INPLASY PROTOCOL

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Conflicts of interest:
None declared.

The Predictive Role of C-Reactive Protein on Sudden Death: A meta-analysis of prospective studies

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Review question / Objective: **This study was a diagnostic research, so the content was decomposed according to PIRO : P: Patients diagnosed with sudden death; I: C-reactive protein; R: There is no gold standard for sudden death, and the definition of sudden death varies from literature to literature. The World Health Organization defines sudden death: "Patients who are normally healthy or seemingly healthy die suddenly due to natural diseases in an unexpectedly short period of time." In our study, sudden death is determined by the history, symptoms, physical examination and electrocardiogram results assesed by doctor. If death events were collected from the patients' medical records, deaths coded using the International Classification of Diseases-9th Revision, codes 410 to 414 for non-SCD and 798.1 for SCD; or the International Classification of Diseases-10th Revision, codes I20 to I25 for non-SCD and I46 for SCD. All deaths registered as sudden deaths were confirmed in interviews with the patient's physician or family members again. O: sudden death.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 20 November 2021 and was last updated on 20 November 2021 (registration number INPLASY2021110074).

INTRODUCTION

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Rationale: C-reactive protein (CRP) is a powerful predictor of cardiovascular disease. However, the relationship between CRP and sudden death (SD) is controversial. So, we performed this meta-analysis to evaluate the association between CRP and SD.

Condition being studied: Sudden death (SD) is one of the most serious human diseases. In SD cases, sudden cardiac death (SCD) account for approximately 85%. Globally, there are 4-5 million people dying of SCD per year. And in western countries, it leads to approximate 20,000 deaths in Australia and 350,000 deaths in America every year. As a non-specific inflammatory biomarker, C-reactive protein (CRP) is directly involved in the process of cardiovascular disease. In recent years, some studies have shown that CRP levels are associated with an increased risk of SD. However, the role of CRP in predicting SD is still controversial. Therefore, we conducted this meta-analysis to provide more biomarker evidence for SD risk assessment.

METHODS

Search strategy: A comprehensive research was conducted on PubMed, Web of Science, Embase, Cochrane data, CNKI and Wan Fang based on the "PRISMA" guideline till November 9, 2020. The following subject terms were combined and applied to research: ("sudden death" or "sudden unexpected death" or "sudden cardiac death" or "SD" or "SCD") and ("C-reactive protein" or "high-sensitive C-reactive protein" or "CRP" or "hsCRP"). Moreover, we manually screened reference in the included studies for potential eligible studies.

Participant or population: Patients diagnosed with sudden death.

Intervention: None.

Comparator: Non-sudden death patients.

Study designs to be included: Prospective studies.

Eligibility criteria: The researches included had to meet the following criteria: (1) The end point covered SD and the relationship between SD and CRP has been investigated; (2) The study design was prospective. The studies were excluded with one of the following conditions: (1) There was no complete data or the data couldn't be transformed; (2) The type of research is letter, review, case report, animal experiment, commentary and grey literature.

Information sources: A comprehensive research was conducted on PubMed, Web of Science, Embase, Cochrane data, CNKI and Wan Fang based on the "PRISMA" guideline till November 9, 2020. Moreover, we manually screened reference in the included studies for potential eligible studies.

Main outcome(s): Twelve prospective studies, a total of 36,646 patients, were included in the present meta-analysis. This study demonstrated that patients with higher CRP levels had a greater risk of SD (HR 1.19, 95%CI 1.09-1.29). CRP was confirmed as an independently predictive factor for SD, when 8 studies were synthesized, whose HR of SD was calculated by multivariate analysis (HR=1.15, 95%CI: 1.05-1.26).

Quality assessment / Risk of bias analysis: The quality of studies included were assessed by NEWCASTLE-OTTAWA QUALITY ASSESSMENT SCALE (NOS). A score equal to or less than 5 was considered as low quality, 6 or 7 as moderate and 8 or 9 as high. Any disagreements were resolved through consensus.

Strategy of data synthesis: Stata software (version 12.0; Stata Corp LP, College Station, TX) was applied for statistical analysis. The relationship between SD and CRP was assessed by Hazard Ratio (HR) with 95% confidence interval (CI). When authors had provided multivariable and univariable analyses simultaneously, the former was selected. Heterogeneity between studies was assessed statistically by $\chi 2$ and I2 tests. When p50%, the significant heterogeneity being present in studies, we chose random-effects model. when p>0.10 and I2<50%, the fixed-effects model was used. Additionally, we performed Begg test and funnel plot to assess if there were publication bias across studies. Two-sided hypotheses of p values less than 0.05 were taken for statistical significance.

Subgroup analysis: Subgroups of meta-analysis were performed based on primary disease, outcomes of cases, variable type of CRP level. Meanwhile, we also carried out subgroup analysis according to the age of patients, follow-up time, country and sample size.

Sensitivity analysis: Sensitivity analysis was conducted to assess the impact of each study on overall heterogeneity. We adopt the method of item-by-item elimination is adopted. After the included studies are sequentially removed, the residual combined effect value and 95% CI are calculated.

Language: There were no language restrictions for retrieval.

Country(ies) involved: China.

Keywords: C-reactive protein; Sudden Death; Sudden Cardiac Death; meta-analysis.

Contributions of each author:

Author 1 - Ruhua Zhou - took part in the data extracted, statistical analysis and drafting of the manuscript.
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Author 3 - Jiaochen Luan - recheck the results and revised the manuscript.
Author 4 - Weiyun Wang - helped to recheck the results and revised the manuscript.
Author 5 - Xinzhi Tang - participated in data extraction.
Author 6 - Yanling Huang - participated in data extraction.
Author 7 - Ziwen Su - participated in data extraction.
Author 8 - Lei Yang - participated in data extraction.
Author 9 - Zejuan Gu - designed the study program and took responsibility for the integrity of the data and the accuracy of the data analysis.