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Contributing factors to hypophosphatemia development in critically Ill ventilated patients: a retrospective cohort study

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Hypophosphatemia (serum phosphate < 2.5 mg/dL) is a major concern when initiating nutritional support. We evaluated which factors contribute to hypophosphatemia development in critically ill patients, as well as the association between hypophosphatemia and mortality. A retrospective cohort study of patients who were ventilated for at least 2 days in a 16-bed mixed ICU. Data collected includes demographics, Acute Physiology & Chronic Health Evaluation 2 (APACHE2) admission score, Sequential Organ Failure Assessment score at 24 h (SOFA24), hourly energy delivery, plasma phosphate levels during the first 2 weeks of admission, ICU length of stay (LOS), length of ventilation (LOV), and mortality (ICU and 90 days). For the hypophosphatemia development model, we considered mortality as a competing risk. For mortality analysis, we used the Cox proportional hazards model considering hypophosphatemia development as a time-varying covariate. 462 patients were used in the analysis. 59.52% of the patients developed hypophosphatemia. Several factors were associated with a decreased risk of hypophosphatemia: age, BMI, pre-admission diabetes diagnosis, APACHE2, SOFA24, first kidney SOFA score, hospital admission time before ICU admission, and admission after liver transplantation. Admission due to trauma was associated with an increased risk of hypophosphatemia. Survival analysis with hypophosphatemia as a time-varying covariate showed a protective effect of hypophosphatemia from mortality (HR 0.447, 95% CI 0.281, 0.712). Age, APACHE2, and SOFA24 score were found to be significantly associated with ICU mortality. Fasting duration in the ICU before nutritional support initiation was not found to be significantly associated with hypophosphatemia. We examined several fasting intervals (12 h, 24 h, 36 h, 48 h, 60 h, 72 h). In each fast interval, we compared the prevalence of hypophosphatemia among patients who fasted the specified length of time, with those who did not fast for the same length of time. In each fasting interval, hypophosphatemia prevalence was lower in the fasting group compared to the non-fasting group. However, this difference was insignificant. BMI, APACHE2, and hospital LOS before ICU admission were inversely associated with hypophosphatemia development. Fasting for up to 72 h in the ICU before starting nutritional support did not affect hypophosphatemia occurrence. Hypophosphatemia was associated with lower mortality.

Keywords Hypophosphatemia, Refeeding syndrome, Fast

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Refeeding syndrome (RFS) is a major concern in critically ill patients, due to its potential adverse cardiovascular and neurologic effects[1]. It is described as a range of metabolic and electrolyte derangements, usually due to reinitiating nutritional support after a period of fasting[2]. Patients are considered to be at risk for RFS after 5–10 days of undernourishment[3]. As RFS is not universally defined, its incidence cannot be clearly determined. Prospective work in an Italian medical ward found an incidence of 18%[4], standing in line with a recent meta-analysis that reported a wide range of 0–62%[5].

Hypophosphatemia (whether mild ($2 \leq Pi < 2.5$ mg/dL), moderate ($1 \leq Pi < 2$ mg/dL), or severe ($Pi < 1$ mg/dL)[6,7] is considered the hallmark of refeeding syndrome[2]. Although hypophosphatemia has several other etiologies not related to RFS, most RFS definitions include hypophosphatemia[8]. Hypophosphatemia is found in 15–35% of critically ill patients[6,9]. While there is an ongoing debate regarding the effect of hypophosphatemia on mortality[4,10–13], its effect on prolonging ventilation and LOS is well described[4,7,9,12].

The duration of fasting and its effect on RFS and hypophosphatemia has not been extensively studied. The American Society for Parenteral and Enteral Nutrition (ASPEN) consensus defines RFS: "…after initiation of calorie provision to an individual who has been exposed to a substantial period of undernourishment"—but doesn't state what is considered a substantial period[2]. Prolonged fasting (at least 72 h) causes physiological and pathophysiological changes, mainly basal metabolic rate decrease, increased fat utilization as an energy source, and vitamin and electrolyte depletion. The reinstitution of energy delivery from carbohydrates causes increases in adenosine triphosphate (ATP) production, which causes hypophosphatemia[2,14,15]. However, most clinical sources do not clearly define the fasting period prior to RFS[4,5,7,16]. Only scarce reports mention fast duration before energy delivery. In these studies, out of 123 patients who fasted between 3-65d, only 36 developed hypophosphatemia attributed to RFS[17–19].

Critically ill patients are considered to be at risk for RFS[2,3]. Controversy exists regarding the initiation of energy delivery to critically ill patients. Some protocols favor restrictive energy delivery[16], while others recommend higher and faster energy delivery[2]. A recent meta-analysis did not find a difference in outcome between both strategies[20]. We have recently demonstrated a correlation between lower daily energy deficit (i.e. higher daily energy delivery) and prolonged ventilation, with a trend toward decreased mortality in patients with hypophosphatemia[21].

This study aimed to evaluate the factors contributing to the development of hypophosphatemia, including fast duration before nutritional support initiation, in critically ill ventilated patients, and to examine the association between hypophosphatemia and mortality in this population.

Methods

This study was approved by the Ethics Committee of Rabin Medical Centre (Approval no. RMC 0392-14). Since data were evaluated retrospectively, anonymously, and solely obtained for the study purposes, a requirement of informed consent was waived by Rabin Medical Centre ethics committee. All study methods were performed in accordance with Helsinki Declaration.

We conducted a retrospective analysis of data from the electronic medical charts of all ventilated patients who were admitted to a 16-bed general mixed medical-surgical adult ICU from Jan 1st 2017, till Oct 31st 2018. For patients who were admitted more than once in the ICU during the study period, only the first admission was used. Unventilated patients were considered ineligible for this study, as their oral calorie intake might not be recorded in their medical records. We excluded patients who were ventilated for less than 48 h (as they could start oral nutrition, which is not reported in the medical chart); who were not delivered energy at all during their admission (as energy delivery cannot be assessed in this population); and those who had hypophosphatemia within 12 h of admission (as it is likely that it appeared secondary to the critical illness per se).

Data obtained included sex, age at admission, body mass index (BMI), hospitalization dates, length of stay in ICU (LOS), readmissions number, the acute physiology and chronic health evaluation 2 (APACHE2) score, the sequential organ failure assessment score at 24 h from admission (SOFA24), ICU admission category (medical, surgical, trauma, obstetrics, transplantation (liver transplantations), length of ventilation (LOV), all phosphate levels in the first 2 weeks of admission (hourly time indexed from admission time), total hourly energy provided from enteral & parenteral nutrition (not including "hidden calories" from drugs or solutions) during the first 2 weeks of admission, ICU outcome (discharge to a hospital ward or a rehabilitation center, or ICU mortality), and mortality for up to 90 days after admission. Continuous variables are presented by median and interquartile range, and categorial variables by numbers and percentage. APACHE2 & SOFA24 score were considered as continuous variables.

APACHE2 (Acute Physiology and Chronic Health Evaluation 2) admission score is a commonly used and well-validated score for hospital mortality of critically ill patients, based on the patient's age, baseline comorbidities, and 12 routine measurements taken during the first ICU admission day[22,23].

SOFA (Sequential Organ Failure Assessment) score is a well-validated score for organ failure and mortality of critically ill patients. It is calculated based on six parameters, each representing a physiologic system. It can be calculated daily during ICU admission[24].

Fast duration was defined as the duration of consecutive hourly 0 kcal delivery to a patient. We describe fast duration in groups of 12-h intervals up to 72 h of fasting, comparing patients who fasted the specific defined fast interval (12/24/36/48/60/72 h) with those who did not fast that whole interval. We focused on fasting during the first 3 days of admission, as our nutritional ward protocol is based on a locally developed protocol which principals are to initiate nutrition at a slow energy delivery rate, and progress to energy delivery target within 2 days (according to patient status)—inline with current restrictive energy delivery guidelines[16].

In cases when a patient received energy delivery, and then started fasting again the longest fast duration was counted, had it occurred before hypophosphatemia developed. Hypophosphatemia occurrence (after the defined

fast duration in the fasting groups) was described in fasting and non-fasting patients within each defined fasting interval; patients who had hypophosphatemia before or during the fasting period were excluded.

Hypophosphatemia was defined as a phosphate level lower than 2.5 mg/dL[6,7]. The primary endpoint was defined as hypophosphatemia development. Secondary endpoints were ICU mortality and 90 days mortality. For hypophosphatemia development we used Fine and Gray's competing risk analysis[25] considering mortality without hypophosphatemia as a competing risk. We analyzed which baseline variables contributed to developing hypophosphatemia. Intermediate variables (such as fast duration, ventilation length, and energy delivered to the patient) were not analyzed because these variables might be influenced by medical decisions taken with consideration of phosphate levels.

For mortality analysis we considered hypophosphatemia development (a variable that is not a baseline characteristic, but one that changes through the admission) as a time varying covariate[26]. The Cox proportional Hazards model was used for this analysis.

Statistical analysis was performed using SAS vs 9.4 (SAS Institute).

Ethical approval and consent to participate
This study was approved by the ethics committee of Rabin Medical Centre (RMC 0392–14).

Results
During the study period, there were 1335 admissions to the ICU. In 542 of them, the patient was ventilated for more than 48 h. There were 23 readmissions of 23 patients; 24 patients were not delivered energy at all; 33 had hypophosphatemia within 12 h of admission. Therefore, 462 patients were included in the final analysis (see Fig. 1 for study flowchart).

Baseline characteristics
Table 1 describes the baseline characteristics of the patients. Table 2 describes the hazard ratio of all characteristics for hypophosphatemia development in univariate analysis, considering mortality as a competing risk. All baseline characteristics but sex and surgical admission reason (compared to medical), were found significant
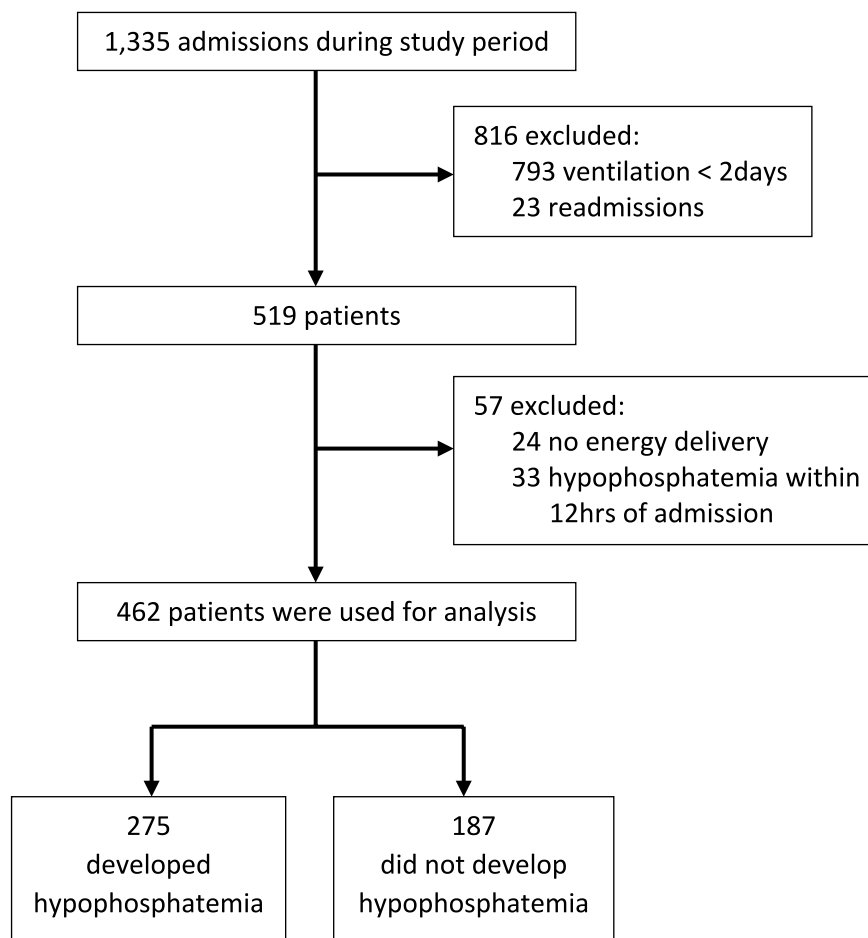

Figure 1. Flowchart of patients inclusion.

N (%)	462 (100%)
Age (yr)	63.45 (49.07, 71.71)
Male gender (n, %)	307 (66.45%)
BMI (kg/m^2)	26.83 (23.44, 30.47)
% Diabetes (n, %)	82 (17.75%)
APACHE2	23 (17, 27)
SOFA24	9 (7, 11)
Kidney SOFA24	0 (0, 2)
Hospital admission time before ICU admission (d)	1 (0, 5)
Admission reason	
Medical	238 (51.52%)
Surgical	126 (27.27%)
Trauma	80 (17.32%)
Transplantation	18 (3.90%)
First phosphate level (mg/dL)*	4.25 (3.5, 5.4)

Table 1. Baseline characteristics of the patients. *First phosphate level—if taken within 6 h from admission.

	Hazard ratio	95% Hazard ratio confidence limits		p value
Age (yr)	**0.987**	**0.981**	**0.994**	**p = 0.0001**
Male gender (n, %)	1.076	0.839	1.381	p = 0.5648
BMI [kg/m^2]	0.971	0.954	0.988	p = 0.0008
% Diabetes (n, %)	0.620	0.439	0.876	p = 0.0067
APACHE2	0.956	0.939	0.973	p < 0.0001
SOFA24	0.946	0.912	0.982	p = 0.0031
Kidney SOFA24	0.627	0.555	0.709	p < 0.0001
Hospital admission time before ICU admission	0.958	0.939	0.977	p < 0.0001
Admission reason (ref = medical)				p < 0.0001
Surgical	1.293	0.984	1.699	
Trauma	1.856	1.353	2.547	
Transplantation	0.291	0.114	0.740	
First phosphate level [mg/dL]*	0.725	0.649	0.811	p < 0.0001

Table 2. Univariate analysis of baseline characteristics for hypophosphatemia development. *First phosphate level—if taken within 6 h from admission.

for hypophosphatemia development). Except for trauma admission reason, all factors were associated with decreased risk for hypophosphatemia development.

Supplemental table S1 describes baseline characteristics by hypophosphatemia development during the first 14 days of admission. As mortality without hypophosphatemia is a competing risk, there are three options for hypophosphatemia development: mortality without hypophosphatemia, survival to ICU discharge without hypophosphatemia, or hypophosphatemia development. Patients who developed hypophosphatemia were younger, had lower BMI, lower prevalence of diabetes, lower APACHE2 score, lower SOFA24 score, and lower renal component on SOFA24 score; they tended to suffer more from trauma. Their first phosphate level was lower. Average time to hypophosphatemia development was 2.79 ± 2.19 d.

Hypophosphatemia description

A total of 2805 phosphate measurements were used for the analysis, with a mean of 6.07 measurements per patient, i.e. a measurement every 1.4 days on average.

275 patients (59.53%) developed hypophosphatemia. Of those, 50 patients (18.18%) developed hypophosphatemia during the first day of their ICU stay; 77 (28%) during the 2nd day; 62 (22.55%) during the 3rd day; and 53 (12.36%) afterward. Most of the patients who developed moderate and severe hypophosphatemia did so during the first 48 h of their stay. See supplement table S2 for hypophosphatemia (according to severity) occurrence by days from ICU admission.

The average time for phosphate level to increase above the threshold of mild, moderate and severe hypophosphatemia (after hypophosphatemia was developed) was 53.83 ± 39.60 h, 39.63 ± 29.16 h, and 18.25 ± 10.97 h, respectively. See supplement table S3 for hypophosphatemia durations.

Multivariate analysis for hypophosphatemia development

For multivariate analysis, we included all baseline characteristics except the Kidney SOFA24 component and the first phosphate level. The former as it is part of the SOFA24 score, which was included in the analysis, and the latter is due to a missing phosphate level within 6 h from admission in 130 patients.

The model demonstrated that among the examined covariates, admission reason (with medical admission reason as reference), BMI, APACHE2 score, hospital admission time before ICU admission, and transplantation admission reason significantly decrease the risk for hypophosphatemia development (Table 3). Substituting SOFA24 score with kidney SOFA24 score slightly changes the results. Kidney SOFA24 score was found to be protective from hypophosphatemia development, while APACHE2 score became not significant. Other covariate significance did not change (supplemental table S4).

Fast duration and hypophosphatemia

For hypophosphatemia development, we considered only baseline variables. Fast duration should be considered as an intermediate variable. i.e., a variable that is changed throughout the hospitalization; moreover, it might be affected by the phosphate level which might change over time. Hence, fast duration was not used as a covariate in the models presented above. Therefore, we evaluated hypophosphatemia occurrence in several different fasting durations. For each fast duration examined, we compared hypophosphatemia occurrence between patients who fasted for the specified duration and those who did not. Hypophosphatemia developed more often in the non-fasting patients, in each fast interval examined. However, these differences in hypophosphatemia rates were not significant between fasting and non-fasting patients, in all fasting intervals examined (see Table 4 and Fig. 2).

Hypophosphatemia and mortality

To examine the association of hypophosphatemia and mortality, we performed a survival analysis with hypophosphatemia as a time varying covariate. Among covariates examined age, APACHE2 and SOFA24 score were found to be significantly associated with ICU mortality; BMI and hypophosphatemia were found to be inversely significantly associated with ICU mortality. Table 5a describes the hazard ratios of the different covariates with 95% confidence intervals. Survival analysis for 90 days mortality (Table 5b) showed similar results, excluding BMI as a significant covariate. Substituting SOFA24 score with kidney SOFA24 score as a covariate showed similar results with an exception in both models (ICU mortality and 90d mortality)—the kidney SOFA24 score was not found to be significantly associated with the outcome (Supplement table S5a and b). Supplement 6 describes further models regarding the interaction between kidney SOFA24, phosphate status, and mortality.

Parameter	Hazard ratio	95% Hazard ratio confidence limits		p value
Age	0.995	0.987	1.003	0.2048
Male gender	0.917	0.700	1.201	0.5293
BMI	**0.976**	**0.958**	**0.994**	**0.0095**
Diabetes	0.769	0.533	1.110	0.1613
APACHE2	**0.967**	**0.944**	**0.990**	**0.0047**
SOFA24	1.001	0.957	1.046	0.9771
Hospital LOS before ICU	**0.959**	**0.938**	**0.980**	**0.0002**
Admission reason (ref = medical)				
Surgical	1.149	0.855	1.543	0.3563
Trauma	1.049	0.750	1.585	0.6518
Transplantation	**0.249**	**0.091**	**0.677**	**0.0065**

Table 3. Multivariate analysis for hypophosphatemia development. Significant values are in bold.

Minimal fast duration	Fasting	Not fasting	p value
12	146/267 (54.68%)	129/195 (66.15%)	0.274
24	85/176 (48.3%)	140/234 (59.83%)	0.419
36	47/109 (43.12%)	150/270 (55.56%)	0.594
48	26/68 (38.24%)	121/260 (46.54%)	0.538
60	16/39 (41.03%)	106/255 (41.57%)	1
72	6/20 (30%)	80/233 (34.33%)	1

Table 4. Hypophosphatemia occurrence rates in fasting and non-fasting patients, based on their minimal fasting duration.
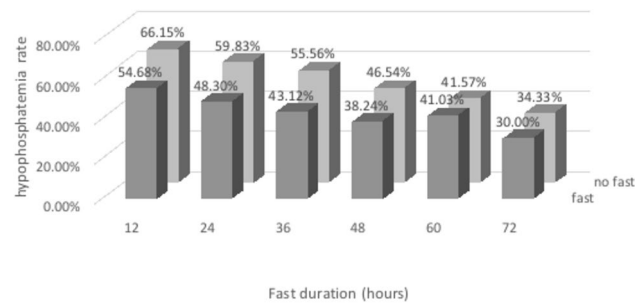
Figure 2. Hypophosphatemia rates among fasting and not-fasting patient in different fasting intervals.

Parameter	Hazard ratio	95% Hazard ratio confidence limits		p value
(a) Multivariate analysis for ICU mortality				
Age	**1.026**	**1.012**	**1.040**	**0.0003**
Male gender	0.689	0.455	1.043	0.0784
BMI	**0.963**	**0.936**	**0.991**	**0.0089**
Diabetes	1.079	0.669	1.741	0.7548
APACHE2	**1.047**	**1.010**	**1.085**	**0.0112**
SOFA24	**1.140**	**1.057**	**1.231**	**0.0007**
Hospital LOS before ICU	1.019	0.997	1.042	0.0889
Admission reason (Ref = medical)				
Trauma	1.589	0.556	4.546	0.3875
Surgical	1.578	0.596	4.178	0.3585
Transplantation	1.077	0.433	2.677	0.8735
Hypophosphatemia	**0.447**	**0.281**	**0.712**	**0.0007**
(b) Multivariate analysis for 90d mortality				
Age	**1.023**	**1.012**	**1.033**	**< 0.0001**
Male gender	0.912	0.667	1.248	0.5660
BMI	0.990	0.971	1.010	0.3352
Diabetes	1.322	0.944	1.850	0.1039
APACHE2	**1.035**	**1.009**	**1.061**	**0.0074**
SOFA24	**1.132**	**1.074**	**1.193**	**< 0.0001**
Hospital LOS before ICU	1.012	0.996	1.028	0.1528
Admission reason (Ref = medical)				
Trauma	1.005	0.582	1.737	0.9851
Surgical	1.136	0.801	1.611	0.4747
Transplantation	0.736	0.361	1.503	0.4006
Hypophosphatemia	**0.510**	**0.373**	**0.697**	**< 0.0001**

Table 5. Survival analysis with hypophosphatemia as a time varying covariate. Significant values are in bold.

Energy delivery and patient outcomes

Table 6 describes the energy delivery and clinical outcomes of the patients. To describe differences between patients who developed hypophosphatemia and those who did not, it is based on the competing risk analysis possible outcomes. Therefore, parameters are calculated until event time (hypophosphatemia for patients who developed it; and either death or discharge for patients who did not develop hypophosphatemia). Patients who developed hypophosphatemia had shorter durations of fasting. They were delivered less energy per hour during their admission. Their LOS and LOV were longer.

Discussion
Associated factors with hypophosphatemia development

Identifying risk factors for hypophosphatemia development in critically ill patients is challenging. Several clinical conditions predisposing to hypophosphatemia have been suggested, such as younger age[12,21], higher APACHE score[10,27], lower APACHE score[21] medical reason of ICU admission[10,27,28], and female sex[27]. Other

	Hypophosphatemia	No hypophosphatemia (N=187)	
		Survivors	No-survivors
N	275 (59.52%)	120 (25.97%)	67 (14.50%)
Longest fast duration (hr)	13 (3, 28)	19 (4. 41.5)	31 (9, 47)
Total energy delivered until event (Kcal)	1484 (635.2, 2933.94)	8909.5, (4695.8, 16,256.64)	6518.4, (1280.8, 11,087.35)
Total energy delivered until event adjusted to time until event (Kcal/hr)	31.34 (16.02, 44.21)	38.05 (29.51, 46.07)	32.65 (15.88, 46.31)
Total energy delivered until event adjusted to time until event and patient weight (Kcal/Kg*hr)	0.39 (0.2, 0.58)	0.47 (0.34, 0.65)	0.43 (0.23, 0.58)
ICU length of stay (d)	12.61 (7, 21.01)	8.83 (5.59, 15.87)	7.85 (3.82, 12.49)
Length of ventilation (d)	10.42 (5.19, 16.79)	7.02 (3.89, 13.83)	7.43 (3.56, 10.60)
ICU Mortality (n,%)	40 (14.54%)	0 (0%)	67 (100%)
		67 (35.83%)	
90-days mortality (n,%)	79 (28.73%)	104 (55.61%)	

Table 6. Clinical course and outcomes.

works demonstrated no difference in these (or other) characteristics between patients who developed hypophosphatemia and those who did not[1,29,30]. As so, there is no consensus regarding the predisposing factors for hypophosphatemia development. Unlike previous studies[1,11,21,27–30], in this study, we performed a multivariate analysis considering mortality as a competing risk, demonstrating several factors associated with increased risk for hypophosphatemia: Lower BMI, lower APACHE2 score, and shorter hospital LOS before ICU admission. Transplantation admission reason is associated with lower risk, while other admission reasons (compared to medical admission reason) carry no risk difference. There is no simple explanation for these effects—neither in our work nor in the other studies mentioned.

Fast duration before nutritional support initiation cannot be used as a covariate in this model, as it is an intermediate variable[31]. However, we found no difference in the rate of hypophosphatemia occurrence between fasting and non-fasting patients, in 6 different fasting intervals up to 72 h of fasting. To our knowledge, the effect of fasting duration before nutrition initiation has not been evaluated in critically ill patients. These results suggest that initiation of nutritional support (with restrictive energy delivery protocol as performed in our ICU) in a critically ill patient is safe (regarding hypophosphatemia development), at least within 72 h of admission. Studies evaluating energy delivery, usually involving ventilated patients[21,28,30,32] (as precise energy delivery of unventilated patients is more challenging to document and may be inaccurate) are scarce; these studies focus on the association between energy delivery/deficit, hypophosphatemia and mortality, but not on fast duration before hypophosphatemia.

Energy delivery is another intermediate variable. In a previous study, we found higher energy delivery throughout ICU admission in patients who developed hypophosphatemia[21]. The results from the current study are somewhat contradictory, as the average hourly energy delivery to the patients who developed hypophosphatemia (30.50 ± 19.28 kcal/h) was lower compared to patients who did not develop hypophosphatemia (both survivors (38.35 ± 14.70 kcal/h) and non-survivors (33.21 ± 21.16 kcal/h). Adjusting energy delivery rate to patient weight reveals this difference is even smaller (see Table 6). It should be noted that we calculated hourly energy delivery to a patient until time of hypophosphatemia (in patients who developed it) and until death/discharge time (in patients who did not develop hypophosphatemia). Therefore, the slightly lower hourly energy delivery in the patients who developed hypophosphatemia merely reflects our restrictive energy delivery protocol. We start nutritional support in our ICU according to a locally developed protocol, mainly initiating nutrition in a slow rate of energy delivery, and progress to the energy target within 1–2 days according to patient status (in line with current guidelines suggesting restrictive energy delivery[16], aiming to prevent hypophosphatemia). Thus, it is possible that comparing average hourly energy delivery until event time only emphasizes the lower energy delivery until achieving the caloric goal. Comparing energy delivery after hypophosphatemia development is not relevant to its development. Nevertheless, total energy delivered is larger in patients who developed hypophosphatemia [21]. As the patients still have an energy deficit, it seems reasonable to assume a very low likelihood of overfeeding in these patients. This is reflected in this study in the weight and length of stay adjusted energy delivery, which is not greater than 0.5 kcal/Kg*h, a number reflecting average energy delivery of 12 kcal/Kg*d.

Hypophosphatemia and admission outcomes

The increased LOV and LOS, in patients who develop hypophosphatemia, is well described[1,7,33], and are supported by our findings.

As for mortality, stating the obvious, multivariate analysis found age, APACHE2, and SOFA24 as significant factors associated both with ICU and 90 days mortality. BMI was associated with decreased ICU mortality (but not 90 days mortality). Hypophosphatemia was significantly associated with decreased ICU and 90 days mortality. The association between hypophosphatemia and mortality is a matter of debate in current literature[7]. Some works demonstrated higher mortality with hypophosphatemia[28,29], while others found no effect of hypophosphatemia on mortality[9,12,13,27], or decreased mortality[10,21]. Mortality from RFS is mostly due to cardiac arrhythmias, secondary

to electrolytes disturbances. The mortality rate from RFS decreased from 38% in past reports to 17% in modern reports. The likely explanation is restrictive energy delivery, which was not as common in the past[34].

The different effect of hypophosphatemia on mortality might be explained by different possible etiologies of hypophosphatemia (sepsis, burns, respiratory alkalosis, RFS) and their impact on mortality[7]. As the hazard ratio of hypophosphatemia and the associated risk of ICU mortality was 0.45 (95% CI 0.28–0.71) and 0.51 (95% CI 0.37–0.7) for 90 days mortality, and the effect of age and prognostic score on this association was much more subtle (the highest hazard ratio for 90 day mortality was of SOFA24 score, 1.13 (95% CI 1.07–1.19), it is possible to assume that in certain cases hypophosphatemia development might serve as a marker of recovery. A lower APACHE score was found to be associated with hypophosphatemia. Hence, one can assume that the protective effect of hypophosphatemia is merely the effect of the lower APACHE score. However, multivariate analysis found both APACHE and hypophosphatemia to be significantly associated with mortality (in opposite directions).

Hypophosphatemia is treated in our ICU according to a locally developed protocol. All ventilated patients are screened daily for hypophosphatemia development. Mild hypophosphatemia is treated with energy delivery decrement (or cessation) and/or enteral phosphate supplementation. Moderate and severe hypophosphatemia are treated with energy delivery cessation and enteral or parenteral phosphate supplementation (moderate or severe hypophosphatemia, respectively). The more severe the hypophosphatemia, the more aggressive the treatment, thus providing an explanation for the shorter duration of time in which patients are found with severe and moderate hypophosphatemia. This correction might mitigate the hypophosphatemia deterioration to cardiac arrhythmias, and explain the lower mortality with hypophosphatemia development, in contrast to what is expected regarding RFS mortality.

Fast, nutritional support, hypophosphatemia, and mortality

Fasting and hypophosphatemia are intermediate variables and thus an attempt at finding an association between them may introduce bias. However, we managed to identify several factors associated with hypophosphatemia development, including BMI, lower APACHE2 score, and lower hospital LOS before ICU admission. We did not observe a difference in hypophosphatemia rates in fasting and non-fasting patients. Also, the small difference in energy delivery to patients who developed hypophosphatemia is probably negligible. Hence, it seems reasonable to assume that progressive initiation of nutritional support, when prescribed based on a restrictive caloric goal, in mixed general critically ill patients, does not contribute to hypophosphatemia development. Aggressive hypophosphatemia screening and correction allows for avoiding some of hypophosphatemia's adverse effects, suggesting a protective effect from mortality due to hypophosphatemia, even after adjusting to other severity scores. Whether hypophosphatemia can be considered as a marker of recovery[21], is beyond the scope of this study.

Strengths and limitations

Our work has several limitations. First, its retrospective nature, makes it difficult to assess causality between factors. Second, we could not statistically estimate the interaction and influence of several intermediate variables, such as hypophosphatemia occurrence and initiation of nutritional support during an admission. Therefore, we performed only descriptive statistics for these variables. Third, we could not estimate the effect of energy delivered to the patient on hypophosphatemia. The main reason for this is the retrospective nature of the study, as a comparison cannot be made between patients who developed hypophosphatemia and those who didn't due to the unclear direction and even the existence of a causal relationship between energy delivered and phosphate levels. Theoretically, this can be estimated only in a prospective study. Fourth, we have no data regarding energy delivery and fasting duration prior to ICU admission, nor regarding energy delivered from hidden calories; hidden calories were shown in a previous study to be quite common in the ICU, while supplying a median of 205 kcal/d[35] or 2.6 kcal/Kg*d[36]. It seems reasonable to assume that this amount of calories can be considered as a substantial undernourishment to qualify as RFS risk factor. Therefore, as energy provided by hidden calories is not close to meeting caloric goal, it seems reasonable to consider the period when a patient doesn't receive nutritional support as fast. However, we could find one report demonstrating lower phosphate levels only during first 2 days of treatment in COVID-19 patients with high doses of propofol (5000 mg/d) compared to non COVID-19 patients treated with a lower dose of propofol (1800 mg/d)[37]. It is possible that "hidden calories" ight have alter the results. Fifth, we did not fully assess the effects acute kidney injury and/or hyperphosphatemia might have on the results. patients suffering from acute kidney injury are highly unlikely to develop hypophosphatemia, yet their prognosis is generally considered worse. Moreover, they are also likely to develop hyperphosphatemia (emphasizing the fact that a patient who did not develop hypophosphatemia was not necessarily normophosphatemic throughout admission. However, multivariate analysis for mortality using kidney SOFA24 score (instead of SOFA24 score) demonstrated that kidney SOFA24 score is not associated with mortality. Moreover, several models examining only Kidney SOFA24, and phosphate status, demonstrated that phosphate status (whether hypophosphatemia or hyperphosphatemia) is an important factor in the clinical pathway between increased kidney SOFA24 and mortality (see supplement 6). We have no data regarding kidney injury developed during the admission.

Nevertheless, this work has several strengths. First, it represents a diverse critically ill patient population. Second, by considering mortality as a competing risk, we can avoid overestimation of hypophosphatemia occurrence, and better describe its associated factors. Third, by considering phosphate level as a time-varying covariate for mortality analysis, we can assume avoiding of immortal life bias. Fourth, our data showed no association between fast duration and hypophosphatemia—a finding with direct implications on clinical practice.

Conclusion

We found that higher BMI, higher APACHE2 score, and longer hospital LOS before ICU admission—are all inversely associated with hypophosphatemia development. Hypophosphatemia occurrence is similar in each fast duration before nutrition support initiation. Hypophosphatemia was found to have an inverse association with mortality which might suggest it has a protective effect.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Author contributions

LS & OR equally contributed to this manuscript. LS—Conceptualization, Methodology, Investigation, Data curation, Writing—Original Draft, Writing—Review & Editing; OR—Conceptualization, Methodology, Investigation, Data curation, Writing—Original Draft, Writing—Review & Editing; TS—Methodology, Software, Validation, Formal Analysis, Writing—Review & Editing; ER—Data curation, Writing—Review & Editing; MH—Investigation, Data curation; IB—Investigation, Data curation; GF—Investigation, Data curation, PS—Conceptualization, Writing—Original Draft, Writing—Review & Editing, Supervision; IK—Conceptualization, Writing—Review & Editing, Supervision.

Competing interests

The authors declare no competing interests.

Additional information

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