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The accuracy of mean corpuscular volume guided anaemia classification in primary care

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Abstract

Background: Anemia can be categorized into micro-, normo- or macrocytic anemia based on the mean corpuscular volume (MCV). This categorization might help to define the etiology of anemia.
Methods: The cohort consisted of patients newly diagnosed with anaemia in primary care. Seven aetiologies of anaemia were defined, based on an extensive laboratory protocol. Two assumptions were tested: (i) MCV <80 fl (microcytic) excludes vitamin B12 deficiency, folic acid deficiency, suspected haemolysis and suspected bone marrow disease as anaemia aetiology. (ii) MCV >100 fl (macrocytic) excludes iron deficiency anaemia, anaemia of chronic disease and renal anaemia as anaemia aetiology.
Results: Data of 4129 patients were analysed. One anaemia aetiology could be assigned to 2422 (59%) patients, more than one anaemia aetiology to 888 (22%) patients and uncertainty regarding the aetiology remained in 819 (20%) patients. MCV values were within the normal range in 3505 patients (85%). In 59 of 365 microcytic patients (16%), the anaemia aetiology was not in accordance with the first assumption. In 233 of 259 macrocytic patients (90%), the anaemia aetiology was not in accordance with the second assumption.
Conclusions: Anaemia aetiologies might be ruled out incorrectly if MCV guided classification is used as a first step in the diagnostic work-up of anaemia. We recommend using a broader set of laboratory tests, independent of MCV.

Key words: Anaemia, blood chemical analysis, clinical pathology, erythrocyte indices, practice guideline, primary care

Introduction

A widely used algorithm in the diagnostic work-up of anaemia is the classification based on mean corpuscular volume (MCV) as first described by Wintrobe (1). This algorithm uses the MCV to categorize the anaemia into either microcytic (MCV <80 fl), normocytic (MCV 80–100 fl) or macrocytic (MCV >100 fl). Each of these categories is presumed to have its own anaemia aetiology or aetiologies, based on the pathophysiologic mechanism. For instance, iron deficiency anaemia (IDA) may underlie microcytic anaemia, and vitamin B12 deficiency may underlie macrocytic anaemia. Most guidelines recommend this classification system as a first step in the diagnostic work-up of anaemic patients (2–5). In the past few years, however, several reports have pointed out limitations of a MCV guided anaemia classification algorithm (6,7). For one thing, the MCV represents a mean value, which still might be within the normal range—especially in the early stage of a disease. Furthermore, the MCV outcome might also be within the normal range when multiple aetiologies occur simultaneously in a patient (6).

Key messages

- The majority of anaemic patients (85%) are normocytic (MCV between 80 and 100 fl).
- Anaemia aetiologies are not restricted to a MCV guided anaemia classification system.
- Almost half of anaemic patients have multiple aetiologies or uncertain anaemia.
- The MCV guided anaemia classification is not applicable for most patients with anaemia.

Although the usefulness of the MCV classification system in clinical practice has been questioned, very few of these reports mentioned specific numbers or analysis on the usefulness and/or limitations of MCV in this setting. In a study in hospitalized patients with anaemia, only 7% of patients with vitamin B12 or folic acid deficiency had macrocytic anaemia (8). Furthermore, Seward *et al.* concluded that MCV was not a useful first criterion for the selection of follow-up laboratory tests in the diagnostic work-up of anaemia in hospitalized patients (9). This conclusion was based on the fact that over half of the patients did not have the anaemia aetiology as would be expected based on MCV results. This study also showed low sensitivities and specificities for MCV to identify the anaemia aetiologies. These both studies that showed the limitation of MCV were performed in clinical settings.

Little is known on the predictive value of MCV in general practices. Therefore, we set out to study the predictive value of MCV as a first step in the diagnostic work-up of microcytic and macrocytic anaemia patients by systematically screening for a variety of aetiologies in a cohort of newly diagnosed patients with anaemia in general practices.

Methods

Study population

The original cohort study was designed by general practitioners, clinical chemists and internists (10). Patient data were selected from a database with patients from general practice. This database holds data of individuals from the general population, aged ≥50 years and newly diagnosed with anaemia (i.e. no anaemia 2 years previously). GPs selected the patients by requesting one of the two available laboratory panels when anaemia was suspected. Both panels consisted of an extensive laboratory work-up for all patients at the time of anaemia diagnosis; i.e. measurement of haemoglobin, MCV, reticulocyte count, thrombocyte count, leucocyte count, lactate dehydrogenase, vitamin B12, folic acid, ferritin, transferrin, serum iron and creatinine (sidenote: creatinine was only included in one of two panels). More detailed information about the study population can be found in a previously published study (10). The project operated from 1 February 2007 until 1 February 2017.

The present study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review board of the Albert Schweitzer Hospital.

Definitions

Seven aetiologies for anaemia were defined most often occurring in primary care based on literature (2,4). These seven aetiologies were anaemia of chronic disease (ACD), renal anaemia, IDA, suspected haemolysis, suspected bone marrow disease, folic acid deficiency and vitamin B12 deficiency. For each aetiology, a definition was drawn up based on the extensive laboratory work-up. Each definition was based on literature and the Dutch general practitioners' guideline of anaemia (2,3,11–14). The definitions are added as Supplemental Data 1 (10). The definitions were strictly applied, which made it possible to have multiple aetiologies in one patient. To avoid incorporation bias, the MCV was not included in the definitions of the seven aetiologies. The laboratory system used in this study automatically conducted an electrophoresis in case of low MCV (<80 fl) in combination with increased erythrocyte count [(>6.2 (male) or >5.4 (female) µl]. Therefore, we excluded in retrospect patients with a haemoglobinopathy.

Based on various MCV guided anaemia classification algorithms and as indicated in several reports (6,15), two assumptions were designed: (i) a MCV <80 fl excludes vitamin B12 deficiency, folic acid deficiency, suspected haemolysis and suspected bone marrow disease as anaemia aetiology; and (ii) a MCV >100 fl excludes IDA, ACD and renal anaemia as anaemia aetiology.

Statistical analysis

Missing laboratory values ranged from 0.0% to 0.9% for all parameters, except for creatinine (19.6%) (Table 2). We employed single imputation using an expectation–maximization algorithm (10,16). The relatively large amount of missing creatinine values could be ascribed to the fact that general practitioners were allowed to follow either one of two pathways when they requested laboratory analysis, one of which did not include creatinine. Single imputation was allowed in view of the large cohort size. Relative frequency was used to analyse the assumptions and the mismatches between the predefined anaemia aetiologies and the MCV values. A sensitivity analysis was conducted using the World Health Organization definitions for anaemia. This included

Table 1. Characteristics of 4129 anaemia patients in primary care (2007–17)

	Median (IQR)/count (%)
Age (per year)	75 (64–84)
Male sex	2028 (49)
Haemoglobin (g/dl)	
Male	12.9 (12.1–13.4)
Female	11.4 (10.6–11.8)
MCV (fl)	91 (86–94)
Reticulocytes (%)	1.0 (0.8–1.4)
Leucocyte count (10^9/l)	7.1 (5.7–9.0)
Thrombocyte count (10^9/l)	269 (216–345)
LDH (E/l)	306 (221–373)
eGFR (ml/min/1.73 m^2)	68.8 (53.7–83.6)
Ferritin (µg/l)	
Male	156 (60–321)
Female	81 (21–207)
Transferrin (g/l)	2.38 (2.05–2.82)
Serum iron (µmol/l)	
Male	11.2 (6.5–15.6)
Female	8.8 (4.9–12.4)
Vitamin B12 (pmol/l)	288 (209–430)
Folic acid (nmol/l)	16 (11–25)

eGFR, estimated glomerular filtration rate; IQR, interquartile ranges; LDH, lactate dehydrogenase.

Table 2. The anaemia aetiologies found in 4129 anaemia patients in primary care (2007–17) plotted against the MCV classification

Anaemia aetiology	Count (%)	Microcytic count (%)	Normocytic count (%)	Macrocytic count (%)
ACD	1536 (37)	26 (2)	1409 (92)	101 (7)
Renal anaemia	130 (3)	6 (5)	118 (91)	6 (5)
IDA	646 (16)	230 (36)	410 (63)	6 (1)
Suspected haemolysis	20 (0.5)	1 (5)	17 (85)	2 (10)
Suspected bone marrow disease	38 (0.9)	5 (13)	32 (84)	1 (3)
Vitamin B12 deficiency	49 (1)	1 (2)	44 (90)	4 (8)
Folic acid deficiency	3 (0.1)	—	3 (100)	—
Multiple aetiologies	888 (22)	70 (8)	695 (78)	123 (14)
Combination of IDA, ACD and/or renal anaemia	363 (41)	18	319	26
Combination of vit. B12 def., folic acid def., susp. BMD and/or susp. haemolysis	7 (0.8)	1	3	3
Combination of both of the above options	518 (58)	51	373	94
Uncertain anaemia	819 (20)	26 (3)	777 (95)	16 (2)
Total	4129 (100)	365 (9)	3505 (85)	259 (6)

anaemia defined as haemoglobin <12.9 g/dl (males) or <11.9 g/dl (females). A second analysis was performed with exclusion of data of patients with multiple aetiologies and uncertain anaemia. Data were analysed using SPSS for Windows, version 24 (IBM Corp., Armonk, NY).

Results

Inclusion and characteristics

A total of 4152 patients with newly diagnosed anaemia were included. Data of 23 patients (0.6%) were excluded from further analyses because a haemoglobinopathy was confirmed by genetic testing. Thus, data of 4129 were analysed in this study. The median age of the study population was 75 years (interquartile range 64–84 years) and 2028 patients (49%) were male. Laboratory characteristics of the study population are shown in Table 1.

MCV as a first step in anaemia diagnostics

One anaemia aetiology could be assigned in 2422 (59%) cases, and more than one anaemia aetiology in 888 (22%) cases. A total of 819 (20%) patients did not meet any of the predefined criteria for anaemia aetiologies and therefore the aetiology of the anaemia remained unclear. Table 2 shows the frequencies of micro-, normo- and macrocytic anaemia for each aetiology. MCV values were within the normal range in the vast majority of patients [n = 3505 (85%)]. The range of MCV values for each anaemia aetiology is visualized in Figure 1.

If MCV is used as a first step, an MCV <80 fl should exclude patients with vitamin B12 deficiency, folic acid deficiency, suspected haemolysis and suspected bone marrow disease as aetiology. However, this assumption did not apply to 59 of 365 microcytic patients (16%), in whom one or more of these aetiologies of anaemia were diagnosed. In line with this, an MCV >100 fl should exclude patients with IDA, ACD and renal anaemia as anaemia aetiology. However, 233 of 259 macrocytic patients (90%) did demonstrate one or more of these aetiologies of anaemia.

A sensitivity analysis maintaining the WHO definitions for anaemia resulted in exclusion of 1310 patients. Of the 2842 patients included, 347 were microcytic (12%), 2305 were normocytic (81%) and 190 were macrocytic (7%). In total, 57 out of 347 microcytic patients (16%) and 172 out of 190 macrocytic patients (91%) demonstrated an anaemia aetiology contradictory to what would be expected. More details concerning this subgroup can be found in Supplemental Data 2.

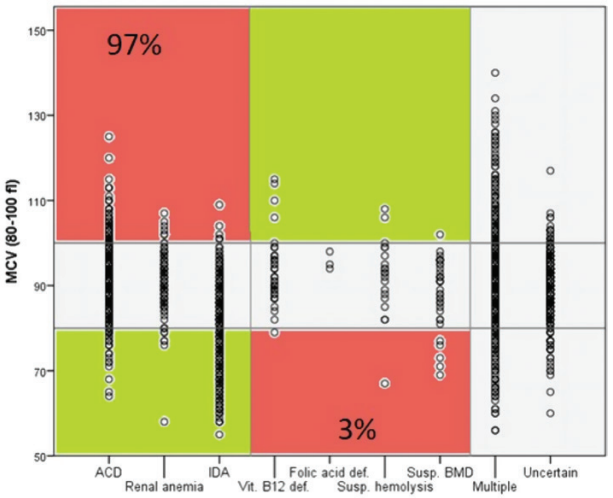

Figure 1. Scatter plot visualizes the anaemia aetiology versus the MCV value in 4129 anaemia patients in primary care. The aetiology of the anaemia is plotted against the patient's MCV value. Each dot represents a case. The cases that fall in the green squares correlate correctly with the MCV guided anaemia classification algorithm. The cases in the red squares would not have been found using the MCV guided anaemia classification system. This represents 3% of the microcytic and 97% of the macrocytic cases. BMD, bone marrow disease; def., deficiency; susp., suspected; vit., vitamin.

MCV assumptions analysis in restricted aetiologies

The above assumptions were tested in a second analysis excluding patients with multiple anaemia aetiologies and those with uncertain anaemia. First, 7 out of 269 microcytic patients (3%) demonstrated an anaemia aetiology contradictory to what would be expected. Second, 113 out of 120 macrocytic patients (94%) demonstrated an anaemia aetiology contradictory to what would be expected.

Conclusions

Principal findings

Our study results implicate that an MCV guided anaemia diagnostic work-up would lead to a suboptimal diagnostic work-up in microcytic and macrocytic anaemia, which might result in inappropriate treatment for most anaemic patients.

The *a priori* probability of an abnormal MCV value is low, since the majority of anaemic patients are normocytic (85%). For these patients, the MCV is not useful as a first step (6).

Our analysis showed that anaemia aetiologies are not restricted to any MCV guided anaemia classification algorithm. In our cohort, 90% of macrocytic- and 16% of microcytic patients demonstrated an anaemia aetiology contradictory to what would be expected based on a MCV guided anaemia classification algorithm. In addition, almost one quarter (22%) turned out to have multiple aetiologies with various combinations, and in 20% of patients the diagnosis of anaemia remained uncertain. For these patients, a MCV guided anaemia classification system is not applicable, although they cannot be singled out during first clinical presentation. Additional analyses excluding this group still violated a MCV guided anaemia classification algorithm in 3% of microcytic and 94% of macrocytic patients.

Strengths and limitations of this study

The cohort studied has some strong features. First, they had all been newly diagnosed with anaemia in general practices, and thus had not yet received additional investigations or treatment for anaemia. Furthermore, the participating general practices represent a typical area of residents in the Netherlands. In addition, in the Netherlands every resident is registered at a general practice. Therefore, the study population is a representation of the general population. Second, the cohort included a large number of patients, which increases the precision of observed point estimates. Furthermore, in all patients an extensive systematic laboratory work-up was conducted at the moment of anaemia diagnosis. In this way, we were able to diagnose or exclude the most common anaemia aetiologies for every patient.

In this study, we used different cut-off values of haemoglobin levels for anaemia compared with the World Health Organization definition (17). The cohort is part of the Dutch population and care is based on the reference values of the participating laboratory. For this reason, we maintained the reference values of the participating laboratory. Nevertheless, we increased the robustness of the study results by adding a sensitivity analysis using the WHO defined cut-off values of haemoglobin levels for anaemia. The sensitivity analysis showed no difference in results outcome. Hence, it can be concluded that the findings of this study have a high external validity.

It is important to realize that this study employed a laboratory-orientated approach to define the anaemia aetiology, and that clinical information is lacking. The diagnosed aetiologies give guidance to further diagnostic work-up, the outcome of which should be matched with the clinical presentation to pursue further investigations and/or treatment.

Implications for clinicians

As it appeared that a large majority of patients from primary care had normocytic anaemia, any MCV guided anaemia classification algorithm is not applicable in most anaemia patients. Furthermore, a MCV guided anaemia classification algorithm seems to have no added value for patients with a micro- or macrocytic anaemia. On top of that, multiple aetiologies of anaemia, in this cohort present in 22% of cases, cannot be diagnosed with this algorithm. Application of a MCV guided anaemia classification based algorithm would lead to a suboptimal diagnostic work-up and might result in an initially inappropriate treatment for most anaemic patients. On top of that, since almost a quarter of anaemic patients have more than one anaemia aetiology, a broad laboratory work-up should be considered in every newly diagnosed anaemia patient.

Supplementary material

Supplementary material is available at *Family Practice* online.

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Declaration

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Ethical approval: all procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional review board of the Albert Schweitzer hospital and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors. This study is part of a large cooperative anaemia project in collaboration with referring general practices, which was approved by the ethics committee of our hospital. The participating general practitioners in the anaemia project had to inform their patients verbally of the participation of the practice in this care improvement project. This method was approved by the institutional review board of the Albert Schweitzer hospital. Consent for publication is not required.

Conflict of interest: none declared.

Prior presentation: none.

Data availability

The dataset used and analysed in the current study is available from the corresponding author on reasonable request.

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