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Natural history of Non-Alcoholic Fatty Liver Disease

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Introduction

Since the first accounts of non-alcoholic fatty liver disease (NAFLD) by Ludwig et al in 1980, there have been a myriad of studies investigating this complex multifaceted disease [1]. Defined as the accumulation of fat in the liver (in excess of 5%) that is not attributable to alcohol or drugs, NAFLD represents a clinical spectrum of disease that includes simple steatosis (non-alcoholic fatty liver; NAFL), steatosis with necroinflammatory changes (non-alcoholic steatohepatitis; NASH), advanced fibrosis, cirrhosis and hepatocellular carcinoma [2]. NAFLD is increasingly being recognised as a clinically important disease and as with any disease, the clinical importance is relative to its prevalence and natural history [3]. NAFLD is closely related to obesity and other metabolic syndrome risk factors, and as such, the clinical burden of NAFLD is considerable and expected to intensify with the burgeoning obesity and diabetes epidemics [4]. Reflecting this, National Health and Nutrition Examination Survey (NHANES) data reported the steady increase of NAFLD prevalence from 5.5% to 11% between 1988 and 2008 in America [5]. Similarly, NAFLD is increasingly acknowledged as the most common chronic liver disease worldwide and is associated with increased healthcare costs and resource utilization [6]. Indeed, NASH related cirrhosis is currently the most rapidly rising indication for liver transplantation and has been anticipated to be the leading cause of liver transplantation by the year 2020 [7].

Currently, the prevalence of NAFLD in the general population has been estimated to range between 20 to 30% and between 5 to 18% in western and Asian studies respectively [8]. Overall, the pooled global prevalence of NAFLD has been reported to be 24.4% [9].

In terms of clinical relevance, the natural history of NAFLD is equally important, but there remains considerable uncertainty and ambiguity about this aspect. The general consensus is that NAFLD is not an entirely benign condition and a subset of patients do progress to significant fibrosis or develop associated morbidity and mortality. In truth, our understanding of the natural history of NAFLD continues to evolve as more data emerges over time. The natural history of NAFLD is dynamic, with interaction and contribution from

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multiple factors including genetic, environmental and lifestyle factors. This review article highlights and discusses the evidence alluding to the natural history of NAFLD as displayed and summarized in Figure 1.

Long term prognosis: mortality outcomes

While there have been a multitude of population or community based and longitudinal tertiary centre cohort studies that have characterised the long term prognosis of NAFLD, results have been limited by differing definitions of NAFLD, referral/ascertainment bias and other confounding factors. Some studies have explored cohorts within the whole gamut of NAFLD, while others have focused on specific subsets of NAFL, NASH or advanced fibrosis.

Among the early landmark studies, a community based study of 420 patients with NAFLD from Olmstead County, Minnesota, with mean follow up of 7.6 years, observed that patients with NAFLD had a 34% higher risk of mortality relative to aged and gender matched general population (standardised mortality ratio 1.34; 95%CI 1.003-1.76; $p=0.03$). The three main causes of death were malignancy, ischemic heart disease and liver disease [10]. Several population-based (NHANES) studies have also interrogated the natural history of NAFLD. Using data of 12,822 subjects from the third National Health and Nutrition Examination Survey (NHANES III) conducted in the period 1988-1994, Ong and colleagues [11] identified 817 subjects with NAFLD; as defined by elevated serum aminotransferases in the absence of other chronic liver disease. Over median follow-up of 8.7 years, with mortality follow up until 31st December 2000, 80 subjects with NAFLD died, demonstrating a higher overall (HR 1.038; 95%CI 1.036-1.041; $p<0.0001$) and liver related mortality (HR 9.32; 95%CI 9.21-9.43; $p<0.0001$). Echoing the study by Adams et al, cardiovascular, malignancy and liver related mortality remain the most important causes of death in patients with NAFLD [11]. In contrast, another study assessing mortality in NHANES III participants [12] did not observe any statistically significant increased risk for all-cause or cause specific mortality in participants with suspected NAFLD. However, on subgroup analysis, suspected NAFLD in the 45 to 54 year old age group was a strong independent risk factor for cardiovascular (HR 8.43; 95% CI 2.43-22.72) and all-cause (HR 4.14; 95% CI 1.26-13.58) mortality [12]. A additional study evaluated the association of NAFLD and mortality using the same NHANES III data set, but defined NAFLD by evidence of hepatic steatosis on ultrasound imaging [13]. Follow up mortality data was also extended to 2006. In this study, NAFLD was not found to be associated with an increased risk of death from all causes, cardiovascular disease, malignancy or liver disease. Interestingly, the prevalence of hepatic steatosis with normal levels of liver enzymes was 16.4% whereas prevalence of hepatic steatosis with increased levels of liver enzymes was 3.1%, which suggest that previous NHANES III based studies that utilized elevated liver enzymes as a surrogate of NAFLD may be flawed as a fair proportion of actual patients with NAFLD, albeit with normal liver enzymes would have been misclassified [13].

Besides evaluating long term outcomes in cohorts with the whole spectrum of NAFLD, other studies have tried to tease out the natural history of NAFLD according to their histological subtypes.

In one of the earliest and important studies on natural history of NAFLD, Matteoni et al [14] related the long term outcomes to different histological phenotypes of NAFLD. The liver histology of 132 patients with biopsy proven NAFLD were analysed and categorised into 4 main groups, of which type 3 and 4 resembled current-day NASH. Over 8 years of follow up, cirrhosis developed predominantly in types 3 and 4, occurring in 21% and 28% of these histologic types, respectively. This was in comparison to only 3% in types 1 and 2 group. While there was no significant difference in overall mortality across the 4 groups, relative to groups 1 and 2, liver related death was increased in NAFLD patients with type 3 and 4 liver histology (11% vs 2%) [14]. Thus, the study by Matteoni provided the first insight that histological features of NAFLD may have prognostic value with regards to natural history.

In another longitudinal cohort study from UK, none of the 40 patients with simple steatosis (non-NASH) had progressed to NASH or cirrhosis over 11 years. However, there were 14 deaths, of which 6 were attributed to extrahepatic malignancy, but none were liver related mortalities [15]. Echoing the notion of a relatively benign history of non-NASH, a separate Danish cohort of 109 patients with simple steatosis followed up over 16.7 years had a comparable life expectancy to the general population. One patient in the cohort developed cirrhosis and subsequently died of liver related causes while there were 26 other non-liver related mortalities in the same cohort [16]. On the other hand, several studies which analysed NASH cohorts found considerably poorer long term outcomes. In an update of the original Matteoni NAFLD cohort, with 18.5 years of follow up, liver related mortality had increased to 18% of the NASH group and 3% of the non-NASH group. This translated into a 14-fold increased risk of liver related mortality in patients with NASH compared to those with non-NASH [17]. This was consistent with two other landmark longitudinal cohort studies from Sweden which demonstrated that relative to the general population, patients with non-NASH had comparable survival whereas patients with NASH were at increased risk of death [18, 19]. Subsequently, in a meta-analysis of three population-based and four community-based studies, with median follow up ranging between 7.3 and 24 years, the pooled overall mortality was higher in patients with NAFLD compared to the general population (OR 1.57; 95% CI 1.18-2.10; $p=0.002$). In addition, while pooled cardiovascular mortality was higher in NAFLD (OR 2.16; 95% CI 1.88-2.49; $p<0.00001$), mortality from extrahepatic malignancy was not increased in NAFLD compared to the general population (OR 0.97; 95% CI 0.66-1.26). Stratifying long term prognosis by histological subtypes (NASH vs simple steatosis), the survival of patients with simple steatosis approximated that of the general population, while patients with NASH had a higher overall mortality compared to those with simple steatosis (OR 1.81; 95% CI 1.24-2.66; $p=0.002$) [20]. Likewise, liver related mortality was significantly higher in patients with NASH, as compared to simple steatosis (OR 5.71; 95% CI 2.31-14.13; $p=0.0002$) [20]. A recent longitudinal Swedish study of 229 biopsy proven NAFLD patients provided updated 33 year follow up data; one of the longest follow up periods available. The diagnosis of NASH remains based on histological interpretation and in recent years, the NAFLD activity score (NAS) has gained wide acceptance in defining NASH [21]. However, it was never intended to replace the pathologist's decision in interpretation of NASH [22]. This study demonstrated that NAFLD patients had increased mortality compared to general population (HR 1.29; 95% CI 1.04-1.59; $p=0.0200$) but on further subgroup analysis, overall mortality

was not increased in patients with high NAS (NAS 5-8) and fibrosis stage 0-2, whereas patients with fibrosis score 3-4, irrespective of NAS, had increased overall and disease specific mortality (HR 3.3, 95% CI 2.27-4.76; $p < 0.001$) [23]. This is supported by the study of Angulo et al, who analysed long term outcomes on 619 NAFLD patients with median 12 year follow up; he found that fibrosis stage was the only independent histological feature on liver biopsy associated with long term overall mortality, liver transplantation and liver related events [24]. This suggest that fibrosis is the most important and significant predictor of long term outcomes in patients with NAFLD.

NAFLD progression: paired biopsied data

Further information about the natural history of NAFLD can be deciphered from studies examining the histological evolution of steatosis, steatohepatitis and fibrosis using evidence from paired biopsies.

Evolution of simple steatosis

While early studies suggest a benign course of natural history in NAFL/simple steatosis [15], recent studies have challenged such dogma that NAFL is not progressive [25]. A longitudinal Asian cohort study of 52 biopsy proven NAFLD patients with repeat biopsies after 3 years found that 39% and 23% of patients with simple steatosis had progressed to borderline and definite NASH respectively [26]. This was consistent with two other studies that reported similar findings; in a cohort of 70 NAFLD patients with paired biopsies, of which 25 patients had simple steatosis, Pais et al documented that 64% of those with simple steatosis had progressed to NASH while 24% developed advanced fibrosis over a mean of 3.7 years [27]. Separately in another cohort of 108 patients (27 with simple steatosis), McPherson et al observed that 44% of their patients with simple steatosis progressed to NASH and 37% had progression of fibrosis, including 22% to advanced fibrosis [28]. Pooled data from 6 studies including 133 patients with simple steatosis were reviewed in a meta-analysis; over 2145.5 person-years of follow-up, 52 patients (39.1%) developed progressive fibrosis, 70 patients (52.6%) remained stable while 11 patients (8.3%) had improvement of fibrosis. Accordingly, the annual fibrosis progression rate in patients with simple steatosis and absence of fibrosis at baseline was 0.07 stages (95% CI 0.02-0.11 stages), which translates to 1 stage of fibrosis progression over 14.3 years [29].

Evolution of NASH

Not unexpectedly, progression of NASH has been well documented in several studies. Powell et al observed that 5 out of 13 NASH patients who underwent serial liver biopsies after 1 to 9 years of follow-up had histological progression of fibrosis [30]. This finding has been echoed by other studies with paired serial biopsies, reporting rates of fibrosis progression among NASH patients between 32% and 53% [26, 31-35]. In a systematic review, Argo et al reported that 37% of the 221 patients with NASH in the review had progressive fibrosis over a mean follow-up of 5.3 years [36]. A more recent meta-analysis of 116 patients with NASH in 7 studies found that overall, 40 patients (34.5%) developed progressive fibrosis and 45 patients (38.8%) remained stable while 31 patients (26.7%) had improvement in fibrosis. Correspondingly, the annual fibrosis progression rate in NASH

patients with absent fibrosis at baseline was 0.14 stages (95% CI 0.07-0.21 stages), reflecting an average of 7.1 years to progress by one stage [29]. Predictive factors associated with progression of fibrosis include age, inflammation at index biopsy, presence of hypertension and a baseline low AST to ALT ratio [29, 36]. Of concern is the recognition of a small subset of patients with NAFLD coined rapid progressors, who can develop rapid progression to advanced fibrosis in a relatively short time. In pooled data from 11 cohort studies including 411 patients with biopsy proven NAFLD, Singh and colleagues identified 5 of 29 patients with NAFL and 2 of 11 patients with NASH that rapidly progressed to advanced fibrosis (stage 3-4) from baseline stage 0 over a mean follow up of 5.9 years [29]. Unfortunately, limited data on the characteristics of these rapid progressors prevent any firm inferences to be derived [29].

Long term outcomes of NAFLD with advanced fibrosis/cirrhosis

Between 10 and 25% of patients with NASH may potentially progress to advanced fibrosis/cirrhosis [14, 18, 37, 38]. One important revelation about the natural history of NASH to cirrhosis was highlighted by Powell et al, who noticed that there was a loss of steatosis and inflammatory changes corresponding to the progression to advanced fibrosis/cirrhosis [30]. Once cirrhosis develops in NASH patients, prognosis is negatively impacted, with potential development of cirrhosis and its complications. Several studies have characterised the long term outcomes of NAFLD with cirrhosis. In an Australian cohort study of 23 patients with NASH associated cirrhosis, outcomes were compared against patients with chronic hepatitis C related cirrhosis; 39% of the patients with NASH cirrhosis developed liver related complications over 7 years follow up and survival was comparable between NASH and hepatitis C related cirrhosis cohorts [39]. In contrast, relative to a hepatitis C cirrhosis cohort, a separate study with 152 patients with NASH cirrhosis observed a lower mortality rates, while risk of development of ascites, hyperbilirubinemia and hepatocellular carcinoma were also lower. However, cardiovascular mortality was higher in the patients with NASH cirrhosis [40]. In a slight variation of the previous studies' findings, a further study of 247 NASH cirrhosis patients reported lower rates of liver related complications and hepatocellular carcinoma than corresponding patients with Hepatitis C cirrhosis but similar overall mortality [41]. Yatsuji et al also reviewed the natural history of a small cohort of 68 Japanese patients with NASH cirrhosis compared to hepatitis C cirrhosis and found similar rates of cirrhosis complications (development of ascites, varices, hepatocellular carcinoma and incidence of hepatic encephalopathy) and survival between the two groups [42]. Further information about the natural history of NAFLD with cirrhosis may come indirectly from data on cryptogenic cirrhosis. There is increasing recognition that NASH accounts for a large proportion of what was previously labelled as cryptogenic cirrhosis, the term as applied to any cirrhosis of uncertain etiology. It has been suggested that cryptogenic cirrhosis often represents "burnt-out" NASH as a significant number of these patients would have the clinical phenotype consistent with NASH, such as higher prevalence of metabolic risk factors, but not the characteristic histopathologic features of NASH, which typically may have disappeared with the development of advanced fibrosis/cirrhosis [30, 43, 44]. The high frequency of NASH developing following liver transplantation among patients with

cryptogenic cirrhosis further strengthens the argument that progressive NASH accounts for a considerable proportion of cryptogenic cirrhosis [45].

Development of Hepatocellular carcinoma

Further evidence of the progressive nature of certain subsets of NAFLD can be found in the context of hepatocellular carcinoma (HCC) development. In parallel to the NAFLD epidemic, the incidence of HCC has been steadily increasing in developed countries such as Europe and United States, previously considered regions of low HCC prevalence [46]. This in part can be a reflection of increasing NAFLD prevalence [47]. Several studies of cohorts involving patients with NAFLD or cryptogenic cirrhosis have reported an association with HCC. A recent Surveillance, Epidemiology and End Results (SEER) database study demonstrated that patients with NAFLD had 2.6 fold increased risk of developing HCC with suggestion that these rates of HCC due to NAFLD are increasing about 10% annually [48]. Advanced fibrosis remains a strong risk factor for development of HCC with cumulative incidence rates reported between 2.4 to 12.8% [49]. Having said that, HCC has also been reported in patients with NAFLD in the absence of cirrhosis, which suggest multiple mechanisms of hepatocarcinogenesis in the context of NAFLD [47, 50].

Conclusion

NAFLD remains among the most common liver diseases worldwide, with increasing prevalence in concert with the obesity and metabolic syndrome epidemic. The evidence on the natural history, albeit with some ambiguity, suggests the potential for some subsets of NAFLD to progress to cirrhosis, liver related complications and mortality. In this setting, NAFLD proves to be a formidable disease entity, with considerable clinical burden, both for the present and the future.

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Key Findings

- Our understanding of the natural history of NAFLD is constantly evolving, with nascent data challenging current dogma.
- There remains some ambiguity regarding long term outcomes in NAFLD, with some conflicting data observed among the various studies of the natural history.
- Certain subsets of NAFL may be progressive while fibrosis remains among the most important predictors of hard long term endpoints such as mortality and liver complications.

Future Unmet Needs

- Further clarification of the natural history is required with well-designed, well-defined studies using prospectively collected data.
- Identifying the predictors of long term outcomes should be used to direct development of clinical trial endpoints in NAFLD.

Implications for the Clinician

- The growing prevalence of NAFLD in combination with the potential of NAFLD to progress to long term negative outcomes suggest a burgeoning clinical burden that clinicians must be prepared to brace.

Figure 1. displays and summarizes the natural history of NAFLD.

Table 1

Studies on long term mortalities in patients with NAFLD

Author	Year	Country	Design	Diagnosis	Mode of Diagnosis	N	Average Follow up (years)	Mortality			
								All cause N (%)	Cardiovascular N (%)	Liver-related N (%)	Extrahepatic malignancy N (%)
Adams [10]	2005	USA	Community	NAFLD	Imaging/Biopsy	420	7.6	53 (13)	15 (4)	7 (2)	15 (4)
Ong [11]	2008	USA	NHANES III	NAFLD	Liver enzymes	817	8.7	80 (10)	20 (2)	5 (0.6)	19 (2)
Dunn [12]	2008	USA	NHANES III	NAFLD	ALT	980	8.7	95 (10)	26 (3)	5 (0.5)	27 (3)
Lazo [13]	2011	USA	NHANES III	NAFLD	Ultrasound	2515	14.5	526 (21)	208 (8)	10 (0.4)	130 (5)
Haflidadottir [51]	2014	Iceland	Tertiary centre	NAFLD	Liver biopsy	151	9.9	42 (28)	20 (13)	3 (2)	6 (4)
Angulo [24]	2015	USA, Europe, Thailand	Tertiary centre	NAFLD	Liver biopsy	619	12	193 (33)	74 (12)	17 (3)	36 (19)
Teli [15]	1995	UK	Tertiary centre	Simple steatosis	Liver biopsy	40	11	14 (35)	NR	0	6
Dam-Larsen [16]	2004	Denmark	Tertiary centre	Simple steatosis	Liver biopsy	109	16.7	27	NR	1	NR
Rafiq [17]	2009	USA	Tertiary centre	Non-NASH	Liver biopsy	74	18.5	42 (57)	NR	2 (3)	NR
				NASH	Liver biopsy	57	18.5	36 (63)	NR	10 (18)	NR
Eksstedt [18]	2006	Sweden	Tertiary centre	Non-NASH	Liver biopsy	58	13.7	7 (12)	5 (7)	0	1 (2)
				NASH	Liver biopsy	71	13.7	19 (27)	11 (15)	2 (3)	4 (6)
Soderberg [19]	2010	Sweden	Tertiary centre	Non-NASH	Liver biopsy	67	21	23 (34)	7 (10)	6 (9)	5 (7)
				NASH	Liver biopsy	51	21	24 (47)	7 (14)	3 (6)	8 (16)

Table 2

Studies on serial biopsy histological progression in patients with NAFLD

Author	Year	Country	N	Subtype	Average Follow up (years)	Fibrosis		
						Improved (%)	Progressed (%)	Unchanged (%)
Powell [30]	1990	Australia	13	NASH	1.9	2 (15)	5 (38)	6 (46)
Teli [15]	1995	UK	12	NAFL	11	NR	1 (8)	NR
Evans [33]	2002	Scotland	7	NASH	8.2	0	4 (57)	3 (43)
Harrison [32]	2003	USA	22	86% NASH	5.7	4 (18)	7 (32)	11 (50)
Fassio [34]	2004	Argentina	22	NASH	4.3	0	7 (32)	15 (68)
Hui [35]	2005	HK	17	82% NASH	6.1	0	9 (53)	8 (47)
Adams [31]	2005	USA	103	93% NASH	3.2	30 (29)	38 (37)	35 (34)
Ekstedt [18]	2006	Sweden	68	NAFLD	13.8	11 (16)	29 (41)	30 (43)
Hamaguchi [52]	2010	Japan	39	NAFLD	2.4	12 (31)	11 (28)	16 (41)
Wong [26]	2010	HK	52	75% NASH	3	13 (25)	14 (27)	25 (48)
Pais [27]	2013	France	70	64% NASH	3.7	20 (29)	20 (29)	30 (42)
Chan [53]	2014	Malaysia	35	97% NASH	6.4	0	18 (51)	17 (49)
McPherson [28]	2015	UK	108	75% NASH	6.6	20 (18)	45 (42)	43 (40)

Table 3

Studies on long term outcomes of NASH cirrhosis

Author	Year	Country	N	Average Follow up (years)	All cause N (%)	Mortality		Morbidity Liver related complications N (%)
						Liver-related N (%)	Cardiovascular N (%)	
Hui [39]	2003	Australia	23	7	6 (26)	5 (22)	NR	9 (39)
Sanyal [40]	2006	USA	152	10	29 (19)	7 (5)	8 (5)	14/101 (14%) ascites 10/149 (7%) HCC
Yatsuji [42]	2009	Japan	68	3.4	19	13	0	13 (19%) ascites 36 (58%) GI varices 9 (13%) Hep Encep 21 (31%) HCC
Bhala [41]	2011	USA/UK/Australia/ Italy	247	7.1	33 (13)	14 (6)	NR	48 (19)