The relationship between hypophosphataemia and outcomes during low-intensity and high-intensity continuous renal replacement therapy

Rinaldo Bellomo, Alan Cass, Louise Cole, Simon Finfer, Martin Gallagher, Inbyung Kim, Joanne Lee, Serigne Lo, Colin McArthur, Shay McGuinness, Robyn Norton, John Myburgh and Carlos Scheinkestel

Phosphate is an essential part of structural cell membrane molecules (eg, phospholipids), energy sources (eg, adenosine triphosphate) and second messengers (eg, adenosine monophosphate).[1] These control mechanisms are disrupted by critical illness[2] and acute kidney injury (AKI) in particular.

When continuous renal replacement therapy (CRRT) is used in the treatment of severe AKI,[3,4] hypophosphataemia may develop, secondary to excess phosphate removal.[5,6] Hypophosphataemia has been associated in some studies with diaphragmatic weakness, increased risk of failed phosphate weaning and decreased myocardial contractility.[7-9] However, these studies did not take into account situations in which phosphate is concomitantly lowered by CRRT rather than by disease alone. As hypophosphataemia during CRRT may develop slowly and phosphate levels are likely to be regularly monitored, the clinical risk may be lower. In this setting, there is limited information on the timing, severity, duration and independent associations of hypophosphataemia with outcome. Such knowledge is important because of the reported greater incidence of hypophosphataemia during higher intensity CRRT in recent dialysis trials.[10,11] If hypophosphataemia independently contributes to a greater risk of mortality or morbidity, its more common occurrence with higher intensity CRRT might, at least partly, explain why such treatment fails to achieve a survival advantage.

The Randomised Evaluation of Normal vs Augmented Level (RENAL) study[12-15] is the largest randomised study of CRRT in patients with AKI to date. Because of its size, the availability of daily serum phosphate measurements and the two levels of CRRT intensity, we used RENAL trial data to explore the timing, severity, duration and predictors of hypophosphataemia during CRRT, and the possible independent association of hypophosphataemia with major clinical outcomes. In particular, we aimed to test the hypothesis that hypophosphataemia is independently associated with an increased risk of death in patients receiving CRRT.

ABSTRACT

Aim: To identify risk factors for development of hypophosphataemia in patients treated with two different intensities of continuous renal replacement therapy (CRRT) and to assess the independent association of hypophosphataemia with major clinical outcomes.

Materials and methods: We performed secondary analysis of data collected from 1441 patients during a large, multicentre randomised controlled trial of CRRT intensity. We allocated patients to two different intensities of CRRT (25 mL/kg/hour vs 40 mL/kg/hour of effluent generation) and obtained daily measurement of serum phosphate levels.

Results: We obtained 14 115 phosphate measurements and identified 462 patients (32.1%) with hypophosphataemia, with peak incidence on Day 2 and Day 3. With lower intensity CRRT, there were 58 episodes of hypophosphataemia/1000 patient days, compared with 112 episodes/1000 patient days with higher intensity CRRT ($P < 0.001$). On multivariable logistic regression analysis, higher intensity CRRT, female sex, higher Acute Physiology and Chronic Health Evaluation score and hypokalaemia were independently associated with an increased odds ratio (OR) for hypophosphataemia. On multivariable models, hypophosphataemia was associated with better clinical outcomes, but when analysis was confined to patients alive at 96 hours, hypophosphataemia was not independently associated with clinical outcomes.

Conclusions: Hypophosphataemia is common during CRRT and its incidence increases with greater CRRT intensity. Hypophosphataemia is not a robust independent predictor of mortality. Its greater incidence in the higher intensity CRRT arm of the Randomised Evaluation of Normal vs Augmented Level trial does not explain the lack of improved outcomes with such treatment.

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Methods

The RENAL study was a multicentre, prospective, randomised trial of two levels of intensity of CRRT in 1508 critically ill patients with AKI, conducted in 35 intensive care units in Australia and New Zealand. The human research ethics committees of the University of Sydney and all participating institutions approved the study.

The methodological details of the RENAL study were recently reported.[12-15] In brief, patients were eligible for enrolment if they were critically ill adults who had AKI, were deemed to require CRRT by the treating clinician and fulfilled other predefined criteria. Eligible patients were randomly assigned to continuous venovenous haemodiafiltration with effluent flow at 40 mL/kg/hour (high intensity) or 25 mL/kg/hour (low intensity). Study treatment was discontinued on death, discharge from the ICU or recovery of renal function to dialysis independence. The primary study end point was death from any cause by Day 90.

Serum phosphate measurement and definitions

In all patients, daily phosphate measurements were performed and recorded every morning until the first occurrence of either death, ICU discharge or completion of 28 days from study randomisation (study treatment period).

For the purpose of this study, and in keeping with local normal reference values, hypophosphataemia was considered present when the serum phosphate level was < 0.6 mmol/L, a stricter definition than was originally applied in the RENAL study.[10] Hypophosphataemia was defined as mild if the serum phosphate level was between 0.4 mmol/L and 0.6 mmol/L, moderate if the serum phosphate level was between 0.2 mmol/L and 0.4 mmol/L, and severe if the serum phosphate level was below 0.2 mmol/L.

Persistent hypophosphataemia was defined by the presence of two serum phosphate levels in the hypophosphataemic range on two consecutive days, and recurrent hypophosphataemia was defined by the presence of two serum phosphate levels in the hypophosphataemic range on two non-consecutive days.

Statistical analysis

Continuous variables were expressed as means with SD for normally distributed variables, and as medians with interquartile ranges for non-normally distributed variables. Comparisons were made using the student *t* test or the Mann–Whitney test, where appropriate. Categorical variables were expressed as proportions and compared using the χ^2 test or the Fisher exact test, as appropriate.

Daily hypophosphataemia-related variables and all baseline variables (biochemical, demographic, clinical and illness severity-related variables) available at randomisation were used to create multivariable models, using survival to 90 days as the primary dependent outcome variable. Multivariable linear regression analysis was used to assess the possible independent relationship between hypophosphataemia and the following dependent variables: mechanical ventilation (MV)-free days, CRRT-free days and ICU-free days at 90-day follow-up. The unadjusted analysis of time to death within 90 days of randomisation is shown as Kaplan–Meier product limit estimates, and survival curves are compared using the log-rank test.

To test whether there was an independent association between mortality and hypophosphataemia, we sought to remove the competing and confounding effect of survival time on the probability of experiencing hypophosphataemia, death or other adverse outcomes. This is because hypophosphataemia was much more common from Day 0 to Day 4 and was still quite common from Day 4 to Day 7. Patients who died before Day 4 or Day 7 had a decreased chance of experiencing hypophosphataemia and hence created an artificial association between hypophosphataemia and decreased risk of death. To correct for this time-related bias, we repeated multivariable analysis for key clinical outcomes after excluding patients who had died before 96 hours and before Day 7.

For an additional sensitivity analysis, we applied competing risk analysis[16] and joint model analysis.[17] For the purpose of joint model development, we first completed two submodels: a longitudinal model of phosphate, taking into account treatment, age, sex and weight, and assuming an interaction between treatment and day after randomisation. Second, we developed a survival Cox model adjusted for treatment and Acute Physiology and Chronic Health Evaluation (APACHE) III score. We also performed Cox proportional hazards modelling for all major outcomes, and pattern analysis to detect whether pattern mixture modelling could be applied. Pattern mixture is an alternative approach for correction for informative dropout.[18] The pattern mixture models allow investigators to relax the assumptions that missing data are missing at random, by permitting group comparisons on available data within subgroups of patients who drop out early.

To adjust for multiple analysis, a two-sided value of $P < 0.01$ was taken to indicate statistical significance. Statistical analyses were performed and independently checked using SAS version 9.1 and R version 2.15.3.

Results

Of the 1508 patients enrolled in the RENAL study, complete daily serum phosphate data were available for 1441 patients (95.6%), for a total of 14 115 phosphate measurements, with survival follow-up available for 1440 patients.

Table 1. Baseline characteristics and outcomes of patients with at least one episode of hypophosphataemia*

Baseline characteristics	Patients without hypophosphataemia	Patients with hypophosphataemia	*P*
Sex	*N* = 979	*N* = 462	
Female, *n* (%)	316 (32.3%)	194 (42%)	0.0003
Male, *n* (%)	663 (67.7%)	268 (58%)	NA
Mechanical ventilation	*N* = 978	*N* = 462	
No, *n* (%)	281 (28.7%)	97 (21%)	0.0018
Yes, *n* (%)	697 (71.3%)	365 (79%)	NA
Non-operative admission diagnosis	*N* = 695	*N* = 334	
Cardiovascular, *n* (%)	340 (48.9%)	184 (55.1%)	0.0026
Genitourinary, *n* (%)	171 (24.6%)	56 (16.8%)	NA
Gastrointestinal, *n* (%)	52 (7.5%)	23 (6.9%)	NA
Haematological, *n* (%)	20 (2.9%)	1 (0.3%)	NA
Metabolic or endocrine, *n* (%)	11 (1.6%)	14 (4.2%)	NA
Neurological, *n* (%)	7 (1%)	4 (1.2%)	NA
Respiratory, *n* (%)	89 (12.8%)	50 (15%)	NA
Transplant, *n* (%)	3 (0.4%)	2 (0.6%)	NA
Severe sepsis at baseline	*N* = 978	*N* = 462	
No, *n* (%)	528 (54%)	204 (44.2%)	0.0005
Yes, *n* (%)	450 (46%)	258 (55.8%)	NA
Mean APACHE III score (SD)	100.8 (25.3), *N* = 977	105.2 (26.2), *N* = 461	0.0029
SOFA respiration category	*N* = 945	*N* = 452	
Normal, *n* (%)	60 (6.3%)	10 (2.2%)	0.0004
Dysfunction, *n* (%)	211 (22.3%)	83 (18.4%)	NA
Failure, *n* (%)	674 (71.3%)	359 (79.4%)	NA
Mean SOFA respiration score (SD)	2.7 (1), *N* = 945	2.9 (0.8), *N* = 452	< 0.0001
SOFA cardiovascular category	*N* = 977	*N* = 460	
Normal, *n* (%)	170 (17.4%)	51 (11.1%)	< 0.0001
Dysfunction, *n* (%)	141 (14.4%)	40 (8.7%)	NA
Failure, *n* (%)	666 (68.2%)	369 (80.2%)	NA
Mean SOFA cardiovascular score (SD)	2.7 (1.6), *N* = 977	3.1 (1.4), *N* = 460	< 0.0001
⩾ 1 non-renal organ failure (SOFA score 3–4)	*N* = 979	*N* = 461	
No, *n* (%)	146 (14.9%)	38 (8.2%)	0.0004
Yes, *n* (%)	833 (85.1%)	423 (91.8%)	NA
Mean potassium (mmol/L) (SD)	4.9 (0.9), *N* = 968	4.6 (0.9), *N* = 462	< 0.0001
Mean urea (mmol/L) (SD)	24.3 (12.7), *N* = 974	21.2 (12.1), *N* = 460	< 0.0001
Mean creatinine, μmol/L (SD)	350.7 (217), *N* = 974	307.2 (187), *N* = 462	0.0002
Mean phosphate, mmol/L (SD)	2.1 (0.8), *N* = 916	1.9 (0.8), *N* = 434	< 0.0001

NA = not applicable. APACHE = Acute Physiology and Chronic Health Evaluation. SOFA = sequential organ failure assessment. * Only significant variables shown.

During treatment, 462 patients (32.1%) developed at least one episode of hypophosphataemia, with an incidence of 58 episodes/1000 patient-days during low-intensity CRRT, compared with 112 episodes/1000 patient-days during high-intensity CRRT ($P < 0.001$). The characteristics of patients who developed at least one episode of hypophosphataemia are compared with those of patients without any episode of hypophosphataemia in Table 1. Patients who experienced hypophosphataemia were more likely to be female and have sepsis and a greater illness severity on admission and more likely to have a lower baseline phosphate level.

Among patients with at least one episode of hypophosphataemia, 158 of 461 (34.3%) had died at 90 days after randomisation, compared with 473 of 979 patients (48.3%) who had never experienced hypophosphataemia ($P < 0.0001$). Survivors were also more likely to have experienced hypophosphataemia overall and mild, moderate, severe, persistent or recurrent hypophosphataemia, than non-survivors (Table 2).

Mean daily phosphate levels, by treatment allocation, are shown in Figure 1, and show a similar pattern of early decrease in phosphate levels and recovery with consistently higher levels during low-intensity CRRT. Figure 2 shows that phosphate levels had similar time-related changes among surviving and non-surviving patients. However, in the first few days, levels were lower among surviving patients. Figure 3 shows the incidence of hypophosphataemia on each day after randomisation, by treatment allocation. The peak incidence of hypophosphataemia was on Day 3 and Day 4 after randomisation.

On multivariable analysis, CRRT intensity, female sex, APACHE III score and hypokalaemia were independent predictors of a greater risk of developing hypophosphataemia, while female sex and calorie intake predicted development to persistent hypophosphataemia (see Appendix 2, Table 2a and Appendix 2, Table 2b at http://www.cicm.org.au/journal.php).

Association with outcome

On multivariable logistic regression analysis, the occurrence of at least one episode of hypophosphataemia during study treatment was independently associated with a significantly *decreased* risk of 90-day mortality (see

Figure 1. Changes in mean serum phosphate levels, by treatment intensity

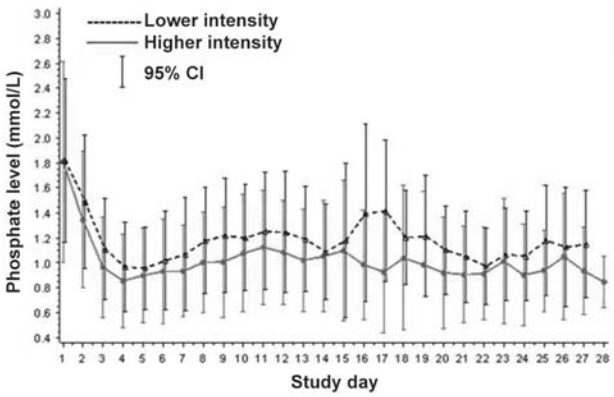


Figure 2. Changes in mean daily serum phosphate levels among survivors and non-survivors

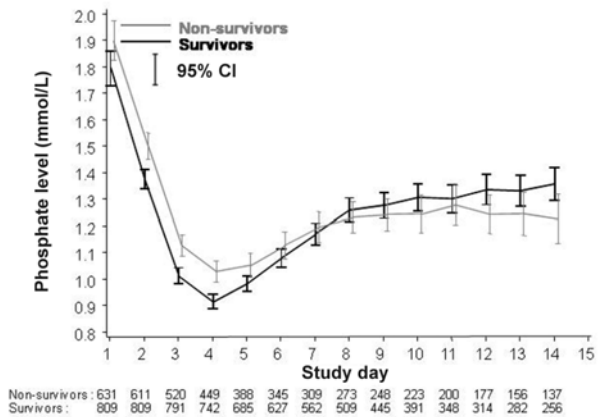


Figure 3. Timing and frequency of the occurrence of hypophosphataemia, by treatment intensity

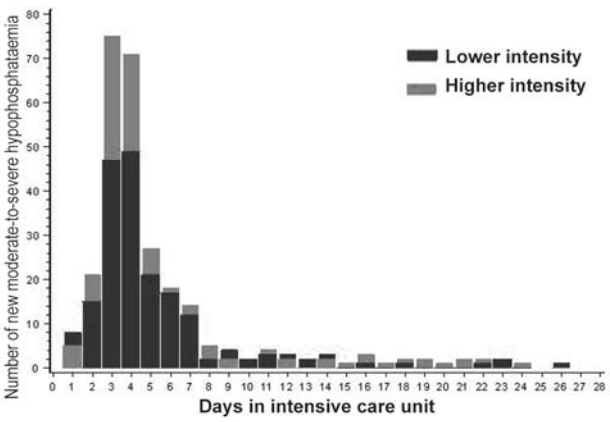


Table 2. Comparison of incidence, severity and persistence of episodes of hypophosphataemia among surviving and non-surviving patients

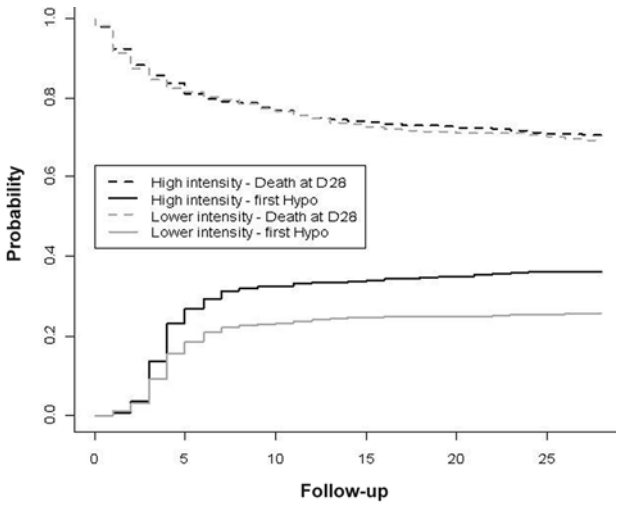
Baseline characteristic	Survivors (*N* = 809)	Non-survivors (*N* = 631)	*P*
⩾ 1 episode of hypophosphataemia, *n* (%)			
No	506 (62.5%)	473 (75%)	< 0.0001
Yes	303 (37.5%)	158 (25%)	
Severity of hypophosphataemia, *n* (%)			
No hypophosphataemia	506 (62.5%)	473 (75%)	< 0.0001
Mild	198 (24.5%)	119 (18.9%)	
Moderate	94 (11.6%)	35 (5.5%)	
Severe	11 (1.4%)	4 (0.6%)	
⩾ 1 episode of persistent hypophosphataemia, *n* (%)			
No	690 (85.3%)	568 (90.0%)	0.0074
Yes	119 (14.7%)	63 (10.0%)	
⩾ 1 episode of recurrent hypophosphataemia, *n* (%)			
No	628 (77.6%)	550 (87.2%)	< 0.0001
Yes	181 (22.4%)	81 (12.8%)	

Appendix 3, Table 3a at http://www.cicm.org.au/journal.php). This finding was not confirmed once the 1183 patients still alive after 96 hours and the 782 patients still alive after 7 days were assessed (see Appendix 3, Table 3b and Appendix 3, Table 3c at http://www.cicm.org.au/journal.php).

Cox proportional hazards modelling confirmed this pattern (see Appendix 4 at http://www.cicm.org.au/journal.php). Similar findings were seen when applying log-rank tests to survival time with Kaplan–Meier plots showing increased time to death with hypophosphataemia. This was corrected once analysis only was applied to patients who survived the first 96 hours (see Appendix 5 at http://www.cicm.org.au/journal.php).

On multivariable linear regression analysis, hypophosphataemia was associated with increased CRRT-free days, MV-free days, ICU-free days and hospital-free days after randomisation until Day 90. These findings were not confirmed once analysis was applied to patients who survived to 96 hours. Competing-risk analysis confirmed that the time to

Figure 4. Cumulative incidence function of the competing events of first hypophosphataemic episode and mortality*



* Shows a significant difference (the Gray test, $P < 0.0001$) in the incidence of hypophosphataemia induced by higher-intensity continuous renal replacement therapy. In both groups, essentially all episodes of hypophosphataemia have occurred by Day 7.

hypophosphataemia was shorter with high-intensity CRRT even when the competing risk of mortality was taken into account (Figure 4). The joint-model analysis also found no relationship between hypophosphataemia and outcome.

Discussion

Key findings

Using data from a large, multicentre, randomised controlled trial of the intensity of CRRT in critically ill patients with AKI, we assessed the incidence, timing and duration of hypophosphataemia and its association with major outcomes. We found that patients with hypophosphataemia had significantly decreased unadjusted mortality compared with patients who did not experience hypophosphataemia, and that surviving patients had a higher incidence of hypophosphataemia than non-surviving patients. Furthermore, when we estimated the independent association between hypophosphataemia and outcome at Day 90, we found that hypophosphataemia was independently associated with a decreased risk of death and with other improvements in patient-centered outcome such as CRRT-free days, MV-free days, ICU-free days and hospital-free days. However, these associations were confounded by the competing effect of mortality because the incidence of hypophosphataemia peaked at Day 4, and patients who died early were therefore less likely to experience such hypophosphataemia. Once we tested the robustness of the findings by adjusting for the biasing effect of survival time on the chance of developing hypophosphataemia, they could not be confirmed.

Comparison with previous studies

The association between acute hypophosphataemia and outcome is poorly understood. Acute hypophosphataemia due to phosphate redistribution alone may have little consequence in the absence of phosphate depletion.[1] Its cause-and-effect relationship with morbidity and mortality has been difficult to establish.[16]

Several studies have reported an association between hypophosphataemia and increased mortality. For example, Shor and colleagues studied 55 patients with sepsis and defined severe hypophosphataemia as iP_{min} (lowest measured phosphate level) < 1 mg/dL (0.32 mmol/L).[19] They found that severe hypophosphataemia during the ICU stay occurred in 47.3% of patients. Those with severe hypophosphataemia had significantly higher mortality rates (80.8% v 34.5%). Zazzo and colleagues prospectively investigated 208 patients admitted to a surgical ICU, and defined hypophosphataemia as $iP_{min} < 0.8$ mmol/L.[7] They found that hypophosphataemia occurred in 28.8% of cases and that mortality was higher in the hypophosphataemic group (30% v 15.2%). Sankaran and colleagues studied 302 patients with bacterial pneumonia admitted to the ICU,[20] and defined hypophosphataemia as $iP_{min} \leq 2.4$ mg/dL (0.77 mmol/L) and found that hypophosphataemia occurred in 44.7% of cases. Patients with hypophosphataemia had higher mortality rates (31.9% v 13.2%).

All these studies were small, used different definitions of hypophosphataemia and did not assess the independent relationship between hypophosphataemia and outcome after the necessary adjustments for illness severity. A recent study of a cohort of ICU patients treated with CRRT has so far assessed the independent association between hypophosphataemia and mortality.[21] Similarly to our study, it found no association between hypophosphataemia and mortality after adjustment for illness severity. In that study, on univariate analysis, mortality was lower in patients who experienced hypophosphataemia, as was the case in our study. This single-centre study found an independent association between hypophosphataemia and an increased risk of tracheostomy in only 321 patients treated with CRRT.[21] Finally, a recent large study of 2730 critically ill patients also found no independent relationship between hypophosphataemia and patient outcome.[22]

We also observed a greater incidence of hypophosphataemia in women. It is unclear whether this phenomenon relates to decreased bone mass in women compared with men, whether the "normal" range of phosphate fails to

represent a true normal for postmenopausal women, or if other factors explain this difference. The additional association between caloric intake and persistent hypophosphataemia is in keeping with expectations in patients at high risk of refeeding syndrome.

These observations create uncertainty about the possible impact of hypophosphataemia on outcome in patients with severe AKI. This is particularly problematic in patients receiving CRRT because recent large trials have shown that hypophosphataemia is particularly common in such patients.[11,12] A very recent study from China assessed the relationship between hypophosphataemia and outcome in a cohort of 760 patients treated with CRRT,[23] and no relationship between the incidence of hypophosphataemia and 28-day mortality was found.

Significance of findings

Our study supports the view that, in AKI patients receiving CRRT, hypophosphataemia is especially common when increased intensity of CRRT is applied. By assessing, for the first time, the relationship between hypophosphataemia and patient outcomes with a prospective, detailed data collection within a large cohort of patients treated with CRRT, our study provides strong evidence that hypophosphataemia has no independent association with outcomes. These observations do not support the notion that the lack of difference in outcome between high-intensity and low-intensity CRRT seen in two recent pivotal, randomised controlled trials of dialysis intensity might have been partly due to the adverse effects of more frequent hypophosphataemia in the high-intensity cohort.

Strengths and limitations

We report observational findings from the largest randomised controlled study of CRRT to date. The data were prospectively collected with specific attention to hypophosphataemia. Phosphate levels were measured daily and independently monitored for accuracy for more than 14 000 measurements, the largest assessment of serum phosphate levels to date. They provide the most comprehensive multicentre description of the epidemiology of hypophosphataemia during CRRT and of its association with outcome to date. Patients had detailed outcome data collected with primary outcome assessment at 90 days. We also had, for all patients, demographic, illness severity and biochemical data that were prospectively collected at baseline and could be used in multivariable models to adjust any association of hypophosphataemia according to baseline patient characteristics. The extent of such detail is much greater than anything previously used for analysis in this field.

On the other hand, data were only available from the time of randomisation. At that time, baseline phosphate levels were lower in patients who subsequently had one or more episodes of hypophosphataemia. It is possible that hyperphosphataemia at randomisation reflected disease severity in a way that was not captured by illness severity scores, and this difference partly explains our findings that patients with hypophosphataemia appeared to do better. Joint modelling analysis found an independent association between hyperphosphataemia during the observation period and mortality. Extended knowledge of phosphate levels before randomisation might then be particularly useful in increasing the validity of our observations. However, we cannot provide information on hypophosphataemia in the days before randomisation. In the RENAL trial, the time between ICU admission and randomisation was more than 2 days, and the mean duration of study time was about 13 days, suggesting that the evolution of serum phosphate levels in the prerandomisation period was unlikely to materially affect the study findings.

The findings of our study are open to interpretation because of the competing effect of mortality with hypophosphataemia (patients who stay in ICU longer are both more likely to live and to experience an episode of hypophosphataemia). However, after excluding patients who died in the first 96 hours or 7 days (when the vast majority of hypophosphataemic episodes had occurred), no independent relationship between hypophosphataemia and outcome could be confirmed. Sensitivity analyses and competing risk analyses all confirmed these findings.

We did not have data on the treatment of hypophosphataemia. However, current practice in Australia and New Zealand ICUs is to administer intravenous phosphate in response to hypophosphataemia,[25,26] as is current practice elsewhere.[24] As hypophosphataemia is unlikely to self-correct, and as it was typically returned to normal within 24 hours in most cases, such treatment can be assumed to have been given to most patients.

Therefore, our results do not imply that hypophosphataemia is of little consequence and should not be corrected. Although it may not carry a statistical association with increased mortality, its development is not desirable and our findings occurred in a clinical environment where treatment was applied. Our findings imply instead that, in a clinical setting where the occurrence of hypophosphataemia is detected by at least daily measurement and its levels corrected by phosphate supplementation, no independent relationship can be identified between hypophosphataemia and increased risk of death. Another potential aspect of our findings is that hypophosphataemia associated with CRRT-induced phosphate losses may have different implications than disease-induced hypophosphataemia.

Conclusions

In the RENAL study, in a clinical environment where hypophosphataemia was generally corrected by phosphate administration, patients with hypophosphataemia had a lower unadjusted mortality rate than those without an episode of hypophosphataemia. Surviving patients had a greater incidence of hypophosphataemia. After correction for multiple confounding variables and the application of different statistical modelling techniques, including time-adjustment, competing risk adjustment, joint modelling, Cox proportional hazards modelling and sensitivity analyses, this favourable association could not be confirmed. Thus, until higher level evidence emerges, hypophosphataemia cannot be considered a major risk factor for increased mortality in patients treated with CRRT. Perhaps, more importantly, the greater incidence of hypophosphataemia during high-intensity CRRT is unlikely to have negatively affected the outcome of these patients during the RENAL trial.

Competing interests

Rinaldo Bellomo has received consulting fees as advisor for Gambro. No other potential conflict of interest relevant to this article was reported.

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Author details

Rinaldo Bellomo, Co-director[1]
Alan Cass, Director[2]
Louise Cole, Staff Specialist[3]
Simon Finfer, Professor[4]
Martin Gallagher, Director, Nephrology Section[5]
Inbyung Kim, Research Fellow[6]
Joanne Lee, Project Coordinator[5]
Serigne Lo, Biostatistician[5]
Colin McArthur, Director, Department of Critical Care Medicine[7]
Shay McGuinness, Staff Specialist, Cardiovascular Intensive Care Unit[7]
Robyn Norton, Director[5]
John Myburgh, Director, Critical Care Section[5]
Carlos Scheinkestel, Director[8]

1 Australian and New Zealand Intensive Care Research Centre, Melbourne, VIC, Australia.
2 Menzies School of Health Research, Charles Darwin University, Darwin, NT, Australia.
3 Intensive Care Unit, Nepean Hospital, Sydney, NSW, Australia.
4 Intensive Care Department, Royal North Shore Hospital, Sydney, NSW, Australia.
5 The George Institute for Global Health, Sydney, NSW, Australia.
6 Intensive Care Unit, Austin Hospital, Melbourne, VIC, Australia.
7 Auckland City Hospital, Auckland, New Zealand.
8 Department of Intensive Care, Alfred Hospital, Melbourne, VIC, Australia.

Correspondence: Rinaldo.bellomo@austin.org.au

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Appendix 1. Randomised Evaluation of Normal vs Augmented Level (RENAL) Replacement Therapy Study committees, teams, site investigators and research coordinators (alphabetical order)

The RENAL Replacement Therapy Study is a collaboration of the Australian and New Zealand Intensive Care Society Clinical Trials Group and the George Institute for International Health.

Writing committee Rinaldo Bellomo (Chair), Alan Cass, Louise Cole, Simon Finfer, Martin Gallagher, Serigne Lo, Colin McArthur, Shay McGuinness, John Myburgh, Robyn Norton, Carlos Scheinkestel, Steve Su.

Management committee Rinaldo Bellomo (Chair), David Ali, Alan Cass, Louise Cole, Simon Finfer, Martin Gallagher, Donna Goldsmith, Joanne Lee, John Myburgh, Robyn Norton, Carlos Scheinkestel.

Steering committee Rinaldo Bellomo (Chair), Ashoke Banerjee, Deepak Bhonagiri, David Blythe, John Botha, John Cade, Louise Cole, Geoff Dobb, John Eddington, Simon Finfer, Arthas Flabouris, Craig French, Peter Garrett, Seton Henderson, Benno Ihle, Chris Joyce, Michael Kalkoff, Jeff Lipman, Colin McArthur, Shay McGuinness, David Milliss, Imogen Mitchell, John Morgan, John Myburgh, Priya Nair, Neil Orford, Asif Raza, Carlos Scheinkestel, Yahya Shehabi, Antony Tobin, Richard Totaro, Andrew Turner, Christopher Wright.

Project management team David Ali, Joanne Lee, Lorraine Little, Alana Morrison, Giovanna Regaglia, Ravi Shukla.

Data safety and monitoring committee Colin Baigent (Chair), Jonathan Emberson, David Wheeler, Duncan Young.

Statistics committee Laurent Billot, Severine Bompoint, Stephane Heritier, Serigne Lo, Avinesh Pillai, Steve Su.

Data management, information technology and programming team Sameer Pandey, Suzanne Ryan, Manuela Schmidt, Gemma Starzec, Bala Vijayan.

Australian Capital Territory site Canberra Hospital: Imogen Mitchell, Rebecca Ashley, Jelena Gissane, Katya Malchukova, Jamie Ranse.

New South Wales sites Blacktown Hospital: Asif Raza, Kiran Nand, Treena Sara. Concord Hospital: David Millis, Jeff Tan, Helen Wong. John Hunter Hospital: Peter Harrigan, Elise Crowfoot, Miranda Hardie. Liverpool Hospital: Deepak Bhonagiri, Sharon Micallef. Mater Calvary Hospital, Newcastle: Jorge Brieva, Melissa Lintott. Nepean Hospital: Louise Cole, Rebecca Gresham, Maria Nikas, Leonie Weisbrodt. Prince of Wales Hospital: Yahya Shehabi, Frances Bass, Michelle Campbell, Victoria Stockdale. Royal North Shore Hospital: Simon Finfer, Susan Ankers, Anne O'Connor, Julie Potter. Royal Prince Alfred Hospital: Richard Totaro, Dorrilyn Rajbhandari. St George Hospital: John Myburgh, Vanessa Dhiacou, Alina Jovanovska, Francesca Munster. St Vincent's Hospital: Priya Nair, Jeff Breeding, Claire Burns. Westmead Hospital: Ashoke Banerjee, Maridy Morrison, Caroline Pfeffercorn, Anne Ritchie.

New Zealand sites Auckland City Hospital/CVICU: Shay McGuinness, Heidi Buhr, Michelle Eccleston, Rachael Parke. Auckland City Hospital/DCCM: Colin McArthur, Jeanette Bell, Lynette Newby. Christchurch Hospital: Seton Henderson, Jan Mehrtens. Whangarei Hospital: Michael Kalkoff, Cathy West.

Queensland sites Mater Adult, Mater Private Hospital: John Morgan, Lorraine Rudder, Joanne Sutton. Nambour General Hospital: Peter Garrett, Nicole Groves, Shona McDonald, Jennifer Palmer. Princess Alexandra Hospital: Chris Joyce, Meg Harwood, Jean Helyar, Benjamin Mackie. Royal Brisbane Hospital: Jeff Lipman, Robert Boots, Claire Bertenshaw, Renae Deans, Cheryl Fourie, Melissa Lassig-Smith.

Tasmanian site Royal Hobart Hospital: Andrew Turner, Tanya Field, Kathryn Marsden.South Australian site Royal Adelaide Hospital: Arthas Flabouris, Jason Edwards, Stephanie O'Connor, Justine Rivett.

Victorian sites Austin Hospital: Rinaldo Bellomo, Claire Mathlin, Donna Goldsmith, Inga Mercer, Kim O'Sullivan. Bendigo Hospital: John Edington, Catherine Boschert, Julie Smith. Epworth Hospital: Benno Ihle, Michael Graan, Samuel Ho. Frankston Hospital: John Botha, Nina Fowler, Jodi McInness, Naomi Pratt. Geelong Hospital: Neil Orford, Tania Elderkin, Melissa Fraser, Anne Kinmonth. Monash Medical Centre: Christopher Wright, Sue Burton, Carly Culhane, Pauline Galt, Rebecca Rutzou. Royal Melbourne Hospital: Megan Roberston, Deborah Barge, Tania Caf, Belinda Howe, Patzy Low. St Vincent's Hospital: Antony Tobin, Nicole Groves, Jennifer Holmes, Roger Smith. The Alfred Hospital: Carlos Scheinkestel, Andrew Davies, Lynne Murray, Rachael Nevill, Shirley Vallance, Sue Varley, Vickie White. Western Hospital: Craig French, Lorraine Little, Heike Raunow.

Western Australian sites Fremantle Hospital: David Blythe, Anna Palermo. Royal Perth Hospital: Geoff Dobb, Melanie Boardman, Jenny Chamberlain, Andree Gould, Geraldine McEntaggart, Samantha Perryman, Linda Thomas.

Appendix 2. Table 2a. Multivariate logistic regression of hypophosphataemia* during intensive care unit stay

Variable and effect (discrete variable)	Odds ratio	95% CI	*P*
Treatment, high intensity v low intensity	0.659	0.46–0.94	0.0229
Mean daily calorie intake (per 500 kcal)	1.781	1.51–2.1	< 0.0001
Mean daily fluid balance (L)	0.626	0.48–0.81	0.0004
Positive mean fluid balance, yes v no	1.874	1.11–3.17	0.0192
Fluid overload at randomisation, yes v no	0.941	0.65–1.36	0.7471
Sex, male v female	0.557	0.38–0.81	0.0022
Severe sepsis at baseline, yes v no	0.983	0.67–1.45	0.9321
APACHE III score	1.009	1–1.02	0.0307
SOFA score			
Respiration, failure v dysfunction	0.244	0.03–1.98	0.1864
Respiration, normal v dysfunction	0.214	0.04–1.03	0.0550
Cardiovascular, failure v dysfunction	1.981	0.96–4.1	0.0655
Cardiovascular, normal v dysfunction	1.347	0.61–2.98	0.4625
Renal, failure v dysfunction	1.106	0.69–1.76	0.6718
Renal, normal v dysfunction	0.978	0.29–3.33	0.9719
Overall (sum of all non-missing organ scores/5)	0.945	0.58–1.55	0.8217
⩾ 1 non-renal organ failure (SOFA score 3–4), yes v no	0.632	0.25–1.59	0.3288
Last serum urea before randomisation (mmol/L)	0.972	0.83–1.14	0.7224
Last creatinine before randomisation (μmol/L)	1.009	1–1.02	0.0700
Potassium (mmol/L)	0.673	0.53–0.85	0.0009
Chloride (mmol/L)	1.001	0.97–1.03	0.9615
Bicarbonate (mmol/L)	0.971	0.93–1.01	0.1649
Urea (mmol/L)	0.991	0.85–1.16	0.9066
Creatinine (μmol/L)	0.992	0.98–1	0.0979
Albumin (g/L)	1.019	0.99–1.05	0.1750
pH	0.345	0.06–2.11	0.2491
Mechanical ventilation, yes v no	2.457	0.32–19	0.3894
Estimated glomerular filtration rate > 60 mL/min, yes v no	1.056	0.71–1.56	0.7863

APACHE = Acute Physiology and Chronic Health Evaluation.
SOFA = sequential organ failure assessment. * Hypophosphataemia defined as a single episode of phosphate concentration < 0.6 mmol/L.

Appendix 2. Table 2b. Multivariate logistic regression for the prediction of persistent hypophosphataemia*

Variable and effect (discrete variable)	Odds ratio	95% CI	*P*
Treatment, high intensity v low intensity	0.574	0.34–0.96	0.0328
Sex, male v female	0.467	0.28–0.79	0.0041
Mean daily calorie intake (/500 kcal)	1.646	1.31–2.07	< 0.0001

APACHE = Acute Physiology and Chronic Health Evaluation. SOFA = sequential organ failure assessment. * Only variables with $P < 0.05$ reported; other variables included treatment, mean daily calorie intake, mean daily fluid balance, positive mean fluid balance, fluid overload at randomisation, sex, severe sepsis at baseline, APACHE III score, SOFA respiratory, cardiovascular and renal scores, ⩾ 1 non-renal organ failure, urea, creatinine, potassium, bicarbonate, albumin, magnesium, pH level at randomisation, mechanical ventilation, estimated glomerular filtration rate.

Appendix 3. Table 3a. Multivariate logistic regression for 90-day mortality (all patients)*

Variable and effect (discrete variable)	Odds ratio	95% CI	*P*
Intercept	NA	NA	0.8154
Hypophosphataemia, yes v no	0.562	0.41–0.77	0.0003
Mean fluid balance, input–output (L)	1.998	1.58–2.53	< 0.0001
Patient age, years	1.038	1.03–1.05	< 0.0001
Patient weight, kg	0.987	0.98–1	0.0186
Time from ICU admission to randomisation, days	1.002	1–1	0.0087
Severe sepsis at baseline, yes v no	1.283	0.95–1.72	0.0992
SOFA liver score, failure v normal	3.431	1.56–7.55	0.0022
International normalised ratio	1.21	1.04–1.41	0.0141
Albumin (g/L)	0.976	0.96–1	0.0249

NA = not applicable. ICU = intensive care unit. SOFA = sequential organ failure assessment. * Only variables with $P < 0.05$ reported; other variables included treatment, mean daily calorie intake, mean daily fluid balance, positive mean fluid balance, fluid overload at randomisation, sex, severe sepsis at baseline, APACHE III score, SOFA respiratory, cardiovascular and renal scores, ⩾ 1 non-renal organ failure, urea, creatinine, potassium, bicarbonate, albumin, magnesium, pH level at randomisation, mechanical ventilation, estimated glomerular filtration rate.

Appendix 3. Table 3b. Multivariable logistic regression for 90-day mortality (patients who lived > 96 hours)*

Variable and effect (discrete variable)	Odds ratio	95% CI	*P*
Intercept	NA	NA	0.4324
Hypophosphataemia, yes v no	0.77	0.56–1.07	0.1149
Mean fluid balance, input–output (L)	1.595	1.21–2.11	0.001
Patient age, years	1.042	1.03–1.05	< 0.0001
Time from ICU admission to randomisation, days	1.002	1–1	0.0202
SOFA liver score, failure v normal	3.234	1.38–7.59	0.007
International normalised ratio	1.224	1.05–1.43	0.0094
Haemoglobin (g/L)	0.991	0.98–1	0.049

NA = not applicable. ICU = intensive care unit. SOFA = sequential organ failure assessment. * Only variables with $P < 0.05$ reported; other variables included treatment, mean daily calorie intake, mean daily fluid balance, positive mean fluid balance, fluid overload at randomisation, sex, severe sepsis at baseline, APACHE III score, SOFA respiratory, cardiovascular and renal scores, ⩾ 1 non-renal organ failure, urea, creatinine, potassium, bicarbonate, albumin, magnesium, pH level at randomisation, mechanical ventilation, estimated glomerular filtration rate.

Appendix 3. Table 3c. Multivariable logistic regression for 90-day mortality (patients who lived > 7 days)*

Variable and effect (discrete variable)	Odds ratio	95% CI	*P*
Intercept	NA	NA	0.581
Hypophosphataemia, yes v no	0.822	0.58–1.16	0.2668
Mean fluid balance, input–output (L)	1.731	1.27–2.36	0.0005
Patient age, years	1.039	1.03–1.05	< 0.0001
Patient weight, kg	0.986	0.97–1	0.03
Time from ICU admission to randomisation, days	1.002	1.00–1	0.0358
SOFA liver score, failure v normal	3.778	1.50–9.51	0.0048
International normalised ratio	1.181	1.01–1.38	0.0351
Haemoglobin (g/L)	0.989	0.98–1	0.0204

NA = not applicable. ICU = intensive care unit. SOFA = sequential organ failure assessment. * Only variables with $P < 0.05$ reported; other variables included treatment, mean daily calorie intake, mean daily fluid balance, positive mean fluid balance, fluid overload at randomisation, sex, severe sepsis at baseline, APACHE III score, SOFA respiratory, cardiovascular and renal scores, ⩾ 1 non-renal organ failure, urea, creatinine, potassium, bicarbonate, albumin, magnesium, pH level at randomisation, mechanical ventilation, estimated glomerular filtration rate.

Appendix 4. Sensitivity analysis: Cox model regression, death at Day 90*

Variable	Hazard ratio**	95% CI**	*P***
Hypophosphataemia, yes v no	0.631	(0.441–0.903)	0.0117
Calorie intake (per 500 kcal)	1.231	(1.066–1.422)	0.0046
Mean daily fluid balance (L)	1.536	(1.199–1.967)	0.0007
Positive mean fluid balance, yes v no	0.932	(0.609–1.426)	0.7442
Fluid overload at randomisation, yes v no	0.815	(0.605–1.099)	0.1797
Patient age	1.016	(1.004–1.029)	0.0115
Sex, male v female	1.086	(0.786–1.501)	0.6158
Severe sepsis at baseline	1.215	(0.879–1.680)	0.2376
APACHE III score	1.010	(1.003–1.016)	0.0034
SOFA respiration score, failure v dysfunction	3.379	(0.631–18.09)	0.1549
SOFA respiration score, normal v dysfunction	1.188	(0.494–2.856)	0.7001
SOFA cardiovascular score	0.869	(0.772–0.977)	0.0190
SOFA renal score, failure v dysfunction	0.764	(0.528–1.105)	0.1525
SOFA renal score, failure v dysfunction	0.818	(0.195–3.425)	0.7833
⩾ 1 non-renal organ failure (SOFA score 3–4), yes v no	1.377	(0.676–2.808)	0.3784
Last serum urea before randomisation (mmol/L)	1.036	(0.947–1.134)	0.4359
Last creatinine before randomisation (μmol/L)	0.998	(0.996–1.001)	0.1844
Potassium (mmol/L)	0.917	(0.762–1.102)	0.3553
Chloride (mmol/L)	0.983	(0.961–1.005)	0.1226
Bicarbonate (mmol/L)	0.989	(0.958–1.021)	0.4879
Urea (mmol/L)	0.988	(0.904–1.081)	0.8001
Creatinine (μmol/L)	1.000	(0.998–1.002)	0.8910
Albumin (g/L)	0.993	(0.972–1.015)	0.5407
Magnesium (mmol/L)	1.577	(1.075–2.312)	0.0197
pH	0.932	(0.239–3.629)	0.9193
Mechanical ventilation, yes v no	0.334	(0.066–1.693)	0.1853
Estimated glomerular filtration rate > 60 mL/min	0.961	(0.689–1.341)	0.8164

APACHE = Acute Physiology and Chronic Health Evaluation. SOFA = sequential organ failure assessment. * Adjusted for hypophosphataemia (yes/no) during study treatment; only patients who survived > 96 hours were included; model stratified by treatment allocation (intensive or conventional). ** Adjusted model; covariates for adjusted model include calorie intake, mean daily fluid balance, positive v negative fluid balance and oedema; baseline characteristics include patient age, sex, intensive care unit admission status (operative or non-operative), sepsis (yes or no), APACHE III score, organ failure (respiratory, coagulation, liver, cardiovascular or renal SOFA score) and prerandomisation blood phosphate concentration dichotomised at the median value.

Appendix 5. Kaplan–Meier curve for hypophosphataemia v no hypophosphataemia, excluding patients who died in the first 96 hours