

# Positive predictive value of the diagnosis coding for vitamin B12 deficiency anemia in the Danish National Patient Register

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**Purpose:** The aim of this validation study was to assess the positive predictive value (PPV) of the International Classification of Diseases, 10th revision (ICD-10) diagnosis of vitamin B12 (cobalamin [Cbl]) deficiency anemia in the Danish National Patient Register (DNPR).

**Patients and methods:** We identified all patients above 18 years of age recorded in the DNPR with a diagnosis of Cbl deficiency anemia (ICD-10 code: D51) admitted to two Danish university hospitals and one Danish regional hospital from 2000 through 2009. We assessed the PPV using biochemical parameters on Cbl deficiency with or without anemia as reference standards. These data were obtained from the Laboratory Information Systems Database. Data on prescriptions with Cbl supplementation drugs were obtained from the Aarhus University Prescription Database.

**Results:** We identified 1089 patients coded with a Cbl deficiency anemia diagnosis in the DNPR. The PPV was 31.5% (95% confidence interval [CI]: 28.8%–34.3%) and 36.8% (95% CI: 34.0%–39.7%) depending on definitions of Cbl deficiency with anemia. When using Cbl deficiency without anemia as a reference standard, the PPV was 51.3% (95% CI: 48.4%–54.3%). The PPV for Cbl supplemented patients was 22.2% (95% CI: 18.0%–26.9%) and for non-Cbl supplemented patients 63.9% (95% CI: 60.5%–67.3%).

**Conclusion:** The PPVs of the ICD-10 diagnosis coding for Cbl deficiency anemia were generally low in the DNPR. Therefore, this register should be used with caution to study patients with Cbl deficiency anemia.

**Keywords:** vitamin B12 deficiency anemia, Danish National Patient Register, Laboratory Information Systems Database, International Classification of Diseases, positive predictive value, validation study

## Introduction

Vitamin B12 (cobalamin [Cbl]) deficiency may lead to anemia<sup>1</sup> and is usually caused by malabsorption in developed countries and by insufficient dietary intake in developing countries.<sup>2,3</sup> The number of Cbl measurements and prescriptions for Cbl supplementation has increased in Denmark.<sup>4</sup> This increasing awareness calls for valid data on this disease entity.

The Danish National Patient Register (DNPR) is a unique data source for research purposes and for quality assessment of the health care system.<sup>5</sup> So far, no studies have assessed the validity of the Cbl deficiency anemia diagnosis in the DNPR.

Hence, the aim of this study was to assess the positive predictive value (PPV) of the International Classification of Diseases, 10th revision (ICD-10) diagnosis coding for Cbl deficiency anemia in the DNPR, using the Laboratory Information Systems (LABKA) Database<sup>6</sup> as a reference standard.

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## Methods

In this validation study, we identified all patients 18 years of age or older recorded in the DNPR with a first time inpatient or outpatient discharge diagnosis of Cbl deficiency anemia (ICD-10 code: D51).<sup>7</sup> We included patients diagnosed at two university hospitals (Aarhus and Aalborg) and one regional hospital (Randers) in Denmark from January 1, 2000 to December 31, 2009.

The DNPR covers all somatic hospitals in Denmark and contains information on patients' civil registration numbers, dates of admission and discharge, code for hospital and department, and up to 20 discharge diagnoses coded by medical doctors according to ICD-8 (1977–1993) and ICD-10 (since 1994). In addition, selected types of hospital-administered treatments are coded. We used the unique civil registration number assigned to all Danish residents to link individual-level data.

We linked patients with Cbl deficiency anemia recorded in the DNPR to the LABKA Database, our reference standard. LABKA contains information on all biochemical analyses performed in hospital laboratories in Northern and Central Denmark recorded according to Nomenclature, Properties, and Units (NPU) codes and/or local analysis numbers (see Table S1). The database has covered the study area since 2000.<sup>6</sup>

No single diagnostic parameter exists for the biochemical diagnosis of Cbl deficiency.<sup>8</sup> Measuring Cbl levels is routinely used, and methylmalonic acid (MMA) levels are used if the laboratory offers this analysis. Total homocysteine (tHcy) levels and mean corpuscular volume (MCV) can also be relevant when assessing Cbl deficiency.<sup>8</sup> These issues complicated the definition of our reference standard and we therefore used both a “strict definition” and a “wide definition” of Cbl deficiency anemia, and Cbl deficiency without concomitant anemia. The three different definitions we operated with are outlined in Table 1.

Lower reference limits for anemia and Cbl deficiency were defined according to Danish reference limits.<sup>9,10</sup> The algorithm for the biochemical assessment of Cbl deficiency is outlined in a review by Hvas and Nexø.<sup>11</sup> This algorithm is widely implemented in Denmark. Briefly, the algorithm suggests measuring plasma Cbl levels first. Levels above 250 pmol/L rule out Cbl deficiency and levels below 125 pmol/L confirm the diagnosis. If the levels are between 125–250 pmol/L then MMA levels should be measured. MMA levels are divided into three categories: levels below 0.28  $\mu\text{mol/L}$  rule out Cbl deficiency, levels

above 0.75  $\mu\text{mol/L}$  confirm Cbl deficiency, and levels between 0.28–0.75  $\mu\text{mol/L}$  are inconclusive. We included the inconclusive ranges for Cbl and MMA<sup>12</sup> in both our wide and strict definitions of Cbl deficiency. Thus, the defined ranges of values were wide enough to avoid missing any patients with Cbl deficiency. In the wide definition, we added tHcy and MCV as diagnostic parameters. We defined 12.0  $\mu\text{mol/L}$  as the cut-off value for tHcy. It is the Danish upper reference limit for patients 30 years or older, modified according to a study by Rasmussen et al,<sup>12</sup> since few patients in our study population were younger than 30 years. We defined macrocytosis as a  $\text{MCV} > 98 \text{ fL}$ .<sup>10</sup>

For each hospitalization, all blood samples taken between date of admission minus 3 months and date of discharge were examined for lowest hemoglobin levels, lowest Cbl levels, highest MMA levels, highest tHcy levels, and highest MCV, in case of multiple records.

We used the Aarhus University Prescription Database (AUPD)<sup>13</sup> to identify patients who redeemed Cbl supplementation prescriptions and the DNPR to identify in-hospital treatment with Cbl. The AUPD contains the variables for civil registration number, name and ATC code of the drug, and date of prescription refill. It covers the study area and period.<sup>13</sup> In Denmark, Cbl supplementation in therapeutic doses can only be obtained by a prescription. Prior use of Cbl was defined as one or more Cbl prescriptions or in-hospital treatment with Cbl within 3 years before admission of the patient.

## Statistical analyses

We computed PPVs as the proportion of patients identified with Cbl deficiency anemia in the DNPR who also had biochemical test results in the LABKA Database fulfilling the criteria of our reference standard definitions. We calculated PPVs for our three definitions of the reference standard: (1) strict and (2) wide definitions of Cbl deficiency anemia, and (3) Cbl deficiency without concomitant anemia. The analyses included all patients identified with a code of Cbl deficiency anemia in the DNPR, also those with no LABKA records. We stratified the analyses according to sex, age at diagnosis (18–39, 40–59, 60–79, 80+), calendar periods (2000–2005, 2006–2009), type of admission (inpatient, outpatient, or both admission types), and prior use of Cbl supplementation therapy. Patients with no LABKA records were included in the group of patients not fulfilling the diagnostic criteria. The PPVs are presented along with corresponding 95%

**Table 1** Definitions used as reference standards for this validation study

<b>Cbl deficiency anemia, strict definition (I and [A or B or C])</b>	<b>Cbl deficiency anemia, wide definition (I and [A or B or C or D or E])</b>	<b>Cbl deficiency without concomitant anemia (A or B or C or D or E)</b>
I. Hemoglobin < 7.0 mmol/L (women)/< 8.0 mmol/L (men)	I. Hemoglobin < 7.0 mmol/L (women)/< 8.0 mmol/L (men)	
A. MMA > 0.75 μmol	A. MMA > 0.75 μmol	A. MMA > 0.75 μmol
B. Cbl < 125 pmol/L	B. Cbl < 125 pmol/L	B. Cbl < 125 pmol/L
C. MMA > 0.28 μmol/L AND Cbl 125–250 pmol/L	C. MMA > 0.28 μmol/L AND Cbl 125–250 pmol/L	C. MMA > 0.28 μmol/L AND Cbl 125–250 pmol/L
	D. Cbl 125–250 pmol/L AND tHcy > 12.0 μmol/L	D. Cbl 125–250 pmol/L AND tHcy > 12.0 μmol/L
	E. Cbl 125–250 pmol/L AND MCV > 98 fL (macrocytosis)	E. Cbl 125–250 pmol/L AND MCV > 98 fL (macrocytosis)

**Notes:** Definitions of cobalamin deficiency anemia and cobalamin deficiency without concomitant anemia. The fulfilling biochemical criteria are outlined.

**Abbreviations:** Cbl, cobalamin; MCV, mean corpuscular volume; MMA, methylmalonic acid; tHcy, total homocysteine.

confidence intervals (95% CI), calculated according to Jeffrey's method.<sup>14</sup> Analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC). The study was approved by The Danish Data Protection Agency (record number: 2005-41-5572).

## Results

We identified 1089 patients with Cbl deficiency anemia according to the DNPR. The median age at diagnosis was 77 years, ranging from 18 to 102 years, and 62% were

women. The proportion of patients without records in the LABKA Database was 4.5% for hemoglobin (anemia) and 4.7% for the Cbl related parameters.

The PPV for Cbl deficiency anemia was 31.5% (95% CI: 28.8%–34.3%) using the strict definition and 36.8% (95% CI: 34.0%–39.7%) using the wide definition (Table 2). The PPV using Cbl deficiency without concomitant anemia as a reference standard was overall 51.3% (95% CI: 48.4%–54.3%), varying from 22.2% (95% CI: 18.0%–26.9%) for patients with a prior Cbl use to 63.9% (95% CI: 60.5%–67.3%) for

**Table 2** Positive predictive values for the coding of cobalamin deficiency anemia in the Danish National Patient Register

	<b>Cbl deficiency anemia</b>		<b>Cbl deficiency without concomitant anemia</b>		
	<b>PPV% (95% CI)</b>		<b>PPV% (95% CI)</b>		
	<b>Strict definition</b>	<b>Wide definition</b>	<b>All patients</b>	<b>With prior Cbl use</b>	<b>With no prior Cbl use</b>
Overall (n = 1089)	31.5 (28.8–34.3)	36.8 (34.0–39.7)	51.3 (48.4–54.3)	22.2 (18.0–26.9)	63.9 (60.5–67.3)
<b>Sex</b>					
Men (n = 409)	42.1 (37.3–46.9)	47.7 (42.9–52.5)	59.7 (54.8–64.3)	31.6 (22.9–41.4)	68.2 (62.9–73.1)
Women (n = 680)	25.1 (22.0–28.5)	30.3 (26.9–33.8)	46.3 (42.6–50.1)	18.4 (13.8–23.7)	61.0 (56.4–65.4)
<b>Age at diagnosis</b>					
18–39 years (n = 116)	34.5 (26.3–43.4)	38.8 (30.3–47.8)	69.0 (60.2–76.8)	45.5 (26.3–65.7)	74.5 (65.0–82.4)
40–59 years (n = 159)	30.8 (24.0–38.3)	38.4 (31.1–46.1)	57.2 (49.5–64.7)	36.1 (22.0–52.4)	63.4 (54.7–71.5)
60–79 years (n = 347)	33.1 (28.3–38.2)	38.9 (33.9–44.1)	52.4 (47.2–57.7)	22.3 (15.4–30.7)	66.8 (60.6–72.6)
80+ years (n = 467)	29.8 (25.8–34.0)	34.3 (30.1–38.7)	44.1 (39.7–48.6)	15.7 (10.7–22.0)	58.8 (53.2–64.2)
<b>Calendar period</b>					
2000–2005 (n = 711)	29.4 (26.1–32.8)	34.9 (31.4–38.4)	49.2 (45.6–52.9)	20.7 (15.8–26.4)	62.2 (57.8–66.4)
2006–2009 (n = 378)	35.4 (30.8–40.4)	40.5 (35.6–45.5)	55.3 (50.3–60.2)	25.2 (17.7–34.0)	67.2 (61.4–72.5)
<b>Patient type</b>					
Inpatient (n = 629)	31.5 (27.9–35.2)	36.6 (32.9–40.4)	43.6 (39.7–47.5)	14.1 (9.8–19.4)	57.2 (52.5–61.8)
Outpatient (n = 308)	25.6 (21.0–30.7)	30.2 (25.3–35.5)	63.0 (57.5–68.2)	41.9 (31.8–52.4)	71.2 (65.0–76.8)
Both inpatient and outpatient (n = 152)	43.4 (35.7–51.4)	51.3 (43.4–59.2)	59.9 (52.0–67.4)	20.5 (10.6–34.0)	75.9 (67.3–83.2)

**Notes:** PPVs are computed using three different reference standards defined by laboratory data from the LABKA Database. For definitions of reference standards see Table 1.

**Abbreviations:** Cbl, cobalamin; CI, confidence interval; DNPR, Danish National Patient Register; LABKA, Laboratory Information Systems Database; PPV, positive predictive value.

patients with no prior Cbl use. In general, PPVs were higher for men than for women.

## Discussion

We studied the validity of coding for Cbl deficiency anemia in the DNPR and generally found low PPVs. This may reflect a potential clinical use of this code for Cbl deficiency independent of anemia as there is no specific ICD-10 code for this condition.

There is no previous investigation of the validity of the ICD-10 diagnosis coding for Cbl deficiency anemia in the DNPR. Other validation studies of ICD-10 diagnosis coding in the DNPR have shown PPVs of 90% or higher,<sup>15–18</sup> although only one of these have investigated diseases or conditions that required laboratory data as a reference standard.<sup>15</sup>

There are several limitations inherent to the definition of a reference standard for Cbl deficiency anemia and the following should be considered when interpreting the results. Our data may indicate that physicians use the ICD-10 code for Cbl deficiency anemia, D51, when patients have had Cbl deficiency anemia in the past. These patients may have normal hemoglobin and/or Cbl related parameters at the time of coding in the DNPR. Accordingly, the PPV was lower among patients with prior use of Cbl supplementation compared with patients with no prior use.

The performances of different biochemical parameters in diagnosing Cbl deficiency have been thoroughly characterized, including the measurement of holotranscobalamin, the metabolically active fraction of circulating Cbl.<sup>19–22</sup> Based on these investigations, strategies have been suggested on how to diagnose Cbl deficiency by assessing biochemical results.<sup>19,21</sup> In the future, these strategies may lead to improvements in the diagnosis of Cbl deficiency.

Furthermore, from these investigations, it is evident that a single blood test result is not definitive in the diagnosis of Cbl deficiency.<sup>8</sup> To address this, we included several parameters in the reference standards that are all applicable for diagnosing Cbl deficiency.<sup>8</sup> Furthermore, physicians may diagnose Cbl deficiency anemia on the basis of symptoms or prior knowledge of the individual patient despite dismissive laboratory results. This would clinically be considered correct according to the current guidelines, as described by Hvas and Nexø.<sup>11</sup> On the basis of these considerations, we may also have underestimated the PPV when using laboratory test results. In addition, we were not able to estimate the sensitivity of the coding of Cbl deficiency anemia since the true prevalence was unknown.

## Conclusion

The PPVs of the ICD-10 diagnosis coding for Cbl deficiency anemia were generally low in the DNPR. Our data indicated that this register should be used with caution in studies on Cbl deficiency anemia.

## Disclosure

The authors report no conflicts of interest in this work. This study received financial support from the Department of Clinical Epidemiology's Research Foundation. The Department of Clinical Epidemiology, Aarhus University Hospital, receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of these studies have any relation to the present study.

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## Supplementary material

**Table S1** Analysis codes used in this validation study

Database	Parameter searched	Type of analysis codes	Analysis codes
LABKA Database	Hemoglobin	NPU	02319, 02321, 21690
		Danish laboratory codes	AAA00359, AAA93003, AAB00012, ASS00126, ASS00996
	Methylmalonic acid	NPU	02780
	Total homocysteine	NPU	04073
	Mean corpuscular volume	Danish laboratory codes	AAA00705
		NPU	01944
Cbl deficiency diagnostics	Danish laboratory codes	AAA00281, AAA00304	
	NPU	01700	
AUPD	Cbl supplementation prescriptions	ATC	A11E, B03BA01, B03BA02, B03BA03, V03AB33
DNPR	Hospital administered Cbl supplementation administration		BOHC2

**Abbreviations:** ATC, anatomical therapeutic chemical; AUPD, Aarhus University Prescription Database; Cbl, cobalamin; DNPR, Danish National Patient Register; LABKA, Laboratory Information Systems Database; NPU, Nomenclature, Properties, and Units.

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