

# Disease Presentation and Natural History of Nonalcoholic Fatty Liver Disease in an Ethnically Diverse United States Patient Population: a Long-Term Follow-up Study

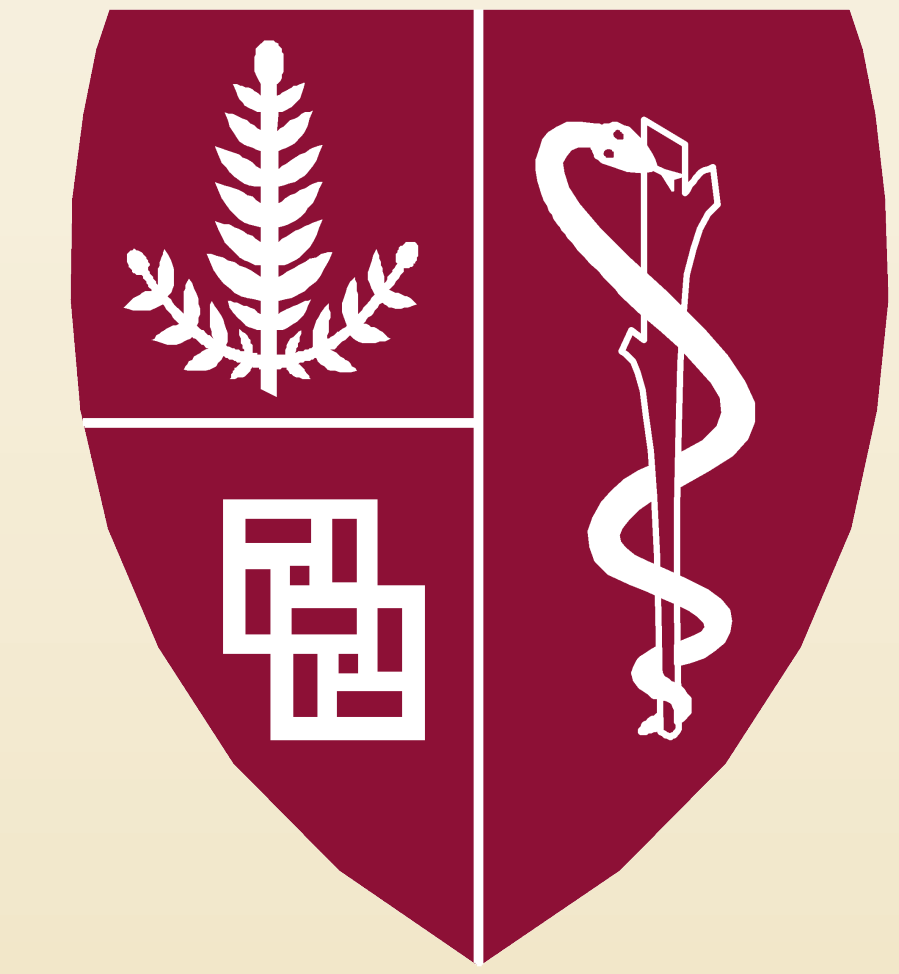
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## OBJECTIVE

Our aim is to characterize disease presentation and natural history of Nonalcoholic fatty liver disease (NAFLD) in an ethnically diverse patient cohort.

## BACKGROUND

- NAFLD is recognized as the most common liver disease in developed countries with an estimated prevalence of 20-30%.
- NAFLD represents a spectrum of disease ranging from simple steatosis of the liver to progressive inflammation and fibrosis, resulting in nonalcoholic steatohepatitis (NASH), which can progress to chronic liver disease, cirrhosis, and/or hepatocellular carcinoma (HCC).
- NASH-related cirrhosis is projected to become the leading indication for liver transplantation in the next 10-20 years.
- The natural history and incidence of disease sequelae from simple steatosis in patients with NAFLD has not been well studied, especially in regards to ethnic influences.

## METHODS

- Retrospective cohort study of 460 consecutive NAFLD patients (128 Asians, 242 Caucasians, and 90 Hispanics) seen at a university medical center between 01/1999 and 12/2005.
- NAFLD was diagnosed by radiologic imaging and/or histologic evaluation.
- Patients were included if they had no known viral infection, excessive alcohol consumption, toxic/drug-induced hepatitis, or autoimmune/genetic liver disease.
- Study endpoints were development of NASH, cirrhosis, decompensation, HCC, and death.

### A. Baseline patient characteristics

- Asians were significantly more likely to be male with a lower BMI, and less likely to be classified as extremely obese (Table 1).
- Comorbidities were similar among the three groups except hypertension was more prevalent among Caucasians (Table 1).

**Table 1. Baseline patient characteristics**

|                                      | Asian<br>n = 128 | Caucasian<br>n = 242 | Hispanic<br>n = 90 | p-value |
|--------------------------------------|------------------|----------------------|--------------------|---------|
| Age (year)                           | 42 ± 13          | 49 ± 14              | 39 ± 12            | <0.001  |
| Sex (male)                           | 68 (53)          | 95 (39)              | 24 (27)            | <0.001  |
| Body mass index (kg/m <sup>2</sup> ) | 28.8 ± 6.5       | 36.7 ± 9.4           | 36.9 ± 9.3         | <0.001  |
| BMI classification                   |                  |                      |                    | <0.001  |
| Normal weight                        | 31 (30)          | 19 (9)               | 6 (9)              |         |
| Overweight                           | 39 (37)          | 39 (18)              | 12 (17)            |         |
| Obese class I                        | 22 (21)          | 45 (21)              | 15 (22)            |         |
| Obese class II                       | 7 (7)            | 43 (20)              | 14 (20)            |         |
| Obese class III                      | 6 (6)            | 71 (33)              | 22 (32)            |         |
| Comorbidities                        |                  |                      |                    |         |
| Hypertension                         | 63 (49)          | 155 (64)             | 53 (59)            | 0.022   |
| Diabetes mellitus                    | 37 (29)          | 85 (35)              | 32 (36)            | 0.43    |
| Hypercholesterolemia                 | 30 (23)          | 70 (29)              | 19 (21)            | 0.27    |
| Hyperlipidemia                       | 69 (54)          | 120 (50)             | 34 (38)            | 0.06    |
| Coronary artery disease              | 13 (10)          | 32 (13)              | 7 (8)              | 0.34    |

- All three groups had similar low, intermediate, and high probability of fibrosis using the APRI and FIB-4 score. Caucasians were more likely to have high probability of fibrosis based on the NFS (12%) compared to Asians (6%) and Hispanics (10%), respectively (p<0.001).

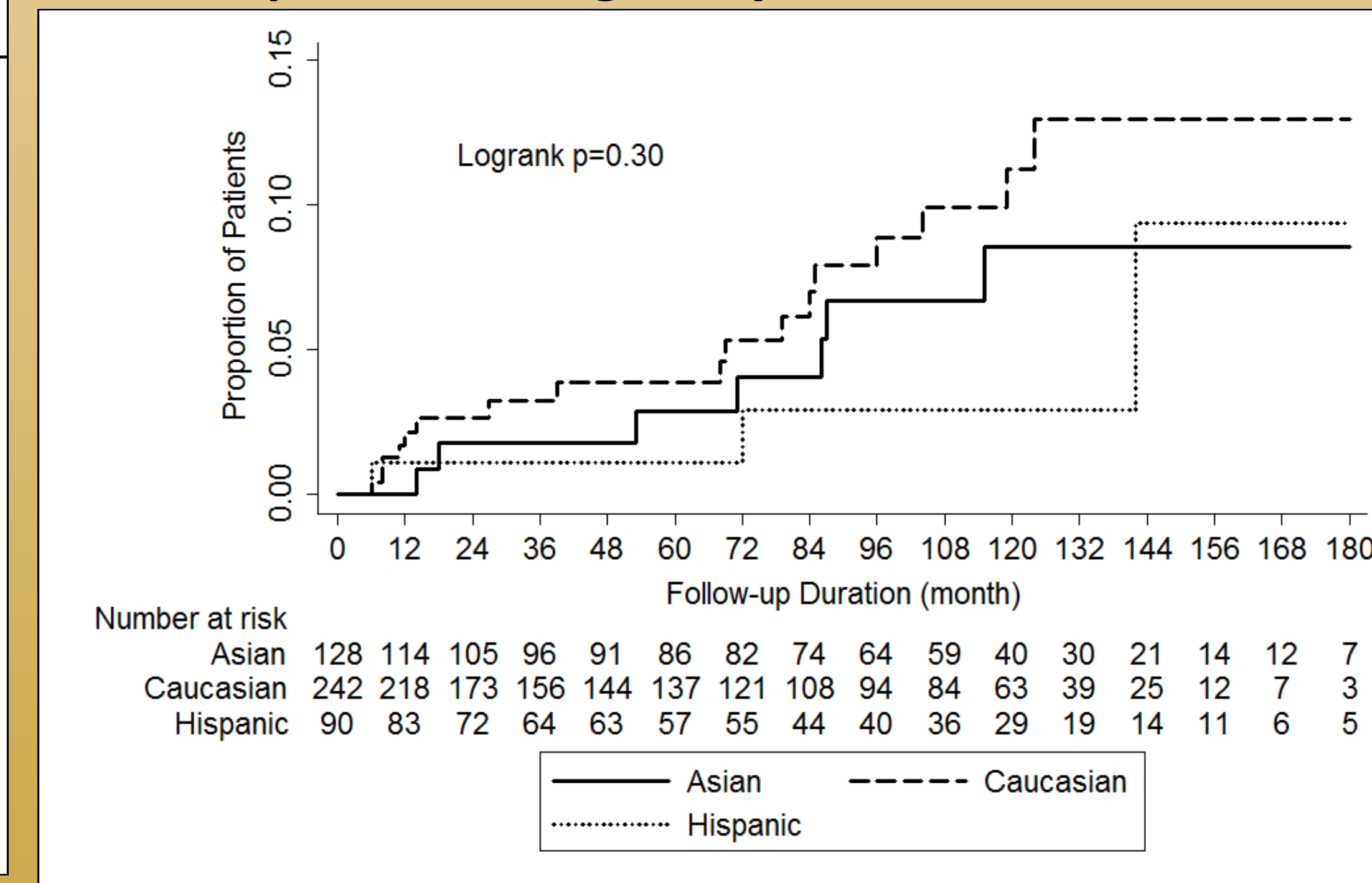
**Table 2. Non-invasive marker panel for fibrosis**

|                              | Asian<br>n = 128 | Caucasian<br>n = 242 | Hispanic<br>n = 90 | p-value |
|------------------------------|------------------|----------------------|--------------------|---------|
| AST to platelet ratio (APRI) |                  |                      |                    | 0.70    |
| Low probability              | 85 (75)          | 181 (80)             | 60 (74)            |         |
| Intermediate probability     | 26 (23)          | 39 (17)              | 18 (22)            |         |
| High probability             | 3 (3)            | 6 (3)                | 3 (4)              |         |
| Fibrosis-4 (FIB-4)           |                  |                      |                    | 0.42    |
| Low probability              | 89 (78)          | 163 (72)             | 65 (82)            |         |
| Intermediate probability     | 20 (18)          | 53 (24)              | 12 (15)            |         |
| High probability             | 5 (4)            | 9 (4)                | 2 (3)              |         |
| NAFLD fibrosis score (NFS)   |                  |                      |                    | <0.001  |
| Low probability              | 68 (75)          | 91 (45)              | 36 (60)            |         |
| Intermediate probability     | 18 (20)          | 86 (43)              | 18 (30)            |         |
| High probability             | 5 (6)            | 25 (12)              | 6 (10)             |         |

### B. Natural disease outcomes

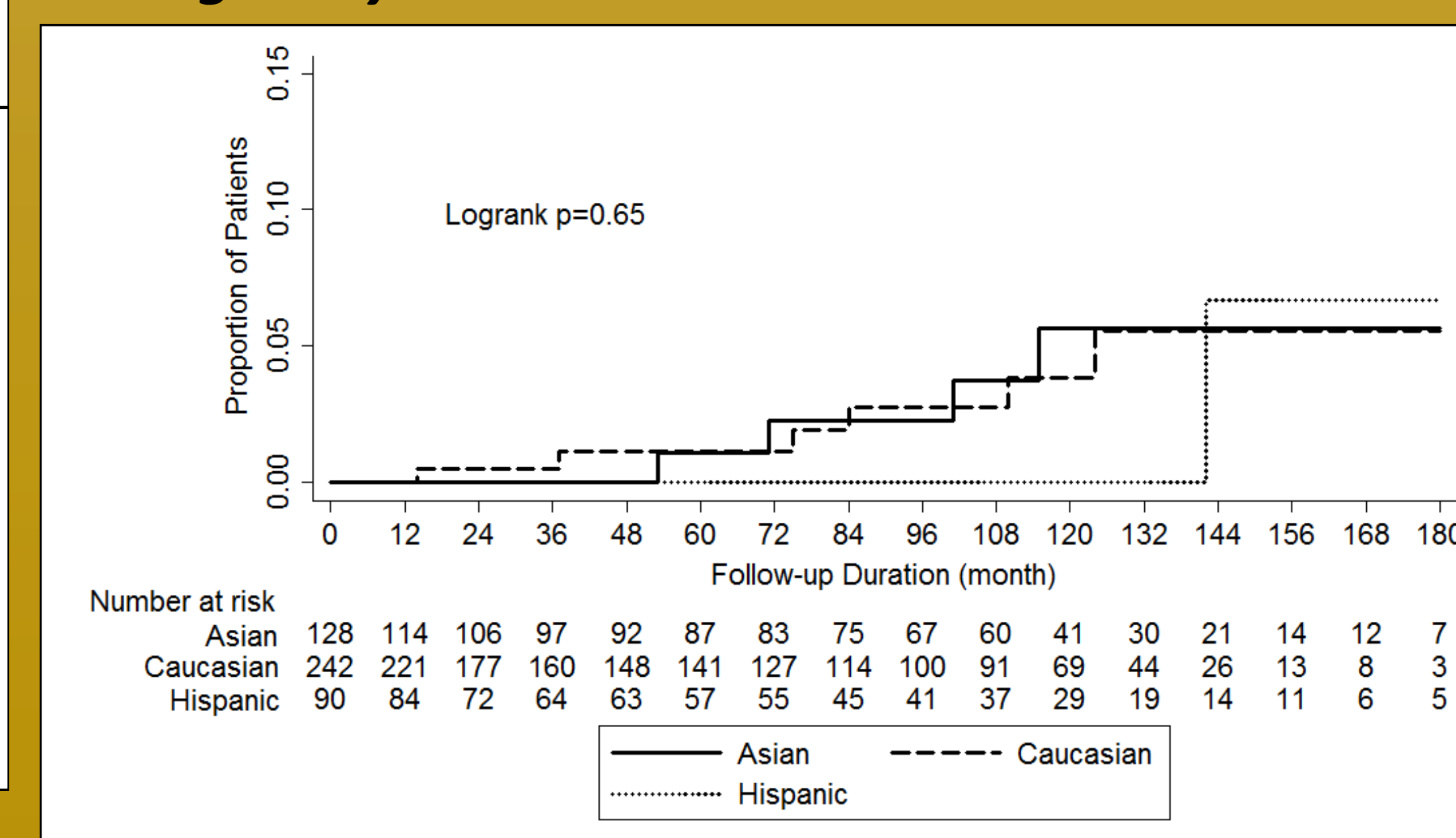
- Median follow-up was 88 (6-232) months.
- There were no statistically significant differences in the 15-year cumulative incidence rates of disease progression to NASH for Asians, Caucasians, and Hispanics (8.5% vs. 13% vs. 9.4%, respectively) (Figure 1).

**Figure 1: Cumulative incidence rates of nonalcoholic steatohepatitis through 15 years**



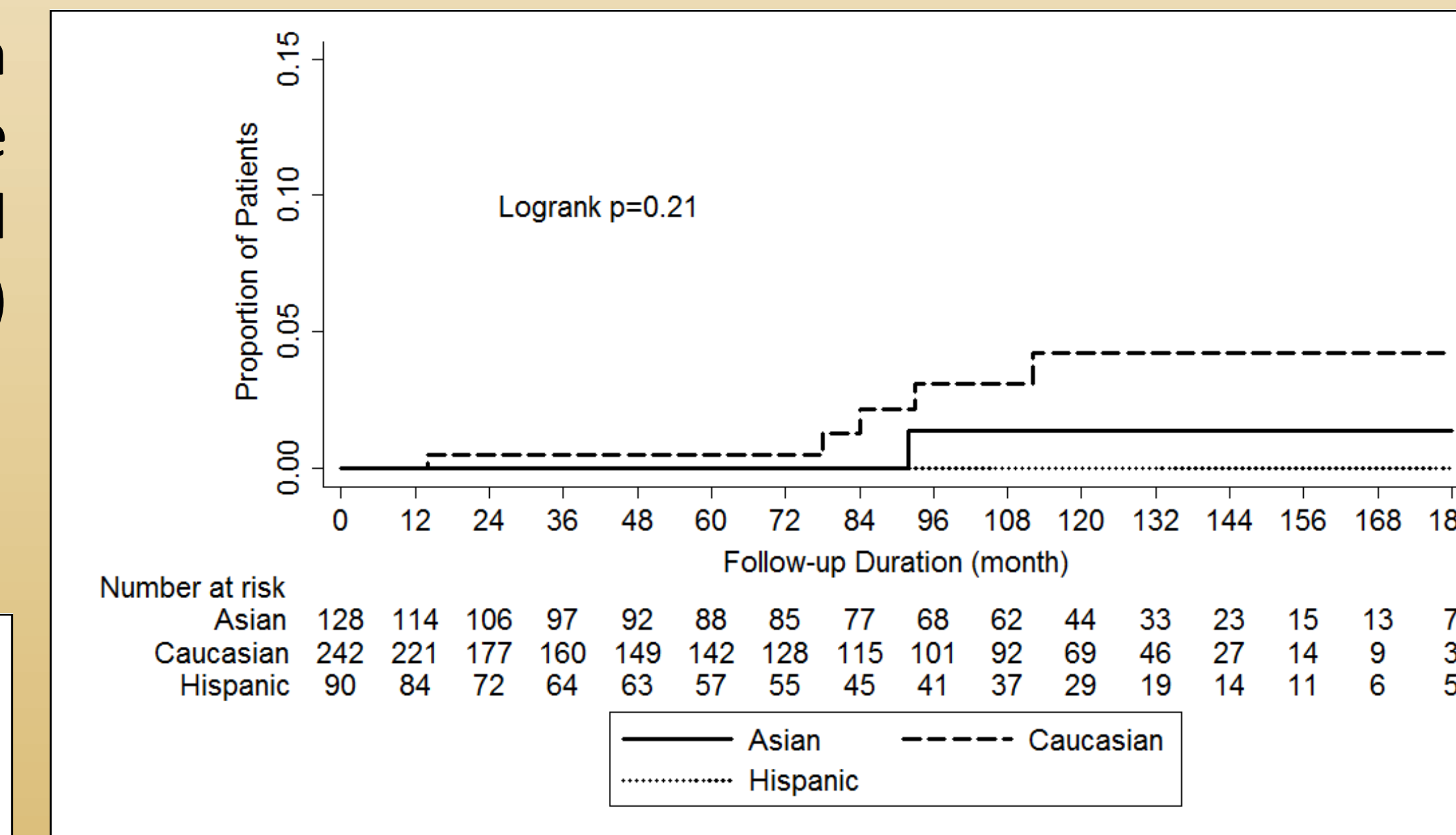
- Asians, Caucasians, and Hispanics had similar 15-year cumulative incidence rates of cirrhosis (5.6% vs. 5.6% vs. 6.7%, p=0.65), hepatic decompensation (1.4% vs. 4.2% vs. 0.0%, p=0.21), liver cancer (1.1% vs. 0.0% vs. 0.0%, p=0.32), and all-cause mortality (14.0% vs. 8.5% vs. 8.4%, p=0.49) (Figure 2-5).

**Figure 2: Cumulative incidence rates of cirrhosis through 15 years**

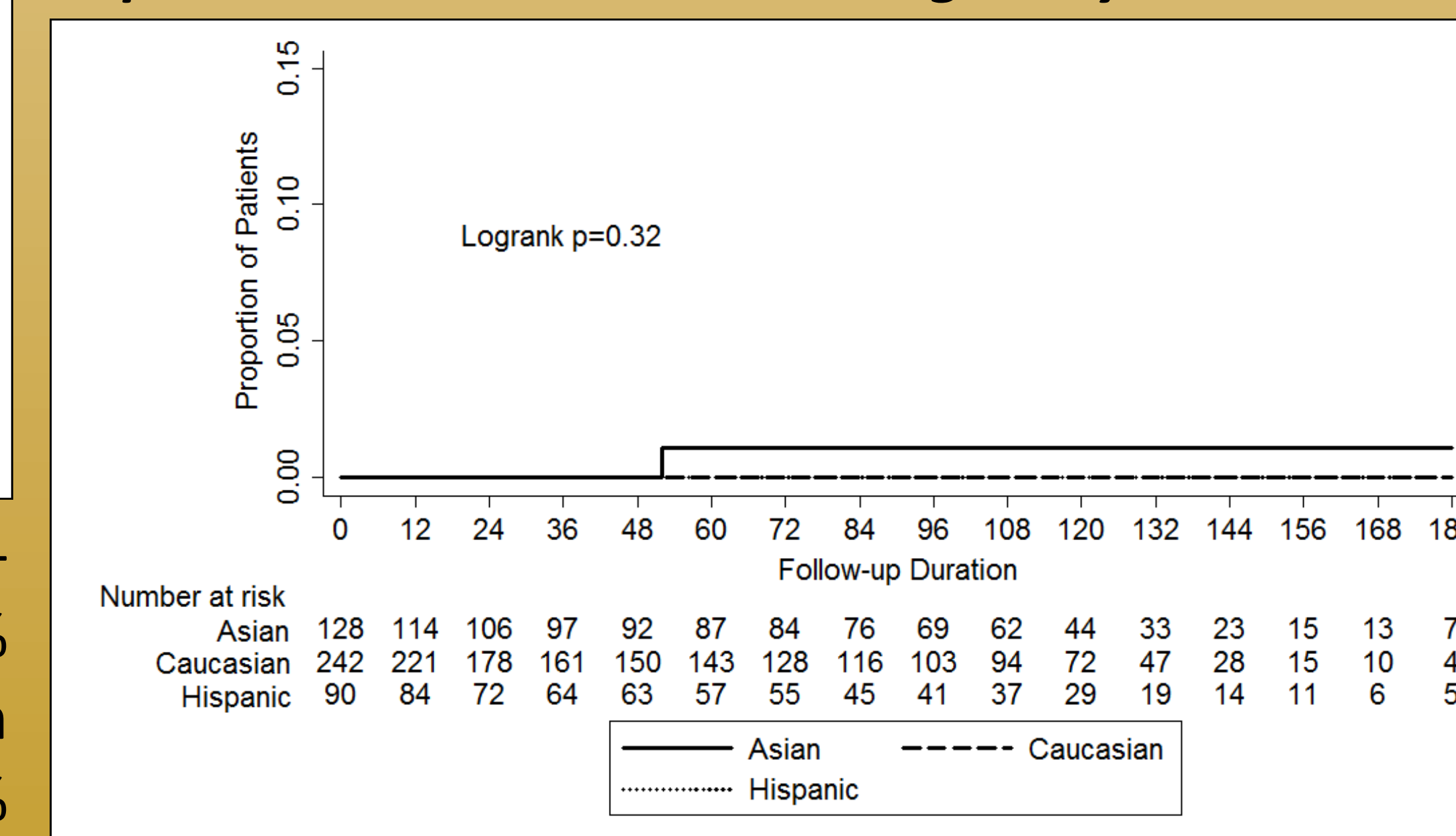


## RESULTS

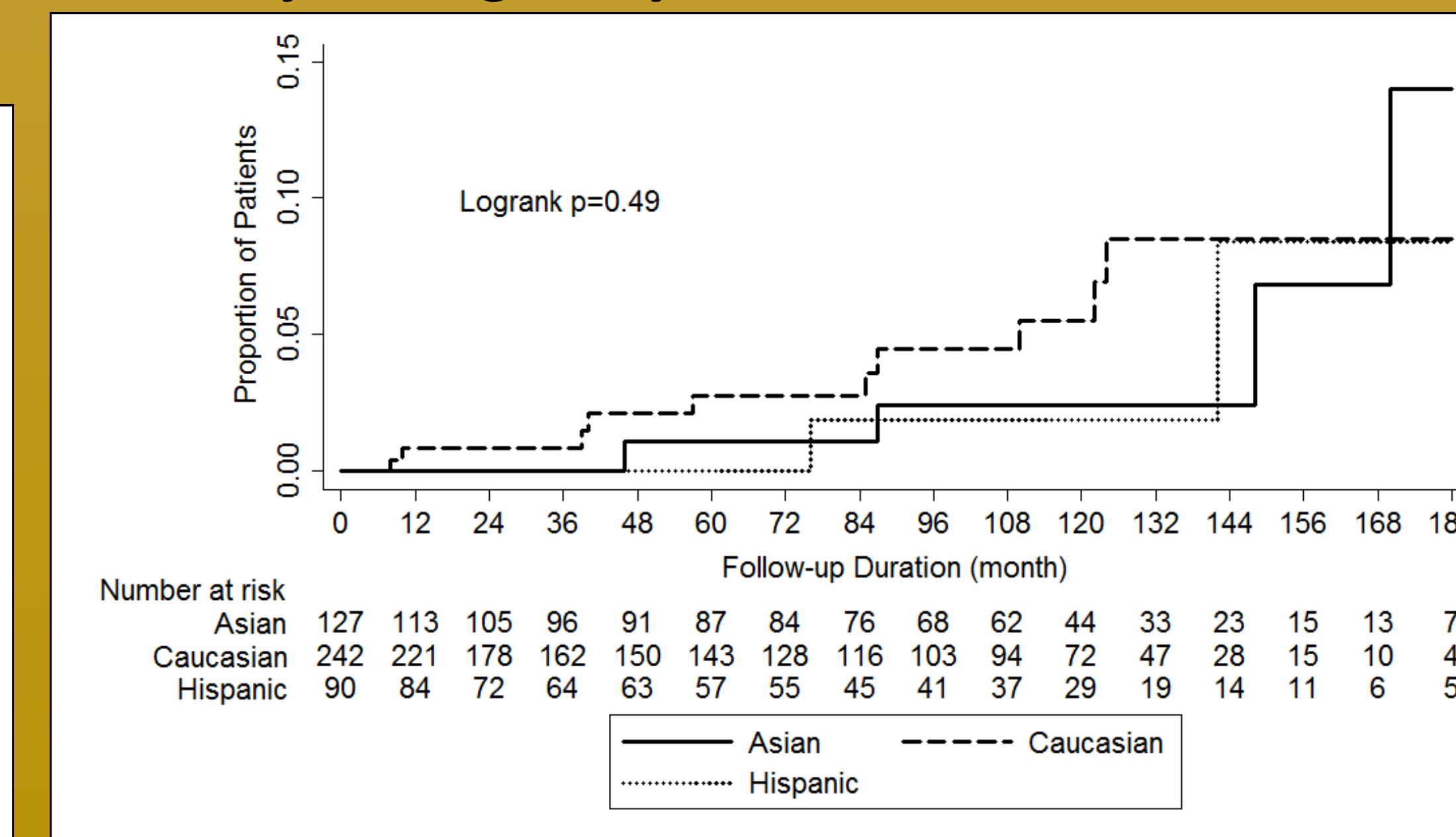
**Figure 3: Cumulative incidence rates of decompensated cirrhosis through 15 years**



**Figure 4: Cumulative incidence rates of hepatocellular carcinoma through 15 years**



**Figure 5: Cumulative incidence rates of all-cause mortality through 15 years**



### C. Predictors of all-cause mortality

- In a multivariate Cox proportional hazards model also inclusive of age, sex, ethnicity, BMI, APRI, and NFS, high probability of fibrosis based on FIB-4 was significantly associated with increase all-cause mortality (HR=23.0, 95% CI=1.05-505.6, p=0.047) compared to low- and intermediate-probability of fibrosis (Table 3).

**Table 3. Predictors of all-cause mortality**

|              | Univariate analysis |            |         | Multivariate analysis |             |         |
|--------------|---------------------|------------|---------|-----------------------|-------------|---------|
|              | HR                  | 95% CI     | p-value | HR                    | 95% CI      | p-value |
| Age          | 1.04                | 1.01-1.08  | 0.011   | 1.05                  | 0.98-1.12   | 0.18    |
| Male         | 1.16                | 0.43-3.12  | 0.77    | 2.27                  | 0.52-9.90   | 0.27    |
| BMI          | 1.01                | 0.95-1.07  | 0.83    | 1.01                  | 0.89-1.14   | 0.88    |
| Asian        | 0.70                | 0.22-2.18  | 0.54    | 0.71                  | 0.05-9.15   | 0.79    |
| Caucasian    | 1.83                | 0.66-5.05  | 0.25    | 1.48                  | 0.15-14.66  | 0.74    |
| Hispanic     | 0.57                | 0.13-2.52  | 0.46    | -                     | -           | -       |
| APRI         |                     |            |         |                       |             |         |
| Low          |                     | Reference  |         |                       | Reference   |         |
| Intermediate | 2.98                | 1.00-8.86  | 0.05    | 2.73                  | 0.50-14.81  | 0.25    |
| High         | 3.32                | 0.41-27.21 | 0.26    | 1.03                  | 0.04-26.36  | 0.99    |
| FIB-4        |                     |            |         |                       |             |         |
| Low          |                     | Reference  |         |                       | Reference   |         |
| Intermediate | 3.55                | 1.02-12.28 | 0.046   | 0.99                  | 0.14-6.79   | 0.99    |
| High         | 10.75               | 2.57-45.05 | 0.001   | 23                    | 1.05-505.63 | 0.047   |
| NFS          |                     |            |         |                       |             |         |
| Low          |                     | Reference  |         |                       | Reference   |         |
| Intermediate | 2.72                | 0.77-9.65  | 0.12    | 1.03                  | 0.18-5.82   | 0.98    |
| High         | 1.77                | 0.20-15.87 | 0.61    | 0.09                  | 0.00-3.13   | 0.18    |

## CONCLUSIONS

Despite differences in initial disease presentation at diagnosis among the various ethnic groups, natural disease progression from simple steatosis to nonalcoholic steatohepatitis, cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, and all-cause mortality was similar among Asians, Caucasians, and Hispanics.

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