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Serum Globulin Predicts All-Cause Mortality for Life Insurance Applicants

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Objective.—Determine the relative mortality in apparently healthy adults with various levels of serum globulin.

Method.—By use of the Social Security Death Master File, mortality in 2010 was determined for 7.7 million life insurance applicants age 20 to 89 providing blood samples with valid globulin results between 1992 and 2006. Relative mortality by Cox regression for bands of globulin values was determined by age-sex group, with age split into 20 to 59 and 60 to 89, with each grouping also including age as a covariate. Further analysis was conducted by excluding applicants with elevations of other test values associated with increased globulin levels and mortality risk.

Results.—After accounting for the mortality impact of frequently associated laboratory test abnormalities including BMI, alkaline phosphatase and albumin, relative mortality was found to increase gradually for globulin values >3.2 g/dL. Values >4.0 were associated with a mortality risk that was approximately doubled. There is also a small increased risk for globulin values <1.9 g/dL.

Conclusion.—The highest 20% of globulin levels were associated with steadily increasing mortality in life insurance applicants. In many cases, other laboratory findings were not informative of the risk.

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Serum globulin levels are routinely reported as part of blood testing on life insurance applicants, but there has been little published research regarding mortality risk associated with different values overall or by age and sex. The globulin level is usually not directly measured but obtained by subtracting albumin from total protein, both of which are measured. A commonly used "normal range" for clinical reporting of serum globulin is 2 to 3.5 g/dL although broader normal ranges are reported as well.

Globulins include alpha-1 globulins, alpha-2 globulins, beta globulins and gamma globulins (immunoglobulins). The first three are made in the liver, with the gamma globulins being made by plasma cells in the bone marrow and tissues. If the globulin level is not elevated, roughly 20% to 40% of total globulin typically consists of gamma globulin.

Elevation of total globulin is most commonly due to an increase of one or more immunoglobulins, including IgG, IgM and IgA. Elevated levels may be the result of a single monoclonal spike consistent with certain hematologic malignancies (such as multiple myeloma) or a polyclonal increase consistent with inflammation or other malignancies.

Other globulins include alpha-1 globulins, which consists mainly of alpha-1 antitrypsin, a protein which is also an acute phase reactant. The alpha-2 components are mainly alpha-2 macroglobulin and haptoglobin, the latter also being an acute phase reactant. Beta globulins are composed mainly of transferrin, which may be increased in iron deficiency but not by inflammation.

Elevated total globulin, usually resulting from increases in immunoglobulins and/or the acute phase reactants, suggests the possibility of multiple myeloma, monoclonal gammopathy, malignancy or inflammation associated with a rheumatic condition or infection. The nature of the globulin increase can be further defined by SPEP (serum protein electrophoresis). Initial clinical evaluation of an elevated globulin might include a history, a repeat globulin level and, if elevated, a CBC and SPEP to better define the nature of the increase.

Decreased globulin levels are most often associated with malnutrition or congenital immune deficiency[1] with the latter likely being obvious by adulthood since immunoglobulin levels would be very low and susceptibility to infection likely to have been high.

The medical literature lacks articles associating globulin level with morbidity or mortality when applied as a screening test. Dispenzieri et al retrospectively examined polyclonal gammopathy findings on SPEP at the Mayo Clinic and found liver disease, connective tissue disease, malignancy and infection to be the most common causes.[2] Multiple laboratory abnormalities, including low albumin, were often apparent, but disease states were presumably more advanced than seen in a screening population and no total globulin levels were provided. No other existing literature was found.

METHODS

As part of the individual life insurance application process in the US, urine and blood samples are routinely collected by the examiner and sent for testing to one of three 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 are in good health because insurance premiums increase substantially for those who are not.

Globulin levels were determined by simple subtraction of the measured albumin level from the total measured protein. Both tests were determined on a Roche Chemistry Analyzer with Roche reagents following Roche guidelines for FDA approved *in vitro diagnosis*. Samples with albumin levels less than 3.5 g/dL or total protein less than 5.1 g/dL were automatically repeated to confirm the laboratory result.

The dataset included applicants age 20 to 89 with valid globulin levels tested from 1992 to 2006 at CRL, without exclusion. Additional analysis was repeated after exclusion of those applicants with abnormalities of BMI, albumin or alkaline phosphatase associated with a relative mortality risk >125% (or if those test values were not available).[3,4] If an applicant had applied multiple times for insurance coverage, only the most recent laboratory result was used. Vital status was determined by reference to the Social Security Death Master File (SS DMF) in May 2010. 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, such applicants were included as well. The median duration of follow-up was 8 years (range 0 to 18 years). Further details of our study population are available in Table 1 by age-sex group.

All statistical analyses were performed using IBM SPSS version 20.

RESULTS

The distribution of lives, deaths and globulin values by age-sex group is shown

Table 1. Study Population Demographics

Age-Sex Group	Total Lives	Deaths	Median Age (Years)	Cases With BMI Available
Female 20 to 59	2,830,420	26,018	39	803,027
Male 20 to 59	4,129,268	73,271	41	1,028,547
Female 60 to 89	280,273	32,701	66	57,567
Male 60 to 89	454,985	62,122	65	89,963
Total	7,694,946	194,112	42	1,979,104

in Tables 2–5. Women and older ages each have globulin values averaging about 0.1 g/dL higher than men or younger ages respectively, for equivalent globulin percentile bands.

Relative mortality by Cox regression (including age as a covariate) based on globulin values split by age-sex group is also shown in Tables 2–5. The reference bands assigned a mortality ratio of 1 are those with globulin values from the 25th to 74th percentile specific to each age-sex group. Relative mortality across this percentile range was nearly flat.

When only age is included as a covariate, globulin values from 1.9 to roughly 3.2 g/dL have a mortality ratio close to 1.0 for all age-sex groups. Relative mortality then begins to increase gradually above 3.2 g/dL, with globulin values ≥3.8 having a risk that is approximately doubled.

In Tables 2–5, relative mortality is also shown when applicants with BMI, albumin or alkaline phosphatase abnormalities each associated with a relative risk of >125% (representing 33% of the group) were excluded and age was still included as a covariate. These 3 results were chosen from the available tests, BP and BMI for exclusion because, if globulin was ≥3.2 g/dL, these results were the most likely (18% to 22% of the time for each) to be sufficiently abnormal to each be associated with an increased

Table 2. Females Age 20 to 59. Distribution and Mortality by Globulin Level for All Cases, and for Cases with BMI, Albumin and Alkaline Phosphatase Values Each with ≤125% Mortality

Distribution of Values and Vital Status, All Cases				Mortality, All Cases			Mortality When BMI, Albumin, AP ≤125%		
Percentile Band	Globulin Values (g/dL)	Dead	Total	MR (Cox)	95% CI Lower	95% CI Upper	MR* (Cox)	95% CI Lower	95% CI Upper
<0.2%	<1.9	74	4293	**1.43**	1.13	1.79	*0.51*	0.13	2.04
0.2–0.29%	1.9-<2	53	4089	**1.15**	0.88	1.51	*0.61*	0.15	2.44
0.3–2.4%	2-<2.2	711	54,607	**1.13**	1.04	1.21	**1.21**	0.92	1.59
2.5–4%	2.2-<2.3	558	49,927	**1.08**	0.99	1.17	**1.16**	0.86	1.55
5–9%	2.3-<2.4	767	74,608	**1.05**	0.97	1.13	**0.99**	0.77	1.27
10–24%	2.4-<2.6	4003	421,268	**0.97**	0.94	1.01	**1.13**	1.00	1.26
25–74% (ref)	2.6-<3.1	11,327	1,379,839	**1.00**			**1.00**		
75–89%	3.1-<3.4	3891	477,519	**1.11**	1.07	1.16	**1.02**	0.90	1.15
90–94%	3.4-<3.6	2143	218,763	**1.31**	1.25	1.37	**1.16**	0.99	1.37
95–97.4%	3.6-<3.7	494	43,027	**1.59**	1.45	1.74	**1.33**	0.94	1.88
97.5–98%	3.7-<4	1031	71,200	**1.92**	1.80	2.05	**1.53**	1.19	1.97
99–99.4%	4-<4.1	275	13,590	**2.51**	2.23	2.83	*1.33*	0.72	2.49
99.5+%	4.1+	691	17,690	**4.57**	4.23	4.93	*2.47*	1.57	3.88

* Shown as non-bold and italic if number of deaths <30, leading to very wide confidence intervals.

Table 3. Females age 60 to 89. Distribution and Mortality by Globulin Level for All Cases, and for Cases with BMI, Albumin and Alkaline Phosphatase Values Each with ≤125% Mortality

Distribution of Values and Vital Status, All Cases				Mortality, All Cases			Mortality when BMI, Albumin, AP ≤125%		
Percentile band	Globulin values (g/dL)	Deaths	Total	MR (Cox)	95% CI Lower	95% CI Upper	MR* (Cox)	95% CI Lower	95% CI Upper
<0.2%	<1.9	106	538	**1.31**	1.09	1.59	*2.37*	1.27	4.43
0.2–0.3%	1.9-<2	74	501	**1.14**	0.90	1.43	*0.58*	0.14	2.31
0.4–2.4%	2-<2.1	455	2788	**1.11**	1.01	1.22	*1.51*	1.00	2.28
2.5–4%	2.1-<2.3	1121	8498	**1.04**	0.97	1.10	**0.76**	0.56	1.04
5–9%	2.3-<2.4	889	7553	**1.00**	0.93	1.07	**0.90**	0.68	1.20
10–24%	2.4-<2.6	4844	40,949	**0.97**	0.94	1.00	**1.03**	0.90	1.18
25–74% (ref)	2.6-<3.2	15,891	147,729	**1.00**			**1.00**		
75–89%	3.2-<3.5	4434	38,877	**1.15**	1.11	1.19	**1.15**	1.01	1.31
90–94%	3.5-<3.7	2273	17,691	**1.32**	1.26	1.38	**1.22**	1.02	1.45
95–97.4%	3.7-<3.9	1046	7228	**1.56**	1.47	1.67	**1.32**	1.01	1.73
97.5–98%	3.9-<4.2	846	5066	**1.82**	1.70	1.95	**1.15**	0.82	1.61
99–99.4%	4.2-<4.4	286	1236	**2.74**	2.44	3.08	*2.57*	1.54	4.28
99.5+%	4.4+	436	1619	**2.99**	2.72	3.28	*3.07*	1.87	5.03

* Shown as non-bold and italic if number of deaths <30, leading to very wide confidence intervals.

mortality risk of >125% across all ages and both sexes.[5] The cut-off of >125% for each rather than a lower risk level was chosen because at least one elevated risk of ≤125% is commonly present (79%) for at least one test or physical measurement result across applicants regardless of age or sex. The potential associations of elevated globulin with high

Table 4. Males Age 20 to 59. Distribution and Mortality by Globulin Level for All Cases, and for Cases with BMI, Albumin and Alkaline Phosphatase Values Each with ≤125% Mortality

Distribution of Values and Vital Status, All Cases				Mortality, All Cases			Mortality When BMI, Albumin, AP ≤125%		
Percentile Band	Globulin values (g/dL)	Deaths	Total	MR (Cox)	95% CI Lower	95% CI Upper	MR* (Cox)	95% CI Lower	95% CI Upper
<0.5%	<1.9	354	12,906	**1.22**	1.10	1.35	*1.55*	1.03	2.31
0.5–0.9%	1.9-<2	268	11,913	**1.07**	0.95	1.20	*0.51*	0.26	1.02
1–2.4%	2-<2.1	1616	70,543	**1.02**	0.97	1.07	**0.86**	0.69	1.08
2.5–4%	2.1-<2.2	1438	74,381	**0.95**	0.90	1.00	**0.97**	0.79	1.19
5–9%	2.2-<2.3	2165	113,865	**0.98**	0.94	1.02	**0.98**	0.83	1.15
10–24%	2.3-<2.5	6428	377,334	**0.94**	0.92	0.97	**0.97**	0.88	1.07
25–74% (ref)	2.5-<3	33,244	2,041,107	**1.00**			**1.00**		
75–89%	3-<3.3	15,896	952,480	**1.15**	1.13	1.18	**1.03**	0.97	1.10
90–94%	3.3-<3.5	4488	246,794	**1.36**	1.32	1.40	**1.11**	0.99	1.25
95–97.4%	3.5-<3.6	2458	109,555	**1.60**	1.54	1.67	**1.27**	1.09	1.48
97.5–98%	3.6-<3.8	1827	65,333	**2.11**	2.01	2.21	**1.34**	1.09	1.63
99–99.4%	3.8-<4	1084	29,937	**2.60**	2.45	2.76	**1.73**	1.32	2.25
99.5+%	4+	2005	23,120	**5.70**	5.45	5.97	**2.93**	2.23	3.84

* Shown as non-bold and italic if number of deaths <30, leading to very wide confidence intervals.

Table 5. Males Age 60 to 89. Distribution and Mortality by Globulin Level For All Cases, and for Cases with BMI, Albumin and Alkaline Phosphatase Values Each with ≤125% Mortality

Distribution of Values and Vital Status, All Cases				Mortality, All Cases			Mortality When BMI, Albumin, AP ≤125%		
Percentile Band	Globulin values (g/dL)	Deaths	Total	MR (Cox)	95% CI Lower	95% CI Upper	MR* (Cox)	95% CI Lower	95% CI Upper
<0.5%	<1.9	246	1425	**1.14**	1.01	1.29	*0.91*	0.46	1.83
0.5–0.9%	1.9-<2	173	1239	**0.95**	0.82	1.11	*1.13*	0.57	2.27
1–2.4%	2-<2.1	1091	6834	**1.03**	0.97	1.09	**1.00**	0.72	1.39
2.5–4%	2.1-<2.2	1008	7625	**0.94**	0.88	1.00	**0.74**	0.53	1.03
5–9%	2.2-<2.3	1631	11,729	**1.02**	0.97	1.07	**1.15**	0.92	1.44
10–24%	2.3-<2.5	4749	39,502	**0.95**	0.92	0.98	**0.81**	0.70	0.94
25–74% (ref)	2.5-<3	26,866	216,440	**1.00**			**1.00**		
75–89%	3-<3.4	17,230	123,560	**1.20**	1.18	1.22	**1.25**	1.15	1.35
90–94%	3.4-<3.5	1916	12,410	**1.37**	1.31	1.44	**1.26**	1.03	1.53
95–97.4%	3.5-<3.7	3539	19,845	**1.59**	1.54	1.65	**1.66**	1.44	1.91
97.5–98%	3.7-<4	1940	9021	**2.02**	1.93	2.12	**1.92**	1.57	2.35
99–99.4%	4-<4.2	780	2821	**2.67**	2.48	2.87	**2.75**	1.99	3.80
99.5+%	4.2+	953	2534	**3.81**	3.57	4.06	**3.52**	2.45	5.05

* Shown as non-bold and italic if number of deaths <30, leading to very wide confidence intervals.

alkaline phosphatase (suggesting liver disease and osteoblastic bone activity) and with low albumin are obvious. Elevated gamma globulin levels have also been shown to be associated with obesity and type 2 diabetes.[6]

Exclusion of applicants with elevated risk associated with BMI or those with missing BMI (those results are available to CRL for only some applicants) substantially reduced the number of applicants in the restricted analysis, resulting in much wider confidence intervals especially for younger women (who have fewer deaths). Mortality ratios where the number of deaths is <30 are subject to substantial random variation and are shown as italic rather than bold in Tables 2–5. Better guidance regarding the trend of mortality at the extremes of globulin values can be obtained using the mortality ratios shown in the column where all those tested are included.

After excluding applicants with these abnormalities from the analysis, globulin values from 1.9 to roughly 3.2 g/dL still retain a mortality ratio close to 1.0. Relative mortality then begins to increase gradually above that, with globulin values of >4.0 g/dL (rather than ≥3.8 for all applicants) having a risk that is approximately doubled.

For low globulin values (<2.0 g/dL), the prevalence of other test abnormalities also associated with increased risk was actually reduced by approximately 40% as compared to globulin values ≥2.0. The one exception was low cholesterol (<140 mg/dL) where the prevalence increased from 2.5% to 6.9% for age ≥50 where it is known to be associated with increased mortality.[7] Risk appears to be somewhat increased for globulin values <1.9 g/dL for all age-sex groups but remains <150%.

DISCUSSION

Because globulin is a non-specific test and because there is a lack of data providing mortality risk guidance, often little action is taken based on screening globulin values. Our data using a pool of life insurance applicants suggests that this test is a useful independent discriminator of all-cause mortality risk across age for both sexes. Values >3.2 g/dL (representing approximately 20%

of life insurance applicants) begin to show additional mortality, and values ≥3.5 (including approximately 5% to 10% of applicants) have mortality increased by at least 25%. Values >4 g/dL are likely associated with more than a doubling of risk, even when the potential impact of other tests are excluded.

In addition to what we have shown in Tables 2–5 based on excluding other test abnormalities, the impact of other tests was also evaluated by including them as variables in a Cox multivariate analysis (not shown). This resulted in very limited reduction in risk associated with elevated globulin as compared to the risk when including only age as a covariate. We have chosen instead to present the results excluding applicants with abnormalities of BMI, albumin and alkaline phosphatase associated with a risk of >125%, which resulted in a greater reduction in mortality attributed to globulin. Because globulin is usually the least specific abnormal test (other than for monoclonal gammopathies) and because risk allocation to other more specific tests is commonly done with limited consideration of the globulin value, this was felt to be more appropriate.

Based on other authors' research including SPEP testing, most globulin elevations are caused by polyclonal and monoclonal immunoglobulin elevations, which can be associated with inflammation, infection, liver disease and malignancy. Other globulin elevations may be driven, in part, by stimulating production of non-immunoglobulin acute phase reactants. All of these globulin components can be associated with disorders (including obesity), resulting in increased mortality risk.

Reduced globulin levels actually associated with risk are far less common than elevations associated with risk. Very low values of globulin, especially when associated with other abnormalities such as low cholesterol, low albumin, weight loss or a history of infections, may be of some concern.

If globulin alone is to be used as an alert that further evaluation is needed, then use of the mortality ratio resulting from inclusion of only age as a covariate may be most appropriate. If all laboratory test values are to be evaluated in a combined fashion (combined scoring of the lab panel), then use of a mortality ratio for globulin after adjustment (by either a multivariate analysis or exclusion) for the other, often more specific, tests may be more appropriate.

CONCLUSION

Globulin is underappreciated as an independent predictor of mortality risk. Values >3.2 g/dL have excess mortality and values >3.5 have substantial extra risk for all ages and both sexes. Other tests may be abnormal, but the extent of those abnormalities is often limited. Very low globulin levels are also associated with a small additional mortality risk.

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