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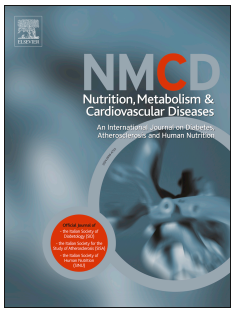

Excessive Vitamin B12 and poor outcome in COVID-19 pneumonia

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Excessive Vitamin B12 and poor outcome in COVID-19 pneumonia

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To the Editor,

The Severe Acute Respiratory Syndrome (SARS) related to COVID-19 infection is a hard-to-treat disease with a poor prognosis. High casualty rate has been reported in the frail elderly where malnutrition and defective micronutrient state may both impair the immune response (1). Rodriguez et all showed that 2% of patients admitted to an Intensive Care Unit (ICU) were Vitamin B12 deficient (2). Low plasma vitamin B12 (B12) and folate levels may also be associated with high homocysteine concentration. Moreover, vitamin B12 supplementation has been showed to add favourably to chronic hepatitis C treatment (3). Aim of our study was to study prospectively vitamin B12 and folate plasma level in patients admitted for COVID Pneumonia. 51 patients diagnosed with SARS-Cov2 pharyngeal nose swab hospitalized at our internal medicine unit from 30Th March to 30Th April 2020 were considered for the study. 2 patients were excluded for ongoing vitamin supplementation. 49 patients (males 64.5%; median age 72 years, IQR= 22 years) underwent extensive blood test, including B12, folates and blood gas analysis. Results were correlated with the outcome with a worse outcome intended as transfer to ICU or death. Continuous variables are expressed as mean ± standard deviation (SD) and as median with Inter-Quartile Range (IQR) depending on data distribution; discrete variables are expressed as number and percentage. Comparison between continuous variables is performed using the Student's T test for unpaired data and/or the Mann-Whitney U test, depending on the distribution of the data. A stepwise multivariate linear regression analysis was performed in order to determine any independent determinants of outcome.

Nine out of 49 patients were transferred to the ICU or died. Patients with poor outcome were significantly older (p=0.01), had lower P/F ratio (p=0.01) and higher plasma level of B12 (p=0.02) compared with those who recovered. In a multivariate regression analysis, only age was independently associated with a worse outcome (β±SEM 0.016±0.005, p=0.001). No significant differences were noticed as regards to folates, transaminases, D-dimer, homocysteine, and fibrinogen (Table I) A shortage of B vitamins may weaken host immune response (1). One might postulate B12 as basic treatment option for COVID-19 illness. However, B12 status has not been previously assessed in this population. Unexpectedly, our data do not support a potential therapeutic role of B12 supplementation for a low 2% rate of B12 deficiency and normal homocysteine levels were not consistent with a significant B12 shortage (4).Unfortunately, we did not perform plasma methylmalonic acid evaluation which is the most sensitive marker for B12 deficiency. However, a potential association between high plasma levels of vitamin B12 and increased risk of mortality is suggested. Moreover, it has been reported that the cyanocobalamin fraction of B12 may worsen prognosis of renal insufficiency patients (4). However, no difference of B12 levels were found when the population was divided for glomerular filtration rate (GFR) by a post-hoc analysis with few patients showing altered GFR. Our study supports recent findings in both the general population and the ICU patients where excessive B12 has been reported to be associated with increased mortality rates (5,6). A number of mechanisms can cause high Vitamin B12 levels in our study population: elevated levels of carrier proteins, decreased Vitamin B12 clearance by the liver and decreased uptake by peripheral tissues. However, it is tempting to speculate a correlation with the cytokine storm of the COVID-19 infection to consider a potential role of excessive vitamin B12 on predicting illness outcome.

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Table I: Population Characteristics of the COVID-19 Patients

	No ICU/alive (#40)	**ICU or death (#9)**	**p value**
Age (years)	70.2±13.4	83.3±10.5	p=0.01
Sex (males, %)	36	37	n.s.
vitB12 (ng/mL)	583±295	1315±1087	p=0.02
Folates (ng/mL)	6.1±7.7	5.7±6.1	n.s.
Fibrinogen (g/L)	6.0±1.8	5.0±2.0	n.s.
Homocysteine µmol/L	9 ± 1.2	11±1.4	n.s.
D-dimer (ng/L)	2910±2310	1350±1130	n.s.
ALT (U/L)	28±17	43±34	n.s.
Lymphocytes (per mm3)	1750±2600	810±409	n.s.
Creatinine (mg/dL)	1.1±0.5	0.8±0.6	n.s.
GFR mL/min/1,73m	64 ±20	61±18	n.s.
P/F ratio ($pO2/\%Ox^{inhaled}$)	280±54	202±91	p=0.01
Protrombin Time (INR)	1.3±0.3	1.1±0.2	n.s.