Published in final edited form as:
Hepatology. 2010 February ; 51(2): 373–375. doi:10.1002/hep.23521.

Long-Term Mortality in Nafld. is Liver Histology of Any Prognostic Significance?

Paul Angulo, MD, FACG, AGAF

Over the last decade, a wealth of data has emerged illustrating both the rather benign clinical course of nonalcoholic fatty liver disease (NAFLD) in many individuals, and the unfavorable prognosis of this condition in others. Several studies on long-term mortality of patients suffering from NAFLD confirmed by imaging and/or liver biopsy have been reported. Studies with an average follow-up of at least 5 years are summarized in Table 1 [1-10]. Compared to the general population of same age and sex, NAFLD is associated with a significantly higher overall mortality [1,2,4] and liver-related mortality [1,2]. The long-term prognosis of patients with NAFLD, however, varies across the disease stage. Although the terms simple steatosis and NASH are often used in studies on long-term prognosis to classify patient risk, differing definitions have been used across the studies. Despite that, however, some conclusions can be derived from pooling data from these studies together (Table 1). Within the first 15 years of follow-up, the prevalence of cirrhosis development is significantly higher in patients with NASH as compared to patients with simple steatosis (10.8% vs. 0.7%, respectively, $x^2 = 23.3$, $p<0.001$). Consequently, the liver-related mortality is also significantly higher in patients with NASH as compared to simple steatosis (7.3% vs. 0.9%, respectively, $x^2 = 16.7$, $p<0.001$). The overall mortality between these two groups, however, is not significantly different, although there is a trend towards a higher overall mortality in the NASH group (40.5% vs. 32.5%, respectively, $x^2=3.61$, $p<0.1$).

None of the studies reported to date comparing overall and liver-related mortality of individuals with biopsy confirmed simple steatosis (as defined by steatosis alone or steatosis with mild inflammation/cellular injury) and the general population of same age and sex has found an increased mortality risk in those with simple steatosis. Thus, when we have to counsel patients with simple steatosis, it is safe to state that simple steatosis is not associated with a prognosis worse than expected in individuals of the same age and sex. On the contrary, the overall and liver-related mortality in patients with NASH is higher than expected in individuals of the same age and sex, but this observation comes from a single study that included only 71 patients with NASH [2]. Unfortunately, since there is no consensus on what the best definition of NASH is, different histological criteria have been used in the various studies for defining NASH [2-4,7]. Most recently, the Pathology Subcommittee of the NIDDK-sponsored NASH-clinical research network (CRN) has proposed a semiquantitative scoring system to grade and stage the several histological features of NAFLD [11]. That scoring system is intended to be used in the design of clinical trials, not to replace the pathologist's judgment on the diagnosis of NASH, and it remains uncertain whether the use of this scoring system for NASH classification provides any prognostic information.

Corresponding Author: Paul Angulo, MD, FACG, AGAF, Professor of Medicine, Section Chief of Hepatology, Division of Digestive Diseases & Nutrition, University of Kentucky Medical Center, 800 Rose Street, Rm MN649, Lexington, KY 40536, (859) 323-3555, (859) 257-8860 fax, paul.angulo@uky.edu.

Financial Support: Supported by an R01 DK82426 grant to Paul Angulo, MD.

In this issue of Hepatology, Soderberg et al. [4] report an 80% (standardized mortality ratio 1.8, 95%CI 1.48, 2.16) increased mortality in 256 patients with elevated liver enzymes who underwent liver biopsy and had a mean follow-up of 21 years. One-hundred and eighteen (46%) patients suffered from NAFLD, and the remaining had liver disease not related to NAFLD. Although the number of patients is too small to derive substantial conclusions, particularly for those with liver disease other than NAFLD, the study provides some interesting observations in the group of patients with NAFLD. First, the NAFLD group had a 70% (standardized mortality ratio 1.7; 95%CI 1.24, 2.25) higher risk of dying as compared to a population of similar age and sex, and this increased risk is almost identical to that reported in two large prior studies [1,2]. Second, using the NASH-CRN histology scoring system [11], patients were divided into those with definitive NASH (n=51) and with no definitive NASH (or non NASH, n=67); the overall mortality in the group with definitive NASH (but not in the non NASH group) was significantly higher as compared to the general population of the same age and sex, similar to what was reported in a prior study [2]. Third, as illustrated in Figure 2a in the paper, overall mortality was almost identical between the definitive NASH and non NASH groups which also had been reported in another recent long-term follow up study [3].

The study by Soderberg at al.[4] essentially reproduces several observations from prior long-term follow-up studies [1-3], but most intriguing is the reported similar overall- and liver-related mortality between the groups with and without definitive NASH. There are two most likely explanations for the lack of difference in survival between the two groups. One explanation is the clear lack of power of the study; with such a small number of patients in each group (51 vs. 67), the study simply did not have enough power for a long-term survival comparison. The second explanation is the way patients were classified (definitive NASH vs. non NASH) for survival comparison. As discussed by the authors, the NASH-CRN scoring system takes into account only the presence and severity of steatosis, hepatocyte ballooning, and lobular inflammation to differentiate between patients with and without definitive NASH [11]. The reported inter-rater agreement on lobular inflammation and hepatocyte ballooning was as low as 0.1 and 0.14 (poor to fair) respectively in one series [12], and increased to only 0.45 and 0.56 (moderate to good) respectively in another series [11]. Similarly, the intra-rater agreement on lobular inflammation and hepatocyte ballooning was 0.37 and 0.62 (moderate to good) respectively in one series [13] and 0.60 and 0.66 (good) respectively in another series [11]. These levels of agreement indicate that mandating lobular inflammation and hepatocyte ballooning for the diagnosis of NASH would make the diagnosis often difficult, if not impossible to reproduce from one pathologist to the next, or from one reading to another reading of the same slides even if the reading is done by the same pathologist. In addition, a series of individuals who had undergone paired liver biopsy with two samples of liver tissue taken simultaneously reported an inter-biopsy agreement on lobular inflammation and hepatocyte ballooning as low as 0.13 and 0.45, respectively [13]. Thus, the diagnosis of NASH may or may not be established in subjects with NAFLD depending on where in the liver parenchyma the biopsy needle is inserted. Furthermore, there are no data from long-term follow-up studies on whether lobular inflammation or hepatocyte ballooning would indicate a greater likelihood of disease progression, and there are no compelling data that lobular inflammation or hepatocyte ballooning *per se* are of any prognostic significance.

As discussed by Soderberg et al. [4], the NASH-CRN scoring system also does not take into account the presence and severity of fibrosis for NASH classification; so not surprisingly, a good proportion of individuals classified as non NASH would be expected to have increased fibrosis. In fact, 45 of the 67 (67.2%) patients classified as non-NASH in the study by Soderberg et al. [4] had increased liver fibrosis, with 8 of them having septal fibrosis or even well established cirrhosis. If all these patients with increased liver fibrosis would have been

labeled definitive NASH, the mortality most definitively would have been significantly higher in the NASH group. Indeed, if we extend the analysis of the data to consider the presence and severity of fibrosis on long-term mortality regardless of other histological features, the study would provide additional and more clinically relevant conclusions. For instance, 40 of the 47 (89.4%) patients who died had increased (stage 1 to 4) fibrosis as compared to 50 of the 71 (70.4%) patients who remained alive ($x^2 = 5.9$, $p<0.02$). In addition, the mortality figure increases markedly in patients with fibrosis stage ≥ 2; 32 of the 47 (68.1%) patients who died had fibrosis stage ≥ 2 as compared to 20 of the 71 (28.2%) patients who remained alive ($x^2 = 18.3$, $p<0.001$). Further, when all patients with fibrosis stage 1-4 were called NASH in the study by Soderberg et al. [4], the overall mortality was markedly higher in the NASH group as compared to the non NASH group as illustrated in Figure 2b in the paper. Similarly, when liver biopsies showing only steatosis or steatosis with nonspecific inflammation were called non NASH, and all other biopsies including those with fibrosis stage 1-4 were called NASH in a recent study [3], the liver-related mortality in the NASH group was significantly higher than in the non NASH group.

Based on all this, it seems the presence and severity of fibrosis dictates both overall and liver-related mortality in patients with NAFLD. Fibrosis stage is in fact the histological feature with the highest inter-rater agreement with reported values of 0.5 (moderate) [12] and 0.84 (excellent) [11], and the highest intra-rater agreement with reported values of 0.69 (good) [13] and 0.85 (excellent) [11]. What still remains unknown, however, is what long-term prognostic information, if any, can be obtained from grading the severity of inflammation and hepatocyte ballooning. The study by Soderberg et al. [4] suggests that requiring those histological features for NASH classification (i.e., using the NASH-CRN scoring system) the long-term mortality of those with definitive NASH is not significantly different from those with non NASH.

Unfortunately, the study by Soderberg et al. [4] along with the two other studies [2,3] that included liver biopsy did not analyze the prognostic relevance of inflammation and hepatocyte ballooning adjusted by presence and severity of fibrosis. Only a large appropriately powered study of several hundreds of patients who underwent liver biopsy and have follow-up data for several years or decades will answer those questions. In the meantime, when the practicing hepatologist is counseling patients in regards to long-term prognosis, it seems important to pay more attention to presence and severity of fibrosis on liver biopsy regardless of the pathologist' labeling of NASH or non NASH.

References

1. Adams LA, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A, Angulo P. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. Gastroenterology. 2005; 129:113–121. [PubMed: 16012941]
2. Ekstedt M, Franzen LE, Mathiensen UI, Thorelius L, Holmqvist M, Bodemar G, Kechagias S. Long-term follow-up of patients with NAFLD and elevated liver enzymes. Hepatology. 2006; 44:865–873. [PubMed: 17006923]
3. Rafiq N, Bai C, Fang Y, Srishord M, McCullough A, Gramlich T, Younossi Z. Long-term follow-up of patients with nonalcoholic fatty liver. Clin Gastroenterol Hepatol. 2009; 7:234–238. [PubMed: 19049831]
4. Soderberg C, Stal P, Askling J, Glaumann H, Lindberg G, Marmur J, Hultcrantz R. Decreased survival of subject with elevated liver function test during a 28 year follow up. Hepatology. 2010
5. Teli MR, James OF, Burt AD, Bennett MK, Day CP. The natural history of nonalcoholic fatty liver: a follow-up study. Hepatology. 1995; 22:1714–9. [PubMed: 7489979]
6. Dam-Larse S, Becker U, Franzmann MB, Larsen K, Christoffersen P, Bendtsen F. Final results of a long-term, clinical follow-up in fatty liver patients. Scand j Gastroenterol. 2009; 44:1236–1243. [PubMed: 19670076]

7. Evans CD, Oien KA, MacSween RN, Mills PR. Non-alcoholic steatohepatitis: a common cause of progressive chronic liver injury? J Clin Pathol. 2002; 55:689–692. [PubMed: 12195000]
8. Hui J, Kench JG, Chitturi S, Sud A, Farrell GC, Byth K, Hall P, Khan M, George J. Long term outcomes of cirrhosis in nonalcoholic steatohepatitis compared with hepatitis C. Hepatology. 2003; 38:420–427. [PubMed: 12883486]
9. Sanyal AJ, Banas C, Sargeant C, et al. Similarities and differences in outcomes of cirrhosis due to nonalcoholic steatohepatitis and hepatitis C. Hepatology. 2006; 43:682–689. [PubMed: 16502396]
10. Yatsuji S, Hashimoto E, Tobari M, Taniai M, Tokushige K, Shiratori K. Clinical features and outcomes of cirrhosis due to non-alcoholic steatohepatitis compared with cirrhosis caused by chronic hepatitis C. J Gastroenterol Hepatol. 2009; 24:284–254.
11. Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, Ferrell LD, Liu YC, Torbenson MS, Unalp-Arida A, Yeh M, McCullough AJ, Sanyal AJ. Nonalcoholic Steatohepatitis Clinical Research Network. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology. 2005; 41:1313–1321. [PubMed: 15915461]
12. Fukusato T, Fukushima J, Shiga J, Takahashi Y, Nakano T, Maeyama S, et al. Interobserver variation in the histolopathological assessment of nonalcoholic steatohepatitis. Hepatol Res. 2005; 33:122–127. [PubMed: 16890173]
13. Ratziu V, Charlotte F, Heurtier A, Gombert S, Giral P, Bruckert E, Grimaldi A, Capron F, Poynard T. LIDO Study Group. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. Gastroenterology. 2005; 128:1898–1906. [PubMed: 15940625]

Abbreviations

NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis

Table 1

Studies on long-term mortality in NAFLD. Tabulated studies are those with an average follow-up of 5 years or longer.

Author [ref]	Diagnosis	n	Cirrhosis Prevalence* n	Liver-related deaths N	Overall deaths n	Average F/U (years)
Adams et al. [1]	NALFD	420	21 (5%)	7 (1.7%)	53 (12.6)	7.6
Ekstedt et al. [2]	NAFLD	129	10 (7.8%)	2 (1.6%)	26 (20.2%)	13.7
Rafiq et al. [3]**	NAFLD	131	NR	12 (9.2%)	78 (59.5%)	18.5
Soderberg [4]	NAFLD	118	9 (7.6%)	9 (7.6%)	47 (39.8%)	21
	Total	**798**	**40 (6%)**	**30 (3.8%)**	**204 (25.6%)**	**15.2**
Teli et al [5]	Simple Steatosis	40	0	0	14 (35)	9.6
Ekstedt et al. [2]	Simple Steatosis	58	0	0	7 (12.1)	13.7
Dam-Larsen et al. [6]&	Simple Steatosis	170	2 (1.2%)	1 (0.6)	48 (28.2%)	20.7
Rafiq et al. [3]**	Simple Steatosis	74	NR	2 (2.7%)	42 (56.8%)	18.5
	Total	**342**	**2 (0.7%)**	**3 (0.9%)**	**111 (32.5%)**	**15.6**
Evans et al. [7]	NASH	26	1 (4%)	0 (0)	4 (15)	8.7
Ekstedt et al [2]	NASH	71	10 (14.1%)	2 (2.8%)	19 (26.8%)	13.7
Rafiq et al. [3]**	NASH	57	NR	10 (17.5%)	36 (63.2%)	18.5
Soderberg [4]	NASH	51	5 (9.8%)	3 (5.9%)	24 (47.1%)	21
	Total	**205**	**16 (10.8%)**	**15 (7.3%)**	**83 (40.5 %)**	**15.5**
Hui et al. [8]	Cirrhotic-stage NAFLD	23	100%	5 (21%)	6 (26%)	5.0
Sanyal et al. [9]	Cirrhotic-stage NAFLD	152	100%	22 (14.5%)	29 (19.1%)	10
Yatsuji et al. [10]#	Cirrhotic-stage NAFLD	68	100%	15 (22.1%)	19 (27.9%)	5.0
Soderberg [4]	Cirrhotic-stage NAFLD	9	100%	4 (44.4%)	8 (88.9%)	21
	Total	**252**	**252 (100%)**	**46 (18.3%)**	**62 (24.6%)**	**10.25**

*cirrhosis prevalence includes all patients diagnosed with cirrhosis at both baseline and during follow-up. NAFLD denotes the inclusion of both patients with simple steatosis and patients with NASH.

**Updated data from Mateoni et al. Gastroenterology 1999;116:1413-1419.

&Updated data from Dam-Larsen et al. Gut 2004;53:750-755.

#Updated analysis from Hashimoto et al. Hepatol Res 2005;33:72-76