

Supplementary Online Table 1. Number of deaths and age- and multivariate-adjusted hazard ratios for mortality by category of hepatic steatosis on ultrasound (N=7,729 with normal, 1,657 with mild, 1,908 with moderate, 848 with severe without additional risk factors*, and 64 with severe with additional risk factors), United States, 1988-2011

Mortality outcome Hepatic steatosis category	No. of deaths	Age-adjusted (N=12,206)			Multivariate-adjusted† (N=11,097)		
		HR‡	95% CI	p-value	HR	95% CI	p-value
All-cause							
Normal	1,617	1.0			1.0		
Mild	388	1.17	0.98 – 1.41	0.082	1.01	0.83 – 1.23	0.91
Moderate	577	1.20	1.06 – 1.35	0.005	0.93	0.79 – 1.11	0.43
Severe without all 3 risk factors	259	1.17	0.98 – 1.40	0.081	0.89	0.76 – 1.06	0.18
Severe with all 3 risk factors	30	2.14	1.38 – 3.30	<0.001	1.18	0.73 – 1.90	0.49
Cardiovascular disease							
Normal	577	1.0			1.0		
Mild	146	1.16	0.86 – 1.56	0.31	0.92	0.67 – 1.26	0.60
Moderate	246	1.41	1.19 – 1.68	<0.001	0.89	0.69 – 1.16	0.39
Severe without all 3 risk factors	85	1.25	0.90 – 1.74	0.18	0.78	0.55 – 1.12	0.18
Severe with all 3 risk factors	10	1.90	0.82 – 4.39	0.13	0.55	0.16 – 1.84	0.32
Cancer							
Normal	485	1.0			1.0		
Mild	111	1.19	0.84 – 1.69	0.33	1.13	0.74 – 1.72	0.56
Moderate	147	1.08	0.83 – 1.41	0.54	1.01	0.73 – 1.42	0.93
Severe without all 3 risk factors	87	1.07	0.75 – 1.51	0.71	0.90	0.65 – 1.27	0.55
Severe with all 3 risk factors	8	1.54	0.66 – 3.58	0.31	1.66	0.66 – 4.14	0.28
Diabetes							
Normal	196	1.0			1.0		
Mild	57	2.01	1.25 – 3.23	0.005	1.15	0.73 – 1.81	0.55
Moderate	111	2.80	1.98 – 3.96	<0.001	1.15	0.78 – 1.71	0.47
Severe without all 3 risk factors	49	1.55	0.87 – 2.74	0.13	0.53	0.33 – 0.86	0.010
Severe with all 3 risk factors	10	9.68	5.58 – 16.81	<0.001	0.77	0.41 – 1.45	0.41

HR, hazard ratio; CI, confidence interval

*Additional risk factors were the following: elevated ALT or AST, elevated BMI, and diabetes.

†Adjusted for age (years), sex, race-ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, other), education (years; <12, 12, >12), drinking (never, former, >0-<1 drink/day, 1-2 drinks/day, >2 drinks/day), smoking (never, former, >0-<1 pack/day, ≥1 pack/day), caffeine from beverages (mg/day as deciles), physical activity (METs per month as deciles), BMI (kg/m²), waist-to-hip ratio, diabetes (diagnosed or A1C≥6.5%), total cholesterol (mg/dL), HDL cholesterol (mg/dL), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), and CRP (mg/dL; ≤0.3, >0.3).

‡Estimated using Cox proportional hazards regression analysis.

Table summary: To further examine the relationship of severe hepatic steatosis on ultrasound with mortality outcomes, we reran our analysis after dividing persons with severe steatosis into 2 subgroups: 1) severe steatosis plus all 3 of the following risk factors: one or both of ALT or AST elevated, overweight or obese, and diabetes (n=64), and 2) severe steatosis without all 3 of the risk factors (n=848). Ten persons were excluded due to missing data on one or more of the 3 risk factors. Among the group with severe steatosis and all 3 risk factors, there were 30 deaths from all causes. Although this group had over twice the mortality from all causes when compared with persons with normal liver and adjusted only for age (HR, 2.14; 95% CI, 1.38-3.30, p<0.001), there was no independent association in multivariate analysis with adjustment for all the factors listed in the footnote above (HR, 1.18; 95% CI, 0.73-1.90, p=0.49). The numbers of deaths with cardiovascular disease, cancer, or diabetes among the subgroup with severe steatosis were small. There was a higher risk of diabetes mortality when adjusted only for age, but with adjustment for baseline diabetes and other factors, no independent association remained. There were also no statistically significant associations with cardiovascular disease or cancer mortality in either age- or multivariate-adjusted analyses. No associations were found among the subgroup with severe steatosis, but without all 3 risk factors.

Supplementary Online Table 2. Number of deaths and multivariate-adjusted hazard ratios for all-cause mortality by subgroups of baseline characteristics among persons with severe hepatic steatosis on ultrasound, United States, 1988-2011

	N	No. of deaths	Multivariate-adjusted		
			HR*	95% CI	p-value
All persons with severe steatosis	922	296	--	--	--
Age (years)			1.08	1.05-1.11	<0.001
Education (years)					
<12	417	168	1.76	1.20-2.58	0.004
12	290	79	1.52	1.03-2.24	0.037
>12	213	48	1.0		
Cigarette smoking					
Never smoker	440	115	1.0		
Former smoker	280	110	1.24	0.72-2.12	0.43
>0-<1 pack/day	122	32	3.01	1.61-5.62	<0.001
≥1 pack/day	77	39	3.05	1.73-5.37	<0.001
Diabetes†					
No	702	172	1.0		
Yes	219	123	2.48	1.65-3.71	<0.001
Systolic blood pressure (mmHg)					
<140	683	164	1.0		
≥140	238	132	1.61	1.13-2.29	0.010
ALT decile‡					
1-3	102	54	1.77	1.18-2.66	0.006
4-9	544	185	1.0		
10	270	53	1.20	0.77-1.86	0.42
Albumin (g/dL)§					
<3.4	17	5	3.39	1.61-7.13	0.002
≥3.4	899	287	1.0		
Platelet count (1000 cells/uL)§					
<200	116	50	1.65	1.05-2.61	0.032
≥200	792	238	1.0		

HR, hazard ratio; CI, confidence interval; ALT, alanine aminotransferase;

*Estimated using Cox proportional hazards regression analysis and adjusted for all factors listed.

†Health care provider diagnosis or A1C≥6.5%.

‡ALT cut-points were 13 and 34 IU/L for men and 9 and 22 IU/L for women.

§Albumin and platelet count cut-points were those of NCHS reference laboratory.

Table summary: To further evaluate the subgroup of participants with severe hepatic steatosis on ultrasound (n=922 with mortality follow-up; 296 with deaths from all causes), we analyzed factors associated with mortality among this subgroup. We first examined the age-adjusted relationship of each variable listed in Table 1 with all-cause mortality. Factors associated with mortality (p<0.10) in individual age-adjusted models were age, race-ethnicity, education, caffeine intake, smoking, diabetes, systolic blood pressure, HDL cholesterol, C-reactive protein, ALT, AST, GGT, alkaline phosphatase, albumin, and platelet count. The relationships of these

variables (except for AST which was highly correlated with ALT ($\rho=0.75$) and GGT which was not measured on all participants) with mortality were further evaluated in multivariate-adjusted analysis using backward selection. Variables were removed one at a time if $p \geq 0.05$, beginning with the highest p-value. Factors that remained independently associated with higher all-cause mortality in the final model with adjustment for each of the other factors in the model were older age, less education, smoking, diabetes, elevated systolic blood pressure, and lower ALT activity, albumin concentration, and platelet count.