Association between the initial serum phosphate level and 30-day mortality in blunt trauma patients

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BACKGROUND: Studies on patients with cardiac arrest or sepsis have reported that high initial phosphate levels are associated with poor outcomes. However, no previous study has investigated the association between initial phosphate levels and outcomes in blunt trauma patients.

METHODS: This study was a retrospective observational study conducted on blunt trauma patients who had been treated at the single regional trauma center between January 2016 and December 2017. Patients' demographic data, initial vital signs, trauma scores, and laboratory parameters including phosphate levels were collected from the trauma registry. The primary outcome was set to 30-day mortality. The secondary outcomes were the total volume of blood transfused, 30-day hospital-free days, and 30-day intensive care unit–free days.

RESULTS: Of the 1,907 included patients, 1,836 were in the survival group, and 71 were in the nonsurvival group. The nonsurvival group had a significantly higher phosphate level than the survival group. Patients in the hyperphosphatemia group had a higher 30-day mortality, fewer 30-day intensive care unit–free days, and higher transfusion volume than those in the other groups. In multivariable logistic regression analysis, hyperphosphatemia was independently associated with 30-day mortality. The receiver operating characteristic curve analysis showed that the area under the curve with the inclusion of phosphate in addition to Injury Severity Score, Revised Trauma Score, and age was 0.911. Area under the curve was also increased when phosphate was simply added to Injury Severity Score and Revised Trauma Score.

CONCLUSION: In blunt trauma patients, hyperphosphatemia was associated with an increased 30-day mortality. (*J Trauma Acute Care Surg.* 2021;91: 507–513.

LEVEL OF EVIDENCE: Prognostic, level III.

KEY WORDS: Hyperphosphatemia; phosphate; mortality; multiple injuries.

Trauma is a major cause of death in individuals younger than 45 years, resulting in substantial social and economic loss.[1] Approximately 9% of all deaths (equal to more than 5 million worldwide) that occur every year are associated with trauma.[2] It is also the most common cause of disability-adjusted life-years in people aged 10 to 50 years.[3] A study reported a mean medical cost of €12,190 in trauma patients and €23,750 in those with severe trauma (Injury Severity Scores [ISSs], 15), indicating a direct relationship between medical cost and severity of trauma.[4]

In the past, deaths from trauma showed a trimodal distribution over time, where the first peak corresponds to deaths within several seconds to minutes after an accident. These deaths are mainly as a result of central nervous system injuries and major vascular traumas, and these can be reduced only through prevention. The second peak corresponds to deaths within several hours after an accident, caused mainly by central nervous system injuries and bleeding. The third peak corresponds to deaths within several days to weeks after an accident mainly caused by sepsis and multiorgan failure.[5] The deaths represented by the second and third peaks can be reduced by improving and advancing the treatments provided in hospitals. In recent years, this distribution has changed. Oyeniyi et al.[6] reported that 74% of the deaths had a unimodal distribution, in which 74% of the patients died within 72 hours, and Minei et al.[7] reported that multiorgan failure as a result of hemorrhage shock occurred soon after trauma. It is thus important to rapidly identify patients with severe trauma and provide them with intensive treatment.

Despite the use of various trauma scoring systems such as the Revised Trauma Score (RTS), ISS, and Trauma and Injury Severity Score as well as biomarkers including lactate, base deficit, and lactate clearance to recognize patients with severe trauma and predict their prognoses, early screening of patients with severe trauma is still difficult.[8,9]

Recent studies have reported that high initial phosphate levels during the acute phase in patients with cardiac arrest or sepsis are associated with poor outcomes, which was considered to be a consequence of cell death due to the ischemic condition.[10,11] Given that cell death occurs because of ischemic injuries

Submitted: January 18, 2021, Revised: April 16, 2021, Accepted: April 27, 2021, Published online: May 5, 2021.

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DOI: 10.1097/TA.0000000000003271

after hemorrhagic shock in trauma patients, high phosphate levels may also be associated with poor outcomes in these patients.[12,13]

However, no study has examined this association in trauma patients. This study examined the association between the initial phosphate levels and prognoses in trauma patients in emergency departments (EDs). We also investigated whether combining phosphate level measurements with other conventional predictors could improve overall prediction outcomes in these patients.

PATIENTS AND METHODS

Study Design, Population, and Setting

We performed a retrospective review of all blunt trauma patients in the trauma registry database of a single regional trauma center (level 1 trauma center in the United States) from January 2016 to December 2017. The study facility was a tertiary academic hospital with more than 500 major trauma patients annually. This study was approved by the Institutional Review Board of Wonju Severance Christian Hospital and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for reporting observational trials.[14]

Patient Enrollment and Outcomes

All adult blunt trauma patients 18 years or older were included in the study. Patients in whom (1) laboratory tests were not performed, (2) who were discharged or transferred to another hospital, (3) who had a cardiac arrest at the time of ED presentation, (4) who died in an ED, and (5) who had invalid data (RTS or ISS) were excluded from the study (Fig. 1). The primary outcome of this study was the 30-day mortality after admission to a trauma center. The secondary outcomes were the total volume of blood transfused, 30-day hospital-free days, and 30-day intensive care unit (ICU)–free days.

Data Collection

Demographic data (age and sex), injury mechanism, and the initial vital signs data on arrival at an ED (blood pressure, heart rate, and respiratory rate [RR]), and trauma scores (Glasgow Coma Scale [GCS], RTS, Abbreviated Injury Scale [AIS], and ISS) were collected from the trauma registries. The RTS consists of three variables, GCS, systolic blood pressure (SBP), and RR, which are assigned coded values from 0 to 4. In this study, RTS with weights to each variable (0.7326 SBP + 0.2908 RR + 0.9368 GCS) was used.[15] The ISS is an anatomical scoring system that provides the overall score for multiple injuries patients.[16] Every injury in each body region is scored on the AIS. The AIS of the three most severely injured regions are squared and added to determine the ISS score. The hospital that conducted this study was a regional trauma center (corresponding to a level 1 trauma center in the United States). When trauma patients visit this hospital, x-rays, and computed tomography are performed in the ED, and these are immediately checked by traumatology specialists. The ISS is calculated based on the damage diagnosed during this process, and the trauma registry including the ISS is managed by dedicated staff. Results of the initial tests performed immediately after the admission to the traumatic center were also collected. These included data on serum phosphate and

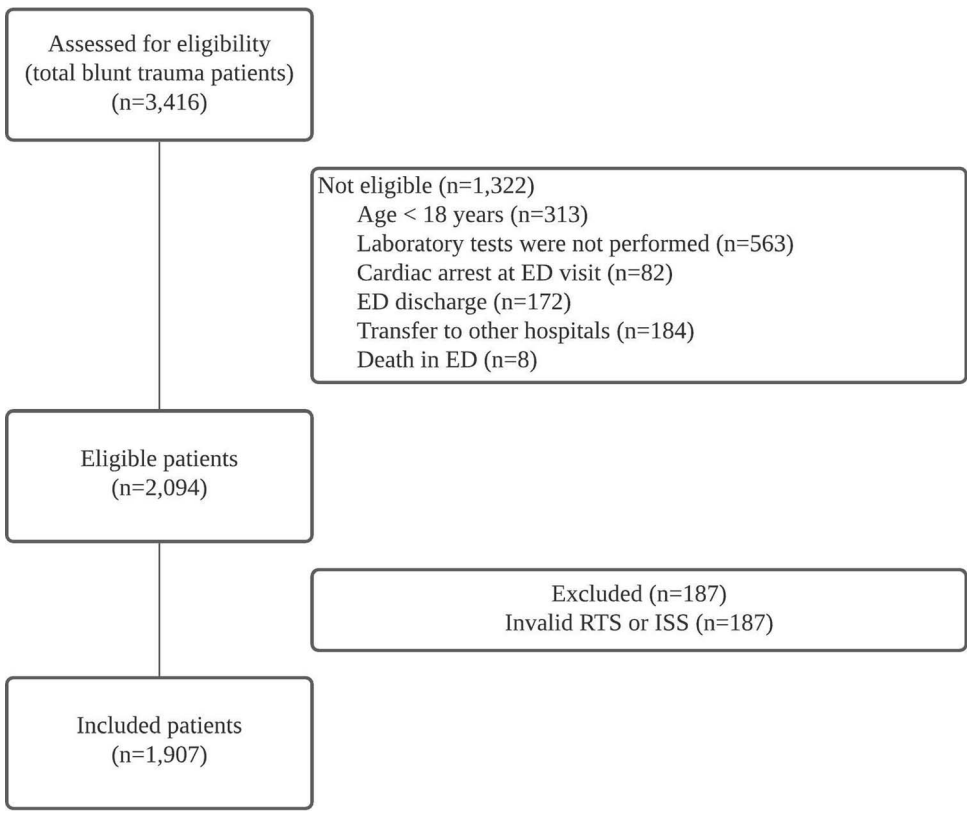

Figure 1. Flow diagram showing patient inclusion.

serum lactate levels. Data on mortality, hospital-free days, ICU-free days, and transfusions (packed red blood cell [RBC] and fresh frozen plasma [FFP]) were additionally collected. The hospital-free days was defined as the days that the patient was alive and not hospitalized (30 − total hospital days = hospital-free days). For patients who died before 30 days and had no hospital-free days, this was recorded as 0. For those who had lengths of stay longer than 30 days, this was recorded as 0.[17] The ICU-free days was defined in a similar manner to days alive and free from the need for intensive care and was calculated using the same method as hospital-free days.[18]

Statistical Analyses

Statistical analyses were performed using SPSS software for Windows (version 25.0 K; SPSS, Chicago, IL). Nominal data are presented as frequencies and percentages, and continuous variables are presented as means and SDs and medians and interquartile ranges after assessments for normality using the Shapiro-Wilk test. The χ^2 test or Fisher's exact test were used for comparisons of nominal variables, while the independent *t* test and Mann-Whitney *U* test were used to compare continuous variables. *p* Values less than 0.05 were considered statistically significant.

The multivariable logistic regression models were constructed using the backward elimination method to identify independent variables of 30-day mortality, as measured by the odds ratio (OR) and 95% confidence intervals. All variables with $p < 0.2$ in the univariate analyses were included in the initial multivariate models. Lactate, RTS, and ISS were dichotomized and included in the analysis with reference to previous studies.[9,19–21] Heart rates were divided into three groups with reference to the previous study (below 70/min, 70–89/min, and above 89/min).[22] Since RTS contains SBP, RR, and GCS, each of those factors were not included in the multivariable logistic regression model. The area under the curve (AUC) of the receiver operating characteristic (ROC) described and compared the models' overall performance. The AUCs were calculated and compared according to the method of Hanley and McNeil using MedCalc version 19.6.3 (MedCalc Statistical Software, Marakierke, Belgium).

The restricted cubic spline curve with four knots was used to represent a nonlinear relationship between the initial serum phosphate level and 30-day mortality. In this analysis, the reference relative OR was set to 3.0 mg/dL of initial serum phosphate level to best interpret changes with increasing phosphate level.

TABLE 1. Baseline Characteristics of 1,907 Patients With Blunt Traumatic Injury

	Survivors (n = 1,836)	Nonsurvivors (n = 71)	Total (n = 1,907)	*p*
Age, y	54 ± 17	66 ± 17	54 ± 17	<0.001
Male (sex)	1,343 (73.1)	52 (73.2)	1,395 (73.2)	>0.999
SBP, mm Hg	137 ± 29	126 ± 45	137 ± 30	0.047
Diastolic blood pressure, mm Hg	79 ± 17	71 ± 23	79 ± 18	0.019
Heart rate, beats/min	86 ± 17	95 ± 26	86 ± 18	0.001
RR, breaths/min	19 ± 3	20 ± 3	19 ± 3	0.011
GCS	14 ± 2	10 ± 5	14 ± 2	<0.001
ISS	13 ± 8.98	27.23 ± 10.48	13.53 ± 9.43	<0.001
AIS_{head}	1.41 ± 1.49	3.17 ± 1.97	1.48 ± 1.55	<0.001
AIS_{face}	0.28 ± 0.67	0.27 ± 0.70	0.28 ± 0.67	0.700
AIS_{chest}	1.08 ± 1.41	1.56 ± 1.75	1.10 ± 1.42	0.016
$AIS_{abdomen}$	0.69 ± 1.18	1.07 ± 1.49	0.70 ± 1.19	0.027
$AIS_{extremity}$	1.05 ± 1.31	1.35 ± 1.71	1.06 ± 1.33	0.246
$AIS_{external}$	0.66 ± 0.58	0.48 ± 0.63	0.65 ± 0.58	0.003
RTS	7.6712 ± 0.5774	6.3776 ± 1.3360	7.6230 ± 0.6683	<0.001
Laboratory findings				
Lactate, mmol/L	2.28 ± 1.55	4.27 ± 3.20	2.36 ± 1.68	<0.001
Phosphate, mg/dL	3.08 ± 1.10	3.67 ± 1.37	3.10 ± 1.12	<0.001
Transfusion	296 (16.1)	28 (39.4)	324 (17)	<0.001
Packed RBC, mL	815 ± 323	1,023 ± 595	833 ± 359	0.113
FFP, mL	807 ± 340	1,110 ± 766	841 ± 418	0.142
30-d ICU-free days	26 ± 7	23 ± 7	26 ± 7	<0.001
30-d hospital-free days	14 ± 10	23 ± 8	14 ± 10	<0.001
Injury mechanism				0.053
Traffic accident	1,271 (69.2)	38 (53.5)	1,309 (68.6)	
Fall down	316 (17.2)	18 (25.4)	334 (17.5)	
Slip down	85 (4.6)	7 (9.9)	92 (4.8)	
Industrial accident	18 (1.0)	1 (1.4)	19 (1.0)	
Other blunt injury	146 (8.0)	7 (9.9)	153 (8.0)	

Nonsurvivors were compared with survivors in the 30 days following their traumatic injury. The data are presented as n (%) or as mean ± SD.
30-Day hospital-free days, days alive and not hospitalized; 30-day ICU-free days, days alive and free from the need for intensive care.

TABLE 2. Outcomes and Clinical Characteristics of Trauma Patients According to Their Initial Serum Phosphate Level

	Phosphate, mg/dL					
	<2.5$_a$ (n = 438)	2.5–4.5$_b$ (n = 1,362)	>4.5$_c$ (n = 107)		*p*	
30-d Mortality	12 (2.7%)	43 (3.2%)	16 (15.0%)	$p_{ab} = 0.662$	$p_{bc} < 0.001$	$p_{ac} < 0.001$
30-d Hospital-free days	14.1 ± 10.3	14.7 ± 10.1	11.4 ± 11.3	$p_{ab} = 0.903$	$p_{bc} = 0.010$	$p_{ac} = 0.083$
30-d ICU-free days	26.1 ± 6.9	26.4 ± 6.2	20.5 ± 9.3	$p_{ab} = 1.000$	$p_{bc} < 0.001$	$p_{ac} < 0.001$
Transfusion						
RBC transfusion, mL	111 ± 319	122 ± 314	471 ± 599	$p_{ab} = 1.000$	$p_{bc} < 0.001$	$p_{ac} < 0.001$
FFP transfusion, mL	152 ± 368	153 ± 364	406 ± 561	$p_{ab} = 1.000$	$p_{bc} < 0.001$	$p_{ac} < 0.001$
Lactate, mmol/L	2.24 ± 1.24	2.18 ± 1.31	5.17 ± 3.75	$p_{ab} = 0.130$	$p_{bc} < 0.001$	$p_{ac} < 0.001$
ISS	12.94 ± 9.04	13.16 ± 9.16	20.55 ± 11.53	$p_{ab} = 1.000$	$p_{bc} < 0.001$	$p_{ac} < 0.001$
RTS	7.74 ± 0.47	7.64 ± 0.63	6.97 ± 1.26	$p_{ab} = 0.012$	$p_{bc} < 0.001$	$p_{ac} < 0.001$

30-day hospital-free days, days alive and not admitted to the hospital; 30-day ICU-free days, days alive and free from the need for intensive care.

$_a$ refers to the hypophosphatemia group (serum phosphate, <2.5 mg/dL); $_b$, normal phosphate group (serum phosphate, 2.5–4.5 mg/dL); $_c$, hyperphosphatemia group (serum phosphate, >4.5 mg/dL); p_{ab}, p value for comparison between hypophosphatemia and normal phosphate group; p_{bc}, p value for comparison between normal phosphate and hyperphosphatemia group; and p_{ac}, p value for comparison between hypophosphatemia and hyperphosphatemia group.

R-package software, version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) with rms package was used for analysis.

Statistical power analysis was performed using G*power 3.1 for the 30-day mortality rate using the two-tail Fisher's exact test. Given a type 1 error of 0.05, 30-day mortality rates of 15% and 3.2%, and the sample sizes of 1,362 and 107, for the patients whose initial serum phosphate level was normal (2.5–4.5 mg/dL) and high (over 4.5 mg/dL), respectively, a statistical power of 0.99 was calculated.

RESULTS

A total of 1,907 adult patients who had experienced blunt trauma were enrolled (Fig. 1). Based on the outcome within 30 days, the patients were divided into survival (n = 1,836) and nonsurvivor (n = 71) groups, and their baseline characteristics were compared. Patients in the nonsurvivor group were older, had lower SBP, and higher heart and RRs than those in the survival group. They had a lower GCS and RTS but a higher ISS compared with the survival group. Higher lactate and phosphate levels were noted in the nonsurvivor group compared with the survival group. The patients in the nonsurvivor group had fewer 30-day hospital-free days and 30-day ICU-free days than the survival group. The injury mechanism did not differ significantly between the two groups (Table 1).

The outcomes according to the phosphate level were compared. Patients in the hyperphosphatemia group (serum phosphate, >4.5 mg/dL) had a higher 30-day mortality, fewer 30-day hospital-free days and 30-day ICU-free days, and higher RBC and FFP transfusion volumes than those in the normal phosphate group (serum phosphate, 2.5–4.5 mg/dL). They also had higher 30-day mortality rates, fewer 30-day ICU-free days, and higher RBC and FFP transfusion volumes than patients in the hypophosphatemia group (<2.5 mg/dL). Furthermore, the serum lactate levels and ISS were higher, and RTS was lower in the hyperphosphatemia group than in the other groups (Table 2).

In the restricted cubic spline curve, OR of 30-day mortality tended to increase, as the initial serum phosphate level was higher than 3 mg/dL, but did not decrease when the initial serum phosphate level was less than 3 mg/dL (Fig. 2).

Next, the multivariable logistic regression analyses were performed to investigate the effects of several independent variables on 30-day mortality. In model 1, the 30-day mortality increased by 1.658 times for every 10 years of age, 2.453 times for hyperphosphatemia, 8.197 times for an ISS of >15, and 8.542 times for an RTS of <7.8408. In model 2, the 30-day mortality increased by 1.643 times for every 10 years of age, 2.672 times for hyperphosphatemia, and 12.915 times for an RTS of <7.8408 (Table 3).

The ROC curve and the area under the ROC curve were derived for the different multivariable logistic regression models. A comparison between the different models yielded a *p* value of 0.048 between model 1 and RTS + ISS + age model (model 1 − phosphate) (Fig. 3*A*). Area under the curve was also increased even when phosphate was simply added to the traditional mortality predictors, ISS and RTS ($p = 0.005$ between

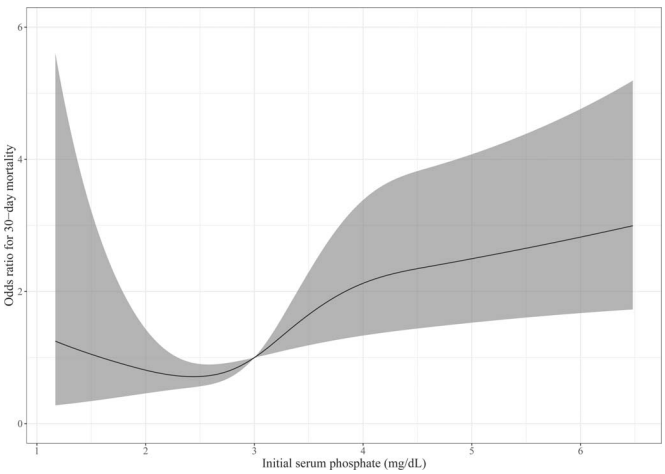

Figure 2. The relation between 30-day mortality and initial serum phosphate levels. The reference was set to 3.0 mg/dL of initial serum phosphate level to best interpret changes with increasing phosphate level.

TABLE 3. Multivariable Logistic Regression Models for 30-Day Mortality

	Adjusted OR (95% CI)	*p*
Model 1		
Age per 10 y	1.658 (1.370–2.006)	<0.001
Phosphate		
2.5–4.5 mg/dL	Reference	
<2.5 mg/dL	1.303 (0.637–2.666)	0.469
>4.5 mg/dL	2.453 (1.164–5.171)	0.018
ISS >15	8.197 (3.573–18.805)	<0.001
RTS <7.8408	8.542 (4.618–15.802)	<0.001
Model 2		
Age per 10 y	1.643 (1.372–1.969)	<0.001
Phosphate		
2.5–4.5 mg/dL	Reference	
<2.5 mg/dL	1.199 (0.594–2.420)	0.613
>4.5 mg/dL	2.672 (1.284–5.560)	0.009
RTS <7.8408	12.915 (6.989–23.863)	<0.001

Model 1 included all variables with $p < 0.2$ in univariate analyses (age, initial serum phosphate/lactate level, diastolic blood pressure, heart rate, ISS, RTS), whereas model 2 included all variables included in model 1 except ISS.

CI, confidence interval.

ISS and ISS + phosphate model, $p = 0.003$ between RTS and RTS + phosphate model) (Figs. 2, 3).

DISCUSSION

In our study, hyperphosphatemia (>4.5 mg/mL), RTS of <7.8408, ISS of >15, and older age were associated with a higher 30-day mortality. In addition, the hyperphosphatemia group had a higher 30-day mortality rate, fewer 30-day hospital-free days and 30-day ICU-free days, and a greater RBC and FFP transfusion volume.

Phosphate is an important constituent of bones, teeth, cell membranes, nucleic acids, high-energy molecules like adenosine triphosphate, intracellular molecules such as 2,3-diphosphoglycerate, glucose-6-phosphate, and many phosphorylated proteins. It is absorbed in the small intestine and excreted through the kidney. Its levels are regulated by the parathyroid hormone, 1,25-dihydroxy vitamin D (1,25(OH)2D, and fibroblast growth factor 23. While parathyroid hormone and F21GF23 reduce the serum phosphate levels, 1,25(OH)2D increases it.[23] The causes of hyperphosphatemia include an acute increase in phosphate load, decreased renal excretion, transcellular shifting, hypoparathyroidism, and pseudohypoparathyroidism.[24] Although its causes in trauma patients are unclear, it is believed to be an acute increase in phosphate load because of tissue hypoxia and tissue injury. In particular, rhabdomyolysis, which may occur in blunt trauma patients, is a risk factor for acute kidney injury and may cause hyperphosphatemia. In addition, hemolysis, which may appear after blood transfusion and crush injury, can induce hyperphosphatemia through a similar mechanism.[23,25,26]

Some studies have investigated the association between hyperphosphatemia and the outcomes of critically ill patients. Miller et al.[27] reported an association between hyperphosphatemia and increased mortality in patients who were on mechanical ventilation because of severe sepsis or septic shock. Their findings suggested that, in addition to being an indicator of septic shock-induced cell death, hyperphosphatemia by itself was toxic. Jung et al.[10] reported an association between high phosphate levels and poor outcomes in patients with cardiac arrest and return of spontaneous circulation. They suggested that the leakage of phosphates from damaged cells under the ischemic conditions may have caused hyperphosphatemia, which in turn could have resulted in endothelial dysfunction and oxidative stress.

Consistent with the aforementioned studies, hyperphosphatemia was associated with an increased 30-day mortality in the blunt trauma patients in our study. In addition, patients in the hyperphosphatemia group had fewer ICU-free days and higher RBC and FFP transfusion volumes. The mechanisms

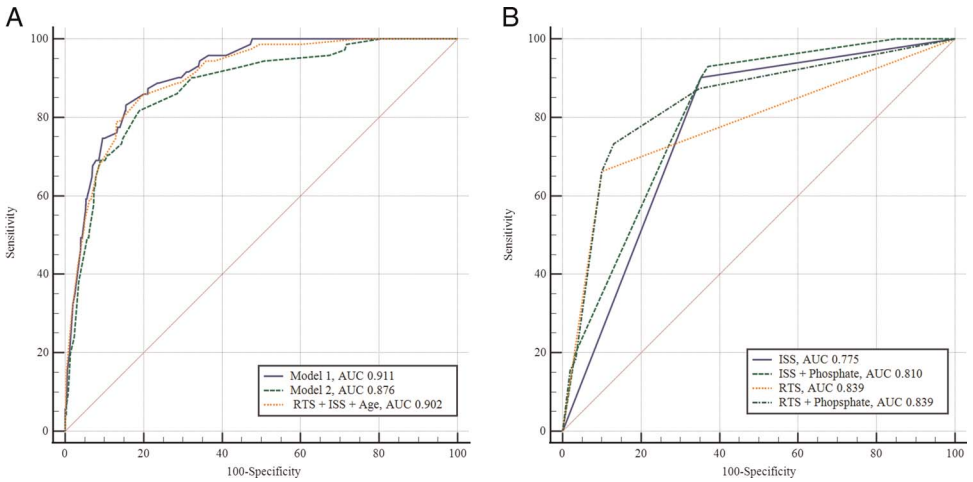

Figure 3. Receiver operating characteristic curves. (*A*) Receiver operating characteristic curves. Model 1, RTS + ISS + age + phosphate; model 2, RTS + age + phosphate. Model 1 versus model 2 ($p = 0.017$), model 1 versus RTS + ISS + age model ($p = 0.048$), model 2 versus RTS + ISS + age model ($p = 0.091$). (*B*) Receiver operating characteristic curves. ISS versus ISS + phosphate ($p = 0.005$), RTS versus RTS + phosphate ($p = 0.003$).

underlying the association between hyperphosphatemia and poor outcomes in trauma patients are not clear, but two putative mechanisms could be considered. The first is ischemic injury due to hemorrhage. Hypovolemia and vasoconstriction after massive blood loss lead to hypoperfusion and further end-organ damage, which results in poor patient outcomes.[12,13] Dundar et al.[28] reported elevated serum phosphate levels with prolonged ischemic time, which were considered a result of continued ischemic injury due to persistent bleeding.

In addition, the serum lactate levels observed support the possibility of ischemic injury due to bleeding. Lactate is a well-known prognostic biomarker whose levels rise in response to tissue ischemia or tissue injury in trauma patients. Baxter et al.[29] reported that elevated lactate levels in an ED are associated with mortality in adult trauma patients. Callaway et al.[30] reported that the initial lactate levels are associated with increased mortality in normotensive trauma patients. Raux et al.[31] found that lactate levels are a better predictor of mortality than the base deficit. In the present study, the hyperphosphatemia group showed higher lactate levels than the other groups. This means that ischemic tissue injury had occurred, which is consistent with the results of aforementioned studies showing that trauma patients with high lactate levels had a poor prognosis.

The second proposed mechanism is phosphate release due to tissue injury. Tissue injury may lead to hyperphosphatemia, as intracellular phosphates are released into the circulation.[32,33] In this study, the hyperphosphatemia group showed higher ISS and lower RTS compared with the other groups, which may mean that multiple or more severe injuries caused a greater phosphate load. Furthermore, ISS and RTS are predictors of mortality in trauma patients. Taken together, these mechanisms may explain the association between hyperphosphatemia and poor outcomes.[9,31,34]

In our study, the ISS and RTS were strongly correlated with 30-day mortality, and when phosphate was included, the AUC was statistically significantly increased. In addition, when phosphate was added to the model, including ISS, RTS, and age (model 1), the AUC was significantly increased. Although the accuracy of model 1, including both ISS and RTS, was higher, model 2, which uses only RTS, may be useful in institutions that cannot calculate the ISS in the ED (Fig. 3). In our study, AIS_{head} was statistically significantly higher in the nonsurvivor group than in the survival group. Given that Oyeniyi et al.[6] reported that more than 60% of trauma-related deaths were due to head injuries and that traumatic brain injuries could be identified within a short time after an emergency room visit, a model including an AIS_{head} instead of an ISS could be useful.[35,36]

Regarding lactate, the univariable logistic regression analysis showed a 3.561-fold increase in mortality when lactate levels were >2.0 compared with when lactate levels were ≤2.0 (OR, 3.561; 95% confidence interval, 2.070–6.126). However, the multivariable logistic regression model (including age, diastolic blood pressure, heart rate, phosphate levels, lactate levels, RTS, and ISS) did not significantly associate lactate levels with mortality.

This study had some limitations. First, it was a single-center, retrospective study; thus, the results cannot be generalized without a multicenter study. Second, since we only investigated the initial serum phosphate level, we could not determine whether the normalization or correction of serum phosphate level is associated with outcomes. Third, patients who did not have laboratory tests performed while they were in the ED were excluded, and this may have led to the exclusion of some patients with severe trauma. Fourth, medical history or medication use, which can affect phosphate metabolism, could not be investigated. For example, while hyperphosphatemia can be caused by hypoparathyroidism, chronic renal disease, and phosphate-containing laxatives, hypophosphatemia can result from primary hyperparathyroidism, vitamin D deficiency, parathyroid hormone-secreting tumors, and medications such as diphenylhydantoin and rifampicin.[23]

In conclusion, in patients who have undergone blunt trauma, hyperphosphatemia was associated with an increased 30-day mortality.

AUTHORSHIP

D.K.L. contributed in the conceptualization, methodology, investigation, data curation, formal analysis, review and editing of the article, and supervision. W.J.J. contributed in the validation and data curation. K.J.L. contributed in the formal analysis. H.J.C. contributed in the visualization. D.W.K. contributed in the writing of the original draft.

ACKNOWLEDGMENT

We thank the Division of Statistics in Medical Research Collaborating Center at Seoul National University Bundang Hospital for the statistical analyses.

DISCLOSURE

The authors declare no conflicts of interest.

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