THE ATLANTIC Journal of Medical Science and Research

Atlantic J Med Sci Res 2026;6(3):410-8
DOI: 10.5455/atjmed.2026.06.073

Original Article

Hypophosphatemia and adverse composite outcome in mechanically ventilated critically Ill children: A single-center retrospective cohort study

Ibrahim Bingol

Gaziantep City Hospital, Department of Pediatric Intensive Care, Gaziantep, Türkiye

Received: 08 July, 2026
Accepted: 27 July, 2026
Published: 14 September, 2026

Corresponding Author: Ibrahim Bingol, Gaziantep City Hospital, Department of Pediatric Intensive Care, Gaziantep, Türkiye
Email: ibrahimbingol@gmail.com

CITATION
Bingol I. Hypophosphatemia and adverse composite outcome in mechanically ventilated critically Ill children: A single-center retrospective cohort study. Atlantic J Med Sci Res. 2026;6(3):410-8. DOI: 10.5455/atjmed.2026.06.073

Abstract

Aim: Hypophosphatemia may impair diaphragmatic contractility and prolong weaning from mechanical ventilation, but pediatric prognostic data are scarce.
Materials and Methods: This single-center retrospective cohort included 206 children (1 month – 18 years) invasively ventilated for at least 48 hours (April 2024 – January 2026). Conditions distorting phosphate homeostasis were excluded. Serum phosphate was measured at admission, day 3 (both required for inclusion), and day 7 in patients still in the pediatric intensive care unit (PICU); hypophosphatemia was defined as < 2.5 mg/dL. The primary outcome was a composite of PICU mortality or prolonged ventilation (≥ 14 days); secondary outcomes were mortality and ventilation duration. Multivariable models were adjusted for age, PRISM III, sepsis, albumin, furosemide, and vasoactive/inotropic exposure. A pre-specified sensitivity analysis used admission hypophosphatemia as the exposure.
Results: Hypophosphatemia occurred at any timepoint in 107 patients (51.9%) and the composite outcome in 71 (34.5%; 46.7% vs 21.2%, p < .001). After adjustment, any-timepoint hypophosphatemia remained associated with the composite outcome (adjusted OR 2.52, 95% CI 1.25 – 5.09, p = .010), driven by the ventilation component (adjusted OR 3.77, 95% CI 1.61 – 8.84, p = .002) rather than mortality (adjusted OR 1.85, p = .158), and with longer ventilation (adjusted ratio 1.57, 95% CI 1.30 – 1.91, p < .001). In the sensitivity analysis the composite association was no longer significant (adjusted OR 1.56, 95% CI 0.79 – 3.09, p = .197), and discrimination was limited (all AUCs < 0.70).
Conclusion: Hypophosphatemia is common in mechanically ventilated children and, when assessed at any timepoint, is associated with mortality or prolonged ventilation; the association is driven by the ventilation component and is lost when restricted to admission values. Hypophosphatemia therefore appears to be predominantly a marker of illness severity rather than an independent, admission-identifiable driver of outcome. Whether serial monitoring and correction improves outcomes requires prospective evaluation.

Keywords: Hypophosphatemia, mechanical ventilation, pediatric intensive care, critical illness, phosphate

INTRODUCTION

Phosphate is an essential intracellular anion required for adenosine triphosphate (ATP) synthesis, oxygen delivery via 2,3-diphosphoglycerate, membrane integrity, and intracellular signaling, and its homeostasis is tightly regulated by parathyroid hormone, fibroblast growth factor 23, and active vitamin D (1). In critical illness, inflammatory cytokine release, acute respiratory alkalosis, renal phosphate wasting from loop diuretics, and continuous renal replacement therapy converge to produce hypophosphatemia, commonly defined as a serum phosphate concentration below 2.5 mg/dL (< 0.81 mmol/L) (1). Severe hypophosphatemia has been mechanistically linked to diaphragmatic dysfunction in adults failing to wean from mechanical ventilation, with phosphate repletion producing a measurable improvement in transdiaphragmatic pressure within hours (2).

In adult intensive care, hypophosphatemia has been consistently associated with prolonged mechanical ventilation, longer length of stay, and increased mortality. Wozniak et al. reported a 1.5-fold increase in ventilation duration and intensive care unit length of stay (3), Wang et al. identified admission hypophosphatemia as an independent predictor of 28-day mortality (4), and Statlender et al. characterized its temporal patterns and contributing factors in mechanically ventilated adults (5). Pediatric evidence is more limited. Kilic et al. reported a 60.2% prevalence in 118 Turkish children, with associations to length of stay and ventilation (6); Lusteau et al. extended this to severe bronchiolitis (7); and Shah et al. found it highly prevalent and associated with longer pediatric intensive care unit (PICU) stays (8). The European Society of Intensive Care Medicine (ESICM) systematic review by Reintam Blaser et al. nonetheless concluded that data remain insufficient to define the optimal phosphate threshold for treatment and the optimal frequency of measurement, particularly in children (9), and the meta-analysis by Sin et al. (12 studies, 7,626 patients) found hypophosphatemia associated with longer intensive care unit (ICU) and hospital stays but not all-cause mortality, suggesting it functions primarily as a marker of disease severity (10).

Against this background, we conducted a single-center retrospective cohort study in a tertiary PICU to evaluate the association between hypophosphatemia and clinically meaningful outcomes in mechanically ventilated children. Because mortality alone has limited power as a stand-alone endpoint in single-center pediatric studies and prolonged ventilator dependency carries substantial morbidity, we adopted a composite primary outcome of PICU mortality or prolonged mechanical ventilation (≥ 14 days), with mortality and ventilation duration analyzed separately as secondary outcomes. By focusing on children requiring at least 48 hours of invasive ventilation and rigorously excluding confounding conditions, we aimed to provide a contemporary characterization that addresses a gap in pediatric critical-care literature, particularly in Turkish and similarly resourced settings.

MATERIALS AND METHODS

Study design and setting

This single-center, retrospective, observational cohort study was conducted in the 30-bed PICU of a tertiary referral center (institutional identity withheld for double-blind peer review). Consecutive patients admitted between April 2024 and January 2026 were screened. The protocol was reviewed and approved by the Gaziantep City Hospital Non-Interventional Clinical Research Ethics Committee (17 June 2026; decision number 593/2026), and written informed consent was waived given the retrospective, anonymized design; the study followed the Declaration of Helsinki.

Study population

Children aged 1 month to 18 years who received invasive mechanical ventilation for at least 48 consecutive hours were eligible, provided serum phosphate values were available at admission (within the first 24 hours) and on day 3; a day-3 value was therefore a requirement for inclusion, and day 7 values were obtained when the patient remained in the PICU, with landmark analyses restricted to patients still in the PICU at those timepoints. Exclusion criteria were chronic kidney disease (any stage), continuous renal replacement therapy at any point, diabetic ketoacidosis as the primary admission diagnosis, tumor lysis syndrome, primary renal tubular disease, known metabolic bone disease or primary hyperparathyroidism, and transfer from another center while already receiving mechanical ventilation. Patients with multiple admissions were included only on their first qualifying admission.

Definition of hypophosphatemia

Hypophosphatemia was defined as a serum phosphate concentration below 2.5 mg/dL (< 0.81 mmol/L) and, on the basis of the lowest of the three protocol measurements (admission, day 3, and day 7), was graded as mild (2.0 – 2.4 mg/dL), moderate (1.0 – 1.9 mg/dL), or severe (< 1.0 mg/dL) (1). Although pediatric phosphate reference ranges are age-dependent, a single threshold was applied because < 2.5 mg/dL is the definition used most consistently in the intensive-care literature (1,9), permitting direct comparison with previous studies. Phosphate was measured at admission (the first sample within 24 hours), on day 3 (48 – 72 hours), and on day 7 if the patient was still in the PICU. Intravenous or oral phosphate replacement was recorded as a binary variable. Replacement was not protocolized and was given at the discretion of the treating clinician after a phosphate value below the study threshold had been documented; it was never administered prophylactically.

Outcomes

The primary outcome was a composite of PICU mortality or prolonged invasive mechanical ventilation, defined as a duration of ≥ 14 days. The 14-day threshold broadly corresponds to the clinical decision point for tracheostomy and the duration after which the risks of prolonged ventilation become substantial. The three mutually exclusive components of the composite—mortality without prolonged ventilation, prolonged ventilation without death, and both—were tabulated, and each dichotomous component was additionally analyzed. Secondary outcomes were PICU mortality alone; invasive ventilation duration (from initiation to successful extubation lasting at least 24 hours); PICU length of stay; weaning failure; reintubation; tracheostomy during the PICU stay; and in-hospital mortality. Weaning failure was defined as failure of a planned extubation within 24 hours (reflecting inadequate extubation readiness), and reintubation as any re-initiation of invasive ventilation within 48 hours of extubation; the two capture overlapping but distinct time windows and were recorded independently. For patients who died while receiving invasive ventilation, ventilation duration was measured from initiation to death (censored at death), and these patients were retained in all analyses.

Data collection and variables

Data were extracted from the institutional electronic medical record into a standardized, password-protected database. Demographic

data included age, sex, and body weight at admission. Disease severity was assessed by Pediatric Risk of Mortality III (PRISM III) (11) and Pediatric Logistic Organ Dysfunction-2 (PELOD-2) (12), both calculated for the first 24 hours. The admission diagnosis was classified into seven mutually exclusive categories: sepsis or septic shock (defined by the 2024 Phoenix Pediatric Sepsis Criteria) (13), respiratory failure, trauma, postoperative state, neurologic disease, inherited metabolic disease, and other or mixed. Admission laboratory parameters included total and ionized calcium, magnesium, potassium, albumin, creatinine, urea, alanine and aspartate aminotransferases, lactate, C-reactive protein (CRP), procalcitonin, arterial pH and bicarbonate, hemoglobin, and glucose. Medications influencing phosphate homeostasis—loop diuretics, corticosteroids, vasoactive or inotropic agents, and salbutamol—were recorded as binary variables; vasoactive and inotropic agents were combined into a single variable because agent selection is heterogeneous and driven by hemodynamic phenotype. Nutritional support was recorded as the day of enteral feeding initiation and the receipt of parenteral nutrition; maintenance fluids were not systematically recorded, and phosphorus intake could not be quantified.

Statistical analysis

Analyses used IBM SPSS Statistics version 26.0 (IBM Corp, Armonk, NY, USA). Normality was assessed with the Shapiro – Wilk test; continuous variables are median (Interquartile range (IQR)) or mean ± standard deviation (SD), compared with the Mann – Whitney U or t test, and categorical variables (n, %) with the chi-square or Fisher exact test. Multivariable logistic regression examined the independent association of hypophosphatemia (any timepoint) with the composite outcome and with PICU mortality, adjusting for age, PRISM III, sepsis, admission albumin, furosemide, and vasoactive/inotropic use; each dichotomous composite component was modeled with the same covariate set. Ventilation duration was log-transformed and modeled by multivariable linear regression with the same covariates. As a pre-specified sensitivity analysis to address potential reverse causation—because day-3 and day-7 hypophosphatemia fall within the outcome window—all multivariable models were repeated using admission hypophosphatemia as the exposure. Receiver operating characteristic (ROC) analysis compared admission, day 3, and the lowest of the three protocol phosphate values for predicting the composite outcome and PICU mortality, and cumulative incidence of the composite event was compared between groups with the log-rank test. A two-sided $p < .05$ was considered statistically significant.

RESULTS

Study population

During the 22-month study period (April 2024 – January 2026), 206 patients met all inclusion and exclusion criteria. Median age was 40 months (IQR 11 – 88) and 117 (56.8%) were male. The most frequent admission diagnoses were respiratory failure (n = 69, 33.5%) and sepsis or septic shock (n = 53, 25.7%), followed by postoperative state (n = 31, 15.0%), neurologic conditions (n = 30, 14.6%), trauma (n = 11, 5.3%), inherited metabolic disease (n = 2, 1.0%), and other or mixed (n = 10, 4.9%). Median PRISM III was 10 (IQR 6 – 15) and PELOD-2 was 4 (IQR 2 – 7) (Table 1). Enteral feeding was initiated at a median of 2 days after admission (IQR 1 – 4), and 72 patients (35.0%) received parenteral nutrition. Overall, PICU mortality was 19.9% (n = 41), prolonged ventilation (≥ 14 days) occurred in 22.3% (n = 46), and the composite primary outcome in 34.5% (n = 71); the composite comprised mortality without prolonged ventilation in 25 (12.1%), prolonged ventilation without death in 30 (14.6%), and both in 16 (7.8%).

Table 1. Baseline characteristics of the study population (n = 206)

Variable	Value
Age, months, median (IQR)	40 (11 – 88)
Male sex, n (%)	117 (56.8)
Body weight, kg, median (IQR)	15.3 (8.7 – 30.6)
Admission diagnosis, n (%)	
Sepsis / septic shock	53 (25.7)
Respiratory failure	69 (33.5)
Trauma	11 (5.3)
Postoperative	31 (15.0)
Neurologic	30 (14.6)
Metabolic disease	2 (1.0)
Other / mixed	10 (4.9)
Severity scores at first 24 h	
PRISM III, median (IQR)	10 (6 – 15)
PELOD-2, median (IQR)	4 (2 – 7)
Admission laboratory values, median (IQR)	
Albumin, g/dL	3.5 (3.3 – 3.8)
Magnesium, mg/dL	2.0 (1.8 – 2.2)
Lactate, mmol/L	2.6 (2.0 – 3.3)
CRP, mg/L	42.0 (29.8 – 84.2)
Medication exposure during PICU stay, n (%)	
Furosemide	122 (59.2)
Corticosteroids	72 (35.0)
Vasoactive / inotropic agents	95 (46.1)
Salbutamol	69 (33.5)
Parenteral nutrition, n (%)	72 (35.0)
Outcomes	
Invasive MV duration, days, median (IQR)	7.0 (4.0 – 12.0)
PICU length of stay, days, median (IQR)	10 (7 – 15)
PICU mortality, n (%)	41 (19.9)
MV ≥14 days, n (%)	46 (22.3)
Composite (mortality OR MV ≥14 d), n (%)	71 (34.5)
Mortality without prolonged MV, n (%)	25 (12.1)
Prolonged MV without death, n (%)	30 (14.6)
Both, n (%)	16 (7.8)

IQR: interquartile range, PRISM III: Pediatric Risk of Mortality III, PELOD-2: Pediatric Logistic Organ Dysfunction-2, CRP: C-reactive protein, MV: mechanical ventilation, PICU: pediatric intensive care unit

Prevalence and severity of hypophosphatemia

Hypophosphatemia was frequent across all three timepoints: 80 of 206 patients (38.8%) at admission and 89 of 206 (43.2%) on day 3—admission and day-3 sampling being required for inclusion, so both denominators comprised the full cohort—and 60 of the 143 patients with an available measurement (42.0%) on day 7. Overall, 107 patients (51.9%) were hypophosphatemic at least once during their course (Table 2). On the basis of the lowest of the three protocol measurements, 27 patients (13.1%) had mild, 47 (22.8%) moderate, and 33 (16.0%) severe hypophosphatemia, while 99 (48.1%) remained normophosphatemic. Phosphate replacement (intravenous or oral) was administered to 73 patients (35.4%), all of whom were hypophosphatemic at one or more timepoints; no patient who remained normophosphatemic throughout received replacement.

Comparison between hypophosphatemic and normophosphatemic patients

Compared with patients who remained normophosphatemic throughout (n = 99), hypophosphatemic patients (n = 107) were more severely ill, with higher PRISM III (median 11 vs 8, p = .002) and CRP (47.2 vs 36.1 mg/L, P = .003). Sepsis (34.6% vs 16.2%, p = .004), furosemide use (69.2% vs 48.5%, p = .004), and vasoactive or inotropic exposure (58.9% vs 32.3%, p < .001) were all more frequent. Ventilation duration (median 9.0 vs 6.0 days, p < .001), PICU length of stay (median 12 vs 8 days, p < .001), the composite outcome (46.7% vs 21.2%, p < .001), and PICU mortality (27.1% vs 12.1%, p = .012) were all significantly worse, whereas reintubation, weaning failure, and tracheostomy did not differ significantly (Table 3).

Table 2. Prevalence of hypophosphatemia by timepoint and severity (n = 206)

Time point / Severity	n	%
Hypophosphatemia by timepoint (cut-off < 2.5 mg/dL)		
Admission (≤ 24 h)	80	38.8
Day 3	89	43.2
Day 7 (n = 143)	60	42.0
Any timepoint	107	51.9
Severity		
Normal (≥ 2.5 mg/dL)	99	48.1
Mild (2.0 – 2.4 mg/dL)	27	13.1
Moderate (1.0 – 1.9 mg/dL)	47	22.8
Severe (< 1.0 mg/dL)	33	16.0

Severity was graded from the lowest of the admission, day-3, and day-7 phosphate measurements; Admission and day-3 phosphate measurements were required for inclusion; the corresponding percentages therefore use the full cohort (n = 206) as the denominator; The day-7 percentage uses the 143 patients with an available day-7 measurement as the denominator; Phosphate replacement therapy (intravenous or oral) was administered to 73 patients (35.4%)

Table 3. Comparison of demographic, clinical, and outcome variables between hypophosphatemic and normophosphatemic groups

Variable	Hypo (+) (n = 107)	Hypo (−) (n = 99)	p
Age, months, median (IQR)	49 (14 – 110)	31 (8 – 64)	0.032
Male sex, n (%)	61 (57.0)	56 (56.6)	1.000
PRISM III, median (IQR)	11 (7 – 16)	8 (5 – 13)	0.002
PELOD-2, median (IQR)	4 (2 – 8)	4 (3 – 6)	0.370
Albumin, g/dL, median (IQR)	3.5 (3.3 – 3.8)	3.5 (3.3 – 3.8)	0.796
Lactate, mmol/L, median (IQR)	2.6 (2.2 – 3.5)	2.5 (2.0 – 3.0)	0.057
CRP, mg/L, median (IQR)	47.2 (34.0 – 90.5)	36.1 (27.0 – 65.2)	0.003
Sepsis, n (%)	37 (34.6)	16 (16.2)	0.004
Furosemide, n (%)	74 (69.2)	48 (48.5)	0.004
Corticosteroids, n (%)	44 (41.1)	28 (28.3)	0.074
Vasoactive / inotropic, n (%)	63 (58.9)	32 (32.3)	<0.001
Parenteral nutrition, n (%)	39 (36.4)	33 (33.3)	0.747
MV duration, days, median (IQR)	9.0 (6.0 – 17.1)	6.0 (3.3 – 8.5)	<0.001
PICU LOS, days, median (IQR)	12 (8 – 20)	8 (6 – 11)	<0.001
Composite outcome, n (%)	50 (46.7)	21 (21.2)	<0.001
PICU mortality, n (%)	29 (27.1)	12 (12.1)	0.012
Reintubation, n (%)	5 (4.7)	8 (8.1)	0.473
Weaning failure, n (%)	6 (5.6)	8 (8.1)	0.669
Tracheostomy, n (%)	12 (11.2)	5 (5.1)	0.176

Groups were defined by any-timepoint hypophosphatemia (serum phosphate <2.5 mg/dL at admission, day 3, or day 7); Continuous variables compared with Mann – Whitney U test; categorical variables with chi-square or Fisher exact test as appropriate; IQR: interquartile range, PRISM III: Pediatric Risk of Mortality III, PELOD-2: Pediatric Logistic Organ Dysfunction-2, MV: mechanical ventilation, LOS: length of stay, PICU: pediatric intensive care unit

Severity stratification and discriminative performance

The composite outcome rose across severity strata: 21.2% (normal), 44.4% (mild), 55.3% (moderate), and 36.4% (severe) (linear-by-linear trend, p = .002; Figure 1A); the lower rate in the small severe stratum (n = 33) most plausibly reflects sampling variability in the smaller strata, whose confidence intervals overlap substantially, rather than a true reversal of the gradient. Median ventilation duration was 6.0, 9.0, 11.0, and 7.0 days, respectively (Figure 1B), the lower severe-group value likely reflecting competing risk from earlier death, ventilation duration being censored at death. ROC discrimination for the composite outcome was limited: admission area under the curve (AUC) 0.651 (95% CI 0.570 – 0.732), day 3 0.632 (95% CI 0.550 – 0.714), and lowest-of-protocol 0.645 (95% CI 0.564 – 0.726) (Figure 2A); for PICU mortality, AUCs were 0.628, 0.583, and 0.624 (Figure 2B). Cumulative incidence of the composite event over the first 28 days was significantly higher in hypophosphatemic patients (log-rank $\chi^2 = 12.76$, $p < .001$).

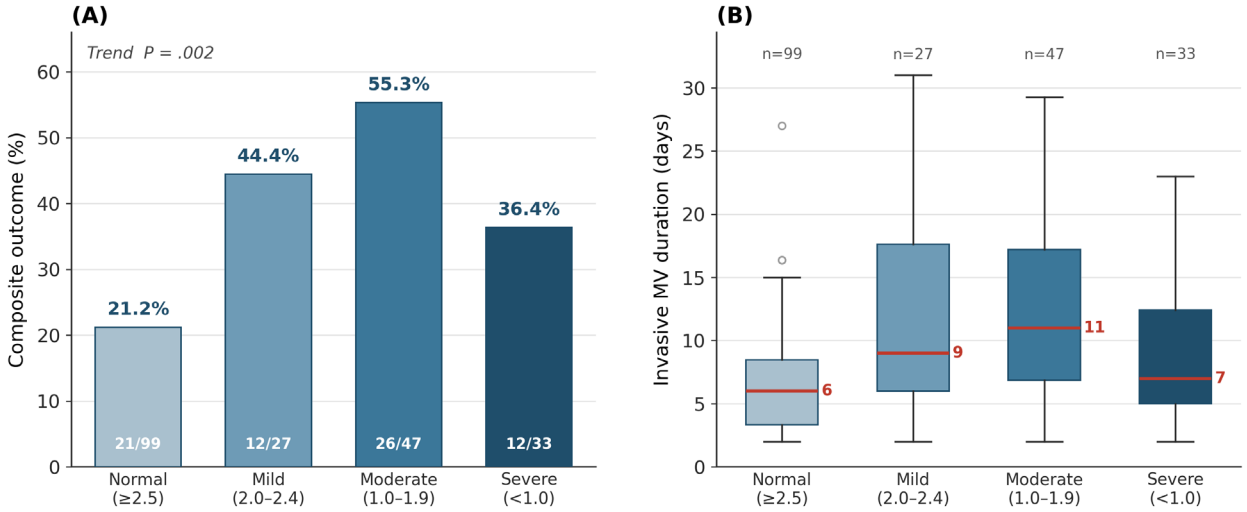

Figure 1. Clinical outcomes stratified by hypophosphatemia severity (lowest of the three protocol phosphate measurements); **(A)** Composite primary outcome (PICU mortality or mechanical ventilation ≥ 14 days) across hypophosphatemia severity strata; The composite outcome rate was 21.2% in normophosphatemic patients and 44.4%, 55.3%, and 36.4% in mild, moderate, and severe hypophosphatemia, respectively; linear-by-linear trend p = .002; The lower rate in the small severe stratum (n = 33) most plausibly reflects sampling variability in the smaller strata; **(B)** Duration of invasive mechanical ventilation by severity, displayed as box-and-whisker plots (median, interquartile range, and outliers); the lower severe-group median reflects, in part, competing risk from earlier death, ventilation duration being censored at death; PICU: pediatric intensive care unit, MV: mechanical ventilation

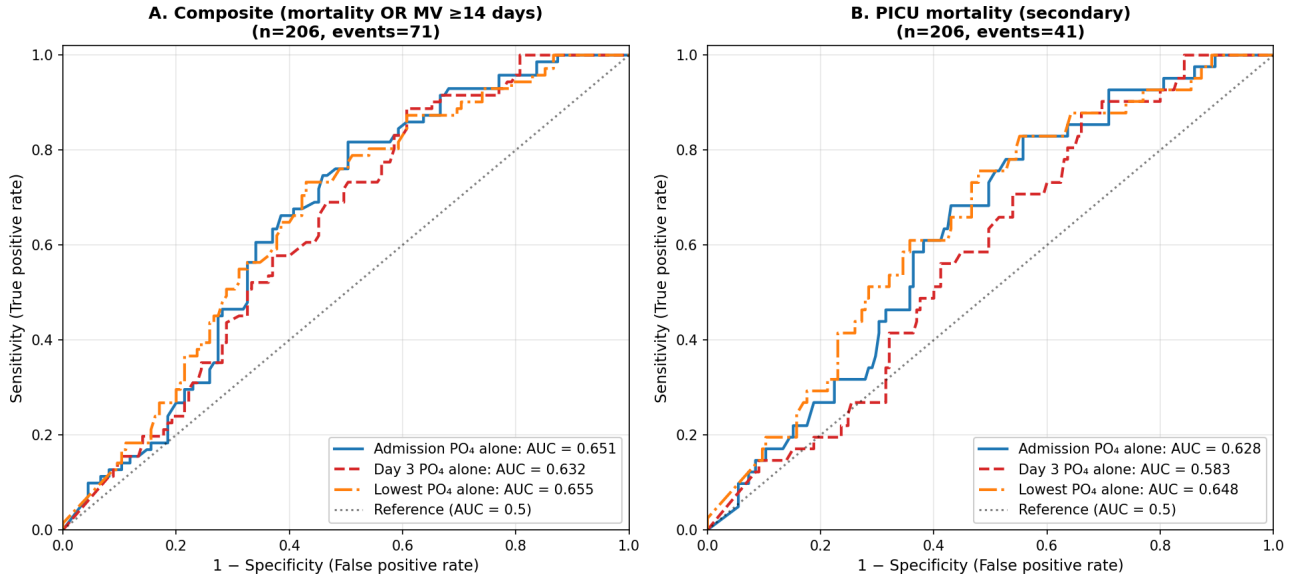

Figure 2. Receiver operating characteristic (ROC) curves for the prediction of **(A)** the composite primary outcome and **(B)** PICU mortality, by serum phosphate values at admission, day 3, and the lowest of the three protocol measurements; AUC: area under the curve, PO_4: phosphate

Multivariable analysis of primary and secondary outcomes

After adjustment for age, PRISM III, sepsis, albumin, furosemide, and vasoactive/inotropic exposure, any-timepoint hypophosphatemia was independently associated with the composite outcome (aOR 2.52, 95% CI 1.25 – 5.09, p = .010), with PRISM III the only other independent correlate (aOR 1.09 per point, 95% CI 1.04 – 1.14, p < .001) (Table 4). Examined by component, this association was confined to prolonged ventilation (aOR 3.77, 95% CI 1.61 – 8.84, p = .002) and was not present for mortality alone (aOR 1.85, 95% CI 0.79 – 4.33, p = .158), for which PRISM III remained dominant (aOR 1.10, 95% CI 1.04 – 1.16, p < .001). For log-transformed ventilation duration, any-timepoint hypophosphatemia was associated with approximately 57% longer ventilation (ratio 1.57, 95% CI 1.30 – 1.91, p < .001), as was sepsis (ratio 1.51, 95% CI 1.23 – 1.85, p < .001) (Table 5; Figure 3).

In the pre-specified sensitivity analysis restricted to admission hypophosphatemia, the association with the composite outcome was attenuated and no longer significant (aOR 1.56, 95% CI 0.79 – 3.09, p = .197); sepsis became the strongest correlate (aOR 2.08, 95% CI 1.03 – 4.21, p = .041). Admission hypophosphatemia was likewise not independently associated with mortality (aOR 1.31, 95% CI 0.58 – 2.96, p = .519) or, in the linear model, with ventilation duration (ratio 1.21, 95% CI 0.99 – 1.49, p = .063).

Table 4. Multivariable logistic regression for the composite primary outcome and PICU mortality

Variable	aOR	95% CI	p
A. Composite primary outcome (events = 71)			
Hypophosphatemia (any timepoint)	2.52	1.25 – 5.09	0.010
PRISM III (per 1-point increase)	1.09	1.04 – 1.14	< 0.001
Sepsis	1.92	0.94 – 3.90	0.073
Albumin (per g/dL)	1.43	0.65 – 3.16	0.376
Furosemide	1.22	0.63 – 2.39	0.552
Vasoactive / inotropic	0.91	0.47 – 1.76	0.776
Age (per month)	1.00	0.99 – 1.00	0.294
B. PICU mortality (secondary; events = 41)			
Hypophosphatemia (any timepoint)	1.85	0.79 – 4.33	0.158
PRISM III (per 1-point increase)	1.10	1.04 – 1.16	<0.001
Sepsis	0.79	0.33 – 1.89	0.589
Albumin (per g/dL)	1.28	0.49 – 3.35	0.611
Furosemide	1.67	0.74 – 3.78	0.214
Vasoactive / inotropic	1.50	0.69 – 3.24	0.305
Age (per month)	1.00	0.99 – 1.01	0.584

aOR: adjusted odds ratio, CI: confidence interval; The exposure was any-timepoint hypophosphatemia; both models were adjusted for age, PRISM III, sepsis, albumin, furosemide, and vasoactive/inotropic exposure (n = 206)

Table 5. Multivariable linear regression for log-transformed mechanical ventilation duration

Variable	Adjusted ratio (e^{β})	95% CI	p
Hypophosphatemia (any timepoint)	1.57	1.30 – 1.91	< 0.001
PRISM III (per 1-point increase)	1.01	1.00 – 1.02	0.185
Sepsis	1.51	1.23 – 1.85	< 0.001
Albumin (per g/dL)	1.07	0.86 – 1.33	0.560
Furosemide	0.96	0.80 – 1.16	0.691
Vasoactive / inotropic	0.83	0.70 – 1.00	0.053
Age (per month)	1.00	1.00 – 1.00	0.060

e^{β}: exponentiated coefficient (multiplicative effect on MV duration), CI: confidence interval; $R^2 = 0.214$; n = 206

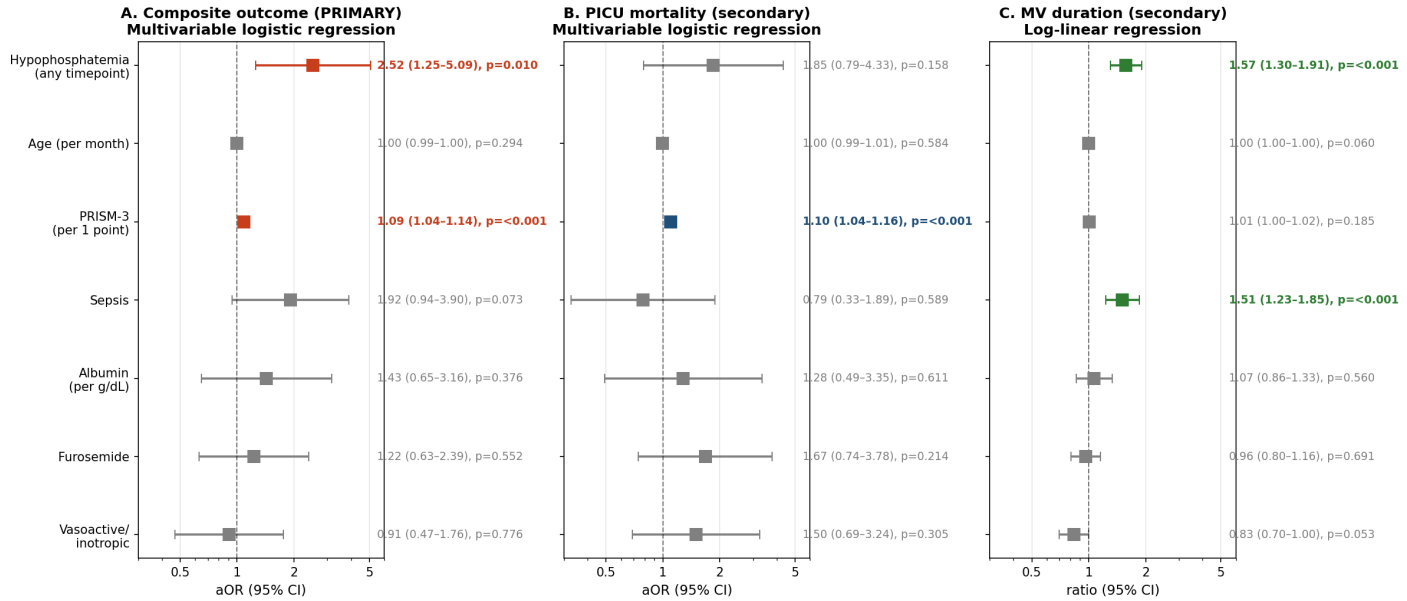

Figure 3. Forest plot summarizing multivariable adjusted associations of any-timepoint hypophosphatemia and other covariates with **(A)** the composite primary outcome (mortality or MV ≥ 14 days), **(B)** PICU mortality (secondary), and **(C)** mechanical ventilation duration (secondary, linear regression on log-transformed duration); Squares indicate adjusted odds ratios (panels A, B) or exponentiated coefficients (panel C); horizontal lines represent 95% confidence intervals; Variables with p < .05 are highlighted in color; non-significant associations in gray

DISCUSSION

In this single-center retrospective cohort of 206 mechanically ventilated critically ill children, hypophosphatemia assessed at any timepoint during the PICU course was independently associated with a composite of PICU mortality or prolonged mechanical ventilation (aOR 2.52, 95% CI 1.25 – 5.09) and with approximately 57% longer ventilation (ratio 1.57, 95% CI 1.30 – 1.91). Two features temper a causal reading of these associations. First, the composite signal was confined to the ventilation component (aOR 3.77) and was absent for mortality alone after adjustment for severity (aOR 1.85, p = .158)—consistent with Sin et al., who concluded that hypophosphatemia acts primarily as a marker of severity rather than a direct driver of mortality (10). Second, and more importantly, the association with the composite outcome did not survive restriction of the exposure to admission hypophosphatemia (aOR 1.56, p = .197). Because any-timepoint hypophosphatemia incorporates day-3 and day-7 values that lie within the outcome window, longer-ventilated and more slowly recovering patients have more opportunities both to be sampled and to develop hypophosphatemia during evolving critical illness; the attenuation in the admission-only analysis is the expected signature of this temporal relationship. Taken together, these findings indicate that hypophosphatemia in this population behaves predominantly as a marker of illness severity and of evolving critical illness rather than as an independent, admission-identifiable driver of adverse outcome. To our knowledge, this is among the first contemporary Turkish pediatric studies to focus specifically on mechanically ventilated children using a composite endpoint that captures both fatal and ventilator-dependent outcomes.

The cumulative prevalence of 51.9% lies toward the higher end of pediatric reports, consistent with our exclusive focus on ventilated children. Kilic et al. reported 60.2% in a general Turkish PICU (6) and Shah et al. 71.6% using age-specific cutoffs (8), whereas adult admission prevalences range from 15.4% in the international ESICM one-day point-prevalence survey (14) to nearly 40% in Wang et al. (4).

The association with prolonged ventilation is biologically plausible. Phosphate is essential for ATP synthesis and 2,3-diphosphoglycerate – mediated oxygen delivery, and severe hypophosphatemia reversibly impairs diaphragmatic contractility; Aubier et al. showed that phosphate repletion improves transdiaphragmatic pressure within hours (2). Sinatra et al. detailed the bidirectional relationship between hypophosphatemia and respiratory dysfunction, including respiratory alkalosis – induced intracellular phosphate shifts, ATP depletion in respiratory muscles, and weaning failure as a downstream phenotype (15). Alsumrain et al. linked hypophosphatemia to failure to wean (16), and Cohen et al. found significant hypophosphatemia (< 0.48 mmol/L) in 34.3% of open-heart surgery patients, associated with prolonged ventilation and increased cardioactive support (17). Our ratio of 1.57 parallels the 1.5-fold increase reported by Wozniak et al. (3), matches Statlender et al. (5), and supports Lusteau et al. in bronchiolitis (7); Federspiel et al. similarly supported repeated rather than single-time-point monitoring (18). Biological plausibility does not, however, establish causation, and our own admission-only analysis argues against a simple causal interpretation: a direct mechanistic effect would be expected to be present from admission, whereas the association emerged only when later, within-window measurements were included.

We adopted a composite endpoint for both methodological and clinical reasons. Single-center pediatric critical-care studies are typically underpowered to detect modest independent effects on mortality through multivariable adjustment, and prolonged ventilator dependency itself carries substantial morbidity—ventilator-associated pneumonia, sedation-related complications, ICU-acquired weakness, tracheostomy, and long-term neurocognitive sequelae—while sharing biological substrates with mortality in the form of failure to recover from critical illness. The composite endpoint therefore captures failure to liberate from critical illness with greater statistical power. With this endpoint, any-timepoint hypophosphatemia retained an independent association (aOR 2.52, p = .010); with mortality alone it did not (aOR 1.85, p = .158); and with admission hypophosphatemia the composite association was lost (aOR 1.56, p = .197). This pattern mirrors Sin et al. (10) and a septic-patient meta-analysis by Wei et al., which found no significant mortality association (19); earlier Turkish pediatric work by Akbaş et al. likewise attributed abnormal phosphate largely to underlying severity captured by PRISM and PELOD scores (20). PRISM III emerging as the dominant predictor across models supports this interpretation. The graded composite trend across strata (21.2%, 44.4%, 55.3%, 36.4%; trend p = .002) is consistent with a severity gradient, the lower rate in the small severe stratum (n = 33) most plausibly reflecting sampling variability in the smaller strata.

Sepsis, furosemide use, and vasoactive or inotropic exposure were more frequent in hypophosphatemic patients, consistent with the recognized contributions of inflammatory cytokines, renal phosphate wasting, and stress-induced intracellular shifts (6), with higher CRP reinforcing the inflammatory contribution. The vasoactive/inotropic association (58.9% vs 32.3%, p < .001) did not persist after adjustment, suggesting it is largely explained by underlying disease severity.

Replacement was administered to 35.4% of patients but was not entered into the models, as it is a post-exposure variable on the causal pathway between hypophosphatemia and outcome; conditioning on it would introduce bias. If replacement is effective, its preferential use in more severely hypophosphatemic patients would bias the observed association toward the null, potentially leading us to underestimate any true association. Its efficacy could not be evaluated in this retrospective design.

Given the high cumulative prevalence and the dynamic temporal pattern, a single admission measurement provides an incomplete picture, and serial monitoring at admission and during the early PICU course is reasonable for detecting a common, readily correctable abnormality. All areas under the curve were below 0.70, a level at which a biomarker has poor discriminatory power when used alone, so phosphate concentrations should not be relied upon as a stand-alone predictor in clinical decision-making. Our data do not, however, support a therapeutic inference: because the composite association was not robust to restriction to admission hypophosphatemia and the effect of replacement could not be evaluated, we cannot conclude that proactive correction shortens ventilation or improves outcome. The 2020 ESICM one-day survey found that only 41% of ICUs had a phosphate repletion protocol and only a minority of hypophosphatemic patients actually received replacement (14), highlighting a substantial implementation gap between recognition and treatment, and the ESICM systematic review emphasized that the optimal threshold, frequency, and timing of correction remain unestablished, particularly in children (9). Whether structured monitoring and correction improves outcomes—and whether hypophosphatemia is a modifiable target or a severity marker—is a question for prospective trials.

Strengths include the focus on the clinically relevant subgroup of mechanically ventilated children, the use of predefined measurement timepoints rather than a single value, a composite endpoint that addresses the limited power of mortality-only analyses, application of the contemporary 2024 Phoenix Pediatric Sepsis Criteria (13), and strict exclusion of conditions that distort phosphate homeostasis. Several limitations temper interpretation. The retrospective single-center design limits generalizability. The principal exposure—hypophosphatemia at any timepoint—incorporates measurements within the outcome window and is therefore susceptible to reverse causation; we addressed this with a pre-specified admission-only sensitivity analysis, which did not confirm an independent association and should temper any causal reading. Ventilation duration for patients who died while ventilated was censored at death, introducing competing-risk effects into the duration analysis. Phosphate replacement, a potential post-exposure mediator, was not modeled. The phosphorus content of nutritional support and maintenance fluids could not be quantified from the records, so residual confounding by phosphate intake cannot be excluded. The secondary mortality model included seven covariates for 41 events (approximately six events per variable, below the conventional threshold of ten), and its estimates should be regarded as exploratory; the composite endpoint, with 71 events, was better powered. A uniform hypophosphatemia threshold of < 2.5 mg/dL was applied for comparability with the predominant intensive-care literature; because pediatric phosphate reference ranges are age-dependent, this may misclassify some younger patients. Severity was graded from the same within-window measurements as the exposure and therefore shares its temporal caveat, so the severity gradient should not be read as strong dose − response evidence. Secondary and sensitivity analyses were exploratory and not adjusted for multiplicity.

CONCLUSION

Hypophosphatemia is common in mechanically ventilated critically ill children and, when assessed at any point during the PICU course, is associated with a composite of mortality or prolonged ventilation—an association driven by the ventilation component and not robust to restriction to admission hypophosphatemia. Together with the loss of the mortality association after adjustment for severity, these findings indicate

that hypophosphatemia in this setting is predominantly a marker of illness severity and of evolving critical illness rather than an independent, admission-identifiable driver of outcome. Serial phosphate monitoring is reasonable given its prevalence and correctability, although its discriminatory performance as a stand-alone predictor was limited (all AUCs < 0.70); whether structured monitoring and correction improves outcomes—and whether hypophosphatemia is a modifiable target rather than a severity marker—requires prospective, preferably multicenter, evaluation with liberation from mechanical ventilation as a clinically meaningful endpoint.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that there is no financial support.

Ethical Approval
Ethical approval was obtained from the Gaziantep City Hospital Non-Interventional Clinical Research Ethics Committee (decision number 593/2026; date 17 June 2026). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent
This was a retrospective study based on anonymized medical records, and the requirement for written informed consent was waived by the ethics committee. No identifying patient information, images, or photographs are included in the manuscript

REFERENCES

1. Geerse DA, Bindels AJ, Kuiper MA, et al. Treatment of hypophosphatemia in the intensive care unit: a review. Crit Care. 2010;14:R147.
2. Aubier M, Murciano D, Lecocguic Y, et al. Effect of hypophosphatemia on diaphragmatic contractility in patients with acute respiratory failure. N Engl J Med. 1985;313:420-4.
3. Wozniak H, Beckmann TS, Dos Santos Rocha A, et al. Hypophosphatemia on ICU admission is associated with an increased length of stay in the ICU and time under mechanical ventilation. J Clin Med. 2022;11:581.
4. Wang L, Xiao C, Chen L, et al. Impact of hypophosphatemia on outcome of patients in intensive care unit: a retrospective cohort study. BMC Anesthesiol. 2019;19:86.
5. Statlender L, Raphaeli O, Shochat T, et al. Contributing factors to hypophosphatemia development in critically ill ventilated patients: a retrospective cohort study. Sci Rep. 2024;14:19771.
6. Kilic O, Demirkol D, Ucsel R, et al. Hypophosphatemia and its clinical implications in critically ill children: a retrospective study. J Crit Care. 2012;27:474-9.
7. Lusteau A, Valla F, Javouhey E, Baudin F. Hypophosphatemia in infants with severe bronchiolitis and association with length of mechanical ventilation. Pediatr Pulmonol. 2023;58:2513-9.
8. Shah SK, Irshad M, Gupta N, et al. Hypophosphatemia in critically ill children: risk factors, outcome and mechanism. Indian J Pediatr. 2016;83:1379-85.
9. Reintam Blaser A, Gunst J, Ichai C, et al. Hypophosphatemia in critically ill adults and children — A systematic review. Clin Nutr. 2021;40:1744-54.
10. Sin JCK, King L, Ballard E, et al. Hypophosphatemia and outcomes in ICU: a systematic review and meta-analysis. J Intensive Care Med. 2021;36:1025-35.
11. Pollack MM, Patel KM, Ruttimann UE. PRISM III: an updated Pediatric Risk of Mortality score. Crit Care Med. 1996;24:743-52.
12. Leteurtre S, Duhamel A, Salleron J, et al. PELOD-2: an update of the Pediatric Logistic Organ Dysfunction score. Crit Care Med. 2013;41:1761-73.
13. Schlapbach LJ, Watson RS, Sorce LR, et al; Society of Critical Care Medicine Pediatric Sepsis Definition Task Force. International consensus criteria for pediatric sepsis and septic shock. JAMA. 2024;331:665-74.
14. Berger MM, Appelberg O, Reintam-Blaser A, et al; ESICM-MEN section. Prevalence of hypophosphatemia in the ICU — Results of an international one-day point prevalence survey. Clin Nutr. 2021;40:3615-21.
15. Sinatra N, Cuttone G, Geraci G, et al. Correlation between hypophosphatemia and hyperventilation in critically ill patients: causes, clinical manifestations, and management strategies. Biomedicines. 2025;13:2382.
16. Alsumrain MH, Jawad SA, Imran NB, et al. Association of hypophosphatemia with failure-to-wean from mechanical ventilation. Ann Clin Lab Sci. 2010;40:144-8.
17. Cohen J, Kogan A, Sahar G, et al. Hypophosphatemia following open heart surgery: incidence and consequences. Eur J Cardiothorac Surg. 2004;26:306-10.
18. Federspiel CK, Itenov TS, Thormar K, et al. Hypophosphatemia and duration of respiratory failure and mortality in critically ill patients. Acta Anaesthesiol Scand. 2018;62:1098-104.
19. Wei S, Li Y, Zhang C, et al. Prognostic value of serum phosphate levels in sepsis: a systematic review and meta-analysis. PeerJ. 2023;11:e16241.
20. Akbaş Y, Koker A, Erkek N. Are we aware that hyperphosphatemia affects mortality and morbidity as much as hypophosphatemia in pediatric intensive care patients? Pediatr Endocrinol Rev. 2019;17:35-40.