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RESEARCH

Expression of nuclear pore protein POM121 in childhood acute lymphoblastic leukemias and its relationship with prognosis

Çocukluk çağı akut lenfoblastik lösemilerinde nükleer por proteini POM121'in ekspresyonu ve prognoz ile ilişkisi

Burcu Genç Cavlak[1], Ayşe Özkan[1], İbrahim Bayram[1], Gülay Sezgin[1], Serhan Küpeli[1], Atila Tanyeli[1]

[1]Çukurova University Faculty of Medicine, Department of Pediatric Oncology and Pediatric Bone Marrow Transplantation Unit, Adana, Turkey

Abstract

Purpose: We aimed to investigate the status of POM121 gene expression, which is one of the nuclear pore proteins in childhood acute lymphoblastic leukemias (ALL), compared with the normal population, and its relationship with prognosis and other clinical findings.

Materials and Methods: Fifty-nine patients with ALL followed up and treated between January 2008 and November 2013, and 36 control subjects were included in the study. A real-time PCR method was used to detect POM121 gene expressions.

Results: The mean value of POM121 expression was 3.75±2.91 in ALL patients and 3.32±3.76 in the control group. The 3 and 10 year overall survival (OS) was better in ALL with lower POM121 expression (77%, 70% versus 68%, 58%, respectively). Although the OS was better in B-ALL patients, with lower POM121 expression (84%, 75% versus 54%, 46%, respectively), in T-ALL, in contrast, the OS results were better in patients with a higher POM121 expression (90%, 90% versus 60%, 60%, respectively). Patients with a higher POM121 expression than the mean of the control group and who had relapse and central nervous system involvement had statistically significantly lower OS results in the 3rd and 10th years (16%, 0% versus 84%, 78%, respectively).

Conclusion: High POM121 expression negatively affects the prognosis in patients with ALL. This is a study to show the relationship between POM121 expression and prognosis in childhood acute lymphoblastic leukemias, POM121 function will be clarified further with more comprehensive studies.

Keywords: Acute lymphoblastic leukemia, POM121 expression, prognosis

Öz

Amaç: Bu çalışmada, çocukluk çağı akut lenfoblastik lösemilerinde (ALL), nükleer por proteinlerinden biri olan POM121'in gen ekspresyonunun normal popülasyona göre durumunu, prognoz ve diğer klinik bulgularla ilişkisini araştırmayı amaçladık.

Gereç ve Yöntem: Ocak 2008 ile Kasım 2013 tarihleri arasında takip ve tedavi edilen 59 ALL'li hasta ve 36 kontrol olgu çalışmaya dahil edildi. POM121 gen ekspresyonunu saptamak için Real time-PCR yöntemi kullanıldı.

Bulgular: POM121 ekspresyonunun ortalama değeri ALL hastalarında 3,75 ± 2,91 ve kontrol grubunda 3,32 ± 3,76 idi. 3 ve 10 yıllık sağkalım düşük POM121 ekspresyonuna sahip olan ALL hastalarında daha iyi idi (sırasıyla %77, %70'e karşı %68, %58). B-ALL hastalarında POM121 ekspresyonu, daha düşük olan hastaların GS sonuçları daha iyi iken (sırasıyla %84, %75'e karşı %54, %46) T-ALL'de, tersine, yüksek olan hastaların GS sonuçları, daha iyi idi (sırasıyla %90, %90'a karşı %60, %60). Nüks ve merkezi sinir sistemi tutulumu olan, kontrol grubunun ortalamasından daha yüksek POM121 ekspresyonu olan hastalar 3. ve 10. yıllarda istatistiksel olarak anlamlı şekilde daha düşük GS sonuçlarına sahipti (sırasıyla %16, %0'a karşı %84, %78).

Sonuç: Yüksek POM121 ekspresyonu, ALL hastalarında prognozu olumsuz yönde etkiler. Bu çalışma, çocukluk çağı akut lenfoblastik lösemilerinde POM121 ekspresyonu ile prognoz arasındaki ilişkiyi göstermeye yönelik yapılan bir çalışmadır ve POM121'in fonksiyonlarını açığa kavuşturmak için daha kapsamlı çalışmalar gereklidir.

Anahtar kelimeler: Akut lenfoblastik lösemi, POM121 ekspresyonu, prognoz.

Address for Correspondence: Ayşe Özkan, Çukurova University Faculty of Medicine, Department of Pediatric Oncology and Pediatric Bone Marrow Transplantation Unit, Adana, Turkey E-mail: drayseozkan79@yahoo.com.tr
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INTRODUCTION

Nuclear pore complexes (NPC) are multiprotein structures found in all eukaryotic cells which are responsible for the passages between the cytoplasm and the nucleus[1]. NPCs also have many cellular functions such as differentiation, cell division, chromatin organization, and epigenetic modification[2]. NPCs are composed of approximately 30 different proteins called nucleoporins[3]. Nucleoporins are typically grouped in subcomplexes and are differentiated according to their different sequence and structural motifs[4].

Many studies have been conducted in the literature on the oncogenic role of nucleoporins in human carcinogenesis in solid tumors[5]. In recent years, numerous studies have been published, which have emphasized the importance of nucleoporins in hematological malignancies[6,7]. Hematological malignancies are usually associated with chromosomal rearrangements, which lead to the expression of chimeric fusion proteins[8]. The proteins known to be part of such oncogenic fusions include the nucleoporins NUP98 and NUP214. The rearrangement of the genes encoding these two nucleoporins plays a role in the pathogenesis of, particularly acute myeloid leukemia, and sometimes myelodysplastic syndrome, and T-cell acute lymphoblastic leukemia (T-ALL)[9].

POM121, one of the nucleoporins, is called the transmembrane nucleoporin and is located in the nuclear envelope together with NUP210 and NDC1[4]. POM121 is also one of the PAX5 fusion genes. PAX5, a transcription factor, encodes the B-cell lineage-specific activator protein and is the main regulator of B-cell development[10]. PAX5 fusion partners include not only transcription factors but also structural proteins such as ELN and POM121[11]. There is a limited number of studies in the literature showing that POM121 plays a role in leukemogenesis[10,12].

In this study, it was aimed to investigate the expression of POM121, one of the nuclear pore proteins, which is considered to be associated with the pathways related to cell proliferation in childhood acute lymphoblastic leukemias (ALL), relative to the normal population, and its relationship with prognosis and other clinical findings.

MATERIALS AND METHODS

Sample

Fifty-nine patients who presented to the Pediatric Oncology Clinic of Çukurova University Hospital between January 2008 and November 2013 and were diagnosed with ALL were included in this study and the prognosis of the disease was evaluated in these patients until January 2020. Thirty-six children who presented to the Pediatrics Department of Çukurova University Faculty of Medicine General Children's Outpatient Clinic for check-up purposes, whose physical examination was normal, and who were found to be hematologically normal with complete blood count were included in the study as the control group for POM121 gene expression.

The following patients were excluded from this study; patients with missing data in their patient files, patients who went to another center after diagnosis or during the treatment process, patients who were diagnosed in an external center and applied to continue treatment after treatment, patients with diagnosed with L3 type ALL and patients whose blood samples were not taken to detect POM12 expression at the time of diagnosis.

Ninety-one patients were diagnosed with ALL between January 2008 and November 2013, 19 of these patients continued their treatments in other centers. 3 patients diagnosed with ALL L3 were excluded from the study. Blood samples for POM121 gene expression could not be obtained from 10 patients. Therefore, a total of 59 patients with ALL were included in the study.

Acute lymphoblastic leukemia patients were subdivided according to the French–American–British classification and immunophenotyping. Patients were immunophenotypically divided into the subgroups of B-ALL and T-ALL. The terminology of "Cluster of Differentiation, CD" was used to identify cell surface antigens. In immunophenotyping studies, those who scored above 20% in CD surface marker antigens were evaluated as positive[13]. Patients were treated with the chemotherapy protocol based on BFM TR-ALL 2000[14]. Ethics committee approval was obtained from Çukurova University Faculty of Medicine, Non Interventional Clinical Research Ethics Committee with the decision number 28/15 dated February 14, 2014. Informed consent was obtained from the patients, control subjects, and/or

legal guardians before enrollment in the study, which was conducted in accordance with local institutional regulations.

Study procedure

Blood samples of 3 ml were taken into a tube with ethylenediaminetetraacetic acid (EDTA) from the patients included in the study at the time of diagnosis and from the controls. First of all, the isolated RNA samples were stored in a freezer at −80°C until the day of the study. White blood cell values of the whole blood samples were detected before starting the study. RNA isolation from leukocyte cells was performed using the High Pure RNA isolation kit. RNAs obtained were translated to cDNA with Transcriptor First Strand cDNA Synthesis Kit and stored at −20°C. A real-time polymerase chain reaction method was used to detect POM121 gene expressions. This study was conducted using a Light Cycler (Roche Applied Science). Housekeeping genes and target genes were analyzed with "Advanced Relative Quantification" calculations on LC 480 Software at a wavelength in accordance with the design.

Statistical analysis

All statistical analyses were performed using the statistical package for social sciences (SPSS v22) software package. Group data were defined as mean ±standard deviation (mean±SD). Pearson correlation test was performed for correlation and Kaplan–Meier method was used for life analysis in the evaluation of the data. In addition, categorical variables (such as gender) were analyzed using the chi-square test. Non-parametric variables were analyzed using the Mann–Whitney U test. P<0.05 was considered statistically significant.

RESULTS

Of the 59 ALL patients, 28 (47.5 %) were diagnosed with ALL L1, 31 (52.5 %) with ALL L2. The number of controls was 36. ALL patients consisted of 39 boys (66.1%) and 20 girls (33.9%), and the boy/girl ratio was 1.95. The control group consisted of 22 boys (61.1%) and 14 girls (38.9%), and the boy/girl ratio was 1.57. The age of the patients ranged from 5 months to 210 months, and the mean age was 91.22±63.39 years. The ages of the children in the control group were between 5 months and 213 months, and the mean age was 87.78±55.80 months.

The mean value of POM121 expression was 3.75±2.91 in ALL patients; the mean value in the control group was 3.32±3.76, and no statistically significant difference was found between them (p=0.539). When POM121 expression was evaluated with gender, relapse, survival, anemia, thrombocytopenia, neutropenia, hepatomegaly, splenomegaly, and lymphadenopathy in patients, there was a significant difference between POM121 expression and neutropenia (p=0.016) (Table 1).

Table 1. POM121 expression in ALL patients and its relationship with certain clinical and laboratory findings.

	ALL POM121 expression (mean±SD) (min–max)	**n**	**p**
Boys	4.18±3.35 0.24-13.45	39	0.117
Girls	2.92±1.54 1.035-7.67	20	
Anemia (−)	2.53±1.31 1.02-3.41	3	*
Anemia (+)	3.81±2.97 0.24-13.45	56	
Neutropenia (–)	4.28±3.15 0.24-13.45	44	**0.016**
Neutropenia (+)	2.20±1.09 1.00-5.10	15	
Thrombocytopenia (−)	3.10±2.53 0.24-10.70	17	0.278
Thrombocytopenia (+)	4.01±3.05 1.02-13.45	42	
Splenomegaly (−)	3.59±3.12 0.24-13.00	30	0.678
Splenomegaly (+)	3.91±.74 1.02-13.45	29	
Hepatomegaly (−)	3.30±2.73 0.24-13.00	28	0.264
Hepatomegaly (+)	4.16±3.06 0.63-13.45	31	
Lymphadenopathy (−)	3.47±2.90 0.24-13.45	35	0.379
Lymphadenopathy (+)	4.16±2.94 0.63-13.00	24	

ALL, acute lymphoblastic leukemia; SD, standard deviation.
*: No statistical analysis was performed because there were fewer than six cases in the groups.

Table 2. POM121 expression in ALL leukemia patients.

	ALL POM121 expression (mean±SD) (min–max)	n	p
ALL L1	3.09±2.24 0.63-8.34	28	0.100
ALL L2	4.34±3.34 0.24-13.45	31	
B-ALL	3.30±2.42 1.00-10.70	38	0.210
T-ALL	5.50±2.98 0.63-13.45	13	
SRG	4.59±3.43 0.24-13.0	19	0.097
MRG	3.52±2.9 0.63-13.5	29	0.96
HRG	2.92±1.72 1.17-6.10	11	
Relapse (−)	4.00±3.07 0.63-13.45	42	0.307
Relapse (+)	3.13±2.49 0.24-10.70	17	
Alive	3.82±3.17 0.63-13.45	38	0.914
Ex	3.65±2.51 0.24-10.70	20	
Lost to follow-up	2.68 2.68	1	

ALL, acute lymphoblastic leukemia; SD, standard deviation; SRG, standard risk group; MRG, intermediate risk group; HRG, high risk group.

In ALL patients, there was a positive correlation between POM121 expression and urea (p=0.001; r=416), creatinine (p=0.001; r=422), uric acid (p=0.001; r=424), and CD117 (p=0.005; r=416). When POM121 expression was compared based on ALL risk groups, immunophenotypes, and ALL subtypes, there were no statistically significant results (Table 2). Immunophenotyping could not be performed in 8 patients at the time of diagnosis.

POM121 expression was divided into two groups: high and low compared with the mean of the control group. Patients with POM121 expression higher than the mean of the control group were referred to as Group 1, and patients with POM121 expression lower than the mean of the control group were referred to as Group 2. ALL patients consisted of 24 patients in Group 1 and 35 patients in Group 2. The effect of POM121 expression being higher and lower than the mean of the control group on overall survival (OS) was investigated in ALL patients. In the 36th, 60th, and 120th months, OS was 68%, 58%, and 58%, respectively, in Group 1, and 77%, 70%, and 70%, respectively, in Group 2 (Figure 1). Overall, OS results of the patients in Group 2, whose POM121 expression was lower than that of the control group, were better. However, the results were not statistically significant (p=0.356).

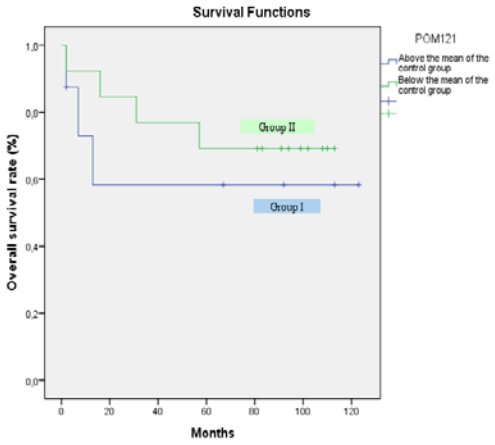

Figure 1. Overall survival of ALL patients.

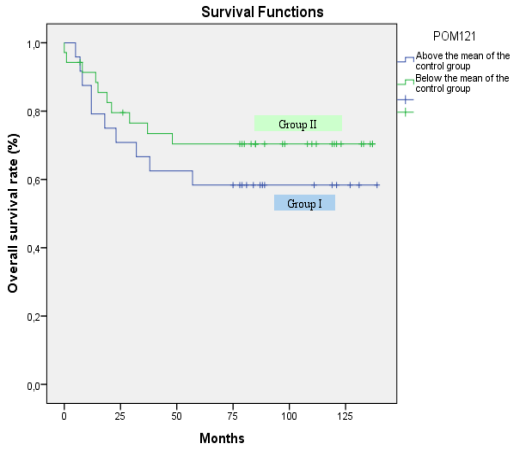

Figure 2. Overall survival of B-ALL patients

When OS results of patients were evaluated according to immunophenotyping, in B-ALL patients, there were 13 patients in Group 1, and 25 patients in Group 2. In B-ALL patients in Group 1, OS was 54%, 46%, and 46% in the 36th, 60th, and 120th months, respectively, and it was 84%, 75%, and 75%, respectively, in Group 2 patients (Figure 2).

Table 3. POM121 expression compared with control group and the effect of clinical and laboratory characteristics on overall survival in ALL patients.

	n	Group 1 (POM121 expression> mean of the control)			n	Group 2 (POM121 expression lower than the mean of the control)		
		3rd year OS	10th year OS	p (Log rank)		3rd year OS	10th year OS	p (Log rank)
Lymphadenopathy								
Yes	12	58	50	0.333	12	75	67	0.624
No	12	75	66		23	77	72	
Hepatomegaly								
Yes	15	66	66	0.257	16	74	67	0.558
No	9	66	45		19	79	74	
Splenomegaly								
Yes	14	78	71	0.075	15	72	65	0.461
No	10	40	40		20	80	74	
Relapse								
Yes	6	16	0	0.001	11	53	32	0.003
No	18	84	78		24	87	87	
CNS involvement								
Yes	6	16	0	0.001	8	60	45	0.159
No	18	84	78		27	81	77	
Gender								
Boy	16	63	63	0.675	23	82	77	0.172
Girl	8	75	50		12	66	57	
Risk group								
SRG	10	70	50	0.023	9	77	77	0.600
MRG	11	82	82		18	76	65	
HRG	3	66	66		8	75	75	
Family history of cancer								
Yes	2	40	-	*	8	75	75	0.759
No	22	70	60		27	77	69	
Cell type								
T-cell	8	88	88	0.066	5	60	60	*
B-cell	13	44	44		25	84	75	
Age								
Older than 6 years	11	65	55	0.688	16	63	63	0.165
2–6 years old	9	56	56		16	94	86	
Under 2 years old	4	100	75		3	67	33	
Anemia								
Yes	23	70	61	*	33	75	72	*
No	1	0	0		2	100	50	
Neutropenia								
Yes	1	100	-	*	14	93	79	0.347
No	23	65	56		21	65	65	
Thrombocytopenia								
Yes	18	78	72	0.002	24	74	65	0.334
No	6	34	17		11	82	82	
WBC								
>100 x 10^9/L	2	100	100	*	4	25	25	*
<100 x 10^9/L	22	58	55		31	84	76	
>50 x 10^9/L	5	100	100	*	8	44	44	0.046
<50 x 10^9/L	19	52	48		27	85	78	
>20 x 10^9/L	10	80	80	0.081	14	62	62	0.260
<20 x 10^9/L	14	57	44		21	86	76	

OS, overall survival; CNS, central nervous system; SRG, standard risk group; MRG, intermediate risk group; HRG, high risk group; WBC, white blood cell. *: No statistical analysis was performed because there were fewer than six cases in the groups.

In T-ALL patients, in the 36th, 60th, and 120th months, 8 patients in Group 1 had an OS of 88% and 5 patients in Group 2 had an OS of 60% (Figure 3). In B-ALL patients, the OS results of patients in Group 2 with a lower POM121 expression were better compared with those of the control group, as in ALL patients, but the results were not statistically significant. In T-ALL, by contrast, patients in Group 1 with a higher POM121 expression than the mean of the control group had better OS results. However, the results were not statistically significant (p=0.065 and p=0.269, respectively).

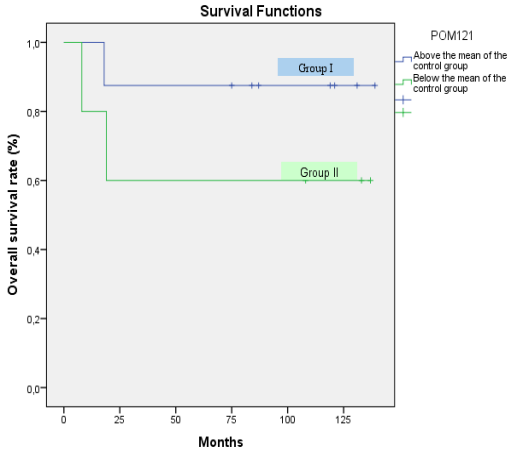

Figure 3. Overall survival of T-ALL patients

DISCUSSION

Attempts have been made to define the role of NPCs in cancer in a detailed manner in several recent reviews[3,15,16]. For the first time in the literature, Blobel et al. showed evidence that Nup214 had an oncogenic role in the development and progression of hematological malignancies in 1994[17]. After this study, it has been shown that some other nucleoporins (Nup62, Nup88, Nup98, Nup358/RanBP2, and Tpr) are also associated with tumorigenesis[18].

There are numerous studies in the literature that analyze the relationship between NPCs and cancer; however, the number of studies that analyze the relationship between POM121, a nucleoporin, and leukemia is limited, and the relationship between POM121 and leukemogenesis could not be demonstrated[10-12,19].

In this study, when the ALL patients and the control group were compared, no statistically significant result was found in terms of POM121 expression (p=0.539). When POM121 expression was assessed with gender, relapse, survival, anemia, thrombocytopenia, neutropenia, hepatomegaly, splenomegaly, and lymphadenopathy in patients, there was a significant difference between POM121 expression and only with neutropenia. In fact, POM121 expression was found to be lower in ALL patients with neutropenia (p=0.016).

There was no significant correlation between POM121 expression and ALL type (ALL L1 and ALL L2), immunophenotype (B-ALL and T-ALL), and risk group (SRG, MRG, and HRG) in our study.

A study by Nebral et al. showed that PAX-5 rearrangements were observed in B-cell precursor ALL at a rate of approximately 2.5% in 446 cases of childhood ALL. In this study, several new PAX5 common genes, such as DACH1, HIPK1, JAK2, and BRD1 including POM121, have been identified. The data of the study showed that they contain not only transcription factors but also structural proteins and genes such as ELN and POM121 are involved in signal transduction; however, these do not play a role in tumor formation[10].

In the present study, the OS results of patients in Group 2, which had lower POM121 expression than the control group in ALL patients, were better. However, the results were not statistically significant. We also found that POM121 expression was significantly lower in the group with neutropenia in ALL patients. The occurrence of neutropenia in these patients can be considered to be associated with a high blast production rate. However, having neutropenia, thus an increased risk of infection, may have led to an inverse relationship. This will be clarified by expanding of the infection parameters and analyzing POM121 expression.

Denk et al. reviewed 12 cases with PAX5 fusion genes in t (7; 9) (q11.2; p13) leukemia and reported that two of them were cases containing the PAX5–POM121 fusion gene, but the relationship of these genes with the prognosis could not be demonstrated[20]. In a study with multiple PAX5 fusion proteins, including PAX5–POM121, it was shown that these proteins share some predominant features including nuclear localization and DNA binding, and this study demonstrated the possible

functions of these proteins, as well as highlighted their effects on development of leukemia[12].

When the OS results of patients were evaluated according to immunophenotyping, in B-ALL patients, the OS results of patients in Group 2, with lower POM121 expression compared with the control group, were better at 36, 60, and 120 months with 84%, 75%, and 75%, respectively. However, the results were not statistically significant (p=0.065). In contrast, in T-ALL, the OS results of patients in Group 1 were better with 88% at the 36th, 60th, and 120th months. However, the results were not statistically significant (p=0.269). This suggests that there is a different mechanism that we are not aware of in T-ALL patients.

When the effects of some clinical and laboratory features and POM121 expression higher or lower than the control mean in ALL patients were compared with the effects on the OS of the patients at the 3rd and 10th years, it was found that ALL patients in Group 1 with relapse and CNS involvement had lower OS compared to Group 2 at the 3rd and 10th years. Thus, it can be said that the higher POM121 expression compared with the control group adversely affects the prognosis.

In a recent study of POM121 by Rampello et al., it has been reported that the nucleoporins, especially POM121 is involved in nuclear envelope herniations (blebs) and Torsin ATPase deficiency is observed in its defects, which may cause a predisposition to leukemia by reducing the sequestration of myeloid leukemia factor 2[21].

There were some limitations in our study. As it is a retrospective study, data of all patients could not be reached. Immunophenotyping could not be performed in eight of the patients at the time of diagnosis. The number of patients was not sufficient for optimal statistical analysis.

In conclusion, in B-ALL patients, the OS results of patients in Group 2 with lower POM121 expression were better compared with mean of the control group. In T-ALL, in contrast, the OS results of patients in Group 1 with a higher POM121 expression were better compared with the mean of the control group. However, not all results were statistically significant. OS results of ALL patients in Group 1 with relapse and CNS involvement, those who were in SRG and, interestingly, those without thrombocytopenia, were statistically significantly lower compered with the group 2. High POM121 expression decreased the OS in B-ALL, but did not have a negative effect on T-ALL. Had there been a higher number of cases in this study, we would have definitely stated that high POM121 expression adversely affects the prognosis in patients with acute leukemia.

This study suggests that high POM121 expression level at admission may be used as a prognostic factor in childhood leukemias. The relapses may be prevented, and survival rates may be increased using more potent treatment protocols against POM121 in patients with high POM121 expressions at diagnosis.

Yazar Katkıları: Çalışma konsepti/Tasarımı: BGC, İB, AT; Veri toplama: BGC, AÖ; Veri analizi ve yorumlama: BGC, AÖ, GS; Yazı taslağı: BGC, AÖ; İçeriğin eleştirel incelenmesi: İB, AT, SK; Son onay ve sorumluluk: BGC, AÖ, İB, GS, SK, AT; Teknik ve malzeme desteği: İB, SK, AT; Süpervizyon: İB, AT, GS; Fon sağlama (mevcut ise): yok.
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