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High vitamin B12 levels are not associated with increased mortality risk for ICU patients after adjusting for liver function: a cohort study

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Abstract

Background and Aims—Recent research has suggested that high vitamin B12 levels may be associated with increased mortality after ICU admission. However, it is known that impaired liver function may lead to elevated B12 since B12 is metabolized through the liver, and therefore high B12 levels may serve as a proxy for poor liver function. The aim of this study is to assess the

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FC drafted the manuscript, contributed to the study design, collected the data, analyzed and interpreted the data, and provided critical revisions to the manuscript. KL conceived of the study, contributed to the study design, provided data interpretation, and contributed to critical revisions of the manuscript. SA and DD contributed to the study design, data acquisition, data interpretation, and critical revisions of the manuscript. CJM contributed to the in study conception and design, data interpretation, critical revisions of the manuscript, and also supervised the study. All authors read and approved the final manuscript.

Conflict of interest
The authors have no conflicts of interest to disclose.

impact that liver function and liver disease have on the relationship between high vitamin B12 levels and mortality in the ICU.

Methods—We performed an observational cohort study using ICU data that were collected from patients admitted to four ICU types (medical, surgical, cardiac care and cardiac surgery recovery) in one large urban hospital from 2001 to 2008. We analyzed the medical records of 1,684 adult patients (age ≥ 18 years) who had vitamin B12 and liver function measurements up to 14 days prior to ICU admission or within 24 hours after admission.

Results—While we found an association between high B12 and mortality when we did not control for any potential confounders, after we adjusted for liver function and liver disease, no significant association existed between B12 and mortality using multivariable logistic regression (30-day mortality: OR=1.18, 95% CI 0.81 to 1.72, p=0.3890; 90-day mortality: OR=1.20, 95% CI 0.84 to 1.71, p=0.3077).

Conclusions—Elevated B12 levels are not a significant predictor of mortality after ICU admission when liver function is controlled for, and may instead be a proxy for poor liver function.

Keywords

Vitamin B12; critical care; liver function; mortality; intensive care unit; liver disease

1. Introduction

Much of the clinical research on vitamin B12 (cobalamin) has focused on B12 deficiency, but less is known about the effects of elevated B12 levels. Several studies have looked at B12 and mortality in elderly populations: some have found an association between high B12 levels and mortality[1–6] and others have not[7, 8]. When studying B12, it is important to account for liver function and liver disease, as impaired liver function is known to affect B12 levels, primarily because B12 is metabolized by the liver[9, 10]. Although some of the above studies did adjust for albumin (ALB)[1, 4, 5], none of them explicitly adjusted for a full liver function panel in a multivariable model. Lin et al[11] found that elevated B12 levels were associated with increased mortality in hepatocellular carcinoma patients (N=90). Dou et al[12] studied N=149 patients with liver failure and found that B12 levels were positively correlated with mortality after adjusting for the Model for End-stage Liver Disease (MELD) score[13]. However, neither study focused on ICU patients.

Few studies have looked at elevated vitamin B12 levels and mortality for ICU patients. Olivieri et al[14] conducted a study of 250 elderly patients with acute myocardial infarction admitted to a cardiac care unit (CCU) and found that vitamin B12 was not a significant predictor for cardiovascular-related mortality. Corcoran et al[15, 16] studied on the effect of vitamin B12 levels on mortality in the ICU and found that there was no association between B12 deficiency and mortality, and that weak correlations existed between B12 levels, CRP, and Sequential Organ Failure Assessment (SOFA) score, a measure of acuity in the ICU[17]. Manzanares and Hardy[18] conducted a review of studies on the relationship between B12 and mortality and noted that the data on B12 and mortality for critical care patients was scarce.

In a recent study, Sviri et al[19] examined B12 in the medical ICU (MICU), N=663, and found that log B12 levels were linearly positively correlated with 90-day mortality risk after adjusting for several other factors including cirrhosis and chronic liver disease but not measures of liver function (OR 1.7, 95% CI 0.9 to 3.1, p<0.05). We hypothesize that poor liver function may be the underlying cause of both the high B12 levels and increased mortality and, furthermore that B12 levels are not linearly associated with mortality risk, i.e., mortality risk may be elevated for patients with either deficient or high B12 levels. In

this study, we investigate whether there is a relationship between high B12 and mortality after adjusting for liver function and liver disease.

2. Materials and methods

We performed an observational cohort study based on electronic medical records that were collected during the course of clinical ICU care and subsequently de-identified. Our study population consisted of all adult patients that had B12 values and liver function values (ALB, ALT, AST, ALP, PT, and TB) recorded in version 2.6 of the Multiparameter Intelligent Monitoring in Intensive Care II (MIMIC-II)[20] database. MIMIC-II contains a wide variety of clinical and demographic information on approximately 24,000 adult patients 18 years or older that were admitted to the ICU at Boston's Beth Israel Deaconess Medical Center from 2001 to 2008. The database is freely available; any researcher who accepts the data use agreement and has completed human subjects training can apply for permission to access the data. We did not need patient consent as all of the data are de-identified. All of the authors have completed human subjects training, and we conducted the study under National Institutes of Health Institutional Review Board exemption number 4193.

We used lab values, including B12 values, recorded from 14 days before ICU admission up to 24 hours after admission. Other variables, such as comorbidities, were based on combinations of International Classification of Diseases, ninth revision (ICD-9) diagnosis codes, which are assigned at the end of the hospital stay.

There is no consensus on the definition of high or elevated B12. Previous studies have chosen a variety of levels to represent high or very high B12 (pmol/l) levels. Some examples include: 664.2[19]; 513[1]; 700 (high) and 1500 (very high)[11]; and 601 (high) and 1000 (very high)[10]. Excess B12 is either stored in the liver, present in the blood without any adverse effects, or excreted. There are no studies investigating the potential clinical effects of high B12 because, in general, there are no known adverse effects caused by elevated B12. It is probably for this reason that there is no cutoff for high B12 based on clinical outcomes. We chose a level of 1000 pmol/l because we wanted to be sure of identifying a cohort with abnormally high levels of B12 that may potentially have adverse clinical outcomes. With regard to B12 deficiency, the cut point for clinical B12 deficiency is ≤ 148 pmol/l[21], although even the definition of deficiency is an area of debate[22, 23]. We chose to categorize the B12 levels into deficient (≤ 148 pmol/l), mid-range (> 148 pmol/l to ≤ 1000 pmol/l), and high (> 1000 pmol/l) groups. By doing so, we were able to estimate the mortality risk for elevated B12 compared to mid-range or deficient levels, and we did not need to make the assumption that mortality risk increases linearly with B12 levels.

We modeled two outcomes: death 30 days and 90 days after admission to the ICU. We used four groups of independent variables in our analysis: vitamin B12 category, demographics, other potential confounders, and liver disease and function. Demographic information included age at admission, gender, race, and insurance coverage. We included the following variables to adjust for liver function: ALT, AST, TB, ALP, ALB, PT, liver cancer, and non-cancerous liver disease. In general, we categorized laboratory tests using quartiles (except B12) because the laboratory values did not appear to have a linear relationship with mortality. The diagnosis of non-cancerous liver disease was defined using the following ICD-9 codes: 570 (liver necrosis), 571.5–9 (chronic liver disease and cirrhosis, excluding the 571.0–571.3 codes explicitly mentioning alcoholic liver disease as we have added alcoholism to the analysis separately), 572* (liver abscess and sequelae of chronic liver disease), and 573* (other disorders of the liver, including hepatitis and hepatopulmonary syndrome), where * indicates the group of codes that begin with that sequence. Liver cancer

was defined using ICD-9 codes 155* (primary liver and intrahepatic bile duct cancer) and 197.7 (secondary liver metastases). Elevated liver function test values were not part of the definition of liver disease; liver function tests were added to the analysis separately.

We considered several other potentially confounding factors for inclusion in the final model. We used the Simplified Acute Physiology Score (SAPS)[24] – with the age component removed so we could observe the effect of age separately – in order to account for the patient's acuity during the first 24 hours of the ICU stay. We considered other ICU-related factors such as first service unit – CCU, CSRU (cardiac surgery recovery unit), MICU, and SICU (surgical ICU) – and non-liver lab tests such as serum creatinine, hemoglobin, and mean corpuscular volume (MCV). We also collected information on B12 supplementation and other interventions (dialysis, total parenteral nutrition (TPN), and inotropic support). Finally, we considered multiple disease conditions for inclusion in the final model: alcoholism, sepsis, respiratory disease, myeloproliferative disease, stroke, coronary artery disease (CAD), hypertension, other cardiovascular disease conditions not captured by any other comorbidities (Other CVD), immunocompromised status, gastrointestinal (GI) hemorrhage, and neuropsychiatric disorders. These potentially confounding variables were considered as candidates in the final model for a variety of reasons, either because they affect or are related to B12 levels (myeloproliferative disease, B12 supplementation, TPN, creatinine, hemoglobin, MCV), are known to affect liver function (alcoholism), or identify common subpopulations in the ICU (first service unit, CAD, stroke, hypertension, other CVD conditions not already captured by other information). We also considered for inclusion variables associated with chronic conditions that are known to be associated with higher mortality in the ICU, namely, dialysis, immunocompromised status, and respiratory disease. These chronic conditions are used in the APACHE-II (acute physiology and chronic health evaluation) score[25] which is an alternative to the SAPS score for measuring acuity in the ICU but, unlike the SAPS score, includes variables for pre-existing conditions. Most comorbidities were captured using ICD-9 codes, except immunocompromised status and alcoholism, which were supplemented with a manual review of the notes. Finally, we also collected variables included in the study by Sviri et al[19] (inotropic support, sepsis, GI hemorrhage, neuropsychiatric disorders).

With regard to B12 supplementation, four patients were known to have received a B12 supplement prior to B12 measurement during their hospital stay. However, we did not have information about B12 supplementation prior to ICU admission for any patient and therefore it is possible that other patients also received B12 supplements prior to measurement. For this reason, we chose to keep the four patients who received B12 supplements in the ICU prior to B12 measurement in the cohort.

2.1 Statistical analysis

For the descriptive statistics comparing the independent variables across B12 levels in Tables 1 and 2, we used nonparametric versions of standard statistical tests in order to accommodate small sample sizes in some subgroups and non-normal data. We used nonparametric ANOVA (Kruskal-Wallis test[26]) to compare continuous variables, such as laboratory values, and Fisher's exact test to compare categorical variables, such as gender and race. Where appropriate, we used the Jonckheere-Terpstra test of trend for continuous predictors[27] and the Cochran-Armitage chi-squared test for trend of proportions to investigate whether the predictors had an increasing or decreasing trend with increasing B12 levels[28]. A p-value <0.05 was considered significant for all hypothesis tests.

We investigated the relationship between B12, mortality, and liver disease and function by fitting a multivariable logistic regression model that adjusted B12 measurement and liver disease and liver function, as well as other potential confounders. This model is referred to

as the "fully-adjusted" model. We attempted to account for potential confounders, as well as factors adjusted for in the multivariable model of Sviri et al[19]. In order to create the fully-adjusted model, we first fitted a model with all B12, demographic, and potentially confounding variables, and then we removed from the model all variables with $p<0.05$ (except B12 and liver function and liver disease variables, as they relate to our primary hypothesis).We performed a global likelihood ratio test to confirm that these variables did not significantly contribute to the model as a group.

In addition, in order to illustrate the attenuation effect on mortality risk due to B12 level, we also showed the results from the intermediate model building steps (from consecutively adding B12, demographic variables, other potential clinical confounders, and finally liver disease and liver function variables). We label these intermediate models, Models 1–3, with "Model 4" referring to our fully-adjusted model. We repeated this analysis for 30-day and 90-day mortality. Collinearity of the independent variables was assessed by using the variance inflation factor (VIF) and generalized variance inflation factor (GVIF)[29] for variables with >2 degrees of freedom (df) (i.e., more than 2 categories); no VIF or $GVIF^{1/(2df)}$ was >2. All data analysis was performed using the R statistical software[30].

We conducted two sensitivity analyses. The first, was an attempt to replicate the results of the Sviri[19] study. The Sviri study[19] was comprised of MICU patients only, and in that study only the 90-day mortality model found a significant relationship between B12 and mortality. For this reason we built an additional model for 90-day mortality based only on MICU patients in order to be able to make more direct comparison to the Sviri study. We applied the same model building algorithm that we used to build the fully-adjusted models (Model 4) to the MICU subset. In the second sensitivity analysis we used different B12 cutoffs for low and high B12, in order to observe if this affected the results. We used 200 pmol/l (the threshold for subclinical deficiency[22]) for low B12 and 664 pmol/l (an upper threshold used by a previous study[19]).

Finally, we also performed a univariate analysis to compare the patients in our study to the rest of the patients in the MIMIC-II database (i.e., the patients without B12 values or values for the liver function tests) in order to investigate possible sources of selection bias (see Table 5). Compared to the rest of the adult patients in the MIMIC-II database, the patients in the B12 study tended to have more comorbidities, but typically there was no more than a 5% difference in prevalence between the B12 and non-B12 groups, with the exception of alcoholism (17.8% compared to 3.5%), sepsis (15.1% compared to 9.7%), liver disease (13.7% compared to 6%), CVD conditions not already captured by other variables (58.2% compared to 50.6%), immunocompromised status (28.1% compared to 6.5%) and neuropsychiatric disorders (32.4% compared to 25.4%). There were also a higher proportion of patients in the MICU in our study than in the rest of the MIMIC-II database (55.6% for the B12 study group compared to 35.8% for the non-B12 group) and less SICU patients (7.5% for the B12 group compared to 27.7% for the non-B12 group). Both sets of patients tended to have similar liver function measures and SAPS scores (a median of 12 for the B12 study patients compared to 10 for the rest of the ICU population).

3. Results

3.1 Univariate analysis

Univariate descriptions of the relationship between B12 levels, the mortality outcomes, demographics, and liver function are given in Table 1. The high B12 group had higher 30-day mortality than other groups and the morality rate increased with increasing B12 (mortality rate for the high B12 group was 32.7% compared to 8.1% and 14.6% for the deficient and mid-range B12 groups, $p<0.0001$). Similar results were found for 90-day

mortality (mortality rate for high B12 group was 40.3% compared to 10.8% and 19.9% for the deficient and mid-range groups, p<0.0001). The differences in age across the B12 groups were statistically significant, but not clinically important (median age 64.4 years for high B12 compared to 66.8 and 68.2 years for the deficient and mid-range groups, p<0.0001). The B12 groups had a similar proportion of females (46.0% compared to 37.8% and 39% for deficient and mid-range groups, p=0.0785). All the liver function measures and rates of liver disease and cancer generally increased with increasing B12 levels with the exception (as might be expected) of albumin which decreased with increasing B12 levels (p<0.0001 for all). These results are in agreement with Dou et al[12], Lin et al[11], Ermens et al[9] and others who found that poor liver function is associated with elevated B12 levels.

The univariate examination of the relationships between B12 and the remaining potentially confounding factors is given in Table 2. SAPS were similar for all B12 groups (for example, median SAPS was 14 for the deficient B12 group and 12 for both the mid-range and high B12 groups, p=0.1260). However, in general, high B12 levels appeared to be associated with conditions and factors usually associated with poorer health compared to deficient and mid-range B12 groups. The high B12 group had proportionately more patients in the MICU (75.0% versus 35.1% and 51.8% for the deficient and midrange groups, respectively, p<0.0001) and less patients in the CCU and CSRU than other B12 groups (9.0% in CCU compared to 16.2% and 14.0% in the deficient and mid-range groups, p=0.0200, and 7.0% in the CSRU compared to 48.6% and 26.9% in the deficient and mid-range B12 groups). The proportion of elective admissions tended to be lower in the high B12 group (2% for high B12 compared to 24.3% and 10.9% for deficient and mid-range groups, p<0.0001), and the proportion of emergency admissions increased with increasing B12 (90.3% for high B12 compared to 75.7% and 81.7% for deficient and midrange, p=0.0002). Higher B12 levels were associated with longer lengths of stay (ICU LOS: median 2.8 days for high B12 compared to 2.4 and 2.2 for deficient and mid-range groups, p=0.0025; Hospital LOS: median 13.5 days for high B12 compared to 7 and 9 days for deficient and mid-range groups, p<0.0001).

There were statistically significant, but not necessarily clinically important, trends for all non-liver lab values across the B12 groups (higher B12 levels were associated with higher creatinine, folate, and MCV levels and lower hemoglobin levels). As might be expected, the deficient B12 group had the highest rate of B12 supplementation compared to the other B12 levels (21.6% compared to 3.8% and 5% for mid-range and high B12 groups, p=0.0002). With regard to other procedures, only rates of dialysis tended to increase as B12 increased (16.7% for high B12 compared to 9.2% and 0% for mid-range and deficient B12, p<0.0001). Finally, the high B12 group tended to have higher rates of alcoholism (p<0.0001), sepsis (p<0.0001), myeloproliferative disease (p<0.0001), and immunocompromised status (p=0.0001) and lower rates of CAD (p<0.0001), Other CVD (p=0.0104), and hypertension (p<0.0001).

3.2 Multivariable models

A summary of Models 1 to 4 are given in Table 3. Model 1 gives the unadjusted estimate of the mortality risk for high and deficient B12 levels compared to mid-range levels, repeated for mortality at 30 and 90 days after ICU admission. Deficient B12 was not significantly different to the mid-range B12 group for any of the models. For the high B12 group, the unadjusted risk was approximately 2.7–2.8 times that of mid-range B12 group (for 30-day: OR 2.83, 95% CI 2.13 to 3.76, p<0.0001; for 90-day: OR 2.72, 95% CI 2.08 to 3.55, p<0.0001). Model 2 represents the risk of B12 adjusted for demographic variables (age, gender, race, and insurance type). The mortality risks for the high B12 group in Model 2 were similar to the unadjusted risks (for 30-day: OR 3.12, 95% CI 2.31 to 4.20, p<0.0001; for 90-day: OR=3.09, 95% CI 2.33 to 4.09, p<0.0001). When we added other potential non-

liver related clinical confounders to Model 2 to create Model 3, the mortality risk for the high B12 patients compared to midrange patients dropped to an approximately 100% increased risk but this difference was still significant compared to mid-range B12 patients (for 30-day: OR 1.93, 95% CI 1.38 to 2.72, p=0.0001; for 90-day: OR=1.97, 95% CI 1.43 to 2.71, p<0.0001).

However, after we adjusted for liver disease and liver function (Model 4) in addition to all the other factors, the mortality risk for the high B12 group decreased to an approximately 20% increased risk compared to mid-range patients, and the difference between high B12 and mid-range B12 was no longer significant (for 30-day: OR 1.18, 95% CI 0.81 to 1.72, p=0.3890; for 90-day: OR=1.20, 95% CI 0.84 to 1.71, p=0.3077). The details of the fully-adjusted model (Model 4) are given in Table 4. Significant predictors for the 30-day mortality model were age (p<0.0001), insurance (p=0.0128), SAPS (p<0.0001), first service unit (p<0.0001), stroke (p<0.0001), immunocompromised status (p<0.0001), alcoholism (p=0.0244), inotropic support (p=0.0331), TB (p=0.0335), ALP (0.0156), and ALB (p<0.0001). As mentioned previously, high B12 was not a significant predictor in the model (p=0.3886) and neither was B12 overall (p=0.6626).

For 90-day mortality we saw broadly similar results, with some difference in the selection of the confounding variables. Again, high B12, deficient B12, and B12 as a whole were not significant (p=0.3148, p=0.6774, and p=0.5719, respectively). Significant predictors in the 90-day mortality model were: age (p<0.0001), dialysis (p=0.0062), first service unit (p<0.0001), sepsis (p=0.0330), respiratory disease (p=0.0060), stroke (p<0.0001), CAD (p=0.0037), CVD (p=0.0354), immunocompromised status (p<0.0001), MCV (p=0.0455), TB (p=0.0165), ALP (p=0.0430), ALB (p<0.0001), liver disease (p=0.0197), and liver cancer (p=0.0035). In general, the 90-day model tended to select chronic conditions such as dialysis or heart disease, and tended to exclude acute predictors that might be expected to have more of a short-term effect, such as inotropic support.

3.2 Sensitivity analyses

We also built a corresponding Model 4 for 90-day mortality based only on the MICU patients (N=936), and again we found that high B12 was not a significant predictor (p=0.8063) of mortality (results not shown). Note that the 90-day, fully-adjusted mortality model based on the MICU patients is the model that most closely mirrors the Sviri et al[19] multivariable model that found that high B12 was a significant predictor of mortality, except that our model is adjusted for liver function. In general, most of the significant predictors in the 90-day MICU model were also significant in the corresponding 90-day model based on the whole ICU sample (age, SAPS, stroke, Other CVD, immunocompromised status, MCV, TB, ALB, and liver cancer). There were some differences; the MICU model dropped dialysis, sepsis, TPN, respiratory disease, CAD, and hypertension. Furthermore, gender was significant in the MICU 90-day model but not in the general 90-day, fully adjusted model; conversely, ALP and liver disease were not significant in the MICU 90-day model but were significant in the general 90-day, fully-adjusted model.

We also tesed the fully-adjusted 30-day and 90-day models in the paper with different cutoff levels for B12 of 200 pmol/l for low B12 and 664 pmol/l for high B12, as described in the methods section. We found similar results, and in fact the mortality risk for high B12 levels was actually smaller with these thresholds than with fully-adjusted model presented in the paper. The risk for high B12 compared to mid-range B12 was not significant for 30-day mortality (OR=1.07; 95%CI 0.76–1.52; p=0.68) or for 90-day mortality (OR=1.11; 95%CI 0.81–1.52; p=0.70).

4. Discussion

We showed that after adjusting for liver function and disease high B12 levels were not associated with higher mortality for ICU patients. It is possible that poor liver function or liver disease cause both elevated B12 levels and negative clinical outcomes, and high B12 levels serve as a proxy for poor liver function. While it is always difficult to definitively exclude an association, to our knowledge, our study is the largest study so far to look at the relationship between elevated B12 and mortality for the ICU population. Also, as far as we are aware, our study is the only one to consider a non-linear association between B12 levels and mortality, contain a comprehensive set of liver function measurements, and include patients from the SICU and CSRU.

It is important to consider liver function when studying B12 as the liver is directly involved in B12 metabolism. The liver typically stores several years' supply of B12 and also synthesizes transcobalamin II (TCII), which is a B12 transport protein. After dietary B12 is absorbed from the terminal ileum into the enterohepatic circulation, TCII promotes uptake of B12 into the liver. TCII also carries B12 in the serum and binds to receptors on non-hepatocyte cell surfaces to facilitate B12 transport into cells[9]. Although TCII carries some B12 and is responsible for promoting cellular B12 uptake, the majority of serum B12 is bound to transcobalamin I/III (also called haptocorrin, or HC), which is synthesized in salivary gland, gastric, and myeloid cells (precursors to red blood cells, platelets, and non-lymphocyte white blood cells). HC does not play a role in cellular B12 uptake; however, B12 bound to HC (HC-B12) is taken up by the liver and is one mechanism by which circulating B12 is cleared[9].

Liver damage can lead to high vitamin B12 levels by several mechanisms: hepatocyte lysis (break- down of the hepatic cells releases stored B12), decreased liver production of TCII (which decreases uptake by tissues and increases the amount of circulating B12), and decreased liver uptake of HC-B12 (which also increases the amount of circulating B12)[9]. Therefore it is plausible that poor liver function is the underlying cause of both higher mortality rates and elevated B12 levels. High B12 levels can also be the result of increased HC production in certain hematologic conditions due to the increased number of myeloid cells (which increases serum HC-B12 levels) and increased ingestion or therapeutic B12 administration[9].

Furthermore, there are several issues with using elevated B12 levels as a biomarker for mortality for ICU patients. First, in contrast to liver function, vitamin B12 is not routinely measured in the ICU in the United States. Second, again unlike liver function, there is no known mechanism to link elevated B12 with mortality. Third, there are already a number of scores that have been developed and validated to measure acuity of illness in the ICU, such as SAPS[24], APACHE-II[25], and SOFA[17], so B12 measurements are not necessary for this purpose. In contrast to elevated B12, B12 deficiency is a known problem for elderly populations[21—23].

The primary limitation of our study is that it is a retrospective, observational study and therefore, as with all observational studies, we were unable to rule out bias due to the non-randomization of unknown confounders or selection bias due to only being able to study patients who had B12 levels taken. However, we attempted to assess this possible source of bias by comparing the 1684 patients included in our study with the 22,814 patients in the MIMIC-II database but not included in this study, and while we found some clinically significant differences (our study group had a higher incidence of alcoholism, immuno-compromised status patients, and patients admitted to the MICU), none seemed to suggest a reason as to why B12 and not liver function was responsible for higher mortality. A

prospective study on the association between high B12 and mortality where B12 values are measured on all participants would be valuable in ruling out possible selection bias, but to date no such study has been conducted. We were also not able to collect information on B12 therapy prior to admission to the hospital. It is possible that this may create some bias as some of the patients on B12 therapy may have appeared in the "high" B12 group that otherwise would have appeared in the "deficient" category, for example. However, in general, it is unlikely that a person could have achieved a B12 level over 1000 pmol/l (our cutoff for high B12) due to B12 therapy alone.

5. Conclusions

After accounting for liver function and liver disease, elevated B12 levels were not a significant predictor of mortality for ICU patients, for either 30 or 90 days after admission. B12 is known to be elevated in patients with liver disease and it is likely that high B12 levels are often a proxy for poor liver function. Moreover, other composite measures of acuity for the ICU population are already in use have good predictive power for mortality. We conclude that elevated B12 is not a good predictor of mortality for ICU patients when liver function is known.

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Abbreviations

ALB	albumin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CCU	coronary care unit
CSRU	cardiac surgery recovery unit
GVIF	generalized variance inflation factor
HC	haptocorrin
ICD-9	International Classification of Disease codes, ninth revision
IQR	inter-quartile range
MCV	mean corpuscular volume
MELD	Model for End-stage Liver Disease
MICU	medical intensive care unit
MIMIC-II	Multiparameter Intelligent Monitoring in Intensive Care II

MMA	methylmalonic acid
PT	prothrombin time
SICU	surgical intensive care unit
TB	total bilirubin
TCII	transcobalamin II
tHcy	total homocysteine
TPN	total parenteral nutrition
VIF	variance inflation factor

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Table 1

Univariate descriptive table of B12, demographics, and liver function.

Covariate	Deficient B12 ≤148 pmol/l N=37	Mid-range B12 148–1000 pmol/l N=1347	High B12 >1000 pmol/l N=300	Total N=1684	P-value Test of association	P-value Test of trend
Mortality						
30-day	3 (8.1)	197 (14.6)	98 (32.7)	298 (17.7)	<0.0001	<0.0001
90-day	4 (10.8)	268 (19.9)	121 (40.3)	393 (23.3)	<0.0001	<0.0001
B12, pmol/l	118 (112.9, 135)	411 (274.1, 586.6)	1383 (1148.8, 1475.6)	465.2 (290.7, 797.7)	<0.0001	<0.0001
Age, years					0.2367	-
<45	3 (8.1)	131 (9.7)	35 (11.7)	169 (10)	0.6179	0.2781
45–60	14 (37.8)	457 (33.9)	118 (39.3)	589 (35)	0.4515	0.1431
60–80	16 (43.2)	481 (35.7)	91 (30.3)	588 (34.9)	0.3434	0.0401
≥80	4 (10.8)	278 (20.6)	56 (18.7)	338 (20.1)	0.4410	0.9090
Age, continuous	66.8 (58.5, 72.7)	68.2 (55.9, 78.3)	64.4 (52.8, 76.7)	67.7 (55.4, 78.1)	0.0822	0.0587
Female	14 (37.8)	525 (39)	138 (46)	677 (40.2)	0.0785	0.0303
Race					0.4232	-
White	31 (83.8)	966 (71.7)	214 (71.3)	1211 (71.9)	0.8187	0.4279
Black	2 (5.4)	123 (9.1)	34 (11.3)	159 (9.4)	0.4827	0.1542
Other	4 (10.8)	258 (19.2)	52 (17.3)	314 (18.6)	0.5409	0.8767
Insurance					0.0237	
Insured	22 (59.5)	434 (32.2)	93 (31)	549 (32.6)	0.0762	0.0675
Medicaid/Self-pay	1 (2.7)	187 (13.9)	40 (13.3)	228 (13.5)	0.1946	0.5644
Medicare	14 (37.8)	702 (52.1)	158 (52.7)	874 (51.9)	0.6168	0.3827
Other	0 (0)	24 (1.8)	9 (3)	33 (2)	0.3316	0.1067
Liver function						
ALT, IU/l	17 (11, 27)	23 (15, 38)	38 (18, 82)	24 (15, 43)	<0.0001	<0.0001
AST, IU/l	26 (18, 43)	27 (19, 49)	50 (26, 125.2)	29 (20, 58.2)	<0.0001	<0.0001
TB, mg/dl	0.6 (0.4, 0.8)	0.5 (0.3, 0.9)	1.1 (0.5, 3.5)	0.6 (0.4, 1.1)	<0.0001	<0.0001
ALP, IU/l	66 (53, 85)	82 (64, 110)	118.5 (79.5, 194.2)	85 (66, 121.2)	<0.0001	<0.0001
ALB, g/dl	3.6 (3.3, 3.8)	3.4 (2.9, 3.8)	2.9 (2.3, 3.3)	3.3 (2.8, 3.8)	<0.0001	<0.0001
PT, seconds	14.5 (13.5, 15.5)	14.4 (13.2, 16.3)	15.8 (14.1, 19)	14.6 (13.3, 16.7)	<0.0001	<0.0001
Liver disease	0 (0)	126 (9.4)	104 (34.7)	230 (13.7)	<0.0001	<0.0001

Covariate	Deficient B12 ≤148 pmol/l N=37	Mid-range B12 148–1000 pmol/l N=1347	High B12 >1000 pmol/l N=300	Total N=1684	P-value Test of association	P-value Test of trend
Liver cancer	0 (0)	19 (1.4)	16 (5.3)	35 (2.1)	0.0004	<0.0001

Data presented as number (%) or median (inter-quartile range).

Table 2

Univariate descriptive table of features of the ICU stay, procedures, and comorbidities.

Covariate	Deficient B12 ≤148 pmol/l N=37	Mid-range B12 148–1000 pmol/l N=1347	High B12 >1000 pmol/l N=300	Total N=1684	P-value Test of association	P-value Test of trend
SAPS	14 (9, 17)	12 (8, 15)	12 (9, 16)	12 (8, 16)	0.1260	0.3991
First service unit					<0.0001	-
CCU	6 (16.2)	188 (14)	27 (9)	221 (13.1)	0.0929	0.0200
CSRU	18 (48.6)	362 (26.9)	21 (7)	401 (23.8)	<0.0001	<0.0001
MICU	13 (35.1)	698 (51.8)	225 (75)	936 (55.6)	0.0005	<0.0001
SICU	0 (0)	99 (7.3)	27 (9)	126 (7.5)	0.1496	0.1057
Admission type[a]					<0.0001	-
Elective	9 (24.3)	147 (10.9)	6 (2)	162 (9.6)	<0.0001	<0.0001
Emergency	28 (75.7)	1101 (81.7)	271 (90.3)	1400 (83.1)	0.5316	0.0002
Urgent	0 (0)	35 (2.6)	7 (2.3)	42 (2.5)	1	0.8695
LOS, days						
ICU	2.4 (1.2, 3.7)	2.2 (1.2, 4.6)	2.8 (1.5, 7)	2.3 (1.2, 4.8)	0.0090	0.0025
Hospital	7 (5, 11)	9 (5, 16)	13.5 (6, 24)	9 (5, 17)	<0.0001	<0.0001
Lab tests						
Creatinine, mg/dl	0.9 (0.7, 1.1)	1 (0.7, 1.6)	1.3 (0.8, 2.4)	1 (0.7, 1.7)	<0.0001	<0.0001
Hemoglobin, g/dl	10.4 (9.3, 11.2)	10.3 (9, 11.7)	10 (8.8, 11.2)	10.2 (9, 11.6)	0.0365	0.0131
Folate, ng/ml[a]	8.9 (6.3, 12.9)	13.1 (9.5, 19.4)	14.8 (10.3, 20)	13.4 (9.6, 19.9)	0.0008	<0.0001
MCV, fL[a]	89 (83, 93)	90 (86, 95)	93 (88, 100)	91 (86, 96)	<0.0001	<0.0001
Procedures						
B12 supplement	8 (21.6)	51 (3.8)	15 (5)	74 (4.4)	0.0002	0.1962
Dialysis	0 (0)	124 (9.2)	50 (16.7)	174 (10.3)	<0.0001	<0.0001
TPN	0 (0)	27 (2)	9 (3)	36 (2.1)	0.4080	0.1746
Inotropic support	9 (24.3)	283 (21)	74 (24.7)	366 (21.7)	0.3350	0.2692
Comobidities						
Alcoholism	4 (10.8)	218 (16.2)	78 (26)	300 (17.8)	0.0003	<0.0001
Sepsis	4 (10.8)	190 (14.1)	82 (27.3)	276 (16.4)	<0.0001	<0.0001
Respiratory disease	2 (5.4)	179 (13.3)	39 (13)	220 (13.1)	0.4288	0.6487
Myeloproliferative disease	0 (0)	6 (0.4)	5 (1.7)	11 (0.7)	0.0675	0.0179

Covariate	Deficient B12 ≤148 pmol/l N=37	Mid-range B12 148–1000 pmol/l N=1347	High B12 >1000 pmol/l N=300	Total N=1684	P-value Test of association	P-value Test of trend
Stroke	2 (5.4)	108 (8)	24 (8)	134 (8)	0.9559	0.8178
CAD	26 (70.3)	544 (40.4)	61 (20.3)	631 (37.5)	<0.0001	<0.0001
Other CVD	20 (54.1)	807 (59.9)	151 (50.3)	978 (58.1)	0.0085	0.0104
Hypertension	26 (70.3)	716 (53.2)	120 (40)	862 (51.2)	<0.0001	<0.0001
Immunocomprimized	6 (16.2)	358 (26.6)	110 (36.7)	474 (28.1)	0.0007	0.0001
Neuropsychiatric	8 (21.6)	420 (31.2)	105 (35)	533 (31.7)	0.1852	0.0855
GI hemorrhage	0 (0)	71 (5.3)	22 (7.3)	93 (5.5)	0.1332	0.0571

Data presented as number (%) or median (inter-quartile range).

[a]Admission type had 80 (4.8%) missing values, folate had 503 (29.9%) missing values, and MCV had 1 (0.1%) missing value.

Table 3

Results from the four models for mortality 30 and 90 days after ICU admission.

Models: 30 days	Description	Deficient B12 OR (95% CI)	P-value	High B12 OR (95% CI)	P-value
Model 1	B12 only	0.52 (0.16, 1.69)	0.2743	2.83 (2.13, 3.76)	<0.0001
Model 2	+Demographics	0.65 (0.19, 2.16)	0.4776	3.12 (2.31, 4.20)	<0.0001
Model 3	+Other potential confounders	0.89 (0.22, 3.57)	0.8651	1.93 (1.38, 2.72)	0.0001
Model 4	+Liver function and diseases	1.32 (0.32, 5.52)	0.7033	1.18 (0.81, 1.72)	0.3890
Models: 90 days					
Model 1	B12 only	0.49 (0.17, 1.39)	0.1790	2.72 (2.08, 3.55)	<0.0001
Model 2	+Demographics	0.58 (0.20, 1.67)	0.3098	3.09 (2.33, 4.09)	<0.0001
Model 3	+Other potential confounders	0.99 (0.30, 3.30)	0.9919	1.97 (1.43, 2.71)	<0.0001
Model 4	+Liver function and diseases	1.30 (0.37, 4.53)	0.6774	1.20 (0.84, 1.71)	0.3077

Table 3 shows the model building procedure. In order to demonstrate the attenuation of the effect of B12 on mortality, we added variables to the B12 predictor sequentially to create the final, fully-adjusted model (“model 4”).Model 1 includes B12 only; model 2 includes B12 and demographic variables; model 3 includes B12, demographic, and other potentially confounding factors; and model 4 includes B12, demographic variables, other potential confounders, and liver function and disease (see Table 4 for details). The odds ratio compares the risk of the deficient or high B12 group to the mid-range B12 group.

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Table 4

Results from final model for mortality for 30 and 90 days after ICU admission.

Covariate	30-day mortality OR (95% CI)	P-value	90-day mortality OR (95% CI)	P-value
B12, pmol/l (Ref=Mid- range)		0.6626		0.5719
Deficient B12	1.28 (0.31, 5.32)	0.7363	1.27 (0.37, 4.41)	0.7060
High B12	1.18 (0.81, 1.72)	0.3886	1.20 (0.84, 1.70)	0.3148
Age, years (Ref=45–65)		<0.0001		<0.0001
<45	0.46 (0.24, 0.90)	0.0224	0.48 (0.26, 0.88)	0.0181
65–80	1.97 (1.22, 3.15)	0.0051	2.25 (1.47, 3.44)	0.0002
≥80	6.44 (3.82, 10.85)	<0.0001	7.22 (4.48, 11.63)	<0.0001
Gender (Ref=Female)	0.94 (0.68, 1.30)	0.7200	1.18 (0.88, 1.58)	0.2725
Race (Ref=White)		0.4647		0.4164
Black	0.71 (0.41, 1.25)	0.2363	0.73 (0.44, 1.20)	0.2141
Other	1.02 (0.67, 1.54)	0.9307	0.89 (0.60, 1.31)	0.5490
Insurance type (Ref=Insured)		0.0128		0.2368
Medicaid/Self-pay	1.67 (0.94, 2.96)	0.0819	1.25 (0.74, 2.12)	0.4017
Medicare	1.42 (0.94, 2.16)	0.0982	1.17 (0.81, 1.70)	0.4081
Other	4.66 (1.72, 12.61)	0.0025	2.65 (1.01, 6.95)	0.0469
Dialysis	-	-	1.82 (1.19, 2.80)	0.0062
SAPS	1.09 (1.06, 1.13)	<0.0001	1.08 (1.05, 1.11)	<0.0001
First service unit (Ref=CCU)		<0.0001		<0.0001
CSRU	0.32 (0.15, 0.68)	0.0031	0.37 (0.19, 0.72)	0.0032
MICU	1.14 (0.67, 1.94)	0.6254	1.05 (0.66, 1.67)	0.8416
SICU	0.19 (0.08, 0.47)	0.0004	0.38 (0.18, 0.77)	0.0072
B12 supplement	0.49 (0.21, 1.13)	0.0941	-	-
Sepsis	1.39 (0.96, 2.03)	0.0839	1.46 (1.03, 2.07)	0.0330
TPN	-	-	2.11 (0.92, 4.85)	0.0780
Respiratory disease	-	-	1.72 (1.17, 2.52)	0.0060
Stroke	3.77 (2.25, 6.32)	<0.0001	3.21 (1.98, 5.21)	<0.0001
CAD	0.77 (0.51, 1.15)	0.2015	0.58 (0.40, 0.84)	0.0037
Hypertension	-	-	0.79 (0.58, 1.07)	0.1310
Other CVD	-	-	1.42 (1.02, 1.98)	0.0354
Immunocompromised	2.30 (1.62, 3.26)	<0.0001	2.43 (1.76, 3.36)	<0.0001
Alcoholism	1.66 (1.07, 2.59)	0.0244	-	-
MCV, fL (Ref≤86)		0.0529		0.0455
Q2 (86, 91]	0.91 (0.57, 1.45)	0.6832	0.82 (0.54, 1.24)	0.3439
Q3 (91, 96]	1.05 (0.64, 1.70)	0.8583	0.93 (0.60, 1.44)	0.7403
Q4 (96, 135]	1.57 (1.00, 2.47)	0.0487	1.39 (0.93, 2.09)	0.1063
Inotropic support	1.53 (1.03, 2.27)	0.0331	-	-
Neuropsychiatric disorder	0.70 (0.49, 1.01)	0.0561	-	-
ALT, IU/l (Ref≤15)		0.3293		0.6625
Q2 (15, 24]	1.21 (0.74, 1.99)	0.4535	1.18 (0.76, 1.83)	0.4598

Covariate	30-day mortality OR (95% CI)	P-value	90-day mortality OR (95% CI)	P-value
Q3 (24, 43]	1.62 (0.96, 2.73)	0.0683	1.35 (0.84, 2.16)	0.2179
Q4 (43, 4170]	1.40 (0.76, 2.58)	0.2828	1.19 (0.68, 2.08)	0.5407
AST, IU/l (Ref≤20)		0.8722		0.7431
Q2 (20, 29]	1.20 (0.70, 2.05)	0.5086	1.13 (0.71, 1.80)	0.6009
Q3 (29, 58.2]	1.03 (0.59, 1.79)	0.9273	0.90 (0.55, 1.48)	0.6861
Q4 (58.2, 4253]	1.14 (0.58, 2.24)	0.6997	1.04 (0.57, 1.91)	0.8996
TB, mg/dl (Ref≤0.4)		0.0335		0.0165
Q2 (0.4, 0.6]	1.49 (0.93, 2.38)	0.0966	1.32 (0.86, 2.02)	0.2075
Q3 (0.6, 1.1]	0.99 (0.61, 1.60)	0.9629	1.33 (0.87, 2.03)	0.1888
Q4 (1.1, 54.2]	1.81 (1.12, 2.94)	0.0160	2.06 (1.32, 3.21)	0.0014
ALP, IU/L (Ref≤66)		0.0156		0.0430
Q2 (66, 85]	1.29 (0.77, 2.16)	0.3367	1.48 (0.94, 2.34)	0.0896
Q3 (85, 121]	1.85 (1.13, 3.03)	0.0140	1.66 (1.07, 2.58)	0.0248
Q4 (121, 4585]	2.02 (1.23, 3.29)	0.0052	1.85 (1.19, 2.89)	0.0065
ALB, g/dl (Ref≤2.8)		<0.0001		<0.0001
Q2 (2.8, 3.3]	0.92 (0.63, 1.32)	0.6427	0.81 (0.57, 1.13)	0.2156
Q3 (3.3, 3.8]	0.45 (0.28, 0.71)	0.0007	0.38 (0.25, 0.58)	<0.0001
Q4 (3.8, 5.6]	0.28 (0.14, 0.53)	0.0001	0.24 (0.14, 0.43)	<0.0001
PT, second (Ref≤13.3)		0.4065		0.8901
Q2 (13.3, 14.6]	1.09 (0.68, 1.74)	0.7338	1.02 (0.67, 1.56)	0.9164
Q3 (14.6, 16.7]	0.95 (0.58, 1.58)	0.8555	1.00 (0.64, 1.56)	0.9989
Q4 (16.7, 150]	1.34 (0.84, 2.13)	0.2221	1.15 (0.75, 1.76)	0.5305
Liver disease	1.61 (0.99, 2.61)	0.0531	1.71 (1.09, 2.67)	0.0197
Liver cancer	2.31 (0.97, 5.46)	0.0576	3.54 (1.52, 8.26)	0.0035

Table 5

Comparing the ICU patients in the B12 study and ICU patients who did not have a B12 measurement at baseline.

Variable	B12 study (N=1684)	Not in B12 study (N=22,814)	P-value
30-day mortality	298 (17.7)	3049 (13.4)	<0.0001
90-day mortality	393 (23.3)	3845 (16.9)	<0.0001
Age, years	67.7 (55.4, 78.1)	65.1 (51, 77.7)	<0.0001
Female	677 (40.2)	9918 (43.5)	0.0087
Race			<0.0001
White	1211 (71.9)	15713 (68.9)	0.0094
Black	159 (9.4)	1601 (7)	0.0003
Other	314 (18.6)	5500 (24.1)	<0.0001
Insurance type			<0.0001
Insured	549 (32.6)	9457 (42.1)	<0.0001
Medicaid/Free/Self-pay	228 (13.5)	2583 (11.5)	0.0131
Medicare	874 (51.9)	9833 (43.8)	<0.0001
Other	33 (2)	578 (2.6)	0.1267
Liver function:			
ALT, IU/L	24 (15, 43)	25 (16, 46)	0.0013
AST, IU/L	29 (20, 58.2)	30 (20, 63)	0.1296
TB, mg/dL	0.6 (0.4, 1.1)	0.6 (0.4, 1)	0.9987
ALP, IU/L	85 (66, 121.2)	80 (61, 111)	<0.0001
ALB, g/dL	3.3 (2.8, 3.8)	3.4 (2.9, 3.9)	<0.0001
PT, seconds	14.6 (13.3, 16.7)	13.8 (12.9, 15.5)	<0.0001
Liver disease	230 (13.7)	1360 (6)	<0.0001
Liver cancer	35 (2.1)	495 (2.2)	0.8625
SAPS	12 (8, 16)	10 (6, 14)	<0.0001
First service Unit			<0.0001
CCU	221 (13.1)	3659 (16)	0.0015
CSRU	401 (23.8)	4653 (20.4)	0.0010
MICU	936 (55.6)	8175 (35.8)	<0.0001
SICU	126 (7.5)	6327 (27.7)	<0.0001
Admission type			<0.0001
Elective	162 (10.1)	3474 (15.8)	<0.0001
Emergency	1400 (87.3)	17581 (79.9)	<0.0001
Urgent	42 (2.6)	945 (4.3)	0.0008
ICU LOS	2.3 (1.2, 4.8)	2 (1.1, 4.1)	<0.0001
Hospital LOS	9 (5, 17)	7 (4, 12)	<0.0001
Non-liver lab values:			
Creatinine, mg/dL	1 (0.7, 1.7)	0.9 (0.7, 1.3)	<0.0001
Hemoglobin, g/dL	10.2 (9, 11.6)	11.4 (9.9, 13.1)	<0.0001
Folate, ng/mL	13.4 (9.6, 19.9)	15 (10.4, 20)	0.0053

Variable	B12 study (N=1684)	Not in B12 study (N=22,814)	P-value
MCV, ng/mL	91 (86, 96)	89 (86, 93)	<0.0001
Procedures:			
B12 supplement	74 (4.4)	298 (1.3)	<0.0001
Dialysis	174 (10.3)	808 (3.5)	<0.0001
TPN	36 (2.1)	467 (2)	0.7892
Inotropic support	366 (21.7)	3557 (15.6)	<0.0001
Comorbidities:			
Alcoholism	300 (17.8)	791 (3.5)	<0.0001
Sepsis	276 (16.4)	2217 (9.7)	<0.0001
Respiratory disease	220 (13.1)	2641 (11.6)	0.0704
Myeloproliferative disease	11 (0.7)	85 (0.4)	0.1002
Stroke	134 (8)	2569 (11.3)	<0.0001
CAD	631 (37.5)	7553 (33.1)	0.0003
Other CVD	978 (58.1)	11610 (50.9)	<0.0001
Hypertension	862 (51.2)	10767 (47.2)	0.0016
Immunocompromised	474 (28.1)	1474 (6.5)	<0.0001
Neuro-psychiatric disorder	533 (31.7)	5847 (25.6)	<0.0001
GI hemmorrhage	93 (5.5)	766 (3.4)	<0.0001

Data presented as number (%) or median (inter-quartile range).