Supplemental Table 1. Univariable and multivariable predictors of progression to cirrhosis among patients with baseline bridging (F3) fibrosis secondary to non-alcoholic steatohepatitis

	Univariable		**Multivariable**	
	Hazard Ratio (95% CI)	**p-value**	**Hazard Ratio (95% CI)**	**p-value**
Age, per yr	1.01 (0.99, 1.03)	0.3483	1.01 (0.99, 1.03)	0.4083
Sex (Female vs. Male)	0.98 (0.67, 1.45)	0.9355	1.12 (0.75, 1.66)	0.5879
Ethnicity (Non-hispanic/Latino vs. Hispanic/Latino)	0.68 (0.41, 1.12)	0.1320	0.63 (0.38, 1.04)	0.0714
BMI, per kg/m^2	1.02 (0.99, 1.05)	0.2178	1.00 (0.97, 1.03)	0.8561
LS by VCTE ≥16.6 kPa	3.86 (2.61, 5.72)	<0.001	3.99 (2.66, 5.98)	<.0001

BMI, body mass index; LS by VCTE, liver stiffness by vibration-controlled transient elastography.

Supplemental Table 2. Univariable and multivariable predictors of progression to cirrhosis among patients with baseline bridging (F3) fibrosis secondary to non-alcoholic steatohepatitis

	Univariable		**Multivariable**	
	Hazard Ratio (95% CI)	**p-value**	**Hazard Ratio (95% CI)**	**p-value**
Baseline LS by VCTE >=16.6 kPa vs. <16.6 kPa	3.86 (2.61, 5.72)	<0.001	4.26 (2.83, 6.40)	<0.001
Age, per yr	1.01 (0.99, 1.03)	0.3483	1.01 (0.99, 1.03)	0.4092
Sex (Female vs. Male)	0.98 (0.67, 1.45)	0.9355	1.08 (0.73, 1.61)	0.6871
Ethnicity (Non-hispanic/Latino vs. Hispanic/Latino)	0.68 (0.41, 1.12)	0.1320	0.65 (0.39, 1.07)	0.0927
BMI, per kg/m^2	1.02 (0.99, 1.05)	0.2178	0.99 (0.96, 1.02)	0.6179
≥20% increase in LS by VCTE vs <20% increase	1.59 (0.97, 2.59)	0.0638	1.98 (1.20, 3.26)	0.0076

BMI, body mass index; LS by VCTE, liver stiffness by vibration-controlled transient elastography.

Supplemental Table 3. Baseline demographics and clinical characteristics of the subgroup of patients with sufficient data for determination of the Agile 3+ and 4 scores

		Bridging Fibrosis (F3) n=629	Compensated Cirrhosis (F4) n=701
Demographics	Age, y	58 (51, 64)	59 (54, 65)
	Women, n (%)	350 (56)	442 (63)
	Diabetes, n (%)	444 (71)	531 (76)
Liver biochemistry	ALT, U/L	53 (36, 80)	43 (32, 61)
	AST, U/L	46 (33, 65)	45 (34, 61)
	AST/ALT ratio	0.86 (0.72, 1.04)	1.02 (0.84, 1.24)
	Platelets, $10^3/\mu L$	206 (166, 256)	161 (125, 206)
Liver histology	NAS ≥4, n (%)	594 (94)	662 (95)[†]
	Steatosis Grades 2–3, n (%)	53 (8)	33 (5)[†]
	Lobular inflammation Grade 3, n (%)	317 (50)	377 (54)[†]
	Hepatocellular ballooning Grade 2, n (%)	489 (78)	570 (82)[†]
Biopsy quality	Length, cm	2.2 (1.6, 3.0)	2.0 (1.5, 2.8)
	Length ≥2 cm, n (%)	383 (61)	388 (55)
Noninvasive tests	NFS	-0.192 (-1.016, 0.500)	0.619 (-0.212, 1.493)
	FIB-4	1.68 (1.23, 2.50)	2.49 (1.73, 3.49)
	ELF	9.94 (9.34, 10.61)	10.60 (9.97, 11.27)
	LS by VCTE, kPa	12.7 (9.7, 17.3)	21.1 (14.3, 28.9)
	Agile 3+	0.76 (0.53, 0.89)	0.95 (0.86, 0.98)
	Agile 4	0.20 (0.08, 0.39)	0.63 (0.34, 0.80)

Data are median (interquartile range) or n/n (%).
ALT, alanine aminotransferase; αSMA, α-smooth muscle actin; BMI, body mass index; ELF, Enhanced Liver Fibrosis score (Siemens Healthcare GmbH, Erlangen Germany); FIB-4, fibrosis-4 index; GGT, γ-glutamyltransferase; LS by VCTE, liver stiffness by vibration-controlled transient elastography; NAFLD Activity Score, NAS.
[†] Total n=699.

Supplemental Table 4. Univariable and multivariable predictors of progression to cirrhosis among patients with bridging (F3) fibrosis secondary to non-alcoholic steatohepatitis

	Univariable		**Multivariable**	
	Hazard Ratio (95% CI)	**p-value**	**Hazard Ratio (95% CI)**	**p-value**
Age, per yr	1.01 (0.99, 1.03)	0.5227	0.99 (0.97, 1.01)	0.3738
Sex (Female vs. Male)	0.93 (0.62, 1.39)	0.7270	0.84 (0.56, 1.26)	0.3958
Ethnicity (Non-hispanic/Latino vs. Hispanic/Latino)	0.68 (0.40, 1.13)	0.1351	0.61 (0.36, 1.03)	0.0619
BMI, per kg/m^2	1.02 (0.99, 1.05)	0.1715	1.00 (0.97, 1.03)	0.8734
Agile 3+ score ≥ 0.90	4.34 (2.89, 6.50)	<.0001	4.75 (3.07, 7.34)	<.0001

BMI, body mass index.

Supplemental Table 5. Performance of liver stiffness by vibration-controlled transient elastography versus the Agile scores for predicting disease progression*

	Progression to Cirrhosis (F4) in Patients with Bridging Fibrosis (F3) (n=629)		**Liver-Related Clinical Events Among Patients with Cirrhosis (F4) (n=701)**	
	Liver stiffness by VCTE	**Agile 3+**	**Liver stiffness by VCTE**	**Agile 4**
c-statistic (95% CI)	0.71 (0.65, 0.76)	0.70 (0.64, 0.76)	0.81 (0.72, 0.90)	0.82 (0.74, 0.90)
Optimal threshold	≥ 16.6 kPa	≥ 0.90	≥ 30.7 kPa	≥ 0.72
Sensitivity	58% (55/95)	55% (52/95)	74% (17/23)	87% (20/23)
Specificity	76% (407/534)	81% (431/534)	79% (535/678)	64% (433/678)
PPV	30% (55/182)	34% (52/155)	11% (17/160)	8% (20/265)
NPV	91% (407/447)	91% (431/474)	99% (535/541)	99% (433/436)

NPV, negative predictive value; PPV, positive predictive value; VCTE, vibration-controlled transient elastography.
* Analysis restricted to patients with complete data for calculation of the Agile scores.

Supplemental Table 6. Univariable and multivariable predictors for the development of liver-related events among patients with baseline cirrhosis (F4) secondary to non-alcoholic steatohepatitis

	Univariable		**Multivariable**	
	Hazard Ratio (95% CI)	**p-value**	**Hazard Ratio (95% CI)**	**p-value**
Age, per yr	1.05 (1.00, 1.11)	0.0644	1.06 (1.00, 1.13)	0.0533
Sex (Female vs. Male)	2.08 (0.84, 5.15)	0.1142	2.39 (0.95, 5.98)	0.0637
Ethnicity (Non-hispanic/Latino vs. Hispanic/Latino)	0.86 (0.30, 2.48)	0.7772	0.82 (0.28, 2.39)	0.7175
BMI, per kg/m^2	0.98 (0.92, 1.03)	0.4082	0.97 (0.91, 1.03)	0.3431
LS by VCTE ≥30.7 kPa	8.24 (3.61, 18.8)	<0.001	10.13 (4.38, 23.41)	<.0001

BMI, body mass index; LS by VCTE, liver stiffness by vibration-controlled transient elastography.

Supplemental Table 7. Univariable and multivariable predictors for the development of liver-related events among patients with baseline cirrhosis (F4) secondary to non-alcoholic steatohepatitis

	Univariable		**Multivariable**	
	Hazard Ratio (95% CI)	**p-value**	**Hazard Ratio (95% CI)**	**p-value**
Age, per yr	1.05 (1.00, 1.11)	0.0644	1.06 (1.00, 1.13)	0.0512
Sex (Female vs. Male)	2.08 (0.84, 5.15)	0.1142	2.37 (0.94, 5.96)	0.0661
Ethnicity (Non-hispanic/Latino vs. Hispanic/Latino)	0.86 (0.30, 2.48)	0.7772	0.80 (0.27, 2.35)	0.6911
BMI, per kg/m^2	0.98 (0.92, 1.03)	0.4082	0.97 (0.92, 1.03)	0.3642
LS by VCTE ≥30.7 kPa	8.24 (3.61, 18.8)	<0.001	10.13 (4.38, 23.41)	<0.001
Weight loss ≥ 5% (yes vs no)	0.46 (0.11, 1.93)	0.2852	0.45 (0.11, 1.89)	0.2729

BMI, body mass index; LS by VCTE, liver stiffness by vibration-controlled transient elastography.

Supplemental Table 8. Univariable and multivariable predictors for the development of ascites, hepatic encephalopathy and portal hypertension-related bleeding among patients with baseline cirrhosis (F4) secondary to non-alcoholic steatohepatitis

	Univariable		**Multivariable**	
	Hazard Ratio (95% CI)	**p-value**	**Hazard Ratio (95% CI)**	**p-value**
Age, per yr	1.06 (1.00, 1.12)	0.0655	1.06 (1.00, 1.14)	0.0603
Sex (Female vs. Male)	2.13 (0.79, 5.75)	0.1338	2.46 (0.90, 6.72)	0.0780
Ethnicity (Non-hispanic/Latino vs. Hispanic/Latino)	0.99 (0.30, 3.34)	0.9920	0.96 (0.28, 3.25)	0.9446
BMI, per kg/m^2	0.97 (0.91, 1.04)	0.3773	0.97 (0.91, 1.04)	0.3505
LS by VCTE ≥30.7 kPa	7.90 (3.25, 19.20)	<.0001	9.77 (3.97, 24.05)	<.0001

BMI, body mass index; LS by VCTE, liver stiffness by vibration-controlled transient elastography.

Supplemental Table 9. Univariable and multivariable predictors for the development of liver-related events among patients with baseline cirrhosis (F4) secondary to non-alcoholic steatohepatitis

	Univariable		**Multivariable**	
	Hazard Ratio (95% CI)	**p-value**	**Hazard Ratio (95% CI)**	**p-value**
Baseline LS by VCTE >=30.7 kPa vs. <30.7 kPa	8.24 (3.61, 18.82)	<0.001	10.04 (4.34, 23.23)	<0.001
Age, per yr	1.05 (1.00, 1.11)	0.0644	1.06 (1.00, 1.13)	0.0508
Sex (Female vs. Male)	2.08 (0.84, 5.15)	0.1142	2.35 (0.94, 5.91)	0.0686
Ethnicity (Non-hispanic/Latino vs. Hispanic/Latino)	0.86 (0.30, 2.48)	0.7772	0.84 (0.29, 2.45)	0.7446
BMI, per kg/m^2	0.98 (0.92, 1.03)	0.4082	0.97 (0.91, 1.03)	0.3511
≥20% increase in LS by VCTE vs <20% increase	0.61 (0.21, 1.76)	0.3618	0.75 (0.26, 2.18)	0.5959

BMI, body mass index; LS by VCTE, liver stiffness by vibration-controlled transient elastography.

Supplemental Table 10. Univariable and multivariable predictors of liver-related events among patients with cirrhosis (F4) secondary to non-alcoholic steatohepatitis

	Univariable		**Multivariable**	
	Hazard Ratio (95% CI)	**p-value**	**Hazard Ratio (95% CI)**	**p-value**
Age, per yr	1.03 (0.98, 1.09)	0.2379	1.02 (0.96, 1.08)	0.5509
Sex (Female vs. Male)	2.11 (0.78, 5.69)	0.1390	1.90 (0.70, 5.18)	0.2094
Ethnicity (Non-hispanic/Latino vs. Hispanic/Latino)	1.55 (0.36, 6.62)	0.5523	1.75 (0.41, 7.49)	0.4532
BMI, per kg/m^2	0.96 (0.90, 1.03)	0.2405	0.95 (0.89, 1.01)	0.1054
Agile 4 score ≥ 0.72	11.48 (3.41, 38.65)	<.0001	11.84 (3.51, 39.99)	<.0001

BMI, body mass index.

Supplemental Table 11. Concordance statistics by logistic regression for baseline LS by VCTE and baseline NITs in predicting liver-related events

NIT	Number of participants	c-statistic (95% CI) of NIT	c-statistic (95% CI) of LS by VCTE	Difference	p-value
FIB-4	728	0.76 (0.66, 0.86)	0.76 (0.65, 0.87)	0.00 (-0.15, 0.15)	0.9685
NFS	732	0.70 (0.60, 0.80)	0.77 (0.66, 0.87)	-0.07 (-0.23, 0.10)	0.4336
ELF	733	0.80 (0.71, 0.89)	0.77 (0.67, 0.87)	0.03 (-0.07, 0.14)	0.5340

LS, liver stiffness; VCTE, vibration-controlled transient elastography; NIT, non-invasive tests; Fibrosis-4 index, FIB-4, NAFLD fibrosis score, NFS; Enhanced Liver Fibrosis test, ELF

Supplemental Table 12. Multivariable predictors of liver-related events among patients with advanced fibrosis (F3-F4) secondary to non-alcoholic steatohepatitis

	Multivariable	
	Adjusted HR (95% CI)	**p-value**
Age	1.05 (1.00, 1.11)	0.0466
Sex (Female vs. Male)	1.63 (0.77, 3.46)	0.2027
Ethnicity (Non-hispanic/ Latino vs. Hispanic/Latino	0.68 (0.26, 1.81)	0.4417
BMI	0.98 (0.93, 1.04)	0.5266
LS by VCTE >=30.7 kPa vs. <30.7 kPa	10.52 (5.15, 21.48)	<.0001
Treatment arm Selonsertib 6 mg vs Placebo Selonsertib 18 mg vs Placebo Simtuzumab low dose vs Placebo Simtuzumab high dose vs Placebo	 2.34 (0.67, 8.15) 1.35 (0.36, 5.01) 3.77 (0.38, 37.12) 2.53 (0.26, 24.47)	 0.1815 0.6574 0.2556 0.4213

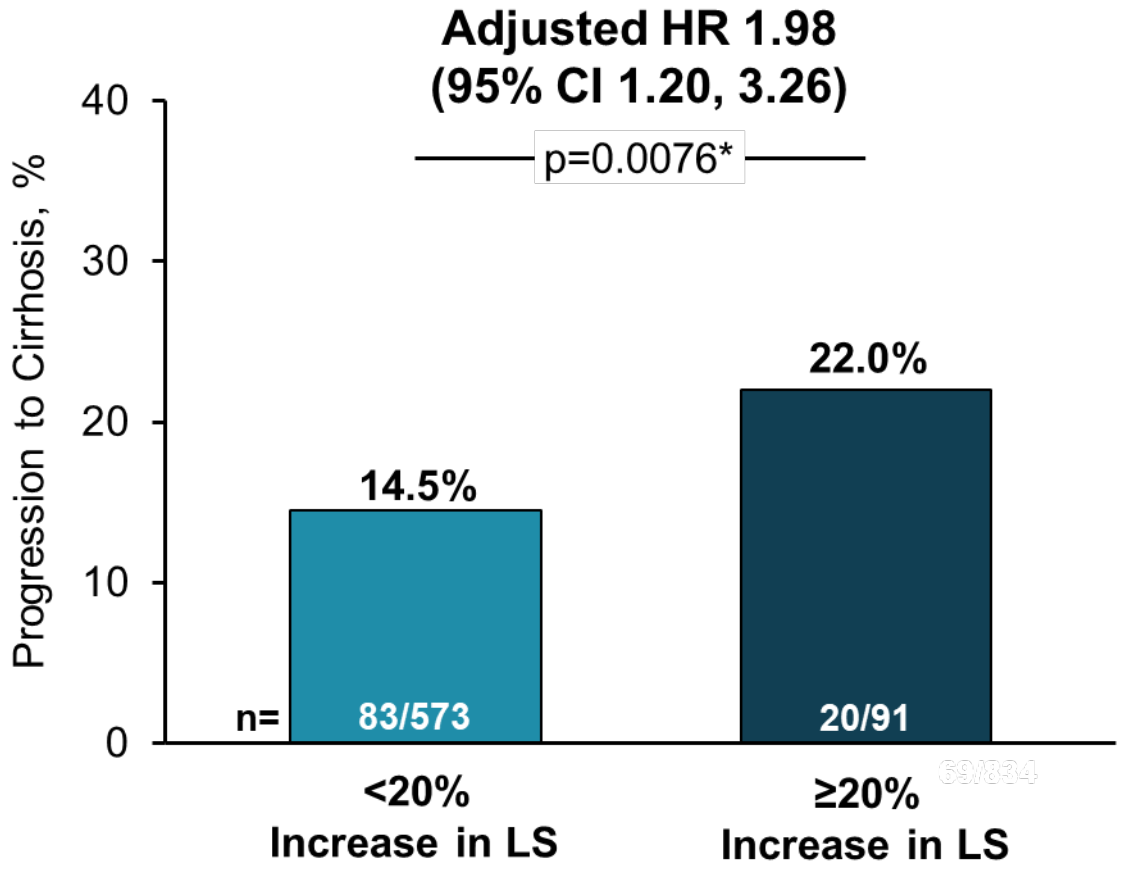
BMI, body mass index; LS, liver stiffness; VCTE, vibration-controlled transient elastography

Supplemental Table 13. Performance of liver stiffness by vibration-controlled transient elastography according to thresholds recommended by the Baveno VII consensus for identification of patients with advanced chronic liver disease [25]

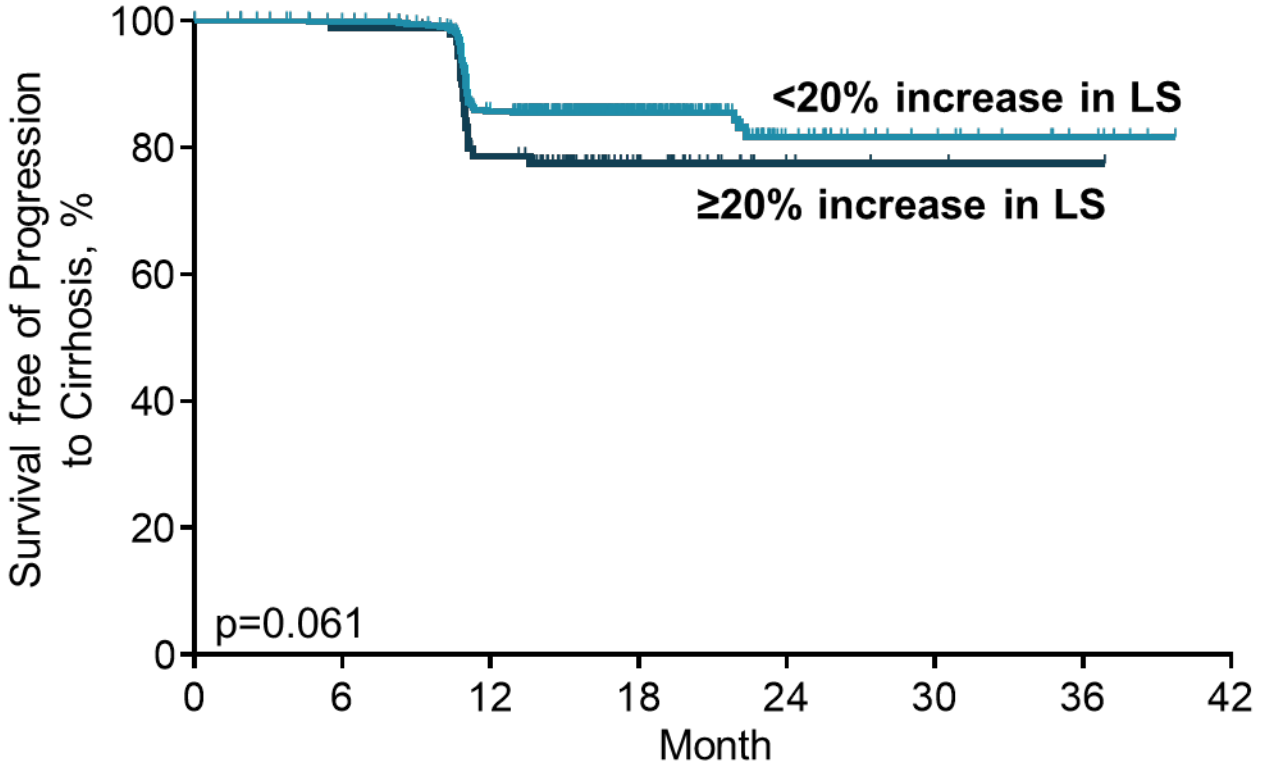
Threshold	Proportion with Event	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	Hazard Ratio (95% CI)
Progression to Cirrhosis (F4) in Patients with Bridging Fibrosis (F3) (n=664)						
LS ≥ 10 kPa	91/483 (19%)	88 (81, 94)	30 (26, 34)	19 (15, 23)	93 (89, 97)	3.01 (1.65, 5.50)
LS < 10 kPa	12/181 (7%)					
LS ≥ 15 kPa*	64/240 (27%)	62 (52, 72)	69 (65, 72)	27 (21, 33)	91 (88, 93)	3.21 (2.16, 4.79)
LS < 15 kPa	39/424 (9%)					
LS ≥ 20 kPa	34/112 (30%)	33 (24, 43)	86 (83, 89)	30 (22, 40)	88 (84, 90)	2.70 (1.79, 4.08)
LS < 20 kPa	69/552 (13%)					
LS ≥ 25 kPa	25/52 (48%)	24 (16, 34)	95 (93, 97)	48 (34, 62)	87 (84, 90)	4.52 (2.88, 7.10)
LS < 25 kPa	78/612 (13%)					
LS ≥ 30 kPa	17/32 (53%)	17 (10, 25)	97 (96, 98)	53 (35, 71)	86 (83, 89)	4.54 (2.69, 7.64)
LS < 30 kPa	86/632 (14%)					
LS ≥ 35 kPa	9/20 (45%)	9 (4, 16)	98 (97, 99)	45 (23, 68)	85 (82, 88)	3.45 (1.74, 6.83)
LS < 35 kPa	94/644 (15%)					
Liver-Related Events in Patients with Cirrhosis (F4) (n=734)						
LS ≥ 10 kPa	26/672 (4%)	96 (81, 100)	9 (7, 11)	4 (3, 6)	98 (91, 100)	2.46 (0.33, 18.10)
LS < 10 kPa	1/62 (2%)					
LS ≥ 15 kPa	25/532 (5%)	93 (76, 99)	28 (25, 32)	5 (3, 7)	99 (96, 100)	4.92 (1.17, 20.78)
LS < 15 kPa	2/202 (1%)					
LS ≥ 20 kPa	22/400 (6%)	81 (62, 94)	47 (43, 50)	6 (3, 8)	99 (97, 100)	3.83 (1.45, 10.12)
LS < 20 kPa	5/334 (1%)					
LS ≥ 25 kPa	21/268 (8%)	78 (58, 91)	65 (0.61, 0.69)	8 (5, 12)	99 (97, 100)	6.43 (2.60, 15.94)
LS < 25 kPa	6/466 (1%)					
LS ≥ 30 kPa*	19/177 (11%)	70 (50, 86)	78 (74, 81)	11 (7, 16)	99 (97, 99)	7.87 (3.44, 17.98)
LS < 30 kPa	8/557 (1%)					
LS ≥ 35 kPa	16/127 (13%)	59 (39, 78)	84 (81, 87)	13 (7, 20)	98 (97, 99)	7.44 (3.45, 16.03)
LS < 35 kPa	11/607 (2%)					

NPV, negative predictive value; PPV, positive predictive value; LS, liver stiffness by vibration-controlled transient elastography. 95% CI for sensitivity, specificity, PPV, and NPV are based on exact limits. * Optimal threshold based on maximal sum of sensitivity and specificity.

Supplemental Figure 1. ≥5kPA (and ≥20%) increase in Liver stiffness (LS) by vibration-controlled transient elastography (VCTE) is associated with increased risk of progression to cirrhosis among patients with baseline bridging (F3) fibrosis secondary to non-alcoholic steatohepatitis

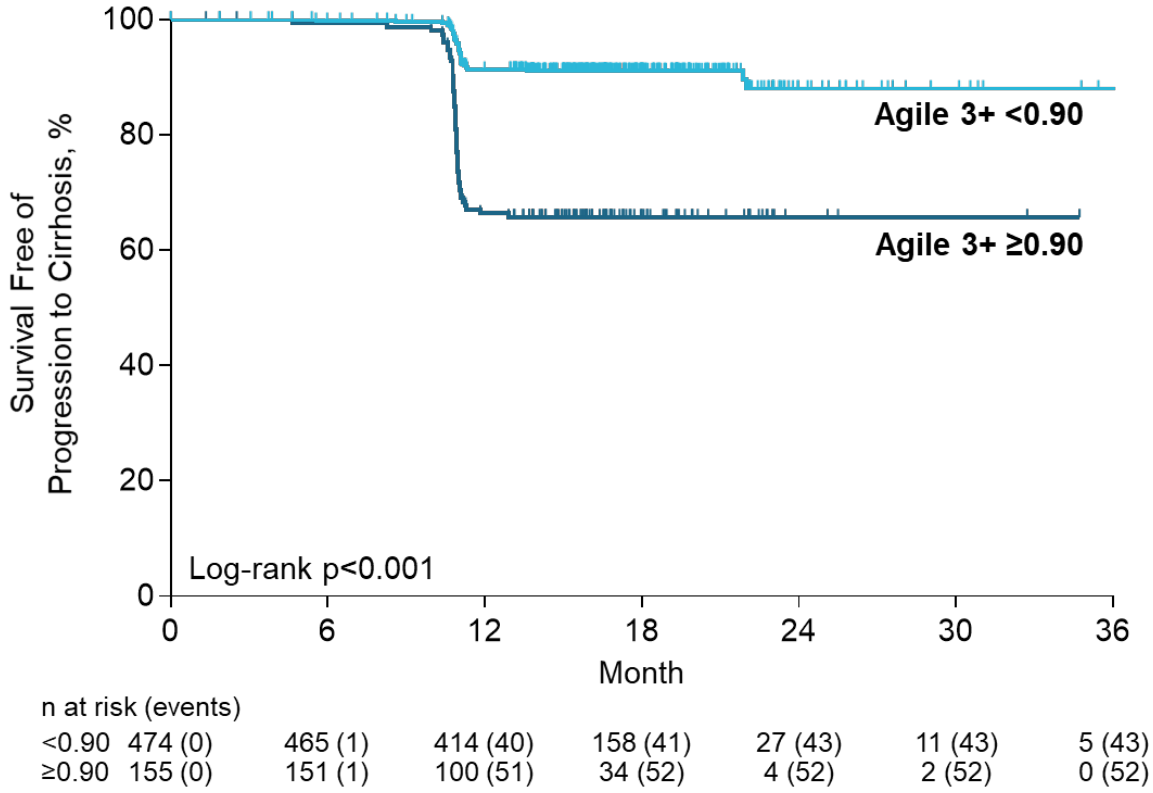


Supplemental Figure 2. Progression to cirrhosis in patients with bridging (F3) fibrosis secondary to non-alcoholic steatohepatitis, stratified by ≥5kPA (and ≥20%) increase in Liver stiffness (LS) by vibration-controlled transient elastography (VCTE)

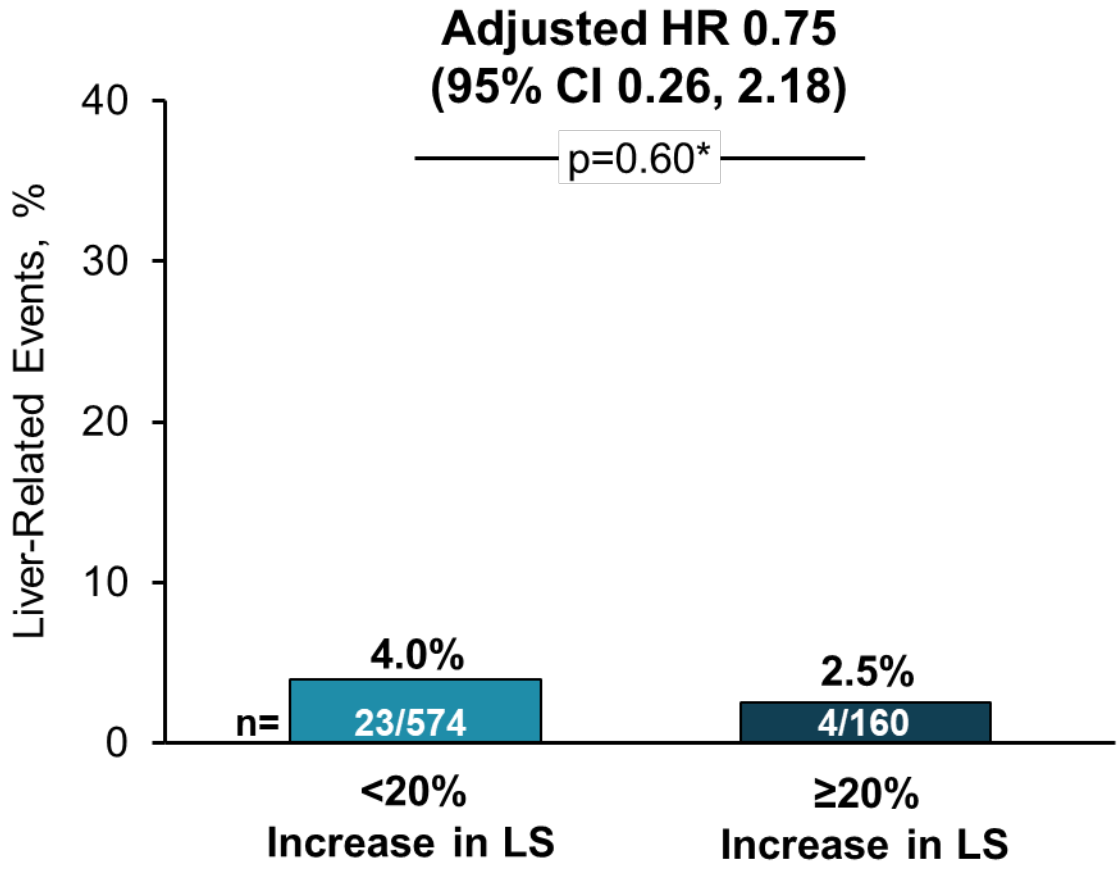


n at risk (events)								
<20%	573 (0)	559 (1)	470 (79)	178 (80)	30 (83)	14 (83)	6 (83)	0 (83)
≥20%	91 (0)	89 (1)	69 (19)	27 (20)	4 (20)	2 (20)	1 (20)	0 (20)

Supplemental Figure 3. Progression to cirrhosis in patients with bridging (F3) fibrosis secondary to non-alcoholic steatohepatitis, stratified by Agile 3+ score ≥ 0.90 versus < 0.90

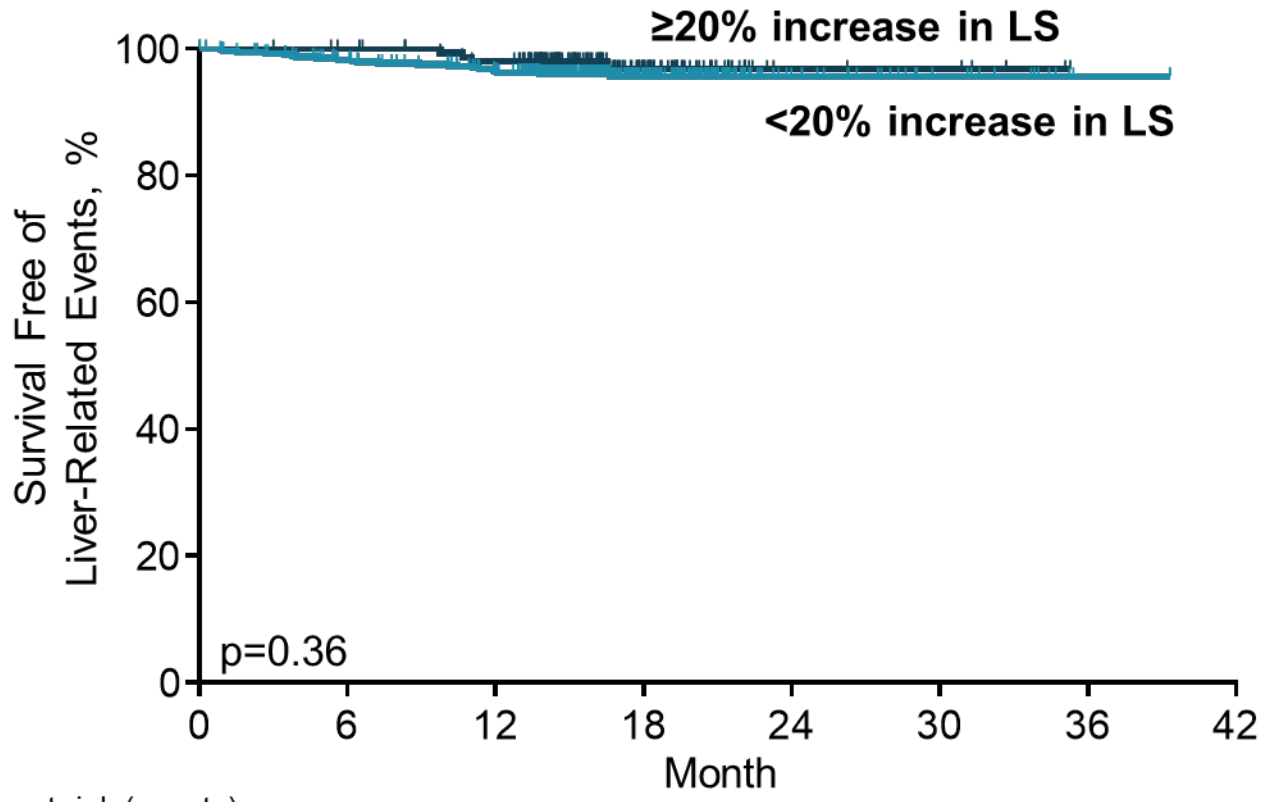


Supplemental Figure 4. Liver-related events in patients with cirrhosis (F4) secondary to non-alcoholic steatohepatitis, stratified by≥5kPA (and ≥20%) increase in Liver stiffness (LS) by vibration-controlled transient elastography (VCTE



*Fisher exact test.

Supplemental Figure 5. Liver-related events in patients with cirrhosis (F4) secondary to non-alcoholic steatohepatitis, stratified by≥5kPA (and ≥20%) increase in Liver stiffness (LS) by vibration-controlled transient elastography (VCTE



n at risk (events)								
<20%	574 (0)	554 (10)	531 (20)	170 (23)	27 (23)	12 (23)	1 (23)	0 (23)
≥20%	160 (0)	157 (0)	150 (3)	52 (4)	6 (4)	5 (4)	0 (4)	0 (4)

Supplemental Figure 6. Liver-related events in patients with cirrhosis (F4) secondary to non-alcoholic steatohepatitis, stratified by Agile 4 ≥ 0.72 versus < 0.72