

NASH Progression Rates Based on Fibrosis and Inflammation (NAS): A Paired Biopsy Analysis From a Natural History Cohort in the US

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BACKGROUND

- Disease progression in nonalcoholic steatohepatitis (NASH) is assessed by:
 - Progression of fibrosis (from F0 to F4 [most severe/cirrhosis])
 - Inflammation (evaluated via the nonalcoholic fatty liver disease activity score [NAS])^{1,2}
- Data on disease progression are essential to support state transition probabilities in economic models
- However, real-world data are limited regarding fibrosis and lacking regarding inflammation (NAS) in patients with NASH

OBJECTIVE

- To estimate NASH progression in a natural history cohort stratified by both baseline fibrosis stage and inflammation (NAS)

METHODS

- Data from patients enrolled in a longitudinal observational cohort study (TARGET-NASH [ClinicalTrials.gov identifier, NCT02815891]) with biopsy-confirmed NASH, paired liver biopsies, and NAS were used to determine the transition probability of NAS and conditional probability of fibrosis progression
- Multinomial logistic regression was adapted to estimate the transition probabilities
- NAS ≥4, an inclusion criterion in NASH clinical trials, was examined categorically

RESULTS

- In total, 152 patients were included in this analysis
 - The majority of patients were White (n=136; 89.5%) and female (n=93; 61.2%)
 - Mean age at enrollment was 55.5 years (standard deviation [SD], 11.72)
 - Mean body mass index (BMI) at enrollment was 33.0 kg/m² (SD, 6.40) with most patients (n=99/150) below the severe obesity category (BMI ≤35 kg/m²)
- On average, the time between the paired liver biopsies was 45.8 months (SD, 44.83)
 - 23.0% (n=35) of patients had the biopsies within 1 year of each other, 20.4% (n=31) had the biopsies 1-2 years apart, and 56.6% (n=86) had the biopsies 2+ years apart
- At 1st biopsy, 46.7% (n=71) of patients had a NAS <4 and 53.3% (n=81) had a NAS ≥4
- Regardless of initial NAS, fibrosis stage more likely remained the same or increased versus decreased: 83.1% (n=59) of patients with NAS <4 (**Table 1**) and 79.0% (n=64) of patients with NAS ≥4 (**Table 2**)
- The annual transition probability in the NAS <4 group (n=27) to NAS ≥4 was 0.29 (95% confidence interval [CI]: 0.10-0.47); in the NAS ≥4 group (n=44), the probability of transitioning to NAS <4 was 0.37 (95% CI: 0.22-0.53) (**Table 3**)

Table 1. 1-year fibrosis transition probabilities among patients with NAS <4 at 1st biopsy

	Fibrosis Progression			
Fibrosis stage at 1 st biopsy	Decreased	Same	Increased	Total
F0	0 (n=0)	0.2 (n=3)	0.8 (n=10)	13
F1	0.11 (n=3)	0.55 (n=12)	0.35 (n=7)	22
F2	0.44 (n=5)	0.34 (n=4)	0.22 (n=2)	11
F3	0.2 (n=4)	0.54 (n=10)	0.26 (n=4)	18
F4	0 (n=0)	1 (n=7)	0 (n=0)	7
Total	12	36	23	71

Table 2. 1-year fibrosis transition probabilities among patients with NAS ≥4 at 1st biopsy

	Fibrosis Progression			
Fibrosis stage at 1 st biopsy	Decreased	Same	Increased	Total
F0	0 (n=0)	0.51 (n=1)	0.49 (n=3)	4
F1	0.06 (n=2)	0.52 (n=11)	0.42 (n=11)	24
F2	0.17 (n=3)	0.32 (n=4)	0.52 (n=8)	15
F3	0.3 (n=8)	0.53 (n=12)	0.16 (n=4)	24
F4	0 (n=4)	1 (n=10)	0 (n=0)	14
Total	17	38	26	81

Table 3. NAS transition probabilities among patients with NAS at 1st and 2nd biopsies

	NAS at 2 nd Biopsy		
NAS at 1 st biopsy	<4	≥4	Total
<4	0.71 95% CI: 0.53-0.90 (n=18)	0.29 95% CI: 0.10-0.47 (n=9)	27
≥4	0.37 95% CI: 0.22-0.53 (n=15)	0.63 95% CI: 0.47-0.78 (n=29)	44
Total	33	38	71

CONCLUSIONS

- Most patients with NASH were unlikely to achieve fibrosis improvement within 1 year regardless of initial NAS (<4 or ≥4)
- NAS transition probabilities reflected annual changes in fibrosis stage
- Calculating NAS is feasible for inclusion in economic models and its inclusion will enable modeling of earlier disease progression in NASH

LIMITATIONS

- This is a small retrospective study due to the requirement of 2 paired biopsies. Looking at changes in fibrosis as a function of changes in NAS in a larger cohort would validate the relationship between the two.
- The model assumes transition is linear, but this is unlikely in practice. The exact time of transition was not observed, transitions may have occurred outside the biopsy dates and a transition between contiguous states (fibrosis stages) is not instantaneous. Therefore, this approach focused on the underlying progression across states rather than the observed progressions

REFERENCES

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