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Defining characteristics and outcomes for patients with non-alcoholic fatty liver disease admitted to hospital with decompensated cirrhosis

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We read with interest the systematic review and meta-analysis by Le *et al* which demonstrates the rapidly increasing worldwide incidence of non-alcoholic fatty liver disease (NAFLD) likely associated with the obesity epidemic[1]. Recently, we have demonstrated that NAFLD is the second most common cause of liver disease in patients admitted to hospital in the United Kingdom (UK) with decompensated cirrhosis (14.4% of admissions) [2]. We strongly agree that targeted public health interventions to reduce incidence and prevalence of NAFLD, and optimal outpatient management strategies are urgently needed to mitigate against NAFLD-related complications[3]. However, efforts to better characterise and stratify this cohort are similarly required. Utilising more robust phenotypic data should allow for the development of robust risk prediction models and may encourage implementation of precision approaches to improve overall patient outcomes.

We analysed data from a UK multicentre, retrospective observational cohort study, including patients admitted to hospitals with decompensated cirrhosis in November 2019[4] (Supplementary Table 1 provides regional submission data). We compared admissions for patients with NAFLD to the rest of the predominately alcohol-related liver disease (ARLD) cohort. Details of methods and statistical analyses are presented in the Supplementary Materials.

The NAFLD cohort were significantly older (69.0 (IQR 62.3-77.0) v 55.5 (IQR 47.0-65.0), p <0.0001*) and less likely to be male (50.6% v 63.5%, p=0.001*) (Table 1A). Whilst we note Le *et al* demonstrated a higher incidence of NAFLD amongst male patients, this may reflect previous findings that mortality is comparable across male and female patients with NAFLD reflecting similar prevalence of advanced disease[5].

No differences were demonstrated in proportion of admissions with a previous history of decompensation or known liver disease, or a history of HCC between cohorts. Admissions for patients with NAFLD were significantly less likely to regularly consume alcohol (18.0% v 61.8%, p<0.0001*) than the rest of the predominant ARLD cohort (Table 1A). However, alcohol consumption has been shown to be underreported in previous cohorts of NAFLD, while markers of alcohol use may have highlighted individual's regularly consuming alcohol above recommended limitsl[6].

Admissions for patients with NAFLD were predominantly related to management of ascites (40.9% v 32.1%, p=0.02*) or encephalopathy (25.6% v 15.8%, p=0.002*), and less likely to be for jaundice (2.8% v 17.2%, p<0.0001*) (Table 1A). Ascites is associated with the highest risk of readmission for patients with NAFLD[7]. Patient-centred, elective outpatient paracentesis provision is therefore a requisite component of modern Hepatology services.

Recently, data has implicated the premature onset of encephalopathy in NAFLD, while the association of hyperammonaemia with deleterious outcomes is also well described.(Ref)
A high index of suspicion for encephalopathy is required in this cohort, in addition to a low threshold in initiating therapies impacting ammoniogenesis.

The reduction in the proportion of patients admitted with jaundice likely reflects the cohort of patients from the predominately ARLD cohort presenting with alcohol-related hepatitis.

Following admission, no differences were noted between cohorts in the proportion of patients managed by a specialist Gastroenterologists/Hepatologist on specialist wards, or, in patients transferred to specialist centres. No differences were appreciated between patient cohorts for mortality during admission (15.8% v 15.6%, p=0.91) despite admissions with NAFLD having significantly lower prognostic scores and being less likely to access critical care (5.1% v 11.7%, p=0.008*) (Table 1A). Whilst this may reflect the older age of this cohort and concomitant comorbidity, previous concerns have been raised regarding limited access to critical care for patients with ARLD, with stigma amongst healthcare professionals suggested as a potential barrier for this cohort[9]. Understanding potential barriers to NAFLD patients accessing critical care is required to optimise management. Admissions for patients with NAFLD were not more likely to result in mortality after adjustment for age, critical care admission or MELD score (adjusted odds ratio 1.16 (95% CI 0.65-2.00) (Supplementary Figure 1). Whilst comparisons between non-survivors and survivors are likely underpowered, conventional prognostic models discriminated admission likely to result in survival (Table 1B). However, no prognostic scores significantly outperforming the other models (p=0.41), with no model achieved an AUC of greater than 0.8 (Supplementary Figure 2). After exclusion of admissions resulting in mortality or critical care admission, length of stay was no different to the rest of the cohort (Table 1A).

Limitations of these analyses are discussed in the Supplementary Materials and include the retrospective design, coverage of only a single month, incomplete coverage of the UK with potentialselection bias, lack of data regarding comorbidities

and the subjective nature of aetiology assignment. Whilst accepting these limitations, this study is however, representative of a large, real-world cohort.

With the likely increased incidence of patients being admitted to hospital with decompensated NAFLD, further work to understand how to optimally manage this cohort are necessary. This cohort is older, and often more co-morbid and will likely require a tailored approach to their care. Understanding barriers to providing best care, including access to critical care, is essential when developing hepatology services of the future.

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Tables

1A)

Variable	N	NAFLD N=176	N	Alternate aetiology of liver disease N=1048	P value
Age	176	69.0 (62.3-77.0)	1048	55.5 (47.0-65.0)	<0.0001*
Male sex	176	89 (50.6%)	1048	665 (63.5%)	0.001*
Current alcohol use	122	22 (18.0%)	813	502 (61.8%)	<0.0001*
Previously known liver disease	176	151 (85.8%)	1048	890 (84.9%)	0.82
Previous known decompensation	176	116 (65.9%)	1048	706 (67.4%)	0.73
Known HCC	176	10 (5.7%)	1048	54 (5.2%)	0.72
Reason for admission					
Ascites	176	72 (40.9%)	1048	336 (32.1%)	0.02*
Encephalopathy	176	45 (25.6%)	1048	166 (15.8%)	0.002*
Gastrointestinal bleeding	176	19 (10.8%)	1048	161 (15.4%)	0.13
Jaundice	176	5 (2.8%)	1048	180 (17.2%)	<0.0001*
Sepsis	176	10 (5.7%)	1048	69 (6.6%)	0.74

Prognostic scores					
MELD score	147	13.0 (11.0-18.0)	955	17.0 (12.0-21.0)	<0.0001*
UKELD score	147	53.0 (51.0-60.0)	955	57.0 (52.0-62.0)	<0.0001*
Child Pugh score	139	8.0 (7.0-10.0)	932	9.0 (8.0-11.0)	0.0005*
Post 24-hour care					
Managed by a specialist	176	125 (71.0%)	1048	776 (74.1%)	0.41
Predominately managed on a specialist ward	176	93 (52.8%)	1043	597 (57.2%)	0.29
Critical care admission during stay	176	9 (5.1%)	1048	123 (11.7%)	0.008*
Transfer to another centre	176	5 (2.8%)	1048	19 (1.8%)	0.37
Admission mortality	171	27 (15.8%)	1029	160 (15.6%)	0.91
Length of stay	142	7.0 (4.0-13.0)	859	7.00 (3.0-13.0)	0.60

1B)

Variable	**N**	**Survivors N=144**	**N**	**Non-survivors N=27**	**P value**
Age	144	69.0 (62.0-76.0)	27	73.0 (65.0-78.0)	0.17
Male sex	144	72 (50.0%)	27	15 (55.6%)	0.68
Current alcohol use	102	20 (19.6%)	17	2 (11.8%)	0.74
Previously known liver disease	144	125 (86.8%)	27	22 (81.5%)	0.54
Previous known decompensation	144	96 (66.7%)	27	17 (63.0%)	0.83
Known HCC	144	8 (5.6%)	27	2 (7.4%)	0.66

Reason for admission					
Ascites	144	59 (41.0%)	27	11 (40.7%)	>0.9999
Encephalopathy	144	38 (26.4%)	27	5 (18.5%)	0.47
Gastrointestinal bleeding	144	16 (11.1%)	27	2 (7.4%)	0.74
Jaundice	144	4 (2.8%)	27	1 (3.7%)	0.58
Sepsis	144	10 (6.9%)	27	0 (0.0%)	0.37
Prognostic scores					
MELD score	119	13.0 (10.0-17.0)	23	21.0 (15.0-27.0)	<0.0001*
UKELD score	119	53.0 (50.0-57.0)	23	59.0 (54.0-61.0)	0.0001*
Child Pugh score	113	8.0 (7.0-9.0)	22	10.0 (8.8-11.0)	0.0002*
Post 24 hour care					
Managed by a specialist	144	100 (69.4%)	27	21 (77.8%)	0.49
Predominately managed on a specialist ward	144	78 (54.2%)	27	12 (44.4%)	0.40
Critical care admission during stay	144	5 (3.5%)	27	4 (14.8%)	0.04

Table 1. Characterising UK NAFLD admissions. 1A) Comparison of admissions for patients with NAFLD compares to patients with alternate aetiologies of liver disease. **1B)** Comparison of NAFLD admissions resulting in patient survival with those that did not. Non-normally continuous data were analysed using Mann-Whitney *U* tests and presented as median (IQR). Categorical data were analysed using Fisher's exact tests and presented as number (%). Statistical significance set as per Benjamini-Hochberg procedure with a false discovery rate of 0.05.

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