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Correlation between the 72-hour fatality ratios and out-of-hospital cardiac arrest ratios in patients with extremely high outlier values of 57 laboratory test items

A single-center retrospective inception cohort study

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Abstract

The association between extremely high outlier values (EHOV) of laboratory test items (LTIs) and short-term prognosis or out-of-hospital cardiac arrest (OHCA) remains unclear. This retrospective study investigated the correlation between 72-hour fatality ratios and OHCA ratios in patients with the top 100 EHOV of 57 LTIs without focusing on the disease group and which test items were predictors of 72-hour fatality. This single-center retrospective inception cohort study enrolled patients aged ≥ 18 years who underwent any combination of laboratory tests at the Saitama Medical Center, Japan between January 1, 2008, and December 31, 2013. The primary outcome was the correlation between the 72-hour fatality ratios and OHCA ratios in patients with the top 100 EHOV for 57 LTIs without focusing on the disease group. The LTIs included hematology, blood chemistry, erythrocyte sedimentation, blood coagulation, and arterial blood gas test results. The secondary outcome was which of the 57 LTIs with the top 100 EHOV were more likely to associate with the 72-hour fatality. We evaluated the correlation between the 72-hour fatality ratios and the OHCA ratios for each laboratory test item using the Passing–Bablok regression method. The 72-hour fatality ratios for the top 100 EHOV of 57 LTIs were significantly positively correlated with the OHCA ratios. The regression coefficient of the regression line was 0.394, and the correlation coefficient (95% confidence interval) was 0.644 (0.458–0.775, $P < .001$). These 72-hour fatality ratios tended to be lower than the OHCA ratios. The top 100 EHOV of 13 LTIs including total bilirubin, direct bilirubin, C-reactive protein, base excess, bicarbonate ion, creatine kinase, uric acid, partial pressure of oxygen, sodium, chloride, blood urea nitrogen, aspartate aminotransferase, and lactate dehydrogenase had 72-hour fatality ratios that were above the upper limit of the linear confidence region of the regression line, with higher 72-hour fatality ratios than the OHCA ratios. The 72-hour fatality ratios for the top 100 EHOV of 57 LTIs tended to be lower than the OHCA ratios. The top 100 EHOV of these 13 LTIs were found to be more likely to associate with 72-hour fatality than OHCA.

Abbreviations: γ-GTP = γ-glutamyl transferase, ALT = alanine aminotransferase, ALP = alkaline phosphatase, AST = aspartate aminotransferase, BE = base excess, BUN = blood urea nitrogen, Ca = calcium, Cl = chloride, CRP = C-reactive protein, CK = creatine kinase, Cr = creatinine, EHOV = extremely high outlier values, FDP = fibrinogen degradation product, ICUs = intensive care units, Ht = hematocrit, Hb = hemoglobin, HbA1c = hemoglobin A1c, HDL-C = high-density lipoprotein cholesterol, IgA = immunoglobulin A, IgD = immunoglobulin D, IgE = immunoglobulin E, IgG = immunoglobulin G, IgM = immunoglobulin M, LTIs = laboratory test items, LD = lactate dehydrogenase, LDL-C = low-density lipoprotein cholesterol, Mg = magnesium, OHCA = out-of-hospital cardiac arrest, $PaCO_2$ = partial pressure of arterial carbon dioxide, PaO_2 = partial pressure of arterial oxygen, K = potassium, RPG = random plasma glucose, RBC = red blood cell, Na = sodium, T-Bil = total bilirubin, TP = total protein, WBC = white blood cell.

Keywords: 72-hour fatality, critical values, extremely high outlier value, laboratory test items, out-of-hospital cardiac arrest, panic values

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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1. Introduction

Clinical laboratory data are routinely collected every day at medical institutions worldwide. However, such data have not yet been used secondarily from a cross-disease perspective to improve the overall quality of medical care.[1] Extreme outlier values are defined as infrequent laboratory data that are statistically below the 0.5 to 1.0th percentiles or above the 99.0 to 99.5th percentiles.[2] Panic or critical values are abnormal values that indicate the existence of a life-threatening pathophysiological state that requires the prompt initiation of treatment and further confirmation using laboratory tests.[3] However, the nature of extremely high outlier values of various laboratory tests (panic values or not) and the role of these values in the actual prognosis have not been sufficiently examined. Several studies have identified the following as the predictors of 72-hour mortality for patients in intensive care units (ICUs),[4] after emergency department visits,[5] and those with trauma[6]: aspartate aminotransferase (AST) level ≥ 3000 U/L,[7] C-reactive protein (CRP) level ≥ 40 mg/dL,[8] and random plasma glucose level ≥ 500 mg/dL.[9] In other words, to the best of our knowledge, no previous studies have analyzed the association between each extremely high outlier value of laboratory test items and short-term prognosis or out-of-hospital cardiac arrest (OHCA) from a cross-disease perspective.

This retrospective study investigated the correlation between 72-hour fatality ratios and OHCA ratios in patients with the top 100 extremely high outlier values of 57 laboratory test items without focusing on the disease group and which test items were predictors of 72-hour fatality.

The results of this study will help physicians estimate which laboratory test item is relevant for the short-term prognosis of patients with extremely high outlier values. Clinicians' prediction of the 72-hour fatality based on the most recent evidence in patients with extremely high outlier values will provide useful information for making treatment decisions and explaining the disease state to patients and their families.

2. Methods

2.1. Study design, setting, participant selection, sampling technique, and sample size estimation

This single-center retrospective inception cohort study enrolled patients aged ≥ 18 years who underwent any combination of 57 laboratory test items at the clinical laboratory in Saitama Medical Center, Japan, between January 1, 2008, and December 31, 2013, irrespective of symptom onset, hospitalization, or setting (i.e., emergency, outpatient, or inpatient). We excluded bone marrow transplantation donors and for cases of the same patient with metachronous duplicates, only the records with the highest value of the targeted laboratory test were retained.

Systematic sampling was used to identify the inception cohorts with the top 100 extremely high outlier values in descending order, for the respective laboratory test items from the enrolled patients. Fifty-seven laboratory test items were reviewed in this study. Therefore, the total number of patients with the top 100 extremely high outlier values was 5700. To compute the required sample size using G*Power,[10] the following parameters were applied: Test family, "Exact"; Statistical test, "Linear multiple regression: Random model"; Type of power analysis, "A priori: Compute required sample size—given α, power, and effect size"; Tails, "Two"; H_1 ρ^2, "0.3" (this means that the alternative hypothesis [H_1] was assumed to be moderately correlated at 0.3); H_0 ρ^2, "0.0" (this means that the null hypothesis [H_0] assumed a coefficient of determination of zero); α err prob, "0.05"; Power (1-β err prob), "0.8"; and Number of predictors, "57" (this means that 57 laboratory test items were employed as predictors). The sample size was calculated as 133. We expanded the actual data size to 5700 to achieve higher power.

2.2. Primary and secondary outcome variables

The primary outcome was the correlation between the 72-hour fatality ratios and OHCA ratios in patients with the top 100 extremely high outlier values of the 57 laboratory test items without focusing on the disease group.

The secondary outcome was which of the 57 laboratory test items with the top 100 extremely high outlier values were more likely to associate with the 72-hour fatality.

2.3. Endpoints and participants

The index date of the inception cohort was defined as the point in time when an extremely high outlier value was observed for the respective laboratory test item. The patients with the top 100 extremely high outlier values for each of the 57 laboratory test items (total 5700 patients) in the inception cohort were categorized into three groups based on their outcomes according to the medical records: death within 72 hour after the index date, OHCA on the index date, or unknown outcome. After excluding patients with unknown outcomes, the 72-hour fatality ratio and OHCA ratio were calculated. Patient age, sex, comorbid diseases, and causative diseases were not considered.

2.4. Issue of interest

The 57 laboratory test items examined in this study included the following tests: hematology (white blood cell [WBC] count, red blood cell [RBC] count, hemoglobin [Hb] level, hematocrit [Ht] level, and platelet count), blood chemistry (levels of total protein [TP], albumin, direct bilirubin, total bilirubin, AST, alanine aminotransferase [ALT], alkaline phosphatase [ALP], γ-glutamyl transferase [γ-GTP], lactate dehydrogenase [LD], creatine kinase [CK], amylase, lipase, CRP, sodium (Na), potassium (K), chloride (Cl), calcium (Ca), inorganic phosphorus, magnesium (Mg), blood urea nitrogen [BUN], creatinine [Cr], uric acid, total cholesterol, high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], triglycerides, immunoglobulin [Ig]A, IgD, IgE, IgG, and IgM, brain natriuretic peptide, random plasma glucose [RPG], hemoglobin A1c [HbA1c], glycoalbumin, ferritin, ammonia, β2-microglobulin, and β-D-glucan), coagulation (prothrombin time international normalized ratio, activated partial thromboplastin time, fibrinogen degradation product [FDP] level, fibrinogen level, and D-dimer level), arterial blood gas analysis (pH, partial pressure of carbon dioxide [$PaCO_2$], partial pressure of oxygen [PaO_2], bicarbonate ion level, base excess [BE], and lactate level), and erythrocyte sedimentation rate.

2.5. Ethics approval

The study protocol was designed in accordance with the tenets of the Declaration of Helsinki[11] and was approved by the Institutional Clinical Ethics Review Board of Saitama Medical Center, Jichi Medical University (Approval No.: Clinical #10-79). Ethics approval did not include the option for sharing data with the public; therefore, we ensured that all patient-record data were fully anonymized. These data did not include any potentially identifiable or sensitive patient information. The requirement for written informed consent from the participants was waived owing to the retrospective nature of the study design.

2.6. Statistical analyses

The statistical package StatFlex Ver. 7.0.11 (Artech Co. Ltd, Osaka, Japan) was used to analyze the Passing–Bablok regression between the 72-hour fatality ratios and OHCA ratios for each laboratory test item. G*Power version 3.1.9.2 (Heinrich

Heine University Düsseldorf, Düsseldorf, Germany)[10] was used for sample size calculation. A P value of <.05 was considered statistically significant.

3. Results

3.1. Patient baseline information, 72-hour fatality ratios, and OHCA ratios (Table 1)

Table 1 shows the following results for each laboratory test item: maximum value and the 100th value 72-hour fatality ratio among the extremely high outlier values, number of deaths within the 72-hour period, number of OHCAs, number of survivals over the 72-hour period, number of unknown outcomes, 72-hour fatality ratio (in descending order), and OHCA ratio. The results are sorted in descending order by the 72-hour fatality ratio. The highest numbers of deaths within the 72-hour period were 32 (AST), 30 (LD), 25 (BUN), 24 (Cl), and 22 (Na). The highest numbers of OHCAs were 97 (K), 85 (ammonia), 83 (inorganic phosphorus), 75 (FDP), 72 ($PaCO_2$), and 72 (lactate). The highest numbers of unknown outcomes were 10 (TP), 9 (ALP), 9 (pH), 8 (BE), and 8 (RPG). The main reason for an unknown outcome was transfer to another hospital or discharge home within 72 hours.

A 72-hour fatality ratio (%) of ≥20% was observed for the following test items: $PaCO_2$ ≥ 163.2 mmHg (67.9%), lactate level ≥ 188.0 mg/dL (63.0%), inorganic phosphorus level ≥ 14.4 mg/dL (47.1%), ammonia level ≥ 681.0 μg/dL (42.9%), LD level ≥ 11,650.0 U/L (42.9%), AST level ≥ 4864.0 U/L (39.0%), D-dimer level ≥ 303.0 μg/mL (30.0%), BUN level ≥ 161.0 mg/dL (26.9%), Cl level ≥ 128.0 mEq/L (25.0%), Na level ≥ 161.0 mEq/L (23.7%), PaO_2 ≥ 404 mmHg (22.0%), and uric acid level ≥ 17.1 mg/dL (21.1%).

Overall, the 72-hour fatality was 0% for the following 14 test items: Ht level ≥ 57.7%, albumin level ≥ 5.6 g/dL, glycoalbumin level ≥ 44.5%, amylase level ≥ 4151.0 U/L, HDL-C level ≥ 133.0 mg/dL, IgA level ≥ 797.0 mg/dL, IgD level ≥ 0.6 mg/dL, IgE level ≥ 5100.0 mg/dL, IgM level ≥ 460.0 mg/dL, LDL-C level ≥ 272.0 mg/dL, total cholesterol level ≥ 445.0 mg/dL, triglyceride level ≥ 1303.0 mg/dL, γ-GTP level ≥ 1667.0 mg/dL, and RBC count ≥ 6.45 million/μL.

An OHCA ratio of ≥20% was observed for the following items: K level ≥ 11.1 mEq/L (99.0%), ammonia level ≥ 681.0 μg/dL (85.9%), inorganic phosphorus level ≥ 14.4 mg/dL (83.0%), FDP level ≥ 710.0 mg/dL (75.0%), lactate level ≥ 188.0 mg/dL (72.7%), $PaCO_2$ ≥ 163.2 mmHg (72.0%), D-dimer level ≥ 303 μg/dL (70.0%), LD level ≥ 11,650.0 U/L (30.0%), and RPG level ≥ 698.0 mg/dL (23.9%).

A 0% OHCA ratio was observed for the following 31 test items: Cl level ≥ 128.0 mEq/L, CK level ≥ 15,367.0 U/L, BE level ≥ 15.4 mEq/L, direct bilirubin level ≥ 15.52 mg/dL, total bilirubin level ≥ 20.56 mg/dL, ALT level ≥ 1887.0 U/L, β-D-glucan level ≥ 135 pg/mL, ALP level ≥ 3647.0 U/L, brain natriuretic peptide level ≥ 3843.2 pg/mL, HbA1c ≥ 12.8%, ferritin level ≥ 4359.5 ng/mL, lipase level ≥ 146.0 U/L, WBC level ≥ 158,400/μL, arterial blood gas pH ≥ 7.643, fibrinogen level ≥ 1005.0 mg/dL, β2-microglobulin level ≥ 35.1 mg/L, TP level ≥ 10.4 g/dL, platelet count ≥ 1,381,000/μL, erythrocyte sedimentation rate ≥ 132.0 mm/h, IgG level ≥ 4470.0 mg/dL, amylase level ≥ 4151 U/L, HDL-C level ≥ 133.0 mg/dL, IgA level ≥ 797.0 mg/dL, IgD level ≥ 0.6 mg/dL, IgE level ≥ 5100.0 mg/dL, IgM level ≥ 460.0 mg/dL, LDL-C level ≥ 272.0 mg/dL, total cholesterol level ≥ 445.0 mg/dL, triglyceride level ≥ 1303.0 mg/dL, γ-GTP level ≥ 1667.0 mg/dL, and RBC count ≥ 645 million/μL.

The 72-hour fatality ratios and OHCA ratios were 0% for the following 11 laboratory test items, despite extremely high outlier values: amylase, HDL-C, IgA, IgD, IgE, IgM, LDL-C, TC, TG, γ-GTP, and RBC count.

3.2. Primary outcome results: the correlation between the 72-hour fatality ratios and OHCA ratios of the 57 laboratory test items (Fig. 1)

There was a significant positive correlation between the 72-hour fatality ratios and OHCA ratios. The regression coefficient of the regression line was 0.394, and the Y-intercept was 0.065; the correlation coefficient (95% confidence interval) was 0.644 (0.458–0.775), which was significant (P < .001). The regression coefficient was 0.394, indicating that the 72-hour fatality ratio of each laboratory test item tended to be lower than the OHCA ratio.

3.3. Secondary outcome results: the laboratory test items among the 57 that were more likely to predict 72-hour fatality than at the point of OHCA (Fig. 1)

The 57 laboratory tests were categorized into groups A, B, and C, with 13, 7, and 37 items, respectively, according to whether the 72-hour fatality ratios were above or below the upper limit of the linear confidence region of the regression line and greater than or less than the OHCA ratios.

In Group A, comprising 13 items, the 72-hour fatality ratio was above the upper limit of the linear confidence region of the regression line and higher than the OHCA ratio (total bilirubin level ≥ 20.56 mg/dL, direct bilirubin level ≥ 15.52 mg/dL, CRP level ≥ 39.0 mg/dL, BE level ≥ 15.4 mEq/L, bicarbonate ion level ≥ 43.1 mmHg, CK level ≥ 15,367.0 U/L, uric acid level ≥ 17.1 mg/dL, PaO_2 ≥ 404.3 mmHg, Na level ≥ 161.0 mEq/L, Cl level ≥ 128.0 mEq/L, BUN level ≥ 161.0 mg/dL, AST level ≥ 4864.0 U/L, and LD level ≥ 11,650.0 U/L).

In Group B, comprising seven items, the 72-hour fatality ratio was below the lower limit of the linear confidence region of the regression line and lower than the OHCA ratio (Ht level ≥ 57.5%, Mg level ≥ 4.6 mg/dL, Ca level ≥ 12.4 mg/dL, activated partial thromboplastin time ≥ 200.0 s, RPG level ≥ 698.0 mg/dL, FDP level ≥ 710.0 mg/dL, and K level ≥ 11.1 mEq/L).

Group C, comprising 37 items, included 11 laboratory test items with 0% OHCA ratio and 72-hour fatality, namely, amylase level ≥ 4151 U/L, HDL-C level ≥ 133.0 mg/dL, IgA level ≥ 797.0 mg/dL, IgD level ≥ 0.6 mg/dL, IgE level ≥ 5100.0 mg/dL, IgM level ≥ 460 mg/dL, LDL-C level ≥ 272.0 mg/dL, total cholesterol level ≥ 445.0 mg/dL, triglyceride level ≥ 1303.0 mg/dL, γ-GTP level ≥ 1667.0 U/L, and RBC count ≥ 6.45 million/μL.

These findings indicated that the 72-hour fatality ratios for the top 100 extremely high outlier values of Group A were higher than the OHCA ratios. The extremely high outlier values of these 13 laboratory test items of Group A were more likely to be associate with the 72-hour fatality than OHCA.

4. Discussion

This study found that the 72-hour fatality ratios for the 57 laboratory test items in patients with the top 100 extremely high outlier values tended to be lower than the OHCA ratios. The top 100 extremely high outlier values of Group A of 13 laboratory test items including total bilirubin, direct bilirubin, CRP, BE, bicarbonate ion, CK, uric acid, PaO_2, Na, Cl, BUN, AST, and LD were more likely to associate with 72-hour fatality than OHCA.

The Guidelines for Clinical Laboratory Tests (JSLM 2018)[12] state that the reference high values for panic data or critical values in adults include 9 items in Group A (LD, AST, BUN, Cl, Na, uric acid, CK, bicarbonate ion, and BE levels), 4 in Group B (K, FDP, RPG, and Ca levels), and 14 in Group C (WBC count, platelet count, $PaCO_2$, pH, and levels of total protein, albumin, ALT, amylase, Cr, lactate, prothrombin time international normalized ratio, fibrinogen, and HbA1c).

Table 1

Comparison of the 72-h fatality ratio and out-of-hospital cardiac arrest ratio for the 57 parameters with the top 100 extremely high outlier values.

			Extremely high outlier values		Outcome (patients)					
Classification	Laboratory test items	Units	Max	100th Max	Deaths within the 72-h period	OHCA	Survival over the 72-h period	Unknown	72-h fatality ratio (%)	OHCA ratio (%)
BGA	P_aCO_2	mmHg	250.0	163.2	19	72	9	0	67.9	72.0
BGA	Lactate	mg/dL	270.0	188.0	17	72	10	1	63.0	72.7
Biochemical	IP	mg/dL	29.2	14.4	8	83	9	0	47.1	83.0
BGA	Ammonia	μg/dL	1604.0	681.0	6	85	8	1	42.9	85.9
Biochemical	LD	U/L	80,900.0	11,650.0	30	30	40	0	42.9	30.0
Biochemical	AST	U/L	37,242.0	4864.0	32	18	50	0	39.0	18.0
Coagulation	D-dimer	μg/mL	3100.0	303.0	9	70	21	0	30.0	70.0
Biochemical	BUN	mg/dL	301.0	161.0	25	6	68	1	26.9	6.1
Biochemical	Cl	mEq/L	148.0	128.0	24	0	72	4	25.0	0.0
Biochemical	Na	mEq/L	193.0	161.0	22	2	71	5	23.7	2.1
BGA	PaO_2	mmHg	660.9	404.3	18	16	64	2	22.0	16.3
Biochemical	Uric acid	mg/dL	57.7	17.1	20	3	75	2	21.1	3.1
Biochemical	CK	U/L	329,500.0	15,367.0	18	0	76	6	19.1	0.0
BGA	BE	mEq/L	33.2	15.4	16	0	76	8	17.4	0.0
BGA	HCO_3^-	mmHg	65.6	43.1	16	1	76	7	17.4	1.1
Coagulation	FDP	mg/mL	6336.0	710.0	4	75	21	0	16.0	75.0
Biochemical	CRP	mg/dL	78.6	39.0	13	5	78	4	14.3	5.2
Biochemical	D-Bilirubin	mg/dL	30.27	15.52	14	0	86	0	14.0	0.0
Biochemical	T-Bilirubin	mg/dL	43.18	20.56	12	0	88	0	12.0	0.0
Coagulation	PT-INR		129.81	9.00	10	14	76	0	11.6	14.0
Biochemical	RPG	mg/dL	1990.0	698.0	7	22	63	8	10.0	23.9
Biochemical	ALT	U/L	9400.0	1887.0	9	0	91	0	9.0	0.0
Biochemical	β-D-glucan	pg/mL	10,300	135	9	0	91	0	9.0	0.0
Biochemical	ALP	U/L	11,280.0	3647.0	8	0	83	9	8.8	0.0
Biochemical	BNP	pg/mL	14,767.8	3843.2	6	0	90	4	6.3	0.0
Biochemical	Ca	mg/dL	19.0	12.4	5	9	79	7	6.0	9.7
Coagulation	APTT	s	252.9	200.0	5	12	83	0	5.7	12.0
Biochemical	Ma	mg/dL	33.3	4.6	5	9	86	0	5.5	9.0
Biochemical	HbA1c	%	20.0	12.8	3	0	94	3	3.1	0.0
Biochemical	Ferritin	ng/mL	584,570.7	4359.5	3	0	95	2	3.1	0.0
Biochemical	Lipase	U/L	3350.0	146.0	3	0	95	2	3.1	0.0
Hematology	WBC count	10^3/μL	487.2	158.4	3	0	97	0	3.1	0.0
BGA	pH		7.829	7.643	2	0	89	9	2.2	0.0
Biochemical	Cr	mg/dL	87.46	15.14	2	3	93	2	2.1	3.1
Coagulation	Fibrinogen	mg/dL	1607.0	1005.0	2	0	98	0	2.0	0.0
Biochemical	β2-MG	mg/L	133.1	35.1	2	0	98	0	2.0	0.0
Hematology	Hb	g/dL	23.7	19.0	1	2	92	5	1.1	2.1
Biochemical	TP	g/dL	15.6	10.4	1	0	89	10	1.1	0.0
Hematology	PC	10,000/μL	568.0	138.1	1	0	95	4	1.0	0.0
Blood	ESR	mm/h	173.0	132.0	1	0	98	1	1.0	0.0
Biochemical	IgG	mg/dL	11,800.0	4470.0	1	0	98	1	1.0	0.0
Biochemical	K	mEq/L	33.2	11.1	0	97	1	2	0.0	99.0
Hematology	Ht	%	73.2	57.5	0	8	86	6	0.0	8.5
Biochemical	Alb	g/dL	7.1	5.6	0	1	99	0	0.0	1.0
Biochemical	GA	%	78.7	44.5	0	1	97	2	0.0	1.0
Biochemical	Amylase	U/L	4814,900.0	4151.0	0	0	100	0	0.0	0.0
Biochemical	HDL-C	mg/dL	217.0	133.0	0	0	97	3	0.0	0.0
Biochemical	IgA	mg/dL	9740.0	797.0	0	0	98	2	0.0	0.0
Biochemical	IgD	mg/dL	5020.0	0.6	0	0	99	1	0.0	0.0
Biochemical	IgE	mg/dL	155,000.0	5100.0	0	0	97	3	0.0	0.0
Biochemical	IgM	mg/dL	10,100.0	460.0	0	0	99	1	0.0	0.0
Biochemical	LDL-C	mg/dL	891.0	272.0	0	0	97	3	0.0	0.0
Biochemical	TC	mg/dL	1216.0	445.0	0	0	93	7	0.0	0.0
Biochemical	TG	mg/dL	4419.0	1303.0	0	0	94	6	0.0	0.0
Biochemical	γ-GTP	U/L	5774.0	1667.0	0	0	95	5	0.0	0.0
Hematology	RBC count	10^4/μL	884	645	0	0	93	7	0.0	0.0

β2-MG = β2-microglobulin, γ-GTP = γ-glutamyl transferase, Alb = albumin, ALP = alkaline phosphate, ALT = alanine aminotransferase, APTT = activated partial thromboplastin time, AST = aspartate aminotransferase, BE = base excess, BGA = blood gas analysis, BNP = B-type natriuretic peptide, BUN = blood urea nitrogen, Ca = calcium, CK = creatine kinase, Cl = chloride, Cr = creatinine, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, FDP = fibrinogen-fibrin degradation products, GA = glycoalbumin, Hb = hemoglobin, HCO_3^- = bicarbonate, HDL-C = high-density lipoprotein cholesterol, Ht = hematocrit, IP = inorganic phosphorus, K = potassium, LD = lactate dehydrogenase, LDL-C = low-density lipoprotein cholesterol, Max = maximum, Mg = magnesium, Na = sodium, OHCA = out-of-hospital cardiac arrest, P_aCO_2 = partial pressure of arterial carbon dioxide, P_aO_2 = partial pressure of arterial oxygen, PLT = platelet, PT-INR = prothrombin time-international normalized ratio, RBC = red blood cell, RPG = random plasma glucose, TC = total cholesterol, TG = triglyceride, TP = total protein, WBC = white blood cell.

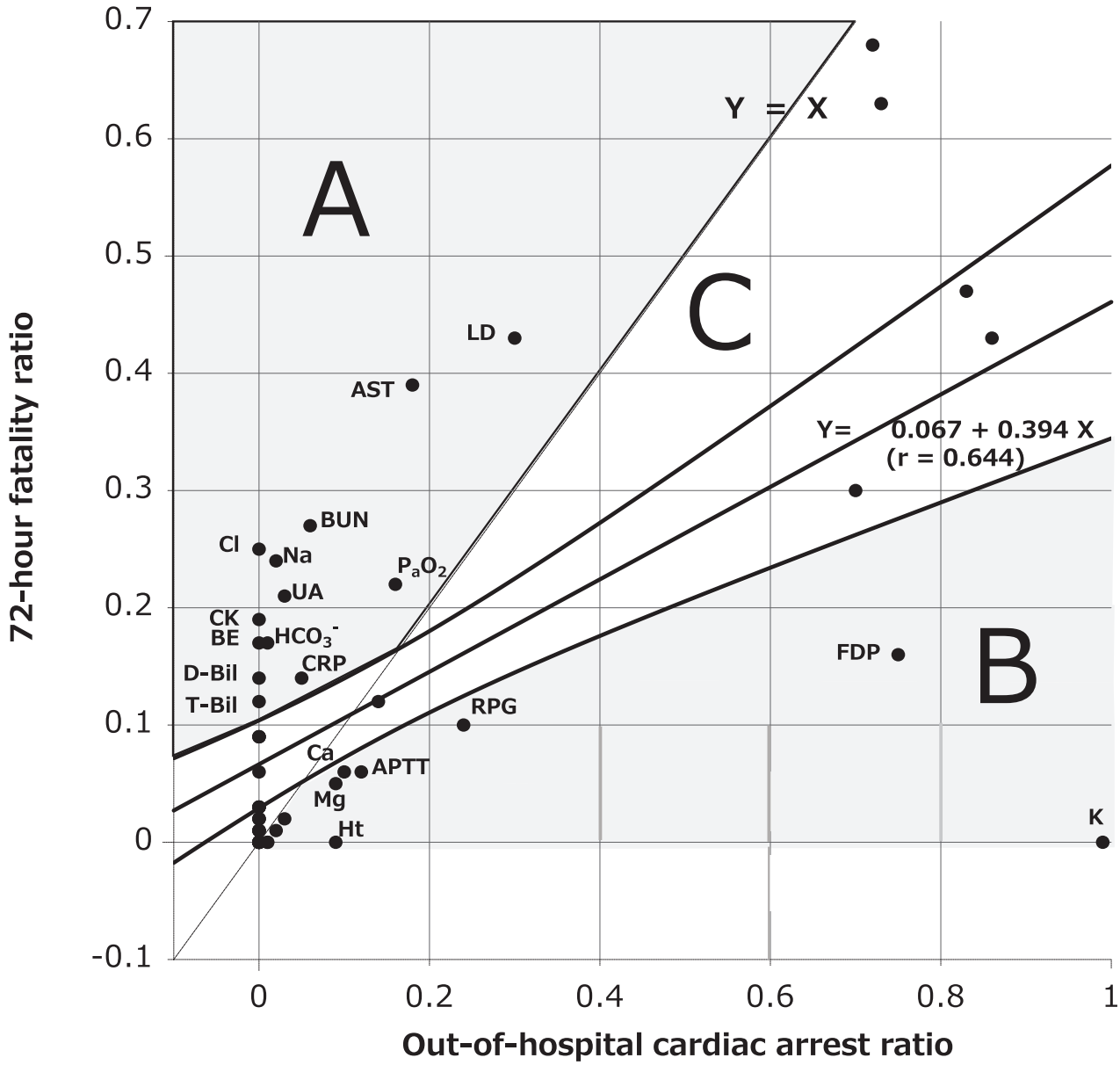

Figure 1. Correlation between the out-of-hospital cardiac arrest ratio and 72-h fatality ratio in patients with the top 100 extremely high outlier values for 57 laboratory test items. "A" indicates the 13 items that had 72-h fatality ratios that were above the upper limit of the linear confidence region of the regression line and higher than the OHCA ratio. "B" indicates the seven items that had 72-h fatality ratios that were below the lower limit of the linear confidence region of the regression line and lower ratios than the OHCA ratio. "C" indicates the remaining 37 items except "A" and "B," including 11 laboratory test items with a 0% OHCA ratio and 72-h fatality. APTT = activated partial thromboplastin time, AST = aspartate aminotransferase, BE = base excess, BUN = blood urea nitrogen, Ca = calcium, CK = creatine kinase, Cl = chloride, CRP = C-reactive protein, D-Bil = direct bilirubin, FDP = fibrinogen fibrinolysis product, HCO_3^- = bicarbonate ion, Ht = hematocrit, K = potassium, LD = lactate dehydrogenase, Mg = magnesium, Na = sodium, OHCA = out-of-hospital cardiac arrest, PaO_2 = partial pressure of arterial oxygen, RPG = random plasma glucose, T-Bil = total bilirubin, UA = uric acid.

The test items in Groups A and B may be related to the period of death and OHCA triggers or changes after OHCA, respectively. We reviewed the laboratory test items that were chosen as predictive indicators, focusing on studies that examined prognosis prediction in patients with terminal cancer using laboratory tests and on studies that examined the relationship between laboratory values above the reference range and outcomes (Table 2).

Hamano et al[13] examined the prediction model from 7-day survival to 90-day survival in patients with advanced cancer. In addition to the heart and respiratory rates, the combination of BUN, albumin, Cr, CRP, and total bilirubin levels and LD, WBC (lymphocyte and neutrophil) count, and the ratio of platelet to lymphocyte counts were found to be useful predictors. Chen et al[14] reported that the combination of WBC count ≥ 11,000/μL, platelet count < 130,000/μL, Cr level ≥ 1.3 mg/dL, and K level ≥ 5.0 mg/dL, in addition to no chemotherapy and heart rate ≥ 120 bpm, was useful in predicting 7-day mortality in patients with advanced cancer. Cheng et al[15] reported that the odds ratio of death within 14 days after hospitalization in critically ill patients with metastatic or advanced cancer was significantly higher with albumin level < 2.5 g/dL, LD level ≥ 1501 U/L, WBC count ≥ 6500/μL, and platelet count < 28,000/μL, in addition to age ≥ 65

Table 2

Laboratory test items (Group A) selected as predictive indices in the earlier reports (continued to Table 3).

			Laboratory test items							
			A (selected)							
Studies	Subject	Estimated survival times	LD	AST	BUN	Na	CK	HCO_3^-	CRP	T-Bil
JSLM2018[12]	Panic data and critical values	N/A	✔	✔	✔	✔	✔	✔		
Hamano et al[13]	Advanced cancer	7–90 d	✔		✔				✔	✔
Chen et al[14]	Advanced cancer	7 d								
Cheng et al[15]	Metastatic or advanced cancer	14 d	✔		✔					
Onishi et al[16]	Terminal illness	14 d			✔	✔			✔	✔
Niki et al[17]	Terminal cancer	2 or 3 wk	✔	✔	✔				✔	
Forrest et al[18]	Inoperable non-small-cell lung cancer	Survival mo							✔	
Kawai et al[19]	Terminally ill cancer	30 d			✔				✔	
Tyler et al[20]	Intensive care unit	Death in the ICU				✔		✔		✔
Saito et al[7]	AST more than 3000 U/L	72 h				✔	✔			
Saito et al[8]	CRP more than 40 mg/dL	72 h								
Watanabe et al[9]	RPG more than 500 mg/dL	72 h					✔			

"A" indicates laboratory test items with 72-h mortality rates that were above the upper limit of the linear confidence region of the regression line and higher rates than the out-of-hospital cardiac arrest rate.
AST = aspartate aminotransferase, BUN = blood urea nitrogen, CK = creatine kinase, CRP = C-reactive protein, HCO_3^- = bicarbonate ion, LD = lactic dehydrogenase, N/A = not applicable, Na = sodium, T-Bil = total bilirubin.

Table 3

Laboratory test items (Groups B and C) selected as predictive indices in the earlier reports.

	Laboratory test items																
	B (selected)					C (selected)											
Studies	K	RPG	Ca	Mg	Ht	WBC count	LYN count	NEUT count	EOS count	RBC count	Hb	PLT count	Alb	ALP	P	Cr	Lactate
JSLM2018[12]	✔	✔	✔			✔					✔	✔	✔			✔	✔
Hamano et al[13]						✔	✔	✔				✔	✔			✔	
Chen et al[14]	✔					✔						✔				✔	
Cheng et al[15]						✔						✔	✔				
Onishi et al[16]						✔			✔								
Niki et al[17]						✔						✔					
Forrest et al[18]													✔				
Kawai et al[19]					✔	✔	✔	✔	✔	✔	✔	✔	✔				
Tyler et al[20]	✔	✔	✔	✔		✔					✔	✔	✔		✔	✔	✔
Saito et al[7]	✔													✔	✔		
Saito et al[8]													✔		✔		
Watanabe et al[9]													✔				

"B" indicates laboratory test items with 72-h mortality rates that were below the lower limit of the linear confidence region of the regression line and lower rates than the out-of-hospital cardiac arrest rate.
"C" indicates selected item that were classified as neither "A" nor "B" in this study.
Alb = albumin, ALP = alkaline phosphatase, Ca = calcium, Cr = creatinine, EOS = eosinophil, Hb = hemoglobin, Ht = hematocrit, K = potassium, LYN = lymphocyte, Mg = magnesium, NEUT = neutrophil, P = inorganic phosphorus, PLT = platelet, RPG = random plasma glucose, WBC = white blood cell.

years. Onishi et al[16] reported that CRP level ≥ 13.3 mg/dL, total bilirubin level ≥ 1.1 mg/dL, Na level < 131 mEq/L, BUN level ≥ 28 mg/dL, WBC count ≥ 17,700/μL, and eosinophil count < 0.2% were useful in predicting death within 14 days in patients with terminal gynecological cancer.

In a study predicting three-week prognosis in terminally ill patients with cancer in a palliative care ward, the WPCBAL score[17] based on six laboratory test items (WBC > 4870/μL, platelet count ≤ 225,000/μL, CRP ≥ 2.75 mg/dL, BUN ≥ 14 mg/dL, AST ≥ 30 U/L, and LD ≥ 264 U/L) was reported to have a higher C-statistic than the Glasgow prognostic score[18] based on two laboratory test items (albumin < 3.5 g/dL, CRP ≥ 1.0 mg/dL) (0.7540 vs 0.6573). Kawai et al[19] reported the usefulness of a combination of CRP ≥ 5.4 mg/dL, albumin < 2.8 g/dL, BUN ≥ 21 mg/dL, WBC ≥ 8600/μL, eosinophil count < 0.8%, ratio of neutrophil to lymphocyte count ≥ 11.1, Hb ≥ 13.2 g/dL, mean RBC volume (Ht/RBC) ≥ 93.7 fL, and platelet count < 159,000/μL in predicting 30-day mortality in patients with terminal cancer.

Tyler et al[20] examined the association between laboratory values above the reference range in the ICU and both patient mortality and length of hospital stay. Significant differences were observed in the following 15 laboratory parameters between the ICU death group and the ICU survival group: levels of albumin, bicarbonate ion, bilirubin, Cr, RPG, Hb, lactate, Mg, inorganic phosphorus, K, Na, Ca, and Ca ions and counts of platelets and WBCs. However, OHCA was not included in the study. High K levels significantly correlated with the cardiac arrest time, and no return of spontaneous circulation to normal was observed at a K level of ≥7.0 mEq/L.[21] In this study, we targeted cases with extremely high outlier K levels (≥11.1 mEq/L). OHCA was observed in 99% of these cases, suggesting that the time course after OHCA was long.

We previously studied the prediction of mortality at 72 hour in patients with extremely high outlier values of AST, CRP, and RPG. The 72-hour mortality rate in patients with AST levels ≥ 3000 U/L was 31.1%, and high levels of ALP, CK, Na, K, and inorganic phosphorus were predictive indices.[7] The

72-hour fatality ratio in patients with CRP levels ≥ 40 mg/dL was 16.0%, and old age, low albumin level, high inorganic phosphorus level, and complications of cardiovascular disease were predictive indicators.[8] The 72-hour fatality ratio in patients with RPG levels ≥ 500 mg/dL was 4.6%, and low albumin level, high CK level, and the presence of malignancy were predictive indicators.[9]

As shown in Tables 2 and 3, the laboratory test items selected as predictive indices in earlier studies differed according to the study subject and time to outcome. Accurate prediction of outcomes in patients with extremely high outlier values of clinical laboratory test items will facilitate the delivery of optimal medical care and allow a greater understanding of the underlying disease conditions.

Our future research will aim to develop a multivariable prediction model for the 72-hour prognosis in patients with extremely high outlier values of laboratory test items that have not yet been examined according to the TRIPOD statement.[22]

Future work, based on an act concerning anonymized medical data that are meant to contribute to research and development in the medical field ("Next Generation Medical Care Infrastructure Act"),[23] will also seek to clarify the relationship between extremely high outlier values of respective laboratory test items and their outcomes using machine learning methods by developing both a hardware and software environment that enables the use of the large quantities of clinical laboratory data that are generated in different medical institutions.

4.1. Limitations

Generalization of these results should be approached with caution as this study had some limitations, such as a retrospective design and the use of the top 100 extremely high outlier values of the 57 laboratory test items measured at a university teaching hospital. Medication use, the time course for treatment, interval time of OHCA, presence or absence of life-saving treatment, diagnosis, sex, and age were not evaluated in this study, although these factors may have affected the results.

4.2. Conclusions and recommendations

The 72-hour fatality ratios for the top 100 extremely high outlier values of 57 laboratory test items was significantly positively correlated with the OHCA ratios, and the 72-hour fatality ratios tended to be lower than the OHCA ratios. In predicting short-term prognosis, clinicians should focus on the extremely high outlier values for the following 13 laboratory test items: total bilirubin, direct bilirubin, CRP, BE, bicarbonate ion, CK, uric acid, PaO_2, Na, Cl, BUN, AST, and LD. The top 100 extremely high outlier values of these 13 laboratory test items were more likely to associate with 72-hour fatality than OHCA.

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