Оригінальні дослідження

Ferritin level predicts in-hospital mortality in hypertensive patients with COVID-19

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article;
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Aim. This study aimed to establish the predictive ability of serum ferritin levels for severe / critical condition development, need for supplemental oxygen, and in-hospital mortality in hypertensive patients with COVID-19-associated pneumonia.

Materials and methods. 135 unvaccinated patients hospitalized for COVID-19-associated pneumonia were enrolled in the study. 78.5 % of patients were hypertensive.

Results. Among hypertensive patients, the median ferritin level at admission was 315.5 (169.0–396.0) ng/mL in patients with moderate condition, 374.0 (171.0–709.5) ng/mL in patients developed severe condition, and 489.0 (362.0–1128.5) ng/mL in patients developed critical condition (P = 0.03). Serum ferritin level at admission was higher in non-survivors (539.0 (440.0–1128.5) ng/mL) than that in survivors (332.5 (172.0–545.0) ng/mL, P = 0.02). Hypertensive patients who required supplemental oxygen had higher median serum ferritin level (446.0 (187.0–763.0) ng/mL) than patients without the requirement of supplemental oxygen (324.0 (165.0–401.0) ng/mL, P = 0.02). There was poor discrimination ability of ferritin level in the prediction of severe / critical conditions (AUC = 0.628, P = 0.02) and the need for supplemental oxygen (AUC = 0.629, P = 0.02). There was an acceptable discrimination ability of ferritin level in the in-hospital mortality prediction (AUC = 0.701, P = 0.03); the Youden index was 0.54, the associated criterion was >438.0 ng/mL with 83.3 % sensitivity and 70.7 % specificity. Ferritin level >438.0 ng/mL at admission was associated with a significant increase in in-hospital mortality (OR = 12.04 (2.47–58.62), P = 0.002).

Conclusions. Serum ferritin level at hospital admission increases with the severity of COVID-19 in hypertensive patients. Serum ferritin level predicts in-hospital mortality in hypertensive patients. However, its predictive ability for the disease progression to severe/critical conditions and the need for supplemental oxygen is poor. A ferritin level of 438.0 ng/mL is proposed to be a cut-off value for the prediction of in-hospital mortality.

Рівень феритину як предиктор внутрішньогоспітальної смертності в пацієнтів із COVID-19 та артеріальною гіпертензією

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Мета роботи – встановити прогностичну значущість рівнів феритину сироватки крові на час госпіталізації щодо тяжкого / вкрай тяжкого перебігу, потреби в кисневій терапії та внутрішньогоспітальної смертності в пацієнтів з артеріальною гіпертензією та пневмонією, що асоційована з коронавірусною хворобою COVID-19.

Матеріали та методи. У дослідженні взяли участь 135 невакцинованих пацієнтів, госпіталізованих з приводу пневмонії, що асоційована з коронавірусною хворобою COVID-19. Артеріальну гіпертензію діагностували в 78,5 % хворих.

Результати. Серед пацієнтів з артеріальною гіпертензією середній рівень феритину під час госпіталізації становив 315,5 (169,0–396,0) нг/мл у пацієнтів із середньотяжким перебігом, 374,0 (171,0–709,5) нг/мл у хворих із тяжким перебігом, 489,0 (362,0–1128,5) нг/мл у пацієнтів із вкрай тяжким перебігом (р = 0,03). Рівень феритину під час госпіталізації був вищим у тих пацієнтів, які померли (539,0 (440,0–1128,5) нг/мл), ніж у тих, хто одужав (332,5 (172,0–545,0) нг/мл, р = 0,02). Хворі на артеріальну гіпетензію, які потребували кисневої терапії, мали вищий рівень феритину сироватки крові (446,0 (187,0–763,0) нг/мл), ніж пацієнти, які не потребували такої терапії (324,0 (165,0–401,0) нг/мл, р = 0,02). Виявили слабкі дискримінаційні властивості рівня феритину сироватки крові щодо прогнозування тяжкого / вкрай тяжкого перебігу (AUC = 0,628, р = 0,02) та потреби в кисневій терапії (AUC = 0,629, р = 0,02). Визначили задовільну дискримінаційну здатність рівня феритину сироватки крові щодо прогнозування внутрішньогоспітальної смертності (AUC = 0,701, р = 0,03); індекс Юдена – 0,54, асоційований критерій становив >438,0 нг/мл із чутливістю 83,3 % і специфічністю 70,7 %. Рівень феритину >438,0 нг/мл під час госпіталізації асоціювався зі значним підвищенням внутрішньогоспітальної смертності (відношення шансів – 12,04 (2,47–58,62), р = 0,002).

Висновки. Рівень феритину сироватки крові під час госпіталізації зростає з тяжкістю коронавірусної хвороби COVID-19 у пацієнтів з артеріальною гіпертензією. Рівень сироваткового феритину є предиктором внутрішньогоспітальної смертності у хворих на артеріальну гіпертензію. Однак його предиктивні властивості щодо тяжкого / вкрай тяжкого перебігу та потреби в кисневій терапії є слабкими. Рівень феритину 438,0 нг/мл можна вважати пороговим значенням щодо прогнозування внутрішньогоспітальної смертності.

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was first described in December 2019 and rapidly spread worldwide leading to the COVID-19 pandemic. As of 1 September 2022, there were over 627 million confirmed cases of COVID-19 including over 6.5 million deaths globally [1]. According to the meta-analysis conducted by Y. Hu et al., mortality ranges from 2.0 % to 4.4 % with pooled estimates of 3.2 % and the prevalence of severe disease ranges

from 12.6 % to 23.5 % with pooled estimates of 18.0 % [2]. Patients with arterial hypertension have 2-fold higher risks of severe disease and mortality [3]. The assessment of biomarkers that may predict disease progression and mortality in hospitalized hypertensive patients is of important value.

It is established that several biomarkers are associated with severe COVID-19 including C-reactive protein, procalcitonin, D-dimer, ferritin, IL-6, IL-10, and soluble IL-2 receptors [4–6]. High ferritin levels in patients with severe COVID-19 may represent hyperinflammation and cytokine storm and may serve as an important predictor of severe disease and mortality [7–9]. Ferritin level appears to be higher in hypertensive patients [10,11]. While the predictive ability of ferritin level was well studied in COVID-19 in the general population, its predictive ability has not been studied in hypertensive patients.

Aim

This study aimed to establish the predictive ability of serum ferritin levels for severe/critical condition development, need for supplemental oxygen, and in-hospital mortality in hypertensive patients with COVID-19-associated pneumonia.

Materials and methods

This was a single-centre prospective clinical study conducted in Ivano-Frankivsk Central City Hospital and Ivano-Frankivsk City Hospital No. 1.

135 adult patients hospitalized for COVID-19-associated pneumonia were enrolled in the study between March and June 2021. All the patients were not vaccinated for COVID-19. 106 (78.5%) patients had arterial hypertension.

Inclusion criterion – pneumonia associated with laboratory-confirmed COVID-19.

Exclusion criteria: pregnancy; age <18 years old; moderate and severe cognitive decline; acute myocardial infarction; acute period of stroke; stage V chronic kidney disease; active cancer.

Pneumonia was confirmed by chest computed tomography or chest X-ray. Coronavirus SARS-CoV-2 as an etiological agent of pneumonia was confirmed with either PCR or ELISA test with the assessment of IgM level.

COVID-19-associated pneumonia severity was assessed according to the Protocol of Medical Care for Treatment of Coronavirus Disease (COVID-19) [12]. A severe clinical condition was defined as the presence of at least one of the following characteristics: respiratory rate ≥30 breaths per minute, oxygen saturation ≤93 %, and pulmonary infiltrates occupying >50 % of the lung area. The critical condition was defined as the presence of at least one of the followings: acute respiratory distress syndrome, sepsis, altered consciousness, and multiple organ dysfunction syndrome.

Besides conventional laboratory tests (complete blood count, urinalysis, biochemical profile, fasting blood glucose), ferritin levels (L2KFE2, Immulite 2000 Ferritin, "Siemens", ELISA test) were measured.

A consent form was signed by each prospective participant before recruitment into the study. All of the procedures in the study met bioethical standards according to the Helsinki Declaration.

Statistical processing of the study results was performed using the software Statistica 10, MedCalc, and MS Excel. Shapiro–Wilk test was used to evaluate the distribution of variables. Descriptive statistics for data with abnormal distribution were presented as the median and interquartile range (Me (Q1–Q3)). Mean with standard deviation (Mean ± SD) was calculated for descriptive statistics for data with normal distribution. T-test, Mann–Whitney U test, Kruskal–Wallis test with post-hock Dunn's test, were performed. Also, the odds ratio (OR), diagnostic test parameters (sensitivity, specificity, predictive values, and likelihood ratios), and the Youden index were calculated. Receiver operating characteristic (ROC) curves were built. A P-value <0.05 was considered significant.

Results

Participants. The mean age was 68.4 ± 1.7 years in hypertensive patients and 59.1 ± 4.9 years in non-hypertensive patients (P = 0.01). Among hypertensive patients, 41 (38.7 %) were males and 65 (61.3 %) were females. Among non-hypertensive patients, 12 (41.4 %) were males and 17 (58.6 %) were females. The mean body mass index was 28.7 ± 1.1 kg/m^2 in hypertensive patients and 28.4 ± 1.9 kg/m^2 in non-hypertensive patients (P = 0.74).

The median systolic blood pressure at the moment of hospital admission was 130.0 (120.0–140.0) mm Hg in hypertensive patients and 120.0 (110.0–130.0) mm Hg in non-hypertensive patients (P < 0.001). The median diastolic blood pressure at the moment of hospital admission was 80.0 (80.0–90.0) mm Hg in hypertensive patients and 80.0 (70.0–80.0) mm Hg in non-hypertensive patients (P = 0.047).

Among hypertensive patients, 48 (45.3 %) received angiotensin-converting enzyme (ACE) inhibitors, 31 (29.2 %) took angiotensin receptor blockers, 35 (33.0 %) received diuretics (thiazide, thiazide-like and loop), 39 (36.8 %) took beta-blockers, and 34 (32.1 %) received calcium channel blockers before hospital admission. Totally, among hypertensive patients, 87 (82.1 %) took at least 1 anti-hypertensive agent before hospital admission. Among non-hypertensive patients, 5 (17.2 %) received beta-blockers, and 3 (10.3 %) took loop diuretics before hospital admission; these medications were taken for reasons other than arterial hypertension. None of the non-hypertensive patients received ACE inhibitors, angiotensin receptor blockers and calcium channel blockers prior to hospitalization.

Among hypertensive patients, 59 (55.7 %) were prescribed ACE inhibitors, 33 (31.1 %) received angiotensin receptor blockers, 45 (42.5 %) were administered diuretics, 38 (35.8 %) took beta-blockers, and 38 (35.8 %) were prescribed calcium channel blockers during the in-patient stay. Among non-hypertensive patients, 7 (24.1 %) were administered beta-blockers, 3 (10.3 %) took diuretics and 1 (3.4 %) received angiotensin receptor / neprilysin inhibitor.

Among hypertensive patients 47 (44.3 %) had a moderate clinical condition, 46 (43.4 %) patients developed a severe clinical condition, and 13 (12.3 %) patients developed a critical clinical condition. Among non-hypertensive patients, 16 (55.2 %) had a moderate clinical condition, 9 (31.0 %) developed a severe clinical condition and 4 (13.8 %) patients developed a critical clinical condition.

Among hypertensive patients, 50 (47.2 %) developed the need for supplemental oxygen. Among non-hypertensive patients, 12 (41.4 %) developed the need for supplemental oxygen during the inpatient stay.

12 (11.3 %) hypertensive patients and 2 (6.9 %) non-hypertensive patients died.

The median serum ferritin level at the moment of hospital admission in hypertensive patients (349.0 (176.0–572.5) ng/mL) and non-hypertensive patients (349.0 (189.0–746.5) ng/mL) was equal (P = 0.92).

The association between ferritin level at the moment of hospital admission and the severity of COVID-19 is shown in *Table 1*. Among hypertensive patients, serum ferritin level at the moment of hospital admission was higher in patients who developed critical condition than that in patients with moderate clinical condition (P = 0.01). Also, there was no significant difference in the serum ferritin level in patients who developed severe and critical conditions (P = 0.16).

Non-hypertensive patients who developed severe clinical condition had a higher serum ferritin level at the moment of hospital admission than patients in moderate clinical condition (P = 0.01). Also, among non-hypertensive patients, there was no statistically significant difference in serum ferritin level between patients in critical clinical condition and the ones in severe (P = 0.08) or moderate (P = 0.84) clinical conditions.

Among all enrolled patients, serum ferritin level was lower in patients with moderate clinical condition compared to patients who developed severe (P = 0.02) and critical condition (P = 0.01). The difference in ferritin levels between patients in severe clinical condition and those in critical clinical condition was not statistically significant (P = 0.62).

Among hypertensive patients, serum ferritin level at the moment of hospital admission was higher in non-survivors (539.0 (440.0–1128.5) ng/mL) than that in survivors (332.5 (172.0–545.0) ng/mL, P = 0.02). Hypertensive patients who required supplemental oxygen had higher median serum ferritin level (446.0 (187.0–763.0) ng/mL) than patients without the requirement of supplemental oxygen (324.0 (165.0–401.0) ng/mL, P = 0.02).

Among hypertensive patients, men had a higher median serum ferritin level than women (396.5 (257.5–923.5) ng/mL in men vs. 304.0 (161.0–443.5) ng/mL in women, P = 0.01). There was no significant difference in the median serum ferritin level between obese patients (body mass index (BMI) ≥30.0 kg/m²) and non-obese patients (BMI <30.0 kg/m²) (402.0 (167.0–733.0) ng/mL vs. 338.0 (202.5–523.5) ng/mL, respectively, P = 0.35).

Predictive ability of ferritin level at admission in hypertensive patients. *Fig. 1* shows poor discrimination ability (AUC = 0.628, P = 0.02) of serum ferritin level in the prediction of severe / critical clinical conditions in hypertensive patients. The Youden index was 0.34 indicating the poor ability of serum ferritin level to predict severe / critical clinical condition; the associated criterion was >402.0 ng/mL with a sensitivity of 53.5 % and specificity of 80.4 %.

As shown in *Fig. 2*, there was a poor discrimination ability (AUC = 0.629, P = 0.02) of serum ferritin level in the prediction of the need for supplemental oxygen in hypertensive patients. The Youden index was 0.37 indicating an overall

Table 1. Serum ferritin levels at the moment of hospital admission in patients who developed moderate, severe and critical clinical conditions

Patient category	Patients in moderate condition¹, ng/mL	Patients in severe condition², ng/mL	Patients in critical condition³, ng/mL	P-value		
Hypertensive patients (n = 106)	315.5 (169.0–396.0)	374.0 (171.0–709.5)	489.0 (362.0–1128.5)	**Kruskal–Wallis test: P = 0.03 Post-hock Dunn's test:**		
					1	2
				2	P = 0.10	–
				3	P = 0.01	P = 0.16
Non-hypertensive patients (n = 29)	264.5 (182.5–363.0)	788.0 (449.0–1080.0)	266.5 (100.0–687.5)	**Kruskal–Wallis test: P = 0.02 Post-hock Dunn's test:**		
					1	2
				2	P = 0.01	–
				3	P = 0.84	P = 0.08
All patients (n = 135)	281.0 (172.0–388.0)	416.5 (185.0–805.0)	446.0 (212.0–993.0)	**Kruskal–Wallis test: P = 0.01 Post-hock Dunn's test:**		
					1	2
				2	P = 0.01	–
				3	P = 0.02	P = 0.62

Table 2. The predictive ability of serum ferritin level for in-hospital mortality in hypertensive patients

Criterion	Sensitivity	Specificity	+LR	-LR	+PV	-PV
≥40.9	100	0	1		11.5	
>64.9	91.67	3.26	0.95	2.56	11	75
>122	91.67	11.96	1.04	0.7	12	91.7
>208	83.33	30.43	1.2	0.55	13.5	93.3
>307	83.33	46.74	1.56	0.36	16.9	95.6
>402	83.33	67.39	2.56	0.25	25	96.9
>438	83.33	70.65	2.84	0.24	27	97
>446	58.33	70.65	1.99	0.59	20.6	92.9
>589	41.67	78.26	1.92	0.75	20	91.1
>733	33.33	83.7	2.04	0.8	21.1	90.6
>960	33.33	90.22	3.41	0.74	30.8	91.2
>1018	25	92.39	3.29	0.81	30	90.4
>1249	16.67	94.57	3.07	0.88	28.6	89.7
>1470	8.33	94.57	1.53	0.97	16.7	88.8
>1500	0	100		1		88.5

+LR: positive likelihood ratio; **-LR:** negative likelihood ratio;
+PV: positive predictive value; **-PV:** negative predictive value.

poor ability of serum ferritin level to predict the need for supplemental oxygen; the associated criterion was >411.0 ng/mL with a sensitivity of 57.1 % and specificity of 80.0 %.

There was an acceptable discrimination ability (AUC = 0.701, P = 0.03) of serum ferritin level in the prediction of in-hospital mortality in hypertensive patients (*Fig. 3*). The Youden index was 0.54 indicating an acceptable ability of serum ferritin level to predict in-hospital mortality; the associated criterion was >438.0 ng/mL with a sensitivity of 83.3 % and specificity of 70.7 %.

The predictive ability of serum ferritin levels for severe / critical clinical condition development and in-hospital mortality is shown in *Table 2*.

Ferritin level >438.0 ng/mL at the moment of hospital admission was associated with a significant increase in the in-hospital mortality (OR=12.04 (2.47–58.62), P = 0.002).
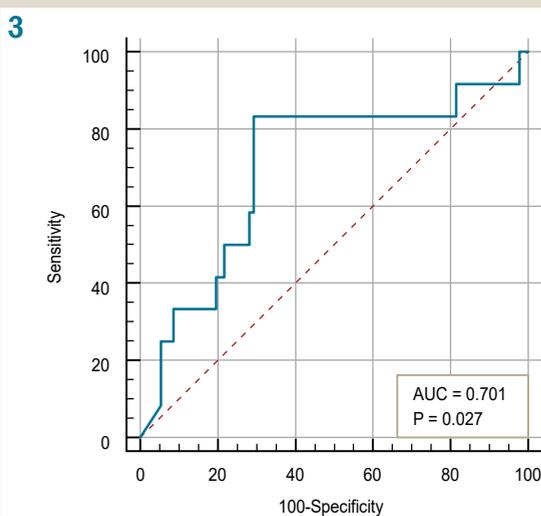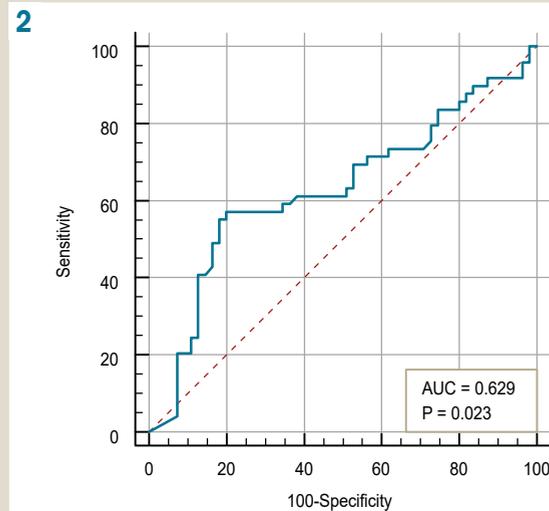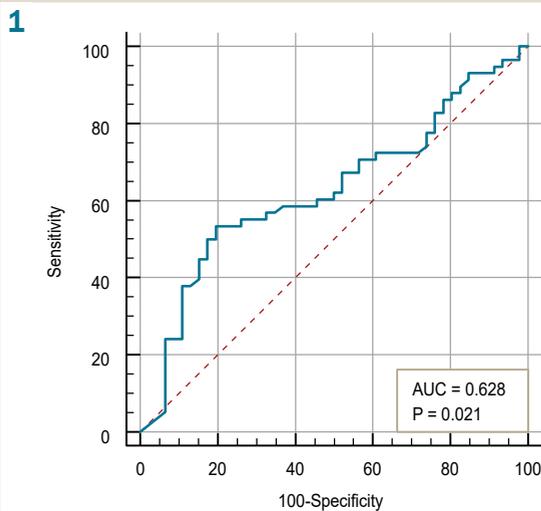
1

AUC = 0.628
P = 0.021

2

AUC = 0.629
P = 0.023

3

AUC = 0.701
P = 0.027

Fig. 1. ROC curve of serum ferritin level at the moment of hospital admission for prediction of severe / critical clinical condition in hypertensive patients.

Fig. 2. ROC curve of serum ferritin level at the moment of hospital admission for prediction of need for supplemental oxygen in hypertensive patients.

Fig. 3. ROC curve of serum ferritin level at the moment of hospital admission for prediction of in-hospital mortality in hypertensive patients.

Discussion

Our study has demonstrated that there was no significant difference in serum ferritin levels between hypertensive and non-hypertensive patients with COVID-19-associated pneumonia. Hypertensive patients who developed critical clinical condition had a higher serum ferritin level at the moment of hospital admission than patients in moderate clinical condition. Among all enrolled patients, serum ferritin levels at the moment of hospital admission increased with the disease severity. Also, among hypertensive patients, ferritin level at the moment of hospital admission was higher in non-survivors than in survivors. Patients who developed the requirement of supplemental oxygen had a higher ferritin level at the moment of hospital admission than patients who did not require supplemental oxygen.

According to the meta-analysis performed by K. Kaushal et al., high ferritin level is associated with more severe disease and poor outcome in COVID-19 [8]. A study performed by D. A. Shakaroun et al. showed that a ferritin level of >490 ng/mL was associated with an increased risk of a lethal outcome, admission to the intensive care unit and need for mechanical ventilation [13]. For every 100 ng/mL increase in ferritin, the odds of in-hospital mortality were 3.2 % increased [14]. High ferritin level was associated with a more severe pulmonary involvement [14].

Our study has shown poor discrimination ability of ferritin level at admission for disease progression to severe / critical condition (AUC = 0.628, P = 0.02) and need for supplemental oxygen (AUC = 0.629, P = 0.02). The optimal cut-off value for severe/critical outcome development was 402 ng/mL. Similar results were published by D. Ji et al., ferritin level >400 ng/mL at presentation was predictive of progression to the severe clinical condition [15]. Our study has shown acceptable discrimination ability of ferritin level at admission for in-hospital mortality (AUC = 0.701, P = 0.03). An optimal cut-off ferritin level for the prediction of mortality was 438.0 ng/mL. The Youden index for the prediction of mortality was higher than the one for the prediction of progression to severe/critical clinical condition.

The results of a cross-sectional study conducted by S. Ahmed et al. [16] have shown that ferritin level was a slightly better predictor of mortality than severity, with an AUC of 0.69 and 0.66, respectively. The study has demonstrated that the optimal cut-off ferritin level was 574.5 ng/mL

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for the prediction of mortality and 354 ng/mL for the prediction of severe disease [16]. These data correspond to the results of our study.

Our study has demonstrated higher ferritin levels in men than in women. Several studies showed controversial results regarding ferritin levels in men and women infected by COVID-19. A study performed by J. Chen et al. has shown higher mean ferritin levels in females (598.74 ng/mL) than in males (511.21 ng/mL) among patients with COVID-19 [17]. However, another study has shown higher ferritin levels in males (1024.54 µg/L) than in females (531.13 µg/L) (P < 0.001) [18]. Also, this study has demonstrated that ferritin level was an independent predictor of disease severity in both males and females [18].

There were some limitations requiring careful extrapolation of the study results. First, all patients included in the study were not vaccinated against COVID-19. Second, there was no mild clinical condition as all patients included in the study had radiologically confirmed pneumonia. Third, the number of patients.

Conclusions

1. Serum ferritin level at the moment of hospital admission increases with the severity of COVID-19 in hypertensive patients.

2. Serum ferritin level predicts in-hospital mortality in hypertensive patients.

3. However, its predictive ability for disease progression to severe / critical conditions and the need for supplemental oxygen is poor.

4. A ferritin level of 438.0 ng/mL is proposed to be a cut-off value for the prediction of in-hospital mortality.

Further perspectives include a comparison between the predictive ability of the ferritin level in men and women, an assessment of the predictive ability of ferritin level dynamic changes in hospitalized patients.

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