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C-Reactive Protein and All-Cause Mortality in a Large Hospital-Based Cohort

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BACKGROUND: C-reactive protein (CRP), an acute-phase protein, is a sensitive systemic marker of inflammation and acute-phase reactions. Testing CRP concentrations at hospital admission may provide information about disease risk and overall survival.

METHODS: All first-ever transmittals to the department of medical and chemical laboratory diagnostics for determination of low-sensitivity CRP (n = 274 515, 44.5% male, median age 51 years) between January 1991 and July 2003 were included [median follow-up time: 4.4 years (interquartile range, 2.3–7.4 years)]. The primary endpoint was all-cause mortality. Multivariate Cox regression adjusted for sex and age was applied for analysis.

RESULTS: Compared to individuals within the reference category (CRP <5 mg/L), hazard ratios (HR) for all-cause mortality increased from 1.4 (5–10 mg/L category) to 3.3 in the highest category (>80 mg/L, all P <0.001). CRP was associated with various causes of death. The relation of CRP to cancer death was stronger than to vascular death. Younger patients with increased CRP had relatively far worse outcome than older patients (maximal HR: ≤30 years: 6.7 vs >60 years: 1.7–3.7). Interestingly, both short- and long-term mortality were associated with increasing CRP concentrations (>80 mg/L: HR 22.8 vs 1.4).

CONCLUSION: Measurement of low-sensitivity CRP at hospital admission allowed for the identification of patients at increased risk of unfavorable outcome. Our findings indicate that close attention should be paid to hospitalized patients with high CRP not only because of very substantial short-term risk, but also long-term excess risk, the basis for which needs to be determined.

C-reactive protein (CRP)[5] is the prototypical acute-phase response protein that increases during systemic inflammation and is currently one of the most frequently studied inflammatory markers in epidemiology.

Following an acute phase stimulus, CRP values may increase by as much as 10 000-fold by de novo hepatic synthesis regulated by proinflammatory cytokines, especially interleukin 6 *(1)*. A major CRP response is observed in infection and sepsis, various autoimmunopathies, tissue necrosis, trauma, and neoplasia *(1)*. CRP concentrations directly correlate with disease activity in many diseases and can contribute to disease progression through a range of proinflammatory properties *(1–3)*. Being an exquisitely sensitive marker of systemic inflammation and tissue damage, CRP is very useful in screening for organic disease, monitoring treatment responses, and detecting interrcurrent infection *(1)*. As a calcium-dependent ligand-binding protein, CRP participates in activation of the complement system *(4)* and contributes to innate immunity *(1)*.

CRP selectively binds to LDL *(5)* and VLDL, is deposited in atherosclerotic plaques *(6)*, and contributes to the pathogenesis of atherosclerosis through complement activation. Procoagulant effects of CRP have also been reported *(1)*. With increasing evidence that CRP, even within the range formerly considered to be normal, is an independent predictor of cardiovascular events *(7–10)* and the availability of routine high-sensitivity (hs)-CRP assays, CRP was the first inflammatory biomarker to be recommended by an expert panel for optional measure-

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[5] Nonstandard abbreviations: CRP, C-reactive protein; hs, high sensitivity.

ment to assess the risk for coronary heart disease as an adjunct to established risk factors *(11)*.

Increased CRP concentrations have been reported to be associated with features of the metabolic syndrome *(12, 13)*, breast and colorectal cancer *(14)*, end-stage renal disease *(15)*, and even mood disorders *(16)*, indicating that low-grade inflammation might be one of the basic pathogenic processes in many common chronic diseases. In this context, it is important to recognize that the CRP response is nonspecific and is triggered by many disorders unrelated to cardiovascular disease. Furthermore, increased baseline CRP concentrations are associated with smoking, coffee consumption, stress, and oral contraceptives *(1)*.

CRP may be an informative predictor of mortality, enabling better risk stratification and risk-adjusted follow-up. Our knowledge is limited as to the impact on intermediate- and long-term outcome of increases in CRP indicative of acute-phase reactions. The effect of increased CRP might be of interest, especially in the hospital environment, where many patients have an identifiable point source for increased CRP and may not have chronic low-grade inflammation. Because of the availability of an objectively defined endpoint, examination of the impact of clinically relevant CRP concentrations on overall survival in a large hospital-based cohort might allow more accurate risk estimates. The use of low-sensitivity CRP measurement may enable early identification of high-risk patients and allow for optimization of therapeutic procedures in these subgroups during both the acute phase and at follow-up. To evaluate the relevance of CRP as a potential predictor for overall survival in a large-scale cohort, we investigated the value of low-sensitivity CRP measurement as marker for the identification of patients with unfavorable long-term survival.

Patients and Methods

PATIENTS

All first-ever transmittals to the Department of Medical and Chemical Laboratory Diagnostics for determination of CRP between January 1991 and July 2003 were included in our study. Inclusion criteria were a valid CRP value and complete patient data including sex, name, and date of birth required for successful record linkage. Exclusion criteria were incomplete patient data. From a total of 950 874 patients admitted to the general hospital of Vienna, 274 515 individuals (28.9%) fulfilled these criteria. Record linkage was performed via database query of the Austrian death registry, resulting in date of death (if it occurred between January 1990 and December 2004) and cause of death encoded either before 2002 according to the International Code of diseases Version 9 (ICD9), or after 2002 according to the ICD10. The Austrian death registry includes all deaths within Austria and the deaths of Austrian citizens in foreign countries if reported to Austrian officials. According to Austrian laws, all patients must undergo a postmortem examination if the final cause of death is not evident from the patient history, resulting in an overall postmortem frequency of 35% in our study. For statistical analysis we used only anonymized data containing no personal information except age in years and sex, and the study was approved by the Ethics Committee of the Medical University of Vienna.

MEASUREMENT OF CRP CONCENTRATIONS

CRP was measured in serum or heparin-plasma as a routine analysis. CRP concentrations were analyzed using a particle-enhanced immunoturbidimetric assay (Tina-quant C-reactive Protein, Roche Diagnostics) according to manufacturers instructions on an automated analyzer [Hitachi 917, Hitachi 947 (Boehringer) and Roche Modular P (Roche Diagnostics]. Within- and between-run imprecision values were approximately 2.5%. Between-analyzer variability was $<5\%$, as assessed by daily comparisons. Because very low CRP concentrations could not be reproduced with adequate accuracy, the lower detection limit was set to 5 mg/L. Thus, owing to lack of availability at the time of determination, the CRP assay used in this study was not a high-sensitivity assay.

DETERMINATION OF OUTCOME VARIABLES

The main outcome variable was all-cause mortality, defined as death occurring after determination of CRP and before December 31, 2004. Noncancer mortality was defined as death occurring from causes other than neoplasia (defined as ICD9 groups 140–239 and ICD10 groups C00 to D48), all-cause vascular mortality was considered to be present in case of ICD9 codes 390–459, ICD10 group I00 to I99, respectively. Mortality due to ischemic heart disease was defined as ICD9 diagnosis coded as 410–414 and ICD10 I20–I25, and death due to cerebrovascular disease was defined as ICD9 groups 430–438 and ICD10 groups I60–I69. Observation time was calculated in years from the time point of CRP determination to death, or until the end of observation time (December 31, 2004) in survivors.

To facilitate analysis, CRP concentrations were divided into 6 categories: Patient samples with CRP <5 mg/L were determined as the reference category, the other categories were 5–10 mg/L, >10 and ≤ 20 mg/L, >20 and ≤ 40 mg/L, >40 and ≤ 80 mg/L, and >80 mg/L.

STATISTICAL ANALYSIS

The influence of CRP on all-cause mortality was assessed in a multivariate Cox regression model adjusted

Table 1. Characteristics of the study population.[a]

	Patient characteristics (N = 274 515)
Sex (male/female)	122 170/152 345 (44.5%/55.5%)
Median age in years (IQR range)	51 (34–66)
Median CRP (IQR range)	<5 mg/L (<5–19.1 mg/L)
Median observation period in years (IQR range)	4.4 (2.3–7.4)
All-cause mortality, n (%)	39 785 (14.5%)
Noncancer mortality, n (%)	22 981 (8.4%)
Cancer mortality, n (%)	16 804 (6.1%)
All-cause vascular mortality, n (%)	14 114 (5.1%)
Mortality due to ischemic heart disease, n (%)	6748 (2.5%)
CRP categories, n (%)	
<5 mg/L	141 470 (51.5%)
5–10 mg/L	36 000 (13.1%)
10.1–20 mg/L	30 179 (11.0%)
20.1–40 mg/L	22 299 (8.1%)
40.1–80 mg/L	20 183 (7.4%)
>80 mg/L	24 345 (8.9%)

[a] Discrete variables are given as counts and percentages, continuous variables as median and interquartile range (IQR).

for sex and age. Age of study patients was calculated at the time of CRP measurement. The assumptions underlying the proportional-hazards model (proportional hazards, lack of interaction, and linearity of continuous variables) were tested and found valid unless otherwise indicated. SPSS Version 12.0™ (SPSS) was used for all analyses. In the model for death, we did not include nonfatal events or hospitalizations that occurred after the index date. Regression diagnostics were performed according to standard recommendations.

ESTIMATE OF SAMPLE BIAS

To give an estimate of a possible sample bias, we compared the observed all-cause mortality in our study to the estimated mortality during our observation period to the general Austrian population. For this purpose, we calculated the individual probability of death within the hypothetical maximum observation period (date of analysis until the last day included in the record linkage analysis) considering individual age, sex, and maximum observation time by using the official Austrian mortality tables provided by Statistik Austria (http://www.statistik.at/fachbereich_03/Stt2000_2002.xls, 2005).

Results

DEMOGRAPHIC CHARACTERISTICS

A total of 274 515 community-dwelling patients attended the Vienna General Hospital and had blood samples taken for CRP. The median age was 51 years (range 0–100 years) at time of analysis, and the median observation period was 4.4 years (range 0–11.28 years). A total of 1 340 000 person-years were studied, and a total of 39 785 deaths (14.5%) were recorded within the observed period (Table 1) (see Table 1 in the Data Supplement that accompanies the online version of the article at http://www.clinchem.org/content/vol?/issue?).

CRP AND OVERALL SURVIVAL

CRP concentrations varied considerably between individuals, with a median of <5 mg/L (interquartile range: <5 mg/L–19.1 mg/L). In a multivariate Cox regression adjusted for sex and age as possible confounders, CRP categories were significantly associated with all-cause mortality (Fig. 1). Compared to individuals within the reference category (CRP <5 mg/L), hazard ratios gradually increased from 1.4 in the 5–10 mg/L category to 3.3 in the highest category (>80 mg/L, all P <0.001, Fig. 2).

The association between CRP and mortality was also significant when we considered mortality from cancer, noncancer, all-cause vascular diseases, ischemic heart or cerebrovascular disease (Fig. 2), and infectious diseases (See Supplemental Data Table 2) as secondary endpoints. The relation of CRP to cancer death was stronger than to vascular death.

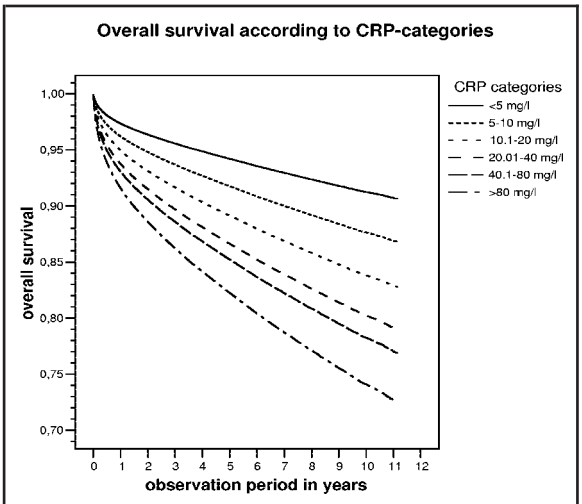

Fig. 1. CRP and overall survival in 274 515 hospital-based patients.

Survival curves were derived from a Cox regression model adjusted for sex and age. In parallel to increasing CRP concentrations, all cause mortality increased progressively.

We also evaluated whether CRP might be predictive for death in different types of cancer (See Supplemental Data Table 3). Interestingly, increased CRP seems to be less predictive for breast and prostate cancer (hazard ratios reaching approximately 2.5 in the highest category) compared to other types of malignancies (including gastric, colorectal, or lung cancer), resulting in hazard ratios up to 5.

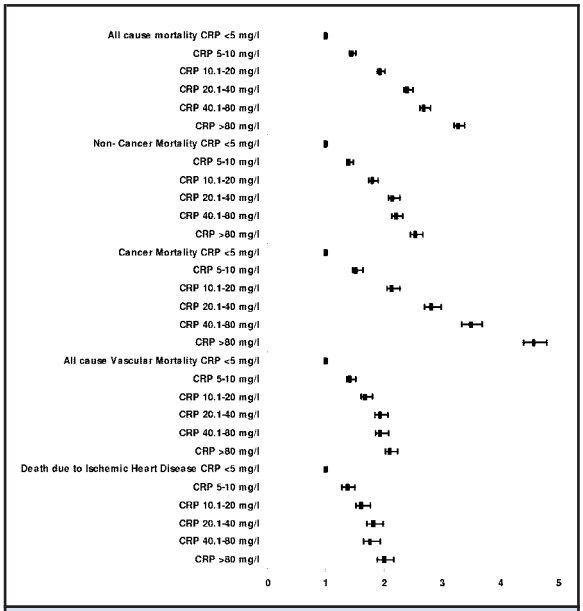

Fig. 2. Hazard ratios for the respective outcome variables were calculated in a Cox regression model adjusted for age and sex, with the lowest CRP category (<5 mg/L) serving as reference category.

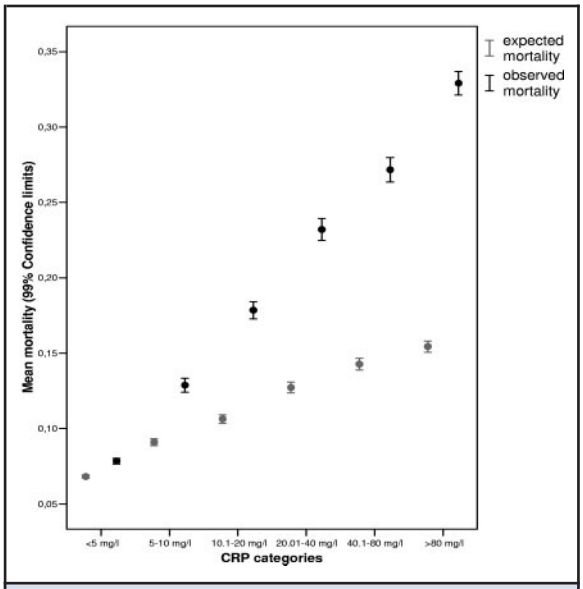

Fig. 3. Comparison of observed all-cause mortality within the CRP categories and expected mortality within the Austrian population at the respective CRP categories.

For better legibility, expected mortality was shifted to the left in the Fig. Although no larger differences between expected and observed mortality were observed in patients within the CRP <5 mg/L category, the gap between observed and calculated mortality increased with increasing CRP.

To provide an estimate for sampling bias in our retrospective hospital-based analysis, we compared expected mortality retrieved from the Austrian mortality tables to observed cases (Fig. 3). Within the reference group there were no major differences between both values, whereas in the other categories the gap between expected and observed deaths continuously increased in parallel to increasing hazard ratios in the Cox regression analysis.

ASSOCIATION OF SEX AND AGE WITH CRP CONCENTRATIONS AND SURVIVAL

CRP concentrations steadily rose with age, and female patients had significantly lower CRP concentrations in all age categories ($P < 0.001$) except for the lower subgroup (25–31 years $P = 0.37$, Fig. 4).

Male sex and young age were significant predictors of increased all-cause mortality. Male patients had a 1.3-fold (95% CI: 1.2–1.4, $P < 0.001$) increased hazard

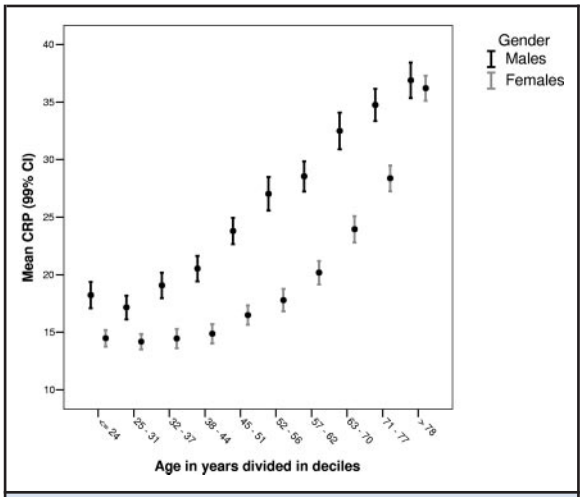

Fig. 4. Mean CRP concentrations (mg/L) according to sex and age.

All sex-related differences in each age category were significant at $P < 0.001$, except the youngest and oldest group ($P < 0.05$) and the age category 25–31 years ($P = 0.37$).

ratio for overall mortality and hazard ratios for different CRP categories significantly differed between men and women.

In contrast, the effect of increased CRP decreased significantly with age. Within younger patients (≤30 years) maximal hazard ratios for overall mortality were significantly higher (hazard ratio 6.7) compared to 1.7 within the oldest subgroups in both sexes (>80 years; See Supplemental Data Table 4a and b). Hazard ratios were similar across ages ≤60, with a drop in the hazard ratios after age 60.

CRP CONCENTRATIONS AND LONG-TERM VS SHORT-TIME SURVIVAL

As expected from an acute-phase marker, particularly high CRP concentrations were more predictive for short-term mortality (with hazard ratios ranging up to 23 for ≤30-day mortality in the highest category) than for intermediate- (>30 days and <1 years) and long-term mortality (>1 years), whereas hazard ratios were considerably lower, reaching 4.5 and 1.4 in the highest CRP category (See Supplemental Data Table 5a; and see Supplemental Data Table 5b for age-related data).

Discussion

Although the role of hs-CRP as a risk predictior in general populations is well established, especially for cardiovascular disease, this study is the first to evaluate the impact of low-sensitivity CRP in risk prediction in acute-phase patients at the time of hospital admission. Our large hospital-based cohort study with a long follow-up period suggests that the measurement of concentrations of low-sensitivity CRP provides strong predictive information, independent of clinical diagnosis, about short- and long-term survival, especially in younger patients (≤30–60 years). Although, as expected, the risk associated with CRP in relation to short-term mortality was substantially higher than with long-term mortality, our data indicate that acute inflammation also has a strong association with long-term outcome, in contrast to the popular findings about low-grade chronic inflammation. With our database we cannot determine whether this effect is confounded by factors correlated with CRP,.

CRP AND CARDIAC DEATH

In the current study, we observed significantly higher CRP concentrations in patients whose deaths were attributable to ischemic heart disease. Our data extend the landmark studies from Ridker et al. *(7–10)*, who established hs-CRP as a risk marker for cardiovascular mortality, to CRP concentrations observed in acute inflammation. In our study, patients within the highest category who had CRP concentrations >80 mg/L, which is indicative for acute inflammation, also had the highest cardiovascular mortality, suggesting that not only chronic but also acute inflammation might contribute to coronary events. Both short- and long-term cardiovascular mortality were associated with increased CRP, although as expected the association was stronger for short-term mortality. These findings suggest that acute inflammation, the most frequent cause for such increased CRP concentrations, might also exert more sustained, long-term effects on cardiovascular risk by mechanisms that remain to be elucidated.

CRP AND CANCER

In our group of 274 515 community-dwelling patients, nearly one-third of the deaths were recorded for cancer (16 804, 6.1%). Interestingly, patients with increased CRP had a higher risk of dying from cancer (Fig. 2) than from other causes independent of acute infection. Of note, the association of CRP with cancer death was stronger than with vascular and ischemic heart disease death. Apart from an increased cardiovascular risk, increased CRP as an inflammatory marker also seems to be predictive for cancer risk. Similar results have been described previously for ovarian *(17)* or colorectal *(18)* cancer.

Additionally, in patients with cancers such as hepatocellular carcinoma, preoperative serum CRP concentrations are an independent and significant indicator of poor prognosis and early recurrence *(19)*. The role of CRP as a predictor of survival has been shown in

multiple myeloma, melanoma, and lymphoma and in ovarian, renal, pancreatic, and gastrointestinal tumors *(20)*. Therefore, CRP concentrations could provide valuable information for palliative care.

SEX, AGE, AND INFLAMMATION

Previously, CRP concentrations were thought to be similar in women and men *(21, 22)*, but this supposition was based on comparisons of CRP concentrations across different studies with heterogeneous study populations rather than on direct comparisons between men and women within the same sample. Moreover, the previous studies were largely performed in volunteers, who may differ from the general population in important ways.

Our study in 274 515 hospitalized patients showed that CRP concentrations steadily increased with age, and female patients had significantly lower CRP concentrations in all age categories ($P < 0.001$) except for the younger subgroup (25–31 years; $P = 0.37$, Fig. 4). These findings contrast with those of a recently reported study in which CRP was measured in 2749 white and black individuals age 30–65 years participating in the Dallas Heart Study *(23)*. This study, however, was performed in an outpatient cohort and thus cannot be directly compared to our study.

The clinical implications of sex differences in CRP concentrations require consideration, because several studies have shown a strong association between CRP concentrations and cardiovascular outcomes in women *(7, 13, 23)*.

Interestingly, the influence of CRP on overall survival was stronger in younger individuals (≤30–60 years) than in older patients. One could speculate that because immune responsiveness generally decreases with age *(24)*, acute inflammation might be better tolerated in older patients, resulting in a more favorable long-term outcomes. Most likely, however, this difference might be attributable to the higher background mortality at higher age and not necessarily changes in immune responsiveness.

STRENGTHS AND LIMITATIONS OF THIS STUDY

We evaluated the association of low-sensitivity CRP with all-cause mortality in a large hospital-based population. Our approach offers a unique evaluation of the performance of risk markers for outcome in a large population (n = 274 515) over a long time period, yielding a total of 1 340 000 person years. Because Austrian laws require that all deaths be recorded in the central death registry, this approach allowed almost complete follow-up of all patients. The only losses to follow-up might have occurred because of spelling errors in names, resulting in faulty record linkage, or missing persons, who are not declared dead until 50 years after date of disappearance. Overall we estimated that these losses to follow-up affect <1% of the study population and were negligible for statistical analysis. In contrast to clinical diagnoses, which are subject to examiner bias and usually vary with different diagnostic criteria, death is usually reliably recorded and misdiagnoses rarely occur. Because of the high postmortem frequency (35%) and the Austrian legal situation, we estimate that diagnoses leading to death are recorded correctly in approximately 95% of cases.

This study had several limitations. As we are well aware, patients admitted for CRP determination are not a representative sample of the healthy Austrian population and might be preselected for worse outcome. However, the included cohort comprises approximately 15% of the total Viennese population, and our reference category had an overall mortality comparable to that within the Austrian population (Fig. 3). Thus, we did not observe evidence for a major selection bias with regard to our outcome variables. Because hospital admission in these patients was frequently triggered by an acute event, CRP concentrations in this study cannot be directly compared to those observed in healthy individuals *(8, 22)*. However, if the implications of increased CRP applied only to acute conditions, one would not expect excess long-term risk. Our data suggest some of the same behavior of CRP in hospitalized patients as in the general population (See Supplemental Data Table 5a–b).

The hospital-based patient cohort is an evident limitation of this study, and adjustment was possible only for age and sex in our analysis and not for other important risk factors that might have influenced CRP concentrations *(1)*. Thus, we cannot determine whether CRP is an independent risk factor, and the hazard ratios are likely overestimates compared to models, which can control for more risk factors. In addition, we cannot exclude the possibility that inclusion of younger patients (≤30 years) who usually have a low mortality rate might have biased our estimates. On the other hand, young people in a hospital population may have serious underlying disease in contrast to nonhospitalized young people, and in our study this expectedly low-mortality patient group (≤30 years) had a relative risk for unfavorable outcome comparable to or higher than patients up to 60 years old (See Supplemental Data Tables 4 and 5b). Moreover, except for the age group of 81+ years, the distribution of the total number of patients in each age category was approximately equal, and the interquartile range for age was 34–66 years.

Another limitation of this study was the absence of data on hs-CRP concentrations. This test was unavailable for routine laboratory analysis at the beginning of our study. To analyze all available data, we had to set a

cutoff at 5 mg/L. Because most of the CRP range used in studies of general populations was grouped in our lowest CRP category (<5 mg/L), our data do not contribute to knowledge about low-grade chronic inflammation. However, determination of hs-CRP may not be necessary in a hospital-based cohort because of generally higher values compared to population-based samples. Furthermore, we are aware that the association of CRP with mortality does not necessarily imply a causal relationship.

In conclusion, the determination of low-sensitivity CRP at the time of hospital admission is valuable for predicting outcome, especially in patients ≤30–60 years, and CRP could serve as a useful triage marker to assess risk of future death. Because patients with CRP >80 mg/L had a 10-year mortality of almost 30% regardless of underlying diagnosis, these patients might particularly benefit from individual prevention strategies. We were able to demonstrate that independently of underlying disease, basal CRP concentrations are a major predictor of both short- and long-term mortality, indicating that acute inflammation also has a strong association with long-term outcome. Our findings suggest that close attention should be paid to hospitalized patients with high CRP not only in the short term, because of very substantial risk, but also during long-term follow-up because of ongoing excess risk.

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