JOURNAL OF INSURANCE MEDICINE
Copyright © 2015 Journal of Insurance Medicine
J Insur Med 2015;45:75–80

MORTALITY

Hemoglobin Screening Independently Predicts All-Cause Mortality

Michael Fulks, MD; Vera F. Dolan, MSPH; Robert L. Stout, PhD

Objective.—Determine if the addition of hemoglobin testing improves risk prediction for life insurance applicants.

Method.—Hemoglobin results for insurance applicants tested from 1993 to 2007, with vital status determined by Social Security Death Master File follow-up in 2011, were analyzed by age and sex with and without accounting for the contribution of other test results.

Results.—Hemoglobin values ≤12.0 g/dL (and possibly ≤13.0 g/dL) in females age 50+ (but not age <50) and hemoglobin values ≤13.0 g/dL in all males are associated with progressively increasing mortality risk independent of the contribution of other test values. Increased risk is also noted for hemoglobin values >15.0 g/dL (and possibly >14.0 g/dL) for all females and for hemoglobin values >16.0 g/dL for males.

Conclusion.—Hemoglobin testing can add additional independent risk assessment to that obtained from other laboratory testing, BP and build in this relatively healthy insurance applicant population. Multiple studies support this finding at older ages, but data (and the prevalence of diseases impacting hemoglobin levels) are limited at younger ages.

Address for correspondence: Clinical Reference Laboratory, 454 Beltrami Drive, Ukiah, California 95482; Ph: 707-463-3200; Fax: 707-463-3209; dolanvp@consultancy.com

Correspondent: Vera F. Dolan, MSPH.

Key words: Anemia, hemoglobin, laboratory tests, life insurance, mortality, polycythemia.

Received: January 23, 2014

Accepted: June 16, 2014

INTRODUCTION

Hemoglobin (Hb) is the oxygen-carrying component of red blood cells and can be measured on an automated analyzer with results expressed in grams/deciliter or, using S.I. units, in g/L (eg, 13.5 g/dL or 135 g/L). Hemoglobin levels run somewhat higher in males (due to androgens) and in those who are aerobically active. Levels are reduced most commonly by iron deficiency as the result of blood or other iron loss which surpasses intake thereby limiting hemoglobin production. Bleeding can be pathologic (eg, colon cancer) or physiologically normal (eg, menstrual). Other specific causes of anemia include vitamin B_{12} malabsorption, nutritional deficiencies, and genetic red blood cell variants such as thalassemia minor, sickle cell trait and sickle cell anemia. Hemoglobin levels are also often reduced by inflammatory and malignant diseases, mainly due to the circulating inflammatory and catabolic factors suppressing red cell production in the bone marrow.

Because the hemoglobin level can be reduced by a variety of medical conditions as well as poor nutritional status and restricted activity, it may serve as a marker of health status and of mortality risk. Anemia is defined by the World Health Organization as a Hb <12 g/dL in females and <13 g/dL in males with that definition mainly targeting iron deficiency as a result of diet.[1] Various studies have used this definition or alternate definitions to assess the morbidity, disability and mortality risk associated with reduced hemoglobin levels.[2-9]

However, these study populations were almost all age 65+ and were recruited from general population samples usually containing more known disease and nutritional issues than is common with individual life insurance applicants who might have less risk associated with low hemoglobin.

Elevated hemoglobin levels (polycythemia) in an apparently healthy older population may also be seen on screening. This might be the only sign or symptom if caused by polycythemia vera, while other causes associated with excess mortality such as hypoxemia (eg, severe COPD, sleep apnea or pulmonary fibrosis) would more likely to be already known. Zakai et al showed some increase in mortality in the highest quintile of hemoglobin values in an elderly population but referenced multiple other studies that had not found such an increase.[2]

METHODS

As part of the individual life insurance application process in the United States, urine and blood samples are routinely collected by an examiner and most often sent for testing to one of two laboratories including Clinical Reference Laboratory (CRL), with which the authors are affiliated. The samples are processed in an automated fashion, and results forwarded to the insurer requesting the testing. Most applicants believe they are in good health because insurance premiums increase substantially for those who are not, discouraging application.

In contrast to the urinalysis and chemistry panel which are ordered routinely at insurance application, hemoglobin testing (based on age and policy amount) is requested by only a small and shifting fraction of insurers and may be limited to certain age and policy amount combinations. Some additional hemoglobin tests may be ordered based on history or other findings as well. This pattern reflects the uncertainty as to its independent value as a predictor of mortality in this population.

Hemoglobin testing at CRL is performed on samples collected in lavender top EDTA tubes using an Advia 120 Hematology analyzer. Complete blood counts were obtained but only the hemoglobin results are reported here. The stability of hemoglobin results at CRL had previously been validated on fresh samples studied over a 10 day time period (CRL data not shown) which exceeds the delay inherent in transport and processing of insurance blood samples.

We studied all 30,231 applicants (0.3% of all blood samples tested) tested for hemoglobin at CRL between 1993 and 2007 and found to have a hemoglobin of $>$6.0 to 20.0 g/dL who also had cotinine testing results available (to account for the potential increase in hemoglobin associated with chronic carbon monoxide exposure). Only 8 hemoglobin results fell outside this value range and were excluded. Follow-up for mortality was conducted October, 2011 by use of the Social Security Death Master File. Match was by Social Security number, name and date of birth. Partial matches were manually reviewed; if the only disparity appeared to be probable name misspelling or transposition of dates, these applicants were included as well. The median duration of follow-up was 13 years (range 0 to 18).

Relative mortality risk was calculated by Cox regression analysis using IBM SPSS version 21. Analyses were split by sex, and both age and tobacco use (defined as urine cotinine $>$200 ng/mL) were included as covariates. Mortality and distribution analysis were initially conducted with both males and females split at age 50, but male results were very similar across all ages so those bands were combined as shown in the results.

RESULTS

The distribution of lives and deaths with relative mortality by Cox regression analysis is shown in Tables 1-3 for females age $<$50 and age 50+ and all males respectively. Hemoglobin bands containing too few deaths to produce a credible mortality ratio are listed as NS (data not sufficient) and those with limited data resulting in very wide 95% confidence intervals are shown in italics.

Table 1. Females Age <50 - Mortality (by Cox) and Distribution by Hemoglobin Level

Hemoglobin (g/dL)	Vital Status			MR*	95% CI	
	Alive	Dead	Distribution	(Cox)	Lower	Upper
>6 to 10	178	1	1.8%	NS	-	-
>10 to 12	1720	15	17.7%	0.9	0.5	1.6
>12 to 13	3414	16	35.0%	0.5	0.3	0.8
>13 to 14 (ref)	3099	36	32.0%	1.0	-	-
>14 to 15	1061	20	11.0%	1.3	0.8	2.3
>15 to 16	191	7	2.0%	*2.3*	*1.1*	*5.2*
>16 to 18	31	0	0.3%	NS	-	-
>18 to 20	2	0	0.0%	NS	-	-
Total	9696	95				

ref = reference band
NS = data not sufficient
MR in italics = wide confidence intervals due to few deaths
* covariates include age and smoking only

For females age <50 (who are likely to be menstruating or possibly pregnant), low hemoglobin does not appear predictive of mortality risk although even mildly elevated hemoglobin is predictive. For females age 50+ and all males, lower hemoglobin values (sex-specific) are associated with progressively increasing risk with a smaller increased risk seen for elevated values.

The analysis shown in Tables 1-3 does not account for other test findings (other than age and smoking status) in assessing the contribution of hemoglobin to mortality prediction. Although medical history is limited in our dataset, the full complement of chemistry screening, urinalysis and reflex testing such as HbA1c and hepatitis screening is available as well as BP and BMI for some applicants.

Our prior research has shown that the contribution of most tests and any test value to mortality predictions is dependent on age and sex, preventing use of the raw test results themselves in a single multivariate analysis covering a range of age or both sexes. However, a mortality risk score was developed by the authors based on all available test results, BP and BMI, which accounts for age and sex.[10] We included that risk score (excluding any contribution from Hb) as another covariate in the Cox regression

Table 2. Females Age 50+ - Mortality (by Cox) and Distribution by Hemoglobin Level

Hemoglobin (g/dL)	Vital Status			MR*	95% CI	
	Alive	Dead	Distribution	(Cox)	Lower	Upper
>6 to 10	38	8	1.0%	3.2	1.6	6.6
>10 to 12	466	47	11.7%	1.3	0.9	1.9
>12 to 13	1213	104	30.0%	1.3	1.0	1.7
>13 to 14 (ref)	1451	103	35.3%	1.0	-	-
>14 to 15	658	73	16.6%	1.4	1.0	1.9
>15 to 16	173	26	4.5%	1.8	1.2	2.7
>16 to 18	31	4	0.8%	*1.3*	*0.5*	*3.6*
>18 to 20	2	0	0.0%	NS	-	-
Total	4032	365				

* covariates include age and smoking only

Table 3. Males All Ages - Mortality (by Cox) and Distribution by Hemoglobin Level

Hemoglobin (g/dL)	Vital Status			MR*	95% CI	
	Alive	Dead	Distribution	(Cox)	Lower	Upper
>6 to 10	20	5	0.2%	5.2	2.1	12.7
>10 to 12	150	33	1.1%	3.1	2.1	4.5
>12 to 13	574	51	3.9%	1.8	1.3	2.4
>13 to 14	2361	90	15.3%	1.1	0.8	1.4
>14 to 15 (ref)	5677	172	36.5%	1.0	-	-
>15 to 16	4881	135	31.3%	1.1	0.8	1.3
>16 to 18	1792	68	11.6%	1.4	1.0	1.8
>18 to 20	32	2	0.2%	*2.3*	*0.6*	*9.3*
Total	15,487	556				

* covariates include age and smoking only

analysis previously done for Tables 1-3. The results of that additional analysis are shown in Tables 4, 5 and 6, respectively for females age <50, 50+ and for all males. Including the impact of those other laboratory test and physical measurement findings generally reduces the risk multiple for the more extreme reductions or increases in hemoglobin levels, but hemoglobin remains highly predictive of all-cause mortality even after this adjustment.

DISCUSSION

Based on our results for life insurance applicants, hemoglobin values ≤13.0 g/dL for females age 50+ and for all males are associated with progressively increased risk of all-cause mortality. This excess risk is only moderately reduced when the impact of other test results (and BP and BMI in some cases) is accounted for. Not surprisingly, this increase in risk is not seen for younger females where pregnancy (dilutional anemia) or mild iron deficiency anemia due to menstruation and inadequate iron intake are much more common than anemia associated with other conditions.

The hemoglobin level associated with an increased risk and the degree of increase is very similar to that noted by Culleton et al.

Table 4. Females Age <50 - Comparison of Age- and Smoking-Adjusted Mortality (By Cox) Including 95% CI With and Without Adjustment for Other Test Results

Hemoglobin (g/dL)	*Age and Smoking Only*	*Age, Smoking and Other Test Results*		
	MR	MR	Lower CI	Upper CI
>6 to 10	NS	NS	-	-
>10 to 12	0.9	0.9	0.5	1.7
>12 to 13	0.5	0.5	0.3	0.8
>13 to 14 (ref)	1.0	1.0	-	-
>14 to 15	1.3	1.2	0.7	2.1
>15 to 16	*2.3*	*2.0*	*0.9*	*4.4*
>16 to 18	NS	NS	-	-
>18 to 20	NS	NS	-	-

ref = reference band
NS = data not sufficient
MR in italics = wide confidence intervals due to few deaths

Table 5. Females Age 50+ - Comparison of Age- and Smoking-Adjusted Mortality (By Cox) Including 95% CI With and Without Adjustment for Other Test Results

Hemoglobin (g/dL)	*Age and Smoking Only*	*Age, Smoking and Other Test Results*		
	MR	MR	Lower CI	Upper CI
>6 to 10	3.2	2.7	1.3	5.5
>10 to 12	1.3	1.3	0.9	1.8
>12 to 13	1.3	1.3	1.0	1.7
>13 to 14 (ref)	1.0	1.0	-	-
>14 to 15	1.4	1.3	1.0	1.8
>15 to 16	1.8	1.8	1.2	2.7
>16 to 18	*1.3*	*1.3*	*0.5*	*3.5*
>18 to 20	NS	NS	-	-

for older community-living adults (Calgary Health Region) when those results were adjusted for renal function, diabetes and comorbidity.[3] The bands of hemoglobin in that study only go as low as <11 g/dL for females and <12 g/dL for males. Zakai et al. using data from the Cardiovascular Health Study on which extensive information was collected on adults age 65+, earlier found a very similar pattern and risk when adjusted for other factors.[2] Because the data are presented by quintile, no discrete risk information is available for hemoglobin values <12.6 g/dL for females and <13.7 g/dL for males.

Denny et al also found a relative risk similar to ours across bands of hemoglobin ⩾10 g/dL in a community population age 71+ when adjusted for history and other test results for hemoglobin values, but less risk than we found on an adjusted basis <10 g/dL.[4] However, in contrast to our results and to the other studies noted above, Denny et al. did not find any increase in risk for females with hemoglobin values in the >12.0 to 13.0 g/dL band. Because 30% of female applicants age 50+ had hemoglobin values in that band, the question of relative risk and any need of further evaluation of this group is both important and not fully answered.

Each of the 3 studies noted above also found increasing mortality as hemoglobin levels increased beyond the expected range. Bands of elevated hemoglobin values are very different across studies so a precise match is difficult, but risk appears to increase at a Hb >15.0 g/dL in females and >16.0 g/dL in males. Our data is largely in agreement but also showed an increased risk in females

Table 6. Males All Ages - Comparison of Age- and Smoking-Adjusted Mortality (By Cox) Including 95% CI With and Without Adjustment for Other Test Results

Hemoglobin (g/dL)	*Age and Smoking Only*	*Age, Smoking and Other Test Results*		
	MR	MR	Lower CI	Upper CI
>6 to 10	5.2	3.9	1.6	9.5
>10 to 12	3.1	2.3	1.6	3.4
>12 to 13	1.8	1.5	1.1	2.0
>13 to 14	1.1	1.0	0.8	1.3
>14 to 15 (ref)	1.0	1.0	-	-
>15 to 16	1.1	1.0	0.8	1.3
>16 to 18	1.4	1.3	1.0	1.7
>18 to 20	*2.3*	*1.6*	*0.4*	*6.6*

beginning at a lower >14.0 to 15.0 g/dL. This band includes 13% of female applicants, making this another important question regarding risk but one without a certain answer.

One curious finding is the reduced MR (0.5) for females age <50 in the Hb >12.0 to 13.0 g/dL band relative to higher Hb values. This is not seen for older females nor in the references cited above (which are limited to older lives). We can provide no clear physiologic explanation (pregnancy?) and think this is most likely reflective of random variation and relatively small sample size. However, we have no other data to compare and cannot rule out actual lower mortality.

Our study has limitations, the largest of which is the small percentage of applicants tested for hemoglobin and the uncertainty regarding how many tests were ordered "for cause" rather than as a routine requirement. Fortunately, there is sufficient existing literature (limited to older ages) so that our findings have support. Sample size and outcomes (death) were limited for some age-sex-hemoglobin band combinations. Health history information was also very limited for our study, but the results of other extensive laboratory testing was available to us and could be included in a multivariate analysis for individual age-sex groups.

CONCLUSION

Hemoglobin screening added additional risk discrimination for male applicants at any age and for female applicants age 50+ independent of the other laboratory results. Both anemia and polycythemia contribute to the excess risk; high and low cut-off values indicating need for further review of the hemoglobin result are sex-specific.

REFERENCES

1. World Health Organization. Iron deficiency anemia assessment, prevention, and control WHO/NHD/01.3. 2001.
2. Zakai NA, Katz R, Hirsch C, et al. A prospective study of anemia status, hemoglobin concentration, and mortality in an elderly cohort: The Cardiovascular Health Study. *Arch Intern Med.* 2005:165: 2214-2220.
3. Culleton BF, Manns BJ, Zhang J, et al. Impact of anemia on hospitalization and mortality in older adults. *Blood*. 2006;107:3841-3846.
4. Denny SD, Kuchibhatia MN, Cohen HJ. Impact of anemia on mortality, cognition, and function in community-dwelling elderly. *Am J Med.* 2006;119: 327-334.
5. Dong, X, de Leon CM, Artz A, et al. A population-based study of hemoglobin, race, and mortality in elderly persons. *J Gerontol*. 2008;63A:873-878.
6. Izaks GJ, Westendorp RGJ, Knook DL. The definition of anemia in older persons. *JAMA*. 1999;281: 1714-1717.
7. Merchant AA, Roy CN. Not so benign haematology: anemia of the elderly. *Br J Haematol.* 2012; 156:173-185.
8. Riva E, Tettamanti M, Mosconi P, et al. Association of mild anemia with hospitalization and mortality in the elderly: the Health and Anemia population-based study. *Haematologica*. 2009;94:22-28.
9. Patel KV, Harris TB, Faulhaber M, et al. Racial variation in the relationship of anemia with mortality and mobility disability among older adults. *Blood.* 2007;109:4663-4670.
10. Fulks M, Stout RL, Dolan VF. Scoring life insurance applicants' laboratory results, blood pressure and build to predict all-cause mortality risk. *J. Insurance Medicine.* 2012;43:169-177.