BMJ Open

High-sensitivity C-Reactive Protein as a Predictor of In-hospital Mortality in Cardiovascular Disease Patients at an Emergency Department: a retrospective cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-015112
Article Type:	Research
Date Submitted by the Author:	16-Nov-2016
Complete List of Authors:	Yoshinaga, Ryo; Iizuka Byoin, Japanese Oriental Medicine Doi, Yasufumi; Iizuka Byoin, Personnel Ayukawa, Katsuhiko; Iizuka Byoin, Emergency Department Ishikawa, Shizukiyo; Jichi Ika Daigaku, Department of General Medicine
Primary Subject Heading:	Emergency medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	High sensitivity C-Reactive Protein, cardiovascular disease, emergency department

Research Article

High-sensitivity C-Reactive Protein as a Predictor of In-hospital Mortality in Cardiovascular Disease Patients at an Emergency Department: a retrospective cohort study

Ryo Yoshinaga, MD[1], Yasufumi Doi, MD, PhD[2],

Katsuhiko Ayukawa, MD[3] and Shizukiyo Ishikawa, MD, PhD[4]

Departments of [1]Japanese Oriental Medicine, [2]Personnel, and [3]Emergency Department, Iizuka Hospital, Iizuka, Japan

[4]Department of General Medicine, Jichi Medical University School of Medicine, Shimotsuke, Japan

Running headline: High-sensitivity CRP and cardiovascular disease

Corresponding author: Dr. Ryo Yoshinaga, Department of Japanese Oriental Medicine, Iizuka Hospital, 3-83 Yoshio-cho, Iizuka-shi, Fukuoka 820-8505, Japan.

Tel: +81-948-22-3800; Fax: +81-948-29-8075.

E-mail: ryoshinagah2@aih-net.com

Word count (excluding title page, abstract, references, figure and tables): 2,894

Abstract word count: 284

Tables/figures: 2 tables, 2 figures

ABSTRACT

Background: It is unknown whether the initial high-sensitivity C-reactive protein (hs-CRP) levels measured in an emergency department (ED) are associated with the prognosis of patients with cardiovascular disease (CVD).

Methods and Results: We retrospectively stratified the cases of 12,211 CVD patients aged ≥18 years into five groups according to hs-CRP levels (<3.0 mg/l, 3.1–5.4, 5.5–11.5, 11.6–33.2, ≥33.3 mg/L) who were followed up prospectively for their post-ED stay at Iizuka Hospital; 1,156 patients had died. The absolute risk (AR) of in-hospital mortality increased significantly with hs-CRP levels: 7.0, 9.6, 11.2, 12.3, and 19.9 AR for the above-described hs-CRP groups. The age- and sex-adjusted hazard ratio (HR) for total mortality was increased significantly in the three ≥5.5 mg/l groups compared to the <3.0 mg/l group (5.5–11.5 mg/l: HR=1.32, 95%CI=1.09–1.60, p=0.005; 11.6–33.2 mg/l: HR=1.38, 95%CI=1.14–1.65, p=0.001; and ≥33.3 mg/l: HR=2.15, 95%CI=1.84–2.51, p<0.001). Similar findings were observed for the CVD subtypes of acute myocardial infarction, heart failure, cerebral infarction, and intracerebral haemorrhage. This association remained unchanged even after adjustment for age, sex and WBC and withstood Bonferroni adjustment for multiple testing. When the causes of death were divided into primary CVD and non-CVD deaths, the association between initial hs-CRP levels and mortality remained significant, but the influence of hs-CRP levels was greater in non-CVD deaths than CVD deaths. The percentage of non-CVD deaths increased with hs-CRP levels; among the patients with hs-CRP levels ≥33.3 mg/l, non-CVD deaths accounted for 37.5% of total deaths.

Conclusion: Our findings suggest that increased hs-CRP is a significant risk factor for in-hospital mortality among CVD patients in an ED. Particular attention should be given to our finding that non-CVD death is a major cause of death among CVD patients with higher hs-CRP levels.

Key Words: High-sensitivity C-reactive protein, cardiovascular disease, emergency department

Strengths and limitations of this study

- The cases of 12,211 patients diagnosed with CVD at a single emergency department were retrospectively analysed.
- Increased CRP level was shown to be a significant risk factor for in-hospital mortality in CVD patients.
- The causes of death in the CVD patients were analysed: the influence of CRP level was much stronger in the non-CVD deaths than in CVD deaths.
- The limitations of this study were its retrospective and single-hospital design and the absence of confounders other than age, sex and WBC.

Introduction

Emergency department (ED) patients with cardiovascular disease (CVD) need a timely evaluation for the diagnosis of CVD and the identification of comorbidities. However, the evaluation of CVD patients transported by an ambulance is often difficult because these patients may have complex medical problems and are sometimes too ill to assist medical staff with important medical information such as time of symptom onset and their medical history. The identification of markers that are associated with in-hospital mortality would be useful in the triage of CVD patients in EDs around the world.

C-reactive protein (CRP) is an acute-phase protein produced by the liver, and the serum levels of this protein increase in response to tissue injury, infection, inflammation, and neoplastic proliferation. The measurement of serum CRP concentrations is inexpensive and is done routinely to assess patients. In addition, the serum hs-CRP level is known to be a predictive marker of the degree of atherosclerosis and future cardiovascular events. Several studies have also observed elevated CRP at the acute phase of CVD values in patients with acute myocardial infarction, ischaemic stroke and acute heart failure.[1–12]

However, there has been controversy over the usefulness of the measurement of CRP as a prognostic marker in ED evaluations. The objective of the present study was to examine the association between the initial hs-CRP levels and in-hospital mortality in patients with CVD and its subtypes, i.e., acute myocardial infarction, heart failure, cerebral infarction and intracerebral haemorrhage.

Patients and Methods

Study design, setting and population

This was a retrospective cohort study at Iizuka Hospital, a teaching hospital with 1,116 beds located at the centre of the Chikuho region of Fukuoka prefecture on Japan's Kyushu Island.

This hospital is the only critical care centre for a population of approximately 430,000 people, and over 8,000 cases are transported by emergency vehicle to the hospital each year, accounting for approximately 40% of the emergency-conveyance patients in the Chikuho region. Ethical approval of this study was obtained from the Ethics Committee of Iizuka Hospital (CRM-27015). The requirement of informed consent was waived by the Ethics Committee because of the retrospective nature of the study. In this study, the cases of 57,443 consecutive patients ≥18 years old who presented to Iizuka Hospital's ED by ambulance between 1 February 2006 and 30 September 2014 were evaluated. Among them, 391 patients had repeated ED visits on two consecutive days, and only the index case was used in order to comply with the assumption of independent observations.

Our review of the hospital's records indicated that, at the time of their ED visit, 2,317 patients had a history of cardiopulmonary arrest, and 298 were pregnant. All of these cases were excluded from the present study. Of the remaining 54,437 records, 12,830 patients were diagnosed with CVD at their ED visit. The hs-CRP level or white blood cell count (WBC) at baseline was not obtained for 619 (4.8%) patients. A final total of 12,211 patients with CVD were included in this study (Fig. 1). Among these patients, 1,156 deaths were recorded, giving an in-hospital mortality rate of 9.5% (confidence interval [CI]: 0.09–0.10).

Data collection and laboratory measurement

The following data were extracted from the medical records for each patient: age, gender, diagnosis in the ED, length of hospital stay (days) and outcome. The cause of death was extracted from the death certificate. Blood samples for initial hs-CRP and WBC were collected soon after the patient arrived at the ED as part of the clinical routine and were analysed immediately for every patient. Serum hs-CRP levels were measured with a latex

agglutination turbidimetric immunoassay (CRP-latex X2 Seiken, Denka Seiken, Tokyo). The hs-CRP measurement range was 0.2–320 mg/l, and the normal range is <3mg/l.

Diagnosis at the emergency department and definition of endpoints

The diagnoses at the ED and the causes of death were classified clinically using the International Classification of Diseases, Tenth Revision (ICD-10). CVD was defined as meeting the criteria in diagnosis codes I00–I99 of the ICD-10, and was divided into acute myocardial infarction (I21–I24), heart failure (I50), intracerebral haemorrhage (I61), cerebral infarction (I63), and "other" according to the ICD-10 classification.

Regarding the diagnosis of CVD at the ED, the emergency room doctors performed careful examinations and primary care. The physical examination, electrocardiograph, X-ray, ultrasonography and blood examination were performed immediately. A complete blood cell count and biochemical examination including pH, lactate, creatine kinase-MB, brain-natriuretic peptide, D-dimer and troponin assay were available as needed. Brain imaging data (computed tomography and/or magnetic resonance imaging) were also available if the patients had neurologic abnormalities or a decreased level of consciousness.

When a patient was suspected of having CVD, the ED doctors were able to contact a cardiologist, neurologist, cardiovascular surgeon, or neurosurgeon 24 hours a day, 365 days a year. Based on the examinations by specialists and the test results, the leading diagnosis of CVD complying with ICD-10 was established at the ED. During the study period, no structural changes such as patient uptake, patient flow, the evaluation at the ED and biomarker analysis occurred. The end point was death from any cause in the hospital. Patients who remained in the hospital on 30 November, 2014 were considered alive in this analysis. Patients who did not require hospitalization and were discharged from the ED were also considered alive, and their stay in the hospital was regarded as 1 day.

We divided the causes of death into two main categories using the ICD-10: CVD deaths and Non-CVD deaths. CVD death was defined as a death from a cause listed in ICD codes I00–I99, and Non-CVD death was defined as a death from a cause other than those listed in codes I00–I99. We classified the Non-CVD deaths into the following three subcategories: infection, neoplasm, and others. Infection-related deaths included deaths from septicaemia, bacteraemia, endocarditis, pulmonary infections (e.g., viral pneumonia, bacterial pneumonia, influenza with respiratory manifestations, abscess of lung or mediastinum), genitourinary infections (e.g., urinary tract infection, pyelonephritis, peri-nephric abscess), gastrointestinal infections (e.g., diverticulitis, *C. difficile* colitis, peri-rectal abscess), peritonitis, soft tissue infections (e.g., cellulitis, necrotizing fasciitis, gangrene), and joint or bone infections (e.g., infective arthritis, osteomyelitis). Neoplasm-related deaths included the deaths from codes C00–D48. Deaths from causes other than those listed above were classified as other deaths.

Statistical analysis

We divided the patients with hs-CRP levels >3.0 mg/l into quartiles. The patients with hs-CRP levels ≤3.0 mg/l were assigned to a separate category which served as the reference group, because the 3.0 mg/l cut-off point corresponds to the "high" CRP level in previous primary prevention studies.[13] We calculated the age- and sex-adjusted or multivariate-adjusted hazard ratios (HRs) for total death from CVD and its subtypes and their 95%CI values using the Cox proportional hazards model. The linear trends of HRs across hs-CRP levels were also tested using the Cox proportional hazards model. The Bonferroni method was used to address issues of multiple subgroup analyses. Bonferroni-corrected statistical significance was defined as $p<0.008 = (0.05/6)$ in the analysis of total death and

p<0.004 = (0.05/12) in the analysis of CVD deaths and Non-CVD deaths. All analyses were performed using the SAS software package ver. 9.4 (SAS Institute, Cary, NC).

Results

The age range of the patients was 18–104 yrs (median 76 yrs; interquartile range 64–84). Fifty-two per cent (6,355) were men; 48% (5,856) were women. The median baseline serum hs-CRP level was 1.8 mg/l (interquartile range 0.6–7.5 mg/l). The median number of hospital days including the date of the ED visit was 14 days (interquartile range 2–32 days).

Table 1 shows the in-hospital mortality and the age- and sex-adjusted and multivariate-adjusted HRs for the in-hospital mortality of CVD according to the patients' hs-CRP levels. A significant association was observed between hs-CRP levels and the absolute risk of in-hospital mortality in the total CVD group (p for trend <0.001). In regard to the subtypes of CVD, the in-hospital mortality of the patients with acute myocardial infarction, heart failure, cerebral infarction, and intracerebral haemorrhage was also significantly increased as the hs-CRP levels increased (p for trend <0.001)

The age- and sex-adjusted HRs for total in-hospital mortality in the patients with hs-CRP levels ≥5.5 mg/l were significantly higher compared to those in the patients with levels <3.0 mg/l (5.5–11.5 mg/l: HR = 1.32, 95%CI = 1.09–1.60, p = 0.005; 11.6–33.2 mg/l: HR = 1.38, 95%CI = 1.14–1.65, p = 0.001; and ≥33.3 mg/l: HR = 2.15, 95%CI = 1.84–2.51, p<0.001). In the same way, the age- and sex-adjusted HRs for the in-hospital mortality of the patients with acute myocardial infarction, heart failure, cerebral infarction, and intracerebral haemorrhage also increased with increasing hs-CRP levels, and were significantly higher in the patients with hs-CRP levels ≥33.3 mg/l compared to those with levels <3.0 mg/l.

In addition, when we determined the age- and sex-adjusted HRs for one increment in log-transformed hs-CRP concentrations, we observed significant upward trends for in-

hospital mortality for both total CVD and its subtypes. This association remained unchanged even after adjustment for age, sex and WBC and withstood Bonferroni adjustment for multiple testing.

As shown in Table 2, when divided the cases separately into CVD deaths and non-CVD deaths, the age- and sex-adjusted HRs of the cause-specific in-hospital deaths increased with increasing hs-CRP levels in both the subgroup of CVD deaths and that of non-CVD deaths (p for trend <0.001). In the patients with hs-CRP levels ≥33.3 mg/l, the age- and sex-adjusted HR for CVD death was 1.44 (95%CI 1.20–1.73, p<0.001) compared to that in the patients with hs-CRP <3.0 mg/l. The HR for non-CVD death, on the other hand, was 12.05 (95%CI 8.06–18.04, p<0.001) in this group. The relationship between the hs-CRP levels and non-CVD deaths was thus much stronger than that between the hs-CRP levels and CVD deaths. Regarding the subtypes of CVD, similar relationships were observed.

Figure 2 shows the proportions of the causes of death. The number of infection deaths showed a significant positive linear trend with the hs-CRP levels (χ^2 = 101.7, p<0.001). Similar associations were observed for neoplasms (χ^2 = 67.4, p<0.001) and the other causes group (χ^2 = 15.7, p=0.003). Among the deaths of patients with hs-CRP levels ≥33.3 mg/l, 37.5% were non-CVD deaths, namely 17.1% infection, 12.1% neoplasm, and 8.3% other causes.

Discussion

The results of this large retrospective cohort study at a local Japanese teaching hospital clearly demonstrated that the risk among CVD patients for in-hospital mortality increased significantly with increasing initial hs-CRP levels taken in the ED. As with total deaths, the risks for cause-specific in-hospital mortality from CVD death and non-CVD death also

increased significantly as the hs-CRP levels increased. The influence of hs-CRP levels on mortality was greater in the non-CVD deaths than in the CVD deaths.

These findings provide important information regarding critical care for patients with CVD. Prompt risk stratification is important in the management of CVD patients in an ED. Hs-CRP is a sensitive and nonspecific marker of systemic inflammation. A patient's initial hs-CRP level may prove to be a simple and readily available adjunct that could help the emergency care staff to identify CVD patients who may be at a high risk of death. Several studies have shown that elevated CRP levels at admission in CVD patients, including those with acute coronary syndrome, ischaemic stroke and acute heart failure, are associated with their mortality.[2,3,7,9,10] These results, together with ours, imply that CRP is a valuable biomarker for identifying CVD patients at high risk of total in-hospital death. In the present study, initial hs-CRP levels ≥5.5 mg/l were associated with greater mortality in CVD patients.

We also observed an association between hs-CRP levels and cause-specific in-hospital mortality from CVD death in this study. When the CVD cases were divided into subtypes of CVD, similar relationships were observed. The mechanisms underlying the association between hs-CRP levels and the risk of atherosclerotic CVD death are still unknown. However, there is a possibility that elevated levels of CRP reflect the extent of infarction and inflammation related to the pathobiology of ischaemic tissue damage.[4,6,14] In terms of heart failure, it is known that inflammatory markers such as tumor necrosis factor (TNF), interleukin (IL)-6, and CRP are elevated in patients with congestive heart failure and correlate with the degree of heart failure.[15–17] These findings and our present results raise the possibility that CRP levels are associated with the severity of cardiovascular diseases that are related to broad vascular damage.

Our present analyses also showed an association between hs-CRP levels and non-CVD deaths, and the influence of hs-CRP levels was much stronger in the non-CVD deaths than in

the CVD deaths. In addition, the proportion of non-CVD deaths increased with the increase in the hs-CRP level, and non-CVD deaths accounted for 37.5% of the total deaths among the patients with hs-CRP levels ≥33.3 mg/l. Hs-CRP can be elevated by underlying conditions other than CVD, such as infection, neoplasm and other diseases. In the present patient series, infection and neoplasm were major causes of non-CVD death. Generally, CVD is a common cause of death globally and has shown a relationship with CRP levels, but CRP is an extremely sensitive marker for many diagnoses — not just CVD. Therefore, the patients with CVD and elevated hs-CRP levels in the present study might have had comorbidities at the ED.

Concerning neoplasms, several studies have reported that CRP levels have prognostic value in a wide variety of operable and inoperable cancers.[18,19] In the present study, some CVD patients with elevated hs-CRP levels on admission might have had a poorer prognosis for cancer and an increased risk of death. Infections, pneumonia and urinary tract infections (UTIs) are the most common infectious complications of ischaemic stroke, and they are independently associated with stroke outcome.[20] Current guidelines for the early management of patients with acute ischaemic stroke recommend that patients with suspected pneumonia or UTIs should be treated promptly with appropriate antibiotics.[21] However, to date, there has been no specific recommendation for the treatment of infectious complications in other subtypes of CVD, such as acute myocardial infarction, heart failure and intracerebral haemorrhage.

In the present study, in addition to cerebral infarction, similar associations were observed between hs-CRP levels and non-CVD death in other subtypes of CVD. Similarly, a prospective cohort study demonstrated that, among patients with ischaemic stroke, elevated CRP levels on admission is a predictor of pneumonia and UTI within 5 days.[22] These findings imply that a search for infections and tailored treatment without delay may be indicated for all types of CVD patients with elevated hs-CRP levels.

There are several limitations of our study that must be acknowledged. The first limitation is that this was a retrospective cohort study at a single hospital. It is possible that our medical care may be different from that at other hospitals throughout the world. However, to maintain its standard of medical care, Iizuka Hospital has affiliations with overseas medical institutions: the University of Pittsburgh Medical Center, El Camino Hospital, and Virginia Mason Institute. In addition, our hospital has been designated a residency training hospital since 1989, and it is renowned in Japan as an educational hospital. We thus believe that standard medical care is provided at our hospital.

Secondly, in this study, the evaluation of hs-CRP values was based on a single measurement in the ED. Since the time to reach the peak hs-CRP level may differ according to the underlying diseases in individual patients, it is possible that the initial hs-CRP levels do not precisely reflect the pathological condition in each disease. This could have weakened the association found in this study, biasing the results toward the null hypothesis. Therefore, the true association may be stronger than that shown in our study.

Thirdly, confounders and covariates other than age, sex and WBC could not be adjusted in this study. It is not our intention to suggest that CRP can replace the clinical evaluation of individual patients with CVD. Rather, we simply report that, in a large cohort, the hs-CRP level was associated with in-hospital mortality. Ideally, our analysis would have assessed whether the hs-CRP measurement added prognostic information beyond commonly used risk assessment scoring systems such as the Acute Physiology and Chronic Health Evaluation (APACHE). Unfortunately, data such as haemodynamics and comorbidities could not be analysed in this study, so we elected instead to focus our analysis only on laboratory data that are routinely available. Further clinical and laboratory investigations are required to explain the association between mortality and the initial ED-measured hs-CRP level in patients with CVD.

Conclusion

The results of the present study clearly demonstrated the potential utility of hs-CRP measurement in the ED triage for patients with CVD as well as its subtypes, i.e., acute myocardial infarction, heart failure, cerebral infarction, and intracerebral haemorrhage. The assessment of hs-CRP at baseline even in CVD patients may improve the ability to identify patients at high risk of death from not only the primary CVD but also other systemic complications.

Author contributions

Conceptualization: R. Yoshinaga, Y. Doi, K. Ayukawa, S. Ishikawa. Methodology: R. Yoshinaga, Y. Doi, K. Ayukawa, S. Ishikawa. *Validation:* R. Yoshinaga, Y. Doi, K. Ayukawa, S. Ishikawa. *Formal analysis:* R. Yoshinaga, Y. Doi, S. Ishikawa. *Writing:* R. Yoshinaga, Y. Doi, K. Ayukawa, S. Ishikawa. *Visualization:* R. Yoshinaga, Y. Doi, K. Ayukawa. *Supervision:* Y. Doi, K. Ayukawa, S. Ishikawa.

Funding

This study received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

None declared.

Data sharing statement

No additional data are available.

References

1. Liuzzo G, Biasucci LM, Gallimore JR, et al. The prognostic value of C-reactive protein and serum amyloid a protein in severe unstable angina. N Engl J Med 1994;**331**(7):417-24.

2. Nikfardjam M, Mullner M, Schreiber W, et al. The association between C-reactive protein on admission and mortality in patients with acute myocardial infarction. J Intern Med 2000;**247**(3):341-5.

3. Chew DP, Bhatt DL, Robbins MA, et al. Incremental prognostic value of elevated baseline C-reactive protein among established markers of risk in percutaneous coronary intervention. Circulation 2001;**104**(9):992-7.

4. Di Napoli M, Papa F, Bocola V. C-reactive protein in ischemic stroke: an independent prognostic factor. Stroke 2001;**32**(4):917-24.

5. Audebert HJ, Rott MM, Eck T, et al. Systemic inflammatory response depends on initial stroke severity but is attenuated by successful thrombolysis. Stroke 2004;**35**(9):2128-33.

6. Keskin O, Ulusoy RE, Kalemoglu M, et al. White blood cell count and C-reactive protein predict short-term prognosis in acute myocardial infarction. J Int Med Res 2004;**32**(6):646-54.

7. Masotti L, Ceccarelli E, Forconi S, et al. Prognostic role of C-reactive protein in very old patients with acute ischaemic stroke. J Intern Med 2005;**258**(2):145-52.

8. Canale ML, Stroppa S, Caravelli P, et al. Admission C-reactive protein serum levels and survival in patients with acute myocardial infarction with persistent ST elevation. Coron Artery Dis 2006;**17**(8):693-8.

9. Elkind MS, Tai W, Coates K, et al. High-sensitivity C-reactive protein, lipoprotein-associated phospholipase A2, and outcome after ischemic stroke. Arch Intern Med 2006;**166**(19):2073-80.

10. Idicula TT, Brogger J, Naess H, et al. Admission C-reactive protein after acute ischemic stroke is associated with stroke severity and mortality: the 'Bergen stroke study'. BMC Neurol 2009;**9**:18.

11. Sheikh AS, Yahya S, Sheikh NS, et al. C-reactive Protein as a Predictor of Adverse outcome in Patients with Acute Coronary Syndrome. Heart Views 2012;**13**(1):7-12.

12. Park JJ, Choi DJ, Yoon CH, et al. Prognostic value of C-reactive protein as an inflammatory and N-terminal probrain natriuretic peptide as a neurohumoral marker in acute heart failure (from the Korean Heart Failure registry). Am J Cardiol 2014;**113**(3):511-7.

13. Buckley DI, Fu R, Freeman M, et al. C-reactive protein as a risk factor for coronary heart disease: a systematic review and meta-analyses for the U.S. Preventive Services Task Force. Ann Intern Med 2009;**151**(7):483-95.

14. Dirnagl U, Iadecola C, Moskowitz MA. Pathobiology of ischaemic stroke: an integrated view. Trends Neurosci 1999;**22**(9):391-7.

15. Tsutamoto T, Hisanaga T, Wada A, et al. Interleukin-6 spillover in the peripheral circulation increases with the severity of heart failure, and the high plasma level of interleukin-6 is an important prognostic predictor in patients with congestive heart failure. J Am Coll Cardiol 1998;**31**(2):391-8.

16. Vasan RS, Sullivan LM, Roubenoff R, et al. Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction: the Framingham Heart Study. Circulation 2003;**107**(11):1486-91.

17. Yin WH, Chen JW, Jen HL, et al. Independent prognostic value of elevated high-sensitivity C-reactive protein in chronic heart failure. Am Heart J 2004;**147**(5):931-8.

18. Roxburgh CS, McMillan DC. Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. Future Oncol 2010;**6**(1):149-63.

19. Clarke SJ, Chua W, Moore M, et al. Use of inflammatory markers to guide cancer treatment. Clin Pharmacol Ther 2011;**90**(3):475-8.

20. Aslanyan S, Weir CJ, Diener HC, et al. Pneumonia and urinary tract infection after acute ischaemic stroke: a tertiary analysis of the GAIN International trial. Eur J Neurol 2004;**11**(1):49-53.

21. Jauch EC, Saver JL, Adams HP, Jr., et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;**44**(3):870-947.

22. Fluri F, Morgenthaler NG, Mueller B, et al. Copeptin, procalcitonin and routine inflammatory markers-predictors of infection after stroke. PLoS One 2012;**7**(10):e48309.

Figure legends

Fig. 1. Flow diagram of the study.

Fig. 2. The proportions of causes of death to total deaths. The number of infection deaths showed a significant positive linear trend with CRP levels (χ^2 = 101.7, p<0.001). Similar associations were observed in neoplasms (χ^2 = 67.4, p<0.001) and other causes of death (χ^2 = 15.7, p=0.003). Among the deaths of patients with CRP levels ≥33.3 mg/l, 37.5% were caused by non-CVD death: 17.1% infection, 12.1% neoplasm and 8.3% other.

Table 1. No. of patients and deaths, in-hospital mortalities, and hazard ratios for total death of cardiovascular disease and its subtypes according to hs-CRP levels

Diagnosis at the emergency department	Total	hs-CRP levels (mg/l) <3.0	3.1–5.4	5.5–11.5	11.6–33.2	≥33.3	*p* for trend (across categories)	Continuous log scale	*p* for trend (continuous)
Cardiovascular disease									
No. of patients	12,211	7,375	1,212	1,200	1,216	1,208			
No. of deaths	1,156	517	116	134	149	240			
In-hospital mortality (%)	9.5	7.0	9.6	11.2	12.3	19.9	<0.001		
Age- and sex-adjusted HR (95%CI)		1 (ref.)	1.18 (0.97–1.45)	1.32† (1.09–1.60)	1.38† (1.14–1.65)	2.15† (1.84–2.51)	<0.001	1.15† (1.12–1.19)	<0.001
Multivariable-adjusted HR(95%CI)		1 (ref.)	1.15 (0.94–1.41)	1.29 (1.07–1.56)	1.33† (1.11–1.60)	2.00† (1.71–2.34)	<0.001	1.14† (1.10–1.18)	<0.001
Acute myocardial infarction									
No. of patients	1,347	796	145	126	125	155			
No. of deaths	89	28	4	12	9	36			
In-hospital mortality (%)	6.6	3.5	2.8	9.5	7.2	23.2	<0.001		
Age- and sex-adjusted HR (95%CI)		1 (ref.)	0.65 (0.23–1.86)	1.80 (0.91–3.57)	1.46 (0.68–3.13)	4.33† (2.60–7.22)	<0.001	1.37† (1.23–1.54)	<0.001
Multivariable-adjusted HR(95%CI)		1 (ref.)	0.62 (0.22–1.76)	1.64 (0.83–3.26)	1.14 (0.51–2.54)	3.44† (2.04–5.82)	<0.001	1.31† (1.16–1.47)	<0.001
Heart failure									
No. of patients	1,742	620	232	249	310	331			
No. of deaths	148	19	11	28	29	61			
In-hospital mortality (%)	8.5	3.1	4.7	11.2	9.4	18.4	<0.001		
Age- and sex-adjusted HR (95%CI)		1 (ref.)	1.27 (0.60–2.66)	2.29† (1.26–4.17)	1.99† (1.11–3.57)	3.55† (2.11–5.97)	<0.001	1.35† (1.22–1.51)	<0.001
Multivariable-adjusted HR(95%CI)		1 (ref.)	1.26 (0.60–2.64)	2.34† (1.28–4.26)	2.07† (1.15–3.72)	3.83† (2.26–6.49)	<0.001	1.39† (1.24–1.55)	<0.001
Cerebral infarction									
No. of patients	2,879	1,823	277	281	271	227			
No. of deaths	261	109	25	34	43	50			
In-hospital mortality (%)	9.1	6.0	9.0	12.1	15.9	22.0	<0.001		
Age- and sex-adjusted HR (95%CI)		1 (ref.)	1.15 (0.74–1.78)	1.73† (1.18–2.55)	2.04† (1.43–2.91)	3.02† (2.15–4.22)	<0.001	1.28† (1.19–1.37)	<0.001
Multivariable-adjusted HR(95%CI)		1 (ref.)	1.07 (0.69–1.66)	1.59 (1.08–2.34)	1.63 (1.12–2.36)	2.20† (1.53–3.17)	<0.001	1.20† (1.11–1.29)	<0.001
Intracerebral haemorrhage									
No. of patients	1,989	1428	167	153	137	104			
No. of deaths	338	201	39	32	29	37			
In-hospital mortality (%)	17.0	14.1	23.4	20.9	21.2	35.6	<0.001		
Age- and sex-adjusted HR (95%CI)		1 (ref.)	1.60 (1.14–2.26)	1.34 (0.92–1.95)	1.33 (0.90–1.97)	2.33† (1.64–3.32)	<0.001	1.14† (1.07–1.21)	<0.001

Multivariable-adjusted HR(95%CI)		1 (ref.)	1.56 (1.10–2.20)	1.32 (0.91–1.92)	1.29 (0.87–1.92)	2.05† (1.42–2.97)	<0.001	1.12† (1.05–1.19)	<0.001
Others									
No. of patients	4,254	2,708	391	391	373	391			
No. of deaths	320	160	37	28	39	56			
In-hospital mortality (%)	7.5	5.9	9.5	7.2	10.5	14.3	0.002		
Age- and sex-adjusted HR (95%CI)		1 (ref.)	1.41 (0.98–2.01)	0.95 (0.63–1.42)	1.28 (0.89–1.82)	1.43 (1.05 to 1.95)	0.032	1.08 (1.02–1.14)	0.009
Multivariable-adjusted HR(95%CI)		1 (ref.)	1.30 (0.91–1.86)	0.74 (0.48–1.14)	1.16 (0.85–1.61)	1.03 (1.02 to 1.04)	0.381	1.04 (0.98–1.10)	0.223

CI: confidence interval; HR: hazard ratio; hs-CRP: high-sensitivity C-reactive protein; WBC: white blood cell count.
Cardiovascular disease: International Statistical Classification of Diseases and related problems 10th revision (below ICD-10) Diseases of the circulatory system (I00–I99);
Acute myocardial infarction: ICD-10 (I21–I24); Heart failure: ICD-10 (I50); Cerebral infarction: ICD-10 (I63); Intracerebral haemorrhage: ICD-10 (I61).
Multivariable adjustment was made for age, sex, and WBC count.
†Statistically significant after applying a Bonferroni correction.

Table 2. No. of cause-specific deaths, hazard ratios for cause-specific death of cardiovascular disease and its subtypes according to hs-CRP levels

Diagnosis at the emergency department	Total	hs-CRP levels (mg/l) <3.0	3.1–5.4	5.5–11.5	11.6–33.2	≥33.3	*p* for trend (across categories)	Continuous log scale	*p* for trend (continuous)
Cardiovascular disease									
No. of patients	12,211	7,375	1,212	1,200	1,216	1,208			
No. of CVD deaths	976	484	106	116	120	150			
CVD-related		1	1.16	1.23	1.20	1.44†	<0.001	1.08†	<0.001
Age- and sex-adjusted HR (95%CI)		(ref.)	(0.94–1.43)	(1.00–1.51)	(0.98–1.46)	(1.20–1.73)		(1.03–1.11)	
CVD-related,		1	1.13	1.20	1.16	1.33†	0.002	1.05†	0.004
Multivariable-adjusted HR(95%CI)		(ref.)	(0.92–1.40)	(1.00–1.48)	(0.95–1.42)	(1.10–1.61)		(1.01–1.09)	
No. of non-CVD deaths	180	33	10	18	29	90			
Non-CVD-related		1	1.55	2.67†	3.84†	12.05†	<0.001	1.77†	<0.001
Age- and sex-adjusted HR (95%CI)		(ref.)	(0.76–3.15)	(1.50–4.75)	(2.32–6.35)	(8.05–18.04)		(1.63–1.93)	
Non-CVD-related,		1	1.52	2.61†	3.72†	11.49†	<0.001	1.75†	<0.001
Multivariable-adjusted HR(95%CI)		(ref.)	(0.75–3.09)	(1.47–4.65)	(2.25–6.16)	(7.66–17.23)		(1.61–1.91)	
Acute myocardial infarction									
No. of patients	1,347	796	145	126	125	155			
No. of CVD deaths	70	25	2	11	7	25			
CVD-related		1	0.37	1.93	1.31	3.51†	<0.001	1.30†	<0.001
Age- and sex-adjusted HR (95%CI)		(ref.)	(0.09–1.56)	(0.94–3.95)	(0.56–3.05)	(1.98–6.23)		(1.14–1.48)	
CVD-related,		1	0.35	1.74	1.01	2.71†	0.001	1.23†	0.002
Multivariable-adjusted HR(95%CI)		(ref.)	(0.08–1.47)	(0.85–3.58)	(0.41–2.47)	(1.50–4.90)		(1.08–1.40)	
No. of non-CVD deaths	19	3	2	1	2	11			
Non-CVD-related		1	2.82	1.21	2.59	10.14†	<0.001	1.73†	<0.001
Age- and sex-adjusted HR (95%CI)		(ref.)	(0.47–17.04)	(0.12–11.75)	(0.42–15.84)	(2.75–37.33)		(1.32–2.28)	
Non-CVD-related,		1	2.71	1.11	2.07	8.64†	0.001	1.67†	<0.001
Multivariable-adjusted HR(95%CI)		(ref.)	(0.45–16.45)	(0.11–10.81)	(0.31–13.72)	(2.32–32.27)		(1.27–2.21)	
Heart failure									
No. of patients	1,742	620	232	249	310	331			
No. of CVD deaths	98	15	10	21	19	33			
CVD-related		1	1.49	2.27	1.76	2.58†	0.004	1.23†	0.001
Age- and sex-adjusted HR (95%CI)		(ref.)	(0.67–3.33)	(1.14–4.51)	(0.88–3.48)	(1.39–4.79)		(1.09–1.39)	
CVD-related		1	1.49	2.29	1.78	2.66†	0.003	1.24†	0.001
Multivariable-adjusted HR(95%CI)		(ref.)	(0.67–3.32)	(1.15–4.56)	(0.90–3.54)	(1.42–4.97)		(1.09–1.41)	
No. of non-CVD deaths	50	4	1	7	10	28			

Age- and sex-adjusted HR (95%CI)		1 (ref.)	0.52 (0.06–4.68)	2.50 (0.72–8.74)	2.92 (0.91–9.42)	6.80† (2.36–19.57)	<0.001	1.69† (1.38–2.08)	<0.001
Non-CVD-related, Multivariable-adjusted HR(95%CI)		1 (ref.)	0.51 (0.06–4.57)	2.52 (0.72–8.80)	3.21 (0.99–10.33)	8.19† (2.82–23.80)	<0.001	1.84† (1.47–2.29)	<0.001
Cerebral infarction									
No. of patients	2,879	1,823	277	281	271	227			
No. of CVD deaths	230	103	22	33	38	34			
CVD-related		1	1.08	1.76	1.95†	2.13†	<0.001	1.21†	<0.001
Age- and sex-adjusted HR (95%CI)		(ref.)	(0.68–1.72)	(1.19–2.61)	(1.34–2.84)	(1.44–3.14)		(1.12–1.30)	
CVD-related		1	0.99	1.59	1.48	1.44	0.012	1.11	0.008
Multivariable-adjusted HR(95%CI)		(ref.)	(0.62–1.57)	(1.07–2.35)	(1.00–2.19)	(0.95–2.20)		(1.03–1.21)	
No. of non-CVD deaths	31	6	3	1	5	16			
Non-CVD-related		1	2.07	0.92	3.08	18.78†	<0.001	1.95†	<0.001
Age- and sex-adjusted HR (95%CI)		(ref.)	(0.51–8.41)	(0.11–7.63)	(0.91–10.49)	(7.27–48.51)		(1.57–2.41)	
Non-CVD-related		1	2.20	0.99	3.87	24.08†	<0.001	2.08†	<0.001
Multivariable-adjusted HR(95%CI)		(ref.)	(0.54–8.99)	(0.12–8.29)	(1.10–13.62)	(8.62–67.25)		(1.65–2.64)	
Intracerebral haemorrhage									
No. of patients	1,989	1,428	167	153	137	104			
No. of CVD deaths	313	196	37	29	28	23			
CVD-related		1	1.56	1.25	1.32	1.49	0.019	1.07	0.061
Age- and sex-adjusted HR (95%CI)		(ref.)	(1.10–2.22)	(0.84–1.84)	(0.88–1.97)	(0.96–2.30)		(1.00–1.14)	
CVD-related,		1	1.52	1.23	1.29	1.30	0.020	1.05	0.166
Multivariable-adjusted HR(95%CI)		(ref.)	(1.07–2.17)	(0.83–1.82)	(0.86–1.92)	(0.82–2.04)		(0.98–1.13)	
No. of non-CVD deaths	25	5	2	3	1	14			
Non-CVD-related		1	3.17	5.13	1.85	32.57†	<0.001	2.26†	<0.001
Age- and sex-adjusted HR (95%CI)		(ref.)	(0.62–16.37)	(1.22–21.58)	(0.21–16.09)	(11.41–92.97)		(1.78–2.86)	
Non-CVD-related		1	3.05	4.97	1.77	28.22†	<0.001	2.21†	<0.001
Multivariable-adjusted HR(95%CI)		(ref.)	(0.59–15.77)	(1.18–20.89)	(0.20–15.38)	(9.76–81.58)		(1.73–2.81)	
Others									
No. of patients	4,254	2,708	391	391	373	391			
No. of CVD deaths	265	145	35	22	28	35			
CVD-related		1	1.45	0.83	1.02	1.01	0.894	1.01	0.750
Age- and sex-adjusted HR (95%CI)		(ref.)	(1.00–2.11)	(0.53–1.30)	(0.67–1.54)	(0.67–1.54)		(0.95–1.08)	
CVD-related		1	1.32	0.57	0.77	1.03	0.119	0.96	0.212
Multivariable-adjusted HR(95%CI)		(ref.)	(0.91–1.91)	(0.35–0.93)	(0.53–1.14)	(1.02–1.04)		(0.90–1.03)	
No. of non-CVD deaths	55	15	2	6	11	21			

Non-CVD-related	1	0.86	2.08	3.62†	4.87†	<0.001	1.44†	<0.001
Age- and sex-adjusted HR (95%CI)	(ref.)	(0.20–3.76)	(0.80–5.40)	(1.63–8.05)	(2.47–9.61)		(1.25–1.65)	
Non-CVD-related	1	0.90	2.24	3.87†	5.30†	<0.001	1.47†	<0.001
Multivariable-adjusted HR(95%CI)	(ref.)	(0.21–3.93)	(0.86–5.85)	(1.73–8.64)	(2.66–10.54)		(1.28–1.69)	

hs-CRP: high-sensitivity C-reactive protein; HR: Age- and sex-adjusted hazard ratio; CI: confidence interval.

Cardiovascular disease: International Statistical Classification of Diseases and related problems 10th revision (below ICD-10) Diseases of the circulatory system (I00-I99); Acute myocardial infarction: ICD-10 (I21–I24); Heart failure: ICD-10 (I50); Cerebral infarction:ICD-10 (I63); Intracerebral haemorrhage: ICD-10 (I61).

Multivariable adjustment was made for age, sex, and WBC count.

†Statistically significant after applying a Bonferroni correction.

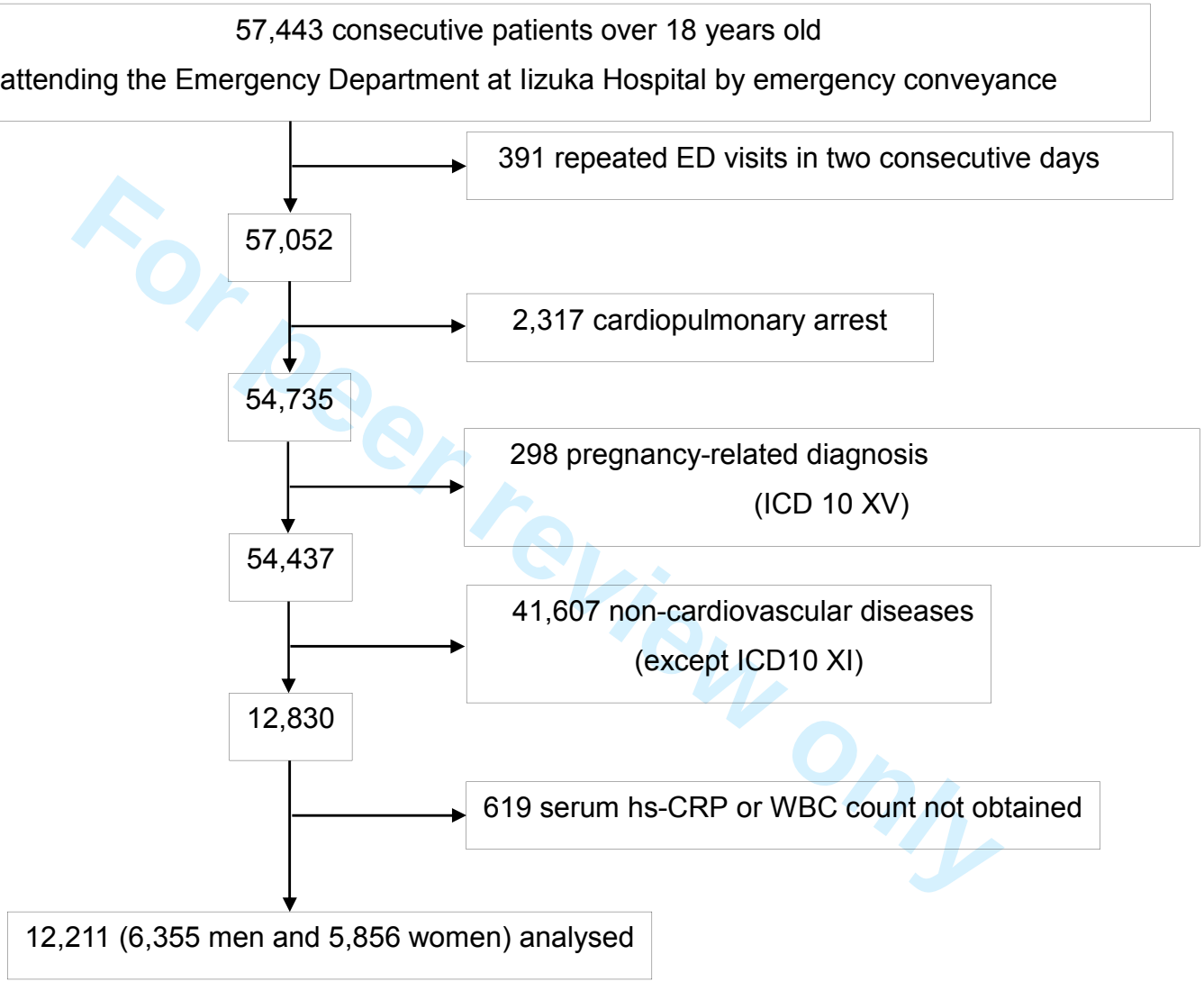
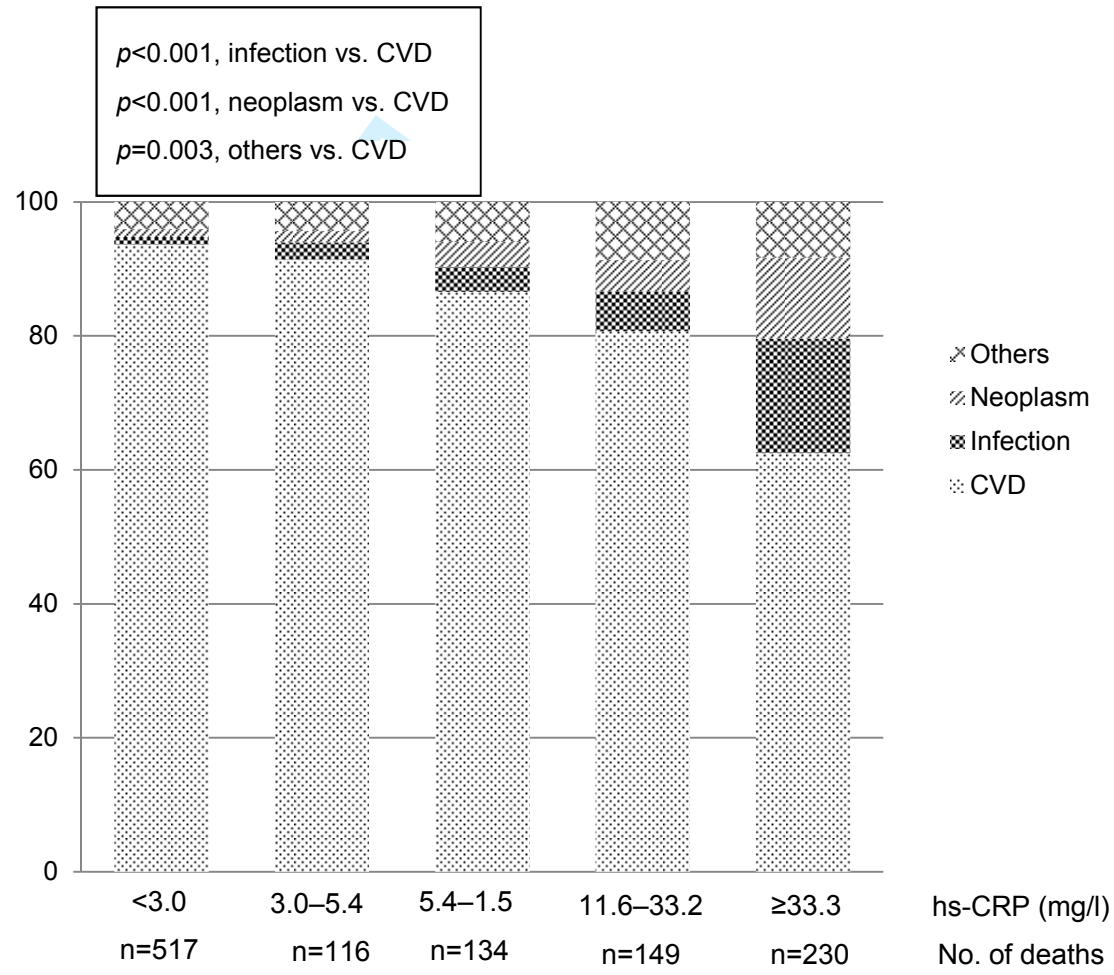


Figure 1

Figure 2



STROBE Statement—checklist of items that should be included in reports of observational studies

Item No	Page No
1(a)	1
1(b)	2
2	4
3	4
4	4,5,6,7
5	4,5,6,7
6(a)	4,5,6,7
6(b)	4,5,6,7
7	6
8	5,6
9	4,5
10	5
11	6
12(a,b,c,d,e)	7,8
13(a,b,c)	8,9
14(a,b,c)	8,9
15	8
16(a,b,c)	8,9
17	8,9
18	9,10
19	12
20	9,10,11,12
21	9,10,11,12
22	13

BMJ Open

High-sensitivity C-Reactive Protein as a Predictor of In-hospital Mortality in Cardiovascular Disease Patients at an Emergency Department: a retrospective cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-015112.R1
Article Type:	Research
Date Submitted by the Author:	22-Jun-2017
Complete List of Authors:	Yoshinaga, Ryo; Iizuka Byoin Doi, Yasufumi; Iizuka Byoin, Personnel Ayukawa, Katsuhiko; Iizuka Byoin, Emergency Department Ishikawa, Shizukiyo; Jichi Ika Daigaku, Department of General Medicine
Primary Subject Heading:	Emergency medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Myocardial infarction < CARDIOLOGY, Heart failure < CARDIOLOGY, Cerebral infarction, intracerebral haemorrhage, C-reactive protein

Research Article

High-sensitivity C-Reactive Protein as a Predictor of In-hospital Mortality in Cardiovascular Disease Patients at an Emergency Department : a retrospective cohort study

Ryo Yoshinaga, MD[1], Yasufumi Doi, MD, PhD[2],
Katsuhiko Ayukawa, MD[3] and Shizukiyo Ishikawa, MD, PhD[4]

Departments of [1]Japanese Oriental Medicine, [2]Personnel, and [3]Emergency Department, Iizuka Hospital, Iizuka, Japan

[4]Department of General Medicine, Jichi Medical University School of Medicine, Shimotsuke, Japan

Running headline: High-sensitivity CRP and cardiovascular disease

Corresponding author: Dr. Ryo Yoshinaga, Department of Japanese Oriental Medicine, Iizuka Hospital, 3-83 Yoshio-cho, Iizuka-shi, Fukuoka 820-8505, Japan.
Tel: +81-948-22-3800; Fax: +81-948-29-8075.
E-mail: ryoshinagah2@aih-net.com

Word count (excluding title page, abstract, strengths and limitations, references, figure and tables): 3,356

Abstract word count: 328

Tables/figures: 3 tables, 2 figures

ABSTRACT

Objective: We investigated whether serum high-sensitivity C-reactive protein (hs-CRP) levels measured in an emergency department (ED) are associated with in-hospital mortality in patients with cardiovascular disease (CVD).

Design: A retrospective cohort study

Setting: ED of a teaching hospital in Japan

Participants: 12,211 CVD patients aged ≥18 years who presented to the ED by ambulance between 1 February 2006 and 30 September 2014 were evaluated.

Main outcome measures: In-hospital mortality

Results: 1,156 patients had died. The absolute risk (AR) of in-hospital mortality increased significantly with the hs-CRP levels (<3.0 mg/l: AR=7.0, 95%CI=6.4–7.6; 3.1–5.4 mg/l: AR=9.6, 95%CI=7.9–11.3: 5.5–11.5 mg/l: AR=11.2, 95%CI=9.4–13.0; 11.6–33.2 mg/l: AR=12.3, 95%CI=10.5–14.1; and ≥33.3 mg/l: AR=19.9, 95%CI=17.6–22.2). The age- and sex-adjusted hazard ratio (HR) for total mortality was increased significantly in the three ≥5.5 mg/l groups compared to the <3.0 mg/l group (5.5–11.5 mg/l: HR=1.32, 95%CI=1.09–1.60, p=0.005; 11.6–33.2 mg/l: HR=1.38, 95%CI=1.14–1.65, p=0.001; and ≥33.3 mg/l: HR=2.15, 95%CI=1.84–2.51, p<0.001). Similar findings were observed for the CVD subtypes of acute myocardial infarction, heart failure, cerebral infarction, and intracerebral haemorrhage. This association remained unchanged even after adjustment for age, sex and WBC and withstood Bonferroni adjustment for multiple testing. When the causes of death were divided into primary CVD and Non-CVD deaths, the association between initial hs-CRP levels and mortality remained significant, but the influence of hs-CRP levels was greater in Non-CVD deaths than CVD deaths. The percentage of Non-CVD deaths increased with hs-CRP levels; among the patients with hs-CRP levels ≥33.3 mg/l, Non-CVD deaths accounted for 37.5% of total deaths.

Conclusion: Our findings suggest that increased hs-CRP is a significant risk factor for in-hospital mortality among CVD patients in an ED. Particular attention should be given to our finding that Non-CVD death is a major cause of death among CVD patients with higher hs-CRP levels.

Key Words: High-sensitivity C-reactive protein, cardiovascular disease, emergency department

Strengths and limitations of this study

The strengths of our study include its large-scale retrospective cohort design with the examination of 12,211 patients diagnosed with CVD, the measurement of hs-CRP at baseline, and the search for cause-specific mortality.

The limitations of our study are (1) the single-center nature of the study (i.e., one teaching hospital) and (2) the confounders such as haemodynamics, comorbidities and other laboratory data could not be investigated.

Introduction

Emergency department (ED) patients with cardiovascular disease (CVD) need a timely evaluation for the diagnosis of CVD and the identification of comorbidities. However, the evaluation of CVD patients transported by an ambulance is often difficult because these patients may have complex medical problems and are sometimes too ill to assist medical staff with important medical information such as time of symptom onset and their medical history. The identification of markers that are associated with in-hospital mortality would be useful in the triage of CVD patients in EDs around the world.

C-reactive protein (CRP) is an acute-phase protein produced by the liver, and the serum levels of this protein increase in response to tissue injury, infection, inflammation, and neoplastic proliferation. The measurement of serum CRP concentrations is inexpensive and is done routinely to assess patients. In addition, the serum hs-CRP level is known to be a predictive marker of the degree of atherosclerosis and future cardiovascular events. [1-4] Several studies have also observed that elevated CRP predicts the prognosis of CVD patients at the acute stage. [5-16]

However, there has been controversy over the usefulness of the measurement of CRP as a prognostic marker in ED evaluations in Japan. The objective of the present study was to examine the association between the initial hs-CRP levels and in-hospital mortality in patients with CVD and its subtypes, i.e., acute myocardial infarction, heart failure, cerebral infarction and intracerebral haemorrhage.

Patients and Methods

Study design, setting and population

This was a retrospective cohort study at Iizuka Hospital, a teaching hospital with 1,116 beds located at the centre of the Chikuho region of Fukuoka prefecture on Japan's Kyushu

Island. This hospital is the only critical care centre for a population of approximately 430,000 people, and over 8,000 cases are transported by emergency vehicle to the hospital each year, accounting for approximately 40% of the emergency-conveyance patients in the Chikuho region. Ethical approval of this study was obtained from the Ethics Committee of Iizuka Hospital (CRM-27015). The requirement of informed consent was waived by the Ethics Committee because of the retrospective nature of the study.

At our hospital, the cases and records of patients who come to the ED are filed separately and are distinguished from those of the general out-patients. In the present study, the patients were recruited from among the ED files, and we evaluated the cases of 57,443 consecutive patients ≥18 years old who presented to Iizuka Hospital's ED by ambulance between February 1, 2006 and September 30, 2014. Among them, 391 patients had repeated ED visits on two consecutive days, and only the index case was used, in order to comply with the assumption of independent observations. At the ED, the leading diagnoses were established clinically using the International Classification of Diseases, Tenth Revision (ICD-10). We reviewed the Hospital's records and the cases and excluded the 2,317 patients who experienced cardiopulmonary arrest and the 298 patients who were pregnant.

Of the remaining 54,437 records, 12,830 patients were diagnosed with CVD, which was defined as meeting the criteria in diagnosis codes I00–I99 of the ICD-10 at their ED visit. The 619 (4.8%) patients whose hs-CRP level or white blood cell count (WBC) at baseline was not obtained were excluded. A final total of 12,211 patients with CVD were included in this study (Fig. 1). We divided the diagnoses with CVD into acute myocardial infarction (I21–I24), heart failure (I50), intracerebral haemorrhage (I61), cerebral infarction (I63), and "other" according to the ICD-10 classification.

Regarding the diagnoses of CVD at the ED, the emergency department physicians performed careful examinations and primary care. The physical examination,

electrocardiograph, X-ray, ultrasonography and blood examination were performed immediately. A complete blood cell count and biochemical examination including pH, lactate, creatine kinase-MB, brain-natriuretic peptide, D-dimer and troponin assay were available as needed. Brain imaging data (computed tomography and/or magnetic resonance imaging) were also available for patients with neurologic abnormalities or a decreased level of consciousness. When a patient was suspected of having CVD, the ED physicians were able to contact a cardiologist, neurologist, cardiovascular surgeon, or neurosurgeon 24 hours a day, 365 days a year. Based on the examinations by specialists and the test results, the leading diagnosis of CVD complying with ICD-10 was established at the ED. During the study period, no structural changes such as patient uptake, patient flow, the evaluation at the ED and the biomarker analysis occurred.

Data collection and laboratory measurement

The following data were extracted from the medical records for each patient: age, gender, diagnosis in the ED, length of hospital stay (days) and outcome. The cause of death was extracted from the death certificate. Blood samples for initial hs-CRP and WBC were collected soon after the patient arrived at the ED as part of the clinical routine and were analysed immediately for every patient. Serum hs-CRP levels were measured with a latex agglutination turbidimetric immunoassay (CRP-latex X2 Seiken, Denka Seiken, Tokyo). The hs-CRP measurement range was 0.2–320 mg/l, and the normal range is <3mg/l.

Definition of endpoints

The endpoints were mortality from any cause during hospitalization. Patients who remained in the hospital on 30 November, 2014 were considered alive in this analysis. Patients who did not require hospitalization and were discharged from the ED were also considered alive, and their stay in the hospital was regarded as 1 day. We divided the causes

of death into two main categories using the ICD-10: CVD deaths and non-CVD deaths. CVD death was defined as a death from a cause listed in ICD codes I00–I99, and Non-CVD death was defined as a death from a cause other than those listed in codes I00–I99. We classified the Non-CVD deaths into the following three subcategories: infection, neoplasm, and others. Infection-related deaths included deaths from septicaemia, bacteraemia, endocarditis, pulmonary infections (e.g., viral pneumonia, bacterial pneumonia, influenza with respiratory manifestations, abscess of lung or mediastinum), genitourinary infections (e.g., urinary tract infection, pyelonephritis, peri-nephric abscess), gastrointestinal infections (e.g., diverticulitis, *C. difficile* colitis, peri-rectal abscess), peritonitis, soft tissue infections (e.g., cellulitis, necrotizing fasciitis, gangrene), and joint or bone infections (e.g., infective arthritis, osteomyelitis). Neoplasm-related deaths included the deaths from codes C00–D48. Deaths from causes other than those listed above were classified as other deaths.

Statistical analysis

We divided the patients with hs-CRP levels >3.0 mg/l into quartiles. The patients with hs-CRP levels ≤3.0 mg/l were assigned to a separate category which served as the reference group, because the 3.0 mg/l cut-off point corresponds to the "high" CRP level in previous primary prevention studies. [17]. We calculated the age- and sex-adjusted or age-, sex-, and WBC-adjusted hazard ratios (HRs) for total death from CVD and its subtypes and their 95%CI values using the Cox proportional hazards model. The linear trends of HRs across hs-CRP levels were also tested using the Cox proportional hazards model. The Bonferroni method was used to address issues of multiple subgroup analyses. Bonferroni-corrected statistical significance was defined as $p<0.008 = (0.05/6)$ in the analysis of total death and $p<0.004 = (0.05/12)$ in the analysis of CVD deaths and Non-CVD deaths. For the distribution plot of hs-CRP levels in the surviving patients, CVD-death and Non-CVD death groups, we

examined hs-CRP values in each group by performing an analysis of variance (ANOVA). Because the distribution of hs-CRP values was skewed, the hs-CRP levels were natural log-transformed for the statistical analyses. All analyses were performed using the SAS software package ver. 9.4 (SAS Institute, Cary, NC).

Results

The age range of the patients was 18–104 yrs (median 76 yrs; interquartile range 64–84). Fifty-two per cent (6,355) were men; 48% (5,856) were women. The median baseline serum hs-CRP level was 1.8 mg/l (interquartile range 0.6–7.5 mg/l). The median number of hospital days including the date of the ED visit was 14 days (interquartile range 2–32 days). Among these patients, 1,156 deaths were recorded, giving an in-hospital mortality rate of 9.5% (confidence interval [CI]: 0.09–0.10).

Table 1 shows the in-hospital mortality and the age- and sex-adjusted and age-, sex-, and WBC-adjusted HRs for the in-hospital mortality of CVD according to the patients' hs-CRP levels. A significant association was observed between hs-CRP levels and the absolute risk of in-hospital mortality in the total CVD group (p for trend <0.001). In regard to the subtypes of CVD, the in-hospital mortality of the patients with acute myocardial infarction, heart failure, cerebral infarction, and intracerebral haemorrhage was also significantly increased as the hs-CRP levels increased (p for trend <0.001)

The age- and sex-adjusted HRs for total in-hospital mortality in the patients with hs-CRP levels ≥5.5 mg/l were significantly higher compared to those in the patients with levels <3.0 mg/l (5.5–11.5 mg/l: HR = 1.32, 95%CI = 1.09–1.60, p = 0.005; 11.6–33.2 mg/l: HR = 1.38, 95%CI = 1.14–1.65, p = 0.001; and ≥33.3 mg/l: HR = 2.15, 95%CI = 1.84–2.51, p<0.001). In the same way, the age- and sex-adjusted HRs for the in-hospital mortality of the patients with acute myocardial infarction, heart failure, cerebral infarction, and intracerebral

haemorrhage also increased with increasing hs-CRP levels, and were significantly higher in the patients with hs-CRP levels ≥33.3 mg/l compared to those with levels <3.0 mg/l.

In addition, when we determined the age- and sex-adjusted HRs for one increment in log-transformed hs-CRP concentrations, we observed significant upward trends for in-hospital mortality for both total CVD and its subtypes. This association remained unchanged even after adjustment for age, sex and WBC and withstood Bonferroni adjustment for multiple testing.

As shown in Table 2, when divided the cases separately into CVD deaths and Non-CVD deaths, the age- and sex-adjusted HRs of the cause-specific in-hospital deaths increased with increasing hs-CRP levels in both the subgroup of CVD deaths and that of Non-CVD deaths (p for trend <0.001). In the patients with hs-CRP levels ≥33.3 mg/l, the age- and sex-adjusted HR for CVD death was 1.44 (95%CI 1.20–1.73, p<0.001) compared to that in the patients with hs-CRP <3.0 mg/l. The HR for Non-CVD death, on the other hand, was 12.05 (95%CI 8.06–18.04, p<0.001) in this group. The relationship between the hs-CRP levels and Non-CVD deaths was thus much stronger than that between the hs-CRP levels and CVD deaths. Regarding the subtypes of CVD, similar relationships were observed.

Figure 2 shows a box plot of the distribution of hs-CRP levels in the surviving patients and the CVD-death and Non-CVD death groups. There were significant differences in the hs-CRP levels among the three groups (p<0.001, respectively). The association was unchanged even after Bonferroni adjustment. The median hs-CRP value was 1.7 mg/l in the surviving group, 3.1 mg/l in the CVD death group, and 32.1 mg/l in the Non-CVD death group. Table 3 shows number of total death, CVD death, Non-CVD death and its subtypes and according to hs-CRP levels. The proportions of Non-CVD death increased with hs-CRP levels: 6.4%, 8.6%, 13.5%, 19.3%, and 37.5% for the above-described hs-CRP groups. Among the deaths of patients with hs-CRP levels ≥33.3 mg/l, 17.1% deaths were caused by infection, 12.1%

deaths were caused by neoplasm, and 8.3% deaths were caused by other causes. The number of infection deaths showed a significant positive linear trend with the hs-CRP levels ($\chi^2 = 101.7$, $p<0.001$). Similar associations were observed for neoplasms ($\chi^2 = 67.4$, $p<0.001$) and the other causes group ($\chi^2 = 15.7$, $p=0.003$).

Discussion

The results of this large retrospective cohort study at a local Japanese teaching hospital clearly demonstrated that the risk among CVD patients for in-hospital mortality increased significantly with increasing initial hs-CRP levels taken in the ED. As with total deaths, the risks for cause-specific in-hospital mortality from CVD death and Non-CVD death also increased significantly as the hs-CRP levels increased. The influence of hs-CRP levels on mortality was greater in the Non-CVD deaths than in the CVD deaths.

These findings provide important information regarding critical care for patients with CVD. Prompt risk stratification is important in the management of CVD patients in an ED. Hs-CRP is a sensitive and nonspecific marker of systemic inflammation. A patient's initial hs-CRP level may prove to be a simple and readily available adjunct that could help the emergency care staff to identify CVD patients who may be at a high risk of death. Several studies have shown that elevated CRP levels at admission in CVD patients, including those with acute coronary syndrome, ischaemic stroke and acute heart failure, are associated with their mortality. [6 7 11 13 14] In addition, several studies have examined the utility of hs-CRP for predicting all-cause mortality in different settings. [18-20] These results, together with ours, imply that CRP is a valuable biomarker for identifying CVD patients at high risk of total in-hospital death. Although hs-CRP levels are much lower in Japanese populations compared to Western populations, [21] our present findings confirmed the utility of measuring the initial hs-

CRP in ED settings in Japan. In the present study, initial hs-CRP levels ≥5.5 mg/l were associated with greater mortality in CVD patients. In addition, the addition of the WBC in the adjustment did not substantially change the HRs in this study. This might be caused by the presence of leukopenia, i.e., a low WBC count. Although both the WBC count and CRP are used as inflammatory biomarkers, patients with leukopenia as the result of a severe inflammatory response or immune suppression might have poorer prognoses.

We also observed an association between hs-CRP levels and cause-specific in-hospital mortality from CVD death in this study. When the CVD cases were divided into subtypes of CVD, similar relationships were observed. The mechanisms underlying the association between hs-CRP levels and the risk of atherosclerotic CVD death are still unknown. However, there is a possibility that elevated levels of CRP reflect the extent of infarction and inflammation related to the pathobiology of ischaemic tissue damage. [8 10 22] In terms of heart failure, it is known that inflammatory markers such as tumor necrosis factor (TNF), interleukin (IL)-6, and CRP are elevated in patients with congestive heart failure and correlate with the degree of heart failure. [23-25] These findings and our present results raise the possibility that CRP levels are associated with the severity of cardiovascular diseases that are related to broad vascular damage. An evaluation of inflammatory risk in CVD patients should thus be routinely performed to identify high-risk patients in need of additional close monitoring. Although the results of the present study suggested that hs-CRP was a strong predictor of cardiovascular mortality, and several studies have indicated the value of determining the CRP level in CVD patients, CRP itself is be unlikely to provide an effective target for intervention and is known to be a downstream surrogate inflammatory marker. Moving upstream in the inflammatory cascade from CRP to IL-6 and IL-1 might provide novel therapeutic opportunities to reduce the cardiovascular event rate. [26] The results of

ongoing clinical trials of inflammation inhibition (such as those of the phase II trial data on canakinumab, a human monoclonal antibody that targets IL-1β [27]) are worthy of attention.

Our present analyses also showed an association between hs-CRP levels and Non-CVD deaths, and the influence of hs-CRP levels was much stronger in the Non-CVD deaths than in the CVD deaths. In addition, the proportion of Non-CVD deaths increased with the increase in the hs-CRP level. Although the actual number of non-CVD deaths was not very large, non-CVD deaths accounted for 37.5% of the total deaths among the patients with hs-CRP levels ≥33.3 mg/l. In addition, the median hs-CRP value was the highest in the Non-CVD death group, 32.1 mg/l. Hs-CRP can be elevated by underlying conditions other than CVD, such as infection, neoplasm and other diseases. In the present patient series, infection and neoplasm were major causes of Non-CVD death. However, a non-CVD death cause might be regarded as a misclassification or a complication of a well-classified CVD. Generally, CVD is a common cause of death globally and has shown a relationship with CRP levels, but CRP is an extremely sensitive marker for many diagnoses — not just CVD. Therefore, the patients with CVD and elevated hs-CRP levels in the present study might have had comorbidities at the ED.

Concerning neoplasms, several studies have reported that CRP levels have prognostic value in a wide variety of operable and inoperable cancers. [28-30] In the present study, some CVD patients with elevated hs-CRP levels on admission might have had a poorer prognosis for cancer and an increased risk of death. Infections, pneumonia and urinary tract infections (UTIs) are the most common infectious complications of ischaemic stroke, and they are independently associated with stroke outcome [31]. Current guidelines for the early management of patients with acute ischaemic stroke recommend that patients with suspected pneumonia or UTIs should be treated promptly with appropriate antibiotics. [32] However, to date, there has been no specific recommendation for the treatment of infectious complications

in other subtypes of CVD, such as acute myocardial infarction, heart failure and intracerebral haemorrhage.

In the present study, in addition to cerebral infarction, similar associations were observed between hs-CRP levels and Non-CVD death in other subtypes of CVD. Similarly, a prospective cohort study demonstrated that, among patients with ischaemic stroke, elevated CRP levels on admission is a predictor of pneumonia and UTI within 5 days. [33] These findings imply that a search for infections and tailored treatment without delay may be indicated for all types of CVD patients with elevated hs-CRP levels.

There are several limitations of our study that must be acknowledged. The first limitation is that this was a retrospective cohort study at a single hospital. It is possible that our medical care may be different from that at other hospitals throughout the world. However, to maintain its standard of medical care, Iizuka Hospital has affiliations with overseas medical institutions: the University of Pittsburgh Medical Center, El Camino Hospital, and Virginia Mason Institute. In addition, our hospital has been designated a residency training hospital since 1989, and it is renowned in Japan as an educational hospital. We thus believe that standard medical care is provided at our hospital.

Secondly, in this study, the evaluation of hs-CRP values was based on a single measurement in the ED. Since the time to reach the peak hs-CRP level may differ according to the underlying diseases in individual patients, it is possible that the initial hs-CRP levels do not precisely reflect the pathological condition in each disease. This could have weakened the association found in this study, biasing the results toward the null hypothesis. Therefore, the true association may be stronger than that shown in our study.

Thirdly, confounders and covariates other than age, sex and WBC could not be adjusted in this study. It is not our intention to suggest that CRP can replace the clinical evaluation of individual patients with CVD. Rather, we simply report that, in a large cohort,

the hs-CRP level was associated with in-hospital mortality. Ideally, our analysis would have assessed whether the hs-CRP measurement added prognostic information beyond commonly used risk assessment scoring systems such as the Acute Physiology and Chronic Health Evaluation (APACHE). Unfortunately, data such as haemodynamics and comorbidities could not be analysed in this study, so we elected instead to focus our analysis only on laboratory data that are routinely available. Further clinical and laboratory investigations are required to explain the association between mortality and the initial ED-measured hs-CRP level in patients with CVD.

Conclusion

The results of the present study clearly demonstrated the potential utility of hs-CRP measurement in the ED triage for patients with CVD as well as its subtypes, i.e., acute myocardial infarction, heart failure, cerebral infarction, and intracerebral haemorrhage. The assessment of hs-CRP at baseline even in CVD patients may improve the ability to identify patients at high risk of death from not only the primary CVD but also other systemic complications.

Author contributions

Conceptualization: R. Yoshinaga, Y. Doi, K. Ayukawa, S. Ishikawa. Methodology: R. Yoshinaga, Y. Doi, K. Ayukawa, S. Ishikawa. *Validation:* R. Yoshinaga, Y. Doi, K. Ayukawa, S. Ishikawa. *Formal analysis:* R. Yoshinaga, Y. Doi, S. Ishikawa. *Writing:* R. Yoshinaga, Y. Doi, K. Ayukawa, S. Ishikawa. *Visualization:* R. Yoshinaga, Y. Doi, K. Ayukawa. *Supervision:* Y. Doi, K. Ayukawa, S. Ishikawa.

Competing interests

None declared.

Data sharing statement

No additional data are available.

References

1. Ridker PM, Cushman M, Stampfer MJ, et al. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997;**336**(14):973-9.

2. Lindahl B, Toss H, Siegbahn A, et al. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. N Engl J Med 2000;**343**(16):1139-47.

3. Boekholdt SM, Hack CE, Sandhu MS, et al. C-reactive protein levels and coronary artery disease incidence and mortality in apparently healthy men and women: the EPIC-Norfolk prospective population study 1993-2003. Atherosclerosis 2006;**187**(2):415-22.

4. Sabatine MS, Morrow DA, Jablonski KA, et al. Prognostic significance of the Centers for Disease Control/American Heart Association high-sensitivity C-reactive protein cut points for cardiovascular and other outcomes in patients with stable coronary artery disease. Circulation 2007;**115**(12):1528-36.

5. Liuzzo G, Biasucci LM, Gallimore JR, et al. The prognostic value of C-reactive protein and serum amyloid a protein in severe unstable angina. N Engl J Med 1994;**331**(7):417-24.

6. Nikfardjam M, Mullner M, Schreiber W, et al. The association between C-reactive protein on admission and mortality in patients with acute myocardial infarction. J Intern Med 2000;**247**(3):341-5.

7. Chew DP, Bhatt DL, Robbins MA, et al. Incremental prognostic value of elevated baseline C-reactive protein among established markers of risk in percutaneous coronary intervention. Circulation 2001;**104**(9):992-7.

8. Di Napoli M, Papa F, Bocola V. C-reactive protein in ischemic stroke: an independent prognostic factor. Stroke 2001;**32**(4):917-24.

9. Audebert HJ, Rott MM, Eck T, et al. Systemic inflammatory response depends on initial stroke severity but is attenuated by successful thrombolysis. Stroke 2004;**35**(9):2128-33.

10. Keskin O, Ulusoy RE, Kalemoglu M, et al. White blood cell count and C-reactive protein predict short-term prognosis in acute myocardial infarction. J Int Med Res 2004;**32**(6):646-54.

11. Masotti L, Ceccarelli E, Forconi S, et al. Prognostic role of C-reactive protein in very old patients with acute ischaemic stroke. J Intern Med 2005;**258**(2):145-52.

12. Canale ML, Stroppa S, Caravelli P, et al. Admission C-reactive protein serum levels and survival in patients with acute myocardial infarction with persistent ST elevation. Coron Artery Dis 2006;**17**(8):693-8.

13. Elkind MS, Tai W, Coates K, et al. High-sensitivity C-reactive protein, lipoprotein-associated phospholipase A2, and outcome after ischemic stroke. Arch Intern Med 2006;**166**(19):2073-80.

14. Idicula TT, Brogger J, Naess H, et al. Admission C-reactive protein after acute ischemic stroke is associated with stroke severity and mortality: the 'Bergen stroke study'. BMC Neurol 2009;**9**:18.

15. Sheikh AS, Yahya S, Sheikh NS, et al. C-reactive Protein as a Predictor of Adverse outcome in Patients with Acute Coronary Syndrome. Heart Views 2012;**13**(1):7-12.

16. Park JJ, Choi DJ, Yoon CH, et al. Prognostic value of C-reactive protein as an inflammatory and N-terminal probrain natriuretic peptide as a neurohumoral marker in acute heart failure (from the Korean Heart Failure registry). Am J Cardiol 2014;**113**(3):511-7.

17. Buckley DI, Fu R, Freeman M, et al. C-reactive protein as a risk factor for coronary heart disease: a systematic review and meta-analyses for the U.S. Preventive Services Task Force. Ann Intern Med 2009;**151**(7):483-95.

18. Koenig W, Khuseyinova N, Baumert J, et al. Prospective study of high-sensitivity C-reactive protein as a determinant of mortality: results from the MONICA/KORA Augsburg Cohort Study, 1984-1998. Clin Chem 2008;**54**(2):335-42.

19. Marsik C, Kazemi-Shirazi L, Schickbauer T, et al. C-reactive protein and all-cause mortality in a large hospital-based cohort. Clin Chem 2008;**54**(2):343-9.

20. Ridker PM. High-sensitivity C-reactive protein as a predictor of all-cause mortality: implications for research and patient care. Clin Chem 2008;**54**(2):234-7.

21. Emerging Risk Factors C, Kaptoge S, Di Angelantonio E, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet 2010;**375**(9709):132-40.

22. Dirnagl U, Iadecola C, Moskowitz MA. Pathobiology of ischaemic stroke: an integrated view. Trends Neurosci 1999;**22**(9):391-7.

23. Tsutamoto T, Hisanaga T, Wada A, et al. Interleukin-6 spillover in the peripheral circulation increases with the severity of heart failure, and the high plasma level of interleukin-6 is an important prognostic predictor in patients with congestive heart failure. J Am Coll Cardiol 1998;**31**(2):391-8.

24. Vasan RS, Sullivan LM, Roubenoff R, et al. Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction: the Framingham Heart Study. Circulation 2003;**107**(11):1486-91.

25. Yin WH, Chen JW, Jen HL, et al. Independent prognostic value of elevated high-sensitivity C-reactive protein in chronic heart failure. Am Heart J 2004;**147**(5):931-8.

26. Ridker PM. From C-Reactive Protein to Interleukin-6 to Interleukin-1: Moving Upstream To Identify Novel Targets for Atheroprotection. Circ Res 2016;**118**(1):145-56.

27. Ridker PM, Howard CP, Walter V, et al. Effects of interleukin-1beta inhibition with canakinumab on hemoglobin A1c, lipids, C-reactive protein, interleukin-6, and fibrinogen: a phase IIb randomized, placebo-controlled trial. Circulation 2012;**126**(23):2739-48.

28. Heikkila K, Ebrahim S, Lawlor DA. A systematic review of the association between circulating concentrations of C reactive protein and cancer. J Epidemiol Community Health 2007;**61**(9):824-33.

29. Roxburgh CS, McMillan DC. Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. Future Oncol 2010;**6**(1):149-63.

30. Clarke SJ, Chua W, Moore M, et al. Use of inflammatory markers to guide cancer treatment. Clin Pharmacol Ther 2011;**90**(3):475-8.

31. Aslanyan S, Weir CJ, Diener HC, et al. Pneumonia and urinary tract infection after acute ischaemic stroke: a tertiary analysis of the GAIN International trial. Eur J Neurol 2004;**11**(1):49-53.

32. Jauch EC, Saver JL, Adams HP, Jr., et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;**44**(3):870-947.

33. Fluri F, Morgenthaler NG, Mueller B, et al. Copeptin, procalcitonin and routine inflammatory markers-predictors of infection after stroke. PLoS One 2012;**7**(10):e48309.

Figure legends

Fig. 1. Flow diagram of the study.

In this study, the cases of 57,443 consecutive patients ≥18 years old who presented to Iizuka Hospital's emergency department by ambulance between 1 February 2006 and 30 September 2014 were evaluated. Excluded from the study were 391 patients had repeated emergency department visits on two consecutive days; 2,317 patients had a history of cardiopulmonary arrest; and 298 were pregnant. Of the remaining 54,437 records, 12,830 patients were diagnosed with cardiovascular disease (CVD). 619 (4.8%) patients whose high sensitivity C-reactive protein level or white blood cell count at baseline was not obtained were excluded. A final total of 12,211 patients with CVD were included in this study

Fig. 2.

Figure 2 shows a box plot of the distribution of hs-CRP levels in the surviving patients and the CVD-death and Non-CVD death groups. There were significant differences in the hs-CRP levels among the three groups ($p<0.001$, respectively). The association was unchanged even after Bonferroni adjustment. The median hs-CRP value was 1.7 mg/l in the surviving group, 3.1 mg/l in the CVD death group, and 32.1 mg/l in the Non-CVD death group.

Table 1. No. of patients and deaths, in-hospital mortalities, and hazard ratios for total death of cardiovascular disease and its subtypes according to hs-CRP levels

Diagnosis at the emergency department	Total	hs-CRP levels (mg/l) <3.0	3.1–5.4	5.5–11.5	11.6–33.2	≥33.3	*p* for trend (across categories)	Continuous log scale	*p* for trend (continuous)
Cardiovascular disease									
No. of patients	12,211	7,375	1,212	1,200	1,216	1,208			
No. of deaths	1,156	517	116	134	149	240			
In-hospital mortality (%)	9.5	7.0	9.6	11.2	12.3	19.9	<0.001		
Age- and sex-adjusted HR (95%CI)		1 (ref.)	1.18 (0.97–1.45)	1.32† (1.09–1.60)	1.38† (1.14–1.65)	2.15† (1.84–2.51)	<0.001	1.15† (1.12–1.19)	<0.001
Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	1.15 (0.94–1.41)	1.29 (1.07–1.56)	1.33† (1.11–1.60)	2.00† (1.71–2.34)	<0.001	1.14† (1.10–1.18)	<0.001
Acute myocardial infarction									
No. of patients	1,347	796	145	126	125	155			
No. of deaths	89	28	4	12	9	36			
In-hospital mortality (%)	6.6	3.5	2.8	9.5	7.2	23.2	<0.001		
Age- and sex-adjusted HR (95%CI)		1 (ref.)	0.65 (0.23–1.86)	1.80 (0.91–3.57)	1.46 (0.68–3.13)	4.33† (2.60–7.22)	<0.001	1.37† (1.23–1.54)	<0.001
Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	0.62 (0.22–1.76)	1.64 (0.83–3.26)	1.14 (0.51–2.54)	3.44† (2.04–5.82)	<0.001	1.31† (1.16–1.47)	<0.001
Heart failure									
No. of patients	1,742	620	232	249	310	331			
No. of deaths	148	19	11	28	29	61			
In-hospital mortality (%)	8.5	3.1	4.7	11.2	9.4	18.4	<0.001		
Age- and sex-adjusted HR (95%CI)		1 (ref.)	1.27 (0.60–2.66)	2.29† (1.26–4.17)	1.99† (1.11–3.57)	3.55† (2.11–5.97)	<0.001	1.35† (1.22–1.51)	<0.001
Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	1.26 (0.60–2.64)	2.34† (1.28–4.26)	2.07† (1.15–3.72)	3.83† (2.26–6.49)	<0.001	1.39† (1.24–1.55)	<0.001
Cerebral infarction									
No. of patients	2,879	1,823	277	281	271	227			
No. of deaths	261	109	25	34	43	50			
In-hospital mortality (%)	9.1	6.0	9.0	12.1	15.9	22.0	<0.001		
Age- and sex-adjusted HR (95%CI)		1 (ref.)	1.15 (0.74–1.78)	1.73† (1.18–2.55)	2.04† (1.43–2.91)	3.02† (2.15–4.22)	<0.001	1.28† (1.19–1.37)	<0.001
Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	1.07 (0.69–1.66)	1.59 (1.08–2.34)	1.63 (1.12–2.36)	2.20† (1.53–3.17)	<0.001	1.20† (1.11–1.29)	<0.001
Intracerebral haemorrhage									

No. of patients	1,989	1428	167	153	137	104			
No. of deaths	338	201	39	32	29	37			
In-hospital mortality (%)	17.0	14.1	23.4	20.9	21.2	35.6	<0.001		
Age- and sex-adjusted HR (95%CI)		1 (ref.)	1.60 (1.14–2.26)	1.34 (0.92–1.95)	1.33 (0.90–1.97)	2.33† (1.64–3.32)	<0.001	1.14† (1.07–1.21)	<0.001
Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	1.56 (1.10–2.20)	1.32 (0.91–1.92)	1.29 (0.87–1.92)	2.05† (1.42–2.97)	<0.001	1.12† (1.05–1.19)	<0.001
Others									
No. of patients	4,254	2,708	391	391	373	391			
No. of deaths	320	160	37	28	39	56			
In-hospital mortality (%)	7.5	5.9	9.5	7.2	10.5	14.3	0.002		
Age- and sex-adjusted HR (95%CI)		1 (ref.)	1.41 (0.98–2.01)	0.95 (0.63–1.42)	1.28 (0.89–1.82)	1.43 (1.05 to 1.95)	0.032	1.08 (1.02–1.14)	0.009
Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	1.30 (0.91–1.86)	0.74 (0.48–1.14)	1.16 (0.85–1.61)	1.03 (1.02 –1.04)	0.381	1.04 (0.98–1.10)	0.223

CI: confidence interval; HR: hazard ratio; hs-CRP: high-sensitivity C-reactive protein; WBC: white blood cell count.
Cardiovascular disease: International Statistical Classification of Diseases and related problems 10th revision (below ICD-10) Diseases of the circulatory system (I00–I99);
Acute myocardial infarction: ICD-10 (I21–I24); Heart failure: ICD-10 (I50); Cerebral infarction: ICD-10 (I63); Intracerebral haemorrhage: ICD-10 (I61).
†Statistically significant after applying a Bonferroni correction.

Table 2. No. of cause-specific deaths, hazard ratios for cause-specific death of cardiovascular disease and its subtypes according to hs-CRP levels

Diagnosis at the emergency department	Total	hs-CRP levels (mg/l)					*p* for trend (across categories)	Continuous log scale	*p* for trend (continuous)
		<3.0	3.1–5.4	5.5–11.5	11.6–33.2	≥33.3			
Cardiovascular disease									
No. of patients	12,211	7,375	1,212	1,200	1,216	1,208			
No. of CVD deaths	976	484	106	116	120	150			
CVD-related		1	1.16	1.23	1.20	1.44†	<0.001	1.08†	<0.001
Age- and sex-adjusted HR (95%CI)		(ref.)	(0.94–1.43)	(1.00–1.51)	(0.98–1.46)	(1.20–1.73)		(1.03–1.11)	
CVD-related, Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	1.13 (0.92–1.40)	1.20 (1.00–1.48)	1.16 (0.95–1.42)	1.33† (1.10–1.61)	0.002	1.05† (1.01–1.09)	0.004
No. of Non-CVD deaths	180	33	10	18	29	90			
Non-CVD-related		1	1.55	2.67†	3.84†	12.05†	<0.001	1.77†	<0.001
Age- and sex-adjusted HR (95%CI)		(ref.)	(0.76–3.15)	(1.50–4.75)	(2.32–6.35)	(8.05–18.04)		(1.63–1.93)	
Non-CVD-related, Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	1.52 (0.75–3.09)	2.61† (1.47–4.65)	3.72† (2.25–6.16)	11.49† (7.66–17.23)	<0.001	1.75† (1.61–1.91)	<0.001
Acute myocardial infarction									
No. of patients	1,347	796	145	126	125	155			
No. of CVD deaths	70	25	2	11	7	25			
CVD-related		1	0.37	1.93	1.31	3.51†	<0.001	1.30†	<0.001
Age- and sex-adjusted HR (95%CI)		(ref.)	(0.09–1.56)	(0.94–3.95)	(0.56–3.05)	(1.98–6.23)		(1.14–1.48)	
CVD-related, Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	0.35 (0.08–1.47)	1.74 (0.85–3.58)	1.01 (0.41–2.47)	2.71† (1.50–4.90)	0.001	1.23† (1.08–1.40)	0.002
No. of Non-CVD deaths	19	3	2	1	2	11			
Non-CVD-related		1	2.82	1.21	2.59	10.14†	<0.001	1.73†	<0.001
Age- and sex-adjusted HR (95%CI)		(ref.)	(0.47–17.04)	(0.12–11.75)	(0.42–15.84)	(2.75–37.33)		(1.32–2.28)	
Non-CVD-related, Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	2.71 (0.45–16.45)	1.11 (0.11–10.81)	2.07 (0.31–13.72)	8.64† (2.32–32.27)	0.001	1.67† (1.27–2.21)	<0.001
Heart failure									
No. of patients	1,742	620	232	249	310	331			
No. of CVD deaths	98	15	10	21	19	33			

CVD-related Age- and sex-adjusted HR (95%CI)		1 (ref.)	1.49 (0.67–3.33)	2.27 (1.14–4.51)	1.76 (0.88–3.48)	2.58† (1.39–4.79)	0.004	1.23† (1.09–1.39)	0.001
CVD-related Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	1.49 (0.67–3.32)	2.29 (1.15–4.56)	1.78 (0.90–3.54)	2.66† (1.42–4.97)	0.003	1.24† (1.09–1.41)	0.001
No. of Non-CVD deaths	50	4	1	7	10	28			
Age- and sex-adjusted HR (95%CI)		1 (ref.)	0.52 (0.06–4.68)	2.50 (0.72–8.74)	2.92 (0.91–9.42)	6.80† (2.36–19.57)	<0.001	1.69† (1.38–2.08)	<0.001
Non-CVD-related, Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	0.51 (0.06–4.57)	2.52 (0.72–8.80)	3.21 (0.99–10.33)	8.19† (2.82–23.80)	<0.001	1.84† (1.47–2.29)	<0.001
Cerebral infarction									
No. of patients	2,879	1,823	277	281	271	227			
No. of CVD deaths	230	103	22	33	38	34			
CVD-related Age- and sex-adjusted HR (95%CI)		1 (ref.)	1.08 (0.68–1.72)	1.76 (1.19–2.61)	1.95† (1.34–2.84)	2.13† (1.44–3.14)	<0.001	1.21† (1.12–1.30)	<0.001
CVD-related Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	0.99 (0.62–1.57)	1.59 (1.07–2.35)	1.48 (1.00–2.19)	1.44 (0.95–2.20)	0.012	1.11 (1.03–1.21)	0.008
No. of Non-CVD deaths	31	6	3	1	5	16			
Non-CVD-related Age- and sex-adjusted HR (95%CI)		1 (ref.)	2.07 (0.51–8.41)	0.92 (0.11–7.63)	3.08 (0.91–10.49)	18.78† (7.27–48.51)	<0.001	1.95† (1.57–2.41)	<0.001
Non-CVD-related Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	2.20 (0.54–8.99)	0.99 (0.12–8.29)	3.87 (1.10–13.62)	24.08† (8.62–67.25)	<0.001	2.08† (1.65–2.64)	<0.001
Intracerebral haemorrhage									
No. of patients	1,989	1,428	167	153	137	104			
No. of CVD deaths	313	196	37	29	28	23			
CVD-related Age- and sex-adjusted HR (95%CI)		1 (ref.)	1.56 (1.10–2.22)	1.25 (0.84–1.84)	1.32 (0.88–1.97)	1.49 (0.96–2.30)	0.019	1.07 (1.00–1.14)	0.061
CVD-related, Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	1.52 (1.07–2.17)	1.23 (0.83–1.82)	1.29 (0.86–1.92)	1.30 (0.82–2.04)	0.020	1.05 (0.98–1.13)	0.166
No. of Non-CVD deaths	25	5	2	3	1	14			
Non-CVD-related Age- and sex-adjusted HR (95%CI)		1 (ref.)	3.17 (0.62–16.37)	5.13 (1.22–21.58)	1.85 (0.21–16.09)	32.57† (11.41–92.97)	<0.001	2.26† (1.78–2.86)	<0.001

Non-CVD-related Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	3.05 (0.59–15.77)	4.97 (1.18–20.89)	1.77 (0.20–15.38)	28.22† (9.76–81.58)	<0.001	2.21† (1.73–2.81)	<0.001
Others									
No. of patients	4,254	2,708	391	391	373	391			
No. of CVD deaths	265	145	35	22	28	35			
CVD-related Age- and sex-adjusted HR (95%CI)		1 (ref.)	1.45 (1.00–2.11)	0.83 (0.53–1.30)	1.02 (0.67–1.54)	1.01 (0.67–1.54)	0.894	1.01 (0.95–1.08)	0.750
CVD-related Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	1.32 (0.91–1.91)	0.57 (0.35–0.93)	0.77 (0.53–1.14)	1.03 (1.02–1.04)	0.119	0.96 (0.90–1.03)	0.212
No. of Non-CVD deaths	55	15	2	6	11	21			
Non-CVD-related Age- and sex-adjusted HR (95%CI)		1 (ref.)	0.86 (0.20–3.76)	2.08 (0.80–5.40)	3.62† (1.63–8.05)	4.87† (2.47–9.61)	<0.001	1.44† (1.25–1.65)	<0.001
Non-CVD-related Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	0.90 (0.21–3.93)	2.24 (0.86–5.85)	3.87† (1.73–8.64)	5.30† (2.66–10.54)	<0.001	1.47† (1.28–1.69)	<0.001

hs-CRP: high-sensitivity C-reactive protein; WBC: white blood cell count;CI: confidence interval.
CVD: Cardiovascular disease: International Statistical Classification of Diseases and related problems 10th revision (below ICD-10) Diseases of the circulatory system (I00-I99); Acute myocardial infarction: ICD-10 (I21–I24); Heart failure: ICD-10 (I50); Cerebral infarction:ICD-10 (I63); Intracerebral haemorrhage: ICD-10 (I61).
†Statistically significant after applying a Bonferroni correction.

Table 3. No. of total death, CVD death, Non-CVD death and its subtypes according to hs-CRP levels

Cause of death	Total	hs-CRP levels (mg/l)					χ^2-test	*p value*
		<3.0	3.1–5.4	5.5–11.5	11.6–33.2	≥33.3		
No. of total deaths	1156	517	116	134	149	240		
No. of CVD deaths n (%)	976 (84.4)	484 (93.6)	106 (91.4)	116 (86.6)	120 (80.5)	150 (62.5)		
No. of Non-CVD deaths n (%)	180 (15.6)	33 (6.8)	10 (8.6)	18 (13.4)	29 (19.5)	90 (37.5)	127.9	<0.001
No. of infection deaths n (%)	64 (5.5)	6 (1.2)	3 (2.6)	5 (3.7)	9 (6.0)	41(17.1)	101.7	<0.001
No. of neoplasm deaths n (%)	49 (4.2)	6 (1.2)	2 (1.7)	5 (3.7)	7 (4.7)	29 (12.1)	67.4	<0.001
No. of other deaths n (%)	67 (5.8)	21 (4.1)	5 (4.3)	8 (5.9)	13 (8.7)	20 (8.3)	15.7	0.003

hs-CRP: high-sensitivity C-reactive protein; Infection deaths: deaths from septicemia, bacteremia, endocarditis, pulmonary infections (e.g., viral pneumonia, bacterial pneumonia, influenza with respiratory manifestations, abscess of lung or mediastinum), genitourinary infections (e.g., urinary tract infection, pyelonephritis, peri-nephric abscess), gastrointestinal infections (e.g., diverticulitis, *C. difficile* colitis, peri-rectal abscess), peritonitis, soft tissue infections (e.g., cellulitis, necrotizing fasciitis, gangrene), and joint or bone infections (e.g., infective arthritis, osteomyelitis). Neoplasm deaths: deaths from International Statistical Classification of Diseases and related problems 10th revision C00–D48. Other deaths; deaths from other than the causes listed above.

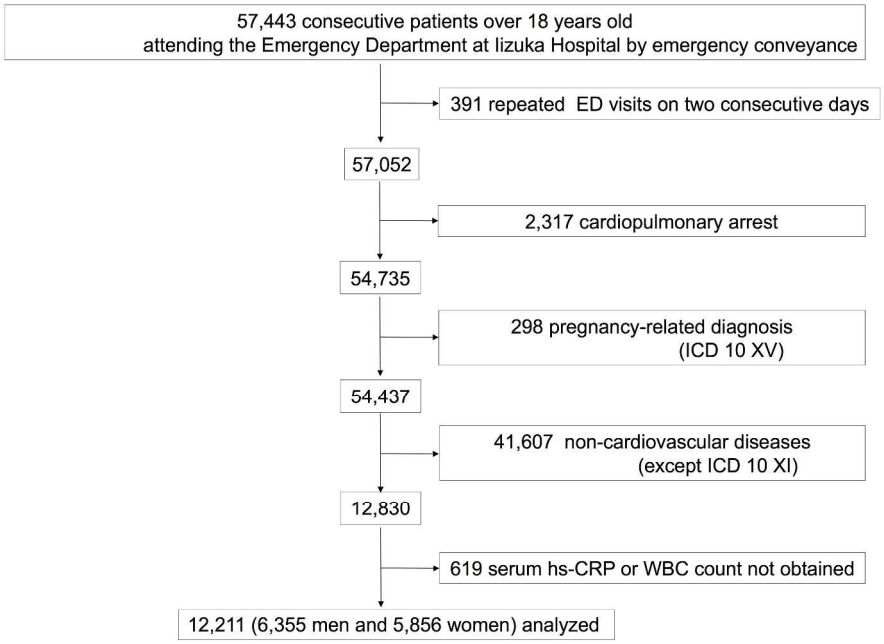


Figure 1

355x266mm (300 x 300 DPI)

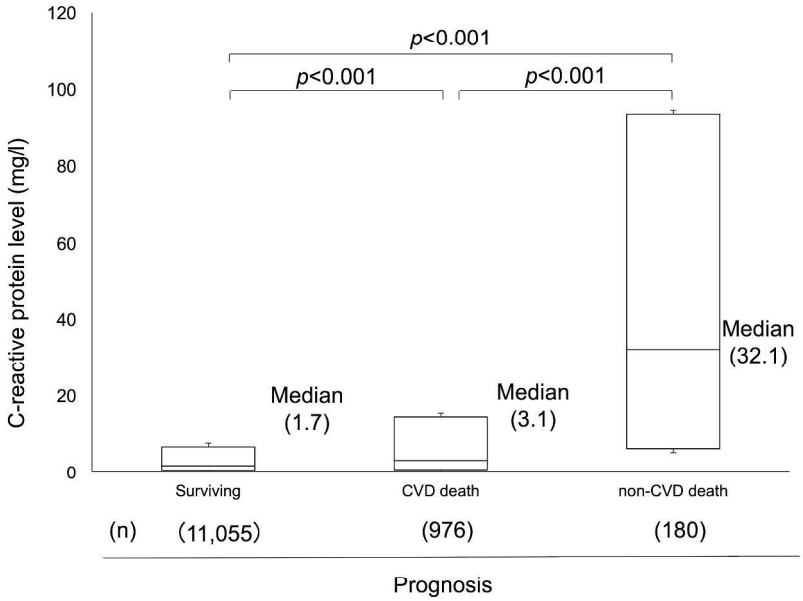


Figure 2

355x266mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (Page No. 1)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (Page No. 2)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (Page No. 4)
Objectives	3	State specific objectives, including any prespecified hypotheses (Page No. 4)
Methods		
Study design	4	Present key elements of study design early in the paper (Page No. 4)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (Page No. 4,5,6)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (Page No. 4,5,6,7) *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed (Page No. 4,5,6,7) *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (Page No. 4,5,6,7)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (Page No. 6,7,8)
Bias	9	Describe any efforts to address potential sources of bias (Page No. 4,5,6,7)
Study size	10	Explain how the study size was arrived at (Page No. 5)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (Page No. 4,5,6,7)

Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (Page No. 7,8)
		(*b*) Describe any methods used to examine subgroups and interactions (Page No. 7,8)
		(*c*) Explain how missing data were addressed (Page No. 7,8)
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed Not applicable *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses (Page No. 7,8)

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (Page No. 4,5,6)
		(b) Give reasons for non-participation at each stage (Page No. 8,9)
		(c) Consider use of a flow diagram Fig1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (Page No.5,6,7, 8,9)
		(b) Indicate number of participants with missing data for each variable of interest Not applicable
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) (Page No. 8,9)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time (Page No. 8,9,10)
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (Page No. 8,9,10) , table1, table2
		(*b*) Report category boundaries when continuous variables were categorized (Page No. 8,9,10) , table1, table2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period (Page No. 8,9,10)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (Page No. 9,10),table3, Fig2
Discussion		
Key results	18	Summarise key results with reference to study objectives (Page No. 10)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (Page No. 13,14)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (Page No. 10,11,12,13)
Generalisability	21	Discuss the generalisability (external validity) of the study results (Page No. 10,11)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable,

for the original study on which the present article is based
(Page No. 14,15)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

High-sensitivity C-Reactive Protein as a Predictor of In-hospital Mortality in Cardiovascular Disease Patients at an Emergency Department: a retrospective cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-015112.R2
Article Type:	Research
Date Submitted by the Author:	23-Aug-2017
Complete List of Authors:	Yoshinaga, Ryo; Iizuka Byoin Doi, Yasufumi; Iizuka Byoin, Personnel Ayukawa, Katsuhiko; Iizuka Byoin, Emergency Department Ishikawa, Shizukiyo; Jichi Ika Daigaku, Department of General Medicine
Primary Subject Heading:	Emergency medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Myocardial infarction < CARDIOLOGY, Heart failure < CARDIOLOGY, Cerebral infarction, intracerebral haemorrhage, C-reactive protein

Research Article

High-sensitivity C-Reactive Protein as a Predictor of In-hospital Mortality in Cardiovascular Disease Patients at an Emergency Department : a retrospective cohort study

Ryo Yoshinaga, MD[1], Yasufumi Doi, MD, PhD[2],
Katsuhiko Ayukawa, MD[3] and Shizukiyo Ishikawa, MD, PhD[4]

Departments of [1]Japanese Oriental Medicine, [2]Personnel, and [3]Emergency Department, Iizuka Hospital, Iizuka, Japan

[4]Department of General Medicine, Jichi Medical University School of Medicine, Shimotsuke, Japan

Running headline: High-sensitivity CRP and cardiovascular disease

Corresponding author: Dr. Ryo Yoshinaga, Department of Japanese Oriental Medicine, Iizuka Hospital, 3-83 Yoshio-cho, Iizuka-shi, Fukuoka 820-8505, Japan.
Tel: +81-948-22-3800; Fax: +81-948-29-8075.
E-mail: ryoshinagah2@aih-net.com

Word count (excluding title page, abstract, strengths and limitations, references, figure and tables): 3,346

Abstract word count: 262

Tables/figures: 3 tables, 2 figures

ABSTRACT

Objective: We investigated whether serum high-sensitivity C-reactive protein (hs-CRP) levels measured in an emergency department (ED) are associated with in-hospital mortality in patients with cardiovascular disease (CVD).

Design: A retrospective cohort study

Setting: ED of a teaching hospital in Japan

Participants: 12,211 CVD patients aged ≥18 years who presented to the ED by ambulance between 1 February 2006 and 30 September 2014 were evaluated.

Main outcome measures: In-hospital mortality

Results: 1,156 patients had died. The in-hospital mortality increased significantly with the hs-CRP levels (<3.0 mg/l: 7.0%, 95%CI=6.4–7.6; 3.1–5.4 mg/l: 9.6%, 95%CI=7.9–11.3: 5.5–11.5 mg/l: 11.2%, 95%CI=9.4–13.0; 11.6–33.2 mg/l: 12.3%, 95%CI=10.5–14.1; and ≥33.3 mg/l: 19.9, 95%CI=17.6–22.2). The age- and sex-adjusted hazard ratio (HR) for total mortality was increased significantly in the three ≥5.5 mg/l groups compared to the <3.0 mg/l group (5.5–11.5 mg/l: HR=1.32, 95%CI=1.09–1.60, p=0.005; 11.6–33.2 mg/l: HR=1.38, 95%CI=1.14–1.65, p=0.001; and ≥33.3 mg/l: HR=2.15, 95%CI=1.84–2.51, p<0.001). Similar findings were observed for the CVD subtypes of acute myocardial infarction, heart failure, cerebral infarction, and intracerebral haemorrhage. This association remained unchanged even after adjustment for age, sex and white blood cell count (WBC) and withstood Bonferroni adjustment for multiple testing. When the causes of death were divided into primary CVD and Non-CVD deaths, the association between initial hs-CRP levels and mortality remained significant, but the influence of hs-CRP levels was greater in Non-CVD deaths than CVD deaths. The percentage of Non-CVD deaths increased with hs-CRP levels; among the patients with hs-CRP levels ≥33.3 mg/l, Non-CVD deaths accounted for 37.5% of total deaths.

Conclusion: Our findings suggest that increased hs-CRP is a significant risk factor for in-hospital mortality among CVD patients in an ED. Particular attention should be given to our finding that Non-CVD death is a major cause of death among CVD patients with higher hs-CRP levels.

Key Words: High-sensitivity C-reactive protein, cardiovascular disease, emergency department

Strengths and limitations of this study

The strengths of our study include its large-scale retrospective cohort design with the examination of 12,211 patients diagnosed with CVD, the measurement of hs-CRP at baseline, and the search for cause-specific mortality.

The limitations of our study are (1) the single-center nature of the study (i.e., one teaching hospital) and (2) the confounders such as haemodynamics, comorbidities and other laboratory data could not be investigated.

Introduction

Emergency department (ED) patients with cardiovascular disease (CVD) need a timely evaluation for the diagnosis of CVD and the identification of comorbidities. However, the evaluation of CVD patients transported by an ambulance is often difficult because these patients may have complex medical problems and are sometimes too ill to assist medical staff with important medical information such as time of symptom onset and their medical history. The identification of markers that are associated with in-hospital mortality would be useful in the triage of CVD patients in EDs around the world.

C-reactive protein (CRP) is an acute-phase protein produced by the liver, and the serum levels of this protein increase in response to tissue injury, infection, inflammation, and neoplastic proliferation. The measurement of serum CRP concentrations is inexpensive and is done routinely to assess patients. In addition, the serum hs-CRP level is known to be a predictive marker of the degree of atherosclerosis and future cardiovascular events. [1-4] Several studies have also observed that elevated CRP predicts the prognosis of CVD patients at the acute stage. [5-16]

However, there has been controversy over the usefulness of the measurement of CRP as a prognostic marker in ED evaluations in Japan. The objective of the present study was to examine the association between the initial hs-CRP levels and in-hospital mortality in patients with CVD and its subtypes, i.e., acute myocardial infarction, heart failure, cerebral infarction and intracerebral haemorrhage.

Patients and Methods

Study design, setting and population

This was a retrospective cohort study at Iizuka Hospital, a teaching hospital with 1,116 beds located at the centre of the Chikuho region of Fukuoka prefecture on Japan's Kyushu

Island. This hospital is the only critical care centre for a population of approximately 430,000 people, and over 8,000 cases are transported by emergency vehicle to the hospital each year, accounting for approximately 40% of the emergency-conveyance patients in the Chikuho region. Ethical approval of this study was obtained from the Ethics Committee of Iizuka Hospital (CRM-27015). The requirement of informed consent was waived by the Ethics Committee because of the retrospective nature of the study.

At our hospital, the cases and records of patients who come to the ED are filed separately and are distinguished from those of the general out-patients. In the present study, the patients were recruited from among the ED files, and we evaluated the cases of 57,443 consecutive patients ≥18 years old who presented to Iizuka Hospital's ED by ambulance between February 1, 2006 and September 30, 2014. Among them, 391 patients had repeated ED visits on two consecutive days, and only the index case was used, in order to comply with the assumption of independent observations. At the ED, the leading diagnoses were established clinically using the International Classification of Diseases, Tenth Revision (ICD-10). We reviewed the Hospital's records and the cases and excluded the 2,317 patients who experienced cardiopulmonary arrest and the 298 patients who were pregnant.

Of the remaining 54,437 records, 12,830 patients were diagnosed with CVD, which was defined as meeting the criteria in diagnosis codes I00–I99 of the ICD-10 at their ED visit. The 619 (4.8%) patients whose hs-CRP level or white blood cell count (WBC) at baseline was not obtained were excluded. A final total of 12,211 patients with CVD were included in this study (Fig. 1). We divided the diagnoses with CVD into acute myocardial infarction (I21–I24), heart failure (I50), intracerebral haemorrhage (I61), cerebral infarction (I63), and "other" according to the ICD-10 classification.

Regarding the diagnoses of CVD at the ED, the emergency department physicians performed careful examinations and primary care. The physical examination,

electrocardiograph, X-ray, ultrasonography and blood examination were performed immediately. A complete blood cell count and biochemical examination including pH, lactate, creatine kinase-MB, brain-natriuretic peptide, D-dimer and troponin assay were available as needed. Brain imaging data (computed tomography and/or magnetic resonance imaging) were also available for patients with neurologic abnormalities or a decreased level of consciousness. When a patient was suspected of having CVD, the ED physicians were able to contact a cardiologist, neurologist, cardiovascular surgeon, or neurosurgeon 24 hours a day, 365 days a year. Based on the examinations by specialists and the test results, the leading diagnosis of CVD complying with ICD-10 was established at the ED. During the study period, no structural changes such as patient uptake, patient flow, the evaluation at the ED and the biomarker analysis occurred.

Data collection and laboratory measurement

The following data were extracted from the medical records for each patient: age, gender, diagnosis in the ED, length of hospital stay (days) and outcome. The cause of death was extracted from the death certificate. Blood samples for initial hs-CRP and WBC were collected soon after the patient arrived at the ED as part of the clinical routine and were analysed immediately for every patient. Serum hs-CRP levels were measured with a latex agglutination turbidimetric immunoassay (CRP-latex X2 Seiken, Denka Seiken, Tokyo). The hs-CRP measurement range was 0.2–320 mg/l, and the normal range is <3mg/l.

Definition of endpoints

The endpoints were mortality from any cause during hospitalization. Patients who remained in the hospital on 30 November, 2014 were considered alive in this analysis. Patients who did not require hospitalization and were discharged from the ED were also considered alive, and their stay in the hospital was regarded as 1 day. We divided the causes

of death into two main categories using the ICD-10: CVD deaths and non-CVD deaths. CVD death was defined as a death from a cause listed in ICD codes I00–I99, and Non-CVD death was defined as a death from a cause other than those listed in codes I00–I99. We classified the Non-CVD deaths into the following three subcategories: infection, neoplasm, and others. Infection-related deaths included deaths from septicaemia, bacteraemia, endocarditis, pulmonary infections (e.g., viral pneumonia, bacterial pneumonia, influenza with respiratory manifestations, abscess of lung or mediastinum), genitourinary infections (e.g., urinary tract infection, pyelonephritis, peri-nephric abscess), gastrointestinal infections (e.g., diverticulitis, *C. difficile* colitis, peri-rectal abscess), peritonitis, soft tissue infections (e.g., cellulitis, necrotizing fasciitis, gangrene), and joint or bone infections (e.g., infective arthritis, osteomyelitis). Neoplasm-related deaths included the deaths from codes C00–D48. Deaths from causes other than those listed above were classified as other deaths.

Statistical analysis

We divided the patients with hs-CRP levels >3.0 mg/l into quartiles. The patients with hs-CRP levels ≤3.0 mg/l were assigned to a separate category which served as the reference group, because the 3.0 mg/l cut-off point corresponds to the "high" CRP level in previous primary prevention studies. [17]. We calculated the age- and sex-adjusted or age-, sex-, and WBC-adjusted hazard ratios (HRs) for total death from CVD and its subtypes and their 95%CI values using the Cox proportional hazards model. The linear trends of HRs across hs-CRP levels were also tested using the Cox proportional hazards model. The Bonferroni method was used to address issues of multiple subgroup analyses. Bonferroni-corrected statistical significance was defined as $p<0.008 = (0.05/6)$ in the analysis of total death and $p<0.004 = (0.05/12)$ in the analysis of CVD deaths and Non-CVD deaths. For the distribution plot of hs-CRP levels in the surviving patients, CVD-death and Non-CVD death groups, we

examined hs-CRP values in each group by performing an analysis of variance (ANOVA). Because the distribution of hs-CRP values was skewed, the hs-CRP levels were natural log-transformed for the statistical analyses. All analyses were performed using the SAS software package ver. 9.4 (SAS Institute, Cary, NC).

Results

The age range of the patients was 18–104 yrs (median 76 yrs; interquartile range 64–84). 52% (6,355) were men; 48% (5,856) were women. The median baseline serum hs-CRP level was 1.8 mg/l (interquartile range 0.6–7.5 mg/l). The median number of hospital days including the date of the ED visit was 14 days (interquartile range 2–32 days). Among these patients, 1,156 deaths were recorded, giving an in-hospital mortality rate of 9.5% (confidence interval [CI]: 0.09–0.10).

Table 1 shows the in-hospital mortality and the age- and sex-adjusted and age-, sex-, and WBC-adjusted HRs for the in-hospital mortality of CVD according to the patients' hs-CRP levels. A significant association was observed between hs-CRP levels and the absolute risk of in-hospital mortality in the total CVD group (p for trend <0.001). In regard to the subtypes of CVD, the in-hospital mortality of the patients with acute myocardial infarction, heart failure, cerebral infarction, and intracerebral haemorrhage was also significantly increased as the hs-CRP levels increased (p for trend <0.001)

The age- and sex-adjusted HRs for total in-hospital mortality in the patients with hs-CRP levels ≥5.5 mg/l were significantly higher compared to those in the patients with levels <3.0 mg/l (5.5–11.5 mg/l: HR = 1.32, 95%CI = 1.09–1.60, p = 0.005; 11.6–33.2 mg/l: HR = 1.38, 95%CI = 1.14–1.65, p = 0.001; and ≥33.3 mg/l: HR = 2.15, 95%CI = 1.84–2.51, p<0.001). In the same way, the age- and sex-adjusted HRs for the in-hospital mortality of the patients with acute myocardial infarction, heart failure, cerebral infarction, and intracerebral

haemorrhage also increased with increasing hs-CRP levels, and were significantly higher in the patients with hs-CRP levels ≥33.3 mg/l compared to those with levels <3.0 mg/l.

In addition, when we determined the age- and sex-adjusted HRs for one increment in log-transformed hs-CRP concentrations, we observed significant upward trends for in-hospital mortality for both total CVD and its subtypes. This association remained unchanged even after adjustment for age, sex and WBC and withstood Bonferroni adjustment for multiple testing.

As shown in Table 2, when divided the cases separately into CVD deaths and Non-CVD deaths, the age- and sex-adjusted HRs of the cause-specific in-hospital deaths increased with increasing hs-CRP levels in both the subgroup of CVD deaths and that of Non-CVD deaths (p for trend <0.001). In the patients with hs-CRP levels ≥33.3 mg/l, the age- and sex-adjusted HR for CVD death was 1.44 (95%CI 1.20–1.73, p<0.001) compared to that in the patients with hs-CRP <3.0 mg/l. The HR for Non-CVD death, on the other hand, was 12.05 (95%CI 8.06–18.04, p<0.001) in this group. The relationship between the hs-CRP levels and Non-CVD deaths was thus much stronger than that between the hs-CRP levels and CVD deaths. Regarding the subtypes of CVD, similar relationships were observed.

Figure 2 shows a box plot of the distribution of hs-CRP levels in the surviving patients and the CVD-death and Non-CVD death groups. There were significant differences in the hs-CRP levels among the three groups (p<0.001, respectively). The association was unchanged even after Bonferroni adjustment. The median hs-CRP value was 1.7 mg/l in the surviving group, 3.1 mg/l in the CVD death group, and 32.1 mg/l in the Non-CVD death group. Table 3 shows number of total death, CVD death, Non-CVD death and its subtypes and according to hs-CRP levels. The proportions of Non-CVD death increased with hs-CRP levels: 6.4%, 8.6%, 13.5%, 19.3%, and 37.5% for the above-described hs-CRP groups. Among the deaths of patients with hs-CRP levels ≥33.3 mg/l, 17.1% deaths were caused by infection, 12.1%

deaths were caused by neoplasm, and 8.3% deaths were caused by other causes. The number of infection deaths showed a significant positive linear trend with the hs-CRP levels ($\chi^2 = 101.7$, $p<0.001$). Similar associations were observed for neoplasms ($\chi^2 = 67.4$, $p<0.001$) and the other causes group ($\chi^2 = 15.7$, $p=0.003$).

Discussion

The results of this large retrospective cohort study at a local Japanese teaching hospital clearly demonstrated that the risk among CVD patients for in-hospital mortality increased significantly with increasing initial hs-CRP levels taken in the ED. As with total deaths, the risks for cause-specific in-hospital mortality from CVD death and Non-CVD death also increased significantly as the hs-CRP levels increased. The influence of hs-CRP levels on mortality was greater in the Non-CVD deaths than in the CVD deaths.

These findings provide important information regarding critical care for patients with CVD. Prompt risk stratification is important in the management of CVD patients in an ED. Hs-CRP is a sensitive and nonspecific marker of systemic inflammation. A patient's initial hs-CRP level may prove to be a simple and readily available adjunct that could help the emergency care staff to identify CVD patients who may be at a high risk of death. Several studies have shown that elevated CRP levels at admission in CVD patients, including those with acute coronary syndrome, ischaemic stroke and acute heart failure, are associated with their mortality. [6 7 11 13 14] In addition, several studies have examined the utility of hs-CRP for predicting all-cause mortality in different settings. [18-20] These results, together with ours, imply that CRP is a valuable biomarker for identifying CVD patients at high risk of total in-hospital death. Although hs-CRP levels are much lower in Japanese populations compared to Western populations, [21] our present findings confirmed the utility of measuring the initial hs-

CRP in ED settings in Japan. In the present study, initial hs-CRP levels ≥5.5 mg/l were associated with greater mortality in CVD patients. In addition, the addition of the WBC in the adjustment did not substantially change the HRs in this study. This might be caused by the presence of leukopenia, i.e., a low WBC count. Although both the WBC count and CRP are used as inflammatory biomarkers, patients with leukopenia as the result of a severe inflammatory response or immune suppression might have poorer prognoses.

We also observed an association between hs-CRP levels and cause-specific in-hospital mortality from CVD death in this study. When the CVD cases were divided into subtypes of CVD, similar relationships were observed. The mechanisms underlying the association between hs-CRP levels and the risk of atherosclerotic CVD death are still unknown. However, there is a possibility that elevated levels of CRP reflect the extent of infarction and inflammation related to the pathobiology of ischaemic tissue damage. [8 10 22] In terms of heart failure, it is known that inflammatory markers such as tumor necrosis factor (TNF), interleukin (IL)-6, and CRP are elevated in patients with congestive heart failure and correlate with the degree of heart failure. [23-25] These findings and our present results raise the possibility that CRP levels are associated with the severity of cardiovascular diseases that are related to broad vascular damage. An evaluation of inflammatory risk in CVD patients should thus be routinely performed to identify high-risk patients in need of additional close monitoring. Although the results of the present study suggested that hs-CRP was a strong predictor of cardiovascular mortality, and several studies have indicated the value of determining the CRP level in CVD patients, CRP itself is be unlikely to provide an effective target for intervention and is known to be a downstream surrogate inflammatory marker. Moving upstream in the inflammatory cascade from CRP to IL-6 and IL-1 might provide novel therapeutic opportunities to reduce the cardiovascular event rate. [26] The results of

ongoing clinical trials of inflammation inhibition (such as those of the phase II trial data on canakinumab, a human monoclonal antibody that targets IL-1β [27]) are worthy of attention.

Our present analyses also showed an association between hs-CRP levels and Non-CVD deaths, and the influence of hs-CRP levels was much stronger in the Non-CVD deaths than in the CVD deaths. In addition, the proportion of Non-CVD deaths increased with the increase in the hs-CRP level. Although the actual number of non-CVD deaths was not very large, non-CVD deaths accounted for 37.5% of the total deaths among the patients with hs-CRP levels ≥33.3 mg/l. In addition, the median hs-CRP value was the highest in the Non-CVD death group, 32.1 mg/l. Hs-CRP can be elevated by underlying conditions other than CVD, such as infection, neoplasm and other diseases. In the present patient series, infection and neoplasm were major causes of Non-CVD death. However, a non-CVD death cause might be regarded as a misclassification or a complication of a well-classified CVD. Generally, CVD is a common cause of death globally and has shown a relationship with CRP levels, but CRP is an extremely sensitive marker for many diagnoses — not just CVD. Therefore, the patients with CVD and elevated hs-CRP levels in the present study might have had comorbidities at the ED.

Concerning neoplasms, several studies have reported that CRP levels have prognostic value in a wide variety of operable and inoperable cancers. [28-30] In the present study, some CVD patients with elevated hs-CRP levels on admission might have had a poorer prognosis for cancer and an increased risk of death. Infections, pneumonia and urinary tract infections (UTIs) are the most common infectious complications of ischaemic stroke, and they are independently associated with stroke outcome [31]. Current guidelines for the early management of patients with acute ischaemic stroke recommend that patients with suspected pneumonia or UTIs should be treated promptly with appropriate antibiotics. [32] However, to date, there has been no specific recommendation for the treatment of infectious complications

in other subtypes of CVD, such as acute myocardial infarction, heart failure and intracerebral haemorrhage.

In the present study, in addition to cerebral infarction, similar associations were observed between hs-CRP levels and Non-CVD death in other subtypes of CVD. Similarly, a prospective cohort study demonstrated that, among patients with ischaemic stroke, elevated CRP levels on admission is a predictor of pneumonia and UTI within 5 days. [33] These findings imply that a search for infections and tailored treatment without delay may be indicated for all types of CVD patients with elevated hs-CRP levels.

There are several limitations of our study that must be acknowledged. The first limitation is that this was a retrospective cohort study at a single hospital. It is possible that our medical care may be different from that at other hospitals throughout the world. However, to maintain its standard of medical care, Iizuka Hospital has affiliations with overseas medical institutions: the University of Pittsburgh Medical Center, El Camino Hospital, and Virginia Mason Institute. In addition, our hospital has been designated a residency training hospital since 1989, and it is renowned in Japan as an educational hospital. We thus believe that standard medical care is provided at our hospital.

Secondly, in this study, the evaluation of hs-CRP values was based on a single measurement in the ED. Since the time to reach the peak hs-CRP level may differ according to the underlying diseases in individual patients, it is possible that the initial hs-CRP levels do not precisely reflect the pathological condition in each disease. This could have weakened the association found in this study, biasing the results toward the null hypothesis. Therefore, the true association may be stronger than that shown in our study.

Thirdly, confounders and covariates other than age, sex and WBC could not be adjusted in this study. It is not our intention to suggest that CRP can replace the clinical evaluation of individual patients with CVD. Rather, we simply report that, in a large cohort,

the hs-CRP level was associated with in-hospital mortality. Ideally, our analysis would have assessed whether the hs-CRP measurement added prognostic information beyond commonly used risk assessment scoring systems such as the Acute Physiology and Chronic Health Evaluation (APACHE). Unfortunately, data such as haemodynamics and comorbidities could not be analysed in this study, so we elected instead to focus our analysis only on laboratory data that are routinely available. Further clinical and laboratory investigations are required to explain the association between mortality and the initial ED-measured hs-CRP level in patients with CVD.

Conclusion

The results of the present study clearly demonstrated the potential utility of hs-CRP measurement in the ED triage for patients with CVD as well as its subtypes, i.e., acute myocardial infarction, heart failure, cerebral infarction, and intracerebral haemorrhage. The assessment of hs-CRP at baseline even in CVD patients may improve the ability to identify patients at high risk of death from not only the primary CVD but also other systemic complications.

Author contributions

Conceptualization: R. Yoshinaga, Y. Doi, K. Ayukawa, S. Ishikawa. Methodology: R. Yoshinaga, Y. Doi, K. Ayukawa, S. Ishikawa. *Validation:* R. Yoshinaga, Y. Doi, K. Ayukawa, S. Ishikawa. *Formal analysis:* R. Yoshinaga, Y. Doi, S. Ishikawa. *Writing:* R. Yoshinaga, Y. Doi, K. Ayukawa, S. Ishikawa. *Visualization:* R. Yoshinaga, Y. Doi, K. Ayukawa. *Supervision:* Y. Doi, K. Ayukawa, S. Ishikawa.

Competing interests

None declared.

Data Sharing

No additional data available.

References

1. Ridker PM, Cushman M, Stampfer MJ, et al. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997;**336**(14):973-9.

2. Lindahl B, Toss H, Siegbahn A, et al. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. N Engl J Med 2000;**343**(16):1139-47.

3. Boekholdt SM, Hack CE, Sandhu MS, et al. C-reactive protein levels and coronary artery disease incidence and mortality in apparently healthy men and women: the EPIC-Norfolk prospective population study 1993-2003. Atherosclerosis 2006;**187**(2):415-22.

4. Sabatine MS, Morrow DA, Jablonski KA, et al. Prognostic significance of the Centers for Disease Control/American Heart Association high-sensitivity C-reactive protein cut points for cardiovascular and other outcomes in patients with stable coronary artery disease. Circulation 2007;**115**(12):1528-36.

5. Liuzzo G, Biasucci LM, Gallimore JR, et al. The prognostic value of C-reactive protein and serum amyloid a protein in severe unstable angina. N Engl J Med 1994;**331**(7):417-24.

6. Nikfardjam M, Mullner M, Schreiber W, et al. The association between C-reactive protein on admission and mortality in patients with acute myocardial infarction. J Intern Med 2000;**247**(3):341-5.

7. Chew DP, Bhatt DL, Robbins MA, et al. Incremental prognostic value of elevated baseline C-reactive protein among established markers of risk in percutaneous coronary intervention. Circulation 2001;**104**(9):992-7.

8. Di Napoli M, Papa F, Bocola V. C-reactive protein in ischemic stroke: an independent prognostic factor. Stroke 2001;**32**(4):917-24.

9. Audebert HJ, Rott MM, Eck T, et al. Systemic inflammatory response depends on initial stroke severity but is attenuated by successful thrombolysis. Stroke 2004;**35**(9):2128-33.

10. Keskin O, Ulusoy RE, Kalemoglu M, et al. White blood cell count and C-reactive protein predict short-term prognosis in acute myocardial infarction. J Int Med Res 2004;**32**(6):646-54.

11. Masotti L, Ceccarelli E, Forconi S, et al. Prognostic role of C-reactive protein in very old patients with acute ischaemic stroke. J Intern Med 2005;**258**(2):145-52.

12. Canale ML, Stroppa S, Caravelli P, et al. Admission C-reactive protein serum levels and survival in patients with acute myocardial infarction with persistent ST elevation. Coron Artery Dis 2006;**17**(8):693-8.

13. Elkind MS, Tai W, Coates K, et al. High-sensitivity C-reactive protein, lipoprotein-associated phospholipase A2, and outcome after ischemic stroke. Arch Intern Med 2006;**166**(19):2073-80.

14. Idicula TT, Brogger J, Naess H, et al. Admission C-reactive protein after acute ischemic stroke is associated with stroke severity and mortality: the 'Bergen stroke study'. BMC Neurol 2009;**9**:18.

15. Sheikh AS, Yahya S, Sheikh NS, et al. C-reactive Protein as a Predictor of Adverse outcome in Patients with Acute Coronary Syndrome. Heart Views 2012;**13**(1):7-12.

16. Park JJ, Choi DJ, Yoon CH, et al. Prognostic value of C-reactive protein as an inflammatory and N-terminal probrain natriuretic peptide as a neurohumoral marker in acute heart failure (from the Korean Heart Failure registry). Am J Cardiol 2014;**113**(3):511-7.

17. Buckley DI, Fu R, Freeman M, et al. C-reactive protein as a risk factor for coronary heart disease: a systematic review and meta-analyses for the U.S. Preventive Services Task Force. Ann Intern Med 2009;**151**(7):483-95.

18. Koenig W, Khuseyinova N, Baumert J, et al. Prospective study of high-sensitivity C-reactive protein as a determinant of mortality: results from the MONICA/KORA Augsburg Cohort Study, 1984-1998. Clin Chem 2008;**54**(2):335-42.

19. Marsik C, Kazemi-Shirazi L, Schickbauer T, et al. C-reactive protein and all-cause mortality in a large hospital-based cohort. Clin Chem 2008;**54**(2):343-9.

20. Ridker PM. High-sensitivity C-reactive protein as a predictor of all-cause mortality: implications for research and patient care. Clin Chem 2008;**54**(2):234-7.

21. Emerging Risk Factors C, Kaptoge S, Di Angelantonio E, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet 2010;**375**(9709):132-40.

22. Dirnagl U, Iadecola C, Moskowitz MA. Pathobiology of ischaemic stroke: an integrated view. Trends Neurosci 1999;**22**(9):391-7.

23. Tsutamoto T, Hisanaga T, Wada A, et al. Interleukin-6 spillover in the peripheral circulation increases with the severity of heart failure, and the high plasma level of interleukin-6 is an important prognostic predictor in patients with congestive heart failure. J Am Coll Cardiol 1998;**31**(2):391-8.

24. Vasan RS, Sullivan LM, Roubenoff R, et al. Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction: the Framingham Heart Study. Circulation 2003;**107**(11):1486-91.

25. Yin WH, Chen JW, Jen HL, et al. Independent prognostic value of elevated high-sensitivity C-reactive protein in chronic heart failure. Am Heart J 2004;**147**(5):931-8.

26. Ridker PM. From C-Reactive Protein to Interleukin-6 to Interleukin-1: Moving Upstream To Identify Novel Targets for Atheroprotection. Circ Res 2016;**118**(1):145-56.

27. Ridker PM, Howard CP, Walter V, et al. Effects of interleukin-1beta inhibition with canakinumab on hemoglobin A1c, lipids, C-reactive protein, interleukin-6, and fibrinogen: a phase IIb randomized, placebo-controlled trial. Circulation 2012;**126**(23):2739-48.

28. Heikkila K, Ebrahim S, Lawlor DA. A systematic review of the association between circulating concentrations of C reactive protein and cancer. J Epidemiol Community Health 2007;**61**(9):824-33.

29. Roxburgh CS, McMillan DC. Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. Future Oncol 2010;**6**(1):149-63.

30. Clarke SJ, Chua W, Moore M, et al. Use of inflammatory markers to guide cancer treatment. Clin Pharmacol Ther 2011;**90**(3):475-8.

31. Aslanyan S, Weir CJ, Diener HC, et al. Pneumonia and urinary tract infection after acute ischaemic stroke: a tertiary analysis of the GAIN International trial. Eur J Neurol 2004;**11**(1):49-53.

32. Jauch EC, Saver JL, Adams HP, Jr., et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;**44**(3):870-947.

33. Fluri F, Morgenthaler NG, Mueller B, et al. Copeptin, procalcitonin and routine inflammatory markers-predictors of infection after stroke. PLoS One 2012;**7**(10):e48309.

Figure legends

Fig. 1. Flow diagram of the study.

In this study, the cases of 57,443 consecutive patients ≥18 years old who presented to Iizuka Hospital's emergency department by ambulance between 1 February 2006 and 30 September 2014 were evaluated. Excluded from the study were 391 patients had repeated emergency department visits on two consecutive days; 2,317 patients had a history of cardiopulmonary arrest; and 298 were pregnant. Of the remaining 54,437 records, 12,830 patients were diagnosed with cardiovascular disease (CVD). 619 (4.8%) patients whose high sensitivity C-reactive protein level or white blood cell count at baseline was not obtained were excluded. A final total of 12,211 patients with CVD were included in this study

Fig. 2.

Figure 2 shows a box plot of the distribution of hs-CRP levels in the surviving patients and the CVD-death and Non-CVD death groups. There were significant differences in the hs-CRP levels among the three groups ($p<0.001$, respectively). The association was unchanged even after Bonferroni adjustment. The median hs-CRP value was 1.7 mg/l in the surviving group, 3.1 mg/l in the CVD death group, and 32.1 mg/l in the Non-CVD death group.

Table 1. No. of patients and deaths, in-hospital mortalities, and hazard ratios for total death of cardiovascular disease and its subtypes according to hs-CRP levels

Diagnosis at the emergency department	Total	hs-CRP levels (mg/l) <3.0	3.1–5.4	5.5–11.5	11.6–33.2	≥33.3	*p* for trend (across categories)	Continuous log scale	*p* for trend (continuous)
Cardiovascular disease									
No. of patients	12,211	7,375	1,212	1,200	1,216	1,208			
No. of deaths	1,156	517	116	134	149	240			
In-hospital mortality (%)	9.5	7.0	9.6	11.2	12.3	19.9	<0.001		
Age- and sex-adjusted HR (95%CI)		1 (ref.)	1.18 (0.97–1.45)	1.32† (1.09–1.60)	1.38† (1.14–1.65)	2.15† (1.84–2.51)	<0.001	1.15† (1.12–1.19)	<0.001
Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	1.15 (0.94–1.41)	1.29 (1.07–1.56)	1.33† (1.11–1.60)	2.00† (1.71–2.34)	<0.001	1.14† (1.10–1.18)	<0.001
Acute myocardial infarction									
No. of patients	1,347	796	145	126	125	155			
No. of deaths	89	28	4	12	9	36			
In-hospital mortality (%)	6.6	3.5	2.8	9.5	7.2	23.2	<0.001		
Age- and sex-adjusted HR (95%CI)		1 (ref.)	0.65 (0.23–1.86)	1.80 (0.91–3.57)	1.46 (0.68–3.13)	4.33† (2.60–7.22)	<0.001	1.37† (1.23–1.54)	<0.001
Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	0.62 (0.22–1.76)	1.64 (0.83–3.26)	1.14 (0.51–2.54)	3.44† (2.04–5.82)	<0.001	1.31† (1.16–1.47)	<0.001
Heart failure									
No. of patients	1,742	620	232	249	310	331			
No. of deaths	148	19	11	28	29	61			
In-hospital mortality (%)	8.5	3.1	4.7	11.2	9.4	18.4	<0.001		
Age- and sex-adjusted HR (95%CI)		1 (ref.)	1.27 (0.60–2.66)	2.29† (1.26–4.17)	1.99† (1.11–3.57)	3.55† (2.11–5.97)	<0.001	1.35† (1.22–1.51)	<0.001
Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	1.26 (0.60–2.64)	2.34† (1.28–4.26)	2.07† (1.15–3.72)	3.83† (2.26–6.49)	<0.001	1.39† (1.24–1.55)	<0.001
Cerebral infarction									
No. of patients	2,879	1,823	277	281	271	227			
No. of deaths	261	109	25	34	43	50			
In-hospital mortality (%)	9.1	6.0	9.0	12.1	15.9	22.0	<0.001		
Age- and sex-adjusted HR (95%CI)		1 (ref.)	1.15 (0.74–1.78)	1.73† (1.18–2.55)	2.04† (1.43–2.91)	3.02† (2.15–4.22)	<0.001	1.28† (1.19–1.37)	<0.001
Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	1.07 (0.69–1.66)	1.59 (1.08–2.34)	1.63 (1.12–2.36)	2.20† (1.53–3.17)	<0.001	1.20† (1.11–1.29)	<0.001
Intracerebral haemorrhage									

No. of patients	1,989	1428	167	153	137	104			
No. of deaths	338	201	39	32	29	37			
In-hospital mortality (%)	17.0	14.1	23.4	20.9	21.2	35.6	<0.001		
Age- and sex-adjusted HR (95%CI)		1 (ref.)	1.60 (1.14–2.26)	1.34 (0.92–1.95)	1.33 (0.90–1.97)	2.33† (1.64–3.32)	<0.001	1.14† (1.07–1.21)	<0.001
Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	1.56 (1.10–2.20)	1.32 (0.91–1.92)	1.29 (0.87–1.92)	2.05† (1.42–2.97)	<0.001	1.12† (1.05–1.19)	<0.001
Others									
No. of patients	4,254	2,708	391	391	373	391			
No. of deaths	320	160	37	28	39	56			
In-hospital mortality (%)	7.5	5.9	9.5	7.2	10.5	14.3	0.002		
Age- and sex-adjusted HR (95%CI)		1 (ref.)	1.41 (0.98–2.01)	0.95 (0.63–1.42)	1.28 (0.89–1.82)	1.43 (1.05 to 1.95)	0.032	1.08 (1.02–1.14)	0.009
Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	1.30 (0.91–1.86)	0.74 (0.48–1.14)	1.16 (0.85–1.61)	1.03 (1.02 –1.04)	0.381	1.04 (0.98–1.10)	0.223

CI: confidence interval; HR: hazard ratio; hs-CRP: high-sensitivity C-reactive protein; WBC: white blood cell count.
Cardiovascular disease: International Statistical Classification of Diseases and related problems 10th revision (below ICD-10) Diseases of the circulatory system (I00–I99);
Acute myocardial infarction: ICD-10 (I21–I24); Heart failure: ICD-10 (I50); Cerebral infarction: ICD-10 (I63); Intracerebral haemorrhage: ICD-10 (I61).
†Statistically significant after applying a Bonferroni correction.

Table 2. No. of cause-specific deaths, hazard ratios for cause-specific death of cardiovascular disease and its subtypes according to hs-CRP levels

Diagnosis at the emergency department	Total	hs-CRP levels (mg/l)					*p* for trend (across categories)	Continuous log scale	*p* for trend (continuous)
		<3.0	3.1–5.4	5.5–11.5	11.6–33.2	≥33.3			
Cardiovascular disease									
No. of patients	12,211	7,375	1,212	1,200	1,216	1,208			
No. of CVD deaths	976	484	106	116	120	150			
CVD-related		1	1.16	1.23	1.20	1.44†	<0.001	1.08†	<0.001
Age- and sex-adjusted HR (95%CI)		(ref.)	(0.94–1.43)	(1.00–1.51)	(0.98–1.46)	(1.20–1.73)		(1.03–1.11)	
CVD-related, Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	1.13 (0.92–1.40)	1.20 (1.00–1.48)	1.16 (0.95–1.42)	1.33† (1.10–1.61)	0.002	1.05† (1.01–1.09)	0.004
No. of Non-CVD deaths	180	33	10	18	29	90			
Non-CVD-related		1	1.55	2.67†	3.84†	12.05†	<0.001	1.77†	<0.001
Age- and sex-adjusted HR (95%CI)		(ref.)	(0.76–3.15)	(1.50–4.75)	(2.32–6.35)	(8.05–18.04)		(1.63–1.93)	
Non-CVD-related, Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	1.52 (0.75–3.09)	2.61† (1.47–4.65)	3.72† (2.25–6.16)	11.49† (7.66–17.23)	<0.001	1.75† (1.61–1.91)	<0.001
Acute myocardial infarction									
No. of patients	1,347	796	145	126	125	155			
No. of CVD deaths	70	25	2	11	7	25			
CVD-related		1	0.37	1.93	1.31	3.51†	<0.001	1.30†	<0.001
Age- and sex-adjusted HR (95%CI)		(ref.)	(0.09–1.56)	(0.94–3.95)	(0.56–3.05)	(1.98–6.23)		(1.14–1.48)	
CVD-related, Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	0.35 (0.08–1.47)	1.74 (0.85–3.58)	1.01 (0.41–2.47)	2.71† (1.50–4.90)	0.001	1.23† (1.08–1.40)	0.002
No. of Non-CVD deaths	19	3	2	1	2	11			
Non-CVD-related		1	2.82	1.21	2.59	10.14†	<0.001	1.73†	<0.001
Age- and sex-adjusted HR (95%CI)		(ref.)	(0.47–17.04)	(0.12–11.75)	(0.42–15.84)	(2.75–37.33)		(1.32–2.28)	
Non-CVD-related, Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	2.71 (0.45–16.45)	1.11 (0.11–10.81)	2.07 (0.31–13.72)	8.64† (2.32–32.27)	0.001	1.67† (1.27–2.21)	<0.001
Heart failure									
No. of patients	1,742	620	232	249	310	331			
No. of CVD deaths	98	15	10	21	19	33			

CVD-related Age- and sex-adjusted HR (95%CI)		1 (ref.)	1.49 (0.67–3.33)	2.27 (1.14–4.51)	1.76 (0.88–3.48)	2.58† (1.39–4.79)	0.004	1.23† (1.09–1.39)	0.001
CVD-related Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	1.49 (0.67–3.32)	2.29 (1.15–4.56)	1.78 (0.90–3.54)	2.66† (1.42–4.97)	0.003	1.24† (1.09–1.41)	0.001
No. of Non-CVD deaths	50	4	1	7	10	28			
Age- and sex-adjusted HR (95%CI)		1 (ref.)	0.52 (0.06–4.68)	2.50 (0.72–8.74)	2.92 (0.91–9.42)	6.80† (2.36–19.57)	<0.001	1.69† (1.38–2.08)	<0.001
Non-CVD-related, Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	0.51 (0.06–4.57)	2.52 (0.72–8.80)	3.21 (0.99–10.33)	8.19† (2.82–23.80)	<0.001	1.84† (1.47–2.29)	<0.001
Cerebral infarction									
No. of patients	2,879	1,823	277	281	271	227			
No. of CVD deaths	230	103	22	33	38	34			
CVD-related Age- and sex-adjusted HR (95%CI)		1 (ref.)	1.08 (0.68–1.72)	1.76 (1.19–2.61)	1.95† (1.34–2.84)	2.13† (1.44–3.14)	<0.001	1.21† (1.12–1.30)	<0.001
CVD-related Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	0.99 (0.62–1.57)	1.59 (1.07–2.35)	1.48 (1.00–2.19)	1.44 (0.95–2.20)	0.012	1.11 (1.03–1.21)	0.008
No. of Non-CVD deaths	31	6	3	1	5	16			
Non-CVD-related Age- and sex-adjusted HR (95%CI)		1 (ref.)	2.07 (0.51–8.41)	0.92 (0.11–7.63)	3.08 (0.91–10.49)	18.78† (7.27–48.51)	<0.001	1.95† (1.57–2.41)	<0.001
Non-CVD-related Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	2.20 (0.54–8.99)	0.99 (0.12–8.29)	3.87 (1.10–13.62)	24.08† (8.62–67.25)	<0.001	2.08† (1.65–2.64)	<0.001
Intracerebral haemorrhage									
No. of patients	1,989	1,428	167	153	137	104			
No. of CVD deaths	313	196	37	29	28	23			
CVD-related Age- and sex-adjusted HR (95%CI)		1 (ref.)	1.56 (1.10–2.22)	1.25 (0.84–1.84)	1.32 (0.88–1.97)	1.49 (0.96–2.30)	0.019	1.07 (1.00–1.14)	0.061
CVD-related, Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	1.52 (1.07–2.17)	1.23 (0.83–1.82)	1.29 (0.86–1.92)	1.30 (0.82–2.04)	0.020	1.05 (0.98–1.13)	0.166
No. of Non-CVD deaths	25	5	2	3	1	14			
Non-CVD-related Age- and sex-adjusted HR (95%CI)		1 (ref.)	3.17 (0.62–16.37)	5.13 (1.22–21.58)	1.85 (0.21–16.09)	32.57† (11.41–92.97)	<0.001	2.26† (1.78–2.86)	<0.001

Non-CVD-related Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	3.05 (0.59–15.77)	4.97 (1.18–20.89)	1.77 (0.20–15.38)	28.22† (9.76–81.58)	<0.001	2.21† (1.73–2.81)	<0.001
Others									
No. of patients	4,254	2,708	391	391	373	391			
No. of CVD deaths	265	145	35	22	28	35			
CVD-related Age- and sex-adjusted HR (95%CI)		1 (ref.)	1.45 (1.00–2.11)	0.83 (0.53–1.30)	1.02 (0.67–1.54)	1.01 (0.67–1.54)	0.894	1.01 (0.95–1.08)	0.750
CVD-related Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	1.32 (0.91–1.91)	0.57 (0.35–0.93)	0.77 (0.53–1.14)	1.03 (1.02–1.04)	0.119	0.96 (0.90–1.03)	0.212
No. of Non-CVD deaths	55	15	2	6	11	21			
Non-CVD-related Age- and sex-adjusted HR (95%CI)		1 (ref.)	0.86 (0.20–3.76)	2.08 (0.80–5.40)	3.62† (1.63–8.05)	4.87† (2.47–9.61)	<0.001	1.44† (1.25–1.65)	<0.001
Non-CVD-related Age-, sex-, and WBC-adjusted HR (95%CI)		1 (ref.)	0.90 (0.21–3.93)	2.24 (0.86–5.85)	3.87† (1.73–8.64)	5.30† (2.66–10.54)	<0.001	1.47† (1.28–1.69)	<0.001

hs-CRP: high-sensitivity C-reactive protein; WBC: white blood cell count;CI: confidence interval.
CVD: Cardiovascular disease: International Statistical Classification of Diseases and related problems 10th revision (below ICD-10) Diseases of the circulatory system (I00-I99); Acute myocardial infarction: ICD-10 (I21–I24); Heart failure: ICD-10 (I50); Cerebral infarction:ICD-10 (I63); Intracerebral haemorrhage: ICD-10 (I61).
†Statistically significant after applying a Bonferroni correction.

Table 3. No. of total death, CVD death, Non-CVD death and its subtypes according to hs-CRP levels

Cause of death	Total	hs-CRP levels (mg/l)					χ^2-test	*p value*
		<3.0	3.1–5.4	5.5–11.5	11.6–33.2	≥33.3		
No. of total deaths	1156	517	116	134	149	240		
No. of CVD deaths n (%)	976 (84.4)	484 (93.6)	106 (91.4)	116 (86.6)	120 (80.5)	150 (62.5)		
No. of Non-CVD deaths n (%)	180 (15.6)	33 (6.8)	10 (8.6)	18 (13.4)	29 (19.5)	90 (37.5)	127.9	<0.001
No. of infection deaths n (%)	64 (5.5)	6 (1.2)	3 (2.6)	5 (3.7)	9 (6.0)	41(17.1)	101.7	<0.001
No. of neoplasm deaths n (%)	49 (4.2)	6 (1.2)	2 (1.7)	5 (3.7)	7 (4.7)	29 (12.1)	67.4	<0.001
No. of other deaths n (%)	67 (5.8)	21 (4.1)	5 (4.3)	8 (5.9)	13 (8.7)	20 (8.3)	15.7	0.003

hs-CRP: high-sensitivity C-reactive protein; Infection deaths: deaths from septicemia, bacteremia, endocarditis, pulmonary infections (e.g., viral pneumonia, bacterial pneumonia, influenza with respiratory manifestations, abscess of lung or mediastinum), genitourinary infections (e.g., urinary tract infection, pyelonephritis, peri-nephric abscess), gastrointestinal infections (e.g., diverticulitis, *C. difficile* colitis, peri-rectal abscess), peritonitis, soft tissue infections (e.g., cellulitis, necrotizing fasciitis, gangrene), and joint or bone infections (e.g., infective arthritis, osteomyelitis). Neoplasm deaths: deaths from International Statistical Classification of Diseases and related problems 10th revision C00–D48. Other deaths; deaths from other than the causes listed above.

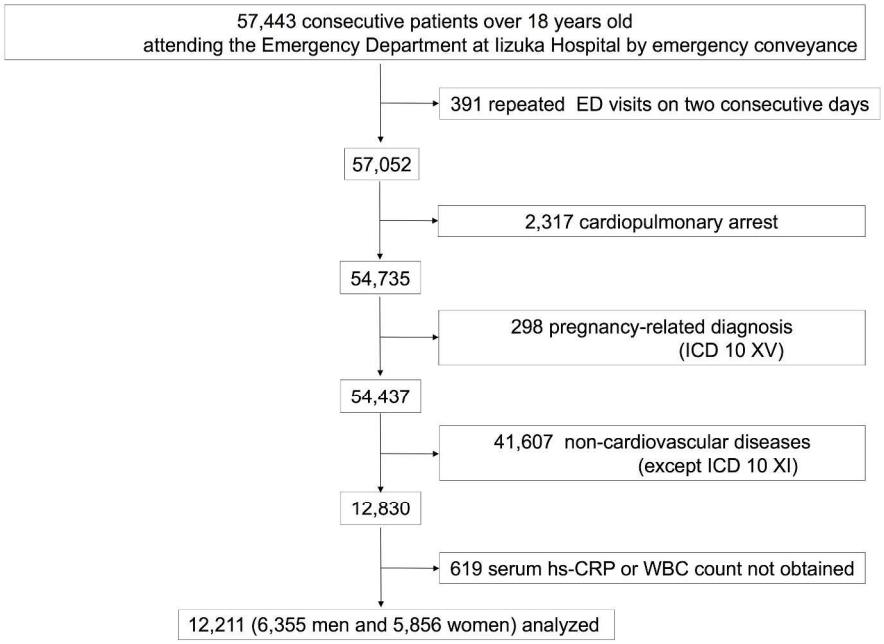


Figure 1

355x266mm (300 x 300 DPI)

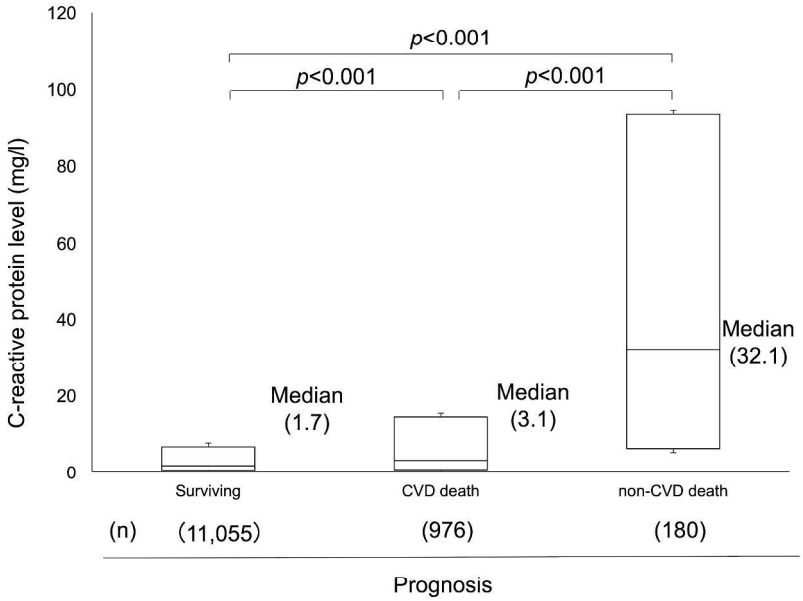


Figure 2

355x266mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (Page No. 1)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (Page No. 2)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (Page No. 4)
Objectives	3	State specific objectives, including any prespecified hypotheses (Page No. 4)
Methods		
Study design	4	Present key elements of study design early in the paper (Page No. 4)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (Page No. 4,5,6)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (Page No. 4,5,6,7) *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed (Page No. 4,5,6,7) *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (Page No. 4,5,6,7)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (Page No. 6,7,8)
Bias	9	Describe any efforts to address potential sources of bias (Page No. 4,5,6,7)
Study size	10	Explain how the study size was arrived at (Page No. 5)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (Page No. 4,5,6,7)

Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (Page No. 7,8)
		(*b*) Describe any methods used to examine subgroups and interactions (Page No. 7,8)
		(*c*) Explain how missing data were addressed (Page No. 7,8)
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed Not applicable *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses (Page No. 7,8)

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (Page No. 4,5,6)
		(b) Give reasons for non-participation at each stage (Page No. 8,9)
		(c) Consider use of a flow diagram Fig1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (Page No.5,6,7, 8,9)
		(b) Indicate number of participants with missing data for each variable of interest Not applicable
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) (Page No. 8,9)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time (Page No. 8,9,10)
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (Page No. 8,9,10) , table1, table2
		(*b*) Report category boundaries when continuous variables were categorized (Page No. 8,9,10) , table1, table2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period (Page No. 8,9,10)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (Page No. 9,10),table3, Fig2
Discussion		
Key results	18	Summarise key results with reference to study objectives (Page No. 10)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (Page No. 13,14)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (Page No. 10,11,12,13)
Generalisability	21	Discuss the generalisability (external validity) of the study results (Page No. 10,11)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable,

for the original study on which the present article is based
(Page No. 14,15)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.