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Evaluation of C-Reactive Protein Levels as Prognostic Indicators in Subarachnoid Hemorrhage Patients

Subaraknoid Kanama Hastalarında C-Reaktif Protein Düzeylerinin Prognostik Gösterge Olarak Değerlendirilmesi

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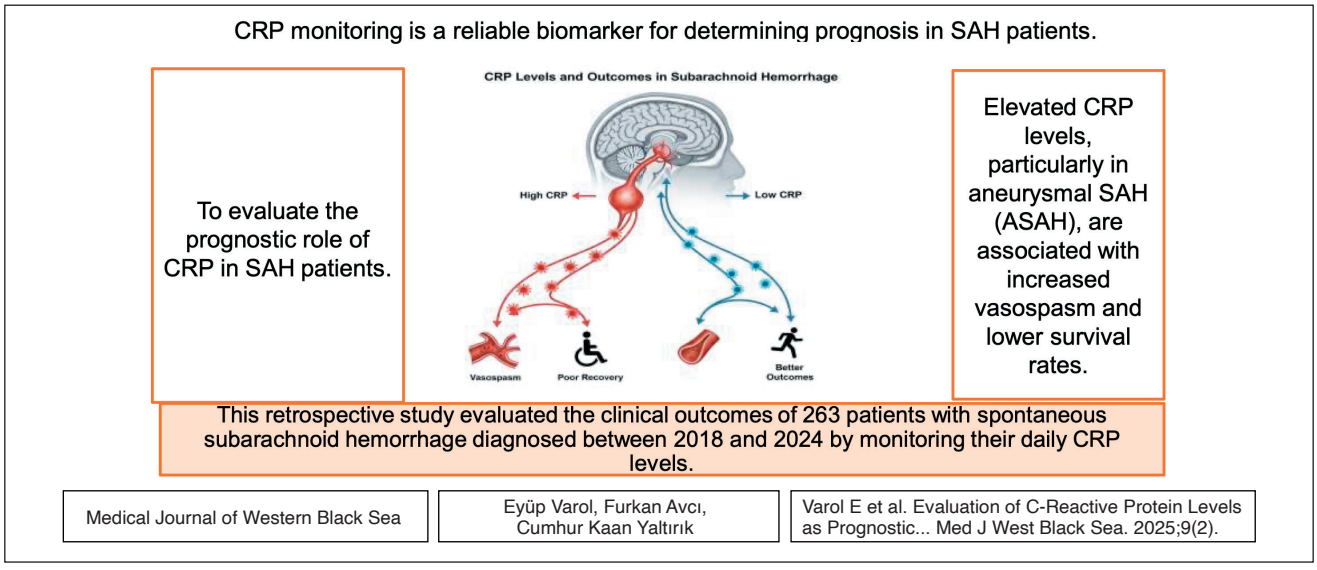
GRAPHICAL ABSTRACT



ABSTRACT

Aim: Subarachnoid hemorrhage (SAH) is a life-threatening condition often leading to severe complications such as cerebral vasospasm, delayed cerebral ischemia, and high mortality rates. Identifying reliable biomarkers to predict clinical outcomes can aid in improving patient management and tailoring therapeutic interventions. This study aims to evaluate the prognostic value of C-reactive protein (CRP) levels in predicting clinical outcomes, including functional recovery, incidence of vasospasm, and mortality, in SAH patients within the first 14 days post-hemorrhage.

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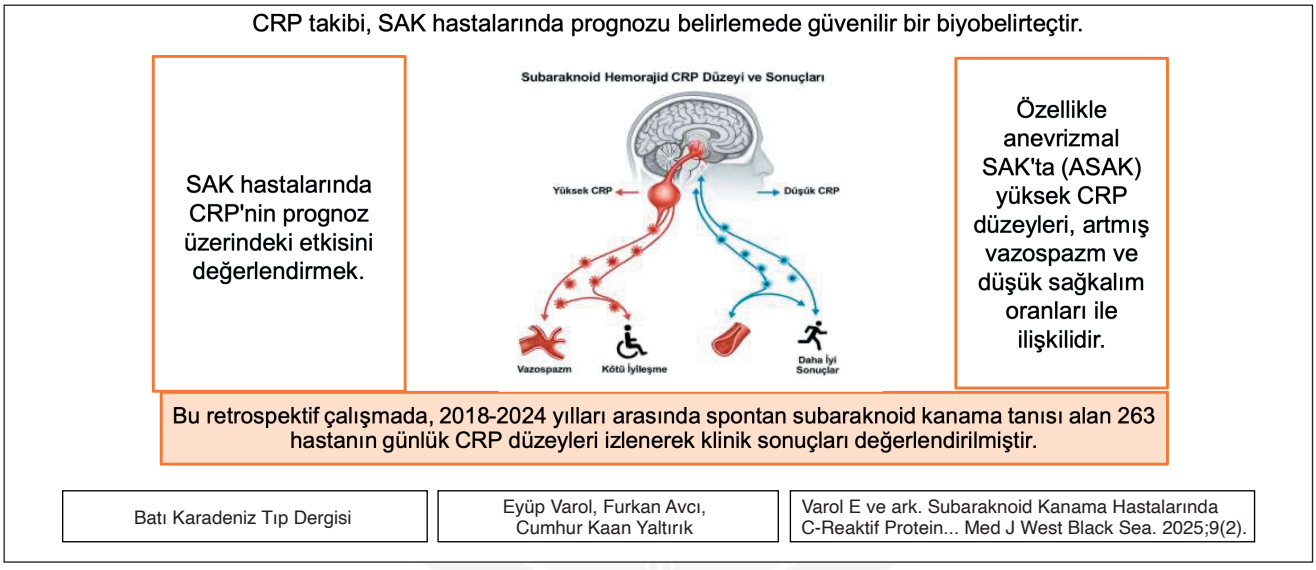
Material and Methods: A retrospective analysis of 263 patients diagnosed with spontaneous SAH between 2018 and 2024 was conducted. Patients were classified into aneurysmal SAH (ASAH) and non-aneurysmal SAH (NASAH) groups based on digital subtraction angiography findings. CRP levels were measured daily for 14 days, and clinical outcomes were assessed using the Modified Rankin Scale and Kaplan-Meier survival analysis.

Results: Patients with ASAH exhibited significantly higher CRP levels (median: 516 mg/L) and longer durations of CRP >100 mg/L compared to NASAH patients. Higher CRP levels correlated positively with worse mRS scores and increased vasospasm incidence. Survival analysis revealed that ASAH patients with CRP >200 mg/L had significantly reduced survival rates (45%) compared to those with lower CRP levels (72%, $p < 0.001$).

Conclusion: Elevated CRP levels are strongly associated with poor functional outcomes, increased vasospasm, and higher mortality in SAH patients, particularly in those with aneurysmal rupture. Incorporating CRP monitoring into routine clinical practice may enhance prognostication and guide targeted therapies.

Keywords: Subarachnoid hemorrhage, C-reactive protein, vasospasm, prognosis, biomarkers

GRAFİKSEL ÖZET



ÖZ

Amaç: Subaraknoid kanama (SAK), genellikle ciddi komplikasyonlara yol açan ve yüksek mortalite oranlarına sahip, yaşamı tehdit eden bir durumdur. Klinik sonuçları öngörebilecek güvenilir biyobelirteçlerin tanımlanması, hasta yönetimini iyileştirmeye ve tedavi yaklaşımlarını bireyselleştirmeye katkı sağlayabilir. Bu çalışmanın amacı, SAK hastalarında ilk 14 gün içinde C-reaktif protein (CRP) düzeylerinin fonksiyonel iyileşme, vazospazm insidansı ve mortalite gibi klinik sonuçları öngörmedeki prognostik değerini değerlendirmektir.

Gereç ve Yöntemler: 2018 ile 2024 yılları arasında spontan SAK tanısı almış 263 hastanın retrospektif analizi yapıldı. Dijital subtraksiyon anjiyografi bulgularına göre hastalar anevrizmal SAK (ASAK) ve anevrizma dışı SAK (ADSAK) olarak sınıflandırıldı. CRP düzeyleri 14 gün boyunca günlük olarak ölçüldü ve klinik sonuçlar Modifiye Rankin Skalası ve Kaplan-Meier sağkalım analizi ile değerlendirildi.

Bulgular: ASAK hastalarında CRP düzeyleri anlamlı olarak daha yüksekti (medyan: 516 mg/L) ve CRP >100 mg/L süresi ADSAK hastalarına göre daha uzundu. Yüksek CRP düzeyleri, daha kötü mRS skorları ve artmış vazospazm insidansı ile pozitif korelasyon gösterdi. Sağkalım analizinde, CRP >200 mg/L olan ASAK hastalarının sağkalım oranı (%45), daha düşük CRP düzeyine sahip olanlara kıyasla (%72) anlamlı olarak daha düşüktü ($p < 0.001$).

Sonuç: Yüksek CRP düzeyleri, özellikle anevrizma rüptürü olan hastalarda, kötü fonksiyonel sonuçlar, artmış vazospazm ve yüksek mortalite ile güçlü bir şekilde ilişkilidir. CRP izleminin rutin klinik pratiğe dahil edilmesi, prognoz tahminini güçlendirebilir ve hedefe yönelik tedavilere yön verebilir.

Anahtar Sözcükler: Subaraknoid kanama, C-reaktif protein, vazospazm, prognoz, biyobelirteçler

INTRODUCTION

Subarachnoid hemorrhage (SAH) is a life-threatening condition characterized by bleeding into the subarachnoid space, often due to a ruptured aneurysm. It accounts for approximately 6-8% of all hemorrhagic strokes with an annual incidence of 6-28 per 100,000 people (1). Despite advancements in medical and surgical treatments, the prognosis for SAH patients remains poor with high mortality and significant long-term morbidity. Approximately 10% of patients die within the first few hours of bleeding, and 25% within the first 24 hours (2).

One of the most challenging aspects of SAH management is predicting clinical outcomes. Early predictors can facilitate timely interventions and optimize resource allocation. Cerebral vasospasm, a severe complication of SAH, typically develops between 3–14 days post-hemorrhage and significantly contributes to delayed cerebral ischemia (DCI) and neurological deterioration. The inflammatory response triggered by SAH has been implicated in vasospasm and poor outcomes, making biomarkers of inflammation an area of significant clinical interest (3). C-reactive protein (CRP), an acute-phase reactant synthesized in the liver, plays a central role in systemic inflammation. Elevated CRP levels have been associated with adverse outcomes in various neurological conditions, including ischemic stroke and traumatic brain injury. In the context of SAH, CRP has emerged as a potential biomarker for predicting complications such as vasospasm, delayed ischemia, and mortality (4,5).

However, its prognostic value remains incompletely understood, particularly in differentiating outcomes between aneurysmal SAH (ASAH) and non-aneurysmal SAH (NASAH) cases.

This study aims to evaluate the relationship between CRP levels and clinical outcomes in SAH patients, with a focus on functional recovery, vasospasm incidence, and survival. By analyzing CRP trends over the first 14 days post-SAH, this study seeks to establish CRP as a reliable prognostic marker and explore its potential role in guiding therapeutic strategies. There are studies in the literature reporting the prognosis of inflammatory markers such as CRP on ASAH patients, but this study aims to contribute to the literature with a large patient sample by examining the effect of CRP on prognosis on SAH in aneurysmal and non-aneurysmal patients separately.

MATERIALS and METHODS

This was a retrospective observational study conducted at a tertiary care center, analyzing patients diagnosed with spontaneous SAH between 2018 and 2024. The study adhered to ethical guidelines, with approval from the institutional ethics committee (Approval ID: B.10.1.TKH.4.34.H.GP.0.01, dated April 25, 2022). Patient consent was obtained at the time of data collection. All authors have confirmed that this study did not involve animal subjects or tissue.

A total of 263 patients presenting with confirmed SAH were included. Diagnosis was established using brain computed tomography (CT) or lumbar puncture findings. Patients were categorized based on digital subtraction angiography (DSA) findings into:

- ASAH: Patients with intracranial aneurysms (n=186).
- NASAH: Patients without aneurysmal findings (n=77).

Inclusion Criteria:

- Age ≥18 years.
- Spontaneous SAH diagnosis confirmed through imaging.
- Monitoring for at least 14 days post-admission.
- Daily CRP measurements available.

Exclusion Criteria:

- Traumatic SAH or other non-spontaneous causes.
- Preexisting inflammatory conditions (e.g., rheumatoid arthritis, lupus).
- Recent infections (<1 year prior to admission).
- Chronic diseases impacting inflammation (e.g., diabetes, hypertension, cardiovascular diseases).
- Missing data on CRP levels or clinical outcomes.

CRP Measurement and Outcome Assessment

CRP levels were measured daily during the first 14 days post-SAH using an immunoturbidimetric assay. The primary outcomes assessed were:

1. Functional outcomes using the Modified Rankin Scale (mRS) at discharge.
2. Incidence of vasospasm confirmed clinically or radiologically.
3. Survival rates analyzed using Kaplan-Meier curves.

CRP cut-off values are determined after statistical analysis by vasospasm group patients.

Statistical Analysis

Statistical analyses were performed using R software (version 4.2.2). Continuous variables were tested for normality using the Shapiro-Wilks test and analyzed with independent samples t-tests or Mann-Whitney U tests. Categorical data were analyzed using Pearson's Chi-square or Fisher's exact tests. Associations between CRP levels and vasospasm risk were evaluated using generalized linear mixed

models. Pearson correlation coefficients were calculated for CRP levels and mRS scores. Kaplan-Meier survival analyses were conducted to compare survival trends, and log-rank tests assessed statistical significance. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 263 patients with spontaneous SAH were included and categorized into ASAH (n=186) and NASAH (n=77) based on DSA findings.

Demographics and CRP Levels

ASAH patients exhibited significantly higher CRP levels and longer durations of CRP >100 mg/L compared to NASAH patients. Elderly patients (>60 years) had the highest CRP levels, especially in the ASAH group (mean: 600 mg/L), while younger patients (<40 years) consistently showed lower CRP values across both groups. The average duration of CRP elevation >100 mg/L was 2.55 ± 0.6 days in ASAH, versus only 0.10 ± 0.03 days in NASAH. A detailed breakdown by age, gender, and CRP levels is presented in Table 1.

CRP and Vasospasm

In the ASAH group, patients with CRP levels >200 mg/L had a significantly higher incidence of vasospasm (72%) compared to those with CRP ≤200 mg/L (45%). A strong positive correlation was observed between peak CRP levels and vasospasm ($r = 0.605$, $p < 0.0001$). Although the association was weaker in NASAH ($r = 0.236$, $p = 0.0388$), it remained statistically significant.

Functional Outcomes

Modified Rankin Scale scores at discharge revealed poorer outcomes in ASAH patients. A total of 25 ASAH patients died (mRS 6), and 30 had severe disability (mRS 3–5), while only 1 NASAH patient died and 3 experienced severe disability. High CRP levels correlated significantly with worse mRS scores in both groups, stronger in ASAH ($r = 0.605$) than NASAH ($r = 0.236$) (Table 2).

Survival Analysis

Kaplan-Meier survival analysis showed that ASAH patients with CRP >200 mg/L had significantly reduced survival (45%) compared to those with lower levels (72%, $p < 0.001$). NASAH patients had higher survival overall (84.2%), with a borderline significant difference between CRP groups ($p = 0.045$). These results are summarized in Table 3 and illustrated in Figure 1.

DISCUSSION

This study demonstrates that elevated CRP levels in the acute phase of SAH are strongly associated with worse clinical outcomes, particularly in patients with ASAH. High CRP levels correlated with increased vasospasm incidence, poor functional recovery, and reduced survival, highlighting CRP as a useful prognostic biomarker in SAH management.

Our findings are consistent with prior studies that link systemic inflammation to complications following SAH. Elevated CRP has previously been associated with increased risk of vasospasm, DCI, and poor neurological recovery (3, 4, 6, 7). In our cohort, CRP levels >200 mg/L were significantly

Table 1: Detailed Age Group, Gender, CRP Levels Data of the Patients

Group	Age Range	Patients (n)	Gender (M/F)	Maximum CRP (mg/L)	Days CRP >100 mg/L (Mean ± SD)
ASAH	<40	30	15/15	400 (350–450)	1.5 ± 0.3
	40–60	100	50/50	500 (440–560)	2.0 ± 0.4
	>60	56	28/28	600 (525–675)	3.0 ± 0.6
NASAH	<40	10	5/5	120 (110–130)	0.05 ± 0.01
	40–60	50	25/25	130 (125–145)	0.07 ± 0.02
	>60	17	8/9	150 (140–165)	0.15 ± 0.03
Reference Values	N/A	N/A	N/A	<100 mg/L	1-14 days

ASAH: Aneurysmal Subarachnoid Hemorrhage, **NASAH:** Non-aneurysmal Subarachnoid Hemorrhage, **CRP:** C-Reactive Protein

Table 2: Functional Outcomes (mRS Scores) by Group

Group	mRS 0–2 gün	mRS 3–5 gün	mRS 6. gün
ASAH	131	30	25
NASAH	76	3	1

ASAH: Aneurysmal Subarachnoid Hemorrhage,
NASAH: Non-aneurysmal Subarachnoid Hemorrhage,
mRS: Modified Rankin Scale

Table 3: Survival Analysis by Group

Group	Overall Survival Rate (%)	Log-ank Test p-value
ASAH	58.6	<0.0001
NASAH	84.2	0.045

ASAH: Aneurysmal Subarachnoid Hemorrhage,
NASAH: Non-aneurysmal Subarachnoid Hemorrhage

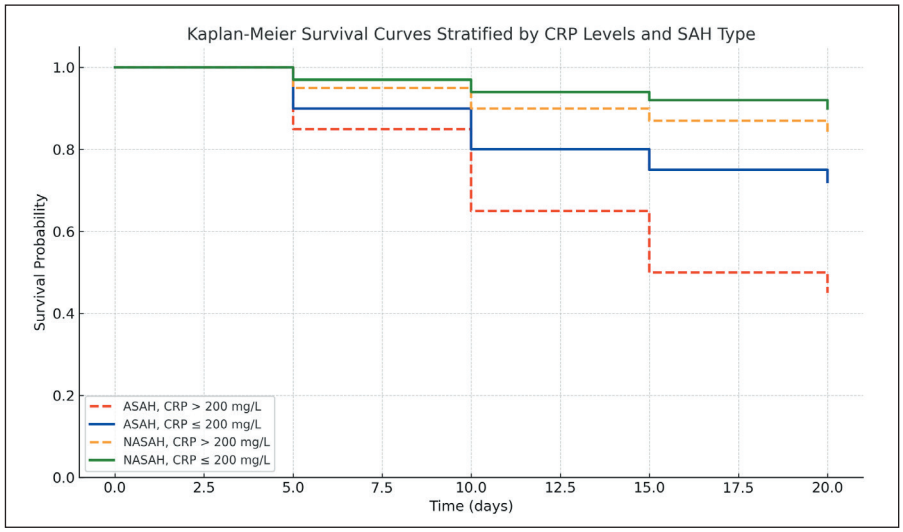


Figure 1: Survival analysis of groups

associated with vasospasm and poor mRS scores in ASAH, confirming the clinical relevance of inflammatory monitoring.

The pathophysiological basis of these findings is supported by evidence that CRP reflects systemic inflammatory responses mediated by cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) (3). These mediators are known to contribute to endothelial dysfunction and impaired cerebral autoregulation, which play critical roles in the development of vasospasm and secondary ischemic injury.

Recent studies further support CRP's role not only as a marker but also as a potential mediator of injury. Harale et al. reported a strong association between high-sensitivity CRP (hs-CRP) and DCI in ASAH, suggesting CRP may exacerbate oxidative stress and reduce nitric oxide availability (8). Similarly, Luna-Peralta et al. identified the CRP/albumin ratio as a predictor of vasospasm, reinforcing the prognostic value of inflammatory profiles (9).

In our study, elderly patients exhibited higher CRP levels and worse outcomes, in line with the concept of "inflammaging," where age-related immune dysregulation amplifies inflammatory responses (10). The marked difference in inflammatory burden between ASAH and NASAH groups further highlights the heterogeneity in SAH pathophysiology. While CRP also correlated with outcomes in NASAH, the effect size was smaller, suggesting additional non-inflammatory mechanisms such as venous or perimesencephalic bleeding may dominate in these cases (11).

The clinical utility of CRP lies in its accessibility and ease of monitoring. Tang et al. proposed incorporating routine CRP measurement into early SAH management to identify high-risk patients (12). Therapeutic strategies, including statin therapy or emerging CRP-targeted treatments, may benefit patients with persistently elevated CRP levels (6). Furthermore, integrating CRP with other biomarkers such as procalcitonin may enhance prognostic accuracy in neurocritical care settings (13).

Although there are studies in the literature reporting the importance of inflammatory mediators in the prognosis of aneurysmal sac disease, this study has a privileged place among other studies in the literature in terms of its sample size and inclusion of both aneurysmal and non-aneurysmal sac patients (14,15).

It is also compatible with the study conducted by Ogden et al. in 2019, in which they determined the inflammatory scores of patients by examining different mediators, including CRP and neutrophil lymphocyte ratio (16). Gel et al. stated that early diagnosis and treatment of ASAH disease has positive effects on mortality and morbidity (17). This study is considered important because it highlights the importance of CRP, an easily accessible and affordable test. Overall, our findings support the integration of CRP monitoring into standard SAH protocols. Identifying patients with high inflammatory burden may allow for tailored interventions and improved outcomes, particularly in ASAH cases where inflammation appears to play a dominant role.

However, this study has several limitations. First, the retrospective and single-center nature of the analysis may limit the generalizability of results and introduce selection bias. Second, while CRP levels showed strong associations with clinical outcomes, this study does not establish causality or explore underlying molecular mechanisms in depth. Third, inflammatory markers other than CRP—such as IL-6 or procalcitonin—were not routinely measured, limiting our ability to assess the full inflammatory profile. Future prospective, multicenter studies incorporating broader biomarker panels are needed to validate CRP›s predictive value and explore targeted anti-inflammatory strategies.

Conclusion

This study provides robust evidence that CRP levels are a reliable biomarker for predicting outcomes in SAH patients. Elevated CRP levels, particularly in ASAH, are associated with higher rates of vasospasm, poor functional recovery, and increased mortality. These findings support the integration of CRP monitoring into routine clinical practice to improve prognostication and guide targeted therapeutic interventions. Further research is needed to refine CRP-based thresholds and explore innovative treatments to mitigate inflammation and improve outcomes in SAH.

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None.

Author Contributions

Eyüp Varol: Design, Writing; **Furkan Avcı:** Data collection or processing, Analysis or interpretation; **Cumhur Kaan Yaltırık:** Concept, Literature Research.

Conflicts of Interest

The authors have no confict of interest to declare.

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None.

Ethical Approval

The study adhered to ethical guidelines, with approval from the institutional ethics committee (Approval ID: B.10.1.TKH.4.34.H.GP.0.01, dated April 25, 2022). Patient consent was obtained at the time of data collection. All authors have confirmed that this study did not involve animal subjects or tissue.

Review Process

Extremely and externally peer-reviewed.

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