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Plasma Interleukin 6 Levels Predict Long-term Mortality in Aneurysmal Subarachnoid

Renjie Zhang
West China Hospital of Sichuan University
Yu Zhang
Affiliated Hospital of Chengdu University
Zheran Liu
West China Hospital of Sichuan University
Yiyan Pei
West China Hospital of Sichuan University
Yan He
West China Hospital of Sichuan University
Jiayi Yu
Chengdu University of Traditional Chinese Medicine
Chao You
West China Hospital of Sichuan University
Lu Ma
West China Hospital of Sichuan University
Fang Fang (fangfang01@scu.edu.cn)
West China Hospital of Sichuan University

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Abstract

OBJECTIVE: Interleukin 6 (IL-6) is an inflammatory cytokine released into the periphery after stroke, involved in the prognosis of aneurysmal subarachnoid hemorrhage (aSAH). We aimed to explore the relationship between serum IL-6 with long-term mortality after aSAH.

METHODS: We retrospectively reviewed the medical records of 18824 SAH patients for collection of serum IL-6 levels during hospitalization from a large, single-center aSAH database of Sichuan University West China Hospital. Patient deaths were determined through a national death record registration system. The primary outcome was long-term mortality. Cox regression models were used to investigate univariate and multivariate relationships between predictors and outcomes. A propensity score-matched analysis was conducted to minimize bias from confounding variables.

RESULTS: In total, we included 1131 aSAH patients with 3288 records of IL-6 collections. Initial serum IL-6 values were elevated in all, ranging from 1.50 to 4522.00 pg/ml. After logarithmic transformation, the IL-6 was associated with long-term mortality (HR 1.32, 95% CI 1.21-1.44). The results maintained significant in the multivariate cox regression and propensity score-matched analysis (adjusted HR 1.23, 95% CI 1.11-1.36, p<0.001; IL-6 >103.00 pg/ml vs IL-6≤103. 00 pg/ml, PSM HR 1.94, 95% CI 1.48-2.55, p<0.001). Similar results were observed in the long-term mortality of survivors at discharge and 1-year mortality.

CONCLUSIONS: Serum IL-6 is independently associated with long-term mortality of aSAH patients. Our study provided new evidence for the investigation of inflammation after aSAH and the association of inflammatory cytokines with the long-term prognosis of aSAH and might support future management decisions.

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating disease with high mortality and disability. Owing to the improvement in clinical management, short-term mortality has declined to approximately 25–30%[1, 2]. However, even after an initially favorable recovery from aSAH, survivors still experience a 1.5-fold excess long-term mortality in comparison to the general population[3]. As reported in 2014, long-term mortality of aSAH is 17.9% at 10 years, 29.5% at 15 years, and 43.6% at 20 years after aSAH[4]. Previous data for long-time outcomes of aSAH are scarce. Thus, finding a biomarker to identify patients at high risk of long-term mortality and facilitate prompt preventive strategies to improve prognosis is urgently required.

In general, an overactive immune response after aSAH put aSAH patients at risk for poor outcomes[5–8]. Of the various cytokines, interleukin 6 is abnormally elevated after aSAH in both cerebrospinal fluid (CSF) and peripheral blood[9, 10]. Several studies have revealed that aSAH patients with high serum IL-6 levels were more likely to develop complications and suffer unfavorable short-term outcomes[11–13]. Till now, there has been no investigation into the association between serum IL-6 and long-term mortality of aSAH. Our study aimed to examine the association between serum IL-6 and long-term mortality in aSAH patients in a large, single-center cohort with accurate and complete long-term data, obtained from the Household Registration Administration System, a national death record registration system.

Methods

Study Design and Data Source

We conducted a retrospective observational study from January 2009 to June 2019 using the electronic health record system of Sichuan University West China Hospital. Data was retrieved with the assistance of the information department, including medical history, diagnoses, resident admission notes, discharge notes, and laboratory and imaging examinations. The study was approved by the West China Hospital Institutional Review Board, with a waiver of informed consent due to minimal risk to patients. Treatment of patients was carried out according to standardized guidelines[14, 15].

Patient Selection

Patients diagnosed with aSAH were included in this study. SAH was identified by neuroimaging, including computed tomography, magnetic resonance imaging, angiography, or cerebrospinal fluid test. Aneurysms were identified by cerebral angiography, magnetic resonance angiography, or computed tomography angiography.

Exclusion criteria included (1) aneurysms caused by trauma or arteriovenous malformations, (2) fusiform aneurysms and nondefinitive aneurysms, and (3) aneurysms treated before ictus, (4) patients without peripheral IL-6 measurements, and (5) record of death missing.

Exposure variable

The exposure variable of this study was serum IL-6. Peripheral blood was collected and measured for serum IL-6 by the West China Hospital Stroke Unit as an alternative infection biomarker as part of a hospital-wide clinical initiative. We collected all IL-6 records during hospitalization. There were 3288 records of IL-6 collections in total. We divided them into five phases: T1 (< 24h) n = 156, T2 (24-72h) n = 356, T3 (day3-6) n = 986, T4 (day7-14) n = 1139 and T5 (day15-30) n = 654. We explored peak IL-6 levels during hospitalization for each patient and furtherly examined the correlation between peak IL-6 levels at five phases with the primary outcome.

Primary and secondary outcomes

The primary outcome was long-term mortality (defined as all-cause mortality at the longest follow-up). Secondary outcomes were mortality at discharge, short-term mortality (defined as 1-year mortality), short-term and long-term mortality in survivors at discharge, and in-hospital neurological complications. Neurological complications included delayed cerebral ischemia, rebleeding, seizures, and hydrocephalus.

Delayed cerebral ischemia was defined as a new focal neurological impairment or a new infarct on CT or MRI, not attributable to other causes. Rebleeding was defined as increased hemorrhage volume confirmed by a repeat computed tomography or magnetic resonance imaging scan.

Follow-up

We used personal identification numbers to identify death records from Sichuan province's Household Registration Administration System. All death records were extracted through the Household Registration System, which should document a citizen’s date of death within one month as required. Therefore, it drastically reduced the loss of follow-up in this study. Suppose the identification number of patients in the electronic medical record system was wrong or non-existent, or their household registration was not in Sichuan province, their household registration cannot be found and these patients are excluded from the study. The median follow-up was 3.8 years for all participants, the longest follow-up period was 10.2 years, and the censoring date was April 1, 2021.

Statistical Analysis

Serum IL-6 levels were log-normalized and boxplots were drawn to illustrate the time course during 1-month hospitalization. For subgroup analysis of different aSAH patient-associated characteristics, post-SAH complications, and clinical outcomes, data were dichotomized into two groups and analyzed by unpaired *t-test*.

Baseline cohort characteristics were presented as proportions and means (SDs) or medians (interquartile ranges). We computed between-group comparisons with ANOVA or chi-square test. All tests of significance were 2-sided, and $P < 0.05$ was considered statistically significant. Multiple imputations were used to impute missing data of continuous variables, and for categorical variables, missing data were coded as other.

We performed Cox regression models to analyze unadjusted and adjusted associations between outcomes and IL-6 levels in each group. Univariable Cox regression was utilized to determine factors influencing the outcomes ($P < 0.10$), implemented into a multivariable Cox regression model. Factors were considered independently associated when they remained statistically significant. Confounders adjusted in the multivariable model were examined in previous studies and clinical practice, including age, sex, smoking, alcohol abuse, hypertension, diabetes mellitus, coronary heart disease (CHD), chronic obstructive pulmonary

disease (COPD), chronic renal failure (CRF), aneurysm location (anterior circulation, posterior circulation), size of the aneurysm, systolic blood pressure (SBP), blood glucose, Hunt & Hess grade, Fisher grade, external ventricular drain, and operation of the aneurysm (no treatment, clip, coil). Additionally, we added in-hospital infection as a confounder for sensitivity analysis to examine whether serum IL-6 was associated with mortality in aSAH patients independently of in-hospital infection.

Furthermore, we developed a propensity score matching to minimize bias using all confounders. Patients were stratified by the cut-off value of IL-6 levels. We performed a 1:1 nearest neighbor matching without replacement with the caliper width set as 0.20 SD. Characteristics of both groups were compared using standardized mean difference, and a difference > 0.1 was considered meaningful.

Kaplan-Meier curves and log-rank tests of the time to event data were used to examine mortality at the longest follow-up. Whether the association between IL-6 and long-term mortality differed across various subgroups was determined by subgroup analysis and p for interaction was calculated.

Receiver operator characteristic (ROC) analysis was performed to assess the ability of IL-6 levels, age, modified Fisher grade, and the multivariable model for IL-6 levels to distinguish between long-term survivor and death. The DeLong test was used to compare areas under the curve (AUCs). The optimal cut-off value of IL-6 was identified by the maximum Youden index.

All analyses were conducted using R software (version 4.1.0, R Foundation for Statistical Computing).

Results

Of the 6228 patients with aSAH admitted to Sichuan University West China Hospital, during the 10 years, a total of 1131 aSAH patients with IL-6 records were included in this study (eFigure1). Baseline characteristics stratified by the long-term mortality were shown in Table 1. At the longest follow-up,73.6% patients (n=833) survived and 26.4% patients (n=298) dead. In demographics, deaths were older (p<0.001) and had higher SBP (p=0.03). In medical history, the dead had a higher proportion of COPD (p<0.001). As expected, there were significantly more patients with clinically and radiologically severe SAH among the deaths (p<0.001 and p=0.001, respectively). More patients of death performed external ventricular drain at admission (p<0.001). However, there was no significant difference in the location and size of aneurysms (p=0.85 and p=0.11, respectively). Patients who received treatment for aneurysms were more likely to survive (p<0.001). Higher blood glucose was found in deaths (p<0.001). The occurrence of in-hospital infection in deaths was 80.2% (n=239). The difference was statistically significant compared with survivors (p<0.001).

The time course of IL-6 levels during hospitalization was illustrated in Figure 1a. Considering the great individual variation, IL-6 levels were presented after logarithmic transformation. In our series, initial serum IL-6 values were elevated in all. The IL-6 values ranged between 1.50 and 4522.00 pg/ml. The median IL-6 level was 39.37 pg/ml and the Inter-Quartile Range was 67.97 pg/ml. During the further clinical course, a substantial rise in IL-6 concentrations was observed on day 2 after SAH, and IL-6 peaks were found on days 2-5, day 13-14, day17, day26, and day29. For subgroup analysis, we compared daily IL-6 levels between low Hunt & Hess grade (I-III) and high Hunt & Hess grade (IV-V), cases with hydrocephalus and without hydrocephalus, and survivors and deaths at the longest follow-up (Figure 1b-d). Statistics differences were found on days 0-2 between different Hunt & Hess grade groups, on days 0,2, 5, 17, 24, 28, and 30 between groups with hydrocephalus or not, and on days 0-2, 5-6, 8-9, 11, 13, 17-18, 20 and 26 between different long-term outcome groups.

IL-6 peak during hospitalization was associated with long-term mortality (HR 1.32 95% CI 1.21-1.44). After adjusting all variates influencing the outcome, including age, smoking, alcohol abuse, SBP, CRF, COPD, Fisher grade, Hunt & Hess grade, external ventricular drain, treatments, blood glucose, and in-hospital infection (Table 2), IL-6 peak still predicted long-term mortality (adjusted HR 1.23 95% CI 1.11-1.36, p<0.001). In the sensitivity analysis of survivors at discharge (Table 4), the finding remained robust even after adjustment (adjusted HR 1.17 95% CI 1.05-1.31, p=0.004).

The correlation between IL-6 peaks at 5 different phases (T1-5) and long-term mortality were furtherly studied (Table 3). In univariate Cox regression analysis, log IL-6 peaks of T1-5 were all significantly associated with long-term mortality (T1 HR 1.76

95% CI 1.27-2.44; T2 HR 1.47 95% CI 1.21-1.77; T3 HR 1.26 95% CI 1.09-1.45; T4 HR 1.27 95% CI 1.12-1.45; T5 HR 1.55 95% CI 1.27-1.88). After adjusting for all covariates in the multivariable Cox regression analysis, findings remained robust at T3-5 (T3 adjusted HR 1.19 95% CI 1.01-1.39, p=0.03; T4 adjusted HR 1.25 95% CI 1.09-1.44, p=0.002; T5 adjusted HR 1.53 95% CI 1.25-1.87, p<0.001). After dichotomized into two groups using the best cut-off values, IL-6 peaks of all phases were significantly associated with long-term mortality after adjustment (T1 adjusted HR 2.84 95% CI 1.06-7.61, p=0.04; T2 adjusted HR 1.76 95% CI 1.06-2.92, p=0.03; T3 adjusted HR 1.81 95% CI 1.27-2.58, p<0.001; T4 adjusted HR 2.43 95% CI 1.74-3.39, p<0.001; T5 adjusted HR 3.47 95% CI 1.99-6.03, p<0.001). In the propensity score-matched analysis, findings remained significant at T2,4-5 (T2 PSM HR 1.84 95% CI 1.02-3.31, p=0.04; T4 PSM HR 2.22 95% CI 1.46-3.38, p<0.001; T5 PSM HR 2.95 95% CI 1.64-5.29, p<0.001).

Additionally, we explored the association between IL-6 peak during hospitalization and in-hospital neurological complications (eTable 3) or short-term mortality (Table 4). Patients with higher IL-6 peaks were more likely to develop hydrocephalus, and rebleeding (OR 1.18 95% CI 1.06-1.30; OR 1.21 95% CI 1.06-1.38, respectively). After adjustment of covariates, there was no significant association between IL-6 peak and neurological complications. In the propensity score-matched analysis, findings only remained prominent in hydrocephalus (PSM OR 1.86 95% CI 1.26-2.74, p=0.002). Besides, IL-6 peak well predicted short-term mortality within all patients or survivors at discharge (adjusted HR 1.36 95% CI 1.22-1.52, p<0.001; adjusted HR 1.32 95% CI 1.17-1.49, p<0.001, respectively). Findings maintained consistent in the propensity score-matched analysis (IL-6 >103.00 pg/ml, PSM HR 2.54 95% CI 1.83-3.53, p<0.001; IL-6 >102.85 pg/ml, PSM HR 1.84 95% CI 1.29-2.62, p=0.001, respectively).

Kaplan-Meier analysis showed that death during follow-up was more frequent in patients with higher IL-6 levels ($p < 0.001$; Figure 2a). It also illustrated that patients with IL-6 levels stratified by IL-6 levels had significantly worse long-term survival except for deaths at discharge ($p < 0.001$; Figure 2b).

We further assessed interactions by variables on serum IL-6 (Figure 3). The interaction was present regarding the aneurysm size and in-hospital infection (p=0.05, p=0.02, respectively). There was no significant effect modification of the association between D-dimer level and mortality on the basis of age ($p = 0.39$), aneurysm location ($p = 0.11$), Fisher grade (p=0.44), Hunt & Hess grade (p=0.36), or aneurysm treatment ($p = 0.10$).

Finally, ROC analysis was performed to determine the ability of IL-6 to distinguish between long-term survivors and deaths (eFigure 2). We compared the ROC curves for IL-6, Fisher grade, and the multivariable IL-6 model (adding all variables significant in multivariable Cox regression analysis). IL-6 showed better ability to predict long-term mortality than Fisher grade (AUC_{IL-6}=0.63, 95% CI 0.59-0.67 vs $AUC_{Fisher\ grade}$=0.56, 95% CI 0.53-0.59, p= 0.004). As expected, multivariable IL-6 model improved the performance of IL-6 ($AUC_{multivariable\ IL\text{-}6\ model}$=0.74, 95% CI 0.71-0.67 vs $AUC_{Fisher\ grade}$=0.74, 95% CI 0.71-0.77, p< 0.001).

Discussion

In this large, single-center cohort study, we reported a systematic analysis of the association of serum IL-6 with mortality among patients with aSAH and we found serum IL-6 was an independent predictor of long-term mortality after aSAH. Additionally, we found that serum IL-6 was associated with short-term mortality after aSAH and neurological in-hospital complications.

Many previous studies explored the association between IL-6 and aSAH, but they focused on complications [12, 13, 16, 17]and short-term outcomes[7, 11, 18]. To our knowledge, there is no data available for discussion about IL-6 and long-term mortality of aSAH patients. However, in cardiovascular[19, 20] and oncology diseases[21–23], we were aware of several studies reporting serum IL-6 as a predictor of long-term mortality. Excessive inflammation has been proved to involve in the pathological process and prognosis of aSAH[24–28]. Furthermore, the proinflammatory cytokines released by aSAH will also deteriorate the development of other pre-existing diseases, then influencing both short-term and long-term outcomes of aSAH patients[4, 29–31]. Many other serum biomarkers have been found to predict long-term mortality of aSAH[32–37].

It was well-known that serum IL-6 elevates after systemic infection. However, many previous studies about the association of IL-6 and aSAH outcomes didn't adjust this important covariate, reducing the credibility of their conclusions[11, 12, 16–18]. In our study, we proved serum IL-6 predicted both short-term and long-term mortality and neurological complications of aSAH patients after adjustment of in-hospital infection. We even verified our conclusions in the subgroup analysis of survivors at discharge.

Interestingly, we noted patients with higher IL-6 levels without in-hospital infection were at higher risk of long-term mortality than those with in-hospital infection. It furtherly supported that the association between high IL-6 levels and long-term mortality of aSAH patients was independent of systemic infection.

Our study has several strengths. Our study collected most records of IL-6 levels of aSAH patients and included more covariates than previous studies. Furthermore, our study is the first to systematically explore the association between serum IL-6 and long-term mortality of aSAH patients. We employed multivariable Cox regression and propensity score-matched analysis to minimize the bias from confounders. Our death records data is accurate and complete, without loss to follow-up.

Nevertheless, our study has several limitations. Due to its retrospective observational design, the timing and number of peripheral blood draw for serum IL-6 levels are not consistent for all patients. Furthermore, we only collected the all-cause mortality rather than cause-specific mortality. Moreover, we found the interindividual range of serum IL-6 was still wide among aSAH patients, which might hinder the interpretation in daily clinical routine.

Conclusion

In summary, high serum IL-6 was associated with long-term and short-term mortality and neurological complications in aSAH patients. Our study provided new evidence for the investigation of inflammation after aSAH and the association of inflammatory cytokines with the long-term prognosis of aSAH and might support future management decisions.

Declarations

Ethical Approval and Consent to participate:

The ethics committee of West China Hospital **(No. 20191133).**

Human and Animal Ethics:

Not applicable.

Consent for publication:

The consent to publish this manuscript has been received from all participants.

Availability of supporting data:

Not applicable.

Competing interests:

None.

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Authors' contributions:

Study concept and design: Renjie Zhang, Yu Zhang, Chao You, Lu Ma, Fang Fang

Acquisition, analysis, or interpretation of data: Renjie Zhang, Yu Zhang, Zheran Liu, Yiyan Pei, Yan He, Jiayi Yu

Statistical analysis: Renjie Zhang, Yu Zhang, Zheran Liu

Drafting of the manuscript: Renjie Zhang

Critical revision of the manuscript for important intellectual content: All authors

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Authors' information:

Authors: Dr. Renjie Zhang1, Dr. Yu Zhang1,3, Dr. Zheran Liu2, Dr. Yiyan Pei2, Dr. Yan He2, Dr. Jiayi Yu4, Prof. Chao You1, Prof. Lu Ma1, Prof. Fang Fang1

References

1. Feigin VL, Lawes CMM, Bennett DA, Barker-Collo SL, Parag V: **Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review**. *The Lancet Neurology*2009, **8**(4):355-369.
2. Galea JP, Dulhanty L, Patel HC, Uk, Ireland Subarachnoid Hemorrhage Database C: **Predictors of Outcome in Aneurysmal Subarachnoid Hemorrhage Patients: Observations From a Multicenter Data Set**. *Stroke*2017, **48**(11):2958-2963.
3. Huhtakangas J, Lehto H, Seppa K, Kivisaari R, Niemela M, Hernesniemi J, Lehecka M: **Long-Term Excess Mortality After Aneurysmal Subarachnoid Hemorrhage: Patients With Multiple Aneurysms at Risk**. *Stroke*2015, **46**(7):1813-1818.
4. Nieuwkamp DJ, de Wilde A, Wermer MJ, Algra A, Rinkel GJ: **Long-term outcome after aneurysmal subarachnoid hemorrhage-risks of vascular events, death from cancer and all-cause death**. *J Neurol*2014, **261**(2):309-315.
5. Ahn SH, Savarraj JPJ, Parsha K, Hergenroeder GW, Chang TR, Kim DH, Kitagawa RS, Blackburn SL, Choi HA: **Inflammation in delayed ischemia and functional outcomes after subarachnoid hemorrhage**. *J Neuroinflammation*2019, **16**(1):213.
6. Savarraj JPJ, Parsha K, Hergenroeder GW, Zhu L, Bajgur SS, Ahn S, Lee K, Chang T, Kim DH, Liu Y*et al*: **Systematic model of peripheral inflammation after subarachnoid hemorrhage**. *Neurology*2017, **88**(16):1535-1545.
7. Muroi C, Hugelshofer M, Seule M, Tastan I, Fujioka M, Mishima K, Keller E: **Correlation among systemic inflammatory parameter, occurrence of delayed neurological deficits, and outcome after aneurysmal subarachnoid hemorrhage**. *Neurosurgery*2013, **72**(3):367-375; discussion 375.
8. Geraghty JR, Lung TJ, Hirsch Y, Katz EA, Cheng T, Saini NS, Pandey DK, Testai FD: **Systemic Immune-Inflammation Index Predicts Delayed Cerebral Vasospasm After Aneurysmal Subarachnoid Hemorrhage**. *Neurosurgery*2021, **89**(6):1071-1079.
9. Suzuki S, Tanaka K, Suzuki N: **Ambivalent aspects of interleukin-6 in cerebral ischemia: inflammatory versus neurotrophic aspects**. *J Cereb Blood Flow Metab*2009, **29**(3):464-479.
10. Erta M, Quintana A, Hidalgo J: **Interleukin-6, a major cytokine in the central nervous system**. *Int J Biol Sci*2012, **8**(9):1254-1266.
11. Nakahara T, Tsuruta R, Kaneko T, Yamashita S, Fujita M, Kasaoka S, Hashiguchi T, Suzuki M, Maruyama I, Maekawa T: **High-mobility group box 1 protein in CSF of patients with subarachnoid hemorrhage**. *Neurocrit Care*2009, **11**(3):362-368.
12. Sarrafzadeh A, Schlenk F, Gericke C, Vajkoczy P: **Relevance of cerebral interleukin-6 after aneurysmal subarachnoid hemorrhage**. *Neurocrit Care*2010, **13**(3):339-346.
13. Wostrack M, Reeb T, Martin J, Kehl V, Shiban E, Preuss A, Ringel F, Meyer B, Ryang YM: **Shunt-dependent hydrocephalus after aneurysmal subarachnoid hemorrhage: the role of intrathecal interleukin-6**. *Neurocrit Care*2014, **21**(1):78-84.
14. Connolly ES, Jr., Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, Hoh BL, Kirkness CJ, Naidech AM, Ogilvy CS*et al*: **Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/american Stroke Association**. *Stroke*2012, **43**(6):1711-1737.
15. Dong Y, Guo ZN, Li Q, Ni W, Gu H, Gu YX, Dong Q: **Chinese Stroke Association guidelines for clinical management of cerebrovascular disorders: executive summary and 2019 update of clinical management of spontaneous subarachnoid**

haemorrhage. *Stroke Vasc Neurol*2019, **4**(4):176-181.

16. Schoch B, Regel JP, Wichert M, Gasser T, Volbracht L, Stolke D: **Analysis of intrathecal interleukin-6 as a potential predictive factor for vasospasm in subarachnoid hemorrhage**. *Neurosurgery*2007, **60**(5):828-836; discussion 828-836.
17. Ridwan S, Grote A, Simon M: **Interleukin 6 in cerebrospinal fluid is a biomarker for delayed cerebral ischemia (DCI) related infarctions after aneurysmal subarachnoid hemorrhage**. *Sci Rep*2021, **11**(1):12.
18. Kao HW, Lee KW, Kuo CL, Huang CS, Tseng WM, Liu CS, Lin CP: **Interleukin-6 as a Prognostic Biomarker in Ruptured Intracranial Aneurysms**. *PLoS One*2015, **10**(7):e0132115.
19. Zhang WR, Garg AX, Coca SG, Devereaux PJ, Eikelboom J, Kavsak P, McArthur E, Thiessen-Philbrook H, Shortt C, Shlipak M*et al*: **Plasma IL-6 and IL-10 Concentrations Predict AKI and Long-Term Mortality in Adults after Cardiac Surgery**. *J Am Soc Nephrol*2015, **26**(12):3123-3132.
20. Szpakowicz A, Pepinski W, Waszkiewicz E, Skawronska M, Niemcunowicz-Janica A, Musial WJ, Kaminski KA: **The rs2228145 polymorphism in the interleukin-6 receptor and its association with long-term prognosis after myocardial infarction in a pilot study**. *Arch Med Sci*2017, **13**(1):93-99.
21. Maeda Y, Takeuchi H, Matsuda S, Okamura A, Fukuda K, Miyasho T, Nakamura R, Suda K, Wada N, Kawakubo H*et al*: **Clinical significance of preoperative serum concentrations of interleukin-6 as a prognostic marker in patients with esophageal cancer**. *Esophagus*2020, **17**(3):279-288.
22. Lindmark E, Diderholm E, Wallentin L, Siegbahn A: **Relationship between interleukin 6 and mortality in patients with unstable coronary artery disease: effects of an early invasive or noninvasive strategy**. *Jama*2001, **286**(17):2107-2113.
23. Kallio J, Hämäläinen M, Luukkaala T, Moilanen E, Tammela TL, Kellokumpu-Lehtinen PL: **Resistin and interleukin 6 as predictive factors for recurrence and long-term prognosis in renal cell cancer**. *Urol Oncol*2017, **35**(9):544.e525-544.e531.
24. Coulibaly AP, Provencio JJ: **Aneurysmal Subarachnoid Hemorrhage: an Overview of Inflammation-Induced Cellular Changes**. *Neurotherapeutics*2020, **17**(2):436-445.
25. Claassen J, Albers D, Schmidt JM, De Marchis GM, Pugin D, Falo CM, Mayer SA, Cremers S, Agarwal S, Elkind MS*et al*: **Nonconvulsive seizures in subarachnoid hemorrhage link inflammation and outcome**. *Ann Neurol*2014, **75**(5):771-781.
26. Bevers MB, Wolcott Z, Bache S, Hansen C, Sastre C, Mylvaganam R, Koch MJ, Patel AB, Møller K, Kimberly WT: **Soluble ST2 links inflammation to outcome after subarachnoid hemorrhage**. *Ann Neurol*2019, **86**(3):384-394.
27. Badjatia N, Monahan A, Carpenter A, Zimmerman J, Schmidt JM, Claassen J, Connolly ES, Mayer SA, Karmally W, Seres D: **Inflammation, negative nitrogen balance, and outcome after aneurysmal subarachnoid hemorrhage**. *Neurology*2015, **84**(7):680-687.
28. Aihara Y, Kasuya H, Onda H, Hori T, Takeda J: **Quantitative analysis of gene expressions related to inflammation in canine spastic artery after subarachnoid hemorrhage**. *Stroke*2001, **32**(1):212-217.
29. Nieuwkamp DJ, Vaartjes I, Algra A, Rinkel GJ, Bots ML: **Risk of cardiovascular events and death in the life after aneurysmal subarachnoid haemorrhage: a nationwide study**. *Int J Stroke*2014, **9**(8):1090-1096.
30. Huttunen T, von und Zu Fraunberg M, Koivisto T, Ronkainen A, Rinne J, Sankila R, Seppa K, Jaaskelainen JE: **Long-term excess mortality of 244 familial and 1502 sporadic one-year survivors of aneurysmal subarachnoid hemorrhage compared with a matched Eastern Finnish catchment population**. *Neurosurgery*2011, **68**(1):20-27.
31. Huttunen J, Kurki MI, von Und Zu Fraunberg M, Koivisto T, Ronkainen A, Rinne J, Jääskeläinen JE, Kälviäinen R, Immonen A: **Epilepsy after aneurysmal subarachnoid hemorrhage: A population-based, long-term follow-up study**. *Neurology*2015, **84**(22):2229-2237.
32. Pan JW, He LN, Xiao F, Shen J, Zhan RY: **Plasma gelsolin levels and outcomes after aneurysmal subarachnoid hemorrhage**. *Crit Care*2013, **17**(4):R149.
33. Lai PM, Du R: **Association between S100B Levels and Long-Term Outcome after Aneurysmal Subarachnoid Hemorrhage: Systematic Review and Pooled Analysis**. *PLoS One*2016, **11**(3):e0151853.
34. Fang F, Wang P, Yao W, Wang X, Zhang Y, Chong W, Hai Y, You C, Jiang Y: **Association between D-dimer levels and long-term mortality in patients with aneurysmal subarachnoid hemorrhage**. *Neurosurg Focus*2022, **52**(3):E8.

35. Fan XF, Chen ZH, Huang Q, Dai WM, Jie YQ, Yu GF, Wu A, Yan XJ, Li YP: **Leptin as a marker for severity and prognosis of aneurysmal subarachnoid hemorrhage**. *Peptides*2013, **48**:70-74.
36. Bian L, Lin J, Liu Y, Lu J, Zhao X: **Copeptin and insulin-like growth factor-1 predict long-term outcomes after aneurysmal subarachnoid hemorrhage: A large prospective cohort study**. *Clin Neurol Neurosurg*2021, **209**:106863.
37. Azurmendi L, Degos V, Tiberti N, Kapandji N, Sanchez-Peña P, Sarrafzadeh A, Puybasset L, Turck N, Sanchez JC: **Neopterin plasma concentrations in patients with aneurysmal subarachnoid hemorrhage: correlation with infection and long-term outcome**. *J Neurosurg*2016, **124**(5):1287-1299.

Tables

Table 1

Baseline characteristics stratified by long-term mortality

Characteristics	All	Survivor	Death	*P* value
	(n=1131)	(n=833)	(n=298)	
Demographics				
Age, y, mean (SD)	56.34 (11.86)	55.21 (11.53)	59.51 (12.22)	<0.001
Male, n (%)	388 (34.3)	276 (33.1)	112 (37.6)	0.19
Smoking, n (%)				0.11
Current	52 (4.6)	44 (5.3)	8 (2.7)	
Ever	209 (18.5)	147 (17.6)	62 (20.8)	
Never	870 (76.9)	642 (77.1)	228 (76.5)	
Alcohol abuse, n (%)	212 (18.7)	150 (18.0)	62 (20.8)	0.33
SBP, mmHg, mean (SD)	147.05 (25.31)	146.08 (24.91)	149.79 (26.27)	0.03
Medical history, n (%)				
Hypertension	314 (27.8)	223 (26.8)	91 (30.5)	0.24
Diabetes	83 (7.3)	60 (7.2)	23 (7.7)	0.87
CHD	27 (2.4)	18 (2.2)	9 (3.0)	0.54
CRF	11 (1.0)	5 (0.6)	6 (2.0)	0.07
COPD	117 (10.3)	64 (7.7)	53 (17.8)	<0.001
Aneurysm characteristics				
Posterior location, n (%)	272 (24.0)	202 (24.2)	70 (23.5)	0.85
Size of aneurysm, cm, mean (SD)	0.75 (0.68)	0.73 (0.60)	0.81 (0.88)	0.11
Hemorrhagic characteristics, n (%)				
Fisher grade III-IV	736 (65.1)	519 (62.3)	217 (72.8)	0.001
Hunt & Hess grade IV-V	218 (19.3)	109 (13.1)	109 (36.6)	<0.001
External ventricular drain	46 (4.1)	17 (2.0)	29 (9.7)	<0.001
Treatment of aneurysms, n (%)				
Clip	870 (76.9)	668 (80.2)	202 (67.8)	<0.001
Coil	81 (7.2)	57 (6.8)	24 (8.1)	
No treatment	180 (15.9)	108 (13.0)	72 (24.2)	
Biology, mean (SD)				
Glucose, mmol/L	7.38 (2.65)	7.11 (2.34)	8.13 (3.25)	<0.001
Complications, n (%)				
Infection in hospital	778 (68.8)	539 (64.7)	239 (80.2)	<0.001

SBP, systolic blood pressure; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; SD, standard deviation

Table 2

Univariate and multivariate cox regression analysis for long-term mortality

Characteristics	Unadjusted		Multivariable Regression Adjustment	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Demographics				
Age	1.03(1.02- 1.04)	<0.001	1.03(1.01- 1.04)	<0.001
Male	1.22(0.92- 1.60)	0.17	NA	NA
Smoking				
Ever	2.32(1.03- 5.21)	0.04	2.44(1.03- 5.78)	0.04
Never	1.95(0.91- 4.21)	0.09	2.03(0.90- 4.57)	0.09
Alcohol abuse	1.20(0.86- 1.67)	0.29	NA	NA
SBP	1.01(1.00- 1.01)	0.03	1.00(0.99- 1.01)	0.93
Medical history				
Hypertension	1.20(0.90- 1.61)	0.21	NA	NA
Diabetes	1.08(0.65- 1.78)	0.77	NA	NA
CHD	1.41(0.63- 3.17)	0.41	NA	NA
CRF	3.40(1.03-11.23)	0.04	3.49(0.94-12.99)	0.06
COPD	2.60(1.76- 3.84)	<0.001	1.82(1.15- 2.89)	0.01
Aneurysm characteristics				
Posterior location	0.96(0.70- 1.31)	0.79	NA	NA
Size of aneurysm	1.17(0.96- 1.42)	0.11	NA	NA
Hemorrhagic characteristics				
Fisher grade III-IV	2.05(1.37- 3.07)	<0.001	1.60(1.03- 2.48)	0.04
Hunt & Hess grade IV-V	3.83(2.81- 5.22)	<0.001	2.48(1.73- 3.54)	<0.001
External ventricular drain	5.17(2.80- 9.57)	<0.001	3.45(1.77- 6.72)	<0.001
Treatment of aneurysms				
Clip	0.45(0.32- 0.64)	<0.001	0.57(0.39- 0.85)	0.005
Coil	0.63(0.36- 1.11)	0.11	0.93(0.50- 1.74)	0.82
Biology				
Glucose, mmol/L	1.15(1.09- 1.20)	<0.001	1.06(1.01- 1.12)	0.03
Log (IL-6), pg/mL	1.32(1.21-1.44)	<0.001	1.23(1.11-1.36)	<0.001
Complications, n (%)				
Infection in hospital	2.21(1.61- 3.04)	<0.001	1.20(0.84- 1.71)	0.31

SBP, systolic blood pressure; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; HR, hazard rate; NA, not available

Table 3

Unadjusted and adjusted associations between IL-6 peaks at different phases and long-term mortality

Timepoints	IL-6, mean (SD), pg/ml	Classifications of IL-6	Events, n (%)	Unadjusted		Multivariable Regression Adjustment		Propensity Score Adjustment	
				Unadjusted HR	*P* value	Adjusted HR	*P* value	Adjusted HR	*P* value
T1 (<24h)	109.72 (460.83)	log (IL-6)	NA	1.76 (1.27-2.44)	0.001	1.4 (0.89-2.20)	0.15	NA	NA
		IL-6>18.93	35/113 (31%)	4.79 (2.24-10.24)	<0.001	2.84 (1.06-7.61)	0.03	3.30 (0.34-31.79)	0.30
T2 (24-48h)	197.61 (517.78)	log (IL-6)	NA	1.47 (1.21-1.77)	<0.001	1.25 (0.99-1.58)	0.06	NA	NA
		IL-6>122.20	72/265 (27.2%)	2.94 (1.84-4.68)	<0.001	1.76 (1.06-2.92)	0.03	1.84 (1.02-3.31)	0.04
T3 (3-6d)	191.87 (614.89)	log (IL-6)	NA	1.26 (1.09-1.45)	0.001	1.19 (1.01-1.39)	0.03	NA	NA
		IL-6>48.54	154/638 (24.1%)	1.94 (1.36-2.75)	<0.001	1.81 (1.27-2.58)	0.001	1.44 (0.96-2.16)	0.08
T4 (7-14d)	144.60 (539.53)	log (IL-6)	NA	1.27 (1.12-1.45)	<0.001	1.25 (1.09-1.44)	0.002	NA	NA
		IL-6>100.02	147/563 (26.1%)	2.53 (1.83-3.51)	<0.001	2.43 (1.74-3.39)	<0.001	2.22 (1.46-3.38)	<0.001
T5 (15-30d)	134.91 (565.15)	log (IL-6)	NA	1.55 (1.27-1.88)	<0.001	1.53 (1.25-1.87)	<0.001	NA	NA
		IL-6>22.12	88/258 (34.1%)	3.30 (1.92-5.68)	<0.001	3.47 (1.99-6.03)	<0.001	2.95 (1.64-5.29)	<0.001

SD, standard deviation; HR, hazard rate; NA, not available

Table 4

Associations between IL-6 peaks and mortality in all patients and survivors at discharge

Outcomes	Classifications of IL-6	Events, n (%)	Unadjusted		Multivariable Regression Adjustment		Propensity Score Adjustment	
			Unadjusted HR	P value	Adjusted HR	P value	Adjusted HR	P value
1-year mortality	log (IL-6)	NA	1.44 (1.30-1.58)	<0.001	1.36 (1.22-1.52)	<0.001	NA	NA
	IL-6>103.00pg/ml	219/1131 (19.4%)	3.01 (2.30-3.95)	<0.001	2.36 (1.78-3.13)	<0.001	2.54 (1.83-3.53)	<0.001
Long-term mortality	log (IL-6)	NA	1.32 (1.21-1.44)	<0.001	1.23 (1.11-1.36)	<0.001	NA	NA
	IL-6>103.00pg/ml	298/1131 (26.3%)	2.44 (1.94-3.07)	<0.001	1.90 (1.50-2.42)	<0.001	1.94 (1.48-2.55)	<0.001
1-year mortality of survivors at discharge	log (IL-6)	NA	1.38 (1.23-1.54)	<0.001	1.32 (1.17-1.49)	<0.001	NA	NA
	IL-6>102.85pg/ml	157/1065 (14.7%)	2.82 (2.05-3.87)	<0.001	2.20 (1.59-3.06)	<0.001	1.84 (1.29-2.62)	0.001
Long-term mortality of survivors at discharge	log (IL-6)	NA	1.25 (1.14-1.38)	<0.001	1.17 (1.05-1.31)	0.004	NA	NA
	IL-6>102.85pg/ml	236/1065 (22.2%)	2.22 (1.72-2.86)	<0.001	1.74 (1.33-2.27)	<0.001	1.53 (1.15-2.04)	0.004

HR, hazard rate; NA, not available

Figures

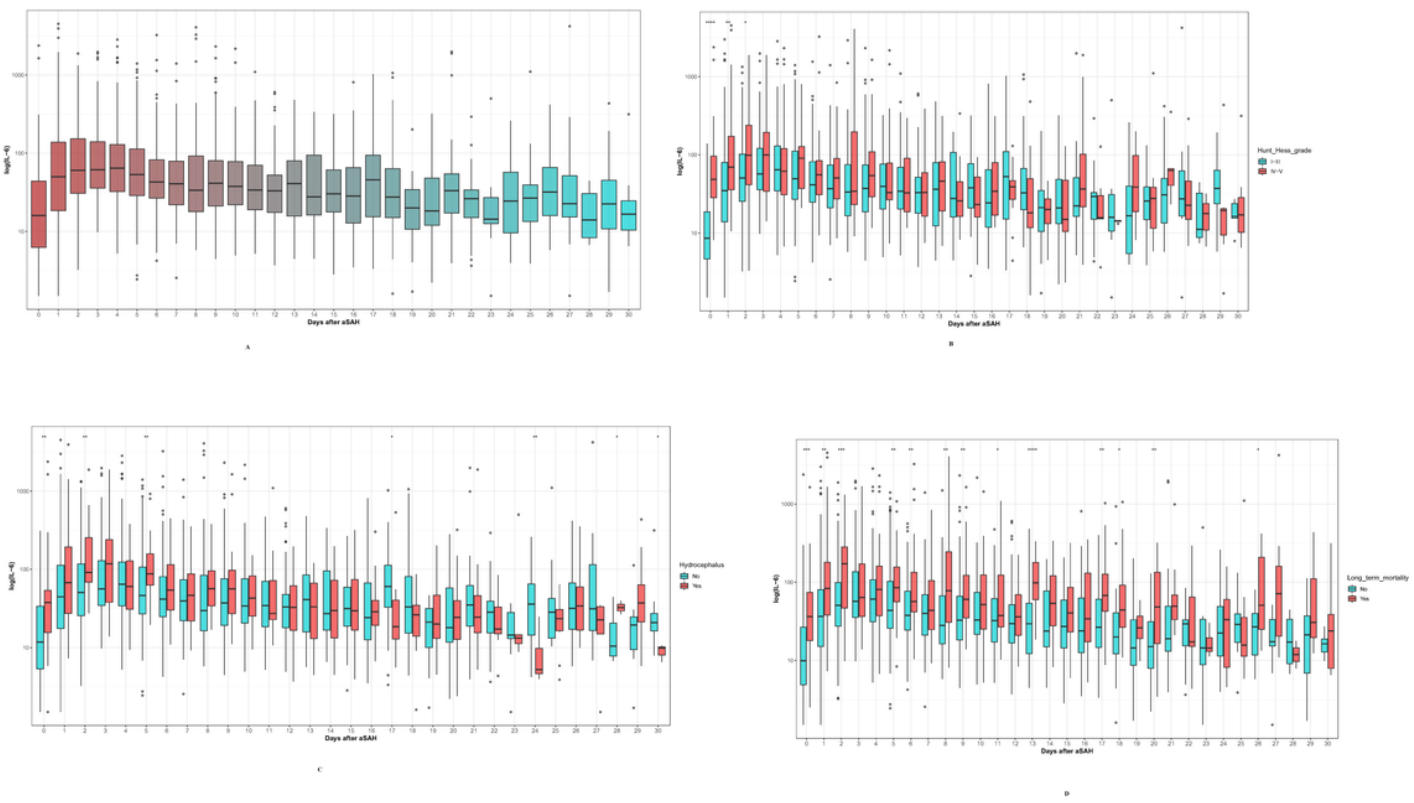

Figure 1

Daily interleukin-6 (IL-6) level during the hospitalization (a), illustrated as box plots and stratified by Hunt & Hess grade at admission (b), the occurrence of hydrocephalus (c), and long-term mortality (d). The median is marked by the black notch within the quartiles. Outliers are plotted as individual points. *: $p \leq 0.05$; **: $p \leq 0.01$; ***: $p \leq 0.001$; ****: $p \leq 0.0001$

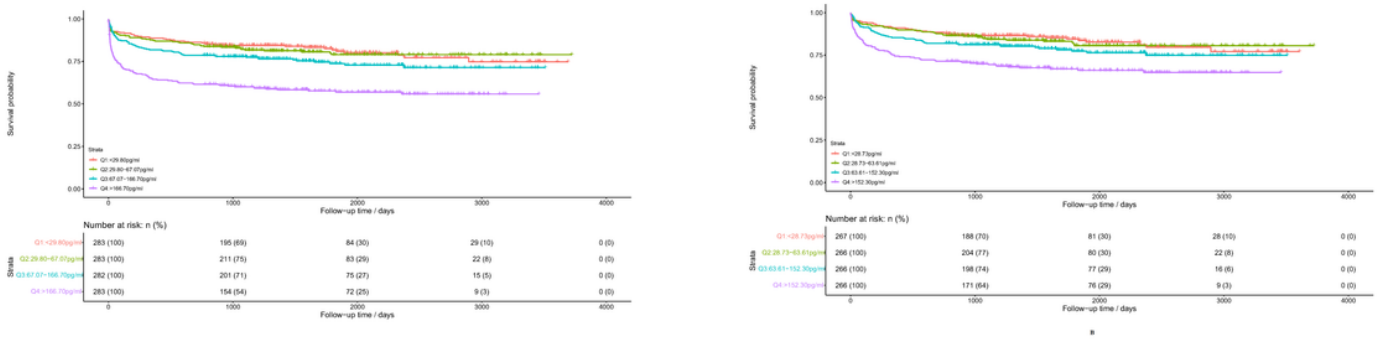

Figure 2

Kaplan-Meier curve for overall survival of all patients (n=1131) by quartiles of IL-6 levels (a). Kaplan-Meier curve for overall survival of survivors at discharge (n=1065) by quartiles of IL-6 levels (b).

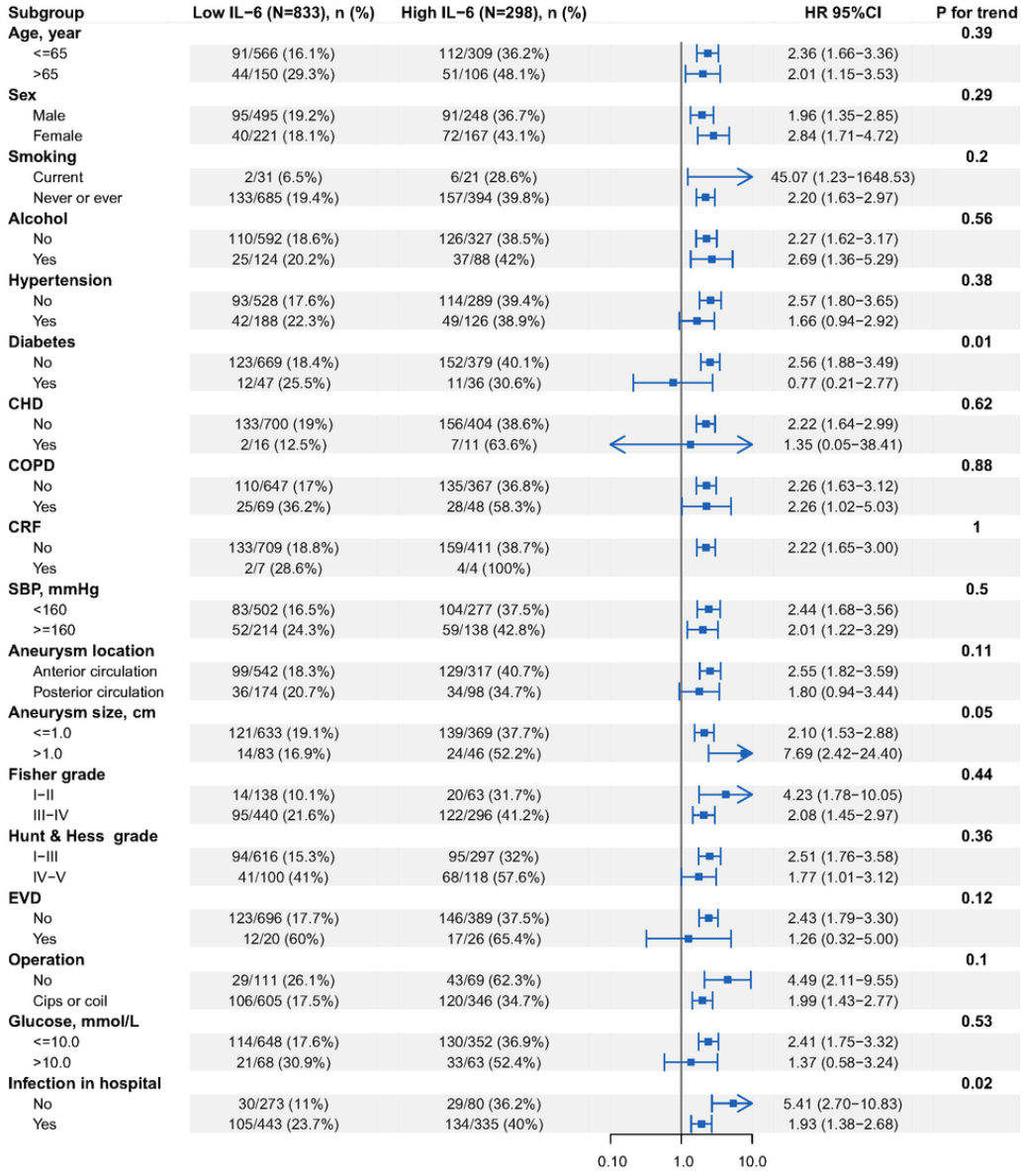

Figure 3

Subgroup analysis of the association between IL-6 levels and long-term mortality with a multivariate Cox regression model

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