



## BIOCHEMICAL PREDICTORS OF CHEMOTHERAPY-INDUCED TOXICITY: A PROSPECTIVE OBSERVATIONAL STUDY EVALUATING THE ROLE OF SERUM ALBUMIN, C-REACTIVE PROTEIN, NEUTROPHIL-TO-LYMPHOCYTE RATIO, AND LACTATE DEHYDROGENASE

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**ABSTRACT** **Background:** Chemotherapy-induced toxicity remains a major cause of treatment interruption, dose reduction, hospitalization, and poor clinical outcomes in cancer patients. Early identification of patients at risk for severe toxicity may improve treatment planning. Biomarkers such as serum albumin, C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), and lactate dehydrogenase (LDH) reflect nutritional status, systemic inflammation, and tumor burden and may predict toxicity. **Objectives:** To evaluate the predictive value of baseline serum albumin, CRP, NLR, and LDH for Grade 3–4 chemotherapy-induced toxicity. **Methods:** This prospective observational study included 150 patients with solid tumors planned for first-line chemotherapy. Before treatment initiation, baseline serum albumin, CRP, NLR, and LDH were recorded as part of routine clinical evaluation. Patients were followed throughout their chemotherapy course, and treatment-related adverse events were assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The relationship between baseline biomarker levels and severe (Grade 3–4) toxicity was evaluated using logistic regression analysis. **Results:** Among 150 patients, 42 (28.0%) experienced severe chemotherapy-induced toxicity (Grade 3–4). Patients who developed severe toxicity had lower serum albumin levels and higher CRP, NLR, and LDH values than those with mild to moderate toxicity. These differences were statistically significant. On multivariate analysis, hypoalbuminemia (<3.5 g/dL), elevated CRP (>10 mg/L), NLR >4, and LDH >300 U/L remained independent predictors of severe toxicity. NLR showed the strongest predictive ability, supporting its role as a simple and cost-effective pretreatment biomarker. **Conclusion:** Baseline serum albumin, CRP, NLR, and LDH are inexpensive and readily available biomarkers that may help identify patients at increased risk for chemotherapy-induced toxicity.

**KEYWORDS :** Chemotherapy toxicity; Albumin; C-reactive protein; Neutrophil-to-lymphocyte ratio; LDH; Biomarkers

### INTRODUCTION

Cancer remains one of the leading causes of morbidity and mortality worldwide and represents a major public health challenge. Despite significant advances in targeted therapy and immunotherapy, cytotoxic chemotherapy continues to be a cornerstone of treatment for many solid tumors [1,2]. However, chemotherapy is frequently associated with treatment-related toxicities that can adversely affect quality of life, necessitate dose reductions, cause treatment delays, and increase healthcare utilization [3].

The occurrence and severity of chemotherapy-induced toxicity vary considerably among patients receiving similar treatment regimens. Although age, performance status, comorbidities, nutritional status, and organ function contribute to treatment tolerance, these variables alone do not fully explain the inter-patient variability observed in clinical practice [4]. Therefore, identification of reliable and inexpensive biomarkers capable of predicting toxicity before treatment initiation remains an important area of oncological research.

Inflammation has emerged as a hallmark of cancer and plays a central role in tumor initiation, progression, angiogenesis, metastasis, and resistance to therapy [5]. Growing evidence suggests that systemic inflammatory response is associated not only with poor oncological outcomes but also with increased treatment-related complications [6]. Consequently, several inflammatory and nutritional biomarkers have been investigated as potential predictors of chemotherapy tolerance.

Serum albumin is one of the most widely used biochemical markers of nutritional and inflammatory status. Hypoalbuminemia is common among cancer patients and has been associated with poor functional status, increased postoperative complications, impaired immune function, and reduced survival [7,8]. Low albumin levels may reflect cancer-related malnutrition, chronic inflammation, or increased catabolic activity, all of which may compromise the body's ability to tolerate systemic therapy.

C-reactive protein (CRP) is an acute-phase reactant synthesized by hepatocytes in response to inflammatory cytokines, particularly

interleukin-6 [9]. Elevated CRP levels have been linked to advanced disease stage, cachexia, poor treatment response, and unfavorable prognosis in multiple malignancies [10]. Persistent systemic inflammation may increase susceptibility to chemotherapy-induced toxicity through impaired tissue repair mechanisms and altered host immunity.

The neutrophil-to-lymphocyte ratio (NLR) has emerged as a simple and reproducible marker of systemic inflammatory response. Elevated NLR reflects an imbalance between tumor-promoting inflammatory activity and antitumor immune surveillance [11]. Several meta-analyses have demonstrated the prognostic significance of NLR across various cancers, including lung, breast, colorectal, and head and neck malignancies [12,13]. Recent studies suggest that elevated baseline NLR may also be associated with increased risk of treatment-related adverse events and poorer chemotherapy tolerance [14].

Lactate dehydrogenase (LDH) is an intracellular enzyme involved in anaerobic glycolysis and is frequently elevated in patients with aggressive tumors and extensive disease burden [15]. Elevated serum LDH levels have been associated with increased tumor proliferation, hypoxia, treatment resistance, and inferior survival outcomes [16]. Because LDH reflects both tumor burden and metabolic activity, it may also serve as a potential predictor of chemotherapy-related complications.

Although several studies have independently evaluated the prognostic significance of albumin, CRP, NLR, and LDH, comparatively few have assessed their combined utility in predicting chemotherapy-induced toxicity [17–20]. Furthermore, data from the Indian population remain limited despite differences in nutritional status, disease presentation, and healthcare delivery systems compared with Western populations [21].

Given that these biomarkers are inexpensive, routinely available, and easily measurable in clinical practice, their incorporation into pretreatment risk assessment may facilitate personalized treatment planning and early supportive care. Therefore, the present study was

undertaken to evaluate the predictive value of baseline serum albumin, CRP, NLR, and LDH for severe chemotherapy-induced toxicity in patients receiving first-line chemotherapy for solid tumors.

## MATERIALS AND METHODS

### Study Design and Setting

This prospective observational study was conducted in the Departments of Medical Oncology and Biochemistry at a tertiary care teaching hospital over 18 months, from January 2024 to June 2025. Written informed consent was obtained from all participants prior to enrollment.

### Study Population

Adult patients with histologically confirmed solid malignancies who were planned to receive first-line systemic chemotherapy were screened for eligibility.

### Inclusion Criteria

1. Age  $\geq 18$  years.
2. Histologically confirmed solid tumor malignancy.
3. Planned for first-line cytotoxic chemotherapy.
4. Eastern Cooperative Oncology Group (ECOG) performance status 0–2.
5. Adequate baseline hematological, renal, and hepatic function.
6. Ability to provide informed consent.

### Exclusion Criteria

1. Active bacterial, viral, or fungal infection at enrollment.
2. Autoimmune or chronic inflammatory disorders.
3. Chronic corticosteroid or immunosuppressive therapy.
4. Severe hepatic dysfunction (Child-Pugh Class C).
5. End-stage renal disease requiring dialysis.
6. Prior exposure to systemic chemotherapy.
7. Patients receiving immunotherapy alone or targeted therapy alone.
8. Incomplete baseline laboratory data.

### Sample Size

A total of 150 consecutive eligible patients were included. The sample size was considered adequate to detect a clinically significant association between baseline biochemical parameters and severe chemotherapy-induced toxicity, with a confidence level of 95% and statistical power of 80%.

### Data Collection

Baseline demographic, clinical, and laboratory data were recorded before initiation of chemotherapy using a structured case record form.

### Demographic Variables

- Age
- Sex

### Clinical Variables

- Primary tumor site
- Disease stage
- ECOG performance status
- Planned chemotherapy regimen
- Presence of metastatic disease
- Comorbidities

### Laboratory Assessment

Venous blood samples were collected within seven days prior to initiation of chemotherapy.

The following biochemical and hematological parameters were measured:

- Hemoglobin (g/dL)
- Total leukocyte count (cells/mm<sup>3</sup>)
- Absolute neutrophil count (ANC)
- Absolute lymphocyte count (ALC)
- Serum albumin (g/dL)
- C-reactive protein (CRP, mg/L)
- Lactate dehydrogenase (LDH, U/L)

Serum albumin, CRP, and LDH were measured on the VITROS 5600 Integrated Chemistry System (Ortho Clinical Diagnostics, USA). Albumin was estimated using the bromocresol green colorimetric method, CRP by a fixed-point immuno-rate sandwich immunoassay, and LDH by a kinetic enzymatic rate method, according to the manufacturer's instructions.

### Neutrophil-to-Lymphocyte Ratio

The neutrophil-to-lymphocyte ratio (NLR) was calculated using the following formula:

$$\text{NLR} = \text{Absolute Neutrophil Count} \div \text{Absolute Lymphocyte Count}$$

### Chemotherapy Administration and Follow-up

Patients received chemotherapy according to standard institutional protocols appropriate for their tumor type and disease stage. Supportive care measures, including antiemetics, hydration, growth factor support, and prophylactic medications, were administered according to treating physician discretion and institutional guidelines.

Patients were followed prospectively from initiation of chemotherapy until completion of six cycles, treatment discontinuation, disease progression, death, or study completion, whichever occurred earlier.

### Assessment of Chemotherapy-Induced Toxicity

All treatment-related adverse events were evaluated at each chemotherapy cycle and graded according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0.

### Hematological Toxicities

- Neutropenia
- Anemia
- Thrombocytopenia
- Febrile neutropenia

### Non-Hematological Toxicities

- Mucositis
- Nausea and vomiting
- Diarrhea
- Peripheral neuropathy
- Hepatotoxicity
- Nephrotoxicity

For the purpose of analysis, severe chemotherapy-induced toxicity was defined as any Grade 3–4 adverse event occurring during the study period.

### Statistical Analysis

Data were entered into Microsoft Excel and analyzed using the Statistical Package for Social Sciences (SPSS), version 29.0.

Continuous variables were expressed as mean  $\pm$  standard deviation (SD) or median with interquartile range (IQR) as appropriate. Categorical variables were presented as frequencies and percentages.

Comparisons between patients with Grade 0–2 toxicity and Grade 3–4 toxicity were performed using:

- Student's t-test for normally distributed continuous variables.
- Mann-Whitney U test for non-normally distributed variables.
- Chi-square test or Fisher's exact test for categorical variables.

Variables demonstrating statistical significance on univariate analysis were entered into a multivariate logistic regression model to identify independent predictors of severe toxicity. Results were reported as odds ratios (ORs) with 95% confidence intervals (CIs).

Receiver operating characteristic (ROC) curve analysis was performed to determine the predictive performance of albumin, CRP, NLR, and LDH. Area under the curve (AUC), sensitivity, specificity, and optimal cut-off values were calculated.

A two-tailed p-value  $< 0.05$  was considered statistically significant.

## RESULTS

A total of 150 patients with histologically confirmed solid malignancies receiving first-line chemotherapy were enrolled. The mean age of the study population was  $54.8 \pm 11.2$  years (range: 24–78 years). There were 88 (58.7%) males and 62 (41.3%) females. Most patients had an ECOG performance status of 0–1 (76.0%), while 24.0% had an ECOG performance status of 2. Metastatic disease was present in 72 (48.0%) patients.

### Baseline Patient Characteristics

The baseline demographic and clinical characteristics of the study population are summarized in Table 1.

**Table 1. Baseline Demographic and Clinical Characteristics of the Study Population (n = 150)**

Characteristic	Value
Age (years), mean ± SD	54.8 ± 11.2
Male, n (%)	88 (58.7)
Female, n (%)	62 (41.3)
ECOG 0–1, n (%)	114 (76.0)
ECOG 2, n (%)	36 (24.0)
Metastatic disease, n (%)	72 (48.0)
Non-metastatic disease, n (%)	78 (52.0)

**Distribution of Tumor Types**

Breast carcinoma was the most common malignancy (22.7%), followed by lung cancer (20.0%), colorectal cancer (16.0%), head and neck cancer (14.7%), and ovarian cancer (12.0%).

**Table 2. Distribution of Primary Malignancies**

Tumor Type	Number (%)
Breast carcinoma	34 (22.7)
Lung carcinoma	30 (20.0)
Colorectal carcinoma	24 (16.0)
Head and neck carcinoma	22 (14.7)
Ovarian carcinoma	18 (12.0)
Others	22 (14.6)
Total	150 (100)

**Incidence of Chemotherapy-Induced Toxicity**

During follow-up, treatment-related toxicities of varying severity were observed. Neutropenia was the most frequent adverse event. Overall, 42 patients (28.0%) developed Grade 3–4 toxicity according to CTCAE version 5.0.

**Table 3. Incidence and Severity of Chemotherapy-induced Toxicities**

Toxicity	Any Grade n (%)	Grade 3–4 n (%)
Neutropenia	62 (41.3)	28 (18.7)
Anemia	40 (26.7)	10 (6.7)
Thrombocytopenia	24 (16.0)	8 (5.3)
Mucositis	26 (17.3)	7 (4.7)
Diarrhea	22 (14.7)	6 (4.0)
Febrile neutropenia	14 (9.3)	14 (9.3)

Overall Grade 3–4 Toxicity: 42 (28.0%)

**Comparison of Baseline Biomarkers According to Toxicity Severity**

Patients who developed Grade 3–4 toxicity demonstrated significantly lower serum albumin levels and significantly higher CRP, NLR, and LDH values compared with patients experiencing Grade 0–2 toxicity.

**Table 4. Baseline Biochemical Parameters According to Toxicity Severity**

Biomarker	Grade 0–2 Toxicity (n=108)	Grade 3–4 Toxicity (n=42)	p-value
Albumin (g/dL)	4.01 ± 0.42	3.28 ± 0.48	<0.001
CRP (mg/L)	7.8 ± 4.1	18.4 ± 8.3	<0.001
NLR	2.8 ± 1.2	5.4 ± 2.1	<0.001
LDH (U/L)	242 ± 67	418 ± 102	<0.001

**Univariate Logistic Regression Analysis**

Univariate logistic regression analysis was performed to evaluate the association between individual biomarkers and severe chemotherapy-induced toxicity.

**Table 5. Univariate Logistic Regression Analysis for Predictors of Grade 3–4 Toxicity**

Variable	Odds Ratio (OR)	95% Confidence Interval	p-value
Albumin <3.5 g/Dl	3.2	1.8–6.8	<0.001
CRP >10 mg/L	2.9	1.5–5.7	0.002
NLR >4	3.8	2.0–7.2	<0.001
LDH >300 U/L	2.6	1.4–5.1	0.004

**Multivariate Logistic Regression Analysis**

Variables significant on univariate analysis were entered into a multivariate logistic regression model. All four biomarkers remained independently associated with severe chemotherapy-induced toxicity.

**Table 6. Multivariate Logistic Regression Analysis for Independent**

**Predictors of Grade 3–4 Toxicity**

Variable	Adjusted OR	95% Confidence Interval	p-value
Albumin <3.5 g/dL	2.8	1.4–5.7	0.003
CRP >10 mg/L	2.2	1.1–4.6	0.020
NLR >4	3.1	1.5–6.2	0.001
LDH >300 U/L	2.0	1.0–4.1	0.040

Hypoalbuminemia, elevated CRP, elevated NLR, and elevated LDH independently increased the likelihood of developing severe chemotherapy-induced toxicity.

**Receiver Operating Characteristic (ROC) Curve Analysis**

Receiver operating characteristic (ROC) curve analysis was performed to assess the predictive performance of each biomarker. NLR demonstrated the highest discriminatory ability among the evaluated parameters.

**Table 7. ROC Analysis of Biomarkers for Prediction of Severe Chemotherapy-induced Toxicity**

Biomarker	AUC (95% CI)	Sensitivity (%)	Specificity (%)
Albumin	0.79	74	71
CRP	0.77	72	69
NLR	0.82	79	75
LDH	0.75	70	68

The area under the curve was highest for NLR (AUC = 0.82), followed by albumin (AUC = 0.79), CRP (AUC = 0.77), and LDH (AUC = 0.75), indicating good predictive performance for severe chemotherapy-induced toxicity.

**ROC Performance of Individual Biomarkers**

Biomarker	AUC	Lower 95% CI	Upper 95% CI	Sensitivity (%)	Specificity (%)
Albumin	0.79	0.71	0.87	74	71
CRP	0.77	0.69	0.85	72	69
NLR	0.82	0.75	0.89	79	75
LDH	0.75	0.67	0.83	70	68

**Optimal Cut-off Values Used**

Biomarker	Cut-off Value
Albumin	<3.5 g/dL
CRP	>10 mg/L
NLR	>4.0
LDH	>300 U/L

**Discussion**

The present prospective observational study investigated the predictive value of baseline serum albumin, CRP, NLR, and LDH for severe chemotherapy-induced toxicity in patients with solid tumors receiving first-line chemotherapy. Patients who developed Grade 3–4 toxicities had significantly lower serum albumin levels and significantly higher CRP, NLR, and LDH levels than those who experienced Grade 0–2 toxicities. Moreover, all four biomarkers remained independently associated with severe toxicity after adjustment for potential confounding variables.

The incidence of Grade 3–4 chemotherapy-induced toxicity in the present cohort was 28%, which is comparable to rates reported in previous studies evaluating adverse events associated with systemic anticancer therapy [3,4]. Severe toxicities remain a major concern in oncology because they frequently result in treatment interruption, dose reduction, hospitalization, increased healthcare expenditure, and compromised therapeutic efficacy. Therefore, identifying high-risk patients before treatment initiation is an important clinical objective.

A key finding of this study was the significant association between hypoalbuminemia and severe chemotherapy-induced toxicity. Patients who developed Grade 3–4 adverse events had significantly lower baseline serum albumin concentrations, and albumin levels below 3.5 g/dL independently predicted toxicity. Serum albumin is widely recognized as an indicator of nutritional status, systemic inflammation, and physiological reserve. Malnutrition and cancer cachexia are common among patients with advanced malignancies and have been associated with impaired treatment tolerance and poorer clinical outcomes. Gupta and Lis reported that low pretreatment serum albumin was consistently associated with adverse outcomes across multiple cancer types [7]. Similarly, Arrieta et al. demonstrated that hypoalbuminemia was associated with increased chemotherapy-

related complications and reduced survival in patients with advanced lung cancer [19]. The present findings reinforce the importance of nutritional assessment before chemotherapy and suggest that serum albumin may serve as a practical biomarker for identifying vulnerable patients.

The study also demonstrated a significant relationship between elevated CRP levels and severe chemotherapy toxicity. CRP remained an independent predictor on multivariate analysis, indicating that systemic inflammation contributes substantially to treatment intolerance. Chronic inflammation promotes metabolic derangements, muscle wasting, immune dysfunction, and reduced physiological resilience, all of which may increase susceptibility to chemotherapy-related adverse effects. Shrotriya et al. reported that elevated CRP levels were consistently associated with poor prognosis and adverse clinical outcomes in cancer patients [10]. Furthermore, McMillan highlighted the central role of systemic inflammatory response in cancer progression and treatment outcomes [6]. The current findings extend these observations by suggesting that CRP may also be useful in predicting chemotherapy-related toxicity.

Among all evaluated biomarkers, NLR demonstrated the highest predictive accuracy, with an area under the ROC curve of 0.82. Patients with elevated NLR values had a markedly increased risk of developing severe toxicity. NLR reflects the balance between systemic inflammation and host immune competence. Elevated neutrophil counts are associated with increased production of pro-inflammatory cytokines and growth factors, whereas lymphopenia reflects impaired antitumor immunity. Templeton et al. demonstrated that elevated NLR was associated with poor outcomes across a broad range of solid tumors [12]. In addition, Guthrie et al. emphasized the clinical relevance of NLR as a readily available marker of cancer-associated systemic inflammation [11]. Recent studies have also suggested that elevated NLR may predict treatment-related complications and reduced chemotherapy tolerance [14]. The findings of the present study support these observations and indicate that NLR may be particularly useful for pretreatment risk stratification.

Elevated serum LDH was another significant predictor of severe chemotherapy-induced toxicity. Patients with higher LDH levels experienced significantly greater rates of Grade 3–4 adverse events, and LDH remained independently associated with toxicity after multivariate adjustment. LDH is a marker of tumor burden, tissue breakdown, hypoxia, and altered tumor metabolism. Increased LDH levels often reflect aggressive tumor biology characterized by enhanced glycolytic activity and rapid cellular proliferation. Petrelli et al. reported that elevated LDH was associated with poor survival outcomes across multiple solid tumors [16]. Similarly, Diem et al. demonstrated that LDH serves as a clinically relevant biomarker reflecting disease aggressiveness and treatment outcomes in oncology [22]. Although LDH has traditionally been studied as a prognostic marker, the present findings suggest that it may also provide valuable information regarding chemotherapy tolerance.

An important strength of this study is the simultaneous evaluation of biomarkers representing different biological domains. Albumin reflects nutritional and inflammatory status, CRP reflects systemic inflammatory activity, NLR reflects immune-inflammatory balance, and LDH reflects tumor burden and metabolic stress. Assessing these markers together may provide a more comprehensive evaluation of patient vulnerability than reliance on any single parameter. Previous investigations have generally focused on individual biomarkers, whereas the present study highlights the potential value of an integrated biomarker-based approach [11,14].

The clinical implications of these findings are noteworthy. All four biomarkers are inexpensive, routinely available, and easily measurable in standard oncology practice. Incorporating these parameters into pretreatment assessment may facilitate early identification of patients at increased risk of severe toxicity. Such patients may benefit from nutritional optimization, enhanced supportive care, closer monitoring, prophylactic interventions, or individualized treatment modifications. Early risk stratification could potentially reduce treatment-related morbidity and improve adherence to planned chemotherapy schedules.

The present study also contributes evidence from an Indian tertiary care setting, where data regarding biomarker-based prediction of chemotherapy toxicity remain limited. Variations in nutritional status,

socioeconomic factors, healthcare access, and disease presentation may influence the applicability of predictive biomarkers across populations. Therefore, validation of these findings in Indian patients is particularly relevant and may support the development of locally applicable risk assessment strategies [21].

Several limitations should be acknowledged. The study was conducted at a single institution, which may limit external validity. The inclusion of multiple solid tumor types and different chemotherapy regimens may have introduced heterogeneity in toxicity patterns. Biomarker levels were assessed only at baseline, and longitudinal changes during treatment were not evaluated. Additionally, other established prognostic indices such as the Glasgow Prognostic Score, Prognostic Nutritional Index, and platelet-to-lymphocyte ratio were not included in the analysis.

Future multicenter studies with larger sample sizes are needed to validate these findings and establish standardized cut-off values for clinical use. Development of composite predictive models integrating biochemical markers with clinical and treatment-related variables may further improve the prediction of chemotherapy toxicity. Interventional studies are also warranted to determine whether biomarker-guided supportive care strategies can reduce adverse events and improve treatment outcomes.

In conclusion, baseline hypoalbuminemia, elevated CRP, elevated NLR, and elevated LDH were independently associated with severe chemotherapy-induced toxicity in patients receiving first-line chemotherapy for solid tumors. Among these biomarkers, NLR demonstrated the strongest predictive performance. These readily available laboratory parameters may serve as practical tools for pretreatment risk assessment and individualized patient management in routine oncology practice.

#### Conclusion

Baseline serum albumin, CRP, NLR, and LDH were significant predictors of severe chemotherapy-induced toxicity in patients receiving first-line chemotherapy for solid tumors. Patients with hypoalbuminemia and elevated inflammatory biomarkers were at substantially higher risk of developing Grade 3–4 adverse events. Among all evaluated parameters, NLR demonstrated the highest predictive accuracy. These inexpensive and routinely available laboratory markers may serve as practical tools for pretreatment risk stratification, enabling individualized treatment planning, closer monitoring, and timely supportive care interventions to improve chemotherapy tolerance and patient outcomes.

#### Strengths

This prospective observational study systematically evaluated readily available biomarkers (albumin, CRP, NLR, and LDH) using standardized CTCAE version 5.0 toxicity criteria. These inexpensive and accessible markers reflect nutrition, inflammation, immunity, and tumor burden, enhancing the clinical applicability of the findings.

#### Limitations

Limitations include the single-center design, modest sample size, heterogeneous tumor types and chemotherapy regimens, and lack of serial biomarker assessment. As an observational study, causal associations cannot be confirmed. Larger multicenter studies are needed for validation.

#### Declarations

##### Consent to Participate

Written informed consent was obtained from all participants.

##### Consent for Publication

Not applicable.

##### Availability of Data and Materials

Data are available from the corresponding author upon reasonable request.

##### Funding

No external funding was received.

##### Conflict of Interest

The authors declare no competing interests.

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