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NICOLAUS COPERNICUS UNIVERSITY IN TORUŃ

MEDICAL RESEARCH JOURNAL

ISSN: 2451-2591

e-ISSN: 2451-4101

Surprisingly low C-reactive protein levels in the statistics of sudden death among patients in the Regional Hospital in Racibórz, Poland

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DOI: 10.5603/mrj.103062

Article type: Original article

Submitted: 2024-10-12

Accepted: 2024-11-05

Published online: 2024-12-04

ORIGINAL ARTICLE

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Surprisingly low C-reactive protein levels in the hospital sudden death statistics. A retrospective Polish single-center analysis

Short title: Wawrzyniec Mantorski et al., Low C-reactive protein levels in the sudden death statistics

DOI: 10.5603/mrj.103062

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ABSTRACT

Identifying patients at high risk of in-hospital mortality within the early days of admission is crucial for guiding medical decisions and allocating resources effectively. This study aimed to explore whether changes in routinely conducted in-hospital admission tests were associated with sudden death among patients (all causes) in the Regional Hospital in Racibórz, Poland. The first laboratory tests of ten biomarkers from 7,827 unique patients were examined, from January 1 to December 31, 2023. Associations between risk factors and all-cause sudden death outcomes were estimated using Cox regression. Based on the estimated concordance statistic, C-reactive protein, among other biomarkers, showed the best fit in the model.
Its values were categorized following the interquartile ranges and death rates for each range were modeled using Poisson regression. Despite acknowledging all other possible causes that may have contributed to the early deaths of patients, a surprisingly low and statistically significant ($p < 0.05$) CRP threshold of 7.4 mg/L was found to differentiate 30-day mortality in patients. Regarding patient deaths, the estimates for hospital wards align with expectations, indicating that an elevated mortality risk was observed in the Intensive Care Unit and Internal Medicine Ward compared to the Emergency Department. The study results shed new light on CRP significance, suggesting the need for further research and verification.

Keywords: in-hospital admission, sudden death, C-reactive protein

Introduction

Identifying patients at high risk of in-hospital mortality within a few days of admission is crucial for guiding medical decisions and allocating resources effectively. Thirty-day survival observation periods for patients after admission to the emergency department have been the subject of many previous studies. The most predictive variables for in-hospital mortality were socio-demographic factors, i.e., older age (greater risk) and admission with a confirmed appointment (reduced risk) [1]. Among the identified risk factors for in-hospital 30-day lethality in laboratory-confirmed cases of influenza were male sex, older age, AH1N1 subtype, and other chronic diseases [2]. In turn, patients admitted to tertiary hospitals, high-volume hospitals, and

hospitals with high or medium timeliness were more likely to survive for 30 days [3]. Significant spontaneous coronary artery dissection in Canada occurred within 30 days after hospital admission [4], while over 11 years of resuscitation efforts for in-hospital cardiac arrest in Sweden showed an overall increase in adjusted 30-day survival rates [5]. In studies in the field of cardiovascular diseases, it is worth mentioning interpretable machine learning models for predicting in-hospital 30-day survival after acute coronary syndrome and urgent coronary artery bypass graft surgery, with creatinine levels identified as the most important predictor [6]. Chemical determinants, such as the levels of soluble urokinase plasminogen activator receptor, were also found to predict adverse events at 30 days in hospital emergency departments in Spain [7].

This study aimed to investigate the risk factors that influenced sudden death among patients 30 days after admission to the Regional Hospital wards in Racibórz, Poland, in the post-COVID-19 era (2023). A classical ensemble statistical framework was employed, using a single-center registry of patient deaths, along with demographic data and clinical characteristics, to build interpretable predictive risk models for short-term fatal events in a typical second-level reference regional hospital in Poland.

Materials and methods

Materials

A retrospective single-center study was conducted using medical records and electronic data from in-hospital admissions in various wards at the 320-bed public Multi-specialist Hospital in Racibórz, Poland. The hospital discharges approximately 2500 patients monthly, with admissions identified by codes from the 10th Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10).

In the case of admissions via the Emergency Department (ED) and planned admissions, hematological/morphological testing is not always necessary as part of the so-called internal medicine package. For example, simple traumatic injuries, such as sprains and even fractures, do not require blood tests.

Exposure ascertainment

The following hematological/morphological biomarkers were of interest for the present study: WBC — white blood cells, RBC — red blood cells, HGB — hemoglobin, HCT — hematocrit, MCV — mean corpuscular volume, MCH — mean corpuscular hemoglobin, MCHC — mean corpuscular hemoglobin concentration, RDW-SD — red cell distribution width (standard deviation), RDW-CV — red cell distribution width (coefficient of variation), and CRP — C-reactive protein. Patients were included in the study if they received care between January 1, 2023, and December 31, 2023, and had at least one measurement of these biomarkers.

Due to repeated visits by some patients and subsequent treatments that might affect hematological/morphological indices, only the first laboratory tests of biomarkers during the study period were examined. In the study, data from 7,827 unique patients was analyzed, resulting in (7,827 patients*10 biomarkers =) 78,270 measurements from a total of 167,101 laboratory tests. Measurements of the blood biomarkers were performed in the hospital's Laboratory Unit using Sysmex XN-2000 (Sysmex Corporation, Japan) analytical systems with EDTA-KE/2.7 ml samples. Additionally, serum Z/4.9 ml samples were used to measure C-reactive protein (CRP).

Outcome ascertainment

The outcome of interest was all-cause mortality (257 cases of death). Patients were considered at risk for mortality from the day after the first hematological/morphological biomarker measurement until the first occurrence of death or censoring, which could occur up to one month (≤ 30 days) before the ED visit or in-hospital admission. The age of the deceased patients ranged from 38 to 99 years.

Methods

Associations between the hospital wards and in-hospital hematological/morphological tests with all-cause sudden death outcomes were estimated using Cox regression. Based on the estimated concordance statistic, the most fitting biomarker for sudden death outcome was

selected. Then, for its interquartile ranges, death rates (observed versus expected events, often referred to as ‘person-years’ summaries) for each range were estimated using Poisson regression [8]. If the exponentiated coefficient from the Cox model is a hazard ratio (HR), then this is known in the Poisson model as the standardized mortality ratio (SMR), with a baseline category set at the lowest value (SMR = 1.00), corresponding 95% confidence interval (95% CI), and p-value (in the present study, a p-value < 0.05 was considered statistically significant).

A similar approach using SMR was employed in the study by Kamarulariffin et al., [9] to predict 30-day mortality from acute myocardial infarction among 41 Malaysian public hospitals. A statistical analysis was performed using the ‘survival’ package [10] in the R statistical platform [11].

Results

All-cause sudden death outcomes, i.e., hazard ratios (HRs), with 95% confidence intervals (95% CI), p-values, and concordance statistics for hospital wards (with death cases) and the analyzed risk factors using Cox regression, are reported in Table 1.

Concerning the possible impact of risk factors, with increasing patient age, the risk of premature death rises, and a 10-year age difference results in a $(1.05^{10}-1)*100\% = 63\%$ increase in mortality within one month of hospital admission, which approximately translates to about two-thirds. Moreover, WBC, RBC, HGB, HCT, MCHC, RDW-SD, RDW-CV, and CRP are statistically significant ($p < 0.05$) predictors of early patient mortality. However, CRP shows the best fit in the Cox regression model, with a concordance statistic of 0.819. From this strictly statistical standpoint, CRP was therefore selected for further statistical and clinical consideration.

The range of first-time laboratory-measured CRP concentrations (7,827 values) varied in patients from 0.2 to 666.4 mg/L. The frequency distribution indicates a left-skewed concentration of values that deviates apparently from the properties of a normal distribution (see the histogram in Figure 1).

The following cases of death with CRP concentrations in mg/L (mean ± standard deviation, median) were recorded according to the chapters of the International Classification of Diseases, 10th Revision: Certain Infectious and Parasitic Diseases — 46 (164 ± 94, 157); Neoplasms — 53 (139 ± 85, 128); Endocrine, Nutritional, and Metabolic Diseases — 9 (70 ± 56,

57); Diseases of the Circulatory System — 117 (140 ± 126, 118); Diseases of the Respiratory System — 12 (119 ± 82, 104); Diseases of the Digestive System — 7 (54 ± 48, 41); Diseases of the Genitourinary System — 9 (133 ± 95, 113); and Symptoms, Signs, and Abnormal Clinical and Laboratory Findings, Not Elsewhere Classified — 4 (112 ± 142, 62). The number of patients and the 30-day deaths in the four interquartile ranges of CRP measurements are presented in Table 2.

The crude sudden death rates of patients reported in Table 2 indicate that their frequency is roughly a few times higher in the interquartile range of CRP from 2 to 7.4 mg/L compared to below 2 mg/L, several-fold higher up to over 40 mg/L, and dozens of times higher above this value. One in ten patients dies within the first month of admission when the biomarker level exceeds this threshold. Additionally, the plot of death fractions across interquartile ranges is shown graphically in Figure 2.

The data in Table 2, particularly the graph in Figure 2, show a dynamic increase in the fraction of deaths across successive interquartile ranges.

The estimated SMRs (with 95% CI and p-values) are reported in Table 3 and are graphically presented in the forest plot in Figure 3.

The results from Table 3 show that early patient mortality (≤ 30 days) is statistically higher ($p < 0.05$) starting from a CRP concentration of 7.4 mg/L compared to the lowest interquartile range of < 2 mg/L. The age-standardized mortality risk for patients with CRP levels in the range of 7.4 to 40.9 mg/L was nearly ten times higher, and for levels above 40.9 mg/L, it was more than 35 times higher.

Additionally, Table 1 shows that the highest mortality rate was recorded in the Intensive Care Unit (ICU), i.e., five times higher than in the ED and three times higher than in the Internal Medicine Department (IMD). In the Trauma and Orthopedic Surgery, Geriatrics, and Observation and Infectious Diseases departments, the risk of patient death was much lower compared to that in the Emergency Department (all the mentioned differences were statistically significant, i.e., $p < 0.05$). It is of note that Table 1 does not include statistical results for the remaining departments of Gynecology and Obstetrics, Ophthalmology, Long-Term Care, Otolaryngology, and Pediatrics, as the results were incalculable due to the lack of clinical responses (patient deaths).

Discussion

While reviewing the literature, the authors noticed that analyses of patient survival in emergency departments, as well as within 30 days of hospital admission (for inpatients), are quite commonly conducted by researchers worldwide. In these types of studies, authors strive to identify the leading risk factors for premature patient mortality and to explore whether these deaths were preventable. However, they often arrive, as expected, at inconsistent (and frequently divergent) results.

Most statistical analyses, in the authors' view, involve patients who have already been specifically diagnosed or are part of a defined research cohort. Indeed, in a 2016–2018 analysis of 30-day in-hospital trauma mortality in patients admitted with an injury mechanism of road or rail-related injury, fall, assault, or burns in four urban Indian university hospitals (in New Delhi, Mumbai, and Ahmedabad), abnormal physiological parameters such as a low SBP, SpO2, and GCS and high HR and RR were observed among non-survivors [12]. Or, in a prospective study of 750 spontaneously enrolled patients with spontaneous coronary artery dissection from 22 Canadian centers (from June 2014 to June 2018), significant cardiovascular complications occurred within 30 days and affected women with myocardial infarction [13].

As can be seen, the 30-day survival of patients from the moment of hospital admission involves a wide range of conditions. The present focus on CRP is not unique. Since CRP is a non-specific liver marker that can be elevated in various conditions — including infections, chronic inflammatory diseases, and even some cancers — it can be effectively used to monitor overall health.

Indeed, in a meta-analysis of prospective studies, Zhou et al. [14] confirmed that CRP is an independent predictor of sudden death. Similar conclusions were drawn in the study by Mazurkiewicz et al. [15]. In a large group of nonagenarian patients, special attention should be given to CRP and albumin levels, as these may serve as useful indicators of hospital mortality in this age group. In the study by Ziakas et al. [16], the association between CRP levels and in-hospital prognosis during a 6-month observation period was also addressed. In turn, Luo et al. [17] suggested that CRP was a better predictor of death than age, neutrophil count, and platelet count, with a cutoff value of 41.4 mg/L. Additionally, in a retrospective study by Milenkovic et al. [18], involving patients with COVID-19 pneumonia, critical threshold values for markers

such as IL-6 ≥ 74.98 pg/mL, CRP ≥ 81 mg/L, procalcitonin ≥ 0.56 ng/mL, and D-dimer ≥ 760 ng/mL were identified as effective predictors of in-hospital mortality. The present analysis also suggests that a one-month observation period from the time of patient admission to the hospital differentiates their mortality based on manifest CRP levels. In short, it is particularly surprising that the present results indicate that after the customary grouping of patients according to quartile thresholds, their hospital mortality is elevated (Table 2, Fig. 2), with a statistically significant difference ($p < 0.05$) starting at a level of 7.4 mg/L and above (Table 3, Fig. 3).

In light of literature reports indicating much higher risk thresholds, it is challenging to explain this clinical finding. The authors are also aware that the significance of this result cannot be overestimated, as other causes underlying the early deaths of patients were not taken into detailed consideration. Only a general comparison with CRP levels was made. Nevertheless, it might serve as a premise for qualifying the biomarker as a prognostic indicator in the early stages of treatment and consideration for antibiotic prescription when elevated CRP levels are detected.

In the authors' opinion, given the differences in mortality risk between hospital departments, the present CRP finding should not be seen as coincidental. The lower mortality rate in the ED compared to other wards (Table 1) may reflect effective hospital organization and collaboration between ED physicians and other departments (the medical guidelines at Racibórz Hospital are strictly enforced by management, limiting patient stays in the ED to a maximum of 6 hours; during this time, patients should receive first aid, basic treatment, and undergo diagnosis for potential further care). Consequently, after basic stabilization and diagnostic procedures, patients are promptly transferred to the appropriate specialized hospital wards. In the ICU, the most severe cases significantly increase the hazard ratios, which are nearly five times greater than those in the ED. Similarly, the HR in the IMD is three times higher, as it often receives terminal oncology patients. These facts highlight the risk of early deaths associated with the patients themselves and emphasize the importance of identifying easily testable prognostic factors.

Conclusions

Based on the collected measurement and epidemiological data, along with the applied statistical methodology, the following conclusions from this research were drawn:

1. Among the standard hematological/morphological biomarkers — WBC, RBC, HGB, HCT, MCV, MCH, MCHC, RDW-SD, RDW-CV, and CRP — CRP demonstrated the best fit for the established Cox regression within the month following patient admission to a typical Polish second-level regional hospital.
2. Despite elevated mean CRP levels in patient deaths, the quartile distribution indicates that the biomarker concentration at which the risk of a fatal event significantly increases ($p < 0.05$) is already > 7.4 mg/L.
3. The remaining results align with the epidemiology of early patient deaths, indicating that elevated mortality risk is typical in wards such as the Intensive Care Unit and Internal Medicine Department. These results affirm the effective organization of work at the hospital and internal causes of patient mortality.
4. The analysis acknowledges the simplifications made, as it does not delve into the details of other causes that may have contributed to the early deaths of patients. Thus, the statistical results on CRP in this study require further research and verification.

Article information

Data availability statement: *The dataset used in this study is available upon request.*
Ethics statement: ***NA***
Author contributions: *Study design: Wawrzyniec Mantorski, Andrzej Tukiendorf, Katarzyna Olszak-Wąsik; data collection: Wawrzyniec Mantorski; statistical analysis: Andrzej Tukiendorf; data interpretation: Andrzej Tukiendorf, Wawrzyniec Mantorski, Iwona Kulik-Parobczy; manuscript preparation: Wawrzyniec Mantorski, Edyta Wolny-Rokicka, Iwona Kulik-Parobczy, Katarzyna Olszak-Wąsik, Andrzej Tukiendorf.; literature search: Wawrzyniec Mantorski, Edyta Wolny-Rokicka, Katarzyna Olszak-Wąsik, Iwona Kulik-Parobczy Andrzej Tukiendorf.*
Funding: ***NA***
Acknowledgments: ***NA***

Conflict of interest: *There is no conflict of interest.*

Supplementary material: ***NA***

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Table 1. HRs with 95% confidence intervals (95% CI), p-values, and concordance statistics for risk factors and hospital wards (with death cases)

Risk factor	HR	95%CI	p-value	Concordance
Age	1.05	(1.04, 1.06)	<0.0001	0.743
Female vs. male	1.00	(0.78, 1.28)	0.9920	0.487
WBC	1.012	(1.010, 1.015)	<0.0001	0.672
RBC	0.721	(0.614, 0.848)	0.0001	0.592
HGB	0.839	(0.787, 0.895)	<0.0001	0.591
HCT	0.967	(0.950, 0.985)	0.0003	0.569
MCV	1.009	(0.993, 1.026)	0.2740	0.558
MCH	1.004	(0.961, 1.049)	0.8620	0.544
MCHC	0.784	(0.712, 0.864)	<0.0001	0.562
RDW-SD	1.034	(1.027, 1.042)	<0.0001	0.729
RDW-CV	1.186	(1.150, 1.222)	<0.0001	0.723
CRP	1.010	(1.009, 1.011)	<0.0001	0.819

Emergency Department (8)	1.00	(ref.)	--	--
General Surgery (25)	0.78	(0.32, 1.88)	0.5786	--
Orthopedic Trauma Surgery (4)	0.20	(0.06, 0.70)	0.0117	--
Internal Medicine Department (139)	2.95	(1.33, 6.55)	0.0079	--
Geriatric Department (3)	0.23	(0.06, 0.91)	0.0361	--
Intensive Care Unit (42)	4.89	(2.06, 11.6)	0.0003	--
Infectious Diseases Department (11)	0.37	(0.14, 1.00)	0.0494	--
Pulmonological Department (25)	1.48	(0.62, 3.56)	0.3795	0.815

Table 2. The number of patients and the 30-day deaths in the four interquartile ranges of CRP levels

Interquartile range:	**I**	**II**	**III**	**IV**
CRP range [mg/L]	[0.2, 2)	[2, 7.4)	[7.4, 40.9)	[40.9, 666.4]
Survived	1949	1931	1935	1755
Dead	3	7	44	203
% of dead	0.2	0.4	2.2	10.4
Times higher	1.0 (ref.)	2.4	14.5	67.5

Table 3. SMRs with 95% CI and p-values for CRP interquartile ranges

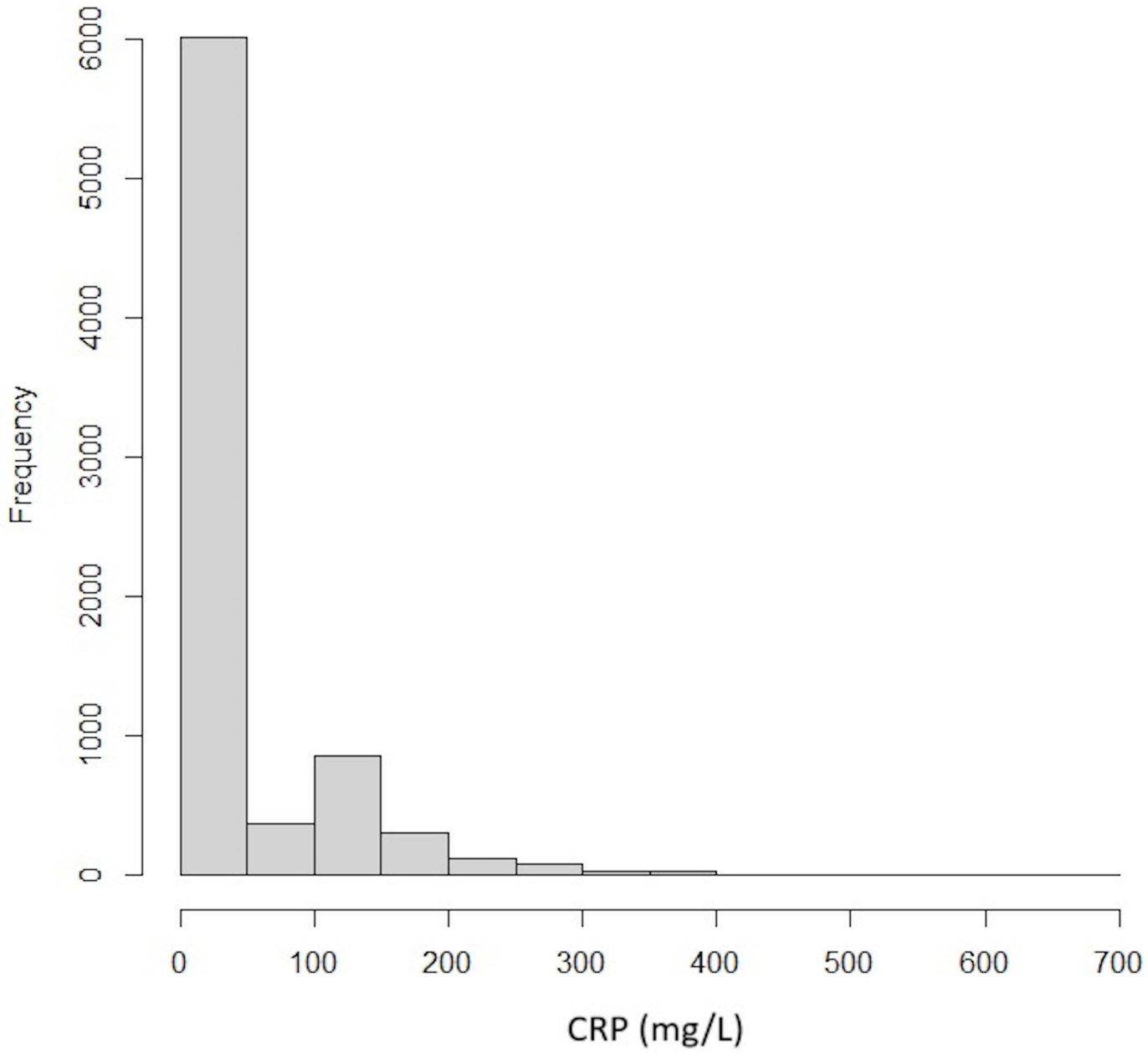
CRP range	**SMR**	**95%CI**	**p-value**

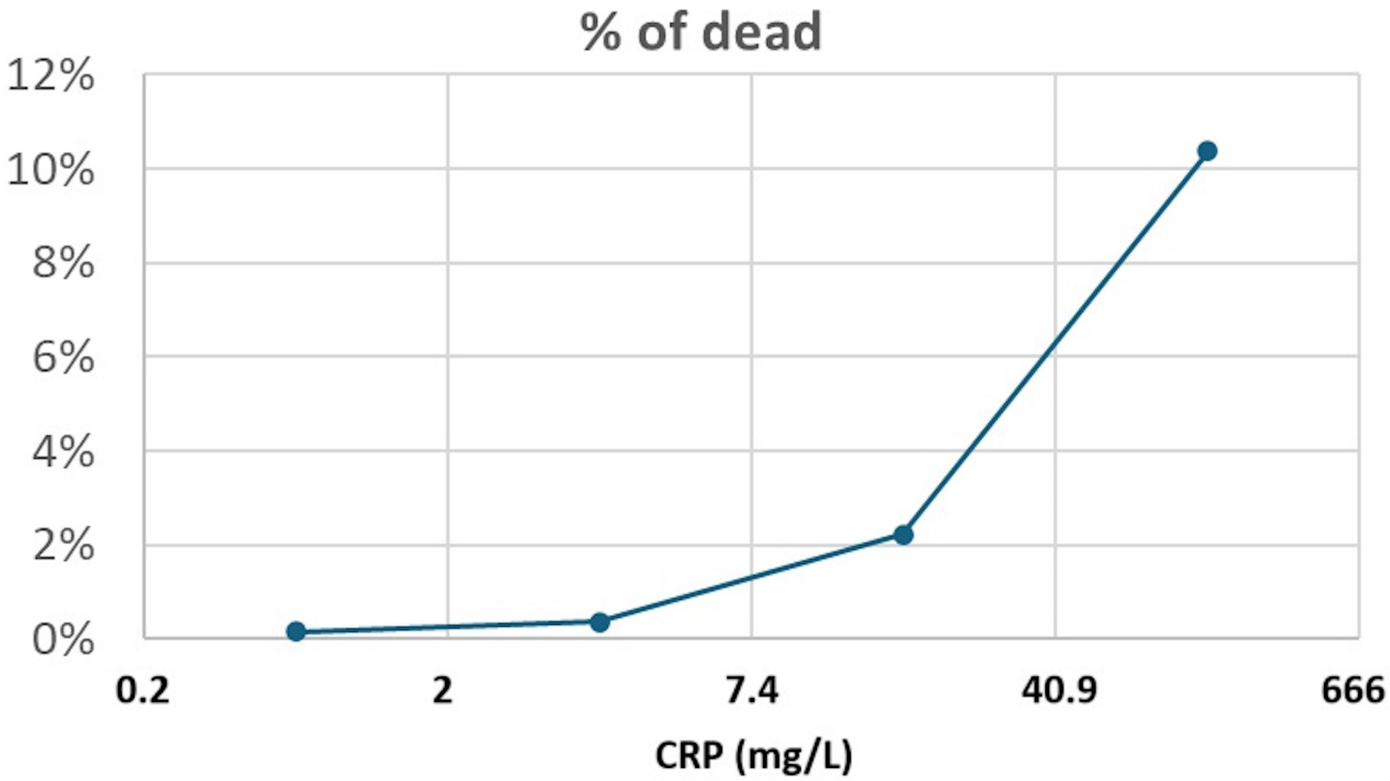
[0.2, 2.0)	1.00 (ref.)	--	--
[2.0, 7.4)	1.92	(0.50, 7.40)	0.3448
[7.4, 40.9)	10.1	(3.15, 33.0)	0.0001
[40.9, 666.4]	35.3	(11.3, 110)	< 0.0001

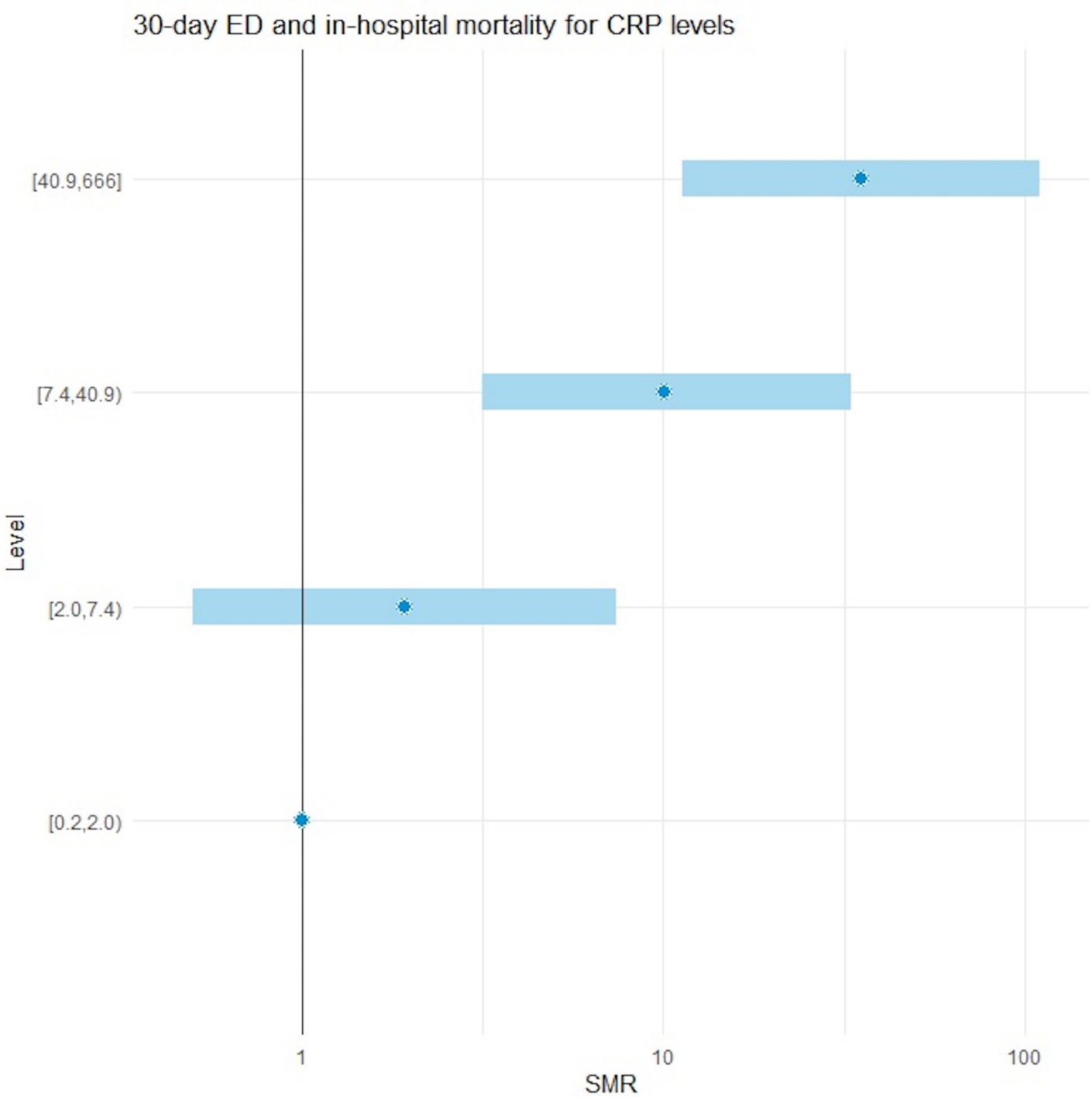
Figure 1. Frequency distribution of first-time laboratory-measured CRP concentrations

Figure 2. Fractions of early patient deaths across interquartile ranges

Figure 3. SMRs with 95% CI for CRP interquartile ranges


Frequency
0
1000
2000
3000
4000
5000
6000
0
100
200
300
400
500
600
700
CRP (mg/L)


% of dead
12%
10%
8%
6%
4%
2%
0%
0.2
2
7.4
40.9
666
CRP (mg/L)


30-day ED and in-hospital mortality for CRP levels
[40.9,666]
[7.4,40.9)
[2.0,7.4)
[0.2,2.0)
Level
1
10
100
SMR