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ОРИГИНАЛНИ СТАТИИ

Factors associated with adverse outcomes in hospitalized older adult patients with COVID-19

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Фактори, асоциирани с неблагоприятен изход при хоспитализирани възрастни пациенти с COVID-19

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Abstract:

Introduction: Older patients with COVID-19 (Coronavirus disease 2019) are at increased risk of adverse outcome. The aim of this study was to evaluate clinical and laboratory factors associated with prognosis in hospitalized patients aged ≥ 49 years. **Materials and Methods:** A retrospective study was conducted among 93 patients with confirmed COVID-19. Demographic data, symptoms at admission, laboratory parameters, serum amyloid A (SAA), and hospital outcome (improvement or severe outcome) were analyzed. The Mann–Whitney U test, Fisher's exact test, and Receiver Operating Characteristic (ROC) analysis were used. **Results:** The patients' age was a factor associated with the results – a significant number of patients with adverse outcome were older patients (p = 0.008), while the patients'sex was not a significantly associated factor (p = 0.999). No statistically significant relationships were found for clinical symptoms, while dyspnea showed borderline significance (p = 0.059). Significant laboratory differences were established for hematocrit (p = 0.028), urea (p=0.001), creatinine (p = 0.001), and D-dimer (p = 0.011). Categorized SAA was not significantly associated with outcome (p = 0.393). ROC analysis showed very good prognostic value of urea (AUC = 0.949) and good value of D-dimer (AUC = 0.838) for predicting adverse outcome (fatal outcome). **Conclusion:** Advanced age, lower hematocrit, and increased levels of urea, creatinine, and D-dimer were associated with adverse outcome in older patients with COVID-19. Urea and D-dimer may be useful markers for early risk stratification.

Key words: COVID-19, older patients, prognosis, biomarkers, urea, D-dimer, serum amyloid A, mortality

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Резюме:

Въведение: Възрастните пациенти са сред най-уязвимите групи при COVID-19, но факторите, свързани с неблагоприятен изход при хоспитализирани болни, невинаги са еднозначно установени. Целта на настоящото проучване е да се анализират демографските, клиничните, лабораторните, образните, микробиологичните и терапевтичните характеристики на възрастни пациенти с COVID-19 и тяхната връзка с изхода от заболяването. **Материал и методи**: Проведено е ретроспективно наблюдателно кохортно проучване сред 93 хоспитализирани възрастни пациенти с потвърден COVID-19. Анализирани са демографски показатели, симптоми при прием, съпътстващи заболявания, лабораторни параметри, образни и микробиологични находки, както и проведената терапия. Изходът е класифициран като подобрение или летален изход. Статистическа значимост е приета при $p < 0.05$. **Резултати**: Полът не показва статистически значима връзка с тежкия изход, докато възрастта е значимо по-висока при пациентите с неблагоприятен изход ($p = 0.008$). От клиничните прояви нито един симптом не достига статистическа значимост, като задухът показва гранична стойност ($p = 0.059$). Сред коморбидностите единствено заболяванията на дихателната система са свързани статистически значимо с неблагоприятен изход ($p = 0.003$). От лабораторните показатели значими разлики се установяват за хематокрит ($p = 0.028$), урея ($p = 0.001$), креатинин ($p = 0.001$) и D-димер ($p = 0.011$). Категоризираният SAA (серумен амилоид А) не показва значима асоциация с изхода ($p = 0.393$). Рентгенографските находки не са свързани значимо с изхода, а сред микробиологичните резултати единствено изолирането на Candida albicans е асоциирано с по-висока честота на неблагоприятен изход ($p = 0.034$). Кислородната сатурация, разделена в пет категории, не показва статистически значима връзка с изхода ($p = 0.663$). ROC анализът показва много добра дискриминационна способност на уреята (AUC = 0.949) и добра дискриминационна способност на D-димера (AUC = 0.838) за предсказване на тежък изход. Кислородотерапията ($p = 0.013$) и кортикостероидната терапия ($p = 0.021$) са по-чести при пациентите с неблагоприятен изход. **Заключение**: В настоящата кохорта по-високата възраст, заболяванията на дихателната система, по-ниският хематокрит и повишените стойности на урея, креатинин и D-димер са свързани с неблагоприятен изход при хоспитализирани възрастни пациенти с COVID-19. Уреята и D-димерът показват добра прогностична стойност, докато повечето начални клинични симптоми, рентгенографските находки и категоризираният SAA не демонстрират статистически значима асоциация с изхода.

Ключови думи: COVID-19, възрастни пациенти, рискови фактори, D-димер, урея

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Introduction

COVID-19 is characterized by significant variability in the clinical course – from mild presentation to severe pneumonia, acute respiratory failure, and fatal outcome. In this context, the identification of prognostic factors associated with adverse outcome is of essential importance for early risk stratification and optimization of the therapeutic approach. Among the early clinical indicators for assessment of disease severity, the reduced SpO_2/FiO_2 index at admission, reflecting the degree of hypoxemia, has been established as an early predictor of severe course and mortality in COVID-19, especially in patients at advanced age, male patients, and patients with increased body mass index (BMI) [1]. In addition, accumulating data show that elevated levels of systemic inflammation at admission are associated with increased risk of in-hospital mortality, and this effect may vary depending on the presence of pre-existing cardiovascular diseases [2]. In this context, a number of laboratory parameters, including lymphopenia, elevated levels of C-reactive protein (CRP), lactate dehydrogenase (LDH), and D-dimer, as well as disturbances in coagulation and organ function, have been established as important indicators of adverse course and increased risk of mortality [3]. Elevated D-dimer levels at admission have been established as an independent prognostic marker associated both with disease severity and with increased risk of in-hospital mortality [4]. In summary, adverse outcome in COVID-19 is associated with advanced age, presence of comorbidities, delayed hospital admission, as well as development

of systemic inflammation, coagulation disorders, and multiorgan damage affecting the heart, kidneys, and liver [5]. In severe course, these processes are characterized by a hyperinflammatory response, coagulation disorders, and acute lung injury, as well as by increased risk of secondary infections and delayed viral clearance [6].

Materials and methods

Methods

A retrospective analysis was conducted of 93 adult patients hospitalized with confirmed Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Demographic, clinical, laboratory, imaging, microbiological, therapeutic, and outcome data were extracted from hospital medical records. The primary endpoint was clinical outcome, classified as improvement or adverse outcome (fatal outcome). All analyses were performed on the full study group (n = 93).

Study Design and Study Population

The present study represents a retrospective observational cohort study conducted at the University Multi-Profile Hospital for Active Treatment of Infectious and Parasitic Diseases "Prof. Ivan Kirov", Sofia, Bulgaria, during the period from 23.09.2023 to 12.12.2023.

The study included 93 adult patients hospitalized with a confirmed diagnosis of COVID-19 within the study period. The diagnosis of SARS-CoV-2 infection was confirmed by a positive result from reverse transcription polymerase chain reaction (RT-PCR) or rapid antigen test for SARS-CoV-2 in accordance with national diagnostic recommendations.

All consecutive hospitalized adult patients meeting the diagnostic criteria for COVID-19 during the study period were assessed for inclusion in the study. Patients were excluded in cases of unclear diagnosis of SARS-CoV-2 infection or absence of essential data in the medical documentation.

The final study cohort included 93 patients with laboratory-confirmed COVID-19. Clinical outcome during hospitalization was classified as improvement or adverse outcome (death).

Data Collection

Clinical and laboratory data were extracted from the patients' medical records.

The following variables were analyzed:

Demographic characteristics: age, sex.

Clinical symptoms assessed included temperature, cough, rhinitis, headache, joint-muscle pain, dyspnea, gastrointestinal symptoms (nausea, vomiting, diarrhea, loss of appetite), disturbances in smell and/or taste.

The patients included in the study had the following comorbidities:

Comorbidities were recorded from the available medical documentation and were categorized according to the affected organ system. For the purpose of the analysis, concomitant diseases were grouped into cardiovascular, respiratory, endocrine/metabolic, renal and urological, neurological, neurodegenerative/cognitive, gastrointestinal, oncological, rheumatological/autoimmune, hematological, musculoskeletal, dermatological, infectious, psychiatric, and other conditions. Individual diagnoses were not analyzed separately because of their heterogeneity and the low number of patients in some subgroups.

In all patients included in the study, baseline vital signs, as well as the following laboratory tests at admission, were analyzed: arterial blood pressure, pulse, oxygen saturation (SaO_2).

Laboratory investigations: complete blood count, C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH), urea, creatinine, liver enzymes (AST, ALT), D-dimer, serum amyloid A (SAA), INR, APTT, blood gas analysis from capillary blood.

Definitions

The possible clinical outcomes were classified into two categories:

Improvement – clinical stabilization and discharge from hospital.

Adverse outcome – fatal outcome during hospitalization.

Comorbidities were considered present when documented in the medical history, discharge summary, or other medical documents of the patient.

Laboratory abnormalities were interpreted according to the reference values of the hospital laboratory.

Statistical Analysis

Numerical variables are presented as median and interquartile range (IQR) due to their non-normal distribution. Categorical variables are presented as absolute number and relative proportion.

Normality of distribution was assessed by the Kolmogorov–Smirnov or Shapiro–Wilk test. For comparison between two groups, Fisher's exact test or the Mann–Whitney U test was used. To identify factors associated with severe COVID-19 course (need for transfer to intensive care unit or fatal outcome), binary logistic regression was used. The multivariable model was constructed using stepwise factor selection (forward selection).

The diagnostic value of factors was assessed by ROC-curve analysis. Optimal cut-off values were determined at the maximum value of the Youden index.

Results were considered statistically significant at $p < 0.05$. All analyses were performed using IBM SPSS statistical software, version 29.

Ethical Considerations

This study is a retrospective, non-interventional analysis of routinely collected clinical data, conducted at the University Multi-Profile Hospital for Active Treatment of Infectious and Parasitic Diseases "Prof. Ivan Kirov" – EAD, Sofia, Bulgaria. All laboratory, clinical, and imaging investigations included in the analysis are part of the routine and mandatory diagnostic investigations performed during hospitalization of patients with COVID-19 according to the current clinical practice in the medical institution.

According to the national legislation of the Republic of Bulgaria and the internal rules of the institution, retrospective analyses of already existing medical documentation, performed without repeated contact with patients, without interventions, and without collection of additional data, using fully anonymized data, do not require formal approval by an ethics committee.

Data Availability

The dataset analyzed within the present study is available from the corresponding author upon reasonable request.

Results

Table 1 presents the demographic and clinical characteristics of older patients with COVID-19. In the studied cohort, no statistically significant association was found between sex and adverse disease outcome ($p = 0.999$). The proportion of adverse events was similar in men (4.4%) and women (6.3%). Age showed a statistically significant relationship with disease outcome, with patients with adverse outcome being older compared to those with improvement ($p = 0.008$). The degree of fever at admission also did not show a significant relationship with outcome ($p = 0.871$). Adverse outcome was observed in 3.3% of patients with normal temperature, 12.5% of those with subfebrile temperature, and 5.8% of those with febrile temperature. No severe cases were registered in the group with highly febrile temperature (≥39.8 °C), although the number of patients in this subgroup was limited ($n = 3$). Regarding respiratory symptoms, rhinitis was not associated with severe disease course ($p = 0.763$). For cough, a tendency toward a higher proportion of adverse outcomes was observed in patients with duration longer than 10 days (11.1%), but the difference did not reach statistical significance ($p = 0.089$). Headache ($p = 0.475$) and myalgia/arthralgia ($p = 0.406$) did not demonstrate a significant relationship with adverse outcome. Dyspnea showed borderline statistical significance ($p = 0.059$). No severe cases were registered among patients without dyspnea, whereas 10.0% of those with dyspnea had an adverse outcome. Gastrointestinal symptoms as a group were not statistically significant ($p = 0.379$). Loss of appetite ($p = 0.396$), nausea ($p = 0.583$), and vomiting ($p = 0.588$) were not associated with a significant difference in outcome. In patients with diarrhea, a higher relative proportion of adverse outcome was observed (14.3% versus 3.8% in those without diarrhea), but without statistical significance ($p = 0.162$). Disturbances in smell and/or taste were not associated with severe disease course ($p = 0.999$), with one patient without adverse outcome registered in this subgroup.

Table 2 presents the comparison of laboratory parameters between patients with improvement and those with adverse outcome.

Among the hematological parameters, only hematocrit (HCT) showed a statistically significant difference between the groups. The median value in patients with adverse outcome was lower (31.5 [31.4–34.0]) compared to the one of the improvement group (38.8 [36.0-43.1]; $p = 0.028$). Hemoglobin demonstrated a tendency toward lower values in severe cases ($p = 0.060$), without reaching statistical significance. Markers of inflammation and leukocyte formula (WBC, Lym, MLR, PLR), as well as platelets (PLT), did not show statistically significant differences between the groups ($p > 0.05$).

Among the biochemical parameters, significant differences were established for:

- Urea – significantly higher in adverse outcome (27.70 [16.70-34.60] versus 7.30 [5.20-10.35]; $p = 0.001$).
- Creatinine – also higher in severe cases (233.6 [213.0-300.2] versus 90.1 [65.2-128.0]; $p = 0.001$).
- D-dimer – higher values in adverse outcome (2.10 [1.89-10.00] versus 1.01 [0.61-2.01]; $p = 0.011$).

The remaining parameters – CRP, liver enzymes (ALT, AST), blood glucose, LDH, ferritin, INR, and APTT – did not reach statistical significance. Regarding gas exchange and acid-base status (pH, HCO_3, pO_2, pCO_2, BE), no statistically significant differences were found between the groups, although the median bicarbonate and base excess were lower in patients with adverse outcome. The duration of hospital stay

did not differ significantly between the groups (p = 0.450). In summary, in the present cohort, statistically significant laboratory differences between the groups were established mainly for parameters reflecting renal function (urea, creatinine), coagulation (D-dimer), and hematocrit, whereas the remaining hematological, inflammatory, and gas exchange parameters did not show a significant association with outcome.

Table 1. Demographic and clinical characteristics of older patients with COVID-19

Parameter	Improvement n (%)	Adverse outcome n (%)	p
Age	72 (76)	83 (90)	0.008
Sex			0.999
Male	43 (95.6%)	2 (4.4%)	
Female	45 (93.8%)	3 (6.3%)	
Temperature at admission			0.871
Normal (36-36.9 °C)	29 (96.7%)	1 (3.3%)	
Subfebrile (37-37.5 °C)	7 (87.5%)	1 (12.5%)	
Febrile (37.6-39.7 °C)	49 (94.2%)	3 (5.8%)	
Highly febrile (≥ 39.8 °C)	3 (100.0%)	0 (0.0%)	
Rhinitis			0.763
None	75 (94.9%)	4 (5.1%)	
< 3 days	2 (100%)	0 (0%)	
3-10 days	8 (88.9%)	1 (11.1%)	
> 10 days	3 (100%)	0 (0%)	
Cough			0.089
None	12 (100%)	0 (0%)	
< 3 days	18 (100%)	0 (0%)	
3-10 days	42 (93.3%)	3 (6.7%)	
> 10 days	16 (88.9%)	2 (11.1%)	
Headache			0.475
None	78 (95.1%)	4 (4.9%)	
Present	10 (90.9%)	1 (9.1%)	
Myalgia/arthralgia			0.406
None	80 (95.2%)	4 (4.8%)	
Present	8 (88.9%)	1 (11.1%)	
Dyspnea			0.059
No	43 (100%)	0 (0%)	
Yes	45 (90.0%)	5 (10.0%)	
Gastrointestinal symptoms (overall)			0.379
None	40 (97.6%)	1 (2.4%)	
Present	48 (92.3%)	4 (7.7%)	
Loss of appetite			0.396
None	53 (96.4%)	2 (3.6%)	
Present	35 (92.1%)	3 (7.9%)	
Nausea			0.583
None	72 (93.5%)	5 (6.5%)	
Present	16 (100%)	0 (0%)	
Vomiting			0.588
None	73 (93.6%)	5 (6.4%)	
Present	15 (100%)	0 (0%)	
Diarrhea			0.162
None	76 (96.2%)	3 (3.8%)	
Present	12 (85.7%)	2 (14.3%)	
Disturbances in smell and/or taste			0.999
None	87 (94.6%)	5 (5.4%)	
Present	1 (100%)	0 (0%)	

Table 2. Laboratory parameters and length of hospital stay according to disease outcome

Parameter	Improvement	Adverse outcome	p
WBC	6.5 (4.9-9.0)	9.2 (6.2-10.1)	0.315
Lym	0.79 (0.50-1.26)	0.53 (0.35-0.56)	0.190
MLR	0.24 (0.13-0.41)	0.40 (0.27-0.50)	0.193
PLR	198.6 (131.4-362.8)	250.9 (117.4-719.2)	0.746
PLT	180.0 (139.0-227.5)	155.0 (133.0-187.0)	0.459
HGB	133.5 (124.0-145.0)	114.0 (104.0-125.0)	0.060
HCT	38.8 (36.0-43.1)	31.5 (31.4-34.0)	0.028
CRP	63.7 (33.9-132.2)	85.6 (81.3-163.0)	0.220
ALT	25.0 (19.5-39.0)	25.0 (15.0-26.0)	0.289
AST	34.0 (25.5-59.5)	31.0 (23.0-36.0)	0.276
Blood glucose	7.2 (5.9-9.1)	9.0 (6.3-13.4)	0.459
LDH	297.0 (230.0-428.0)	364.0 (215.0-369.0)	0.979
Ferritin	266.6 (125.3-567.6)	157.4 (150.2-597.9)	0.776
Urea	7.30 (5.20-10.35)	27.70 (16.70-34.60)	0.001
D-dimer	1.01 (0.61-2.01)	2.10 (1.89-10.00)	0.011
INR	1.00 (0.88-1.11)	1.01 (0.98-1.10)	0.464
pH	7.43 (7.40-7.45)	7.42 (7.37-7.44)	0.527
HCO3	23.0 (21.4-24.5)	18.5 (14.7-23.7)	0.151
Creatinine	90.1 (65.2-128.0)	233.6 (213.0-300.2)	0.001
APTT	29.0 (27.8-34.0)	39.2 (25.4-53.0)	0.800
pO2	58.4 (53.2-66.4)	59.0 (56.4-61.9)	0.947
pCO2	35.5 (33.0-38.5)	28.0 (26.1–35.8)	0.140
BE	−0.85 (−2.70-0.80)	−5.10 (−9.60-0.00)	0.177
Length of hospital stay (days)	7 (6-8)	5 (2-9)	0.450

Table 3 presents the distribution of patients according to SAA levels, categorized into three groups (< 10, 10-300, and > 300), in relation to disease outcome. The largest proportion of patients falls into the group with values > 300, where 6.9% had an adverse outcome. In the 10-300 group, an adverse outcome was observed in 3.1% of patients. At values < 10 (n = 3), no adverse outcome was recorded. Although the relative proportion of adverse outcomes was higher at values > 300 compared with the other categories, the difference between the three groups did not reach statistical significance (p = 0.393). Therefore, with this categorization of SAA, no statistically significant association was established between marker level and adverse outcome in the studied cohort. The number of patients in the < 10 group was small, which limits the possibility of additional conclusions regarding this subgroup. Nevertheless, the inclusion of serum amyloid A in the analysis was justified by its role as a sensitive acute-phase protein, which is rapidly synthesized in response to pro-inflammatory cytokines (especially IL-6, IL-1, and TNF-α) and may reflect the early intensity of the systemic inflammatory response. In COVID-19, hyperinflammation and immune dysregulation are key mechanisms for progression to severe disease, which is why SAA represents a potential biomarker for the assessment of severity and prognosis. Although no statistically significant relationship with the final outcome was demonstrated in the present cohort, its investigation contributes to a more comprehensive characterization of the inflammatory profile of patients and remains a subject of interest for future studies with a larger sample size.

Table 3. Distribution of patients according to serum amyloid A (SAA) categories and disease outcome

Category	Improvement n (%)	Severe outcome n (%)	p
< 10	3 (100%)	0 (0%)	
10-300	31 (96.9%)	1 (3.1%)	
> 300	54 (93.1%)	4 (6.9%)	0.393

In Figure 1, the ROC curves present the discriminative ability of urea and D-dimer for predicting severe outcome (transfer to the ICU and/or fatal outcome). The area under the curve (AUC) for urea is 0.949 (95% CI 0.897-1.002; p < 0.001), and for D-dimer – 0.838 (95% CI 0.712-0.964; p < 0.001). The optimal cut-off values, determined by the maximum Youden index, are > 15.49 for urea (sensitivity 100%, specificity 89.7%) and > 1.78 for D-dimer (sensitivity 100%, specificity 71.3%). The ROC analysis shows that urea

has a very high discriminative ability for distinguishing between patients with favorable and unfavorable outcomes (AUC = 0.949). A value close to 1.0 indicates excellent test accuracy within the present sample. D-dimer also demonstrates good discriminative ability (AUC = 0.838), but lower compared to urea. For both indicators, the p-value is < 0.001, which shows that the discriminative ability is statistically significant compared to the reference line (AUC = 0.5).

The determined cut-off values provide 100% sensitivity for both markers in this cohort. Specificity is higher for urea (89.7%) compared to D-dimer (71.3%), indicating a better ability of urea to identify patients without severe outcome. Within the present data, urea demonstrates better overall diagnostic effectiveness compared with D-dimer for predicting severe outcome.

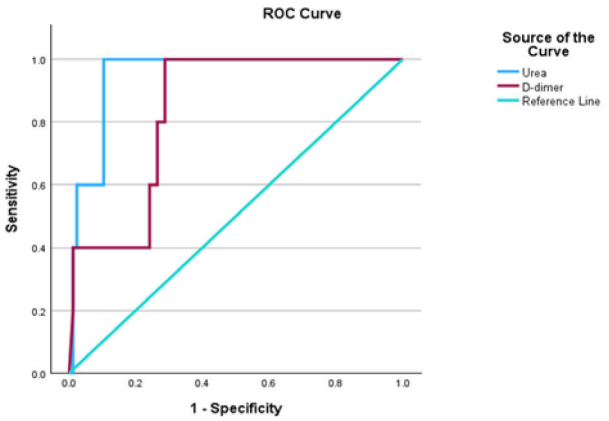

Fig. 1. ROC analysis of urea and D-dimer for predicting severe outcome in patients with COVID-19

Discussion

The literature data show that the clinical manifestations of COVID-19 are nonspecific and vary considerably among patients. A similar pattern is also observed in the present study, where none of the analyzed symptoms showed a statistically significant association with disease outcome, with the exception of a trend for dyspnea [7]. This is also consistent with systematic reviews, according to which individual symptoms have limited value for distinguishing between patient groups [8].

Regarding comorbidities, diseases of the respiratory system were the only group with a statistically significant association with adverse outcome. These results are comparable with publications on asthma and chronic respiratory diseases, which show an increased risk of complications or more severe disease course in some patients [9, 10].

For the laboratory parameters in our cohort, no significant association was established for WBC, CRP, and ferritin, although such associations have been described in other studies. In contrast, statistically significant differences were observed for urea, creatinine, D-dimer, and hematocrit, which points to the role of renal dysfunction, coagulation activation, and hematological disturbances in severe disease course [2, 3].

The obtained results are also consistent with other publications according to which elevated values of D-dimer, BUN, and creatinine at admission are associated with higher mortality and more severe COVID-19 course. In our study, D-dimer, urea, and creatinine were also significantly higher in patients with adverse outcome, while some of the remaining indicators did not reach statistical significance [4, 11, 12, 13].

The ROC analysis additionally confirms the importance of these findings, with urea showing very good, and D-dimer good discriminative ability for predicting severe outcome.

Published meta-analyses report that elevated SAA values are associated with more adverse outcome in COVID-19. In the present study, a similar trend toward a higher frequency of severe outcome at higher SAA values was observed, but without reaching statistical significance [14, 15, 16].

Conclusion

In the present study of hospitalized older patients with COVID-19, the more adverse outcome was mainly associated with advanced age, lower hematocrit, and elevated values of urea, creatinine, and D-dimer. Urea and D-dimer showed good prognostic value in the ROC analysis. Most clinical symptoms and categorized SAA did not demonstrate a statistically significant association with outcome, which highlights the greater importance of age and early laboratory parameters for risk assessment.

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