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C-Reactive Protein as a Prognostic Marker in Intracerebral Hemorrhage: A Systematic Review and Meta-Analysis

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Abstract

Background: Intracerebral hemorrhage (ICH) is a devastating subtype of stroke with high rates of morbidity and mortality. Inflammation is a key driver of secondary brain injury following ICH, and C-reactive protein (CRP) is a cardinal biomarker of systemic inflammation. While numerous studies have investigated the prognostic role of CRP in ICH, its utility remains a subject of debate, with conflicting findings across the literature. **Objective:** This systematic review and meta-analysis aimed to synthesize the available evidence and quantitatively assess the association between CRP levels and adverse clinical outcomes in patients with spontaneous ICH. **Methods:** A comprehensive literature search was conducted in PubMed, Embase, SinoMed, and the Cochrane Library from inception to June 2026. We included observational studies that evaluated the association between CRP levels and subsequent poor outcomes in adult patients with spontaneous ICH. Two independent reviewers performed study selection, data extraction, and quality assessment using the Newcastle-Ottawa Scale. Common and Random effects models were used to pool odds ratios (ORs) and 95% confidence intervals (CIs). Heterogeneity was assessed using the I^2 statistic, and publication bias was evaluated with funnel plots. **Results:** A total of 15 observational studies involving 14,285 patients met the inclusion criteria. The qualitative assessment indicated that most studies were of moderate to high quality. The meta-analysis revealed that elevated CRP levels were significantly

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associated with an increased risk of poor outcome (pooled OR: 1.27, 95% CI: 1.06 - 1.51, $p < 0.001$; $I^2 = 90.3\%$). Similarly, high CRP levels were a significant predictor of poor functional outcome (pooled OR: 1.19, 95% CI: 1.04 - 1.35, $p < 0.001$; $I^2 = 84.3\%$) and mortality (pooled OR: 1.51, 95% CI: 1.08 - 2.12, $p < 0.001$; $I^2 = 84.3\%$). High CRP levels were a significant predictor of early hematoma growth (pooled OR: 1.11, 95% CI: 1.06 - 1.17, $p < 0.001$; $I^2 = 0\%$). Sensitivity analyses confirmed the robustness of the primary findings. There was no evidence of significant publication bias. **Conclusion:** This systematic review and meta-analysis provides strong evidence that elevated CRP levels are independently associated with a higher risk of poor outcome in patients with spontaneous ICH. CRP is an accessible, inexpensive, and valuable biomarker that can aid in early risk stratification and may help identify patients who could benefit from targeted anti-inflammatory therapies.

Keywords

C-Reactive Protein, Intracerebral Hemorrhage, Prognostic Marker, Meta-Analysis

1. Introduction

Intracerebral hemorrhage (ICH), the extravasation of blood into the brain parenchyma, is the second most common subtype of stroke, accounting for 10% - 15% of all cases globally [1]. Despite advances in critical care, ICH remains a major public health concern, associated with disproportionately high rates of mortality and long-term disability compared to ischemic stroke [2]. The pathophysiology of brain injury after ICH is biphasic, involving an initial mechanical injury from the hematoma followed by a more prolonged phase of secondary brain injury. This secondary phase is driven by a complex cascade of events, including oxidative stress, blood-brain barrier disruption, and, critically, a robust inflammatory response [3].

The inflammatory response following ICH is initiated by the presence of blood products in the brain parenchyma, which triggers the activation of resident microglia and astrocytes and the infiltration of peripheral immune cells [4]. This leads to the release of numerous pro-inflammatory mediators, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which contribute to perihematomal edema and neuronal cell death [5] [6]. The intensity of this systemic and local inflammation has been linked to worse clinical outcomes, highlighting the need for reliable biomarkers to quantify this response and predict patient prognosis [3].

C-reactive protein (CRP) is a phylogenetically conserved pentameric protein and a classic acute-phase reactant [7]. It is synthesized primarily by hepatocytes in response to pro-inflammatory cytokines, most notably IL-6, and its plasma concentration can increase up to 1000-fold during inflammation or infection [8]. For decades, CRP has been used as a sensitive, albeit non-specific, marker of inflammation.

More recently, high-sensitivity CRP (hs-CRP) assays have established its role as a powerful predictor of future cardiovascular events in healthy individuals and in patients with established cardiovascular disease [9] [10]. Its prognostic utility has also been demonstrated in a wide range of other conditions, including infections like COVID-19 [11], various cancers [12] [13], and type 2 diabetes [14].

In the context of ICH, elevated CRP levels are commonly observed and are thought to reflect the intensity of the post-hemorrhage inflammatory response [15]. Several studies have reported a strong association between higher admission CRP levels and adverse outcomes, including in-hospital mortality [2] and poor long-term functional status [16]. However, the evidence is not entirely consistent. For instance, one large multicenter analysis found no association between baseline CRP and 30-day mortality or the extent of perihematomal edema [17]. Furthermore, the question of causality remains complex. Mendelian randomization studies, which use genetic variants as proxies for exposure to minimize confounding, have produced conflicting results; some found no causal link between genetically predicted CRP and ICH risk [18], while others have suggested a surprising protective causal relationship, particularly for lobar ICH [19] [20].

Given these inconsistencies and the potential clinical importance of a widely available prognostic biomarker, a comprehensive evaluation of the evidence is warranted. A recent meta-analysis confirmed the prognostic value of CRP [4], but new, large-scale studies have since been published. Therefore, we conducted an updated systematic review and meta-analysis to provide a robust, quantitative summary of the association between CRP levels and the risk of mortality and poor functional outcome in patients with spontaneous ICH.

2. Methods

2.1. Search Strategy

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive literature search was performed in PubMed, Embase, SinoMed, and the Cochrane Library for all relevant articles published from database inception to June 2025. The search strategy combined medical subject headings (MeSH) and text words related to intracerebral hemorrhage (e.g., "Intracerebral Hemorrhage," "Cerebral Hemorrhage") and C-reactive protein (e.g., "C-Reactive Protein," "CRP," "inflammatory markers") and clinical outcomes (e.g., "prognosis," "outcome," "mortality," "morbidity"). No language restrictions were applied initially. The reference lists of retrieved articles and relevant reviews were also manually screened for additional eligible studies.

2.2. Inclusion and Exclusion Criteria

Studies were included if they met the following criteria: 1) study design was an observational cohort (prospective or retrospective) or case-control study; 2) the study population consisted of adult patients (≥18 years) with a primary diagnosis of spontaneous ICH; 3) the exposure of interest was the level of CRP measured during hospitalization; 4) the study reported at least one of the primary outcomes: mortality, poor functional outcome, early hematoma growth, overall survival, delayed mobilization; and 5) the study provided sufficient data to calculate an odds ratio (OR), hazard ratio (HR), or relative risk (RR) with a corresponding 95% confidence interval (CI), or provided raw data from which these could be calculated.

Studies were excluded if they: 1) involved non-spontaneous ICH (e.g., due to trauma, tumor, aneurysm rupture, or arteriovenous malformation); 2) were case reports, case series with fewer than 20 patients, reviews, editorials, or conference abstracts; 3) did not measure CRP; or 4) did not report on the specified clinical outcomes.

2.3. Data Extraction and Quality Assessment

Two reviewers independently screened the titles and abstracts of all identified articles. The full texts of potentially eligible articles were then retrieved and assessed for final inclusion. Any disagreements were resolved by consensus or by consulting a third reviewer.

We extracted the following data from each included study: publication year, first author, country, study design, sample size (with male count and proportion), mean age, CRP measurement timing, follow-up duration, statistical model, outcomes, study design (single-center/multicenter), and CRP cut-off values, and the adjusted effect estimates (ORs or HRs) with their 95% CIs for the association between CRP and outcomes. If a study reported multiple adjusted models, we extracted the estimate from the most fully adjusted model.

The methodological quality of the included observational studies was independently assessed by two reviewers using the Newcastle-Ottawa Scale (NOS). The NOS evaluates studies based on three domains: selection of study groups, comparability of groups, and ascertainment of exposure or outcome. Scores range from 0 to 9 stars, with studies scoring ≥ 7 considered high quality, 5 - 6 as moderate quality, and <5 as low quality.

2.4. Statistical Analysis

The primary outcomes were mortality, poor functional outcome, early hematoma growth, overall survival, and delayed mobilization. We pooled the adjusted ORs from individual studies using a random-effects model (DerSimonian and Laird method), which accounts for both within-study and between-study variation. For studies reporting HRs, these were considered as approximations of ORs, a valid assumption when the outcome is relatively rare. When studies reported CRP as a continuous variable, we used the provided OR per unit or standard deviation increase. When CRP was categorized, we compared the highest versus the lowest category.

Statistical heterogeneity among studies was quantified using the I^2 statistic, with values of <50% and >50% indicating low and high heterogeneity, respectively. The Cochran's Q test was also used, with a p-value < 0.10 indicating significant heterogeneity.

Potential publication bias was assessed visually by inspecting the symmetry of a funnel plot and quantitatively using Egger's linear regression test, where a p-value < 0.05 was considered indicative of significant bias. All statistical analyses were performed using R 4.3.3 and Stata software, version 17.0.

3. Results

3.1. Study Selection

The initial database search yielded 841 records. After removing 89 duplicates, 752 titles and abstracts were screened. Of these, 673 were excluded as they were irrelevant, were not original research (e.g., reviews, editorials), or did not meet the population or exposure criteria. The full texts of the remaining 79 articles were assessed for eligibility. A further 64 articles were excluded for various reasons, including having a population with mixed stroke types without separate data for ICH, not measuring CRP on admission, not reporting the outcomes of interest, or not providing sufficient data for meta-analysis. Ultimately, 15 studies met all inclusion criteria and were included in the systematic review and meta-analysis. The selection process is outlined in **Figure 1**.

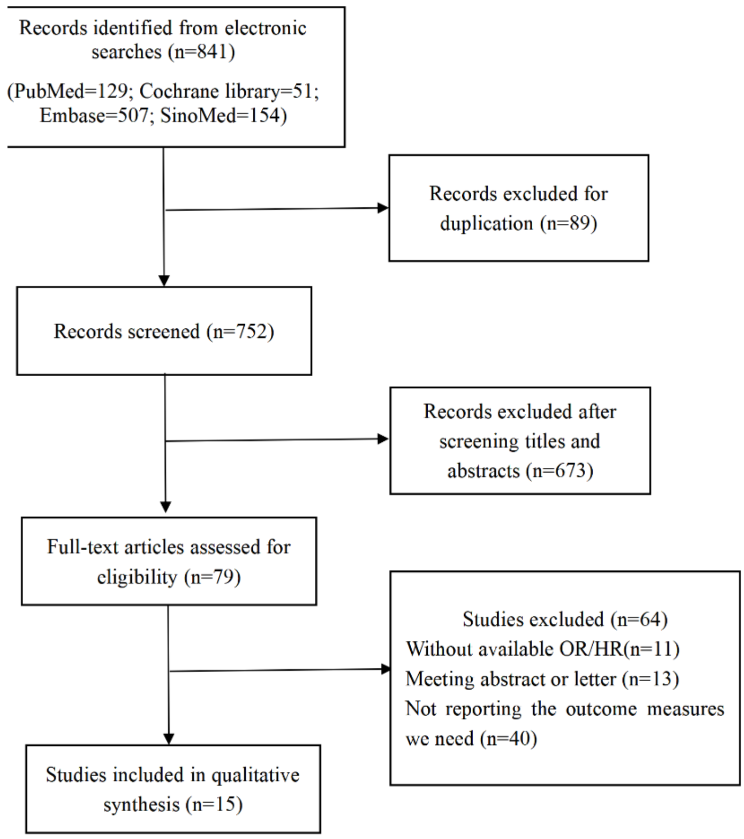

Figure 1. Flow diagram of the selection of eligible studies.

3.2. Study Characteristics

The 15 included studies were published between 2011 and 2022 and comprised a total of 14,285 patients with spontaneous ICH. Of these, 11 were conducted in Asia, 3 in Europe, and 1 in Africa. All studies were observational, with 7 being retrospective cohort studies and 7 being prospective cohort studies, 1 being a pro-retrospective cohort study. The sample sizes ranged from 46 to 9589 patients. The mean or median age of patients was typically between 50 and 80 years. The definition of elevated CRP varied across studies, with cut-off values ranging from 5 mg/L to over 30 mg/L, while some studies analyzed CRP as a continuous variable. The primary outcomes were mortality, poor functional outcome, hematoma expansion, and overall survival, with follow-up periods ranging from in-hospital to 12 months. The quality of the included studies, as assessed by the NOS, was generally good, with 12 studies rated as high quality (score ≥ 7) and 3 as moderate quality (score 5 - 6). Detailed information on the included studies is provided in **Table 1**.

3.3. Meta-Analysis of Clinical Outcomes

3.3.1. Association between CRP and Poor Outcome

Sixteen studies provided data on the association between admission CRP levels and poor outcome (including mortality, poor functional outcome, early hematoma growth, overall survival, and delayed mobilization). The random-effects meta-analysis showed that elevated CRP was significantly associated with an increased risk of mortality. The pooled OR was 1.30 (95% CI: 1.06 - 1.58, $p < 0.001$). There was moderate to high heterogeneity among the studies ($I^2 = 90.9\%$, p for heterogeneity < 0.001). This finding indicates that patients with higher CRP levels have a significantly greater risk of poor outcome following ICH.

3.3.2. Association between CRP and Poor Functional Outcome

Eight studies provided data on the association between CRP levels and poor functional outcomes. The random-effects meta-analysis showed that elevated CRP was significantly associated with an increased risk of poor functional outcome. The pooled OR was 1.19 (95% CI: 1.04 - 1.35, $p < 0.001$). There was moderate to high heterogeneity among the studies ($I^2 = 92.6\%$, p for heterogeneity < 0.001). This finding indicates that patients with higher CRP levels have a significantly greater risk of poor functional outcome following ICH.

3.3.3. Association between CRP and Mortality

Eight studies provided data on the association between CRP levels and mortality. The random-effects meta-analysis showed that elevated CRP was significantly associated with an increased risk of mortality. The pooled OR was 1.51 (95% CI: 1.08 - 2.12, $p < 0.001$). There was moderate to high heterogeneity among the studies ($I^2 = 84.3\%$, p for heterogeneity < 0.001). This finding indicates that patients with higher CRP levels have a significantly greater risk of death following ICH.

Table 1. The main characteristics of included studies.

Year	First Author	Country	Study design	Sample size (male, %)	Mean age	CRP measurement timing	follow-up duration	Statistical model	Outcome 1	Outcome 2	Outcome 3	Outcome 4	Study type	Cutoff value
2011	Margarita L. Alexandrova	Bulgaria	P	46 (23, 50%)	63 ± 12	Admission	1 week	M	Mortality (1 week)				S	5 mg/L
2013	Mario Di Napoli	Italy	P	399 (215, 53.9%)	71.6 ± 12.8	within 6 hours of onset	30 days	M	EHG (24 h or earlier)	Mortality (30 days)			M	10 mg/L
2014	Pekka Löppönen	Finland	R	807 (436, 54%)	69 ± 12	Admission	3 months	M	Functional Outcomes (3 months)				S	NR
2016	Xin-Jiang Yan	China	P-R	112 (66, 58.9%)	63.2 ± 9.6	Admission	6 months	U	Functional Outcomes (6 months)	Mortality (1 week)	Mortality (6 months)	OS (6 months)	S	NR
2017	Asli Bolayir	Turkey	R	296 (138, 46.6%)	76.3 ± 11.4	Admission	60 days	M	Mortality (60 days)				S	NR
2017	Youssef Zied Elhechmi	Tunisia	R	91 (56, 61.5%)	64.35 (61.54-67.17)	24 ± 6 hours	30 days	M	Mortality (30 days)				S	30 mg/L
2017	Wen-Jian Ji	China	P	128 (77, 60.2%)	64 (44-78)	Admission	6 months	U	Functional Outcomes (6 months)				S	NR
2019	Lin Bian	China	P	164 (95, 57.9%)	66 (IQR, 56-76)	Admission	90 days	M	Functional Outcomes (90 days)				S	NR
2020	Xue-Qin Huangfu	China	P	159 (88, 55.3%)	64 (42-78)	Admission	90 days	U	Overall survival (90 days)				S	NR
2021	Ram Sagar	India	P	250 (162, 64.8%)	54.9 ± 12.8	Within 72 hours of onset	3 months	M	Functional Outcomes (3 months)	Mortality (3 months)			S	14.5 mg/L
2021	Qian Liu	China	P	1451 (978, 67.4%)	60.41 ± 12.3	Admission	12 months	M	Functional Outcomes (at discharge)	Functional Outcomes (at 3 months)	Functional Outcomes (at 12 months)		S	NR
2022	Bulent Gulensoy	Turkey	R	170 (89, 52.4%)	66.29 ± 13.99	Admission	30 days	M	Mortality (30 days)				S	7.5 mg/L
2022	Yoshinori Naito	Japan	R	322 (178, 55.3%)	69.3 ± 14.0	Admission	Until discharge	M	Delayed Mobilization (at discharge)				S	NR
2022	He-Ling Chu	China	R	301 (222, 73.8%)	61.4 ± 13.1	Admission	3 months	M	Functional Outcomes (3 months)	Mortality (30 days)	EHG, (24h or earlier) (within 24 hours)		M	8.2 mg/L
2022	Dan-Dan Wang	China	R	9589 (6086, 63.5%)	e: 61.8 ± 12.9 f: 62.7 ± 13.2 g: 64.5 ± 14.0 c, age for CRP ≤ 3 group; d, age for 3 < CRP ≤ 10 group; e, age for CRP > 10 group	Admission	Until discharge	M	Functional Outcomes (at discharge)	Mortality (at discharge)			M	10 mg/L

Note: R, retrospective; P, prospective; P-R, pros-retrospective; NR, not report; M, multivariate; U, univariate; OS, overall survival; S, single-center; M, multicenter; EHG, early hematoma growth.

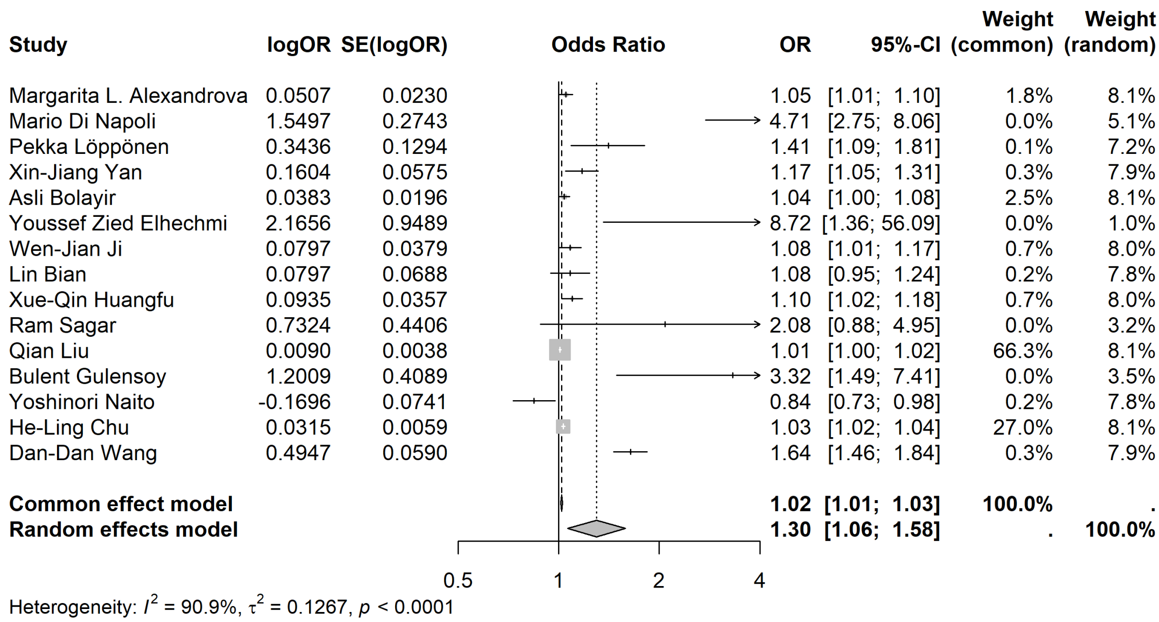

Figure 2. Forest plot of the association between CRP and poor outcome.

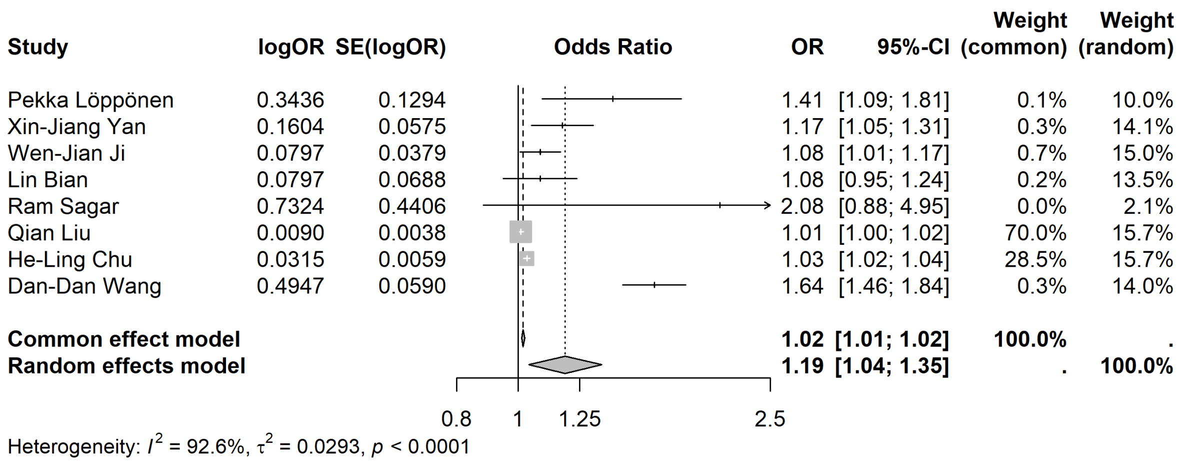

Figure 3. Forest plot of the association between CRP and poor functional outcome.

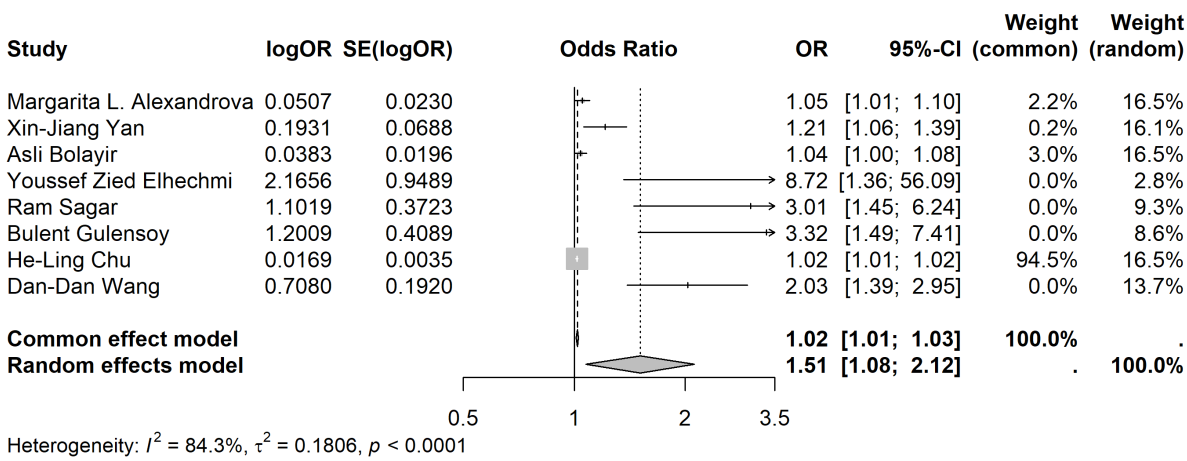

Figure 4. Forest plot of the association between CRP and Mortality.

3.3.4. Association between CRP and Overall Survival

Two reported on the association between admission CRP and overall survival. The pooled OR was 2.14 (95% CI: 0.48 - 9.57, p > 0.05). This demonstrated that elevated CRP levels were not significantly associated with a higher likelihood of overall survival.

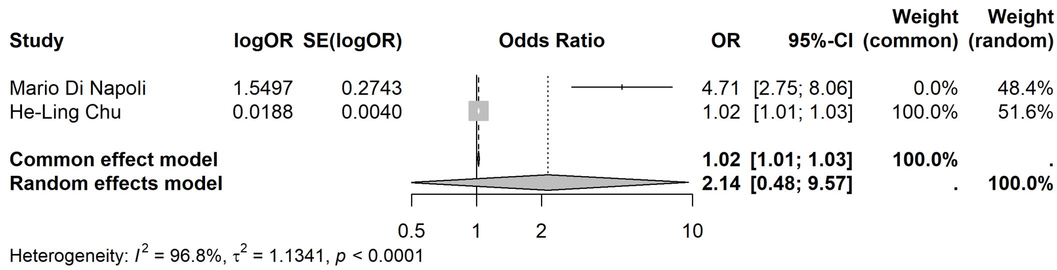

Figure 5. Forest plot of the association between CRP and overall survival.

3.3.5. Association between CRP and Early Hematoma Growth

Two studies reported on the association between admission CRP and early hematoma growth. The pooled analysis demonstrated that elevated CRP levels were significantly associated with a higher likelihood of early hematoma growth. The pooled OR was 1.11 (95% CI: 1.06 - 1.17, p < 0.001). Significant heterogeneity was also observed in this analysis (I^2 = 0%, p for heterogeneity < 0.001). This result suggests that a strong initial inflammatory response, as indicated by high CRP, is predictive of early hematoma growth in ICH survivors.

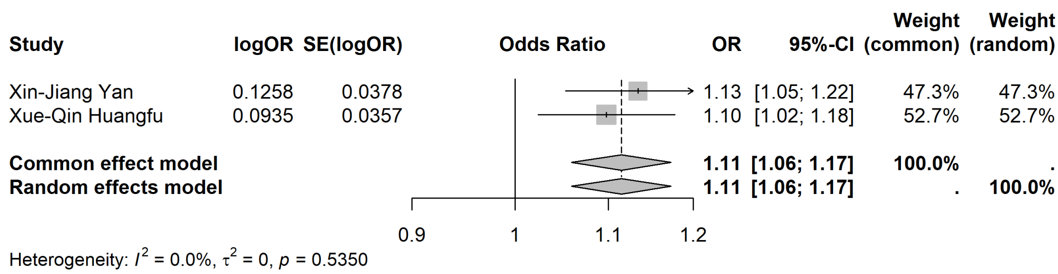

Figure 6. Forest plot of the association between CRP and early hematoma growth.

3.4. Sensitivity Analyses

The sensitivity analysis, conducted by omitting one study at a time, showed that no single study unduly influenced the overall pooled estimates, confirming the robustness of our findings.

3.5. Publication Bias

Visual inspection of the funnel plots for poor outcomes revealed general symmetry, which showed no evidence of significant publication bias.

4. Discussion

This systematic review and meta-analysis, encompassing 15 studies and 14,285

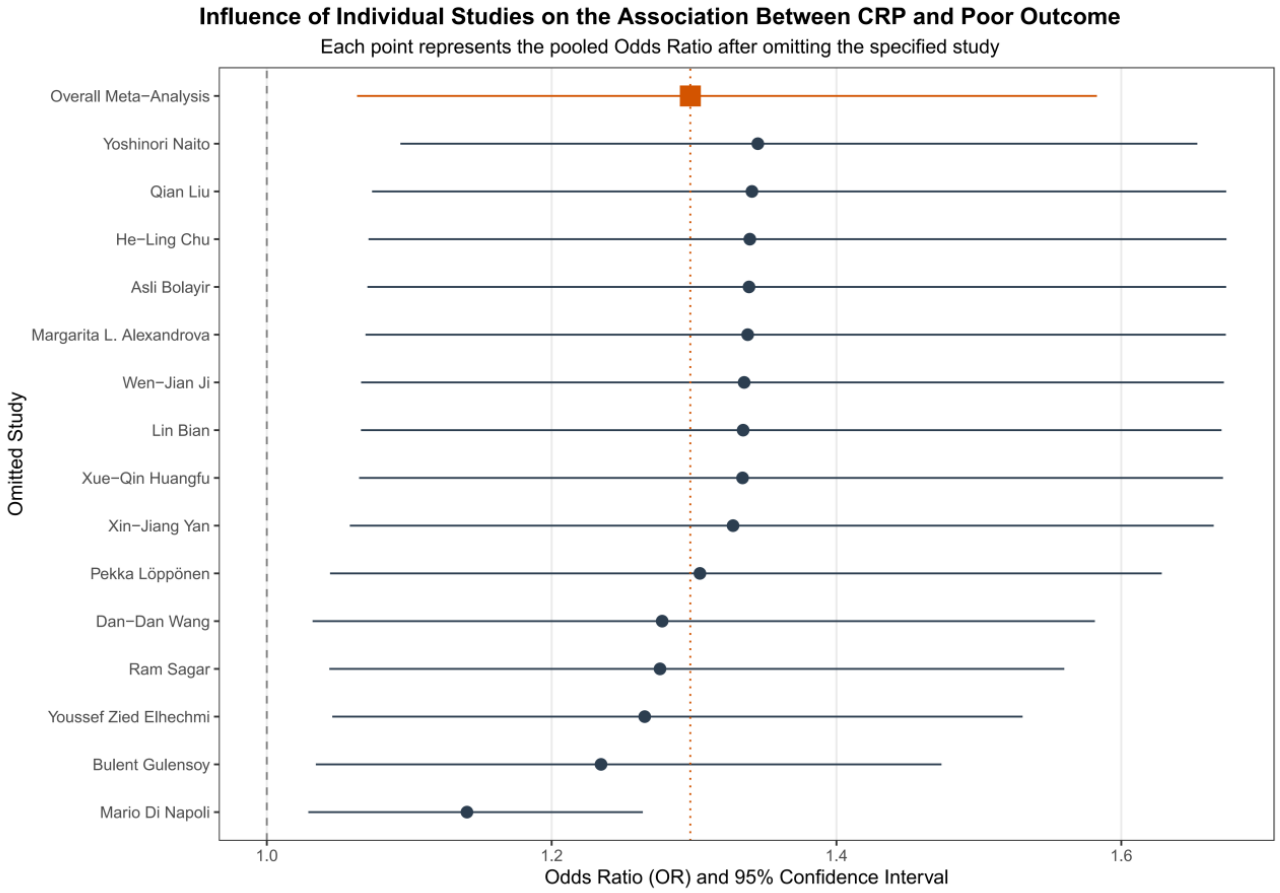

Figure 7. Sensitivity analysis for the association between CRP and poor outcome.

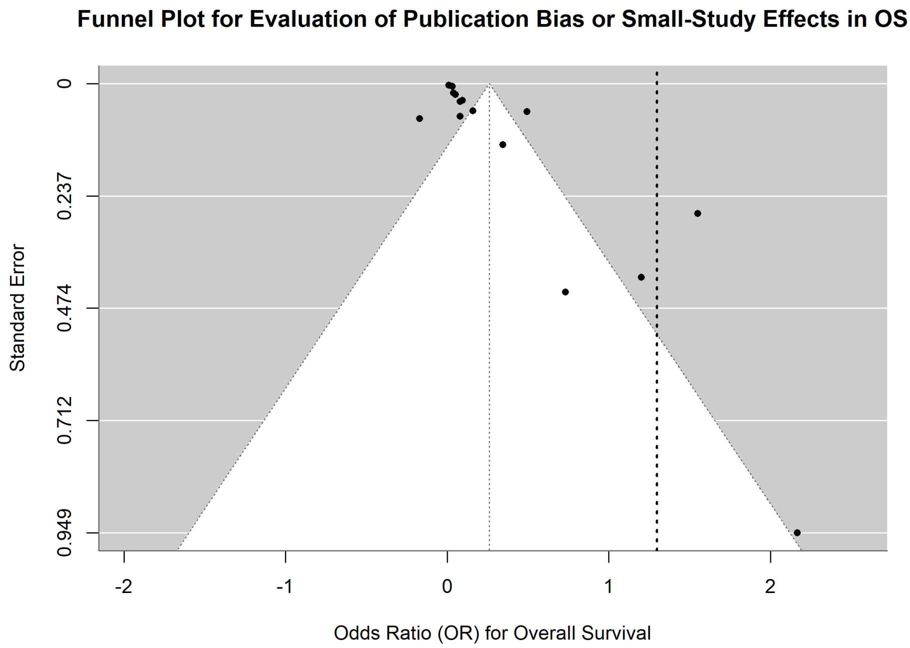

Figure 8. Funnel plot for evaluation of publication bias or small-study effects.

patients, provides compelling evidence that an elevated CRP level is a strong and independent predictor of poor outcome in patients with spontaneous ICH. Our findings consolidate and extend the results of previous studies, confirming that the intensity of the early systemic inflammatory response is a critical determinant of prognosis after ICH.

4.1. Biological Plausibility and Pathophysiological Mechanisms

The robust association between CRP and adverse outcomes in ICH is biologically plausible and likely reflects several underlying pathophysiological mechanisms. First, CRP serves as a sensitive marker of the systemic inflammatory cascade triggered by the initial hematoma [3]. Blood components, particularly hemoglobin and iron, are potent activators of microglia and infiltrating leukocytes, leading to the production of pro-inflammatory cytokines like IL-6, which in turn stimulates hepatic CRP synthesis [21]. A higher CRP level thus reflects a more intense inflammatory state, which is known to exacerbate secondary brain injury through mechanisms such as blood-brain barrier breakdown, vasogenic edema, and direct neuronal toxicity [6].

Beyond being a passive marker, there is growing evidence that CRP may be an active participant in the inflammatory process. The native pentameric CRP (pCRP) can dissociate into a more pro-inflammatory monomeric form (mCRP) at sites of tissue damage [8]. This mCRP has been shown to have direct pathogenic effects relevant to ICH, including activating the complement system and inducing the expression of adhesion molecules on endothelial cells, which facilitates leukocyte infiltration into the brain parenchyma [13] [15]. Therefore, high CRP levels may signify a self-amplifying cycle of inflammation that worsens brain injury.

4.2. Comparison with Existing Literature

Our findings are largely consistent with a previous meta-analysis by Guo *et al.*, which also concluded that elevated NLR, WBC, and CRP were associated with poor outcomes in ICH [4]. Our updated analysis, including several recent large studies, strengthens this conclusion and provides more precise effect estimates. While our results represent the consensus of a large body of evidence, it is important to acknowledge conflicting reports. For example, Sobowale *et al.* found no link between baseline CRP and 30-day mortality [17]. Such discrepancies may arise from differences in study populations, the timing of CRP measurement (as CRP levels peak around 3 days post-ICH [6]), and statistical adjustment for different confounders. The high heterogeneity observed in our meta-analysis underscores these inter-study variations.

The complex findings from Mendelian randomization studies, suggesting either no causal link or a protective effect of CRP on ICH onset [18] [20], do not contradict our findings. These studies assess the causal role of lifelong, genetically determined CRP levels on the risk of developing ICH, not its prognostic role after an ICH event has occurred. Our results firmly establish CRP as a powerful prognostic biomarker that reflects the acute pathological processes unfolding after hemorrhage, regardless of its role in causing the initial event.

4.3. Clinical Implications

The results of this meta-analysis have significant clinical implications. CRP is a routine, inexpensive, and rapidly available laboratory test in virtually all hospitals. Its integration into the early assessment of ICH patients can provide valuable prognostic information.

1) **Risk Stratification:** Admission CRP can help clinicians identify patients at high risk for deterioration and adverse outcomes. This information can supplement established clinical scoring systems, such as the ICH Score, potentially improving their predictive accuracy [22]. High-risk patients could be triaged to higher levels of care and more intensive monitoring.

2) **Therapeutic Guidance:** The strong link between inflammation and poor outcomes provides a compelling rationale for investigating anti-inflammatory therapies in ICH. Elevated CRP could serve as an enrichment biomarker to select patients most likely to benefit from such interventions in future clinical trials.

3) **Composite Biomarkers:** Recent research has explored composite markers that combine CRP with markers of nutritional status, such as the CRP/Albumin ratio (CAR). These ratios have shown promise as even more powerful prognostic indicators in ICH, as they capture both the inflammatory burden and the patient's physiological reserve [2] [23].

4.4. Limitations

This meta-analysis has several limitations that should be considered. First, all included studies were observational, which carries an inherent risk of residual confounding, despite statistical adjustments in the primary studies. Second, there was significant heterogeneity among the studies in terms of patient populations, CRP cut-off values, timing of outcome assessment, and definitions of poor functional outcome. This variability likely contributed to the high I^2 values observed. Third, we could not fully account for potential confounders that also elevate CRP, such as underlying infections, which are common in ICH patients and are themselves associated with poor outcomes. Finally, as with any meta-analysis, there is a potential for publication bias, although our statistical tests did not detect it.

5. Conclusion

This comprehensive systematic review and meta-analysis demonstrates that an elevated C-reactive protein level is a robust and clinically significant predictor of both increased mortality and poor functional outcome in patients with spontaneous intracerebral hemorrhage. As a widely available and inexpensive biomarker, CRP can be a valuable tool for early risk stratification, helping to identify high-risk patients who may warrant more intensive management. These findings underscore the critical role of the inflammatory response in the pathophysiology of secondary brain injury after ICH and support the continued investigation of targeted anti-inflammatory strategies. Future research should focus on standardizing CRP measurement protocols, exploring the prognostic value of serial CRP measurements, and incorporating this biomarker into multimodal predictive models to improve the care of patients with this devastating condition.

Authors' Contributions

YZW, XEF, BHZ, YL, YBY, and ZYS designed this research; YZW, XEF, and YBY performed the statistical analysis; all authors performed the data extraction and drafted and revised the manuscript. All authors read and approved the final manuscript.

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Ethics Approval and Consent to Participate

This study received approval from the Ethics Committee of the First Hospital of Lanzhou University. Patient data were anonymized throughout the research. The findings of this study will be published in a globally influential, open-access academic journal.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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