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ARAŞTIRMA / RESEARCH

Evaluation of lipid levels and LDL-C/HDL-C ratio as possible risk markers of intracerebral hemorrhage

Lipid düzeylerinin ve LDL-C/HDL-C oranının intraserebral hemorajilerde olası bir risk belirteci olarak değerlendirilmesi

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Abstract

Purpose: The aim of this study is to analyze the utility of lipid parameters individually and the low-density lipoprotein cholesterol/high-density lipoprotein cholesterol (LDL-C/HDL-C) ratio as a possible risk marker for intracerebral hemorrhages (ICH).
Materials and Methods: This was a multicenter, retrospective case-control study that included 226 patients with ICH and 226 controls. Lipid parameters were evaluated after 12 h of fasting in patients whose ICH was confirmed by brain computed tomography, and no underlying vascular, traumatic, or metabolic cause could be found.
Results: The mean LDL-C levels and mean total cholesterol (TC) levels did not differ in in the patient and control groups. The mean HDL-C levels in the patient groups were significantly lower whereas triglyceride (TG) levels were significantly higher. In the patient and control groups, LDL-C/HDL-C ratio was 2.65±1.10 and 2.94±1.13 (p=0.006), TG/HDL-C ratio was 3.60±2.72 and 4.47±3.25 (p=0.002), and TC/HDL-C ratio was 4.37±1.49 and 4.83 ± 1.56 (p=0.002), respectively.
Conclusion: Increased TG and decreased HDL-C levels were found to be associated with ICHs. However LDL-C/HDL-C, TC/HDL-C, and TG/HDL-C ratios were low in the patient group. Therefore, we can conclude that these lipid ratios give clearer and more significant results in determining the risk of hemorrhage.
Keywords: LDL-C/HDL-C ratio; triglyceride/HDL-C ratio; hemorrhagic stroke; cholesterol; cerebrovascular disease

Öz

Amaç: Bu çalışmanın amacı lipid parametrelerinin tek tek ve düşük dansiteli lipoprotein kolesterol/yüksek dansiteli lipoprotein kolesterol (LDL-C/HDL-C) oranına bakarak intraserebral hemoraji (ISH) için bir olası risk belirteci olarak kullanılabilirliğini analiz etmektir.
Gereç ve Yöntem: Çok merkezli, retrospektif vaka-kontrol çalışmasıdır. İntraserebral hemorajisi olan 226 hasta ve 226 kontrol çalışmaya dahil edilmiştir. İntraserebral hemorajisi beyin bilgisayarlı tomografide teyit edilen ve altta yatan vasküler, travmatik ve metabolik bir neden bulunamayan hastalardan 12 saatlik açlık sonrası lipid parametreleri değerlendirildi.
Bulgular: Yaptığımız araştırmada LDL-C ve total kolesterol (TC) ortalaması hasta ve kontrol gruplarında anlamlı farklılık göstermedi. Hasta gruplarında HDL-C ortalamaları anlamlı düzeyde düşükken, trigliserid (TG) düzeyleri yüksekti. Hasta ve kontrol grupları arasında LDL-C/HDL-C oranı sırasıyla 2,65 ± 1,10 ve 2,94 ± 1.13 (p=0,006), TG/HDL-C oranı 3,60 ± 2,72 ve 4,47 ± 3,25 (p=0,002) son olarak TC/HDL-C oranı 4,37 ± 1,49 ve 4,83 ± 1,56 (p=0,002) tespit edildi.
Sonuç: Artan TG ve azalan HDL-C düzeylerinin ISH ile ilişkili olduğu görülmüştür. Bununla beraber LDL-C, TC ve TG'nin HDL-C ile arasındaki oranlarının hasta grubunda daha düşük olduğu analiz edildi. Bu nedenle hemoraji riskini belirlemede bu lipid oranlarının daha net ve anlamlı sonuçlar verdiğini önerebiliriz.
Anahtar kelimeler: LDL-C/HDL-C oranı; trigliserid/HDL-C oranı; hemorajik stroke; kolesterol; serebrovasküler hastalık

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INTRODUCTION

Cerebrovascular diseases (CVD) lead to substantial mortality and morbidity in advanced ages. They are grouped under two main types ischemic and hemorrhagic. Intracerebral hemorrhage (ICH) accounts for approximately 10%–15% of all CVD cases[1]. Hemorrhagic strokes are less common than ischemic strokes, but they are clinically severe and have worse prognosis[1]. Spontaneous ICH, which is the subject of this study, usually develops due to severe hypertension (HT). HT is a well-known risk factor for all CVD, and there is a linear relationship between hyperlipidemia and ischemic stroke. In other words, high total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglyceride and low high-density lipoprotein cholesterol (HDL-C) levels increase the risk of ischemic stroke. Furthermore, the relationship between hemorrhagic stroke and lipid parameters remains unclear. Some studies have shown a low serum TC level to be a possible risk factor for long-standing ICH[2].

Although there are studies showing a direct correlation between high HDL-C level and the risk of ICH, such a correlation could not be found in some studies[3,4]. The precise role of cholesterol in the pathogenesis of ICH is unclear, but some studies suggest that low cholesterol levels make the cerebrovascular endothelium fragile and vulnerable to leakage and rupture[5]. In addition, low cholesterol levels in patients with ICH lead to altered cerebral blood flow and increased permeability of the blood–brain barrier[6]. According to another hypothesis, low TC levels are also associated with the presence of cerebral microhemorrhages, which are thought to be asymptomatic precursors of symptomatic ICH[7,8]. Researchers have speculated that similarities between ICH and cerebral microhemorrhage risk factors may enable the early detection of people at high risk of ICH development[5].

High LDL-C/HDL-C, TG/HDL-C ratios have recently been emphasized for patients with ischemic CVD and cardiovascular diseases, and they have been found to be directly related to the risk of atherogenicity[9]. However, there are limited studies on the effects of these ratios on ICH. Therefore, our aim is to examine the relationship between lipid concentrations and ICH, for which there is no clear consensus yet. Our hypothesis is that there may be a possible inverse relationship between LDL-C level and ICH risk. We also expect the decrease in the LDL-C/HDL-C ratio to support this inverse ratio. We also calculated LDL-C/HDL-C, TC/HDL-C, and TG/HDL-C levels to provide a more detailed analysis and planned to show the relationship of the obtained values with ICH.

MATERIALS AND METHODS

Study design and patient selection

Present research was designed retrospective and case-control study. It was carried out as a multicenter study in three different provinces. The hospitals participating in the study are centers with fully equipped tertiary neurology intensive care units. These centers are located in the Eastern and Southeastern Anatolia region of Turkey. The study was approved by the Malatya Turgut Ozal University Clinical Research Ethics Committee (Date:30 September 2021, Ethics committee number:71), and informed consent was obtained. This study was performed in consistency with the the guideline of the Helsinki Declaration.

Electronic medical records were scanned for clinical, laboratory, and radiological data, and 361 patients with the diagnosis of hemorrhagic CVD hospitalized between 2012 and 2020 were screened. Brain CTs and clinical data of the patient and control groups were checked by two neurologists. Those with subarachnoid, epidural, subdural, intralesional hemorrhage were excluded from the study. ICH patients who had history of ischemic or hemorrhagic CVD, hematological disease, malignancy and lipid metabolism disorders were rejected from the study. According to these criteria, 135 patients were excluded from the study. The control group was selected from individuals who had no previous CVD, lipid metabolism disorder, malignancy, or head trauma. According to guidelines HT is diagnosed when systolic blood pressure (SBP) is ≥140 mm Hg and/or their diastolic blood pressure (DBP) is ≥90 mm Hg following repeated examination. Individuals with SBP/DBP >140/90 mmHg and at least one antihypertensive medical treatment were included in the hypertensive patient group[10]. In a healthy humans, the optimum LDL-C level should be <100 mg/dl. Statins are a group of medicines that can help lower the level of LDL-C in the blood. Atorvastatin is commonly used at hyperlipidemia treatment[11]. Atorvastatin treatment and daily dose were questioned since it is a drug that may affect the outcome of the study. In the power analysis, effect size: 0.959, α:0.05, β-1:0.95 were taken. When LDL-C levels are 133±12 mg/dl in the patient group, 121±13.1 mg/dl in the control group, and the ratio between both groups is calculated as N1/N2 =1, at least 50 subjects were required.

Laboratory parameters and radiological imaging

Computed tomography (CT) was used for diagnosis via cranial imaging. Computed tomography is widely considered as the gold standard to image brain hemorrhage. ICH is identified by brain CT as an intra-axial hyperdense region of hemorrhage[12]. In the centers participating in the study, brain CTs were taken on a Siemens® device. Intraparenchymal hemorrhagic areas were categorized based on their location (the lobar regions, thalamus, basal ganglia, brain stem, and cerebellum). Venous blood samples were collected from the patients after they had fasted for 12 h. Samples were placed in EDTA blood collection tubes, and lipid parameters were studied. Abbott Architect ® C16000 and Beckman Coulter ® AU 5800 devices were used for analysis. It was seen that the reference values and measurement units used in the three centers were the same.

The studied lipid parameters were used to calculate LDL-C; it was calculated using the following formula: [LDL-C = TC − (HDL-C + TG/5)]. According to the studied lipid type, TC < 200 mg/dL, LDL-C < 130 mg/dL, HDL-C > 40 mg/dL, and TG < 150 mg/dL were considered normal. The ratios of the lipid parameters (LDL-C, TG, and TC) with HDL-C were calculated.

Statistical analysis

The data obtained at the end of the data collection phase were transferred to a computer and analyzed. SPSS® 26.0 (SPSS Inc., Chicago, IL, USA) package program was used for statistical analysis. All baseline parameters were analyzed. Arithmetic mean, standard deviation, and minimum and maximum values were used to summarize numerical data. Frequency distributions and percentages were used to summarize categorical data. Categorical variables are defined as percentages, and continuous variables are defined as mean±SD. Pearson's correlation test was used for comparing age, gender, and HT diagnosis between the groups. Chi-square test was used to compare categorical data (groups, gender, HT history). The relationship of lipid parameters and ratios between groups was analyzed with the Indepented-Samples T test. Anova table and eta test was used to compare statin doses between groups. $p < 0.05$ was considered significant in all statistical analyses.

RESULTS

A total of 452 (226 patients, 226 controls) individuals were included in the study. When gender distribution of the groups was analyzed, a strong correlation was found between the female (F) and male (M) genders. F/M in the patient group was 107/119 whereas F/M in the control group was 104/122 ($p = 0.778$). The mean age of the patient and control groups was 65.26 ± 11.84 years and 64.58 ± 12.52 years, respectively, and no significant difference was found between the groups ($p = 0.305$).

It was seen that both the groups were similar in terms of gender and age distributions. A potent relationship was not observed between the daily statin dose between the two groups (Table 1). Spontaneous ICH is most commonly encountered with severe HT. As a result, the rates of HT diagnosis in both the groups were examined, which showed that 157 and 150 people had a diagnosis of HT in the patient and control groups, respectively (Table 2).

The relationship between lipid parameters and LDL-C/HDL-C, TG/HDL-C, and TC/HDL-C ratios between the two groups was investigated. The mean HDL-C level was 47.5 ± 15.88 mg/dL and 43.38 ± 12.64 mg/dL ($p = 0.002$) and mean TG level was 143.62 ± 71.65 mg/dL and 166.88 ± 81,762 mg/dL ($p = 0.001$) in the patient and control groups, respectively. LDL-C levels (114.58 ± 32.39 mg/dL, $p = 0.124$) and TC levels (192.69 ± 43.70 mg/dL, $p = 0.452$) were lower in the patient group compared to the control group, but these differences were not statistically significant. Very-low-density lipoprotein cholesterol (VLDL-C) level was lower in the patient group (29.10 ± 13.95 mg/dL) compared to the control group ($p = 0.001$). In the patient and control groups, LDL-C/HDL-C ratio was 2.65 ± 1.10 and 2.94 ± 1.13 ($p = 0.006$), TG/HDL-C ratio was 3.60 ± 2.72 and 4.47 ± 3.25 ($p = 0.002$), and TC/HDL-C ratio was 4.37 ± 1.49 and 4.83 ± 1.56 ($p = 0.002$), respectively (Table 3). According to these results, it was determined that the ratio of the three lipid parameters to HDL-C showed a significant difference between the groups.

Table 1. Demographic data of sample

	Patients	Controls	Total	*p*
Age	65.26±11.84	64.08±12.52	64.67±12.19	*0.305*
Gender, n Female	107 (23.7%)	104 (23%)	211 (46.7%)	*0.805*
Male	119 (26.3%)	122 (27%)	241 (53.3%)	
HT history, n Yes	157 (34.7%)	150 (33.2%)	307 (67.9%)	*0.481*
No	69 (15.3%)	76 (16.8%)	145 (32.1%)	
Statin therapy, n Yes	31 (6.8 %)	40 (8.8 %)	71 (15.7 %)	*0.233*
No	28 (6.1 %)	26 (5.7 %)	54 (11.9 %)	
Dosage (mg/day)	19.6±24.2	11.5±21.2	15.3±22.9	*0.471*

*HT:Hypertansion

Table 2. Correlation Of Clinical Features Between Patient and Control Groups

		Groups	Gender	Age	HT history
Groups	Pearson Correlation	1	0.013	-0.048	-0.033
	Sig. (2-tailed)		0.778	0.305	0.482
	N	452	452	452	452
Gender	Pearson Correlation	0.013	1	0.043	-0.121*
	Sig. (2-tailed)	0.778		0.366	0.010
	N	452	452	452	452
Age	Pearson Correlation	-0.048	0.043	1	0.165**
	Sig. (2-tailed)	0.305	0.366		0.000
	N	452	452	452	452
HT history	Pearson Correlation	-0.033	-0.121*	0.165**	1
	Sig. (2-tailed)	0.482	0.010	0.000	
	N	452	452	452	452

* Correlation is significant at the 0.05 level (2-tailed) ** Correlation is significant at the 0.01 level (2-tailed).; †HT:Hypertansion

Table 3. The analysis of lipid parameters and ratios between patient and control groups.

	Group	Mean (mg/dL)	Std. deviation	t	95% CI (lower-upper)		*p*
LDL-C	1	114,58	32,390	1,540	-11,131	1,349	*0,124*
	2	119,47	35,060				
HDL-C	1	47,50	15,883	3,053	1,469	6,777	*0,002*
	2	43,38	12,649				
VLDL-C	1	29,10	13,958	3,223	-7,436	-1,803	*0,001*
	2	33,72	16,412				
TC	1	192,69	43,702	0,753	-10,876	4,850	*0,452*
	2	195,70	41,328				
TG	1	143,62	71,652	3,217	-37,477	-9,054	*0,001*
	2	166,88	81,762				
LDL-C/ HDL-C	1	2,6588	1,10752	2,749	-0,49692	-0,08264	*0,006*
	2	2,9485	1,13319				
TG/HDL-C	1	3,6009	2,72112	3,083	-1,42579	-0,31568	*0,002*
	2	4,4716	3,25937				
TC/HDL-C	1	4,3792	1,49294	3,177	-0,74137	-0,17469	*0,002*
	2	4,8373	1,56487				

*Group 1: Patients †Grup 2: Controls ‡Std: Standard §LDL-C: low-density lipoprotein-cholesterol ||HDL-C: High-density lipoprotein cholesterol ¶VLDL-C: Very-low-density lipoprotein cholesterol ßTC: Total cholesterol ØTG: Triglyceride.

Lobar hemorrhage was the most common hemorrhage 45.2 % (n:102), thalamus 20% (n:45), basal ganglia 21.6 (n:48), cerebellum 11.6 % (n:26) whereas brain stem hemorrhage was the least common 9.8 % (n:22).

DISCUSSION

There are two well-known risk factors for spontaneous ICHs. The first of these is advanced age, and the second is HT. Severe HT usually occurs in the acute phase of ICH and persists for several days. In the present study, we evaluated lipid parameters that can be considered as possible risk factors for ICH individually and their ratio with HDL-C. Confounding factors were eliminated, and the groups were matched for factors that may reduce the reliability of the study. In other words, attention was paid to the fact that there was a strong and positive correlation between the groups in terms of mean age, gender distribution, and the number of individuals diagnosed with HT. In the present study, it was found that HDL-C levels were higher and TG and VLDL-C levels were lower in those with ICH compared to the control group individuals. However, LDL-C and TC concentrations were not significantly different between the two groups. Unlike other studies in the literature, we analyzed the LDL-C/HDL-C, TC/HDL-C, and TG/HDL-C ratios. The results showed that there was a highly significant difference between the groups. Therefore, these ratios may be used as parameters in the future to show the probability of ICH development with more precision.

In the literature, the relationship between cholesterol levels and ICH remains to be controversial. However, there are sources that have long considered low serum TC levels to be a possible risk factor for ICH[2]. Several pathophysiological mechanisms have been proposed to support this hypothesis. First, low cholesterol levels may play a role in promoting arterial medial layer smooth muscle cell necrosis[13]. The other mechanism is that the endothelial tissue impaired due to low cholesterol levels may cause microaneurysms, the main pathological finding of ICH, and thus contribute to the onset of bleeding[14]. Another study supporting this hypothesis reported that low serum TC levels are associated with an increased risk of symptomatic ICH and the presence of asymptomatic cerebral microhemorrhage[5].

In a study conducted in Japan, the inverse relationship between serum cholesterol level and increased risk of hemorrhagic stroke was shown for the first time. Subsequently, in the Multiple Risk Factor Intervention study, it was found that risk of fatal ICH was three times higher in those with TC < 4.13 mmol/L (<159.7 mg/dL) compared to those with TC > 4.13 mmol/L[15,16]. An analysis of 12 cohort studies from Asia showed a 27% increase in the risk of hemorrhagic stroke for a 0.6 mmol/L (23 mg/dL) reduction in cholesterol concentrations[17]. However, some inconsistencies between the results were also reported. In the Korea Medical Insurance Corporation study, which was also conducted in Asia, low TC level was not shown to be an independent risk factor for hemorrhagic stroke[18].

A positive correlation was found between clinical severity and LDL-C level in ischemic stroke. The National Institutes of Health Stroke Scale (NIHSS), which provides information about clinical severity and prognosis in ischemic stroke, was used in a recent study. In this study, LDL-C level was 103.3 ± 27.1 mg/dL in those with NIHSS ≤ 16, whereas LDL-C level was 128.4 ± 39.5 mg/dL in those with NIHSS > 16 ($p < 0.05$)[19]. Based on this result, we can say that the severity and prognosis of ischemic stroke can vary even at different levels of LDL-C concentration, which is a definite atherogenic risk factor. However, such a correlation between clinical severity and lipid level could not be established yet in hemorrhagic stroke cases. Nevertheless, this issue was evaluated in only one study in terms of mortality due to cholesterol and ICH. The authors argued that there was an association between cholesterol levels and mortality in hemorrhagic stroke cases[10]. Cholesterol levels may reflect the nutritional status of patients with ICH. A low cholesterol level may be a precursor to nutritional deficiencies, low serum albumin levels, or a preliminary finding of other debilitating diseases. Therefore, it may cause increased mortality in patients with ICH[20].

A large systematic meta-analysis was conducted using the Pubmed and Emphase databases between 1980 and 2013 to investigate the relationship between ICH and cholesterol levels. Twenty-three studies were included in this comprehensive meta-analysis study, and cholesterol levels were evaluated in 7960 patients with ICH. In conclusion, this study showed that TC level was inversely related to the risk of hemorrhagic stroke. A 1 mmol/L (38.6 mg/dL) increase in TC concentration was associated with a 15% reduction in the risk of hemorrhagic stroke. Likewise, low LDL-C levels were found to increase the risk of ICH.

However, researchers could not detect a significant relationship between HDL-C and ICH[18]. Although there were statistically significant results in this study, it received self-criticism by its authors. The lack of case-control studies was chief among these self-criticisms. In addition, it was emphasized that case-control studies on this subject are limited. Since the present study includes a control group, it can be a more robust data source for future meta-analysis studies.

Individuals older than 55 years of age were followed up prospectively in Rotterdam I-II studies, which lasted for approximately 20 years and included 9068 people who did not have a stroke. It was found that ICH developed in a total of 85 people among those who were followed up. In addition, microhemorrhages were seen in 162 of 789 patients who had no stroke symptoms and underwent brain magnetic resonance imaging for other reasons. According to the results of the study, it was reported that the risk of ICH increased with decreasing TC levels and increasing HDL-C levels. However, no significant relationship was found between LDL-C level and ICH in this study. There was a negative correlation between TG level and both asymptomatic patients with microhemorrhage and those with ICH. Based on this result, it was argued that low TG level is a strong predictive factor for ICH. This is because no such link was found between LDL-C or TC level and microhemorrhage.[5] The present study also supports the hypothesis that low TG levels may cause damage to the vascular endothelial tissue.

In three prospective studies, it was observed that the risk of hemorrhagic stroke decreased with increasing TG levels. Although one of these studies suggested that the relationship between TG levels and hemorrhagic stroke may be stronger in men, other studies showed no gender-related differences[21]. In another study, decreased VLDL-C and TG levels were associated with an increased risk of ICH[3]. In the present study, mean TG level was found to be 143.62 ± 71.65 mg/dL and 166.88 ± 81.76 mg/dL in the patient and control groups, respectively ($p = 0.001$). The mean VLDL-C level was 29.10 ± 13.95 mg/dL in patients with ICH and 33.72 ± 16.41 mg/dL in the control group ($p = 0.001$).

As new atherogenic indexes, the importance of LDL-C/HDL-C, TC/HDL-C, and TG/HDL-C ratios in the prognostic evaluation of ischemic CVD and cardiovascular diseases has increased recently[22]. In other words, it is thought that TC/HDL-C and LDL-C/HDL-C ratios better reflect atherogenic risk compared to lipid parameters alone. As a result, it was observed that the risk of ischemic CVD increased as this rate increased[23]. In the present study, we tried to take advantage of this ratio between cholesterol levels. We based our hypothesis on the lower cholesterol rate observed in those with ICH. When we looked at the literature, we found that there is not much data on the relationship between ICH and other lipid parameter and HDL-C ratios. Therefore, the present study is extremely important as it is the first such study in the literature. In the present study, we examined the relationship of these three ratios between patient and control groups. The LDL-C/HDL-C ratio was 2.65 in the patient group and 2.94 in the control group ($p = 0.006$). LDL-C/HDL-C ratio was found to be lower in patients with ICH. Likewise, TG/HDL-C and TC/HDL-C ratios were 3.60 and 4.37, respectively, in the patient group and 4.47 and 4.83, respectively, in the control group ($p = 0.002$ and $p = 0.002$). However, the mean LDL-C level was 114.58 mg/dL in the patient group, which was lower than that in the control group; however, there was no significant difference in LDL-C levels between the two groups ($p = 0.124$). In this respect, it would be more reasonable to consider the LDL-C/HDL-C ratio instead of the LDL-C level alone for evaluating the relative risk of ICH. Indeed, an inverse relation with the risk of atherogenicity can be seen again. In other words, low LDL-C/HDL-C ratio was seen to increase the risk of ICH. We see similar results in the other two ratios (TG/HDL-C and TC/HDL-C) as well. In many previous studies showing the correlation between individual lipid parameters and ICH, such correlations could not be found for some lipid parameters and inconsistent results were obtained. For example, in the present study, there was no correlation between LDL-C level and ICH when the patient and control groups were compared. Therefore, in future studies, it will be useful to look at the ratio of lipids with each other in determining both the risk of atherogenicity and the risk of ICH. Based on these observations, we can put forward the following hypothesis: LDL-C/HDL-C, TG/HDL-C, and TC/HDL-C ratios may be act as early warning systems for ICH in the asymptomatic period, i.e., in the microhemorrhage stage.

Our study has several limitations. The present study was limited by the limited sample size. Other a possible limitation of our study, the duration of statin treatment was unknown. Finally, another limitation is that a history of microhemorrhage was not excluded in the patient group.

The results of present study, low TG levels and high HDL-C levels were observed in those with ICH. However, such a relationship was not found between LDL-C, TC levels, and ICH. Furthermore, it was determined that low LDL-C/HDL-C, TG/HDL-C, and TC/HDL-C ratios were associated with an increased risk of ICH. These lipid ratios may play a role in determining the risk of hemorrhagic stroke in the coming years. Therefore, prospective studies with larger patient groups should be conducted for further evaluation.

Yazar Katkıları: Çalışma konsepti/Tasarımı: AA, ÜÖ; Veri toplama: ÜÖ, AA, SÇ; Veri analizi ve yorumlama: AA; Yazı taslağı: AA; İçeriğin eleştirel incelenmesi: ÜÖ, SÇ; Son onay ve sorumluluk: AA, SC, ÜÖ; Teknik ve malzeme desteği: ÜÖ; Süpervizyon: SÇ; Fon sağlama (mevcut ise): yok.
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