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Determining diagnostic markers of vitamin B12 status in older adults- Data from the Trinity Ulster Department of Agriculture Ageing cohort study

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Vitamin B12 deficiency is a significant public health issue, particularly within the elderly population with estimates of those affected ranging from 5–40% depending on the marker of measurement. However, diagnosis is difficult because haematological symptoms of deficiency are often absent and many present with diffuse, non-specific neurological symptoms. Biochemical markers of B-12 status have been previously investigated for their clinical utility, specificity and sensitivity in determining true status; however, few studies have investigated these in large, well-characterised clinically appropriate populations (particularly older adults and those with renal impairment).

Participants (*n* 5201) were recruited to the TUDA ageing cohort study from the University of Ulster, Coleraine and those attending the memory and bone clinics in the Geriatric Unit of St. James Hospital, Dublin. Those receiving B12 treatment/supplementation were excluded (*n* 521) from the final analysis. Blood samples were analysed for total serum cobalamin, holotranscobalmin (Holo TC), homocysteine (tHcy), red cell folate (RCF) and serum folate at Trinity College Dublin. Methylmalonic acid (MMA) determination was performed on a subset of samples (*n* 1399) at the University of Bergen, Norway. Hematologic and renal function data were available through the main study database and the estimated glomerular filtration rate (eGFR) was calculated by use of the Cockcroft–Gault equation. A separate reference population of 459 healthy volunteers (228 Male, 231 Female; 18–84yrs) from the National Adult Nutrition Survey (NANs) was used to determine a reference interval for HoloTC (23·4 pmol/l) and for total serum cobalamin (129·1 pmol/l).Vitamin B12 deficiency was defined as a MMA concentration (>0·45 μmol/l).

Table 1. Performance of Holo TC & Serum cobalamin to detect B12 deficiency in eGFR ranges using reference cut-off intervals[1]

eGFR Range (ml/min)	*n*	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV[2], % (95% CI)	NPV[3], % (95% CI)
≥60					
Holo TC	612	52·91 (45·1–60·5)	88·44 (85·0–91·2)	64·08 (55·6–71·9)	82·80 (79·0–86·1)
Serum Cobalamin	612	39·53 (32·1–47·2)	70·45 (65·9–74·6)	34·34 (27·7–41·4)	74·88 (70·4–78·9)
30–59					
Holo TC	635	40·09 (33·5–46·9)	95·45 (92·9–97·2)	82·08 (73·4–88·8)	75·43 (71·5–79·0)
Serum Cobalamin	628	32·26 (26·0–38·9)	70·45 (65·9–74·6)	55·12 (46·0–63·9)	70·6 (66·4–74·6)
<29					
Holo TC	133	30·16 (19·2–43·0)	95·71 (87·9–99·0)	86·36 (65·0–96·9)	60·36 (50·6–69·5)
Serum Cobalamin	133	17·74 (9·2–29·5)	95·59 (87·6–99·0)	78·57 (49·2–95·0)	56·03 (46·5–65·2)

[1]Reference cut-off from NANs study; [2]Positive predictive value; [3]Negative predictive value.

In a ROC plot analysis (with MMA >0·45 μmol/L classified as B12 deficient status), the areas under the curve (AUCs) demonstrated that Holo TC wasthe best-performing indicator of deficient status (AUC 0·78; 95% CI 0·76–0·81). The differences in AUC between HoloTC and serum cobalamin (0·64; 0·61–0·67), serum folate (0·53; 0·50–0·57), RCF (0·58; 0·53–0·62) and GFR (0·59; 0·56–0·62) were significant ($P < 0·0001$). These findings support the use of Holo TC as a first line diagnostic marker for determination of B12 status in older adults, including those with renal impairment.

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