

# The effect of blood albumin and total lymphocyte count on short-term results in elderly patients with hip fractures

Kan albümin ve total lenfosit sayısının ileri yaş kalça kırıklı olgularda kısa dönem sonuçlarının üzerine etkileri

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## BACKGROUND

A study was performed to determine the effects of blood albumin and total lymphocyte count on the postoperative one-year period in 74 elderly hip fracture patients.

## METHODS

In 2006, 74 patients (52 female, 22 male) with hip fracture who were 65 years of age or older were included in the study. Admission albumin levels and total lymphocyte counts were recorded. The outcomes examined were mortality, length of hospital stay and ambulatory ability. Ambulatory ability was assessed according to Parkland and Palmer criteria.

## RESULTS

There were 61 patients aged 65-84 years, and 13 patients aged 85-105 years. Forty-one patients (55.4%) had hypoalbuminemia and 23 patients (31.1%) had low total lymphocyte count. Low albumin and total lymphocyte counts were associated with higher mortality ( $p=0.011$ ). Patients with low albumin levels had longer length of hospital stay ( $p=0.002$ ). Patients with normal albumin and total lymphocyte counts had higher mobility score meaning better function ( $p=0.012$ ). Multivariate analysis yielded that low total lymphocyte count, American Society of Anesthesiologists (ASA) 3-4 and female gender remained significant independent predictors of one-year mortality. No single blood parameter was found to be effective on ambulatory status.

## CONCLUSION

Risk of mortality in elderly hip fracture patients increases with female gender, ASA 3-4 and low total lymphocyte counts. Hypoalbuminemia is associated with longer hospitalization. Identification of these risk factors can help in the case management for a more favorable outcome.

**Key Words:** Ambulatory status; hypoalbuminemia; total lymphocyte count; mortality.

## AMAÇ

Yetmiş dört ileri yaş kalça kırıklı hastada kan albümin ve 'total lenfosit sayısının' (TLS) ameliyat sonrası 1 yıllık dönemdeki etkileri değerlendirildi.

## GEREÇ VE YÖNTEM

2006 yılında 65 yaş ve üstü 74 (52 kadın, 22 erkek) hasta çalışma kapsamına alındı. Başvuru anındaki albümin ve TLS kaydedildi. Bunlar ile mortalite, hastanede kalış süresi ve yürüyebilme becerisi arasındaki ilişki araştırıldı. Yürüyebilme becerisi Parkland ve Palmer ölçütleri ile değerlendirildi.

## BULGULAR

Hastaların 61'inin yaşı 65-84 olup 13'ü ise 85-105 idi. Hastaların 41'inde (%55,4) hipoalbuminemi ve 23'ünde (%31,08) ise düşük TLS saptandı. Albümin düzeyi ve TLS düşük olan hastalarda mortalite daha yüksekti ( $p=0,011$ ). Ayrıca, albümin düzeyi düşük olduğunda hastanede yatma süresi daha uzundu ( $p=0,002$ ). Albümin düzeyleri ile TLS normal olan hastalarda daha iyi fonksiyonu gösteren yürüyebilme becerisi ile ilgili puanlar daha yüksek olarak bulundu ( $p=0,012$ ). İleri yaşın mortalite ve fonksiyonel sonuçlara etkisi bulunmadı ( $p>0,05$ ). Çok değişkenli analiz sonucunda düşük TLS, ASA 3-4 ve kadın cinsiyetin ameliyat sonrası bir yıllık dönemde mortaliteyi etkileyen güçlü ve bağımsız etkenler olduğu bulundu. Tek başına hiçbir kan parametresinin yürüyebilme becerisi üzerine etkisi saptanmadı.

## SONUÇ

İleri yaş kalça kırıklı hastalarda mortalite riski kadın cinsiyet, ASA 3-4 ve düşük lenfosit sayısı varlığında artmaktadır. Hipoalbuminemi hastalarda hastanede kalış süresi daha uzun olmaktadır. Bu risk faktörlerinin saptanması olgularda daha iyi sonuç almaya yardımcı olabilir.

**Anahtar Sözcükler:** Yürüyebilme becerisi; hipoalbuminemi; total lenfosit sayısı; mortalite.

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Malnutrition is an important factor leading to poorer outcomes after certain surgical procedures in elderly patients and is also reported in several studies to be associated with significant morbidity and mortality with hip fractures.<sup>[1-4]</sup> Nutrition can be assessed with highly sensitive indicators such as skin antigen testing, nitrogen balance, prealbumin levels or transferrin levels.<sup>[5-7]</sup> Prospectively designed studies are limited in number.<sup>[8,9]</sup> In these studies, both routine parameters like serum albumin (alb) and total lymphocyte count (tlc) and highly sensitive indicators like transferrin and nitrogen balance have been used for nutritional assessment. In this study, we aimed to assess the extent to which the blood alb and tlc affect the short-term postoperative results in hip fracture patients aged 65 years or older.

## MATERIALS AND METHODS

In 2006, 74 patients (52 female, 22 male) with hip fracture who were 65 years of age or older, ambulatory before fracture and whose fractures were nonpathologic in origin were included in the study. All patients were treated operatively and followed a similar postoperative protocol consisting of early mobilization and ambulation with weight-bearing as tolerated. Patients were given cefazolin sodium 1 gram (g) intravenous four times a day for 2 days postoperatively. Enoxaparin sodium 0.6 milliliter (ml) subcutaneously was used once a day for thromboembolic prophylaxis for 3 weeks and acetyl salicylic acid 100 milligram (mg) per oral was continued once a day thereafter. All patients were contacted by senior one of us to obtain follow-up information for the first 12 months postoperatively or until death. The patients were interviewed either during routine follow-up visits in the hospital or by telephone. If the patient was not available, a family member or a caregiver was interviewed.

Tlc and blood alb levels on the day of admission were recorded for each patient. Additionally, age, gender, length of hospital stay, time to mobilization after surgery, comorbidities, American Society of Anesthesiologists (ASA) classification of patients, and the time period elapsed between injury and surgery were recorded. In order to determine the effect of advanced age on the postoperative outcome, we also divided patients into two groups as patients between 65-84 and those 85 or older. The length of hospital stay was evaluated by dividing the patients hospitalized '≤7 days' and '>7 days'.

For each outcome, we assessed the effect of two markers:

1. preoperative alb level (< or ≥ 3.5 grams/deciliter [g/dl])
2. preoperative tlc (< or ≥ 1500 cells/ml)

In addition, the following four possible combinations of the two variables were analyzed in order to determine their effects on outcomes:

1. preoperative alb ≥3.5 g/dl and tlc ≥1500
2. preoperative alb ≥3.5 g/dl and tlc <1500
3. preoperative alb <3.5 g/dl and tlc ≥1500
4. preoperative alb <3.5 g/dl and tlc <1500

General health status was defined by the number of preexisting significant comorbidities including diabetes mellitus, congestive heart failure, ischemic heart disease, previous cerebrovascular accident, renal disease, neurological disorders, hypertension, and chronic obstructive pulmonary disease. These comorbidities have been shown to be the most important.<sup>[10,11]</sup> In order to assess the extent to which these comorbidities affected the postoperative short-term results, we categorized patients as having '<2' and '≥2' comorbidities. The patients were also categorized with regard to the comorbidities according to ASA rating of operative risk as patients with ASA 1-2 or ASA 3-4.

The functional status of the patients was assessed according to Parkland and Palmer mobility score.<sup>[12]</sup> This scoring system consists of three categories of mobility activity such as being able to get about the house, get out of the house and go shopping. It gives 3 points to each category, with 9 points indicating the highest mobility function and 0 indicating the lowest.

Informed consent to be included in the study was signed by all patients and the study was approved by the local ethics committee of the hospital.

## Statistical Analysis

Statistical analysis was performed using SPSS 13.0 version for Windows program (SPSS Inc., Chicago, IL, USA). The continuous variables were evaluated with mean (±SD) or median value when required. Categorical variables were evaluated with frequency (%) and Pearson chi-square test, Fisher's exact, Kolmogorov-Smirnov and Mantel-Haenszel chi-square tests. For comparison of the means between patient groups, Student's t-test, one-way ANOVA, and when necessary, Mann-Whitney U test

and Kruskal-Wallis test as nonparametric tests were used. The two-way mixed design ANOVAs (with independent measures on mortality) were performed with Greenhouse-Geisser adjustment when necessary. The relationships between patient characteristics and survival were analyzed by the Kaplan-Meier and Cox regression analyses (Forward LR). A p value less than 0.05 was regarded as significant.

## RESULTS

The mean age was 77.3 (65-105) years (76.86±8.85 (65-105) for males and 78.29±8.05 years (65-96) for females). There were 61 patients aged 65-84 and 13 patients aged 85-105 years. The evaluation regarding

the advanced age of patients yielded no difference in alb and tlc levels, mortality, gender, time to mobilization, comorbidities, and Parkland and Palmer mobility score.<sup>[12]</sup>

The mean levels of tlc and alb were 1637.5 (604-3722) cells/ml and 3.29 (1.7-4.3) g/dl, respectively. Forty-one patients (55.4%) had an alb level <3.5 g/dl preoperatively. Twenty-three patients (31.1%) had tlc <1500 cells/ml. Twenty-four patients (32.4%) had an alb level <3.5 g/dl but tlc ≥1500 cells/ml, 6 patients (8.1%) had an alb level ≥3.5 g/dl but tlc <1500 cells/ml, and 17 patients (22.97%) had both a preoperative alb level <3.5 g/dl and tlc count <1500 cells/ml.

**Table 1.** Characteristics of the patients according to mortality

Patient characteristics (n, %)	Survival (n=59)	Death (n=15)	p
Gender			
Female	41 (78.8)	11 (21.2)	<sup>a</sup> p>0.05
Male	18 (81.8)	4 (18.2)	
Age			
65-84	47 (77)	14 (23)	<sup>a</sup> p>0.05
85 and over	12 (92.3)	1 (7.7)	
Time period between injury and surgery (day)			
1	49 (80.3)	12 (19.7)	<sup>a</sup> p>0.05
≥2	10 (76.9)	3 (23.1)	
No. of Comorbidities			
<2	29 (100)	- (0)	<sup>b</sup> p<0.001
≥2	30 (66.7)	15 (33.3)	
ASA			
1-2	48 (94.1)	3 (5.9)	<sup>a</sup> p<0.001
3-4	11 (47.8)	12 (52.2)	
Time to mobilization after surgery			
≤2	46 (78)	13 (22)	<sup>a</sup> p>0.05
≥3	13 (86.7)	2 (13.3)	
Parkland and Palmer mobility score*			
0-3	7 (50)	7 (50)	<sup>c</sup> p=0.001
6	17 (70.8)	7 (29.2)	
9	34 (100)	- (0)	
Albumin level			
<3.5 g/dl	28 (68.3)	13 (31.7)	<sup>b</sup> p=0.006
≥3.5 g/dl	31 (93.9)	2 (6.1)	
Total lymphocyte count			
<1500 cells/ml	13 (56.5)	10 (43.5)	<sup>a</sup> p=0.002
≥1500 cells/ml	46 (90.2)	5 (9.8)	
Preop. Nutritional Status			
Alb ≥3.5 g/dl and tlc ≥1500	26 (96.3)	1 (3.7)	<sup>c</sup> p=0.011
Alb ≥3.5 g/dl and tlc <1500	20 (83.3)	4 (16.7)	
Alb <3.5 g/dl and tlc ≥1500	5 (83.3)	1 (16.7)	
Alb <3.5 g/dl and tlc <1500	8 (47.1)	9 (52.9)	

\* N=72; <sup>a</sup>p: Fisher's exact test; <sup>b</sup>p: Pearson chi-square test; <sup>c</sup>p: Kolmogorov-Smirnov test.

**Table 2.** Evaluation according to Parkland and Palmer score

	Parkland and Palmer Score			p
	0-3	3-6	6-9	
Female	10	11	22	NS
Male	1	8	7	
Age: 65-84	11	20	28	NS
Age: 85-105	3	4	6	
Alb $\geq$ 3.5 g/dl	3	9	21	p=0.023
Alb $<$ 3.5 g/dl	11	15	13	
Tlc $\geq$ 1500	6	16	28	p=0.024
Tlc $<$ 1500	8	8	6	
Alb $\geq$ 3.5 g/dl and Tlc $\geq$ 1500	2	6	19	p=0.012

alb: Albumin; tlc: Total lymphocyte count; NS: Not significant.

Sixty-one patients (82.4%) were operated one day after hospital admission and the remaining 13 (17.57%) were operated two or more days after hospital admission. Mobilization was achieved on the postoperative 1st day in 59 (79.7%) patients and after the postoperative 1st day in 15 patients (20.3%).

The number of comorbidities was none in 11 (14.9%), 1 in 17 (22.97%) and 2 or more in 46 (62.2%). Mortality rate was higher in patients with  $\geq$ 2 comorbidities (p<0.001) (Table 1). The alb and tlc values were found to be normal in patients having <2 comorbidities. No difference was found in the number of comorbidities with regard to gender. The patients with <2 comorbidities were operated earlier than the patients with  $\geq$ 2 comorbidities (p=0.012). Similarly, they were also mobilized earlier than the patients with  $\geq$ 2 comorbidities (p=0.036).

The mean hospitalization period was 8.4 $\pm$ 3.06 days (4-18). After excluding 2 in-hospital deaths, 35 patients (12 with hypoalbuminemia) were hospitalized  $\leq$ 7 days while 37 patients (26 with hypoalbuminemia) remained in the hospital >7 days (p=0.002). The evaluation regarding tlc and length of hospital

**Table 3.** Patient characteristics according to ASA criteria

	ASA 1-2 (n=51)	ASA 3-4 (n=23)	p
Age	77.37 $\pm$ 9.08	78.96 $\pm$ 6.11	p=0.05
Female	33	19	NS
Male	18	4	
Alive	48	11	p<0.001
Deceased	3	12	
Alb $\geq$ 3.5 g/dl	30	3	p<0.001
Alb $<$ 3.5 g/dl	21	20	
Tlc $\geq$ 1500	40	11	p=0.014
Tlc $<$ 1500	11	12	
Length of hospital stay	7.35 $\pm$ 2.41	9.74 $\pm$ 3.25	p=0.001
Time period between injury and operation	1.20 $\pm$ 0.63	3.13 $\pm$ 3.4	p=0.003

ASA: American Society of Anesthesiologists.

stay revealed no significant difference.

The postoperative function evaluated according to Parkland and Palmer mobility score<sup>[12]</sup> yielded no difference with regard to gender, advanced age, ASA, and hospitalization period. However, patients with alb  $\geq$ 3.5 g/dl and tlc  $\geq$ 1500 had higher mobility score, meaning better function (p=0.012). The patients with alb  $\geq$ 3.5 g/dl had better mobility score than patients with abnormal values (p=0.03). The patients with tlc  $\geq$ 1500 had better mobility score (p=0.024) (Table 2). None of the parameters alone had an effect on postoperative functional outcome in multivariate analysis.

Fifty-one patients were in ASA 1-2 (68.9%) and 23 (31.1%) in ASA 3-4. ASA 1-2 patients were hospitalized less and operated earlier than ASA 3-4 patients (p=0.001, p=0.003). The mean alb of ASA 1-2 and ASA 3-4 patients were 3.512 and 3.083, respectively (p<0.05). However, mean tlc levels, age and gender between ASA 1-2 and ASA 3-4 patients yielded no differences. ASA 1-2 and ASA 3-4 patients showed no difference regarding time to mobilization. Three patients in the ASA 1-2 and 12 patients

**Table 4.** Results of multivariate analysis

Patient characteristics	p	HR	95% CI for HR
ASA 3-4 (vs 1-2)	p<0.001	19.328	3.777 - 98.919
Preoperative tlc <1500 cells/ml (vs $\geq$ 1500 cells/ml)	p=0.008	6.275	1.619 - 24.326
Gender Female (vs male)	p=0.018	7.676	1.412 - 41.718

ASA: American Society of Anesthesiologists; HR: Hazard ratio; CI: Confidence interval; tlc: Total lymphocyte count.

in the ASA 3-4 group died during the follow-up period ( $p < 0.001$ ) (Table 3). Patients with hospital admission value of alb  $< 3.5$  g/dl and tlc  $< 1500$  cells/ml and with ASA score 3-4 had a lower mean survival time. When ASA score groups were adjusted, association between tlc  $< 1500$  cells/ml on hospital admission and survival time remained statistically significant (Log rank chi-square=5.317,  $p=0.021$ ).

Fifteen (20%) patients were recorded as deceased during the postoperative one-year period. Ten of 23 patients with tlc  $< 1500$  and 13 of 41 patients with alb  $< 3.5$  g/dl died ( $p=0.002$ ,  $p=0.006$ ). Nine of 17 patients with tlc  $< 1500$  and alb  $< 3.5$  died ( $p=0.011$ ) (Table 1). Two patients (2.7%) died during the hospitalization period. The alb and tlc levels were both abnormal in these two patients. Results of multivariate analysis with all variables based on the order of variables entering the model are presented in Table 4. When the other variables were controlled, the risk of mortality was significantly increased with tlc  $< 1500$  cells/ml on hospital admission (hazard ratio [HR]=6.275 95% confidence interval [CI]=1.619-24.326), female gender (HR=7.676 95% CI=1.412-41.718) and ASA score of 3-4 (HR=19.328 95% CI=3.777-98.919).

The evaluation regarding the remainder of the variables yielded no significant differences.

## DISCUSSION

Increased rates of malnutrition in elderly patients with hip fracture have been reported.<sup>[2,3,8]</sup> Koval et al.<sup>[2]</sup> in their retrospective study, reviewed 490 patients with hip fracture and found that 18% of patients had hypoalbuminemia and 57% of them had low tlc. Similarly, Patterson et al.<sup>[8]</sup> reported 60% of hip fracture patients were in a protein-depleted condition during the first week of hospitalization. Jensen et al.<sup>[3]</sup> reported that incidence as 42.4% in 129 consecutive orthopedic patients, with almost double that rate in patients with multiple trauma and femur fractures compared to 28.6% of patients undergoing elective total hip replacement. In the current study, we found hypoalbuminemia in 41 patients (55.4%) and 23 patients (31.1%) had low tlc, and those results are consistent with the literature. Our result differs somewhat from Koval et al.<sup>[2]</sup> in that we found higher rates of alb-depleted patients whereas tlc counts were relatively higher.

Albumin serves certain physiologic roles in wound healing. It is a protein synthesized in the liver and

has a longer half-life than the other visceral proteins such as transferrin, prealbumin and retinol-binding protein. It also maintains intravascular oncotic pressure, transfers amino acids from the liver, and transports zinc and fatty acids.<sup>[5,13]</sup> Hypoalbuminemia is an accepted indicator of global protein depletion.<sup>[4]</sup> Decreased levels of alb have been reported to be associated with an increased hospital stay, impaired wound healing, increased rates of wound infection, pneumonia and sepsis, an increased incidence of postoperative complications, delayed physical rehabilitation, and a decreased likelihood of survival.<sup>[2,4,8,14-17]</sup> Koval et al.<sup>[2]</sup> reported that alb level was predictive of length of hospital stay, in-hospital mortality and recovery of basic activities of daily living after hip fracture. They also added that patients with preoperative alb level  $< 3.5$  g/dl were more likely to have an increased length of hospitalization or to die during hospitalization and were less likely to recover their prefracture level of function in basic activities of daily living than patients with higher alb level. Similarly, Pioli et al.<sup>[17]</sup> showed that serum alb level was a strong independent predictor of in-hospital and late mortality. Incalzi et al.<sup>[16]</sup> investigated the in-hospital mortality in elderly hip fracture patients and reported similar findings. Contrary to these, Mizrahi et al.<sup>[14]</sup> found no relationship between admission alb levels and length of hospital stay. Two of our patients died during hospitalization, both of whom had hypoalbuminemia, and like Koval et al.,<sup>[2]</sup> the patients with hypoalbuminemia were hospitalized more in our study. Patterson et al.<sup>[8]</sup> evaluated the protein depletion and metabolic stress in hip fracture patients and found protein depletion in 37 (58%) of their patients. The patients with protein depletion had a higher prevalence of complications, were less likely to return to their prefracture environment and tended to stay in the hospital longer. They also found that protein-depleted patients had a significantly lower probability of survival one year after the hip fracture. In our study, we found that 13 of 41 patients with alb  $< 3.5$  g/dl died during the first year follow-up, but the multivariate analysis yielded that low alb level was not an independent predictor of one-year mortality.

A decreased number of lymphocytes has been shown to be a significant risk factor for the development of postoperative sepsis and mortality,<sup>[2,18,19]</sup> but controversial findings have also been reported.<sup>[10,20]</sup> Koval et al.<sup>[2]</sup> reported that patients with tlc count  $< 1500$  cells/ml on hospital admission was predictive of one-year mortality after hip fracture. Contrary to

this, Foster et al.<sup>[9]</sup> reported that tlc count was not predictive of mortality in a series of 40 patients with hip fracture. Symeonidis and Clark<sup>[20]</sup> reported that their patients with hypoalbuminemia and normal tlc had significantly higher risk of one-year mortality than patients with hypoalbuminemia and low tlc. Their finding was somewhat different from that of Koval et al.<sup>[2]</sup> In the current study, we found that patients with tlc <1500 cells/ml died during first year follow-up, and low tlc level was the strong independent predictor of one-year mortality after multivariate analysis.

The effect of alb and tlc on postoperative functional status is debatable.<sup>[2,14,21]</sup> Koval et al.<sup>[2]</sup> found that normoalbuminemic hip fracture patients had better functional outcome but the tlc count had no effect. Similarly, Hershkovitz et al.<sup>[21]</sup> found in their study that low alb levels on admission were associated with a less favorable functional outcome. However, Mizrahi et al.<sup>[14]</sup> evaluated the effect of admission blood alb level on rehabilitation in hip fracture patients and found normoalbuminemic patients had better rehabilitation scores. However, after adjustment for age, they concluded that alb level alone had become a nonsignificant variable on functional outcome because normoalbuminemic patients had been somewhat younger than the rest of their patients. In the current study, we found that patients with normoalbuminemia and normal tlc had better functional scores, similar to Koval et al.<sup>[2]</sup> However, multivariate analysis yielded that none of them had an independent effect on functional outcome. We also showed after dividing the patients into two groups according to age between 65-84 or  $\geq 85$  to determine the effect of age on functional outcome that there was no relation between advanced age and function, contrary to the results of Mizrahi et al.<sup>[14]</sup>

The effect of gender on mortality after hip fracture surgery is controversial.<sup>[13,17,22]</sup> Pioli et al.<sup>[17]</sup> evaluated mortality rates in hip fracture patients for a one-year period and found male gender to be significant determinant of mortality. Kenzora et al.<sup>[13]</sup> found no significant difference in mortality rates with respect to gender in hip fracture patients. Forsen et al.<sup>[22]</sup> showed in their study that male hip fracture patients had higher mortality than females in the first year after the injury. Beringer et al.<sup>[23]</sup> also found that male gender was associated with higher mortality in hip fracture patients in Northern Ireland. Bass et al.<sup>[24]</sup> conducted a large sample study and reported that males with hip fracture had higher mortality risk than females with hip fracture. In the current study,

we found that female gender was a strong independent determinant for one-year mortality.

Advanced age has been reported to be effective on mortality in patients with hip fracture.<sup>[13,22]</sup> Kenzora et al.<sup>[13]</sup> found a significantly higher rate of mortality in intertrochanteric fracture patients older than 70 years of age. Forsen et al.<sup>[22]</sup> found that female hip fracture patients who were  $\geq 85$  years of age had excess mortality especially during the first three months postoperatively. We had a relatively small group of patients with advanced age in the current study, but found no significant difference regarding the advanced age. We believe that studies with larger sample groups should be done.

There are certain advantages to our study. First, the study design prevented potential mistakes of file review problems because they were all recorded when the patients were hospitalized, and none of the patients included in the study was lost in the follow-up period, which can be considered the strength of the study. The exclusion criteria were limited to pathologic fractures and patients who had been nonambulatory before fracture. These factors all contribute to the strength of the results of this study. However, a weakness of the current study is that the number of patients was not large enough for subgroup evaluation. We suggest further researches with large patient groups in order to make powerful comparisons.

In conclusion, blood alb and tlc significantly affect the postoperative one-year mortality and functional outcome in elderly patients with hip fractures. We think that the short-term results regarding function and mortality can be estimated with tlc and alb levels, which are inexpensive and easy to study. Our study indicates that ASA 3-4, lower lymphocyte count and female gender appear to be significant independent risk factors accounting for mortality in those patients. Identifying these predictive factors may be helpful in improving case management and determining prognosis, especially during the first year after hip fracture management.

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