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Systematic review of risk factors for fibrosis progression in non-alcoholic steatohepatitis☆

Curtis K. Argo*, Patrick G. Northup, Abdullah M.S. Al-Osaimi, Stephen H. Caldwell

Division of Gastroenterology and Hepatology, University of Virginia Health System, JPA and Lee St., MSB 2091, PO Box 800708, Charlottesville, VA, USA

***Background/Aims*: Non-alcoholic steatohepatitis (NASH) is a growing public health problem. Evaluation of risk factors for fibrosis in NASH will help to target resources to reduce development of cirrhosis. This study had two aims; the first to compile longitudinal histological data to characterize the natural history of fibrosis progression in NASH, and second, to identify predictive factors for progression to advanced fibrosis (stage 3 or greater) in NASH.**

***Methods*: Subjects had to have a histological diagnosis compatible with NASH on their initial biopsy, received no intervention of proven histological benefit, and undergone two liver biopsies with at least an interval of one year between them.**

***Results*: Ten studies were selected comprising 221 patients. 37.6% had progressive fibrosis over a mean follow-up interval of 5.3 years (SD, 4.2 years, median, 3.7 years, range 1.0–21.3 years). Proportional hazards regression analysis demonstrated that age (HR = 0.98, $p = 0.009$) and inflammation on initial biopsy (any inflammation, HR = 2.5, $p = 0.001$; grade 1, HR = 2.5, $p = 0.001$; grade 2, HR = 2.4, $p = 0.003$) are independent predictors of progression to advanced fibrosis. Other traditional parameters (e.g. obesity, diabetes, hypertension) were not statistically significant predictors.**

***Conclusions*: Presence of inflammation on the initial biopsy and age are independent predictors of progression to advanced fibrosis in patients with NASH.**

***Keywords*: Fatty liver; Steatohepatitis; Fibrosis; Cirrhosis; Inflammation**

1. Introduction

The emergence of non-alcoholic fatty liver disease (NAFLD) has closely mirrored the epidemic of obesity and diabetes mellitus, and it is a burgeoning health problem with no clear answers regarding its natural history [1]. NAFLD encompasses several conditions: benign fatty liver and different forms of non-alcoholic steatohepatitis (NASH) which include steatosis with inflammation, steatosis with inflammation and mild to advanced fibrosis, steatosis with fibrosis alone, cirrhosis, and end-stage liver disease [2–12]. Mortality associated with NASH is a critical issue: in diabetics, many of whom are at risk for NASH, projections of mortality risk secondary to liver disease approach that of cardiovascular disease [13].

NASH may progress insidiously to advanced fibrosis and is responsible for the majority of cases of cryptogenic cirrhosis [14–17]. Patients with NASH and cirrhosis are at risk of complications of portal hypertension and hepatocellular carcinoma [18–24]. These complications contribute to lower life expectancy for cirrhotic NASH patients: estimates of 5- and 10-year survival in NASH were 67%

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* Corresponding author. Tel.: +1 434 9242626; fax: +1 434 9240491.
E-mail address: cka3d@virginia.edu (C.K. Argo).

Abbreviations: NASH, non-alcoholic steatohepatitis; SD, standard deviation; HR, hazard ratio; NAFLD, non-alcoholic fatty liver disease; BMI, body-mass index; CI, confidence interval; NS, not significant.

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and 59%, respectively [25]. Despite these estimates of reduced survival for NASH patients, the risk factors for progression of non-alcoholic steatohepatitis (NASH) to advanced fibrosis remain unclear. Using univariable and multivariable analysis, several single-biopsy studies have proposed possible risk factors including age, increased body-mass index (BMI), high inflammation grade on biopsy, diabetes, metabolic syndrome, and abnormal aminotransferases (Table 1) [26–33]. However, because of their cross-sectional nature, these studies can only serve as introductory investigations in establishing risk factors for fibrosis progression in NASH.

We evaluated pooled, individual-level, primary data from longitudinal, systematic, histologically-based studies to identify independent predictors for development of advanced fibrosis in patients with NASH. Because larger, more definitive studies are lacking, our review offers an important perspective on the challenges facing health care providers treating NASH patients and its expected societal burden.

2. Methods

2.1. Criteria for consideration of studies for review

2.1.1. Types of studies

Our analysis is a systematic review of the medical literature, with all 10 studies published as peer-reviewed case series or retrospective cohort studies. Patients in all studies were identified through pathology database searches using specific diagnostic terms related to NASH [33–38,41–44]. No abstracts contained data of sufficient completeness to satisfy the criteria for inclusion.

2.1.2. Types of participants

Studies evaluating a controlled intervention (medication or lifestyle intervention) with established effects on underlying liver histology were excluded. This group consisted of studies of lifestyle interventions (reduced calorie diets and physical activity, either alone or in combination [45–52]) and medications (thiazolidinediones [53–60], metformin [60–64], and vitamin E [64–68]). Gastric reduction surgeries have also been shown to alter liver histology and fibrosis in obese patients and thus were excluded [69–73]. Patients with NASH due to established secondary causes including genetic lipodystrophies, use of tamoxifen or amiodarone, industrial solvent exposure, or history of small bowel resection or jejunoileal bypass were also excluded.

2.1.3. Types of outcomes

Inclusion in this review required documentation of two liver biopsies with an interval of at least one year between them meeting the histological diagnostic criteria for NASH on the initial biopsy [7,39,40]. Requirements for diagnostic histological criteria for NASH were met in those papers where an accepted pathological staging system was used [33–38,44]. In older studies published prior to the establishment of these standards [41–43], biopsies were required to demonstrate steatosis and a lobular pattern of inflammation consistent with NASH, or steatosis with fibrosis and no other detectable etiology of liver disease for inclusion. While helpful in confirming NASH, findings of ballooning in zone 3 or presence of Mallory bodies were not required for inclusion in this analysis; however, documentation of fibrosis was necessary. Inflammation was defined as the presence of lobular inflammation. Advanced fibrosis was defined as the presence of stage 3 or 4 fibrosis on biopsy. This definition was selected given current knowledge of the extent of sampling variability on interpretation of fibrosis from liver biopsy in NAFLD [74,75]. Explicit description of the methods used to exclude prohibitive levels of alcohol consumption (>20 g/day in females, >30 g/day in males) was mandatory.

2.1.4. Search methodology

The MEDLINE, PubMed, and EMBASE databases were systematically searched for all articles published between 1966 and 2008 using the following MeSH terms and keywords: "fatty liver," "liver," "liver diseases," "steatohepatitis, "steatosis,""liver cirrhosis," "cirrhosis," "fibrosis," and "risk factors." Various combinations of the above terms yielded 476 citations. Titles and abstracts of articles were examined for terms referring to histological evaluation and fibrosis in NASH patients and abstracts were reviewed when available to determine the applicability of an article to this analysis. The reference sections of selected articles and of recent reviews of NAFLD or NASH published since 1990 were also reviewed to locate additional articles. Consultation with experts in NASH research was sought to identify pre-publication papers. Ten publications were identified for inclusion. Abstract submissions from major gastroenterology and hepatology meetings from 2000 to 2008 were reviewed by hand, but no abstract contained sufficiently complete information for inclusion, and communication with the primary authors was unsuccessful in formulating complete datasets.

Table 1
Risk factors for fibrosis in NAFLD patients identified in cross-sectional, single-biopsy studies.

Author (year)	*N*	Risk factor identified	Odds ratio	*p*-Value
Angulo (1999)	144	Age $\geqslant$ 50	NR	0.001
		BMI $\geqslant$ 31.1 (M), 32.5 (F)	NR	0.002
		Diabetes mellitus	NR	0.009
		AST/ALT ratio > 1	NR	0.03
Garcia-Monzon (2000)	32	Age $\geqslant$ 50	NR	0.003
Ratziu (2000)	93	Age $\geqslant$ 50	5.6	0.01
		BMI $\geqslant$ 28	4.4	0.02
		Necroinflammation present	35.0	0.001
Marchesini (2003)	120	Metabolic syndrome	3.5	0.03
Park (2004)	43	BMI	NR	0.03
		Age	NR	<0.001
Gramlich (2004)	132	Hepatocyte ballooning	NR	0.04
		Mallory bodies present	NR	<0.001
Ong (2005)	55	Abnormal AST	NR	0.01
		Waist-hip ratio	NR	<0.005

BMI, body-mass index; M, male; F, female; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HTN, hypertension; NR, not reported.