also investigated the reasons why patients lost follow-up, highlighting factors such as lack of insurance and financial resources, difficulties in accessing metabolism centers due to economic problems, and reluctance to return to a restricted diet (10). Additionally, adult patients may not want to wait in the same clinic as children and may no longer perceive the disease as a serious issue.

Reaching adulthood from the newborn screening period without mental disability is possible with a significant amount of labor, time,

and money from the healthcare system and with the efforts of dedicated families. To sustain this effort for the development of an independent, productive, and stable society, we must continue to remind our adult patients who have lost follow-up care, their value and the importance of continuous treatment. For adult patients, transition services, or solutions like telemedicine during crises such as the pandemic, as well as overcoming physical and economic challenges due to the limited number of metabolic disease management centers in our country, can be crucial. Implementing telemedicine for routine follow-ups can improve adherence to treatment plans and ensure consistent monitoring. Studies from various centers have shown that telemedicine effectively maintains patient engagement and metabolic control, with high patient satisfaction. It was highlighted that telemedicine played a crucial role in re-engaging patients who had lost follow-up, bringing them back into regular monitoring (11). These findings suggest that telemedicine could be a valuable tool for long-term management of PKU, particularly during the pandemic. The feedback from patients in these studies was overwhelmingly positive, suggesting that telemedicine could be a valuable tool in the long-term management of PKU (12-16). These measures can help prevent them from lost follow-up and ensure the continuity of their metabolic control.

Interestingly, we found a significant improvement in median blood Phe levels during pandemic. This could be attributed to the reduced social distractions and increased focus on dietary compliance during lockdown periods. Previous research supports this observation, indicating that adolescents and adults had better metabolic control during lockdown due to fewer social interactions and temptations that might lead to dietary lapses. Due to the requirement to leave their homes only for emergencies, patients were compelled to consume homemade meals instead of dining at restaurants or eating out. In the study conducted by Rovelli et al. (17), which included 192 patients, the median Phe level decreased by 22.5% during the pandemic ($p < 0.001$). Zubarioğlu et al. (18) highlighted that during the pandemic, 92 patients had better Phe levels, applied fewer washout diets, and attributed this to the benefits of telemedicine applications. In the study conducted by Herle et al. (9), which included 77 PKU patients, no change in Phe levels was observed during the pandemic period. However, a significant decrease in number of Phe measurements was observed, particularly in patients over the age of 16. In the study conducted by Becsei et al. (19), which included 83 patients with classical PKU, an increase in Phe levels was observed in adolescents during the non-pandemic period. Similar to other studies, it has been reported that the number of measured Phe levels decreased, and some patients lost follow-up (9). We believe that the significant decrease in the number of measured Phe levels can be attributed to the postponement of appointments due to the chronic nature of the disease. At this point, collaborating with local healthcare services and ensuring that patients continue their blood tests via mail could be a solution.

During the COVID-19 pandemic, parents of children with classical PKU were concerned about increased risks and sought guidance. We informed them that no specific data linked PKU to higher COVID-19 risk, emphasizing that severe illness was more common

in those with advanced age, male gender, or chronic conditions (20). Our findings indicated that PKU patients did not face higher severe COVID-19 risks, with none of our monitored patients experiencing severe illness. Despite disruptions in metabolic monitoring and dietary management, PKU patients' clinical outcomes were not significantly affected by COVID-19.

The limitations of our study are its retrospective design and the lack of information on Phe levels if patients provided these measurements at other centers. During the active COVID-19 infection period, we were unable to consistently monitor the Phe levels of our patients. The strength of our study lies in its inclusion of the largest sample size in the literature and having the highest number of PKU patients who contracted COVID-19.

In conclusion, the COVID-19 pandemic has underscored the importance of adaptable healthcare delivery models. Ensuring the continuity of care through innovative approaches like remote monitoring and telehealth consultations can mitigate the impact of future disruptions and improve overall patient outcomes. The insights gained from this single-center experience could inform broader healthcare strategies for managing chronic conditions in a during pandemic world. Healthcare services should intensify their efforts in enhancing adherence and monitoring strategies for patients with classical PKU. The results of our study could provide a valuable foundation for discussions on future potential scenarios. Future strategies should focus on enhancing telemedicine services, ensuring the availability of dietary products, and providing targeted support to different patient groups to improve overall care and outcomes for PKU patients. The lessons learned from this study can inform the development of measures to be implemented in the event of another possible lockdown. The healthcare system can organize more quickly when faced with a similar crisis.

REFERENCES

1. Van Spronsen F, Huijbregts S, Bosch A, Leuzzi V. Cognitive, neurophysiological, neurological and psychosocial outcomes in early-treated PKU-patients: a start toward standardized outcome measurement across development. *Mol Genet Metab* 2011;104:S45-S51.
2. Homaei SC, Barone H, Kleppe R, Betari N, Reif A, Haavik J. ADHD symptoms in neurometabolic diseases: Underlying mechanisms and clinical implications. *Neurosci Biobehav Rev* 2022;132:838-56.
3. Özalp I, Coşkun T, Ceyhan M, Tokol S, Oran O, Erdem G, et al. Incidence of Phenylketonuria and Hyperphenylalaninaemia in a Sample of the Turkish Newborn Population. in: Addison, GM, Harkness RA, Isherwood DM, Pollitt RJ. (eds) *Practical Developments in Inherited Metabolic Disease: DNA Analysis, Phenylketonuria and Screening for Congenital Adrenal Hyperplasia*. Springer 1st ed 1986:237-39.
4. Akar H, Karaboncuk Y, Çıki K, Kahraman A, Erdal İ, Coşkun T, et al. COVID-19-related anxiety in phenylketonuria patients. *Turk J Pediatr* 2021;63:790-800.
5. Coşkun T, Çoker M, Mungan NÖ, Özel HG, Sivri HS. Recommendations on phenylketonuria in Turkey. *Turk J Pediatr* 2022;64:413-34.
6. Chiesa A, Spécola N, Poubel M, Vela-Amieva M, Jurecki E, Vilela DR, et al. Adherence to PKU guidelines among patients with phenylketonuria: A cross-sectional national multicenter survey-based study in Argentina, Brazil, and Mexico. *Mol Genet Metab Rep* 2024;38:101026.
7. Berry SA, Brown C, Grant M, Greene CL, Jurecki E, Koch J, et al. Newborn screening 50 years later: access issues faced by adults with PKU. *Genet Med* 2013;15:591-9.
8. Walkowiak D, Mikołuc B, Mozrzyimas R, Kałużny Ł, Didycz B, Jagłowska J, et al. The impact of the First 2020 COVID-19 Lockdown on the metabolic control of patients with Phenylketonuria. *Nutrients* 2021;13:2024.
9. Herle M, Brunner-Krainz M, Karall D, Goeschl B, Möslinger D, Zobel J, et al. A retrospective study on disease management in children and adolescents with phenylketonuria during the Covid-19 pandemic lockdown in Austria. *Orphanet J Rare Dis* 2021;16:367.
10. Burton BK, Leviton L. Reaching out to the lost generation of adults with early-treated phenylketonuria (PKU). *Mol Genet Metab* 2010;101:146-8.
11. Walkowiak D, Mikołuc B, Mozrzyimas R, Kałużny Ł, Didycz B, Korycińska-Chaaban D, et al. The impact of the COVID-19 pandemic on the perception of health and treatment-related issues among patients with Phenylketonuria in Poland—The results of a National Online Survey. *Int J Environ Res and Public Health* 2021;18:6399.
12. Walkowiak D, Mikołuc B, Mozrzyimas R, Kałużny Ł, Didycz B, Korycińska-Chaaban D, et al. Phenylketonuria patients' and their caregivers' perception of the pandemic lockdown: the results of a National Online Survey. *Children* 2022;9:131.
13. Çelik MY, Canda E, Erdem F, Uçar SK, Çöker M. Impact of the COVID-19 Pandemic on Inherited Metabolic Diseases: Evaluation of Enzyme Replacement Treatment Adherence with Telemedicine. *J Pediatr Res* 2022;9:391-6.
14. Cannizzo S, Quoidbach V, Giunti P, Oertel W, Pastores G, Relja M, et al. The COVID-19 pandemic impact on continuity of care provision on rare brain diseases and on ataxias, dystonia and PKU. A scoping review. *Orphanet J Rare Dis* 2024;19:81.
15. Koç Yekedüz M, Doğulu N, Sürücü Kara İ, Öncül Ü, Bakırarar B, Kullu P, et al. Pros and cons of telemedicine for inherited metabolic disorders in a developing country during the COVID-19 pandemic. *Telemed J E Health* 2022;28:1604-12.
16. McBride H, Evans S, Pinto A, Daly A, Ashmore C, Ilgaz F, et al. Patient and carer perceptions of video, telephone and in-person clinics for Phenylketonuria (PKU). *Orphanet J Rare Dis* 2024;19:303.
17. Rovelli V, Zuvadelli J, Ercoli V, Montanari C, Paci S, Dionigi AR, et al. PKU and COVID19: how the pandemic changed metabolic control. *Mol Genet Metab Rep* 2021;27:100759.
18. Zubarioglu T, Hopurcuoglu D, Uygur E, Ahmadzada S, Oge-Enver E, Isat E, et al. The impact of telemedicine for monitoring and treatment of phenylketonuria patients on metabolic outcome during coronavirus disease-19 outbreak. *Telemed J E Health* 2022;28:258-65.
19. Becsei D, Kiss E, Szatmári I, Arató A, Reusz G, Szabó AJ, et al. A retrospective analysis of metabolic control in children with PKU in the COVID-19 era. *Mol Genet Metab Rep* 2022;32:100897.
20. Dessie ZG, Zewotir T. Mortality-related risk factors of COVID-19: a systematic review and meta-analysis of 42 studies and 423,117 patients. *BMC Infect Dis* 2021;21:855.