

Table 1. Associations between hepatocytic ballooning and fibrosis stage in patients with NASH.

Author/Year	Sample	Dataset	Methods	Statistical Analysis	Ballooning degree	Fibrosis stage	Main findings
Fujii et al., 2009	Liver biopsy specimens of human	39	Immunohistochemistry (double staining)	Mann-Whitney U test Spearman rank correlation	Adipophilin-positive ballooned hepatocytes Adipophilin-negative ballooned hepatocytes	Brunt System*	Frequency of adipophilin-positive ballooned hepatocytes was significantly associated with fibrosis
Rangwala et al., 2011	C57Bl/6 mice Liver biopsy specimens of human	C57Bl/6 mice: not mentioned Liver biopsy specimens of human:7	Immunohistochemistry Western blot analysis	Student's t-test	0(none) 1(few) 2(many)	Brunt System*	Trichrome staining revealed the accumulation of ballooned hepatocytes in areas of matrix deposition. Numbers of sonic Hedgehog-positive hepatocytes correlated with degree of ballooning and fibrosis stage. Liver biopsies of NASH demonstrating conic Hedgehog-positive ballooned hepatocytes,

							which are surrounded by gli-2-positive myofibroblasts.
Guy et al., 2015	Liver biopsy specimens of human	59	Immunohistochemistry Cohort studies	Student's t tests, Chi-square test and Wilcoxon rank-sum test	0(none) 1(few) 2(many)	Brunt System*	NASH improvement significantly reduced hepatocytic ballooning and accompanying pathology, including accumulation of progenitors and myofibroblasts.
Younossi et al., 2017	Liver biopsy specimens of human	209	Cross-sectional studies	Chi-square or Mann-Whitney test	0(none) 1(rare) 2(frequent) 3(severe/numerous)	Steatofibrosis [†] No steatofibrosis	Ballooning was significantly associated with advanced fibrosis in cross-sectional studies but was not a predictor of mortality in NAFLD.
Kakisaka et al., 2018	Liver biopsy specimens of human	125	Cross-sectional studies	Linear regression analysis	Presence of ballooned hepatocytes Absence of ballooned hepatocytes	FIB-4 index [#] Brunt System*	Presence of ballooned hepatocytes was negatively associated with the delta FIB-4 index in the NASH patient group; presence of ballooned hepatocytes was a risk factor for progression of liver fibrosis.

Kleiner et al., 2019	Liver biopsy specimens of human	132	Cohort study	Fisher's exact test Analysis of covariance	0 (none) 1 (few) 2 (many)	NASH CRN [‡]	A decrease in ballooning and the composite NAS between the initial and final biopsies were all significantly associated with fibrosis regression.
Brunt et al., 2019	Liver biopsy specimens of human	PIVENS:221 FLINT:200	Retrospective analysis	Fisher's exact test and Student's t test	0 (none) 1 (few) 2 (many)	NASH CRN [‡]	There was a strong link between histologic resolution of NASH (including ballooning, <i>P</i> < 0.05) and improvement in fibrosis.

Abbreviations: NASH: nonalcoholic steatohepatitis; LRM: liver-related mortality; PIVENS trial: Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients; FLINT trial: Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment; gli, glioblastoma.

[†]Steato-fibrosis was defined as steatosis (>5%) in the presence of moderate or marked fibrosis (stage >1); in the scoring protocol, pericellular/perisinusoidal fibrosis and portal fibrosis were graded into four categories on a scale of 0 to 3 as follows: (0) none, (1) mild or few, (2) moderate, or (3) marked or many.

[‡]0: none; 1a: zone 3 perisinusoidal, delicate; 1b: zone 3 perisinusoidal, dense; 1c: portal only; 2:1a or 1b+periportal; 3: bridging; 4: cirrhosis.

*0: none; 1: zone 3 perisinusoidal; 2:1+periportal; 3: bridging; 4: cirrhosis.