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Inflammation, vitamin deficiencies and organ failure in critically ill patients

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SUMMARY

It is unknown whether biochemical vitamin deficiencies in critical illness are associated with severity of illness, organ dysfunction, inflammation or mortality. This nested cohort study recruited 98 patients admitted as emergencies to the intensive care unit, who had a stay of greater than 48 hours. Patient data were prospectively collected. Within the first 48 hours of admission, concentrations of C-reactive protein, vitamins A, E, B_1, B_{12} and folate were measured on arterial blood. These measures were then repeated at least once during the later (>48 hours) period of their stay. Seventy patients (71%) had completed vitamin studies eligible for inclusion in the analysis. Ten patients died (14.3%) during their hospital stay and mortality was associated with age, admission source and severity of illness scores. Vitamin B_{12} concentration was weakly associated with C-reactive protein concentrations on admission to the intensive care unit (r on days one and two=0.4 [P=0.002], 0.36 [P=0.04], respectively) and with the Sequential Organ Failure Assessment score between days two and four (Spearman's r=0.361 [P=0.04], 0.42 [P=0.02] and 0.48 [P=0.02], respectively). Vitamin A concentration was weakly associated with the C-reactive protein concentrations on days one and five (Spearman's r=-0.5 [P=0.001], -0.4 [P=0.03], respectively). Change in deficiency status of any of the vitamins over time in the first week of intensive care admission did not appear to influence mortality. We conclude that while weak correlations were identified between vitamins A and B_{12} and C-reactive protein and Sequential Organ Failure Assessment scores, the importance of these associations and their relationship to hospital mortality remain to be determined.

Key Words: critical illness, vitamins

Nutritional support in the critically ill is now considered a standard of care[1]. The optimal routes, timing and formulation remain controversial[2-4]. Current studies addressing the composition of antioxidants, vitamins and trace elements have resulted in the terms "immunonutrition" and "pharmaconutrition" being used to identify that pharmacological rather than replacement doses of many compounds are now being incorporated into the available preparations[5-8]. In addition to ensuring adequate caloric and protein intake, supplementation of micronutrients such as omega-3 fatty acids, glutamine, selenium and antioxidant vitamins has also been suggested to be important[6,7].

The association between vitamin concentrations and disease risk may be confounded by the effects of inflammation[9]. During episodes of infection, serum concentrations of retinol, carotenoids and the tocopherols are significantly decreased[10-12]. Sepsis, burns and trauma are associated with dramatic reductions in the concentrations of circulating antioxidant vitamins[13,14] and treatments during acute sepsis, such as continuous renal replacement therapy, are associated with increased losses of water-soluble compounds[15]. It is possible that vitamin deficiencies are a confounder of poorer outcomes because of their association with severe inflammation. While previous work has been done to examine the relationship between the acute phase response and vitamin concentrations in postoperative patients, this relationship has not been examined in a cohort of critically ill patients with a sustained inflammatory response[16].

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It is unknown whether vitamin requirements are increased in the critically ill or whether measured concentrations simply reflect the severity of systemic inflammation. If low vitamin concentrations are a 'marker' of severe systemic inflammatory response, then resolution of these low concentrations might indicate resolution of illness and response to therapy. Furthermore, patients with the lowest concentrations might therefore be at the greatest risk of death. In order to address these issues and to specifically examine the associations between vitamin concentrations, inflammatory markers and severity of illness in the critically ill, we designed a nested cohort study.

METHODS

This nested cohort study was conducted in a tertiary intensive care unit (ICU) of a university teaching hospital in Western Australia. Patients from all medical specialties are represented in this ICU, except for acute liver transplantation. After obtaining approval from the institutional Quality Improvement Division of the local ethics committee, 129 consecutive emergency and unplanned ICU admissions to the ICU over a period of two months were studied. We have previously published the relationship between the admission concentrations of vitamins and mortality in this cohort of patients[17]. In this sub-study, we included only patients who stayed in the ICU for over 48 hours.

The information collected included demographics, Acute Physiology and Chronic Health Evaluation II (APACHE II) score and Sequential Organ Failure Assessment (SOFA) score[18], diagnosis, source of admission, nutritional and vitamin supplementation supports provided and mortality outcome. Max SOFA was the maximum SOFA score of the patient within their first week in ICU and delta SOFA (Δ SOFA) was the difference between admission SOFA and max SOFA during the first seven days of ICU admission. 'Admission' arterial blood concentrations of C-reactive protein (CRP), red cell thiamine, red cell folate and also vitamins A, E and B_{12} were obtained on admission to ICU (within the first 48 hours) and were measured daily until the sixth day of ICU admission. Further measurements of these data were not planned after the sixth day of ICU admission. In this study, treating clinicians were blinded to the results of these blood tests and vitamin supplementation was based entirely on treating clinicians' clinical discretion.

To examine changes in vitamin status during ICU stay, the study comprised two periods: an 'admission' period (the first 48 hours of ICU stay) and a 'later' period (from 48 hours to day six). For each of the two study periods, patients were classified as deficient (D) if the vitamin concentration was below the reference ranges quoted for healthy adult subjects, or replete if they were above this (R). Thus, each patient could be classified as R-R, R-D, D-R or D-D when the status of vitamin deficiency in both periods was classified, respectively.

Unit nutrition and vitamin supplementation protocols

The standard enteral nutrition protocol is to start feeding as soon as possible if no contra-indications exist. The volume is usually started at 20 to 30 ml/hour and is increased until the usual daily calorie (30 Kcal/kg/day) and protein (1 to 1.5 g/kg/day) requirements are met. Gastric intolerance is not regarded as significant unless the gastric aspirate is over 300 ml and in this case, intravenous metoclopramide is initiated. If this fails, post-pyloric feeding is instituted. Total parenteral nutrition is reserved only for patients who have contraindications to enteral feeding. Supplementation with the water-soluble vitamins are not standardised in the unit. There is considerable inter-specialist variation in practice. General rules are that patients at risk of thiamine or folate deficiency (particularly those with a history of alcohol abuse, increased losses through continuous haemodialysis and patients with increased cellular turnover) receive either a single bolus dose on admission or daily intravenous supplements for five days. Concentrations are not routinely measured.

Vitamin assays

Vitamin A (alpha-carotene and beta-carotene) and vitamin E (alpha-tocopherol), were extracted from serum or plasma, along with vitamin E acetate as internal standard, into hexane. The concentrations were measured by high-performance liquid chromatography on a programmable wavelength detector and compared with known standards[19].

Red-cell thiamine concentrations (vitamin B_1) were measured using a direct microbiological thiamine assay, employing a chloramphenicol resistant *Lactobacillus fermenti* strain as previously described[20]. Red-cell folate concentrations were determined by competitive immunoassay using the Immunolite 2000® kit. Serum vitamin B_{12} concentrations were determined by enzyme-linked immunosorbent assay using the Immunolite 2000® kit. Serum CRP concentrations were measured by an immunoenzyme analyser (Hitachi 917, Tokyo, Japan). The normal ranges of the vitamins measured are thiamine: 190 to 400 nmol.l^{-1}, folate:

260 to 1450 nmol.l^{-1}, B_{12}: 160 to 725 pmol.l^{-1}, vitamin A: 1 to 4 μmol.l^{-1} and vitamin E: 18 to 46 μmol.l^{-1}.

For the examination of thiamine and folate concentrations, we limited the analysis to patients who did not receive supplementation with these vitamins during their stay in ICU.

Statistics

Categorical variables and continuous variables with skewed distributions were analysed by χ^2 and Mann-Whitney tests, respectively. Non-parametric Spearman's rank correlation coefficient was used to assess the correlations between vitamin concentrations and indices of severity of illness, including the APACHE II score, SOFA score and CRP concentrations. A P value <0.05 was considered significant and all statistical tests were performed with SPSS for Windows (version 15, 2001, SPSS Inc., Chicago, IL, USA).

TABLE 1
Differences between survivors and non-survivors

	All patients n=70	Died n=7	Survived n=63	*P* value
Age, median (IQR)	48 (30-71)	72 (62-79)	48 (30-67)	0.035†
Gender (M/F)	48/22	5/2	43/20	1.0‡
APACHE II score, median (IQR)	19 (14-24)	24 (21-29)	18 (14-22)	0.008†
Admission SOFA, median (IQR)	8 (5-10)	11 (10-15)	7 (5-9)	0.008†
Max SOFA, median (IQR)	9 (6-11)	13 (11-22)	9 (5-11)	0.014†
Δ SOFA-max, median (IQR)	1 (0-2)	2 (0-2)	1 (0-2)	0.469†
CRP, median (IQR), mg.l^{-1}	69 (11-188)	105 (19-305)	69 (10-170)	0.435†
Albumin, median (IQR), g.l^{-1}	31 (26-38)	31 (24-34)	31 (26-38)	0.635†
Enteral feeding, n (%)	41 (58.6)	3 (32.9)	38 (60.3)	0.438‡
Diagnostic subgroups, n (%)				0.504§
Multi-trauma	12 (17.1)	0	12 (19)	
Traumatic brain injury	6 (8.6)	1 (14.3)	5 (7.9)	
Neurosurgical	10 (14.3)	1 (14.3)	9 (14.3)	
Sepsis	8 (11.4)	1 (14.3)	7 (11.1)	
Emergency surgery	11 (15.7)	1 (14.3)	10 (15.9)	
Poisoning	7 (10)	0	7 (11.1)	
Medical*	14 (20)	2 (28.6)	12 (19)	
Burns	2 (2.9)	1 (14.3)	1 (1.6)	
Admission source, n (%)				0.015§
Emergency department	27 (38.6)	2 (28.6)	25 (39.7)	
Wards	8 (11.4)	3 (42.9)	5 (7.9)	
Other hospital	12 (17.1)	1 (8.3)	11 (17.5)	
Operating theatre	23 (32.9)	1 (14.3)	22 (34.9)	
Length of stay, n (%)				0.361§
3 days	10 (14.3)	2 (28.6)	8 (12.7)	
4 days	11 (15.7)	2 (28.6)	9 (14.3)	
5 days	9 (12.9)	0	9 (14.3)	
6 or more	40 (57.1)	3 (42.8)	37 (58.7)	

† Mann-Whitney U-test, ‡ Fisher's exact test, § Pearson χ^2 value. APACHE=Acute Physiology and Chronic Health Evaluation, SOFA=Sequential Organ Failure Assessment, max=maximum, Δ=delta, CRP=C-reactive protein concentration in mg/l. * Medical diagnoses comprising cardio-respiratory failure, hepatic failure, diabetic comas and seizure disorders.

RESULTS

Among a total of 129 patients, 98 had an ICU stay of three or more days and of these 70 (71%) had complete vitamin data throughout the whole first days of ICU admission and were eligible for further analysis. Ten patients died (14.3%) during their hospital stay (seven of those in the ICU) and hospital mortality was significantly associated with age, APACHE II score, admission and max SOFA scores, and admission source (Table 1). Patients admitted to the ICU from the wards were least likely to survive but diagnostic subgroup and length of stay were not significantly associated with mortality.

When the relationships between vitamin concentrations and severity of illness and inflammation were assessed (Figures 1 to 4), only two vitamins (vitamin B_{12} and vitamin A) showed a weak correlation with the severity of illness or inflammation as measured by SOFA score and CRP. Vitamin B_{12} concentration was weakly associated

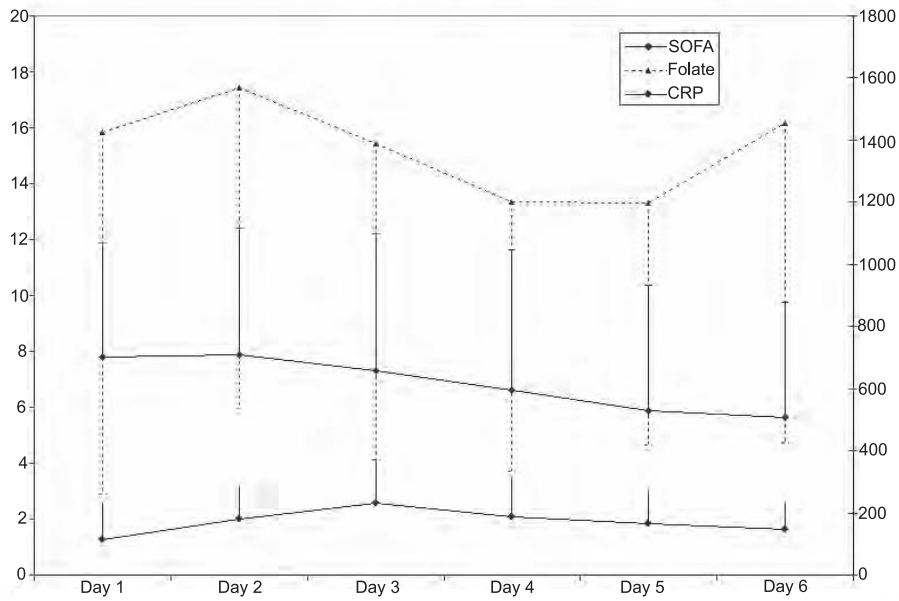

FIGURE 1: Changes in concentrations of folate, CRP and SOFA scores. CRP and folate are plotted against secondary (right) axis. See text for units.

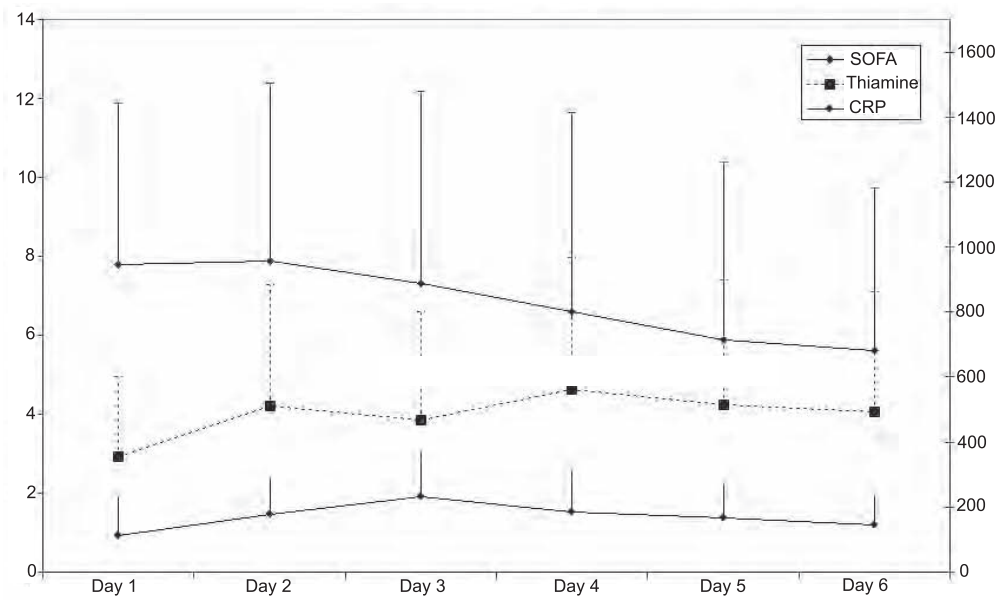

FIGURE 2: Changes in concentrations of thiamine, CRP and SOFA scores. CRP and thiamine are plotted against secondary (right) axis. See text for units.

with CRP concentrations on admission to ICU (Spearman's r on days one and two=0.4 [P=0.002], 0.36 [P=0.04], respectively) and with the SOFA score between days two and four (Spearman's r=0.361 [P=0.04], 0.42 [P=0.02] and 0.48 [P=0.02], respectively). Vitamin A concentration was weakly associated with the CRP concentrations on days one and five (Spearman's r=-0.5 [P=0.001], -0.4 [P=0.03], respectively). None of the reported vitamin concentrations had any significant correlation to the APACHE II scores. Changes in vitamin status for each of the five vitamins are shown in Table 2. When the relationship between mortality and four different states of different vitamin deficiencies (D-D, D-R, R-R, R-D) were assessed by univariate analysis, none of the vitamins were

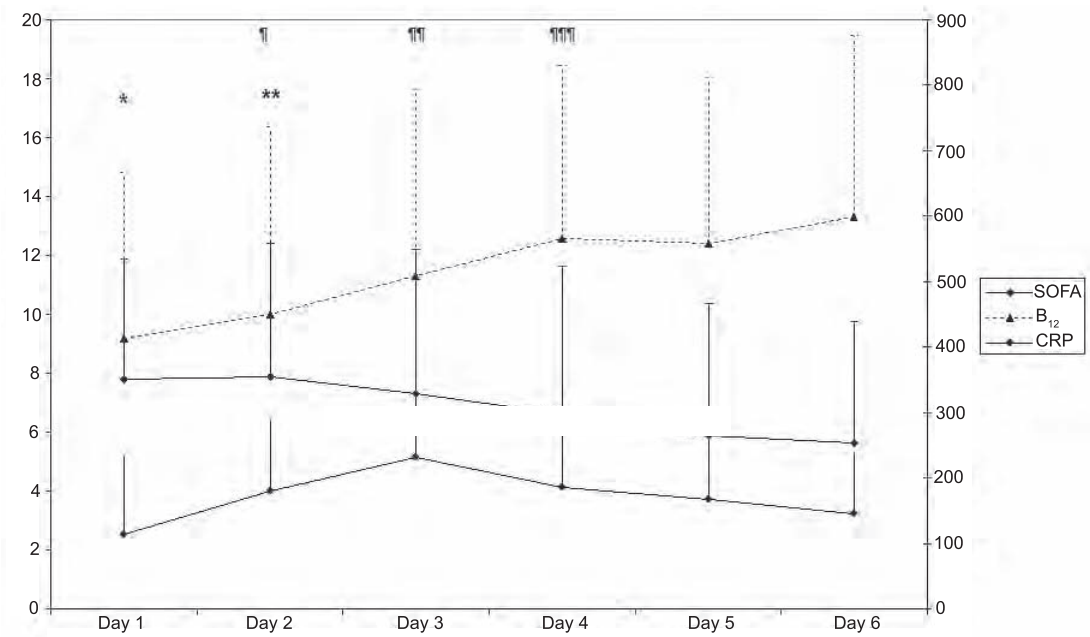

FIGURE 3: Changes in concentrations of vitamin B_{12}, CRP and SOFA scores. CRP and B_{12} are plotted against secondary (right) axis. See text for units. Spearman's r on days one* and two**=0.4 (P=0.002), 0.36 (P=0.04) for B_{12} and CRP. Spearman's r on days two¶, three¶¶ and four¶¶¶=0.361 (P=0.04), 0.42 (P=0.02) and 0.48 (P=0.02) for B_{12} and SOFA score.

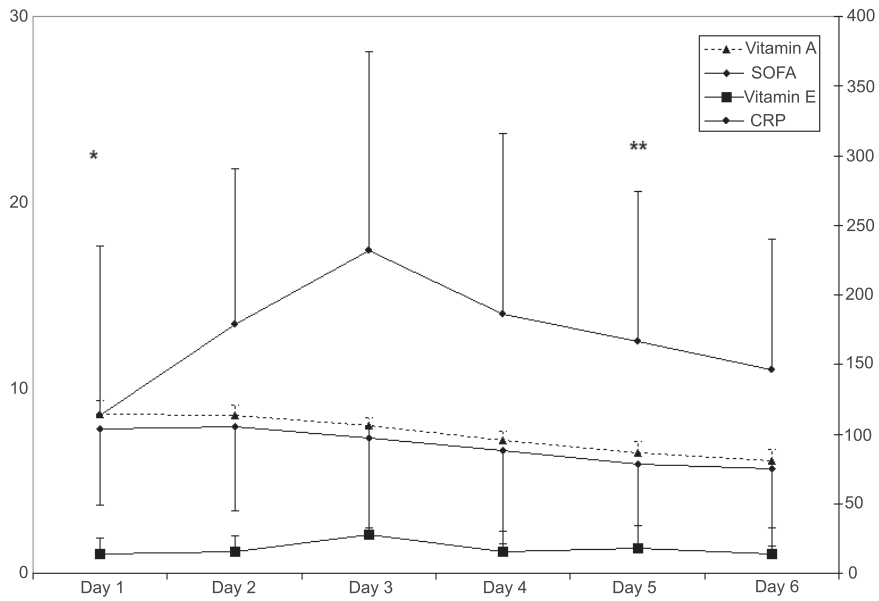

FIGURE 4: Changes in concentrations of vitamins A and E, CRP and SOFA scores. CRP is plotted against secondary (right) axis. See text for units. Spearman's r on days one* and five**=-0.5 (P=0.001), -0.4 (P=0.03), respectively for vitamin A and CRP.

significantly associated with mortality. When compared to those patients who did not have missing data, the patients that were excluded due to missing data had a shorter length of ICU admission and a lower max SOFA score (Mann-Whitney U-test, $P=0.001$ and 0.031, respectively). There were no other differences identified.

TABLE 2
Change in vitamin status and hospital mortality

Vitamin A, n=67	Total†	Died‡	Survived‡	*P* value§
Entire cohort	67	10	57	0.504
R-R	12 (17.9)	2 (16.7)	10 (83.3)	
R-D	16 (23.9)	4 (25)	12 (75)	
D-D	35 (52.2)	4 (11.4)	31 (88.6)	
D-R	4 (6)	0	4 (100)	
Vitamin E, n=62	Total	Died	Survived	*P* value§
Entire cohort	62	9	53	0.225
R-R	32 (51.6)	4 (12.5)	28 (87.5)	
R-D	4 (6.5)	2 (50)	2 (50)	
D-D	18 (29)	2 (11.1)	16 (88.9)	
D-R	8 (12.9)	1 (12.5)	7 (87.5)	
Thiamine (B_1)*, n=38	Total	Died	Survived	*P* value§
Entire cohort	38	7	31	0.164
R-R	31 (81.6)	5 (16.1)	26 (83.9)	
R-D	4 (10.5)	1 (25)	3 (75)	
D-D	2 (5.3)	0	2 (100)	
D-R	1 (2.6)	1 (100)	0	
Folate*, n=23	Total	Died	Survived	*P* value§
Entire cohort				N/A
R-R	23	5 (21.7)	18 (78.3)	
R-D	0	0	0	
D-D	0	0	0	
D-R	0	0	0	
Vitamin B_{12}, n=70	Total	Died	Survived	*P* value††
Entire cohort	70	10	60	0.146
R-R	65 (92.9)	8 (12.3)	57 (87.7)	
R-D	0	0	0	
D-D	0	0	0	
D-R	5 (7.1)	2 (40)	3 (60)	

† Percentage refers to total group number. ‡ Percentage refers to row percentage within the individual vitamin status group. § Pearson χ^2 value. †† Fisher's exact test. R-R=replete on admission and remained so during intensive care unit (ICU) stay, R-D=replete on admission but subsequently became deficient during ICU stay, D-R=deplete on admission but subsequently became replete during ICU stay, D-D=deplete on admission and remained so during ICU stay. * Analysis restricted to those patients who did not receive thiamine or folate supplementation during their stay.

DISCUSSION

The question of whether vitamin deficiencies independently exacerbate the outcome from critical illness and whether measurable concentrations of these compounds reflect disease severity or inflammation has not been addressed prior to this study. We were unable to demonstrate any association between the concentrations of vitamins A, E, B_1, B_{12} or folate with APACHE II score or the admission SOFA score in unplanned admissions to the ICU. Vitamin B_{12} concentrations appeared to reflect the inflammatory response as determined by CRP concentrations on the first two days of admission and SOFA scores on days two to four. Vitamin A concentrations correlated negatively with CRP on days one and day five. We did not identify any relationship of thiamine, folate and vitamin E concentrations to either organ failure scores or CRP concentrations during the six-day study period. These findings mirror our previous work examining the association of admission concentrations with ICU mortality[17]. The major difference is that in this cohort with a stay longer than 48 hours, vitamin E concentrations no longer correlated with CRP concentrations. This may be explained by the fact that eight patients died within the initial 48-hour period and were therefore ineligible to be included in this cohort. They had greater CRP concentrations and severity of illness scores on admission. This may mean that vitamin E concentrations reflect systemic inflammation only in the most critically ill patients admitted to ICU.

The biphasic association of vitamin A concentrations with CRP on days one and five is difficult to explain in the context of critical illness. The recently elaborated influence of vitamin A on many components of the human immune system[21] is intriguing. Whether adverse immune effects are the result of the consumption of this endogenous antioxidant that occurs in critical illness, particularly sepsis, remains to be determined, and it would require a much larger observational trial than ours to determine this endpoint[13,22-24]. It may also be that the relationship of vitamin A concentrations to inflammatory responses change over time and that after the initial massive consumption that occurs in sepsis, the later changes are reflective of other metabolic changes, as has been suggested by a recent study[25]. An additional question that needs to be answered is whether supplementation

titrated to serum concentrations would attenuate the changes in oxidative stress seen in studies in the critically ill. Inadequate intake during critical illness does exacerbate the severity of oxidative stress experienced by these patients[26]. One trial of antioxidant vitamin supplementation demonstrated an improvement in outcome (although baseline mortality was very high in this study)[27,28].

Our findings of an association between B_{12} concentrations and organ failure scores and CRP concentrations are interesting and novel. The association with CRP on days one and two may reflect the disease severity that becomes manifest on days two to four as increasing organ failure scores. There is little literature on the role of this vitamin in critical illness, but one previous study observed higher B_{12} concentration in non-survivors[29] and this is also consistent with our data. Some work has also been done in other groups of severely ill patients. B_{12} supplementation of haemodialysis patients decreases high-sensitivity-CRP concentrations[30]. Supplementation with antioxidant or B-group vitamins produces equivalent decreases in oxidative stress and CRP in acute stroke patients[31], but in healthy volunteers, B_{12} supplementation did not affect CRP[32]. This is the first time that this association has been demonstrated in the critically ill for vitamin B_{12} and certainly warrants further investigation.

We proposed to examine whether a change in vitamin status was associated with an increase in mortality. We postulated that if vitamin concentrations were representative of the inflammatory process, then patients with increasing inflammation would demonstrate changes in concentrations that would be reflective of improvement in clinical condition. Rather than use actual concentrations we classified patients into one of four categories. Our findings are inconclusive and did not demonstrate an association between change in deficiency status over time and hospital mortality.

This is a small observational study and is therefore prone to bias. Our cohort represents a heterogeneous group of diseases requiring intensive care and individual group sizes are too small to make any meaningful inferences. The results of the vitamin assays were not available to the treating clinicians and therefore did not influence the decision to supplement with vitamins or to feed patients, and should not therefore have impacted upon outcome. All patients who received folate or thiamine supplementation were excluded from consideration for the role of deficiencies of these vitamins. This should guarantee that the possible combination of clinician assessment and disease would not skew the results. Despite this, unmeasured residual confounding is highly possible and may have affected our results.

We chose to prospectively examine patients admitted to emergency as they tend to have a greater severity of illness and a higher attendant mortality[33]. Of the 98 patients who stayed in the ICU longer than two days, we had complete vitamin data on only 70. This was due to errors in sampling time, laboratory processing and haemolysis of a number of samples, but may have eroded the power of the study. These patients had a shorter duration of ICU stay and a lower max SOFA score and thus represented a less critically ill group of patients, but did not differ in overall mortality. Although this was a source of self-selection bias, it actually resulted in our analysis being limited to those patients with a greater degree of organ dysfunction. Fortuitously, this was the group of patients in which we expected to observe the associations, if in fact they existed.

We excluded from analysis patients who received empirical thiamine or folate supplementation. We chose to use the deficiency 'status' of patients rather than the actual concentrations of vitamins at each time-point in the analysis. Since none of the patients had conflicting vitamin assays during either the admission or later period, it was a robust method to use. We used CRP as a marker of acute phase response and inflammation, and perhaps measures of inflammatory cytokines would have been more informative[34]. CRP is however, a useful tool, as CRP concentrations have been previously used to predict organ failure and mortality in the critically ill[35] and hospital mortality on discharge from ICU[36]. Future studies may examine the relationship between vitamin concentrations and specific cytokines (both pro- and anti-inflammatory) to further elucidate the relationships that we have identified.

In summary, this small preliminary study has shown some weak correlations between severity of illness and vitamin B_{12} concentration, in a heterogenous cohort of emergently admitted critically ill patients, which have not been previously recognised. A biphasic negative association was also demonstrated for vitamin A. No associations were identified for the other vitamins. These data suggest that vitamins B_{12} and A may be influenced by the inflammatory response in the critically ill. The significance of this association needs to be confirmed by a large observational study. Whether interventions aimed at modifying vitamins B_{12} and A will change the process of inflammation and organ

function remains speculative and needs to be confirmed by a well-powered randomised controlled trial.

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