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Association between baseline intact parathyroid hormone levels, COVID-19 severity, and long-term outcomes in patients undergoing hemodialysis: A multicenter retrospective study

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Abstract. *The COVID-19 pandemic poses unique challenges for vulnerable populations, including patients undergoing maintenance hemodialysis (HD). This study explores the relationship between baseline intact parathyroid hormone (iPTH) levels and COVID-19 severity, post-acute hospitalization, and mortality rates in HD patients.*

Methods. *A multicenter retrospective cohort study was conducted across multiple centers, encompassing 142 patients undergoing HD treatment in three regions of Ukraine. The study spanned from March 2020 to May 2022. Baseline iPTH levels, demographic characteristics, and relevant clinical indicators were systematically recorded. Key endpoints included the severity of COVID-19, post-acute hospitalization, and mortality rates.*

Results. *Of the initially eligible 165 patients, 23 were excluded, resulting in a final cohort of 142 patients. During the acute phase of COVID-19, distinct patterns emerged in terms of hospitalization rates, oxygen support requirements, and mortality. Lower iPTH levels were significantly associated with severe COVID-19-associated pneumonia ($p < 0.0001$). A 20-month follow-up revealed a significant association between serum iPTH concentration < 174 pg/mL and increased rates of post-acute COVID-19 hospitalization [HR 6.3 (95% CI 2.9; 13.7)] and all-cause mortality [HR 34.3 (95% CI 6.9; 74.5)].*

Conclusion. *This multicenter retrospective study suggests potential links between baseline iPTH levels and COVID-19 outcomes in patients undergoing HD. Serum iPTH concentration ≤ 174 pg/mL was significantly associated with increased post-acute hospitalization and mortality rate in our patient cohort. The findings emphasize the need for further research to elucidate underlying mechanisms and establish the prognostic value of iPTH in this specific patient population.*

Key words: *COVID-19, intact parathyroid hormone, pneumonia, long-term outcomes, hospitalization, mortality.*

Conflict of interest statement. The authors declare no competing interest.

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Взаємозв'язок між рівнем паратиреоїдного гормону крові та тяжкістю і віддаленими наслідками COVID-19 у пацієнтів, які лікуються методом гемодіалізу: багатоцентрове ретроспективне дослідження

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Резюме. Пандемія COVID-19 створює унікальні виклики для вразливих груп населення, включаючи пацієнтів, які лікуються методом гемодіалізу (ГД). У цьому дослідженні аналізувався взаємозв'язок між рівнем інтактного паратгормону (іПТГ), тяжкістю COVID-19, віддаленою госпіталізацією та смертністю ГД пацієнтів.

Методи. Багатоцентрове ретроспективне когортне дослідження проведено із залученням 142 пацієнтів з трьох регіонів України, які лікувались методом ГД з березня 2020 року по травень 2022 року. Аналізувались вихідні рівні іПТГ (до інфікування COVID-19), демографічні та клінічні характеристики хворих. Ключові кінцеві точки включали тяжкість COVID-19, необхідність госпіталізації після гострого періоду COVID-19 та рівень смертності.

Результати. Низькі рівні іПТГ статистично значущо асоціювались з тяжкістю COVID-19-асоційованої пневмонії та необхідністю кисневої підтримки під час гострої фази хвороби ($p < 0,0001$). Пацієнти з концентрацією іПТГ сироватки крові < 174 пг/мл мали достовірно вищий рівень госпіталізації [HR 6,3 (95% ДІ 2,9; 13,7)] і смертністю від усіх причин [HR 34,3 (95% ДІ 6,9; 74,5)] протягом 20 місяців спостереження після COVID-19.

Висновок. Це багатоцентрове ретроспективне дослідження свідчить про потенційний зв'язок між вихідним рівнем іПТГ і віддаленими клінічними наслідками COVID-19 у ГД пацієнтів. Концентрація іПТГ сироватки крові ≤ 174 пг/мл статистично значущо асоціюється зі збільшенням рівня госпіталізації та смертності в нашій когорті пацієнтів. Результати підкреслюють необхідність подальших досліджень для з'ясування механізмів, що лежать в основі та встановлення прогностичного значення іПТГ у цій когорті пацієнтів.

Ключові слова: COVID-19, інтактний паратгормон, пневмонія, віддалені результати, госпіталізація, смертність.

Introduction. The COVID-19 pandemic has posed unprecedented challenges to global healthcare systems, highlighting the intricate interplay between pre-existing health conditions and the severity of the viral infection [1]. Among those significantly affected are patients undergoing maintenance hemodialysis (HD), who are known to have a higher risk of severe disease and mortality due to their compromised immune systems and the presence of multiple comorbidities [2, 3]. Half of the infected patients necessitated hospitalization, with 24.5% being admitted to intensive care units and an overall mortality rate of 26.8% [4]. Another study reported a 35.7% mortality rate over 12 months, with a mere 11% of fatalities occurring during the initial admission [5]. These statistics underscore the imperative need for in-depth investigations into COVID-19 risk factors within the HD population.

The intersection of COVID-19 with chronic kidney disease and HD presents unique challenges and necessitates a deeper understanding of the factors that contribute to disease severity and outcomes in this vulnerable population. Emerging evidence suggests that parathyroid hormone (PTH) status, a critical regulator of calcium and phosphorus homeostasis, may play a pivotal role in influencing mortality in patients undergoing HD [6–8]. Some studies suggest that COVID-19 might affect the function of parathyroid glands, potentially leading to hypoparathyroidism [7, 9]. In addition, low serum levels of vitamin D, which is closely related to PTH function, have been associated with severe acute respiratory failure and poor prognosis in COVID-19 patients [10]. This suggests a potential link between mineral metabolism and the immune response to SARS-CoV-2.

In light of these observations, **our study aims** to explore the association between baseline intact PTH (iPTH) status, COVID-19 severity, post-acute hospitalization and mortality rates in patients undergoing HD. The rationale for focusing on iPTH is twofold: first, iPTH has known effects on immune function, which could influence the body's response to viral infections [11]; second, HD patients often exhibit dis-

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ordered mineral metabolism, including alterations in iPTH levels, which could impact their susceptibility to and prognosis of COVID-19 [10].

Patients and Methods. We conducted a multi-center retrospective cohort study encompassing patients undergoing HD in three regions of Ukraine (Kyiv, Odesa, and Zaporizhzhia) during the period from March 2020 to May 2022. The study received approval from the Bioethics and Deontology Commission of the State University “Institute of Nephrology of the National Academy of Sciences of Ukraine (Protocol No. 2 dated 04/06/2021). Due to the retrospective nature of the study, patients were not required to provide informed written consent.

The study included patients who met specific criteria, such as a documented history of COVID-19, a minimum duration of HD treatment for at least 3 months, an age exceeding 18 years, the absence of life-threatening comorbid conditions, and surgical parathyroidectomy before SARS-CoV-2 infection, and the availability of two serum iPTH levels within a year before the onset of infection. To ensure the validity of our findings, we excluded patients with temporary vascular access, diabetes, oncology, systemic disease, or those who had experienced major adverse cardiovascular events before contracting COVID-19. This was done to eliminate the potential impact of these comorbidities on both serum iPTH levels and the clinical outcomes of COVID-19.

All patients were routinely dialyzed three times a week, 4 h per session with bicarbonate-based dialysate, volumetric ultrafiltration control, single-use synthetic (polysulphone) dialyzers, and heparin as a standard anticoagulant. Dialysis prescription was guided by the goal of achieving a value of $Kt/V \geq 1.2$.

In addition to demographic characteristics, routine clinical and laboratory indicators (Kt/V , body mass index (BMI), hemoglobin, serum electrolytes, C-reactive protein (CRP), D-dimer, and chest computed tomography (CT) results of SARS-CoV-2-infected patients were recorded in an electronic database.

The study focused on several key endpoints: the severity of COVID-19, defined by CT findings indicating pulmonary involvement and the requirement for oxygen support, post-acute hospitalization for any reason, and mortality. The iPTH levels were collected at baseline (the mean of 2 last measurements dated before COVID-19 onset). COVID-19-associated pneumonia was estimated based on CT findings of pulmonary involvement and assessed using the following scoring system: 1 indicating less than 5% involvement, 2 indicating 5–25% involvement, 3 indicating 26–49% involvement, 4 indicating 50–75% involvement, and 5 indicating more than 75% involvement. The follow-up period after SARS-CoV-2 infection was 20 months, concluding either upon the occurrence of the specified event or the study's termination on May 30, 2022.

Statistical analysis was conducted using the MedCalc® Statistical Software version 22.016 (MedCalc Software Ltd, Ostend, Belgium, with consideration given to normal distribution verification using the Kolmogorov-Smirnov criterion. Data were presented as median and interquartile ranges [Me (Q25-Q75)], and comparisons were made using the Kruskal-Wallis test. The 2 test was employed to assess differences in frequencies among groups. The threshold value of iPTH for predicting the negative consequences of COVID-19 was determined using the Receiving Operation Characteristic (ROC) analysis. Furthermore, the association of baseline iPTH levels with long-term COVID-19 outcomes was assessed using Kaplan-Maier analysis and compared with the log-rank test.

Results. Out of the initially eligible 165 patients, 23 were excluded from the study. This exclusion included 18 patients with incomplete data and 5 patients who underwent transplantation during the follow-up period post-COVID-19. The final analysis included a cohort of 142 patients, ensuring a more homogeneous and comparable group for in-depth examination. A graphical representation of the study flow is shown in Figure 1.

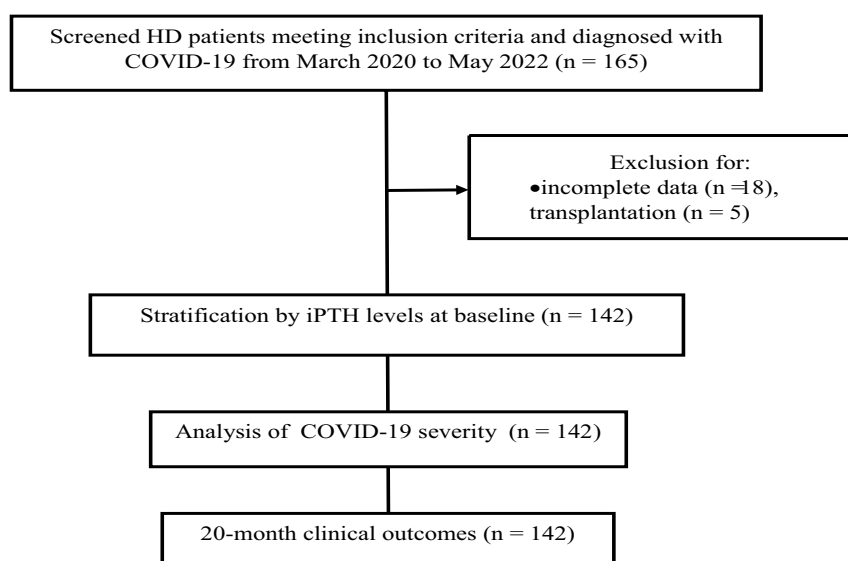


Fig. 1. STROBE flowchart: Participant selection and the study progression.

In our study cohort, the baseline serum iPTH levels ranged from 72.2 to 1030 pg/mL, with an average level of 338.5 (186.1-486.4) pg/mL. As shown in Table 1, HD patients in the lowest quartile (Q) of iPTH levels,

prior to contracting SARS-CoV-2, exhibited a shorter dialysis vintage and lower CRP concentrations compared to patients in the Q2 and Q3 groups.

Table 1

Baseline characteristics of the study participants stratified by iPTH levels

Indicator	Q 1 iPTH < 186.1 pg/mL (n = 37)	Q 2 iPTH 186.1-486.4 pg/mL (n = 80)	Q 3 iPTH > 486.4 pg/mL (n = 25)	p-value
Male sex, n (%)	17 (60.7%)	45 (54.9%)	19 (59.4%)	0.07
Age, years	58.5 (53-62)	57 (44.5-55)	56 (43.7-62)	0.43
HD vintage, months	40 (24-56) _{2,3}	43 (28-60)	48 (32-76)	0.01
Kt/V	1.3 (1.27-1.4)	1.3 (1.24-1.52)	1.3 (1.28-1.45)	0.74
BMI, kg/m ²	27.8 (23.4-29.8)	27.0 (23.7-30.1)	27.5 (23.8-30.9)	0.78
Hemoglobin, g/L	110 (91.2-120)	100 (90-110.5)	98 (89-111.3)	0.95
Systolic blood pressure, mmHg	130 (125-145)	130 (125-140)	135 (120-140)	0.88
Diastolic blood pressure, mmHg	80 (80-95)	75 (70-95)	85 (70-95)	0.56
iPTH, pg/ml	110.2 (88.3-124.5) _{2,3}	327 (225-410) _{1,3}	709 (648-800) _{1,2}	<0.0001
Phosphorus, mmol/L	1.78 (1.58-2.01)	1.74 (1.57-2.11)	1.85 (1.68-2.13) ₂	0.03
Calcium, mmol/L	2.19 (2.11-2.24)	2.23 (2.18-2.32)	2.31 (2.18-2.35)	0.27
Cholesterol, mmol/L	4.3 (3.2-5.6)	4.8 (4.4-5.6)	4.7 (3.7-5.0)	0.18
CRP, mg/l	22.2 (15.7-33.4) _{2,3}	12.2 (7.97-16.1)	10.9 (5.9-18.6)	0.02

Abbreviations: BMI – body mass index, BP – blood pressure, CRP – C-reactive blood protein, HD – hemodialysis, iPTH – intact parathyroid hormone, Kt/V – urea clearance.

During the acute phase of COVID-19, 108 (76%) patients did not require oxygen support, 40 (28.2%) were hospitalized, 34 (24%) patients required oxygen supplementation, and 17 (12%) passed away during the period of observation. The chest CT findings in all HD

patients were scored from 2 to 4 for pulmonary involvement. The baseline iPTH level was significantly lower in patients with severe COVID-19-associated pneumonia compared with those with mild and moderate pneumonia scores (Fig. 2).

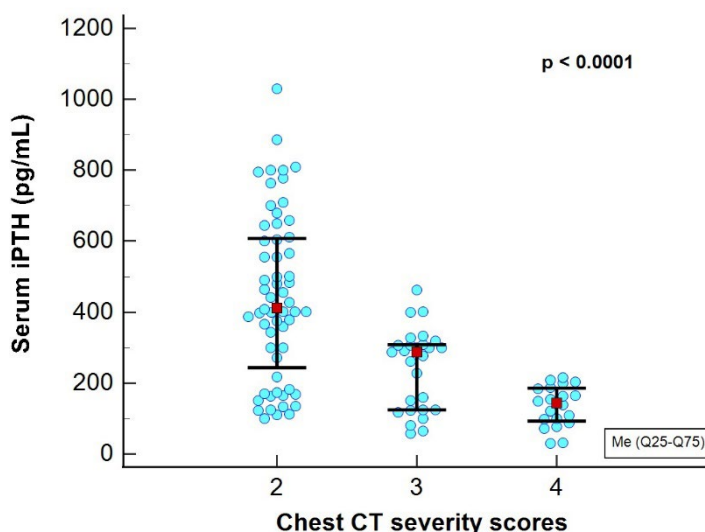


Fig. 2. Serum iPTH levels according to the chest CT severity scores in the COVID-19-infected HD patients (Kruskal-Wallis test).

During the follow-up period, 43 (30.3%) patients who survived acute COVID-19 required hospitalization and 8 (5.6%) died. The long-term mortality rate

was significantly associated with the severity of acute COVID-19 and baseline serum iPTH levels (Fig. 3).

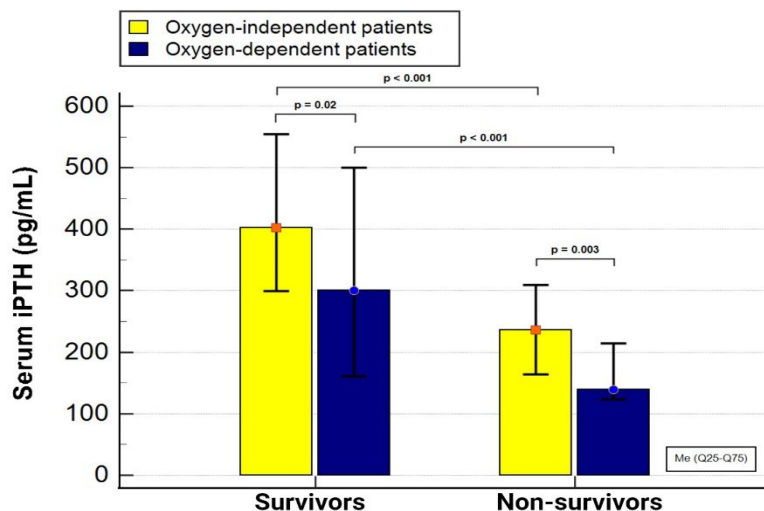


Fig. 3. Serum iPTH levels in patients undergoing HD stratified by COVID-19 outcomes.

The ROC analysis revealed that the most appropriate cut-off point for baseline iPTH concentration as a predictor for post-acute hospitalization in HD patients was ≤ 174 pg/mL with a sensitivity of 74.5 % and specificity of 82.1 %. The area under the ROC curve was 0.78 (95% CI 0.71; 0.85), $p < 0.0001$ (Fig. 4).

The Kaplan-Meier analysis, utilizing iPTH levels based on ROC analysis findings, revealed a significant association between serum iPTH concentration < 174 pg/mL and increased rates of post-acute COVID-19 hospitalization (Fig. 5) and all-cause mortality (Fig. 6).

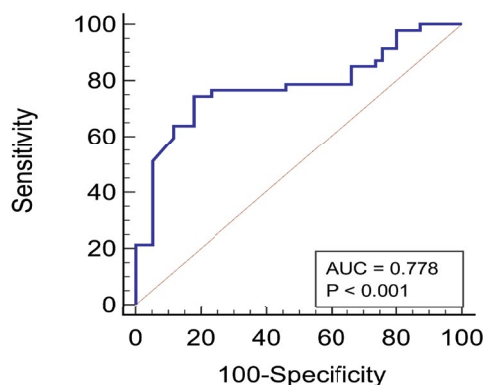
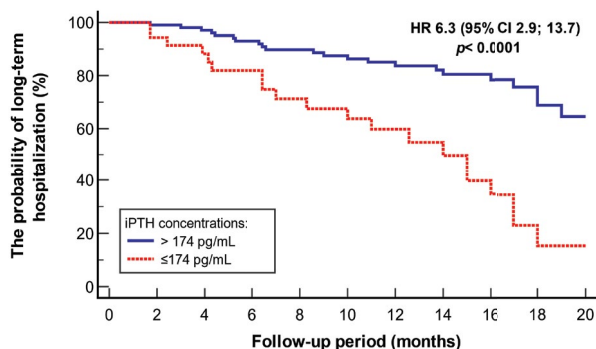


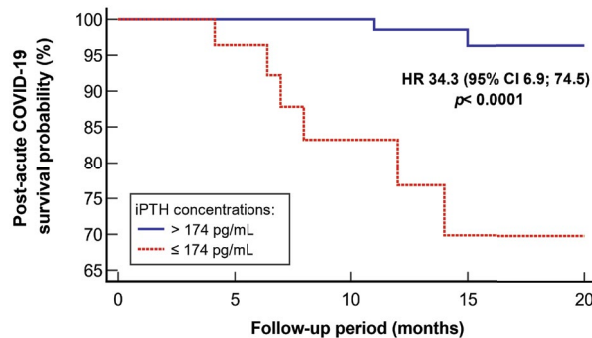
Fig. 4. ROC curve for predicting post-acute COVID-19 hospitalization in patients undergoing HD.



Number at risk

Follow-up period (months)	0	2	4	6	8	10	12	14	16	18	20
Group: > 174 pg/mL	107	104	97	87	79	72	57	47	28	17	0
Group: ≤ 174 pg/mL	35	33	28	23	19	17	12	10	6	2	0

Fig. 5. Probability of long-term hospitalization in survivors of acute COVID-19 among patients undergoing HD.



Number at risk

Follow-up period (months)	0	5	10	15	20
Group: > 174 pg/mL	107	93	73	39	0
Group: ≤ 174 pg/mL	35	24	16	7	0

Fig. 6. Post-acute survival probability in patients undergoing HD.

Discussion. Our study aimed to investigate the relationship between baseline serum iPTH levels and the severity and outcomes of COVID-19 in patients undergoing HD. The results revealed several key findings that have implications for the management of HD patients during the COVID-19 pandemic. We observed that HD patients with lower iPTH levels before contracting SARS-CoV-2 exhibited higher CRP concentrations compared to patients with Q2 and Q3 iPTH level groups. This is consistent with previous research that has suggested a link between low serum PTH levels and markers of protein-energy wasting and inflammation in dialysis patients [12]. In fact, proinflammatory cytokines such as interleukin-1 beta and interleukin-6 have been shown to inhibit PTH secretion [12, 13].

The association between lower baseline iPTH levels and severe COVID-19-associated pneumonia is an intriguing finding that emerged from our study. One possible explanation could be related to the role of iPTH in immune function. PTH receptors are located in circulating human lymphocytes and act as immunoregulatory factors [14]. Lower iPTH levels could potentially lead to impaired immune responses, making patients more susceptible to severe infections, including COVID-19-associated pneumonia. Another potential explanation could be related to the association between low iPTH levels and chronic inflammation [13]. Chronic inflammation can exacerbate the severity of COVID-19, potentially explaining why patients with lower iPTH levels experienced more severe pneumonia. A further hypothesis is related to the role of PTH in calcium metabolism. COVID-19 patients have been observed to have hypocalcemia, and imbalances in vitamin D and PTH levels may contribute to this [15, 16]. As calcium is essential for various cellular processes, including immune responses, abnormal calcium levels due to altered PTH secretion could potentially influence the severity of COVID-19. Nonetheless, the relationship between PTH levels and pulmonary function is complex and not fully understood. A study published in the Korean National Health and Nutrition Examination Survey found that higher PTH levels were associated with decreased pulmonary function and increased mortality in patients with chronic obstructive pulmonary disease (COPD) [17]. However, the study did not find an association between lower PTH levels and poor pulmonary function. Contrary, another study found that PTH levels were significantly lower in COPD patients compared with controls [18]. The data on the association between PTH levels and COVID-19-associated pneumonia are also scarce and limited to case reports [19] or theoretical [9] studies in the general population. Further research is needed to confirm this association and to explore the potential mechanisms underlying it.

Lastly, we found that the long-term hospitalization and mortality rates were significantly associated with the severity of acute COVID-19 and baseline serum iPTH levels. Specifically, the Kaplan-Meier analysis revealed a significant association between serum

iPTH concentration < 174 pg/mL and increased rates of post-acute COVID-19 hospitalization and all-cause mortality. This finding underscores the potential prognostic value of baseline iPTH levels in predicting the outcomes of COVID-19 in HD patients. Notably, there is a gap in the literature with no direct studies analyzing the impact of iPTH levels on long-term hospitalization and mortality in the HD cohort. However, some studies indirectly confirm our findings. It has been demonstrated that both very low and high serum iPTH concentrations may be associated with increased all-cause [7, 8] and infection-related mortality in dialysis patients [14]. Low iPTH levels in HD patients can lead to low bone turnover and formation. This reduction in bone activity diminishes the capacity to regulate circulating calcium and phosphorus levels, potentially making patients more susceptible to arterial vascular calcification and increased mortality rate [20]. Interestingly, the overall trend observed in serum phosphate levels mirrored that of iPTH, demonstrating a U-shaped pattern in the adjusted relative risk estimates [20]. In turn, several studies have shown that imbalances in calcium and phosphate metabolism can be associated with worse outcomes in COVID-19 patients. For instance, hypocalcemia, which can be associated with low iPTH levels, has been identified as an independent risk factor for long-term hospitalization in COVID-19 patients [21]. Hypophosphatemia has been associated with severe lung injuries in COVID-19 patients, resulting in increased hospitalization and mortality risk in the general population of COVID-19 patients [22–24].

Our study has several limitations that should be acknowledged. Firstly, the retrospective nature of the design introduces inherent biases and impedes the establishment of causal relationships. The exclusion criteria, such as the omission of patients with specific comorbidities, may lead to selection bias, limiting the generalizability of results to a broader hemodialysis population. Moreover, the study cohort's limited size may compromise statistical power and generalizability. Additionally, relying on two baseline iPTH measurements within a year before COVID-19 onset may not fully capture dynamic changes in iPTH levels over time. Lastly, the study lacks detailed information on the specific treatment protocols followed for COVID-19, including variations in medication regimens, which could impact outcomes.

Conclusions. In conclusion, our study suggests that low baseline serum iPTH levels might be associated with the severity and adverse long-term COVID-19 outcomes in patients undergoing HD. Serum iPTH concentration ≤ 174 pg/mL was significantly associated with increased post-acute hospitalization and mortality rate in our patient cohort. These findings could have important implications for the management of these patients during the COVID-19 pandemic. However, further research is needed to confirm our findings and to explore the potential mechanisms underlying the observed associations.

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

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Data availability. The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors’ contribution.

L. Snisar: conceptualization, data analysis, and manuscript writing;

A. Rysyev: data collection and statistical processing;

I. Poperechnyi: data collection;

V. Filonov: data collection;

T. Ostapenko: data analysis and manuscript reviewing;

V. Marchenko: data collection;

V. Dzhur: data collection.

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