Clinical Nutrition 40 (2021) 3615–3621

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Prevalence of hypophosphatemia in the ICU – Results of an international one-day point prevalence survey

M.M. Berger [a, *], O. Appelberg [b], A. Reintam-Blaser [c], C. Ichai [d], O. Joannes-Boyau [e], M. Casaer [g], S.J. Schaller [f], J. Gunst [h], J. Starkopf [i], for the ESICM-MEN section [1]

[a] Lausanne University Hospital, Lausanne, Switzerland
[b] University of Tartu, Tartu University Hospital, Tartu, Estonia
[c] Lucerne Cantonal Hospital, Dpt of Intensive Care Medicine, Lucerne, Switzerland
[d] Université Côte d'Azur, Mixed Intensive Care Unit, Nice, France
[e] Centre hospitalier universitaire de Bordeaux, Bordeaux, France
[f] Charité, Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, And Berlin Institute of Health, Dpt of Anesthesiology and Operative Intensive Care Medicine, Berlin, Germany
[g] Department of Intensive Care Medicine, University Hospital Leuven, Leuven, Belgium
[h] KU Leuven, Dpt of Cellular and Molecular Medicine, Clinical, Dpt and Laboratory of Intensive Care Medicine, Belgium, Leuven
[i] University of Tartu, Tartu University Hospital, Estonia

ARTICLE INFO

Article history:
Received 3 October 2020
Accepted 16 December 2020

Keywords:
Critically ill
Electrolyte
Nutrition
Repletion
Standard operating procedure
Monitoring

SUMMARY

Background & aims: Hypophosphatemia (HypoP) is associated with organ dysfunction and mortality. Despite its potential severe consequences, HypoP remains poorly characterized in terms of real prevalence and timing of onset. The primary objective was to determine the prevalence of HypoP defined as blood phosphate <0.8 and < 0.65 mmol/l on one particular day at international level.
Methods: One-day point prevalence survey conducted by the Section of Metabolism, Endocrinology and Nutrition (MEN) of the European Society of Intensive Care Medicine (ESICM) during week 11–2020.
Results: In total, 56 adult and 4 paediatric ICUs, from 22 countries participated: 41 ICUs were mixed medico surgical, the 19 others being cardiac, medical or surgical. Phosphate measurements were performed daily in 21 ICUs, and 1–3 times per week in 39 ICUs. On D-Day 909 patients (883 adults) were present and 668/883 (75.7%) had serum/plasma phosphate determined, revealing a HypoP in 103 (15.4%) patients aged 62 [18 to 85] years. Of those, 49 patients presented phosphate <0.65 mmol/l: cases of hypophosphatemia were detected at any time of patient's ICU stay. No HypoP was observed in children. A treatment protocol existed only in 41.1% of adult ICUs, independently of ICU type, or size. Only 41/98 of the HypoP patients (29/41 of patients with phosphate <0.65 mmol/l) were receiving phosphate.
Conclusion: HypoP is present at least in 15.4% of ICU patients, and may occur at any time during the ICU stay. The absence of phosphate repletion protocols in 60% of participating ICUs is an unexpected finding, and confirms the necessity for the development of ICU phosphate protocols and guidelines.
ClinicalTrials identifier: NCT04201899

1. Introduction

Phosphorus is an essential component of the human body. It is a key element in organic molecules essential for cellular functioning [1,2], including biochemical energy transfer via adenosine triphosphate (ATP), maintenance of genetic information with nucleotides DNA and RNA, intracellular signalling via cyclic adenosine monophosphate (cAMP), and membrane structural integrity via glycerophospholipids. In blood, the phosphorus content is about 12 mg/dL (3.87 mmol/l) with about a third present as inorganic phosphorus (Pi, phosphate), which is the form measured in the

* Corresponding author. CHUV Lausanne University Hospital, CH - 1011 Lausanne. Switzerland.
E-mail addresses: Mette.Berger@chuv.ch (M.M. Berger), oskar.appelberg@gmail.com (O. Appelberg), annika.reintam.blaser@ut.ee (A. Reintam-Blaser), ichai@unice.fr (C. Ichai), olivier.joannes-boyau@chu-bordeaux.f (O. Joannes-Boyau), michael.casaer@uzleuven.be (M. Casaer), stefan.schaller@charite.de (S.J. Schaller), jan.gunst@kuleuven.be (J. Gunst), Joel.Starkopf@kliinikum.ee (J. Starkopf).
[1] Complete list of investigators in appendix.

https://doi.org/10.1016/j.clnu.2020.12.017

blood serum or plasma [3] and considered hereafter. In adults, normal phosphate concentration in serum or plasma is 0.81–1.45 mmol/l (2.5–4.5 mg/dL) [3]. Approximately 55% of serum phosphate is free, 35% is complexed with small cations, and 10% is protein-bound [3]. The determination of intra-cellular phosphate levels is very difficult, as phosphate is complexed with carbohydrates, lipids and proteins [4,5]: it's value is not available in clinical settings.

Hypophosphatemia (HypoP), a serum or plasma phosphate level below the reference interval, is demonstrated in different ICU subpopulations, affecting preferentially patients requiring continuous renal replacement therapy [6], diabetic ketoacidosis [7], respiratory alkalosis [8], or patients admitted with short or long term malnutrition [9]. The international NutritionDay survey showed that it may affect up to 35% of ICU admissions [10]. But we could observe in our systematic review that a universal definition of the cut-offs of severity is lacking [11]: the grading <0.65 mmol/l as "moderate" and <0.32 mmol/l as "severe" comes from old studies conducted on non-ICU populations [12,13]. As critically ill patients develop electrolyte changes much faster than chronic patients, particularly due to insulin administration for glucose control, and as the symptoms are difficult to detect whereas consequences may be more severe, the authors decided to use "severe" and "very severe" respectively for the two cut-offs in this survey. Severe hypophosphatemia is associated with organ dysfunction, rhabdomyolysis, muscle weakness and higher mortality. A recent Chinese meta-analysis of 10 trials reported that the presence of HypoP was associated with increased severity of illness ($p = 0.002$), a longer duration of mechanical ventilation ($p = 0.0003$) and length of ICU stay ($p = 0.02$), as well as a higher ICU mortality ($p < 0.00001$) [14]. However, the true prevalence of HypoP is unknown [15]. While apparently simple, the treatment of HypoP whatever its origin with intravenous (i.v.) or enteral phosphate, requires diagnosis (measurement) and may require additional measures to improve patient management [16], and reduce mortality. Despite the potential severe consequences of HypoP, well defined characterisation of critically ill patients at risk and the role of contributing or causing factors (such as a refeeding syndrome, or ICU treatments as renal replacement therapy or insulin-therapy) remain poorly quantified and characterized.

The primary objective of this survey was to determine the prevalence of HypoP defined as serum or plasma Pi < 0.8 mmol/l on one particular day (D-Day) at international level, while gathering information about the internal ICU policies/guidelines for the management of HypoP among ICUs worldwide.

2. Methods

This one-day point-prevalence survey was conducted by the Section of Metabolism, Endocrinology and Nutrition (MEN) of the European Society of Intensive Care Medicine (ESICM). The survey was endorsed by the research committee of the ESICM and registered on Clinical Trials (NCT04201899). The centres were recruited by an invitation sent by the central ESICM office to the 394 ESICM members who had mentioned the MEN section as first interest. Altogether 93 physicians answered and tried to get Ethics approval in their respective institutions within the time planned for the survey.

2.1. Ethical approval and consent to participate

The principal ethics institutions delivering the Ethical approval, were the Erasme University (Brussels, Belgium) as N°P2019/403, and the Commission Cantonale d''Ethique de la Recherche sur l'Être Humain (Switzerland): N° CER-VD 2019–02343 for the 10 Swiss centres). Individual consent was waived by all institutions based on the importance of conducting a real prevalence survey, and the very limited personal data included in the survey. Ethical approval was obtained at a country or centre-level depending on local regulations, being under the responsibility of the sites' principal investigators.

2.2. Prevalence survey

The survey included two parts: 1) the ICU practices, and 2) a few characteristics of patients presenting HypoP on the D-Day (supplemental material). Data were entered on an electronic case report form (e-CRF) (REDCap®). The following ICU characteristics were collected: number of beds, number of patients present on D-Day, frequency of phosphate analysis, and HypoP treatment strategies. The recorded variables in patients with HypoP on D-Day were: age, days in ICU, ongoing phosphate administration, nutritional or renal replacement therapy (RRT) on D-Day. No outcome data was collected.

The primary endpoint was the prevalence of serum or plasma Pi < 0.8 mmol/l and Pi < 0.65, on one D-Day during week 11 of 2020 (9–13th March 2020), the day being selected locally by the participating sites. Phosphate data were expressed in mmol/l (SI units) using the conversion factor mg/dl = mmol/L * 3.1.

2.3. Statistical analysis

Data are presented as number (percentage) for categorical and median [IQR P_{25}; P_{75}] for continuous variables. Data were analysed using non-parametric tests for continuous variables (visual testing showed non-normal distribution for all tests), and contingency analysis (Pearson's test) for discrete variables. Linear simple regression was calculated between the time in ICU and lowest phosphate value. A value of $p < 0.05$ was considered significant. The statistical package used was JMP version 15.0., SAS, California.

3. Results

In total, 60 ICUs, including 4 paediatric ICUs, from 22 countries participated (Fig. 1), with seven only reporting general ICU characteristics but no patient data. Local ethical approval was obtained, except in seven ICUs from five countries (Argentina, Egypt, Netherlands, Peru, UK) which therefore limited their participation to general ICU characteristics with no patient data. When the number of responding ICUs is compared to the total number of ICUs in the different countries, only 1% of ICUs were participating.

- ICU characteristics

Most adult ICUs (37 of 56, 66.1%) were mixed medico-surgical (Table 1). The 4 paediatric ICUs were mixed medico-surgical.

Phosphate determination was almost equally performed on serum (46.7%) and plasma (40.0%), while the matrix was unknown in 13.3% of sites. Results were delivered in mmol/l in 61.7% and in mg/dl in 38.3% of ICUs. Recorded local upper and lower normal values for phosphate varied slightly and were: 1.45 [1.45; 1.47] mmol/l and 0.81 [0.80; 0.82] mmol/l.

Frequency of phosphate determination varied: 21 (19 adult+2 paediatric) sites measured serum/plasma phosphate at least once daily, while 39 (37 adult + 2 paediatric) measured phosphate one to three times weekly. This frequency was also different according to the ICU type being more frequent in the larger ICUs ($p = 0.0274$) and in surgical and mixed medico-surgical ICUs ($p = 0.0086$) (Table 2). In paediatric ICUs monitoring policy was similar to the adults. In ICUs with a high proportion of tested patients, HypoP was

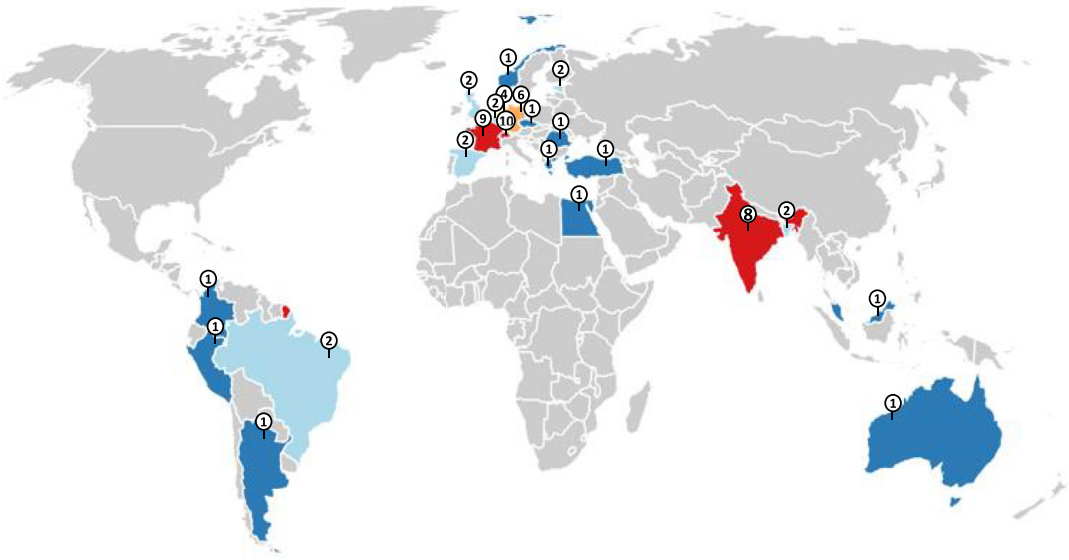

Fig. 1. Geographic ICU distribution of ICUs participating per country (dark blue - 1 ICU, light blue- 2ICUs, orange 3-7 ICUs, red 8–10 ICUs).

Table 1
Characteristics of the participating adult ICUs according to their size, with detail of participating paediatric ICUs. Exact Pi values were documented only for 98 adult patients.

ICU information	Total	Small ICU (≤12 beds)	Middle ICU (13–40 beds)	Large ICU (>40 beds)
Number of ICUs by size	56	16	38	2
ICU type				
Mixed medico surgical	37	6	29	2
Surgical	9	2	7	0
Medical	8	6	2	0
Cardiac	2	2	0	0
Total patients in the ICU				
Adults	883	130	675	78
Paediatric	26	26	0	0
N with Pi analysis				
Adult	668 (75.7%)	83 (63.8%)	512 (75.9%)	73 (93.6%)*
Paediatric	19 (73.1%)	19	0	0
Adult Patients with Pi < 0.8 mmol/l	103 (15.4%)	12 (14.5%)	79 (15.4%)	12 (16.4%)
Pi < 0.65 mmol/l	49/98 (50%%)	7	41	1
Pi < 0.32 mmol/l	16/98 (16.3%)	4	12	0
Phosphate measure frequency				
At least once daily**	20 (35.7%)	7	12	1
1–3 x per week	36 (64.3%)	9	26	1
Phosphate repletion protocol **	23 (41.1%)	5	16	2

* p = 0.086; ** paediatric ICUs: 2/4 reported having a phosphate protocol, and 2/4 analysed Pi at least once daily.

more frequently detected (p = 0.008), and Pi < 0.65 mmol/l more frequently observed (p = 0.016).

Phosphate protocol: a hypoP treatment protocol existed only in 41.1% of ICUs. Absence of protocol was independent of ICU type or size. In case of Pi < 0.65 mmol/l, most ICUs would treat and provide intravenous phosphate (72.4%), while 24.1% would combine enteral and i.v., and only two adult ICUs would use the enteral route (3.4%) alone. In ICUs who provided more detailed information, 3/9 ICUs reported the use of phosphate containing re-injection solutions or dialysates for continuous RRT, to reduce the risk of hypophosphatemia [17,18].

- Prevalence of HypoP and patient characteristics

On D-Day 883 adult patients were present in the ICUs and 668 (75.7%) had phosphate determined, revealing hypophosphatemia in 103 (15.4%) adult patients (complete data only in 98 patients) (Table 1). Of those, 49 patients (50%) presented with

Table 2
Frequency of phosphate determination according to ICU type in adult patients present on D-Day (median [IQR]).

Variable/ICU type	Mixed medico surgical	Surgical	Medical	Cardiac	P value
Median number of patients with Pi determination	11 [7; 18]	12 [11; 17]	6 [1; 10]	1 [1; 1]	0.0274
% of patients with Pi measurement	90 [59; 100]	95 [89; 100]	82 [8–100]	13 [9; 17]	0.0086

Pi < 0.65 mmol/l, and 16 had values < 0.32 mmol/l. Cases of HypoP were detected at any time of patient's ICU stay. The lowest phosphate level of 0.10 mmol/l was recorded in two patients on days 7 and 8: one was receiving phosphate while the other was not. Fifty one (52%) of the 98 HypoP cases were documented within the first 5 days in the ICU (Fig. 2). HypoP patients were aged 62 [18 to 85] years, similar across the categories of admissions. Table 3 provides available patient data and the comparison according to admission category. Of note, the distribution of ICU-length of stay is by design unknown.

3.1. Paediatric patients

26 were present on D-Day in four ICUs, and 19 had phosphate determination (73.1%), but no HypoP was observed.

3.2. Time in ICU of documented HypoP

Median time of moderate HypoP (0.65–0.79 mmol/l) was 4 [2; 10] days, while time of HypoP <0.65 mmol/l was 6 [2; 8] days (p = 0.668), and time to the very severe Pi < 0.32 mmol/l values (n = 14) was 7 [4; 10] days (p = 0.044).

3.3. Relation to nutrition

69 patients (70.4%) were fed on D-Day (51 (52%) on enteral, 21 (21.4%) on parenteral, three being on combined enteral and parenteral). HypoP <0.65 mmol/l was observed more often in fed patients as compared to non-fed patients (39/49 versus 30/49: p = 0.046). The three patients on combined feeding had Pi < 0.65 mmol/l.

3.4. Relation to RRT

Only 15 (15.3%) of the 98 patients with HypoP were on RRT. In these 15 patients, HypoP was documented between the 1st and 39th day of their stay. The proportion of patients with Pi < 0.65 mmol/l was non-significantly higher in RRT versus non-RRT patient s (64.7% versus 46.9% in non-RRT: p = 0.182). In the 10 ICUs reporting these 15 patients, all were using continuous RRT, 3/10 were using phosphate containing solutions: the with-P reported 3 HypoP (2 with Pi < 0.65), and those without P reported 12 HypoP (with 8 < 0.65) cases. Ten out of 15 patients on RRT received additional phosphate.

3.5. Phosphate therapy

41.8% of the HypoP patients were receiving additional phosphate. Among the 49 patients with Pi < 0.65 mmol/l, only 28 were receiving phosphate (57.1%). Phosphate administration differed significantly between patients depending on being on RRT or not (Phosphate in 10/5 (66.7%) on-RRT versus 31/83 (37.3%) no-RRT: p = 0.034), possibly reflecting better attention to patients on RRT. The presence of a protocol was associated with a few more HypoP patients being treated (16/50 vs 23/48; p = 0.044).

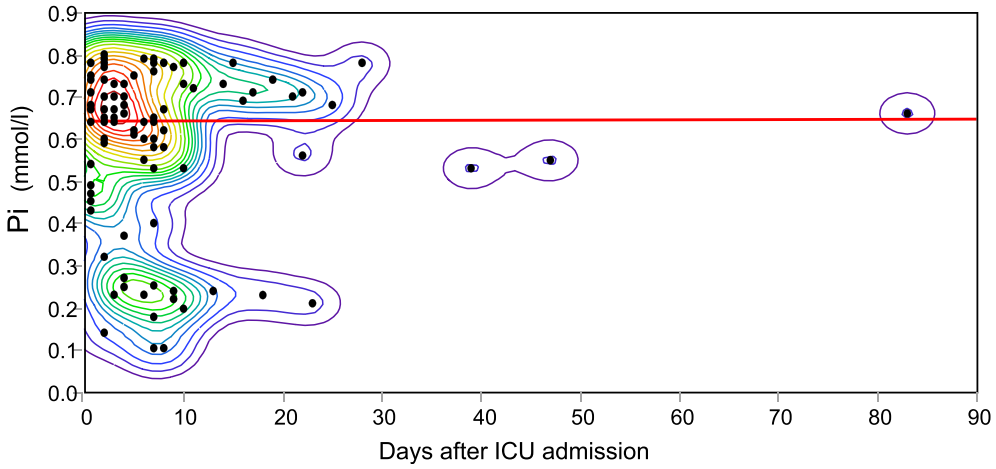

Fig. 2. Density distribution of hypophosphatemia by length of ICU stay (the red horizontal line indicates Pi < 0.65 mmol/l).

Table 3
Characteristics of the adult patients with hypophosphatemia (individual values only in 98/103 HypoP patients).

	Total n	Medical	Elective surgery	Emergency surgery	Elective cardio-surgical	P value
HypoP <0.80 mmol/l	98	56	15	21	6	0.147
HypoP <0.65 mmol/l (% of total)	49	27 (55.1%)	7 (14.3%)	12 (24.5%)	3 (6.1%)	0.904
On RRT (% of total)	15	7 (46.7%)	6 (40.0%)	2 (13.3%)	0	0.029
On artificial feeding	69 (70.4%)	37	13	16	3	0.268
EN	51 (52.0%)	31 (60.8%)	8 (15.7%)	10 (19.6%)	2 (3.9%)	0.738
PN	21 (21.4%)	6 (28.6%)	6 (28.6%)	8 (38.1%)	1 (4.7%)	0.015
EN + PN	3 (4.3%)	1	0	2	0	ns

Abbreviations: EN = enteral nutrition, PN = Parenteral nutrition, EN + PN = combined.

4. Discussion

This is the first international point-prevalence survey reporting on the frequency of hypophosphatemia. It shows that HypoP is present at least in 15% of critically ill patients. This electrolyte abnormality may occur at any time during the stay, even in patients with prolonged ICU stay. Only half of the low values was observed within the first five ICU days. Severe HypoP (Pi < 0.65 mmol/l) was present in 7.3% of patients with phosphate determination and occurred within the first 6 days as a median, which means that about half of the cases were observed even later.

It is likely that this 15.4% prevalence is an underestimation for several reasons. First, only 75.7% of the patients present in the ICUs had blood phosphate determination on the study day, some ICUs testing only once in a week. While some of the participating ICUs probably did more testing on their individually chosen D-Day, others did not change their routines. The results of a previous international survey by the MEN section regarding micronutrient practice gave similar results [19]: 120 (35.9%) respondents reported to daily measure phosphate, whereas 75 (22.5%) reported not to do routine measurements. This proportion of testing hence seems to correspond to standard practice as shown in a Danish cohort [20]: out of 190 patients admitted to their ICU, 122 (64.2%) had serum phosphate levels measured during the first 24 h of admission, of whom 25 (20.5%) were low. Hypophosphatemia in the Danish cohort was not associated with ICU or 28-day mortality. Low testing may also be related to special measures, such as the use of phosphate containing re-injection solutes during RRT [17,18,21], or a systematic i.v. Phosphate administration in patients after stabilization and/or confirmation of higher than usual phosphate needs, reducing the perceived need for daily measurements. Indeed, HypoP during RRT is more due to the duration of RRT and to the solutes than to the RRT method itself [21]: if re-injection solutions or dialysates contain phosphate at about 1 mmol/l, the patient will rarely experience hypophosphatemia [17,18]. Of the 10 ICUs reporting the 15 cases of HypoP during RRT, three were using phosphate containing solutions: 12 HypoP including the most severe occurred in those not using integrated phosphate.

Our study sites were almost equally divided using phosphate measurements in blood plasma or in serum. Determinations in plasma are shown to be slightly (0.06–0.1 mmol/l) lower than in serum [22]. This may explain the negligible variation in reported reference values.

A relatively high number of patients, 7.1% in the present study, had a severe hypophosphatemia (Pi < 0.65 mmol). The qualification “severe” is neither universally applied, nor is the threshold for imperative treatment well defined, some authors keeping the term severe for values Pi < 0.32 mmol/l [17,21]. However, we know from the literature that patients with Pi < 0.65 mmol/l are at particular risk of serious consequences such as cardiac arrhythmias, muscle weakness, respiratory failure, dysphagia and ileus contributing to poor ICU outcome [14]. In our opinion this suggests that serum phosphate levels should be obtained daily (or at least more than once a week) for most of ICU patients and not only at admission.

There are many causes of HypoP, but the four major mechanisms are [14,16,20]: 1) the redistribution of phosphate from the extracellular fluid into cells (due to increased insulin secretion during feeding, exogenous insulin/catecholamines infusion or respiratory alkalosis), 2) decreased intestinal absorption of phosphate, 3) increased urinary phosphate excretion, and 4) removal by RRT. Moreover, hypophosphatemia results frequently from not only one, but multiple associated causes in critically ill patients.

HypoP is a component of the refeeding syndrome (RFS), a life-threatening complication [14]. The prevalence and impact on long-term outcomes of RFS in the critically ill are still unknown. The presence and the impact of RFS on transfer to the ICU and mortality was analysed in a subgroup 947 out of the 2088 patients included in the nutritional study EFFORT that tested individualised nutritional support in medical non critically ill inpatients at nutritional risk [23]. RFS was confirmed in 14.6% of patients, and a significant increase of 180-days mortality rates was observed (29.8% vs 21.9%, adjusted odds ratio of 1.53 (95% CI 1.02 to 2.29, $p < 0.05$). Patients with RFS also had an increased risk for ICU admission (4.3% vs 1.6%), adjusted odds ratio 2.71, $p < 0.05$) and longer length of hospital stay (adjusted difference 1.57 days, $p = 0.01$).

An argument in favour of 0.65 mmol being considered as severe is the fact that correcting HypoP during RFS in ICU patients, might not be sufficient to improve outcome as shown by an Australian study [16]: the study inclusion criteria was a Pi < 0.65 mmol/l within 72 h after starting nutritional support. The patients were randomised to phosphate repletion alone, or to repletion plus restricted feeding progression. While the phosphate replacement dose did not differ between the study groups, a 60-day mortality reduction was observed in the phosphate plus calorie-restriction group [16]. While phosphate administration might be insufficient, its administration should certainly not be omitted. There is to our knowledge no study comparing phosphate to placebo in the context of Pi < 0.65 mmol/l.

Recognizing the prevalence and the potential dangerousness of HypoP should prompt for creation of standard operating procedures (SOP). The low number of patients receiving phosphate treatment was disturbing: only 41.8% of the patients were receiving phosphate therapy, a little more in the severe HypoP patients with (28/49 i.e. 57.1%). This is probably connected to the fact that only 41.1% of ICUs had a repletion protocol in place at the time of the survey. The absence of SOP seems to be common practice. We therefore need to highlight that if phosphate levels are not measured, a hypophosphatemia will not be corrected. Although this is evident, we insist on this point as 64.3% of centres measure Pi only 1–3 times per week. In the previously mentioned MEN survey [19], only 173 (59.2%) of the 292 respondents reporting on supplementation, regularly supplemented phosphate.

4.1. Limitations

The main limitation of the study is the scarce number of participating ICUs estimated at approximately 1% of all ICUs in the respective countries, which limits the generalisability of the results. As the study was conducted through the MEN section of ESICM, participating ICUs and clinicians are more likely to have a focus on metabolism and nutrition. Such potential bias would obviously only result in underestimation of this problem; non-participating ICU's might measure phosphate even less frequently, with the risk of HypoP being more often overlooked [21]. Furthermore, we did not collect detailed patient information about the severity of illness, the reason of admission, the duration of mechanical ventilation, ICU stay, complications, or outcome. The individual data collected was also limited to those patients in the study population who did develop HypoP on D-Day precluding identification of characteristics typical for these patients. This limitation occurred by design: in absence of funding and dedicated research personnel, only a limited number of data was collected to reduce the participating clinicians' collection workload. It was also done in order to facilitate the local ethical clearance. Despite the few variables collected, seven ICUs could not obtain clearance within the three months that were available to participate in the survey, and several others did not even attempt to get clearance. . The information regards RRT modalities was completed posthoc: continuous RRT was used in the 15 patients, and 3/10 ICUs were using phosphate in the

replacement solutions. Finally, prevalence on one day does not enable understanding the progression of an abnormality. Longitudinal repeated measurements might have observed more pathological values or, on the other hand, might have revealed spontaneous normalisation of pathologic values over time.

5. Conclusion

The one-day point-prevalence survey demonstrated that HypoP is present in 15.4% of ICU patients, and may be observed at any time during the ICU stay. Half of the hypophosphatemic patients had a severe alteration defined as Pi < 0.65 mmol/l. The prevalence number is likely to be an underestimation since systematic daily measurements occurred only in 35.7% of ICUs. Moreover, the study was conducted in ICUs with metabolic interest: it is therefore likely that phosphate measurements are even less frequent, and HypoP not recognised more frequently in the ICUs without that specific interest. The high prevalence, occurrence at random times during the whole ICU stay, and clinical consequences of HypoP justify a more systematic and repetitive determination of phosphate within ICU hospitalisation. Abnormal values can only be timely detected and treated if phosphate determination belongs to routine: an inclusion of Pi in the blood gas point-of-care analysers would facilitate the monitoring. Considering the severity of the consequences of HypoP, the creation of phosphate protocols with prospective validation studies including outcome variables should be encouraged, and development of guidelines within societies interested in metabolism and critical care should be undertaken.

Ethical approval

The principal ethics institutions delivering the Ethical approval. Were the Erasme University (Brussels, Belgium) as N°P2019/403, and the Commission Cantonale d''Ethique de la Recherche sur l'Être Humain (Switzerland): N° CER-VD 2019–02343: 10 Swiss centres). Ethical approval was obtained at a country or centre-level depending on local regulations, being under the responsibility of the sites' principal investigators.

Consent to participate

Consent was waived by all respective ethical committees by based on the importance of conducting a real prevalence survey, and the very limited personal data recorded in the survey.

Availability of data

The REDCap@ survey data were collected at the university of Tartu, Tartu, Estonia, The data were transferred to The university of Lausanne after signature of a Data Transfer agreement, where they are available and stored on a secured server of the Lausanne University hospital.

Consent for publication

All the contributing investigators saw the final version of the manuscript and agreed to its publication.

Funding

There was no industrial funding. A grant from the Fonds de Recherche Eléments Traces (N°2020-10-656) of the Dpt of Adult Intensive Care-CHUV supported the Ethics Committee fees. Access to REDCap® was provided by the University of Tartu. The individual authors were supported by their individual hospital departments.

Authors' contributions

Berger MM (BMM), coordinated the working group, conducted the study, obtained the Erasme university ethical approval, and drafted the manuscript. BMM, Reintam-Blaser A, Ichai C, Joannes-Boyau O, Casaer M, Schaller SJ, Gunst J and Starkopf J conceived the study, collected data, participated in analysing the data and wrote the manuscript. Oskar Appelberg (OA) conceived the REDCap® questionnaire, collected data, participated in the statistical analysis, and in the writing of the manuscript. BMM and OA conceived the figures. Participating investigators for the 60 ICUs answered the survey, and approved the final version of the manuscript.

Conflict of interest

None of the authors has any conflict to declare related to the present study.

Acknowledgments

We would like to express our gratitude to Mrs. Samia Abed Maillard (Chief project manager, Lausanne university hospital, CHUV) and Mrs. Sherihane Bensemane (Biologist, ESICM central office) for assistance with project development and the Ethics clearance process, and to all participating centres.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2020.12.017.

List of abbreviations:

ATP	adenosine triphosphate
cAMP	cyclic adenosine monophosphate
D-day	day chosen for the one-day point-prevalence survey
e-CRF	electronic case report form
EN	enteral nutrition
ESICM-MEN	European Society of Intensive Care Medicine – Metabolism, Endocrinology & Nutrition Section
HypoP	hypophosphatemia
ICU	intensive care unit
Pi	inorganic phosphate
PN	parenteral nutrition
REDCap	Research Electronic Data Capture: web application for building and managing online surveys and database
RRT	renal replacement therapy
RFS	refeeding syndrome
SOP	Standard Operating Procedure

References

[1] Peacock M. Phosphate metabolism in health and disease. Calcif Tissue Int 2020. https://doi.org/10.1007/s00223-020-00686-3. e-pub Apr 7.
[2] Gaasbeek A, Meinders AE. Hypophosphatemia: an update on its etiology and treatment. Am J Med 2005;118:1094–101.
[3] Bazydlo LAL, Needham M, Harris NS. Calcium, magnesium, and phosphate. Lab Med 2014;e45-e50:e44.
[4] Bansal VK. Serum inorganic phosphorus. In: rd, Walker HK, Hall WD, Hurst JW, editors. Clinical methods: the history, physical, and laboratory examinations; 1990. Boston.
[5] Manghat P, Sodi R, Swaminathan R. Phosphate homeostasis and disorders. Ann Clin Biochem 2014;51:631–56.
[6] Song YH, Seo EH, Yoo YS, Jo YI. Phosphate supplementation for hypophosphatemia during continuous renal replacement therapy in adults. Ren Fail 2019;41:72–9.

[7] Liu PY, Jeng CY. Severe hypophosphatemia in a patient with diabetic ketoacidosis and acute respiratory failure. J Chin Med Assoc 2004;67:355–9.
[8] Paleologos M, Stone E, Braude S. Persistent, progressive hypophosphataemia after voluntary hyperventilation. Clin Sci (Lond) 2000;98:619–25.
[9] McKnight CL, Newberry C, Sarav M, Martindale R, Hurt R, Daley B. Refeeding syndrome in the critically ill: a literature review and clinician's guide. Curr Gastroenterol Rep 2019;21:58.
[10] Berger MM, Reintam-Blaser A, Calder PC, Casaer M, Hiesmayr MJ, Mayer K, et al. Monitoring nutrition in the ICU 2019;38:584–93.
[11] Reintam Blaser A, Gunst J, Ichai C, VCasaer MP, Benstoem C, Besch G, et al. Hypophosphatemia in critically ill adults and children: a systematic review. Clin Nutr 2021;40:1744–54.
[12] Betro MG, Pain RW. Hypophosphataemia and hyperphosphataemia in a hospital population. Br Med J 1972;1:273–6.
[13] Larsson L, Rebel K, Sorbo B. Severe hypophosphatemia-a hospital survey. Acta Med Scand 1983;214:221–3.
[14] Liu B, Cheng Y, Shen F, Wang Y, Wu Y, Yao L, et al. Hypophosphatemia is associated with poor prognosis of critically ill patients: a meta-analysis of 1 555 patients. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2018;30(1):34–40.
[15] Friedli N, Stanga Z, Sobotka L, Culkin A, Kondrup J, Laviano A, et al. Revisiting the refeeding syndrome: results of a systematic review. Nutrition 2017;35:151–60.
[16] Doig GS, Simpson F, Heighes PT, Bellomo R, Chesher D, Caterson ID, et al. Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial. Lancet Respir Med 2015;3:943–52.
[17] Broman M, Carlsson O, Friberg H, Wieslander A, Godaly G. Phosphate-containing dialysis solution prevents hypophosphatemia during continuous renal replacement therapy. Acta Anaesthesiol Scand 2011;55:39–45.
[18] Godaly G, Carlsson O, Broman M. Phoxilium((R)) reduces hypophosphataemia and magnesium supplementation during continuous renal replacement therapy. Clin Kidney J 2016;9:205–10.
[19] Vankrunkelsven W, Gunst J, Amrein K, Bear DE, Berger MM, Christopher KB, et al. Monitoring and parenteral administration of micronutrients, phosphate and magnesium in critically ill patients: the VITA-TRACE survey. Clin Nutr 2021;40:590–9.
[20] Federspiel CK, Itenov TS, Thormar K, Liu KD, Bestle MH. Hypophosphatemia and duration of respiratory failure and mortality in critically ill patients. Acta Anaesthesiol Scand 2018. https://doi.org/10.1111/aas.13136. e-pub 23 April.
[21] Pistolesi V, Zeppilli L, Fiaccadori E, Regolisti G, Tritapepe L, Morabito S. Hypophosphatemia in critically ill patients with acute kidney injury on renal replacement therapies. J Nephrol 2019;32:895–908.
[22] Burtis CA, Ashwood ER, Bruns DE. Tietz textbook of clinical chemistry and moleculat diagnostics. In. Edited by. 2016. 02-21 05:10:00, https://pdfs.semanticscholar.org/3834/df7822925163007478abdb6b0ca39af0d2a9.pdf.
[23] Friedli N, Baumann J, Hummel R, Kloter M, Odermatt J, Fehr R, et al. Refeeding syndrome is associated with increased mortality in malnourished medical inpatients: secondary analysis of a randomized trial. Medicine (Baltim) 2020;99:e18506.