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Extremely Low Serum Alanine Transaminase Level Is Associated with All-Cause Mortality in the Elderly after Intracranial Hemorrhage

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Objective : Extremely low alanine transaminase (ALT) levels are associated with all-cause mortality in frail elderly individuals; the clinical significance of ALT as a reliable biomarker is now being considered. Predicting mortality with routine tests at the time of diagnosis is important for managing patients after intracranial hemorrhage. We aimed to investigate whether an extremely low ALT level is associated with mortality in the elderly after intracranial hemorrhage.

Methods : A retrospective review was performed on 455 patients with intracranial hemorrhage admitted to a university-affiliated tertiary care hospital from February 2014 to May 2019. Multivariate Cox regression analysis was performed for all ages and for each age group to determine whether an extremely low ALT level is an independent predictor of mortality only in the elderly.

Results : Overall, 294 patients were enrolled, and the mean age of the subjects was 59.1 years, with 99 (33.8%) aged ≥65 years. The variables associated with all-cause mortality in all subjects were age, C-reactive protein (CRP) levels, hemoglobin (Hb) levels (<11 g/dL), and initial Glasgow coma scale (GCS) scores. In young patients, CRP, low Hb levels, and initial GCS scores were significantly associated with all-cause mortality. However, in the elderly (≥65 years), the variables significantly associated with all-cause mortality were extremely low levels of ALT (<10 U/L) (adjusted hazard ratio, 3.313; 95% confidence interval, 1.232–8.909; p=0.018) and initial GCS scores.

Conclusion : Extremely low ALT level (<10 U/L) at the time of diagnosis is a significant risk factor for all-cause mortality in the elderly after intracranial hemorrhage.

Key Words : Alanine transaminase · Frail elderly · Frailty · Intracranial hemorrhages · Mortality.

INTRODUCTION

Measurement of serum alanine aminotransferase (ALT) is the most commonly requested laboratory test[19]. Serum ALT is a major biomarker for monitoring liver function and is a predictor of overall health status[15]. High levels of serum ALT indicate damage to the liver, and some studies have shown that high ALT levels may be associated with mortality[17,22].

However, extremely low ALT levels have recently been shown to affect all-cause mortality, and have emerged as a re-

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liable biomarker[6,16]. There is a negative correlation between the metabolic function of the liver and age[11,21,23]. ALT is an enzyme synthesized in the liver and is known to be decreased in the elderly[11]. A recent meta-analysis revealed that extremely low ALT levels are associated with mortality and frailty in the aged population[19].

Frailty refers to the state of a decreased response to external stress following reduction of the physiological capacity to maintain homeostasis[12]. However, frailty itself does not cause death, and one-third of elderly people have frailty without diseases[13]. If the human body experiences extreme stress, its overall physical capacity is reduced. Elderly individuals with frailty have a significant reduction in the rate of recovery from their decreased physical capacity in stressful situations, which can lead to death[3].

Intracranial hemorrhage is a disease with high mortality, that causes significant physical stress in survivors[25,28]. To our knowledge, no studies have investigated the association between extremely low ALT levels and mortality in elderly patients after intracranial hemorrhage. We hypothesized that extremely low ALT levels are associated with frailty, and therefore, may be associated with all-cause mortality in the elderly after an intracranial hemorrhage, which is one of the most stressful situations. Predicting mortality with routine tests at the time of diagnosis is important for managing patients efficiently. Thus, we aimed to explore whether an extremely low ALT level is associated with all-cause mortality in elderly patients after intracranial hemorrhage.

MATERIALS AND METHODS

This retrospective chart review study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Institutional Review Board of Catholic Kwandong University, International St. Mary's Hospital (IRB No. IS20RISI0004).

Subjects

We retrospectively reviewed 455 patients with intracranial hemorrhage admitted to a university-affiliated tertiary care hospital between February 2014 and May 2019. A retrospective medical record review was conducted on patients who were diagnosed with intracranial hemorrhage by computed tomography or magnetic resonance imaging (MRI). The following exclusion criteria were applied : 1) patients in whom it was not the first episode of stroke; 2) those with a history of tumors and cardiac problems; 3) those aged ≤18 years; 4) those with incomplete medical records or laboratory data; and 5) those with suspected liver damage (serum ALT levels >40 U/L).

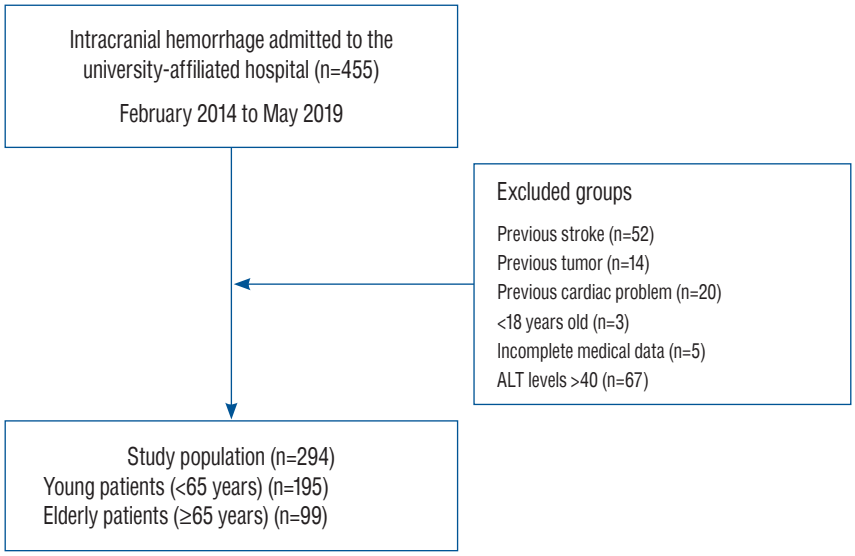

Fig. 1. Strengthening the reporting of observational studies in epidemiology diagram of the study population. From the 455 patients, 52, 14, and 20 patients were excluded because they had a history of previous stroke, tumor, or cardiac problems, respectively. Among the remaining 369 patients with intracranial hemorrhage, three patients under 18 years old, five patients with incomplete medical records and laboratory data, and 67 patients whose serum ALT levels greater than 40 were excluded. Finally, 294 subjects were enrolled in the study. ALT : alanine transaminase.

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Data collection

Age, sex, weight, height, and body mass index (BMI) were collected as biometric data. The cause and type of hemorrhage, medical history, and history of smoking and/or alcohol

Table 1. General characteristics and comparison between elderly and young groups

	Total (n=294)	Elderly (n=99)	Young (n=195)	*p*-value
Age (years)	59.1±15.8	77.5±7.7	49.8±9.3	0.000
Sex				0.564
Female	146 (49.7)	52 (52.5)	94 (48.2)	
Male	148 (50.3)	47 (47.5)	101 (51.8)	
Initial GCS	11.1±4.7	10.1±5.0	11.5±4.6	0.011
Death	42 (14.3)	24 (24.2)	18 (9.2)	0.001
Survival time (months)	26.0±18.4	22.9±19.6	27.6±17.6	0.035
Cause				0.000
Trauma	53 (18.0)	31 (31.3)	22 (11.3)	
Spontaneous	241 (82.0)	68 (68.7)	173 (88.7)	
Hemorrhage type				0.000
EDH, SDH	48 (16.3)	29 (29.3)	19 (9.7)	
ICH, IVH	156 (53.1)	51 (51.5)	105 (53.8)	
SAH	90 (30.6)	19 (19.2)	71 (36.4)	
Laboratory findings at diagnosis				
Extremely low ALT (<10 U/L)	28 (9.5)	14 (14.1)	14 (7.2)	0.087
Low albumin (<3.5 g/dL)	98 (33.3)	54 (54.5)	44 (22.6)	0.000
Low Hb (<11 g/dL)	80 (27.2)	34 (34.3)	46 (23.6)	0.069
Creatinine	0.9±1.0	0.8±0.9	0.9±1.1	0.735
CRP	23.5±46.2	29.3±47.0	20.5±45.7	0.124
BMI				0.022
Underweight (<18.5)	48 (16.3)	22 (22.2)	26 (13.3)	
Normal weight (18.5–24.9)	163 (55.4)	57 (57.6)	106 (54.4)	
Overweight (25.0–29.9)	73 (24.9)	20 (20.2)	53 (27.2)	
Obese (≥30)	10 (3.4)	0 (0.0)	10 (5.1)	
DM	41 (13.9)	19 (19.2)	22 (11.3)	0.095
Hypertension	121 (41.2)	62 (62.6)	59 (30.3)	0.000
Dyslipidemia	32 (10.9)	19 (19.2)	13 (6.7)	0.002
Smoking history	67 (22.8)	14 (14.1)	53 (27.2)	0.018
Alcohol consumption	115 (39.1)	23 (23.2)	92 (47.2)	0.000

Values are presented as mean±standard deviation or number (%). GCS : Glasgow coma scale, EDH : extradural hemorrhage, SDH : subdural hemorrhage, ICH : Intracranial hemorrhage, IVH : intraventricular hemorrhage, SAH : subarachnoid hemorrhage, ALT : alanine aminotransferase, Hb : hemoglobin, CRP : C-reactive protein, BMI : body mass index, DM : diabetes mellitus

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consumption were investigated as medical data related to all-cause mortality. The initial Glasgow coma scale (GCS) was used to investigate the severity of intracranial hemorrhage. The following laboratory findings, known to affect mortality rate, were collected from the data at the time of diagnosis : ALT, albumin, creatinine, C-reactive protein (CRP), and hemoglobin (Hb) levels. We obtained the date of death from the National Health Insurance database.

Data preprocessing

Factors known to have a linear association with mortality, such as age, initial GCS scores, creatinine, and CRP, were used as continuous variables[2,5,9,10,20].

As in the previous studies, albumin, Hb, BMI, and ALT were categorized into risk and reference groups. Serum albumin levels <3.5 g/dL and serum Hb levels <11 g/dL are known risk factors for increased mortality[7,14]. Based on the cutoff val-

Table 2. The univariate regression analysis for predicting death after intracranial hemorrhage

	Total (n=294)		Elderly (n=99)		Young (n=195)	
	HR	*p*-value	HR	*p*-value	HR	*p*-value
Age (years)	1.029	0.004*	1.005	0.841	0.998	0.925
Sex		0.909		0.762		0.759
Female	Ref.		Ref.		Ref.	
Male	1.036	0.909	1.132	0.762	0.865	0.759
Initial GCS	0.760	0.000*	0.806	0.000*	0.718	0.000*
Cause		0.518		0.096		0.996
Trauma	Ref.		Ref.		Ref.	
Spontaneous	0.752	0.518	0.402	0.096	1.004	0.996
Hemorrhage type		0.268		0.309		0.528
EDH, SDH	Ref.		Ref.		Ref.	
ICH, IVH	2.157	0.151	2.091	0.193	33339.516	0.928
SAH	1.498	0.489	2.602	0.139	18421.813	0.932
Laboratory findings at diagnosis						
Extremely low ALT (<10 U/L)	4.298	0.000*	6.135	0.000*	1.563	0.551
Low albumin (<3.5 g/dL)	11.872	0.000*	3.661	0.010*	32.272	0.000*
Low Hb (<11 g/dL)	7.887	0.000*	4.809	0.000*	12.744	0.000*
Creatinine	1.417	0.000*	1.315	0.043*	1.497	0.000*
CRP	1.018	0.000*	1.017	0.000*	1.019	0.000*
BMI		0.057		0.210		0.291
Underweight (<18.5)	Ref.		Ref.		Ref.	
Normal weight (18.5–24.9)	0.523	0.069	0.537	0.168	0.606	0.397
Overweight (25.0–29.9)	0.248	0.009	0.345	0.116	0.239	0.099
Obese (≥30)	0.740	0.694	No data		1.298	0.763
DM	0.820	0.677	0.840	0.750	0.441	0.426
Hypertension	1.323	0.365	0.976	0.955	0.879	0.806
Dyslipidemia	1.114	0.821	0.840	0.750	0.790	0.819
Smoking history	1.178	0.640	1.606	0.346	1.330	0.568
Alcohol consumption	0.830	0.564	1.287	0.574	0.879	0.879

*p<0.05. HR : hazard ratio, GCS : Glasgow coma scale, EDH : extradural hemorrhage, SDH : subdural hemorrhage, ICH : Intracranial hemorrhage, IVH : intraventricular hemorrhage, SAH : subarachnoid hemorrhage, ALT : alanine aminotransferase, Hb : hemoglobin, CRP : C-reactive protein, BMI : body mass index, DM : diabetes mellitus

ues, patients were categorized into the low-level group and the reference group. In the case of BMI, both extremes, underweight and obese, are known to be associated with mortality; thus, BMI was used as a categorical variable for the following

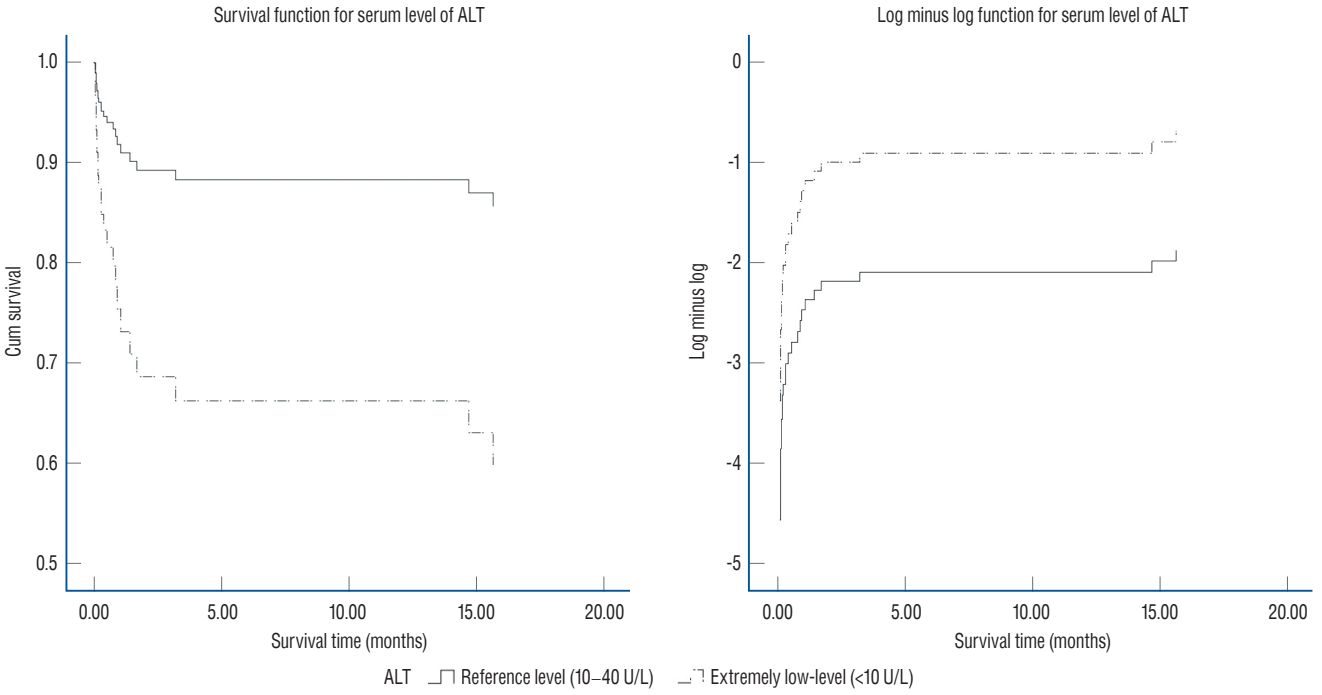

Fig. 2. Cumulative survival and log minus log curve in the elderly group. The Cox proportional model was constructed according to the ALT level, and it was found that there was a difference in survival rate in the elderly group, even though the confounders were controlled. Since the log minus log functions did not cross each other in this study, the application of the Cox proportional hazard model is appropriate. Elderly people with extremely low ALT levels (<10 U/L) at the time of intracranial hemorrhage had a higher mortality rate than those with reference ALT levels (10–40 U/L). ALT : alanine aminotransferase.

Table 3. Independent predictors of death after intracranial hemorrhage using a multivariate Cox regression analysis

	Adjusted HR	95% CI		*p*-value
		Lower	Upper	
Total				
Age (years)	1.023	1.001	1.045	0.040*
CRP	1.012	1.007	1.016	<0.001*
Low Hb (<11 g/dL)	3.592	1.778	7.258	<0.001*
Initial GCS	0.837	0.765	0.916	<0.001*
Young				
CRP	1.012	1.005	1.019	0.001*
Low Hb (<11 g/dL)	5.635	1.759	18.054	0.004*
Initial GCS	0.803	0.695	0.927	0.003*
Elderly				
Extremely Low ALT (<10 U/L)	3.313	1.232	8.909	0.018*
CRP	1.008	1.000	1.016	0.051
Initial GCS	0.844	0.750	0.949	0.005*

*p<0.05. HR : hazard ratio, CI : confidence interval, CRP : C-reactive protein, Hb : hemoglobin, GCS : Glasgow coma scale, ALT : alanine aminotransferase

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four groups : underweight (<18.5), normal weight (18.5–24.9), overweight (25.0–29.9), and obese (≥30)[18,27]. A meta-analysis revealed that mortality increased with every 5 U/L decrement in serum ALT level[19]. In this study, subjects with normal ALT levels were divided into the extremely low ALT level group (<10 U/L) and the reference group (10–40 U/L).

Statistical analyses

The subjects were divided into the two following groups : those aged <65 years and those aged ≥65 years. Survival analyses were performed for all ages and for each age group, to determine whether an extremely low ALT level was an independent predictor of mortality only in the elderly.

Data were analyzed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). The differences between the two groups were assessed using an independent t-test for continuous variables and a chi-square test or Fisher's exact test for categorical variables. Categorical variables were described using frequency and percentages. Continuous variables were described using the mean (standard deviation) for normally distributed variables. Multivariate Cox regression analysis was used to evaluate the association between ALT and all-cause mortality while controlling for potential confounders. *p*-values less than or equal to 0.05 were considered statistically significant.

RESULTS

A total of 294 patients were included in the study. The mean age of the subjects was 59.1 years, and 99 (33.8%) were aged ≥65 years. The number of deaths during the investigation was 42 (14.3%), and the mean survival time was 26.0 months. The overall characteristics are described in Table 1.

We used a Cox regression analysis to evaluate the association with all-cause mortality. The variables used to control potential confounders included age, sex, trauma, hemorrhage type, extremely low ALT level (<10 U/L), low albumin level (<3.5 g/dL), low Hb level (<11 g/dL), serum creatinine and CRP levels, BMI, and a history of diabetes, hypertension, dyslipidemia, smoking, and alcohol consumption. The results of the univariate regression analysis for predicting death are shown in Table 2.

In a multivariate analysis of patients of all ages, extremely low ALT levels were not found to be significantly associated with all-cause mortality. However, analysis of each age group revealed that extremely low ALT levels were significantly associated with all-cause mortality only in the elderly group (Fig. 2).

The variables associated with all-cause mortality in all subjects were age (adjusted hazard ratio [HR], 1.023; 95% confidence interval [CI], 1.001–1.045; p=0.040), CRP (adjusted HR, 1.012; 95% CI, 1.007–1.016; p<0.001), low Hb levels (adjusted HR, 3.592; 95% CI, 1.778–7.258; p<0.001), and initial GCS scores (adjusted HR, 0.837; 95% CI, 0.765–0.916; p<0.001). In the young age group, CRP (adjusted HR, 1.012; 95% CI, 1.005–1.019; p=0.001), low Hb levels (adjusted HR, 5.635; 95% CI, 1.759–18.054; p=0.004), and initial GCS scores (adjusted HR, 0.803; 95% CI, 0.695–0.927; p=0.003) were significantly associated with all-cause mortality. In the elderly group, the variables significantly associated with all-cause mortality were extremely low ALT levels (adjusted HR, 3.313; 95% CI, 1.232–8.909; p=0.018) and initial GCS scores (adjusted HR, 0.844; 95% CI, 0.750–0.949; p=0.005). Variables found to be associated with all-cause mortality in the multivariate Cox regression analysis are shown in Table 3.

DISCUSSION

The aim of this study was to determine whether extremely low ALT levels affect all-cause mortality in elderly patients after intracranial hemorrhage. In this study, cases with a high risk of death were excluded from the study. In addition, patients with ALT levels above 40 were also excluded from the study, as high levels of ALT could lead to death due to hepatotoxicity. Consequently, elderly people with extremely low ALT levels (<10 U/L) at the time of intracranial hemorrhage had a three-fold higher mortality rate than those with normal ALT levels (10–40 U/L).

Extremely low ALT levels were associated with all-cause mortality only in the elderly population, as observed in previous studies[6,7,11,16,19,21]. There was one study in which the low ALT level was not associated with mortality; however, that study specified the ALT criteria as the median value of the study population, which was 17 U/L[8]. Meta-analysis revealed that mortality increased with every decrease of 5 U/L in ALT levels. In this study, the cutoff point of the ALT was set to <10 U/L and significant results were obtained[19]. According to previous studies, extremely low ALT levels can reflect frailty. In

elderly people with frailty, the liver degenerates, thereby reducing its production of ALT, resulting in an extremely low serum ALT concentration[4,16]. The meta-analysis of mortality in patients with cardiovascular diseases caused by frailty showed significant results, suggesting that extremely low ALT levels affect mortality in patients with intracranial hemorrhage associated with frailty[24]. In our study, the Cox proportional model was constructed according to the ALT, and it was found that there was a difference in survival rates in the elderly group, even though the confounders were controlled. This result is consistent with that in previous studies, and it was confirmed that extremely low ALT level is an independent predictor of all-cause mortality in elderly patients after intracranial hemorrhage. It is worth mentioning that laboratory findings at the time of diagnosis have a significant association with mortality, even though other well-known risk factors were controlled.

The mechanism of death due to frailty is known as insult accumulation. Death is mainly caused by disease, but the disease does not always cause death. Patients suffering from most diseases will recover rather than expire. However, people with frailty have a significantly reduced rate of recovery from the state of decreased physical capacity; moreover, they are more susceptible to other diseases, and this condition continues to accumulate, leading to death[1].

Frailty is known to be improved through rehabilitation. The theoretical reason for us to expect that rehabilitation approaches are effective in improving frailty is clear. Some experimental data also suggest that rehabilitation is effective for the elderly with frailty and pre-frailty. However, no study has yet investigated the relationship between mortality and rehabilitation in high-risk patients after an intracranial hemorrhage[5]. Therefore, further research is needed to identify the effects of rehabilitation on intracranial hemorrhage patients with extremely low ALT levels (<10 U/L).

Thrift et al.[26] reported that the mortality rates for all types of stroke vary between 15–30%, depending on the country and the health care system. The mortality rate in this study was 14.3%, which might be different from countries with poor healthcare systems when the results of this study are interpreted and applied to them. However, generalizing the results of this study is reasonable because the correlations between known risk factors such as age, initial GCS scores, low Hb levels, CRP, and mortality rates are similar to those shown in previous studies[2,10,20,29].

This study is limited by its retrospective design and small sample size. Additionally, since the cause of death was not investigated, it is impossible to confirm whether it is cause-specific to the disease. Therefore, when mentioning the mortality rate, we refer to death caused by the overall cause. The all-cause mortality investigated in this study included both survival and deaths during the acute stage. In the future, the association among extremely low ALT levels, frailty, and mortality needs to be confirmed through cohort studies rather than through cross-sectional studies. In addition, further research is needed to identify the effects of rehabilitation on patients with extremely low ALT levels and their mortality.

CONCLUSION

An extremely low ALT level (<10 U/L) at the time of diagnosis is a significant risk factor of all-cause mortality in elderly patients after intracranial hemorrhage; therefore, normalizing ALT levels may help in treating such patients.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

INFORMED CONSENT

This type of study does not require informed consent.

AUTHOR CONTRIBUTIONS

Conceptualization : DYK, KCC
Data curation : DYK, KCC
Formal analysis : DYK
Methodology : DYK
Project administration : DYK, KCC
Visualization : DYK
Writing - original draft : DYK
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