Differentiation of Iron Deficiency and the Anemia of Chronic Disease

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The predictive value positive of serum iron studies and erythrocyte indices in differentiating between iron deficiency anemia and the anemia of chronic disease (ACD) were determined in 82 hospitalized patients with an iron-binding saturation of 15 percent or less. Iron deficiency, determined by serum ferritin of 20 ng/mL or less, was present in only 31 percent of patients with a serum iron level of 10 μg/dL or less; 39 percent of patients with a transferrin saturation of 5 percent or less, and 54 percent of patients with a total iron-binding capacity (TIBC) of 350 μg/dL or greater; conversely, iron deficiency was present in only 3 percent of patients with a TIBC of 250 μg/dL or less. Iron deficiency was present in 83 percent of patients with a mean corpuscular volume (MCV) of 75 μm^3 or less, but only 2 percent of patients with an MCV of 86 μm^3 or greater. It is concluded that the MCV has strong predictive value positive (and negative) when below (or above) the values just cited, but that serum iron studies do not have sufficient predictive value to justify their use in the routine differentiation between iron deficiency anemia and the ACD in hospitalized patients when no other cause for anemia is likely.

One of the most frequent problems in the diagnosis of anemia is the differentiation between iron deficiency and the anemia of chronic disease (ACD). Although the typical clinical manifestations of iron deficiency and the ACD are well established,[1-3] little information has been published on the predictive value of the individual laboratory parameters commonly used to differentiate between the two conditions. This study was undertaken to determine the accuracy of serum iron studies (serum iron, total iron-binding capacity, and transferrin saturation) and the erythrocyte indices (mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH]) in identifying the presence of iron deficiency anemia among hospitalized patients also at risk for ACD.

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Methods

This study included all adult patients (aged 16 years or older) admitted to the University of Utah

Medical Center for a six-month period, July to December 1982, who had serum ferritin assays performed and a total iron-binding capacity (TIBC) of 15 percent or less. The serum ferritin level was the reference value used to determine whether iron deficiency was present. Patients admitted to the psychiatric service were not included. Also, patients were deleted from the study group if they had received regular iron therapy during the previous month, had no complete blood count available, had a complicating disease involving abnormal iron metabolism (eg, hemochromatosis), or had one of four conditions known to be associated with normal ferritin levels in the presence of deficient bone-marrow iron stores (rheumatoid arthritis, hepatic disease, leukemia and lymphoma, and active inflammatory bowel disease).[4-8]

Patients were considered to have hepatic disease if there was a twofold elevation of one or more liver function tests (alkaline phosphatase, total or direct bilirubin, gamma glutamyl transpeptidase [GGT], serum glutamic-oxaloacetic transaminase [SGOT], serum glutamic-pyruvic transaminase [SGPT]) without an evident nonhepatic etiology. The liver function tests and complete blood counts used were the most recent values obtained before the serum iron studies were drawn.

When a patient had more than one set of iron studies during the time period of the project, only the study with the lowest transferrin saturation was used. Iron studies were performed according to established methods. Serum ferritin determinations were done according to the Fer-Iron* method for the first three months of the study, at which time the clinical laboratories changed to the Quantimune** ferritin assay (correlation coefficient = 0.96 between methods on 38 paired samples). Complete blood counts and red blood cell indices were determined by Coulter counter.

Normal values, expressed as 95 percent confidence intervals and for all ages and sexes combined, were serum iron 55 to 170 μg/dL and TIBC 187 to 442 μg/dL, with mean TIBC 324 μg/dL for patients less than 60 years old and 280 μg/dL for those over 60. Normal serum ferritin values used in the clinical laboratories were obtained from previously published normal values and were not specific for this hospital.

Iron deficiency was considered to be present if the serum ferritin was 20 ng/mL or less.[5] Although somewhat higher than in some studies,[7,9,10] this value was chosen to minimize the possibility of misclassifying iron deficiency anemia as not present. Predictive values positive were obtained for the serum iron studies (serum iron, TIBC, transferrin saturation) and erythrocyte indices (MCV, MCH) according to the method illustrated for transferrin saturation in Table 1.

Results

One hundred thirty-three patients met the general criteria for the study, from which 21 patients were excluded for liver disease, 17 for active rheumatoid arthritis, six for leukemia or lymphoma, and seven for having received regular iron therapy. The remaining 82 patients constitute the final study group cited below.

The predictive value positive for each of the test variables in identifying iron deficiency, as defined by a serum ferritin of 20 ng/mL or less, is summarized in Table 2. The serum iron level was not a reliable predictor of iron deficiency; even extremely low levels ($\leq$10 μg/dL) were more likely to be associated with the ACD than with iron deficiency. The TIBC was associated with a very low predictive value positive (3 percent) when it was 250 μg/dL or less, but even TIBC values of 350 μg/dL or more were predictive of iron deficiency in only 54 percent of the patients.

The extent of depression of the transferrin saturation did not reliably predict the presence of iron deficiency; iron deficiency was present in less than one half of the patients with a transferrin saturation of 5 percent or less, and only two of eight patients (25 percent) with transferrin saturations of 1 percent or less had demonstrable iron deficiency. The predictive value positive for the MCV and MCH were nearly identical, reflecting a high degree of correlation between these two parameters ($r = .982$). The predictive value positive increased as the MCV decreased; only 2 percent of patients with an MCV of 86 μm^3 or greater had iron deficiency, while 83 percent of patients with an MCV of 75 μm^3 or less had iron deficiency.

Predictive values were also calculated using a

*Ramco Laboratories, Inc., Houston, Texas.
**Bio-Rad Laboratories, Richmond, California.

Table 1. Positive Predictive Values of Serum Iron Studies and Erythrocyte Indices for Iron Deficiency

	Patients with Serum Ferritin ≤20 ng/mL No.	Total Patients No.	Predictive Value Positive No. (%)	P Value*	Ferritin Range (ng/mL)	Ferritin Median (ng/mL)
Serum iron (μg/dL)						
<11	9	30	30		2-884	174
11-20	8	22	36	.14	3-516	162
21-30	3	17	18		7-414	55
>30	1	12	8		15-293	80
TIBC (μg/dL)						
<251	1	35	3		17-884	276
251-300	5	20	25	.000	19-675	39
301-350	8	14	57		5-200	14
>350	7	13	54		2-155	20
Transferrin saturation (%)						
<6	14	36	39		2-884	138
6-10	6	32	19	.001	7-565	140
11-15	1	14	7		15-293	98
MCV (μ^3)						
<76	10	12	83		2-155	7
76-80	5	10	50	.000	5-374	22.5
81-85	5	19	26		12-675	99
>85	1	41	2		10-884	200
MCH (μμg)						
≤24	9	11	82		2-155	7
24.1-26	5	9	56	.000	5-374	20
26.1-28	5	18	28		10-675	86
>28	2	43	5		19-884	200

*Mantel-Haenszel chi-square analysis

serum ferritin of 50 ng/mL as the separation point for iron deficiency. This level was chosen because occasional patients with chronic inflammatory diseases have serum ferritins in the low-normal range despite being iron deficient.[8] The predictive values positive for the iron studies were not substantially enhanced or were still unreliable in identifying iron deficiency: 37 percent of patients with a serum iron of 10 μg/dL or less were iron deficient by these criteria, as were 44 percent with a transferrin saturation of 5 percent or less. The predictive value positive of a TIBC of 250 μg/dL or less was 6 percent and 69 percent when the TIBC was greater than 350 μg/dL. Ninety-two percent of patients with an MCV of 75 μm^3 or less were identified as iron deficient.

Eight patients had hemoglobin or hematocrit values that were within the normal range for this hospital; these values were at the lower limit of the normal range except in one instance in which the patient had a complicating pulmonary problem, and microcytosis existed. The transferrin saturation for this group of patients ranged from less than 1 percent to 11 percent (median of 5 percent).

Discussion

Although the clinical manifestations of iron deficiency anemia and ACD have been well-described, usually the laboratory abnormalities associated with these conditions have been presented descriptively or with respect to their sensitivity, or specificity for each condition. These values measure the probability that a patient

Table 2. Disease Condition: Serum Ferritin			
Test Variable	**≦20 ng/mL**	**>20 ng/mL**	**Totals**
Transferrin saturation ≦5%	a	c	a + c
Transferrin saturation >5%	b	d	b + d
Totals	a + b	c + d	

$$\text{Predictive Value Positive} = \frac{a}{a + c}$$

known to have a disease will have a positive (or negative) test. However, the clinician is most interested in the predictive value positive (or negative) of a particular laboratory test in arriving at a diagnosis.[11] These values represent the probability of the presence (or absence) of a disease if a particular test is positive (or negative). This study demonstrates several useful conclusions about the predictive values of several common laboratory tests used to differentiate between iron deficiency anemia and the anemia of chronic disease in hospitalized patients.

First, the data in this study indicate that in hospitalized patients with complicating medical problems, neither the serum iron level nor the extent of depression of the transferrin saturation will reliably predict the presence or absence of iron deficiency as judged by the serum ferritin level. Transferrin saturations less than 5 percent had previously been reported to be uncommon in ACD; two studies found no patients with ACD who had transferrin saturations at that level,[1,7] and it has been stated that transferrin saturations less than 5 percent almost certainly indicate iron deficiency.[12]

These conclusions, however, do not appear to pertain to the patients in this study hospitalized for acute illness. The majority of patients with transferrin saturations of 5 percent or less did not have demonstrable iron deficiency, and iron deficiency was present in only 25 percent (2 of 8 patients) of patients with transferrin saturations of 1 percent or less.

Second, the TIBC was mainly useful in excluding iron deficiency rather than successfully predicting its presence. Although iron deficiency may be associated with a normal or low TIBC in some patients,[1] this study indicates that in hospitalized patients a TIBC of 250 μg/dL or less was associated with iron deficiency in only 3 percent of cases. Conversely, TIBC levels that were high normal or elevated were not highly predictive of iron deficiency; iron deficiency was present only approximately one half the time when the TIBC was 350 μg/dL or greater. When the TIBC was at this level, iron deficiency was suggested when the serum iron was markedly decreased.

Third, the MCV (and the MCH, with which it is highly correlated) offers reasonably strong predictive values for the presence or absence of iron deficiency only in certain instances. Iron deficiency was present in 83 percent of cases when the MCV was 75 μm^3 or less and was rare when the MCV was 86 μm^3 or greater; values between these levels constitute a "gray zone" in which an accurate prediction of the presence or absence of iron deficiency cannot be made with confidence using this single variable. Beck et al[13] developed a sequential computer-assisted decision analysis using multiple variables. It was highly successful in predicting the presence or absence of iron deficiency in a somewhat different population than this study; a similar indeterminate zone was found in which the MCV could not reliably predict iron stores.

Fourth, this study suggests, albeit indirectly, that the measurement of serum iron, TIBC, and transferrin saturation may not be justified as a routine procedure on all hospitalized patients when the prime diagnostic considerations are iron deficiency anemia and the ACD. The serum iron and transferrin saturation do not have strong predictive value in differentiating between the ACD and iron deficiency, and the TIBC has only limited utility. To make their use more cost effective and diagnostically precise, the serum iron studies may be better limited to those patients with anemia in whom serum iron studies may provide a clear distinction between competing possible causes. Similar considerations about the predictive value and resultant cost effectiveness of the laboratory workup for patients with possible megaloblastic anemia have been published.[14]

Multivariate analyses have combined several diagnostic tests into algorithms with good predictive value.[13] These depend, however, on computer-based programs that are not commonly available to most clinical physicians, who must differentiate

between these two causes of anemia from the data available from individual laboratory studies. This study indicates that these individual laboratory tests (serum iron studies and erythrocyte indices) have significant limitations when used alone to differentiate iron deficiency anemia from the ACD.

These predictive values apply only to the patient group defined in this study, ie, hospitalized patients with a high probability of having either iron deficiency or the ACD, as demonstrated by a transferrin saturation of 15 percent or less. The actual predictive values might change somewhat in a different patient group, such as chronically ill anemic patients who were unselected for low transferrin saturation. There is reason to think that the general conclusions of this study would still apply if other causes for anemia are not apparent. However, in a markedly different patient group, such as anemic women of child-bearing age who are otherwise healthy, the actual predictive values might change considerably, illustrating the principle that the predictive value of a laboratory test depends in large measure upon the characteristics of the patient group in which it is applied.[15]

The validity of the data presented here depends on three assumptions: first, that the serum ferritin level represents an accurate measurement of bone-marrow iron stores; second, that the patient group included in this study is representative of all anemic hospitalized patients at this institution; and third, that there was an acceptable correlation between the two methods used to measure serum ferritin during the course of this study.

The first assumption appears to be justified by several studies done in similar (although not identical) patient populations, which demonstrate that the serum ferritin is an accurate predictor of bone-marrow iron stores excepting in those diseases that were excluded in this study.[16,17] Other authors have used criteria similar to those used in this study for the diagnosis of iron deficiency, also.[18]

Furthermore, patients with intermediate ferritin levels (20 to 100 ng/mL), who might occasionally be misclassified by the use of an arbitrary designation of 20 ng/mL as indicating iron deficiency,[17] generally had higher MCVs than those patients with ferritin levels definitely indicating iron deficiency. Although examination of the bone marrow for storage iron remains the reference standard for diagnosing iron deficiency, it is seldom done now in uncomplicated iron deficiency, and the serum ferritin has become an acceptable substitute.

The other two assumptions also appear justified. Although not all hospitalized anemic patients have serum iron studies done, there appears little reason to anticipate sufficient bias in the selection of which patients have iron studies done to affect the results of this study. Finally, although the method of measuring serum ferritin was changed during the time period of the study, there was a high correlation between the two methods ($r = .96$) and variance was lowest at low levels of serum ferritin.

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