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MORTALITY

Albumin and All-Cause Mortality Risk in Insurance Applicants

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Objective.—Determine the relationship between albumin levels and all-cause mortality in life insurance applicants.

Method.—By use of the Social Security Death Master File, mortality was determined in 1,704,566 insurance applicants for whom blood samples were submitted to Clinical Reference Laboratory. There were 53,211 deaths observed in this healthy adult population during a median follow-up of 12 years. Results were stratified by 6 age-sex groups: females: ages 20 to 49, 50 to 69 and 70+; and males: ages 20 to 49, 50 to 69 and 70+. The middle 50% of albumin values specific to each group was used as the reference band for that group. The mortality in bands representing other percentiles of albumin values higher and lower than the middle 50% were compared to the mortality in the reference band for each age-sex group. The highest percentile bands represent the lowest albumin values.

Results.—Relative risk exceeded 150% of each age- and sex-specific reference band for all groups between the 90^{th} and 95^{th} percentile of albumin values. This translates into 150% risk thresholds at approximately 3.8 mg/dL for all females and for males 70+, and 4.1 mg/dL for males ages 20 to 69. Conversely, the highest 25% of albumin values were associated with approximately a 20% reduction in risk in males and a variable 10% reduction in risk in females when compared to the middle 50% of albumin values. Excluding those with total cholesterol ≤160 mg/dL, or with AST, GGT or alkaline phosphatase elevations, had little impact on relative risk except at the lowest 0.5% of albumin values.

Conclusion.—When stratified by age and sex, albumin discriminated between all-cause mortality risks in healthy adults at all ages and across a wide range of values independent of other laboratory tests.

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INTRODUCTION

Albumin is a serum protein synthesized in the liver with a half-life of approximately 21 days. It accounts for about 50% of the protein content of blood and at least 75% of the colloid oncotic pressure. Serum concentration may be decreased in those who have poor nutrition, advanced liver disease, or are in a catabolic state associated with cancer or an inflammatory disease. Albumin levels have long been used clinically to monitor

nutritional status in those who are acutely or chronically ill.

However, albumin's value as a screening test to detect those at higher risk of death and the appropriate alert values in the absence of other established risks is less clear. In the Established Populations for Epidemiologic Study (EPESE) of community-dwelling individuals age 71+, albumin levels from 4.3 g/dL decreasing to <3.4 g/dL were associated with progressively increasing levels of risk of cardiac, cancer and all-cause mortality.[1] This association was present independent of disability status and when early deaths were censored. In another study of older community-dwelling individuals, the Longitudinal Aging Study Amsterdam (LASA), there was an association between decreasing levels of albumin over time and cardiovascular disease, but not with all-cause mortality.[2] In the Framingham Offspring Study, in a much younger population, lower albumin levels were associated with increased cardiovascular risk in both sexes and all-cause mortality in women but not in men, even after confounders were accounted for.[3] In a 1998 meta-analysis, a consistent association between low albumin and both cardiovascular disease and all-cause mortality was found for those with albumin values in the bottom tertile.[4] However, in the British United Provident Association (BUPA) study of men, no association was found between mortality and low albumin values.[5]

Our investigation utilizing serum from unselected adult individual life insurance applicants was designed to answer questions about the relative mortality risk associated with various levels of albumin in a generally healthy population. It extends our prior studies on risk discrimination by liver enzymes to include the synthetic function of the liver.[6,7]

METHODS

The population studied for this article is the same as that analyzed for our study of mortality risk and LFTs, which is described in depth in that article.[6] Briefly, by use of the Social Security Master Death File, mortality was examined in 1,704,566 insurance applicants for whom blood samples were submitted to Clinical Reference Laboratory and albumin results obtained. There were 53,211 deaths observed after a median follow-up of 12 years (range 10 to 14 years). The only exclusion criterion was a urine protein/creatinine ratio of ≥1 g/g of creatinine. This level of proteinuria was uncommon (0.2% of insurance applicants) and correlates with protein excretion over 24 hours of 1 gram or more,[8] which is still well below the level that might be expected to result in reduced serum albumin by urinary loss.

Results are presented for 6 age-sex groups: females ages 20 to 49 (F <50), ages 50 to 69 (F 50–69) and ages 70+ (F 70+); and males ages 20 to 49 (M <50), ages 50 to 69 (M 50–69) and ages 70+ (M 70+). This split is based on the relatively homogeneous distributions and mortality ratios within each of those age-sex groups found during preliminary evaluation using narrower age bands, and mean and median albumin values by year of age. Mean ages of the 6 groups were 36.4, 57.3, 74.4, 37.7, 56.7 and 74.1 years, respectively.

Albumin values were grouped using percentile bands of their distribution within these age-sex groups; the lowest albumin values were assigned to the highest percentile bands, while the highest albumin values were assigned to the lowest percentile bands. The middle 50% band of albumin values in each subpopulation (25^{th} to 74^{th} percentile) was assigned a mortality ratio of 100%. Mortality results for other percentile bands of albumin values within each subpopulation were compared to this reference mortality, creating mortality ratios or relative risk estimates. Because of difficulty in finding albumin cut-offs that resulted in exactly the percentage indicated in each band, some bands contain more or less than the percentage indicated. Exact numbers of lives for each band are provided in Tables 1–6.

Table 1. Mortality in Females Ages 20 to 49

Percentile	Albumin	Vital Status		Mortality	Lower	Upper
Band	Values	Alive	Dead	Ratio	95% CI	95% CI
<5%	>4.9	30,087	191	86%	74%	99%
5–<10%	4.9–>4.8	22,849	182	107%	93%	124%
10–<25%	4.8–>4.6	34,577	210	82%	72%	94%
25–<75%	4.6–>4.2	222,039	1648	100%		
75–<90%	4.2–>4	84,888	773	122%	114%	131%
90–<95%	4–>3.8	39,950	421	142%	129%	156%
95–<97.5%	3.8–>3.6	15,474	175	152%	131%	176%
97.5–<99%	3.6–>3.55	4390	54	165%	127%	215%
99–<99.5%	3.55–3.3	5878	53	121%	93%	159%
99.5+%	<3.3	3932	45	154%	115%	205%

Table 2. Mortality in Females Ages 50 to 69

Percentile	Albumin	Vital Status		Mortality	Lower	Upper
Band	Values	Alive	Dead	Ratio	95% CI	95% CI
<5%	>4.8	9072	484	97%	89%	106%
5–<10%	4.8–>4.65	6764	366	99%	89%	109%
10–<25%	4.65–>4.5	9955	494	91%	83%	99%
25–<75%	4.5–>4.1	58,928	3233	100%		
75–<90%	4.1–>3.95	20,645	1289	113%	107%	119%
90–<95%	3.95–>3.85	5492	435	141%	129%	154%
95–<97.5%	3.85–>3.75	3174	276	154%	137%	172%
97.5–<99%	3.75–>3.65	1665	164	172%	149%	200%
99–<99.5%	3.65–>3.5	844	103	209%	174%	251%
99.5+%	≤3.5	804	154	309%	267%	357%

Table 3. Mortality in Females Ages 70+

Percentile	Albumin	Vital Status		Mortality	Lower	Upper
Band	Values	Alive	Dead	Ratio	95% CI	95% CI
<5%	>4.7	621	166	89%	78%	102%
5–<10%	4.7–>4.6	547	161	96%	84%	110%
10–<25%	4.6–>4.4	3871	1105	94%	89%	99%
25–<75%	4.4–>4	5818	1800	100%		
75–<90%	4–>3.8	2527	869	108%	102%	115%
90–<95%	3.8–>3.75	651	268	123%	112%	137%
95–<97.5%	3.75–>3.6	337	196	156%	139%	174%
97.5–<99%	3.6–>3.5	239	107	131%	112%	153%
99–<99.5%	3.5–>3.3	153	77	142%	118%	170%
99.5+%	≤3.3	55	52	206%	169%	250%

Table 4. Mortality in Males Ages 20 to 49

Percentile	Albumin	Vital Status		Mortality	Lower	Upper
Band	Values	Alive	Dead	Ratio	% CI	95% CI
<5%	>5.1	32,242	338	82%	74%	92%
5–<10%	5.1–>5	29,256	318	85%	77%	95%
10–<25%	5–>4.8	209,691	2182	82%	78%	85%
25–<75%	4.8–>4.45	313,830	4002	100%		
75–<90%	4.45–>4.35	77,052	1180	120%	113%	127%
90–<95%	4.35–>4.2	53,488	912	133%	125%	142%
95–<97.5%	4.2–>4	51,365	1178	178%	168%	188%
97.5–<99%	4–>3.95	9807	300	236%	211%	264%
99–<99.5%	3.95–3.8	4750	173	279%	241%	323%
99.5+%	<3.8	4793	294	459%	411%	513%

Table 5. Mortality in Males Ages 50 to 69

Percentile	Albumin	Vital Status		Mortality	Lower	Upper
Band	Values	Alive	Dead	Ratio	95% CI	95% CI
<5%	>4.95	12,350	659	80%	74%	86%
5–<10%	4.95–>4.85	10,474	598	85%	78%	92%
10–<25%	4.85–>4.75	16,904	924	81%	76%	87%
25–<75%	4.75–>4.3	155,908	10,606	100%		
75–<90%	4.3–>4.1	22,479	2110	135%	129%	140%
90–<95%	4.1–>4	15,148	1639	153%	146%	161%
95–<97.5%	4–>3.9	13,733	1806	182%	175%	191%
97.5–<99%	3.9–>3.75	2425	397	221%	202%	242%
99–<99.5%	3.75–>3.65	1136	247	280%	250%	314%
99.5+%	≤3.65	1124	393	407%	374%	443%

Table 6. Mortality in Males Ages 70+

Percentile	Albumin	Vital Status		Mortality	Lower	Upper
Band	Values	Alive	Dead	Ratio	95% CI	95% CI
<5%	>4.85	644	181	78%	68%	88%
5–<10%	4.85–>4.7	517	161	84%	73%	96%
10–<25%	4.7–>4.5	2265	777	90%	85%	96%
25–<75%	4.5–>4.1	8760	3451	100%		
75–<90%	4.1–>3.95	3136	1572	118%	113%	123%
90–<95%	3.95–>3.8	828	509	135%	126%	144%
95–<97.5%	3.8–>3.7	742	499	142%	133%	152%
97.5–<99%	3.7–>3.5	138	119	164%	144%	187%
99–<99.5%	3.5–>3.4	102	86	162%	139%	189%
99.5+%	≤3.4	42	49	191%	158%	230%

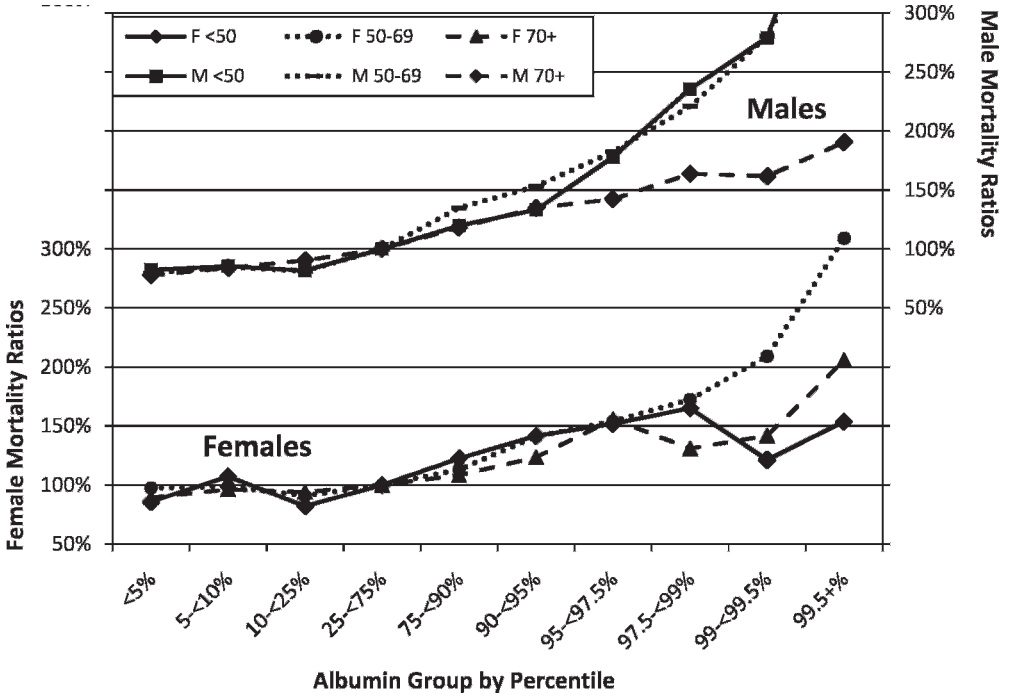

Figure 1. *Mortality ratios by age and sex for each percentile band.*

Analysis was performed with SPSS for Windows, version 17.0.2 (SPSS Inc.).

RESULTS

We looked at the mortality associated with a range of albumin values for each of the age-sex groupings. Tables 1–6 provide a distribution of albumin values by percentile band, the number of deaths, the mortality ratios (MR), and the 95% confidence intervals (CI) for each MR in each of the 6 age-sex groups.[9] Each data point has at least 30 deaths and except for women with the highest 25% of albumin values (fewest deaths), the 95% CIs are relatively narrow. In men, albumin values higher than the middle 50% band have a mortality ratio as low as 80%, and values lower than this reference band have steadily increasing mortality risk. In women, albumin values higher than the middle 50% band have a lesser and more variable reduction in mortality compared to the middle 50%, while values lower than this reference band have steadily increasing mortality risk similar to males. One exception is the F <50 group for albumin levels below 3.5 mg/dL, where mortality dips. We postulate that this is secondary to pregnancy-related dilutional hypoalbuminemia, where values would typically fall into this band without increased mortality risk. All other groups show consistently increasing risk at these albumin values.

The data from Tables 1–6 are combined in Figure 1 to allow comparison of the mortality pattern in all 6 age-sex groups. Except as noted above for F<50, male and female mortality patterns are generally similar, but both high and low albumin values in men have greater relative mortality impact.

We also explored the interaction of albumin with low total cholesterol and with elevated liver enzymes. Figure 2 shows the MRs in the males 50–69 group when all applicants in that group were considered (same data as Table 5); when applicants with total cholesterol (TC) ≤160 mg/dL were excluded; and when applicants with elevated AST, GGT or alkaline phosphatase values (LFTs) at their 95th percentile or higher were excluded. This figure is representative of the other 5 age-sex groups (not shown). A discernable mortality difference begins at

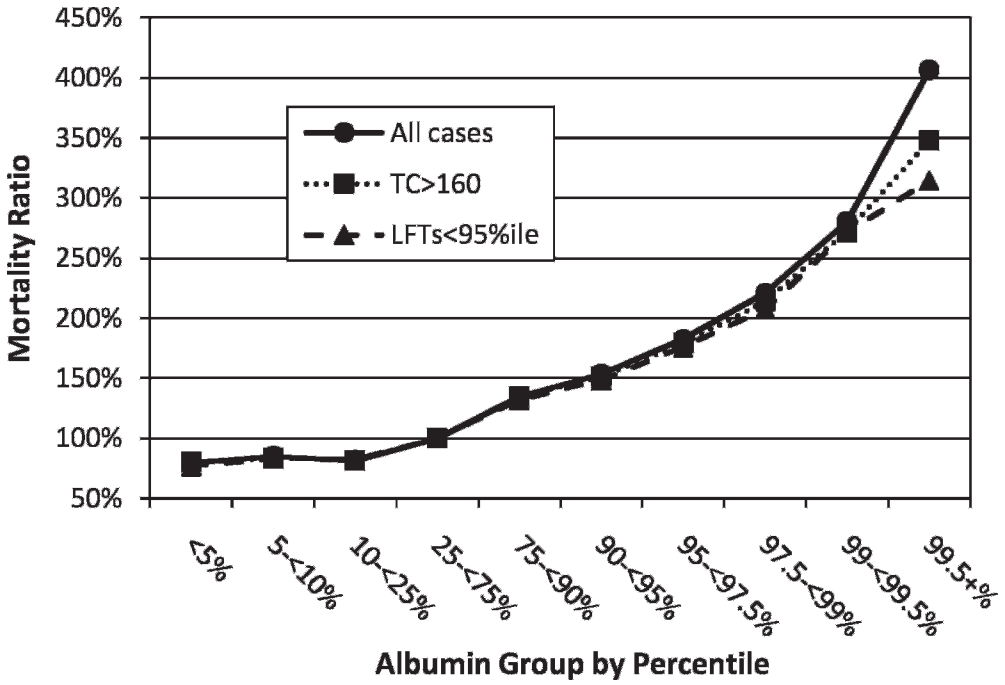

Figure 2. *Mortality ratios in males ages 50–69 by albumin level and exclusion of low cholesterol or high AST, AP or GGT.*

the 95th percentile of albumin values and a difference amounting to more than 50 percentage points begins only at the 99th percentile. At ages <70 years, LFTs have the larger impact and at age 70+, low TC has the larger impact.

DISCUSSION

Though the impact is greater in men and at younger ages, albumin is predictive of mortality risk for all age-sex groups across a wide range of values. Relative risk exceeded 150% of each age- and sex-specific reference band between the 90th and 95th percentile of albumin values for all groups. This translates into 150% risk thresholds at approximately 3.8 mg/dL for all females and for males 70+, and at approximately 4.1 mg/dL for males ages 20 to 69. Any risk-based cut-off value chosen to indicate the need of further evaluation will therefore be different between these groups. Albumin can also play a role in identifying individuals at lower than average risk for all-cause mortality, although this impact appears greater in men than in women. The ability to identify this consistent pattern of increasing risk in all groups, something not always seen in prior studies, may simply be the result of our larger database and/or different selection criteria.

We also examined the relative risk associated with albumin levels for all applicants compared to the risk for applicants after excluding those with low cholesterol, and after excluding those with any other LFT elevation, both of which might be covariates. The total cholesterol cut-off of ≤160 mg/dL was selected for this study based on the threshold associated with increasing mortality risk in insurance applicants (CRL data not shown), and research on albumin, total cholesterol levels and frailty.[10] Even with these exclusions, we found little difference in mortality except in the lowest 1% of albumin values, indicating that the mortality impact of albumin was relatively independent of low total cholesterol or other LFT elevations.

Beyond age, sex, and laboratory values from blood and urine, no other examination or historical information was available for applicants during this time period, preventing separate analysis of the value of albumin in the presence of medical history, low BMI, or high blood pressure. The lack of other

applicant information is a limitation, but community population studies have found that albumin remains an independent predictor of mortality, even when such information is taken into account.[1–4]

CONCLUSIONS

Albumin level predicted mortality risk in this healthy population of insurance applicants in an age- and sex-specific manner both at high values (reduced risk) and low values (increased risk) relative to the middle 50% of albumin values. This finding was largely independent of the risk associated with low total cholesterol and elevations of other LFTs, and was present for all ages and both sexes.

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