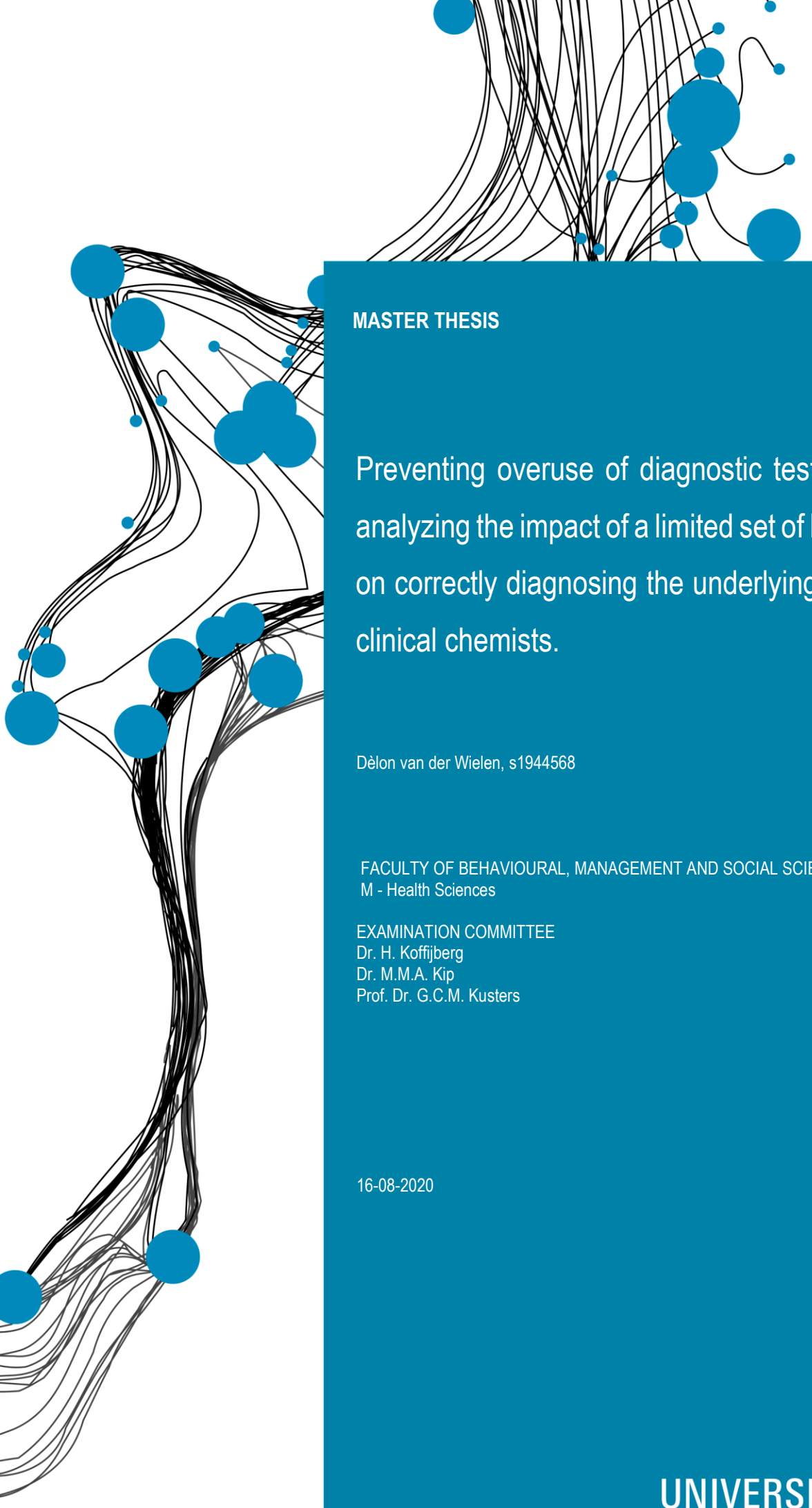

MASTER THESIS

Preventing overuse of diagnostic tests: a case study into analyzing the impact of a limited set of laboratory test results on correctly diagnosing the underlying cause of anemia by clinical chemists.

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ABSTRACT

Background: In this study the percentage of correctly diagnosed underlying cause of anemia by clinical chemists is investigated. Clinical chemists were asked to use a full set of laboratory test results and a limited set of six laboratory test results. Methods: An online survey was build and distributed among 372 clinical chemists and clinical chemists in training affiliated with Netherlands Society for Clinical Chemistry and Laboratory Medicine (NVKC). This survey contained three sections: demographic questions, three cases with all available laboratory test results (n=15) free of choice and three cases with a smaller set of laboratory test results (n=6) containing: Hemoglobin, ferritin, C-reactive protein (CRP), mean corpuscular volume (MCV), Transferrin and folic acid . All cases were derived from a large database of real records suffering from a newly diagnosed anemia. After requesting laboratory test results, respondents were asked to determine an underlying cause of anemia. The respondents were presented three cases in the third section of the survey, in this section the respondents were asked for an underlying cause of anemia based on the limited set of laboratory results. Results: 68 clinical chemist responded to the online survey and diagnosed 58,8% of the presented cases with personally requested laboratory test results correctly compared with the diagnoses given by an expert panel. 56,6% of the cases presented with the limited subset of six laboratory test results were diagnosed correctly. MCV, hemoglobin and ferritin were requested the most. The value of Fleiss' kappa showed that diagnosing iron deficiency (IDA) was carried out best. After analyzing the combinations of requested laboratory test results, no exact agreement was found between the combinations of requested laboratory test results and the limited set of laboratory test results. Conclusion: based on the almost equal percentages of correctly diagnosing the underlying cause of anemia, evidence was found that a limited set of laboratory test results will contribute to prevent the overuse of diagnostic tests in correctly diagnosing the underlying cause of anemia by clinical chemists in the Netherlands.

1 INTRODUCTION

Anemia is a common finding in Dutch general practice, especially among elderly people (>65 years). Anemia is not an illness on its own, but more a symptom caused by a big variety of different diseases. Anemia is a pathological condition characterized by a decreased number of circulating red blood cells and defined by a diminished level of hemoglobin concentrations in whole blood. There is clinical evidence that anemia is also associated with a series of severe complications in cardiovascular disease such as thromboembolic events (e.g.venous thrombosis and stroke). The primary functions of red blood cells are to transport inhaled oxygen from the lungs to the body's tissues, but red blood cells also clean the human body by binding carbon dioxide waste at the body's tissues and transport it to the lungs for exhalation [1][2]. In the Netherlands, anemia is defined as a lower hemoglobin level than the lower limit of the reference value of each type of patient[3].

Most commonly, anemia is diagnosed by a low hemoglobin level or a low hematocrit (< 13.7 g/dL (8.5 mol/L) for men and <12.1 g/dL (7.5 mol/L) for women), also mean corpuscular volume (MCV), reticulocyte count and many other parameters can be useful to diagnose anemia correctly. Anemia is a common diagnosis for clinicians, but to diagnose the correct underlying cause of anemia, many different criteria are needed.[3]

In order to classify the underlying cause of anemia, which initially is based on the hemoglobin level, additional research consists of the determination of the MCV and ferritin levels. The goal of these two determinations are to determine whether or not the patient's anemia could be classified as iron deficiency anemia (IDA). When anemia of chronic disease (ACD), infectious disease or a hematological condition, is suspected based on the anamnesis and the history of the patient, serum iron, transferrin, leukocytes, thrombocytes, Erythrocyte sedimentation rate (ESR) and Modification of Diet in Renal Disease (MDRD=eGFR) levels are determined. An ACD, in particular chronic inflammation, is the result of a disturbed level of iron in the hemoglobin molecule and a shortened life cycle of the red blood cell, this could also occur several weeks after an acute infection. Chronic kidney failure could cause a diminished production of erythropoietin resulting anemia (renal anemia). Bone marrow stem cell diseases or bone marrow suppression could result in a dysfunctional production of erythrocytes. When vitamin B12-and/or folic acid deficiency is expected based on the anamnesis or the history of the patient, also these levels should be determined. Vitamin B12 and folic acid are involved in the production of hemoglobin, a deficiency could lead to a decreased production [3]. Stouten (2016) performed a study about the current and future diagnostics of anemia in the Netherlands, in this study characteristics and test result of a large group of patients (n=2513) presented in Dutch general practices with symptoms of anemia are used. This study has shown that in Dutch general practice patients were diagnosed most with ACD causing the anemia (29,8%). The second most diagnosed cause of anemia was IDA (18,7%). Third, renal anemia was found in 12,3% of the cases used in this study. In this research the focus will therefore be on these three classifications namely:

IDA, ACD and renal anemia[4]. In current practice general practitioners mostly make use of the guideline provided by the Dutch College of General Practitioners (NHG) or the guideline provided by the Dutch Society of Clinical Chemistry Laboratory Medicine (NVKC) to diagnose the correct underlying cause of anemia in adults[5]. Important to mention, but excluded in this study, women with heavy menstrual bleeding and anemia, additional testing is not required because the GP can assume that iron deficiency is the main cause of anemia. When heavy menstrual bleeding is not one of the symptoms, additional testing is recommended. Based on data retrieved from the anamnesis and the history of the patient, the GP could decide to request specific testing. In order to get the correct underlying cause of anemia, a flow chart can be used that selects additional tests based on previous test results to get the correct diagnosis (reflexive testing). In the Netherlands, the NHG-guideline, or a derivative of this, is mainly used as guideline. However, there are different points of view with regard to the use of the NHG-guideline: delegates from internal medicine in the Netherlands states that the NHG-guideline is incomplete and very complex, Also a group of general practitioners has questions about the use of this workflow. Due to the complexity of this guideline, it is also difficult to implement this in the daily routine of the clinical chemical laboratories [6]. In response to this, Oosterhuis et al.(2007) developed and introduced a substantive and alternative flow chart, in particular reflexive testing becomes easier to implement in the current routine and to use in the laboratories. The intended effect of reflexive testing is to determine a correct diagnosis more quickly with less diagnostic laboratory tests, which is also less stressful for the patient (possibility of getting the correct diagnosis with only one blood sample). This changes the role of the clinical chemist and the general practitioner, since the laboratory is likely more involved in the interpretation of the laboratory results with additional comments to the general practitioner[7]. Schop et al.(2018) conducted a study about the effectiveness of using a routine- (GP's were asked to select the laboratory test for further diagnostic examination from a list of 14 parameters) versus an extensive laboratory work-up (GP's were presented with the full list of test results from the 14 parameters), in order to diagnose the correct underlying cause of anemia by GP's. They found out that an extensive laboratory work-up is could result in preventing overuse of diagnostic tests in finding the correct underlying cause of anemia. However, the percentage of incorrect diagnoses was still significant[8]. Another study conducted by Oonk (2018) indicated that an extensive laboratory work-up with a subset of nine laboratory tests containing: ferritin, CRP, reticulocytes, serum iron, erythrocyte sedimentation rate (ESR), MDRD, hemoglobin, leukocytes and folic acid, was the statistically most efficient subset for diagnosing an underlying cause of anemia. This research also showed that a limited set of laboratory tests results containing: ferritin, CRP, MCV, Transferrin and folic acid, was the most efficient subset for diagnosing the correct underlying cause. These subsets were all based on statistics rather than tested in daily practice [9]. With the assumption that the extensive laboratory work-up and the derived limited subset could theoretically prevent the overuse of diagnostic treatment in diagnosing the correct underlying cause of anemia, the focus of this study is on the effectiveness of using a routine work-up versus the use of a limited subset of laboratory test results. Understanding that the role of clinical chemist in the workflow of diagnosing the underlying cause of anemia may change, this study examines to what extent clinical chemists are able to correctly diagnose the underlying cause of the anemia using these two laboratory work-ups.

2 METHODS

In order to determine whether using a routine work-up or providing a small subset of laboratory test results will result in different effectiveness in correctly diagnosing the underlying cause of anemia, an online survey using Qualtrics was used. This survey was distributed among 312 clinical chemists and 60 clinical chemists in training affiliated with the NVKC by email. The online survey was available from 20th of January 2020 until 1st of March 2020 [10]. The cases used in the online survey were obtained from a prospective database of anemia patients (n=2389). Initially the database consisted of 3325 patients older than 50 years with a newly diagnosed anemia. Due to missing data 643 patients were excluded, patients with a too complex clinical picture were also excluded (n=293). the prospected database (n=2389) was eventually divided in four subgroups: IDA (n=389), ACD (n=751), renal anemia (n=307) and other (also unknown cause) (n=942). For each case in the database an extensive laboratory work-up was performed containing MCV, ferritin, vitamin B12, transferrin, hemoglobin, reticulocytes, thrombocytes, lactate dehydrogenase (LDH), folic acid, CRP, ESR, leukocytes, creatinine, MDRD and serum iron. These tests were in accordance with the current guidelines used in clinical practice. The underlying cause of anemia of each case in the database were determined by an expert panel, consisting of an experienced GP, internist and clinical chemist. These determinations were all based on 10 redefined causes (i.e. IDA, ACD, renal anaemia, possible bone marrow disease, possible haemolysis, haemoglobinopathy, vitamin B12 deficiency, folic acid deficiency, other and unknown). As shown in the study by Stouten et al. (2018) ACD, unknown, IDA and renal anemia had the highest prevalence therefore these underlying cause of anemia were included in this study. the prospected database (n=2389) was eventually divided in four subgroups: IDA (n=389), ACD (n=751), renal anemia (n=307) and unknown (n=942). Based on the prevalence of the four subgroups, 201 cases were selected and used for this research. To determine whether the clinical chemists were able to make a correct diagnosis of the underlying cause of anemia based on a limited set of laboratory tests, the most difficult cases to diagnose were selected. This selection is made by computing a code in Microsoft excel which mimics exactly the NHG-guideline based on the test results of the patients [11]. Each of the 201 cases was analyzed by this code and the outcome (probable cause of anemia) compared with the diagnosis of the expert panel. Every inequality between the diagnosis of the code and the diagnosis of the expert panel and the cases diagnosed with ''unknown cause" were considered as difficult cases (n=28). 21 cases were randomly selected to be presented to the clinical chemists [12]. Before distributing the online survey, a small test panel of five clinical chemists were asked to assess the content of the survey and the understandability of the questions. the feedback given by test panel has been used to update the online survey and distribute it among the clinical chemists. At the start of the online survey clinical chemist were

asked for demographic characteristics like working experience, the use of guidelines and the kind of institution they work in. Each survey included three cases randomly derived from the subset of 21 ‘’difficult cases” in which the clinical chemist was able to request laboratory results they thought to be useful for a correct diagnosis. To meet the current way of working the most and provide enough possibilities to request laboratory test result, clinical chemists had the opportunity to request laboratory results over five rounds. In this way reflexive testing could be simulated. The clinical chemist could choose from the 15 different laboratory tests as mentioned before, which is the same set of laboratory tests used in the study among GP's. After each round of requesting laboratory tests, the clinical chemist was presented with the test results and associated reference values. Subsequently, the clinical chemist could give a diagnosis of suspected underlying cause of anemia (IDA, ACD, renal anemia, other or unknown) or could request more laboratory results. After diagnosing three cases with personally ordered laboratory test results, the clinical chemists were presented with three cases with a limited subset of laboratory test results without the opportunity of requesting more results, respondents were then invited to determine an underlying cause of anemia. These tests included in the limited subsets of laboratory tests are the same as the most effective limited subset found by Oonk (2008). The small set of six laboratory test results consists of hemoglobin, MCV, CRP, ferritin, transferrin and folic acid.

2.1 Statistical analysis

Characteristics of the whole sample of clinical chemists were provided by using standard descriptive statistics. These characteristics included the working experience (years), working environment and which guidelines the clinical chemists uses. Working experience is a ratio variable giving the mean of working experience in years with in addition the minimum and maximum value and the standard deviation. Both working environment and the use of guidelines are ordinal variables giving the frequencies and percentages of the whole sample. Before the data of the online surveys were analyzed using SPSS version 26, the data was prepared for data analysis [13]. Since 15 different laboratory tests could be requested, the codes of the tests, whether or not requested, were re-coded using geometric coding. Geometric encoding is a way of encoding data that results in a single variable representing the combinations of answers to a question. This variable could be used for statistical analysis. A more closer look of data preparation is described in the appendix. Standard descriptive statistics compared the diagnoses of the clinical chemists with the diagnoses of the expert panel. The table shows the agreement in frequencies and percentages. To determine the degree of agreement between two or more assessors (also known as 'judges' or 'observers'), the Fleiss 'kappa was used. When using this analysis the inter-rater agreement is shown by 2 tables: "Overall agreement" and "agreement on individual categories". In these tables, the kappa (k) and significance coefficient are most important. The kappa can be interpreted using table 1 [14].

Table 1: Classification of Fleiss' kappa.

Value of k	Strength of agreement
<0.20	Poor
0.21-0.40	Fair
0.41-0.60	Moderate
0.61-0.80	Good
0.81-1.00	Very good

3 RESULTS

In the period the online survey was available, 68 (18.3%) of the 372 respondents completed the survey, of which 7.4% are employed at a academic hospital, 8.8% at a first-line diagnostic center, 45% at a top clinical hospital and 33.8% of respondents at a non-top clinical hospital. The survey consisted of three parts, namely: demographic data, case diagnosis with self-application of tests and case diagnosis with a limited set of laboratory test results. One respondent did not fill in the part of the diagnostics case with the limited subset. All demographic data is shown in table 1 of the appendix. In total, 204 cases were assessed by 68 respondents on the basis of their own requested laboratory tests. In total 1712 laboratory results were requested for these assessments. Of which 752 (43.9%) in the first round, 732 (42.8%) in the second round, 176 (10.3%) in the third round, 46 (2.7%) in the fourth round and 6 (0.4%) in the fifth round. Table 2 provides a detailed overview of the number of laboratory tests requested in each round.

Parameter	Round 1	Round 2	Round 3	Round 4	Round 5
MCV	**186**	7	1		
Hemoglobin	**185**	9	1		
Ferritin	**85**	**81**	2	1	
Leukocytes	51	35	14	3	2
Thrombocytes	50	35	8	4	2
CRP	41	45	17	3	
Reticulocytes	33	**73**	16	1	
ESR	25	37	6		
MDRD	20	56	16	6	
Creatinine	15	59	18	7	
Vit. B12	14	**66**	13	3	
Transferrin	13	53	12	6	
Folic acid	12	62	13	3	1
Serum iron	11	49	11	5	
LDH	9	50	13	2	1
All tests	2	15	15	2	
Total	752	732	176	46	6

Table 2: detailed overview of requested tests by respondents of the online survey

The most common combinations of laboratory tests requested in the first round were MCV + hemoglobin (27,5%, n = 56), MCV + hemoglobin + ferritin (14,2%, n = 29), and MCV + hemoglobin + thrombocytes + leukocytes (4,9%, n = 10). see figure 1.
In the second round, no major differences were seen in combinations of requested tests results, the three most requested laboratory tests were: ferritin (11,1%, n = 81), reticulocytes (10,0%, n = 73) and vitamin B12 (9,0%, n = 66). In addition, most requests were made across the entire spectrum of available tests and the frequencies are close to each other. Two outcomes of possible combinations of

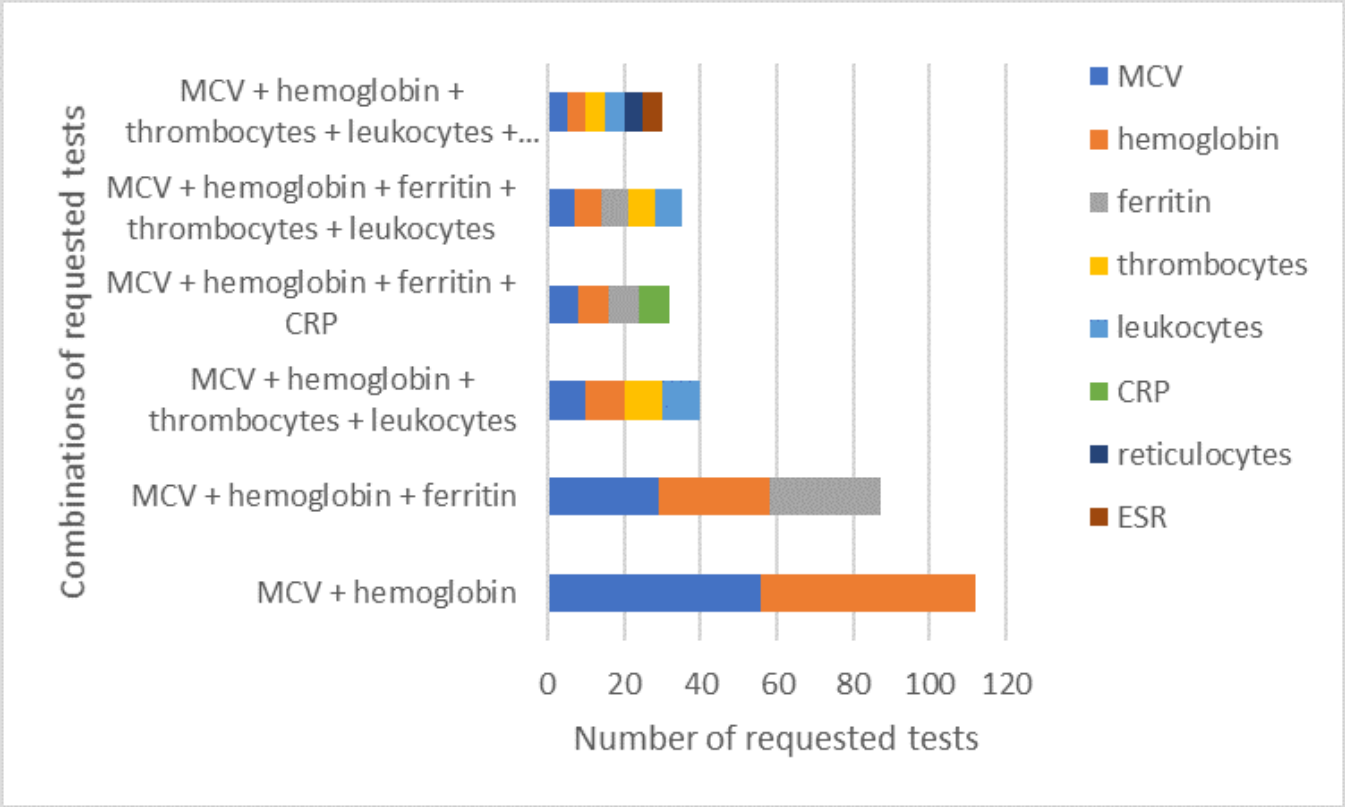

Figure 1: Stacked bar of the most requested combinations of laboratory test results in round 1

requested laboratory test results were more frequently requested than other combinations, however these were not actual combinations, but a single requested test result: Ferritin (11,3%, n = 23) and all tests at once (n = 15). Also in the third round 'all tests in once' (7,4%, n = 15). In the other rounds no combinations were found that were requested more frequently than other combinations. Also the total combination of requested laboratory test results per case is analyzed. This shows a wide variety of combinations, the most frequent combination of requested tests results over five rounds found is the request of all tests by clinical chemists. The respondents' diagnosis were all compared to those of the expert panel. This revealed that 120 (58.8%) cases were correctly diagnosed and 84 (41.2%) were misdiagnosed. The diagnosis of the respondents with the limited set of laboratory results gave 116 (56.9%) correct diagnosis compared to 88 (43.1%) incorrect diagnoses. The diagnoses selected by the clinical chemists between using the personally requested laboratory tests and using the limited subset did not result in a significantly different (p=.181) outcome. As mentioned respondents had up to 5 rounds to request laboratory test results, most respondents formulated a diagnosis in the second round (n=104), no combinations of requested laboratory test results were found that is equal to the smaller set of six laboratory test results presented in the second part of the survey. On average respondents requested 8,3 diagnostic tests in order to formulate a correct diagnosis, respondent with incorrect diagnosis requested on average 5,7 diagnostic tests. All combinations requested by the respondents are shown available in the supplemental data.

Fleiss' kappa was run to determine if there was agreement between the respondents and the expert panel on the diagnosis of each assessed case in which they were able to choose between IDA, ACD, renal anemia, other and unknown based on the chosen laboratory tests. Fleiss' kappa showed that there was fair agreement between the respondents and the expert panel, k=.364 (95% CI, .361 to .367), p < .0005. Between the different diagnoses Fleiss' kappa showed, in contrast to the other diagnoses; Other k=.422 (95% CI, .418 to 427), ACD k=.158 (95% CI, .154 to .162), Renal anemia k=.023 (95% CI, .027 to .018) and Unknown k=.303 (95% CI, .298 to .307), a good strength of agreement on IDA was found k=.805 (95% CI, .800 to .809), p < .0005. Fleiss' kappa was also run to determine if there was agreement between the respondents and the expert panel on the diagnosis of each assessed case in which they were presented to a fixed set of laboratory results. Fleiss' kappa showed that there was fair agreement between the respondents and the expert panel, k=.273 (95% CI, .270 to .276, p < .0005). Furthermore, the working environment (P = 0.272), the use of guidelines (P = 0.262) and the work experience (p = 0.633) had no influence on whether or not a correct diagnosis was made. Comparing the correctly diagnosed cases with the misdiagnosed cases of the routine work-up, no differences were found in requested laboratory test results, see figure

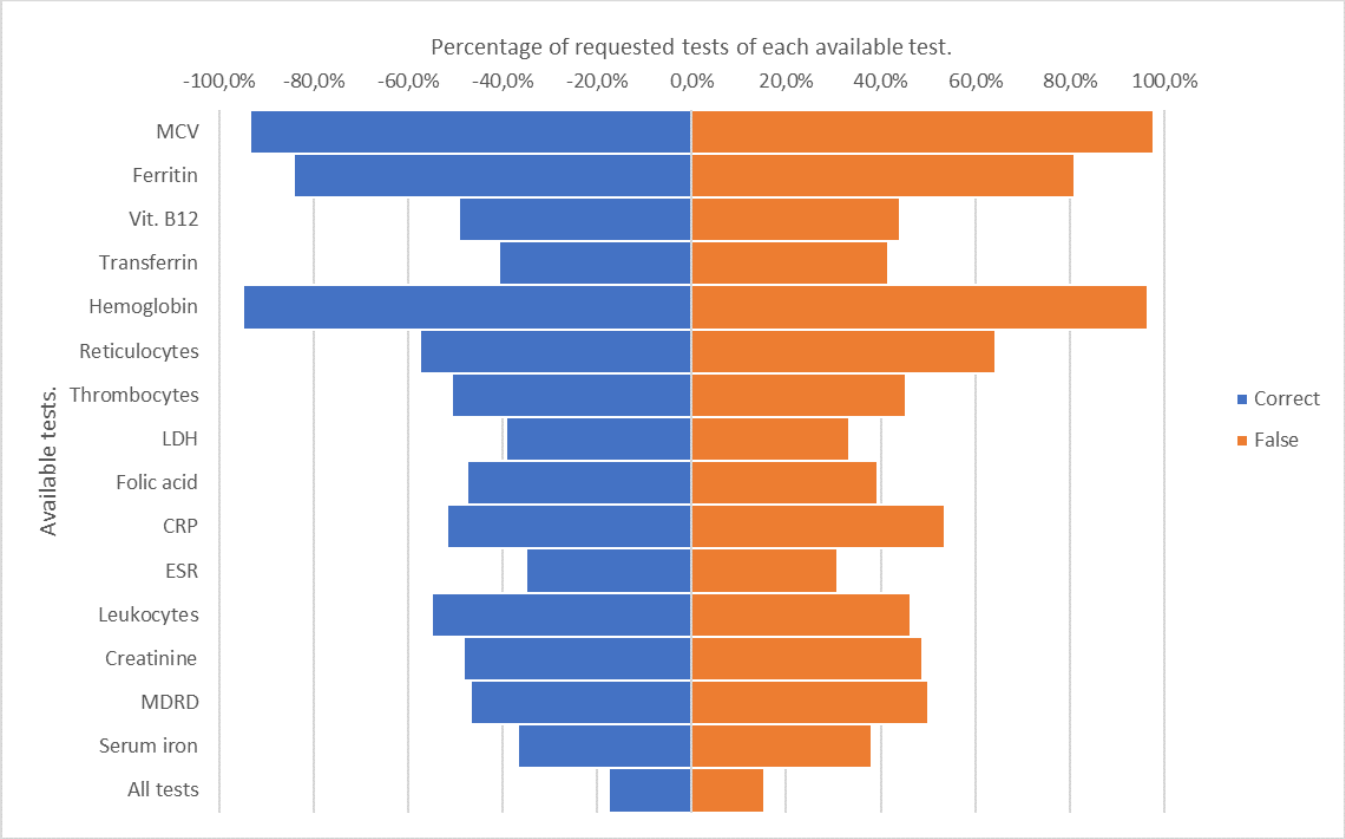

Figure 2: Mirror bar chart representing how many tests are requested by clinical chemists for diagnosing the correct underlying cause of anemia

2. This figure shows the total of requested test results of both the correct and misdiagnosed cases, a detailed overview is shown in table 2 in the appendix. In this study no evidence was found to support the limited set of laboratory test results resulting in a higher amount of correctly diagnosed cases: ferritin (P = 0.662), CRP (P = 0.626), MCV (P = 0.352), transferrin (P = 0.299) and folic acid (P = 0.590).

4 DISCUSSION

The results of this study showed roughly no difference in correctly diagnosing the underlying cause of anemia by clinical chemists using the routine work-up and using a limited subset of six laboratory tests results. This means that using less laboratory test results, clinical chemist were able to reproduce an equal number of correctly diagnosed cases. Looking at the difference between the different categories of underlying cause of anemia (IDA, ACD, renal anemia, other and unknown) using Fleiss' kappa, a bigger difference is notable. This analysis showed a good strength of agreement for diagnosing IDA as underlying cause of anemia. ACD on the other hand appeared quite difficult to diagnose (=.158). As mentioned in a study conducted by Halwachs-Baumann (2012) the underlying pathophysiological principles and therapeutic interventions are significantly different, almost same parameters are involved in diagnosing the correct underlying cause of anemia and especially in distinguishing IDA and ACD [15]. Gollomp et al. (2018) conducted a study about diagnosing ACD and also presented the differences between the values of different parameters [16]. As stated before, multiple laboratory test results are of great value in diagnosing IDA or ACD. Weiss also showed parameter values, which also were included in this study, that can differentiate ACD from IDA namely: serum iron, transferrin and ferritin [17]. According to Weiss (2005) ACD shows a reduced serum iron level, a reduced to normal tranferrin level and a normal to increased ferritin level. The most difficult cases selected for this study showed marginal low values or even normal values of the parameters. Since serum iron is not included in the limited subset of six laboratory test results, the difference between ACD and IDA could be more difficult to tackle. Assessing these cases with the smaller subset of laboratory tests could result in misdiagnoses of patients. The CRP parameter (included in the routine work-up) however could play a big role in distinguish IDA from ACD when this parameter is included in the smaller subset of laboratory test results [17]. This parameter is an indication for inflammatory processes in the human body and is produced by the liver. While CRP can have a major influence on diagnosing the correct underlying cause of the anemia, this parameter is not

integrated as standard in the NHG guidelines. 44.1% of the respondents use the NHG standard, with the influence of CRP possibly remaining under the radar [18]. Previous research has statistically shown that the limited subset consisting of: ferritin, CRP, MCV, transferrin and folic acid could result in a similar percentage of correctly diagnosed patients, resulting in the use of less diagnostic tests. No indications have been found that a particular parameter from the limited subset of six laboratory test results is more or less related to correctly diagnosing the underlying cause of anemia. Since most tests were requested in the first three rounds (89.4%), with no clear combinations of requested test results found, it seems that the respondent preferred multiple test results to get a more generalized picture of the patient's anemia instead of targeted tests on the basis of the results obtained. Supported in several previous studies[9][8], hemoglobin, MCV and ferritin are by far the most requested tests in the first round. This is also in line with when these requests are compared with the NHG guideline and the NVKC guideline. In these guidelines, possible underlying causes are also separated at the beginning of the workflow on hemoglobin, MCV and Ferritin levels (NHG-guideline) and hemoglobin and ferritin levels (NVKC guideline). Although various studies describe that the role of MCV should be less central in the workflow, it is clear that clinical chemists attach great value to the value of MCV. A study conducted in an American hospital showed that the sensitivity of MCV was significantly low in patients with abnormalities in vitamin B12, folic acid and ferritin levels. As a result, MCV did not provide the required information to request the correct order of tests to identify the correct underlying cause of the anemia [19]. This study showed no great difference in correctly diagnosing an underlying cause of anemia by clinical chemists. However, looking at the differences between the categories of underlying causes of the anemia the small subset (k=.273). of laboratory tests showed a lower kappa value resulting in a lower strength of agreement versus the routine work-up (k=.364).

4.1 strengths and limitations

In order to get a clear insight of the working method of clinical chemists in the Netherlands, with regard to the diagnosis of an underlying cause of an anemia, an attempt has been made to get the most representative group possible. All clinical chemists affiliated with the NVKC have been contacted for this by email.This distribution is similar to the distribution among all Dutch clinical chemists, as published by the NVKC, and is therefore seen as a representative sample of the population. [20] A possible limitation of this study is that respondents are not presented with the full real situation of the patient. They indicate that they need additional information about eating/drinking habits and lifestyle, as well as clinical information, which of major importance, to derive a more accurate result from the presented data. The anamnesis, physical condition and medical history are important here. In this study, only the age and sex of the patients were given as additional information. Since the same demographic data were presented in both the personally ordered work-up and the limited subset of laboratory tests, this does not affect the comparison between these two methods. However, it can affect the correct diagnosis of the case by the clinical chemist. A further limitation in this study is the distribution of the various diagnoses among the cases. In this study, more than half (n = 38) was diagnosed by the expert panel as "unknown", only nine cases with "IDA" as diagnosis and fifteen cases as "ACD" were diagnosed. Because all difficult cases were selected, there was no case with the diagnosis of "renal anemia". With this skewed distribution of different diagnoses, it is difficult to determine which diagnosis may or may not be more difficult to make than the other. Because technical difficulties, it was not possible to design one questionnaire that automatically selects random cases from a database, decided was to make a questionnaire in seven different versions. in this way, not all "difficult" had an opportunity to be assessed by the respondents, resulting in excluding cases. However, the design was the same for all versions, only the cases were different. As a result, each selected case was assessed several times by different respondents. Furthermore, the cases included in the personally ordered part of version one were presented in a in the limited set part of version two. The cases included in the personally ordered part of version two were then presented in the limited set part of version three and so on. In this way, every case was assessed by two groups of clinical chemists each time. One group based on personally ordered and the other group based on the limited set.

5 CONCLUSION

The limited subset of six laboratory test results did not result in a higher nor a lower percentage of clinical chemists correctly diagnosing the underlying cause of anemia using an exceptional set of real patient records. Both methods show high frequencies of incorrectly diagnosed patient cases. However, based on these results overuse of diagnostic tests could be prevented, since using less laboratory test results does not affect the chance of correctly diagnosing the underlying cause of anemia. however, as mentioned before, further studies should focus on the role of the clinical chemist and the GP in the whole process of diagnosing patients. Further, more insights are needed in the different approaches assessing patients with anemia. Literature showed that different approaches are available for clinical chemists, which could result in giving different diagnoses.

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Respondents characteristics				
	Mean	Minimum	Maximum	Standard deviation
Working experience	12	1	33	8,3
Respondents characteristics(frequencies and percentages)				
Working environment	Academic hospital	Top clinical hospital	Non-top clinical hospital	First-line diagnostic center
Frequency	5 (7,4%)	31 (45,6%)	23 (33,8%)	6 (8,8%)
Use of guideline	NHG-guideline	NVKC-guideline	Home-made guideline	Other guidelines
Frequency	32 (47,1%)	19 (27,9%)	12 (17,6%)	5 (7,4%)

Table 1: Demographic data respondents online survey

Total requested tests % (n)		
	Diagnosis	
Test	*Correct (n=120)*	*False (n=84)*
MCV	93,3% (112)	97,6% (82)
Ferritin	84,2% (101)	81,0% (68)
Vit. B12	49,2% (59)	44,0% (37)
Transferrin	40,8% (49)	41,7% (35)
Hemoglobin	95,0% (114)	96,4% (81)
Reticulocytes	57,5% (69)	64,3% (54)
Thrombocytes	50,8% (61)	45,2% (38)
LDH	39,2% (47)	33,3% (28)
Folic acid	47,5% (57)	39,3% (33)
CRP	51,7% (62)	53,6% (45)
ESR	35,0% (42)	31,0% (26)
Leukocytes	55,0% (66)	46,4% (39)
Creatinine	48,3% (58)	48,8% (41)
MDRD	46,7% (56)	50,0% (42)
Serum iron	36,7% (44)	38,1% (32)
All tests	17,5% (21)	15,5% (13)
Total requested tests	*1018*	*694*

Table 2: The total amount of tests requested by clinical chemists for diagnosing the correct underlying cause of anemia

Data preparation analysis

When a respondent did not choose a laboratory test, it was coded with '0'. When a test has been chosen, the following values are assigned to the different tests: MCV=1; ferritin=2; vit. B12=4; transferrin=8; hemoglobin=16; reticulocytes=32; thrombocytes=64; LDH=128; Folic acid=256; CRP=512; ESR=1024; leukocytes=2048; creatinine=4096; MDRD=8192; serum iron=16384 and all tests=32768. Subsequently, the codes of the tests that have been requested were summed up to get a unique code for each combination of requested tests. A disadvantage of this type coding is that long unclear codes were formed. To tackle this problem, the numerical code for the tests has been recoded by one letter codes: MCV = A, Ferritin = B, vitamin B12 = C and so on. Subsequently, the variables were converted to "string variables", with the functions CONCAT and RSTRING these individual letters could be merged into one letter code. The maximum length of the is fifteen letters (all tests requested separately). Since tests could be requested in five rounds, different codes with the same letters were possible, for example:

- Round 1: MCV (A), vitamin B12 (C) and Hemoglobin (E)
- Round 2: Ferritin (B) and Transferrin (D)

Requesting this combination results in the code: ACEBD If the requests made in round 2 were made in round 1 and those for round 1 in round 2, you will receive the following code:

- Round 1: Ferritin (B) and Transferrin (D)
- Round 2: MCV (A), Vit. B12 (C) and Hemoglobin (E)

The combination request results in the code: BDACE, although the order of the letters is different, it represents the exact same combination of test results. To find duplicates of combinations, all individual letter combinations have been alphabetized, so that each code starts with the next letter in the alphabet. As a result, in the abovementioned example 2x ABCDE is formulated. These letter combinations ensure that every combination of requested tests could be analyzed either per round or overall.