

# Pattern of change of C-reactive protein levels and its clinical implication in patients with acute poisoning

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## Abstract

**Objectives:** C-reactive protein is well known as an inflammatory indicator in injury, infection, and cancer. However, little is known about its role in poisoning. C-reactive protein levels first increase and then decrease within several days during poisoning management. This study aimed to verify the C-reactive protein change pattern and its clinical co-infection possibility in patients with poisoning.

**Methods:** Daily C-reactive protein levels of the patients with poisoning, who were admitted for more than 5 days, were measured. Microbial cultures were conducted, and fever ( $\geq 38^{\circ}\text{C}$ ) and infection-related symptoms were investigated.

**Results:** In the enrolled 56 patients, the initial median C-reactive protein levels at hospital day 1, 2, 3, 4, and 5 were 0.28, 4.85, 10.91, 10.57, and 6.68 mg/dL, respectively. C-reactive protein level was the highest at hospital day 3 and decreased thereafter. No statistical difference was observed in the daily and maximal C-reactive protein levels between the culture-positive and culture-negative groups. The levels at hospital days 3–5 and the maximal level were 8.4, 9.2, 5.49, and 11.02 mg/dL, respectively, in non-fever group. The levels at hospital days 3–5 and the maximal level were 7.4, 9.2, 4.74, and 10.81 mg/dL, respectively, in non-symptoms group. Levels at hospital days 3–5 and the maximal level were 5.21, 4.93, 3.7, and 5.28 mg/dL, respectively, in all-negative (culture-negative without fever or infection symptoms) group.

**Conclusions:** Acute rise and fall of C-reactive protein levels can be observed in the infection-unlikely patients with poisoning. The levels were similar to bacterial infection levels, possibly due to the drug reaction itself, rather than for superimposed infections.

## Keywords

Acute-phase proteins, inflammation, metabolism

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## Introduction

The World Health Organization reports more than 300 million patients with pesticide intoxication annually.<sup>1</sup> The rate of suicide has been increasing in Korea and the associated socio-economic cost is estimated to be approximately 5.8 billion dollars. The most common mode of suicide attempt is poisoning.<sup>2,3</sup> Although acute poisoning for suicide is frequent, antidotes for specific poisons are still limited. Thirty types of antidotes have been introduced till date, 20 of which are available in Korea. Some of them are dedicated as orphan drugs and are available at dedicated toxicology centres only. Very few cases of poisoning can be diagnosed based on a laboratory test in the hospital. Therefore, physicians have to majorly rely on history taking, physical examinations, and toxidromes when treating such patients with acute poisoning.

Various clinical findings, and electrocardiography and blood or urine sample results are required to predict the severity, prognosis, and complications related to poisoning. Arterial blood gas, complete blood count, and electrolytes are checked

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almost routinely. C-reactive protein (CRP) levels are also used frequently for the purpose.

CRP affects the host immune response mainly by anti-inflammatory reaction and is well known as an inflammatory indicator that is elevated in injury, trauma, infection, cancer, and autoimmune diseases. High CRP level is an indicator of bacterial infection, severe symptoms, and poor prognosis.<sup>4</sup> CRP is a high-risk indicator for cardiovascular disease and stroke and is elevated upon metabolic stress.<sup>5–8</sup>

However, very little is known about the role of CRP in acute poisoning. A couple of studies had been reported previously regarding prognosis prediction by CRP in specific substance poisoning.<sup>9,10</sup> In our experiences, CRP is increased and then decreased, within several days, during the management of patients with intoxication, who were less likely to have any infection. Very limited evidence exists regarding the clinical implication of elevated CRP in poisoning. If the latter occurs due to an infection, various diagnostic tests, such as radiological imaging, including computed tomography (CT); culture; and spinal tapping would need to be performed. If CT is performed, side effects might occur due to the contrast or ionised radiation. If antibiotics are administered, there may be potential risks during the metabolism of poison via liver or kidney. In other words, hospital duration, expenses, and medical concerns would be greatly increased. This study, therefore, aimed to verify the pattern of CRP change and its clinical co-infection possibility in patients with acute poisoning.

## Methods

### Study design and setting

This was a retrospective observational study conducted from June 2017 to May 2020 at Dankook University Hospital, the academic tertiary medical centre in South Korea. The hospital is affiliated to the regional emergency centre and toxicology centre. The number of visiting patients in the emergency department (ED) annually is approximately 42,000 and the number of beds is 860.

### Study protocol

Patients with acute poisoning, who were admitted in our hospital for more than 5 days during the study period with daily CRP and various cultures (blood, urine, and sputum) conducted, were included in the study. Exclusion criteria were as follows: those younger than 10 years of age, those who refused admission, those with incomplete medical records, those who were admitted or expired in less than 5 days, and those with trauma. Diagnosis of acute poisoning was made based on clearly identified history taking, treatment responses (patient or the witness's statement or immediate response to antidote use, such as flumazenil), or laboratory drug test results. Underlying diseases, including systemic lupus erythematosus and rheumatic arthritis, were also investigated, since CRP

elevation could be altered in patients with rheumatic diseases.<sup>11</sup> Laboratory results, including daily CRP levels, and appropriate cultures for fever and infection symptoms during the hospitalisation, were investigated. Fever was defined by a body temperature of more than 38°C. CRP level was determined by immunoassay method using C-reactive protein Gen.3 (COBAS 8000 E801; Roche Diagnostics, Rotkreuz, Switzerland). The normal range was below 0.5 mg/dL.

### Ethics statement and study approval

The study was reviewed and approved by the institutional review board (IRB) of our hospital (DKUH 2021-03-002-002). The need for informed consent was waived from the IRB owing to the retrospective nature of the study. This study was conducted in accordance with the STROBE cross-sectional reporting guidelines.<sup>12</sup>

### Statistical analysis

Categorical variables are represented as numbers and percentages. Continuous variables are shown as mean  $\pm$  standard deviation or median (interquartile range). CRP levels were compared using the Mann–Whitney test, since the levels did not show normal distribution. Kolmogorov–Smirnov and Shapiro–Wilk tests were further used to evaluate the normality. Correlation was analysed via the Spearman's correlation method. SPSS version 26 (IBM SPSS Inc., Chicago, IL, USA) was used and  $p$  value  $< 0.05$  was considered statistically significant.

## Results

A total of 708 intoxicated patients visited our ED during the study period. Among them, 652 were excluded and the remaining 56 patients were enrolled. Mean age was 67.7 years and 35 (62.5%) of them were males (Table 1). Those with underlying diseases were 33 (58.9%) in number; no patient had rheumatic disease. Pesticide poisoning was seen in 32 (57.1%) cases. Single drug-intoxicated patients were 37 in number (66.1%) and those intoxicated with more than 2 kinds of poisons were 14 in number (25%). Of them, 10 (17.9%) were treated with antidotes and 15 (26.8%) received gastric lavage. Forty-two (75%) were admitted in the intensive care unit (ICU). Mean duration of ICU admission was 8.1 days and mean duration of hospitalisation was 12.8 days.

The initial median CRP level at hospital day (HD)1 was 0.28 mg/dL, whereas that at HD2 was 4.85 mg/dL, at HD3 was 10.91 mg/dL, at HD4 was 10.57 mg/dL, and at HD5 was 6.68 mg/dL. CRP level at HD3 was the highest and decreased thereafter (Table 2, Figure 1).

The daily CRP and the maximal CRP levels were compared between the comorbidity and the non-comorbidity group. No statistical difference was observed ( $p$ -value = 0.588, 0.091, 0.405, 0.731, 0.980, 0.868, respectively).

**Table 1.** Baseline characteristics of the patients with intoxication.

Variables	N=56
Age (years)	67.7 ± 18.6
Male	35 (62.5)
Underlying medicosurgical issues	33 (58.9)
Hypertension	28 (50)
Diabetes mellitus	13 (23.2)
Liver disease	1 (1.8)
Ischemic heart disease	2 (3.6)
Stroke	7 (12.5)
Malignancy	5 (8.9)
Underlying psychological disease	19 (33.9)
Underlying rheumatic disease	0 (0)
Pesticide poisoning	32 (57.1)
Number of poisons	
Single drug	37 (66.1)
Multiple drugs	14 (25)
Unknown	5 (8.9)
Types of poisons	
Glufosinate ammonium	14 (25)
Organophosphate	8 (14.3)
Pyrethroid	5 (8.9)
Indoxacarb	3 (5.4)
Emamectin benzoate	1 (1.8)
Other pesticides	2 (3.6)
Benzodiazepine	13 (23.2)
Clonazepam	3 (5.4)
Quetiapine	3 (5.4)
Trazodone	3 (5.4)
Lithium	2 (3.6)
Vitamins	2 (3.6)
Haloperidol	1 (1.8)
Valproate	1 (1.8)
Levothyroxine	1 (1.8)
Dapsone	1 (1.8)
Oxycodone	1 (1.8)
Flocoumafen	1 (1.8)
Chlorpromazine	1 (1.8)
Unknown	5 (8.9)
Suicide attempt	43 (76.8)
Systolic blood pressure (mmHg)	136.6 ± 34.8
Diastolic blood pressure (mmHg)	77.7 ± 20.9
Heart rate (/min)	88.1 ± 18.9
Respiration rate (/min)	18.7 ± 6.9
Body temperature (°C)	36.3 ± 0.8
GCS (median)	10
Specific antidote use	10 (17.9)
Flumazenil	2 (3.6)
Pralidoxime/atropine	8 (14.3)
Gastric lavage	15 (26.8)
Charcoal ingestion	33 (58.9)
Antibiotic use	56 (100)
ICU admission	42 (75)
ICU admission duration (days)	8.1 ± 8.3 (2–32)
Total admission duration (days)	12.8 ± 10.7 (4–55)

(continued)

**Table 1.** (continued)

Variables	N=56
Outcomes	
Survival to discharge	42 (75)
Expired	2 (3.6)
Hopeless discharge or transfer	5 (8.9)
DAMA	6 (10.7)
Transfer due to patient request	1 (1.8)

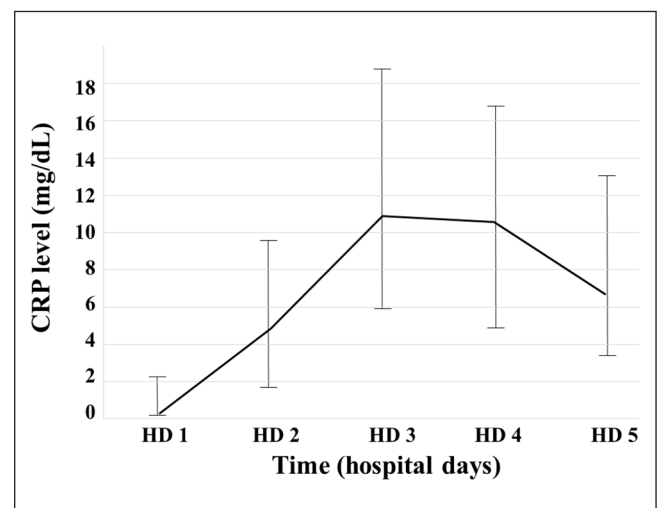
Data are shown as N (%) or mean ± standard deviation.  
GCS: Glasgow Coma Scale; ICU: intensive care unit; DAMA: discharge against medical advice.

Microorganisms were identified in 16 (28.6%) patients while 40 were negative in culture (71.4%); 13 (23.2%) were positive in sputum culture, 6 (10.7%) were positive in urine culture, and 1 (1.8%) was positive in blood culture. No statistical difference in the daily and maximal CRPs was observed between the culture-positive and culture-negative groups (Table 2, Figure 2(a)).

Thirty-two (57.1%) patients developed fever (>38°C). The CRP levels were 12.98 mg/dL at HD3, 11.08 mg/dL at HD4, and 7.65 mg/dL at HD5. Maximal CRP was 15.94 mg/dL. The levels at HD3–5 and maximal CRP were significantly higher in fever group than in the non-fever group (Table 2, Figure 2(b)).

Thirty-four (60.7%) patients developed infection symptoms, such as cough, sputum, dyspnoea, dysuria, and diarrhoea. The CRP levels were 13.73 mg/dL at HD3, 11.59 mg/dL at HD4, and 7.62 mg/dL at HD5. Maximal CRP was 15.65 mg/dL. The levels at HD3–5 and maximal CRP were significantly higher in the infection symptom group than in the non-symptom group (Table 2, Figure 2(c)).

Twelve (21.4%) patients developed no fever or infection symptom and had no microbial growth (all-negative group). The median CRP levels were higher in 3–4 days and

**Figure 1.** The median CRP values of patients with intoxication. CRP: C-reactive protein; HD: hospital day.

**Table 2.** Comparison of serial CRP values with culture results, fever, infection symptoms.

Variables	CRP at HD1 (mg/dL)	CRP at HD2 (mg/dL)	CRP at HD3 (mg/dL)	CRP at HD4 (mg/dL)	CRP at HD5 (mg/dL)	Maximal CRP (mg/dL)
All (N=56)	0.28 (0.08–2.02)	4.85 <sup>a</sup> (1.56–9.40)	10.91 <sup>a</sup> (5.86–18.77)	10.57 <sup>b</sup> (4.78–16.79)	6.68 (3.29–12.96)	14.03 (7.64–21.26)
Non-comorbidity (n=23)	0.23 (0.06–1.50)	2.68 (1.54–5.61)	13.0 <sup>a</sup> (5.58–23.08)	10.44 <sup>a</sup> (5.87–21.86)	6.56 (2.31–13.44)	12.04 (8.37–29.29)
Comorbidity (n=33)	0.42 (0.08–2.34)	6.36 <sup>a</sup> (2.78–10.75)	10.81 (5.59–15.95)	10.57 <sup>a</sup> (4.47–16.31)	7.34 (3.47–12.91)	14.09 (6.81–19.98)
p	0.588	0.091	0.405	0.731	0.980	0.868
Non-culture (n=40)	0.34 (0.11–2.45)	4.83 (1.99–10.19)	10.81 <sup>a</sup> (4.74–17.35)	9.76 <sup>b</sup> (4.17–17.22)	6.26 (2.32–10.15)	12.19 (5.7–21.26)
Any-culture <sup>†</sup> (n=16)	0.22 (0.05–1.71)	5.44 <sup>a</sup> (1.24–9.4)	13.91 (8.04–22.19)	10.74 (7.22–16.79)	8.04 (11.09–22.19)	14.86 (11.09–22.19)
p	0.314	0.821	0.274	0.629	0.336	0.261
Non-fever (n=24)	0.28 (0.06–1.87)	4.78 (1.26–6.09)	8.4 <sup>a</sup> (2.74–14.69)	9.2 <sup>a</sup> (1.67–12.47)	5.49 (1.55–7.67)	11.02 (4.93–16.71)
Any-fever (n=32)	0.34 (0.09–2.46)	5.77 <sup>a</sup> (1.56–11.72)	12.98 (7.45–21.26)	11.08 <sup>a</sup> (8.09–21.5)	7.65 (4.57–16.71)	15.94 (10.51–29.87)
p	0.613	0.186	0.040	0.032	0.004	0.013
Non-infection symptom (n=22)	0.5 (0.15–2.14)	4.2 <sup>a</sup> (1.44–6.11)	7.4 <sup>a</sup> (2.73–14.51)	9.2 <sup>a</sup> (2.18–12.13)	4.74 (1.79–7.83)	10.81 (4.59–15.99)
Any infection symptom (n=34)	0.19 (0.05–2.18)	5.69 (1.56–12.13)	13.73 (7.35–21.81)	11.59 <sup>a</sup> (7.58–20.85)	7.62 (4.69–15.37)	15.65 (10.71–29.48)
p	0.227	0.074	0.036	0.048	0.014	0.004
All-negative* (n=12)	0.84 (0.13–2.54)	4.44 (1.49–6.21)	5.21 <sup>a</sup> (1.82–14.69)	4.93 <sup>a</sup> (1.67–11.92)	3.7 (1.5–6.68)	5.28 (4.4–13.76)
Any-positive (n=44)	0.26 (0.06–1.95)	5.57 <sup>a</sup> (1.56–10.7)	12.98 (7.06–20.53)	11.08 <sup>a</sup> (6.93–19.18)	7.45 (4.24–14.45)	14.86 (10.51–23.19)
p	0.358	0.338	0.032	0.075	0.017	0.005

Data are shown as median (interquartile range).

CRP: C-reactive protein; HD: hospital day.

<sup>a</sup>One of the CRP values was missing.

<sup>b</sup>Two CRP values were missing.

\*All-negative group refers to the patients with no infection symptom or fever during hospitalisation and no growth of microorganisms in the cultures.

<sup>†</sup>The sputum cultures were positive in 13 patients, urine cultures were positive in 6, and blood culture was positive in 1.

decreased thereafter (5.21 mg/dL at HD3 and 4.93 mg/dL at HD4) in all-negative group (Table 2, Figure 2(d)).

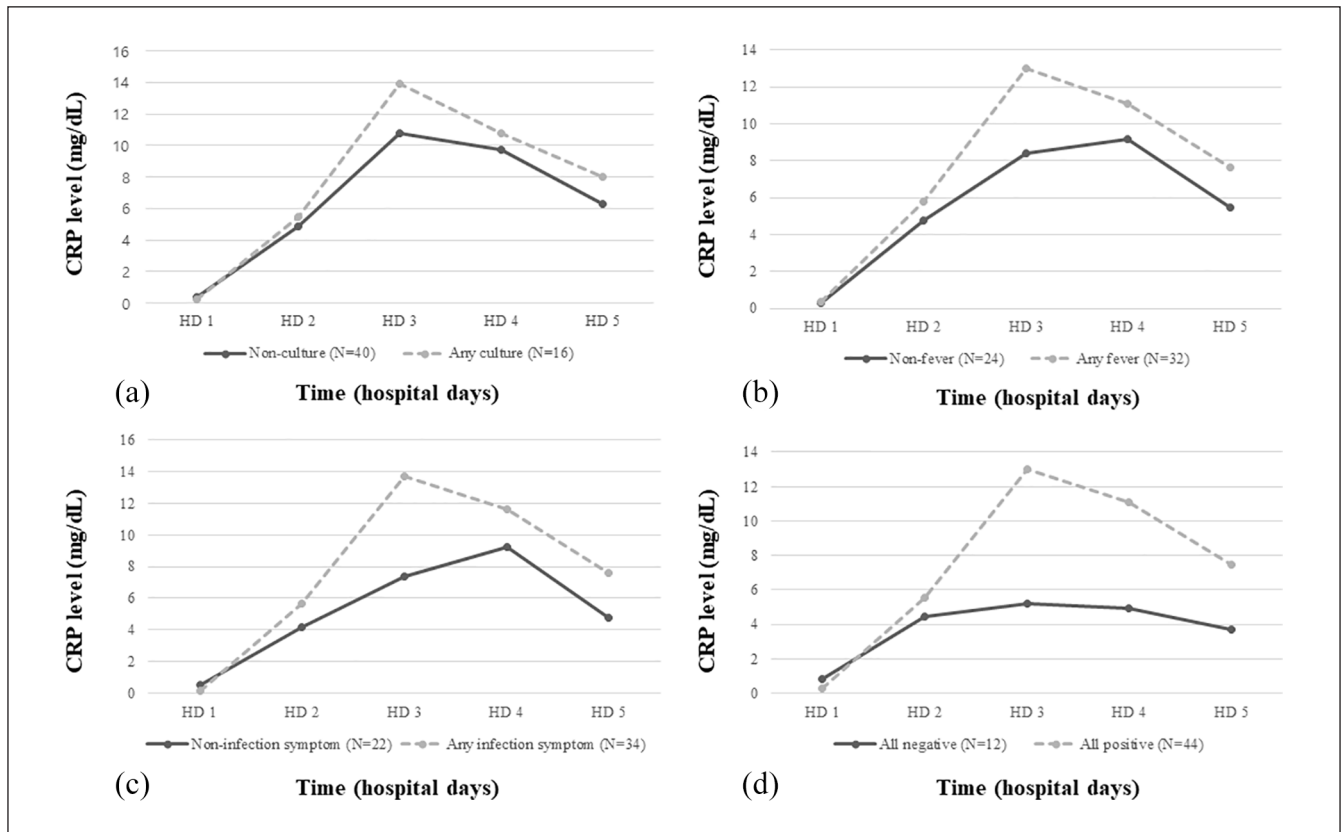
No correlations were noted between the initial CRP levels and the length of stay (LOS)/Acute Physiology and Chronic Health Evaluation II (APACHE II) score. However, weaker correlation was noted between maximal CRP levels and LOS, while moderate correlation was observed between maximal CRP levels and the APACHE II score (Table 3).

## Discussion

Various conditions, such as infection, autoimmune disease, tumour, trauma, and injury, can cause inflammation. In such situations, the concentration of specific substances, namely, acute-phase reactants (APR), may get changed, thereby affecting the host defence system. APRs are increased (positive APR) or decreased (negative APR) by at least 25% of their concentration during inflammation.<sup>13</sup> Erythrocyte sedimentation rate, alpha-1 antitrypsin, haptoglobin, albumin, hepcidin, procalcitonin, and CRP are some known APRs,<sup>14–16</sup>

CRP being the most widely used positive APR indicator. It is a homopentameric structure, synthesised in the endothelial cell, adipocyte, and lymphocyte, predominantly in the liver.<sup>17,18</sup> It has both anti-inflammatory and pro-inflammatory effects; however, the primary reaction is associated with its anti-inflammatory role, which eliminates foreign pathogens and damaged cells and activates the complement system.<sup>19,20</sup> CRP is very useful in treating infectious diseases, since it can differentiate between bacterial and viral infections, and act as an indicator of antibiotics use.<sup>21–23</sup> Although the exact normal range of CRP level is unknown, in general, its levels lower than 0.3 mg/dL are considered normal; 0.3–1 mg/dL represents low-grade inflammation; and >1 mg/dL represents clinically significant inflammation.<sup>24</sup> Low-grade inflammation is related to various metabolic stresses, such as hypertension, diabetes mellitus, insulin resistance, obesity, and atherosclerosis.<sup>7,8</sup> Relatively higher CRP level can be found in elderly individuals, especially women.<sup>25</sup>

In our experience, acute rise and fall of CRP levels occur within several days during management of patients with



**Figure 2.** The median CRP values compared across groups. (a) Comparison of non-culture vs any-culture group. (b) Comparison of non-fever vs any-fever group. (c) Comparison of non-infection symptoms vs any-infection symptoms group. (d) Comparison of all-negative vs any-positive group.

CRP: C-reactive protein; HD: hospital day.  
The interquartile range bars are deleted.

poisoning. Median CRP levels peaked at HD3 and HD4 in our results (10.91 mg/dL at HD3 and 10.57 mg/dL at HD4). Nevertheless, definite reasons or underlying mechanism of CRP elevation in patients with acute poisoning are still unclear. Decreased mentality was frequent in patients with acute poisoning, due to alcohol, sedative, and so on. Therapeutic performance such as gastric lavage was frequently performed. These are the risk factors for aspiration pneumonia. Therefore, CT for detection of it and antibiotic use are very frequent for the possibility of pneumonia. In our study, all 56 (100%) patients received antibiotics, considering that the CRP elevation could be related to infection. Since expenses increase and complications may occur due to unnecessary radiological imaging and antibiotic administration, proper approach to CRP elevation was considered important. One of the 56 patients in our study developed pseudomembranous colitis owing to prolonged antibiotic administration. Therefore, this study was conducted to identify CRP elevation and reveal a possible superimposed infection to minimise the concerns mentioned above. Since diagnosis of infection cannot be reliably made solely based on one diagnostic tool, culture results, fever, and infection symptoms were investigated along with.

**Table 3.** Correlation coefficients between CRP levels and the clinical outcomes.

	LOS	APACHE II
Initial CRP	-0.044	0.239
Maximal CRP	0.291*	0.434**

\* $p < 0.05$ ; \*\* $p < 0.01$ .

CRP: C-reactive protein; LOS: length of stay; APACHE II: Acute Physiology and Chronic Health Evaluation II.

As shown in Table 2, culture results were positive in 28.6% cases. No difference in daily CRP levels and maximal CRP level were observed compared with that in the culture-negative group. Moreover, median CRP levels were higher than 10 mg/dL at HD3 and maximal CRP was 12.19 mg/dL in the culture-negative group. The maximal CRP in poisoning was similar to or higher than the range known in bacterial meningitis, acute pyelonephritis, and severe community-acquired pneumonia (10–30 mg/dL).<sup>21,26</sup> Positive result in culture study confirmed infection. Although being culture-negative did not exclude the possibility of infection, no difference in daily CRP levels and maximal CRP level across the groups was observed, and similar pattern and levels of

CRP elevation in the culture-negative group implied the possibility of CRP elevation in patients with poisoning without infection.

CRP levels during the first two HDs were not different between the fever group and non-fever group. Those at HD3–5 and the maximal CRP level were higher in the fever group. However, CRP levels at HD3–5 in non-fever group were also elevated (5.49–9.2). Fever indicates inflammation, not infection; therefore, CRP elevation may be predictable in patients with fever. However, CRPs at HD3–4 and maximal CRP in non-fever patients were also elevated for a similar extent of bacterial infection. This implied the possibility of CRP elevation in patients with poisoning even in the absence of infection.

Infection symptoms were investigated next and the following were identified: cough, sputum, dyspnoea, dysuria, and diarrhoea. The most common symptom, the sputum, developed in 30 patients, of which, 17 were pesticide-intoxicated, 4 were organophosphate poisoning cases, 2 were pyrethroid poisoning cases, 9 were glufosinate ammonium poisoning cases, and 2 were indoxacarb poisoning cases. The sputum is a typical toxidrome feature of the previously described pesticide poisoning. If patients developed sputum, they may or may not have the infections. However, if they were assumed to have superimposed infections, the CRP levels at HD3–4 were high and maximal CRP (10.81 mg/dL) was similar to that in the bacterial infection level in non-symptom group. This finding implied possible CRP elevation in poisoning.

Patients without fever or infection symptoms and with no growth of microorganism in the cultures were defined as all-negative group; the others (with at least one positive in three) belonged to any-positive group. If no positive result was obtained in the three clinical findings, we considered the possibility of co-infection to be very low. Median CRP levels at HD3–4 were high (5.21 mg/dL at HD3, 4.93 mg/dL at HD4) and they decreased subsequently; maximal CRP was 5.28 mg/dL in this group. Similar pattern of CRP elevation was noted in the all-negative group.

Based on the findings, CRP elevation was suggested to not be considered a co-infection condition. Moreover, routine antibiotic administration or unnecessary radiological imaging would not be required. Although the precise mechanism of CRP elevation in poisoning could not be verified in this study, the drug reaction itself could possibly cause CRP elevation in early phase. CRP levels at HD3–4 were high, similar to that in bacterial infection in the co-infection-unlikely group.

The initial CRP levels did not show any correlation with LOS or APACHE II score. However, it was seen that higher the maximal CRP levels, longer the LOS and higher the APACHE II score. Patients with high CRP levels were assumed to have been hospitalised longer for reasons such as long duration of observation or use of antibiotics.

Very few articles have reported the role of CRP in poisoning. Wu et al.<sup>9</sup> and Lee et al.<sup>10</sup> had reported higher CRP levels to be related to poor prognosis and Lee et al. had reported

the difference between initial CRP levels and that at 24 h to be a high mortality indicator in severe organophosphorus pesticide poisoning. However, initial CRP level was higher in the survival group (20.3 mg/dL in survivors, 9.4 mg/dL in non-survivals) and not related to the prognosis in this report (D-CRP cut-off: 28.4 mg/dL). Tsai et al. had reported CRP to be related to mortality, and not to acetylcholinesterase.<sup>27</sup>

In general, CRP is used as a monitoring or prognostic indicator in infectious diseases. Higher CRP level is related to poor prognosis. In a previously published article, lower CRP clearance, which determined the difference of serial measurements, was a mortality indicator.<sup>28</sup> CRP is also a useful indicator for various conditions. Higher mortality, and more operations and ICU admissions were in high-CRP group in abdominal surgery (cut-off: 15 mg/dL).<sup>29</sup> Unfavourable neurological outcome was reported in high-CRP group of subarachnoid haemorrhage.<sup>30</sup> Secondary rise of CRP level may be indicative of postoperative complications after orthopaedic surgery.<sup>31</sup> As with poisoning, the specific role of CRP still needs to be identified. Acute rise and fall pattern of CRP has been observed in the infection-unlikely patients with poisoning. Further studies would be necessary to identify the exact mechanism of CRP elevation in poisoning.

The study has a few limitations. First, those admitted for more than 5 days were enrolled to verify the pattern of CRP change. Patients who expired in early phase were excluded. Therefore, understanding the severity or prognosis with CRP levels was not possible. Furthermore, this was conducted in a single toxicology centre and cases were less in number. Although poisonous substances may vary, the mechanisms or pharmacokinetics of each drug were not considered in the study. Further studies are needed to precisely determine the pattern and mechanism of change in CRP levels according to specific substances or treatments such as antibiotic administration. Finally, to the best of our knowledge, the pattern of CRP level changes in poisoning has never been reported. Therefore, we included all patients for whom data on five consecutive CRP levels and culture results were available. Since this could lead to the selection bias, the statistical power for sample size was not calculated.

## Conclusion

In all patients admitted in the hospital for more than 5 days, CRP levels were elevated and the peak was observed in 3–4 days; thereafter, the levels decreased. However, the cultures were negative in 71.4% of the patients and fever and infection symptoms were negative in 42.9% and 39.3% of patients, respectively. The levels were similar to bacterial infection levels. This could be due to the drug reaction itself, and not due to any co-infection.

## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Ethical approval

Ethical approval for this study was obtained from the institutional review board of Dankook University Hospital (DKUH 2021-03-002-002).

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## Informed consent

The written informed consent was waived from the institutional review board owing to the retrospective nature of the study.

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