Steatosis in Cirrhosis: A Prognostic Marker for Liver-Related Outcomes in MASLD

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Background and Aims

The association between fibrosis and liver-related outcomes is well established. However, the predictive utility of histological components have not been well studied. We aim to study the utility of the qFIBs[1] and its components (qfibrosis, qInflammation, qBallooning, qSteatosis) in predicting risk of Liver Related Events (LRE) in Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD).

Method

108 liver biopsy images were retrieved and the composite LREs of liver-related death, hepatic encephalopathy (HE), ascites and hepatocellular carcinoma (HCC) were studied with the Non-alcoholic Steatohepatitis Clinical Research Network (NASH-CRN) score and qFIBs. Firth-corrected Cox regression was performed due to the occurrence of few events, together with log-rank tests and Kaplan-Meier analyses.

Results and Discussion

LREs (liver-related deaths=5, HE=4, HCC=4, ascites=8) occurred in 12% of the cohort (n=13/108). Median follow up was 7.83 years. Patients with more advanced fibrosis had a six-fold risk of developing LREs (qF3/4 vs qF0/1/2, HR 6.41, 95% CI 1.10 - 37.23), compared to a seven-fold risk with NASH-CRN (F3/4 vs F0/1/2, HR 7.19, 95% CI 1.74 - 29.82). A lower qSteatosis showed a twenty-three-fold increased risk of developing LREs (HR 23.51, 95% CI 1.23-448.16). On further analysis, it was found that majority of the patients with lower qSteatosis were also cirrhotic. Interestingly, among the cirrhotic group (n=33), a lower qSteatosis grade, rather than being a protective factor, correlated with poorer outcomes (qS0/1=24 vs qS2/3=9, 100% of LREs occurred in the qS0/1 group), likely due to the reduction of steatosis in dynamic fat changes in end stage liver disease.

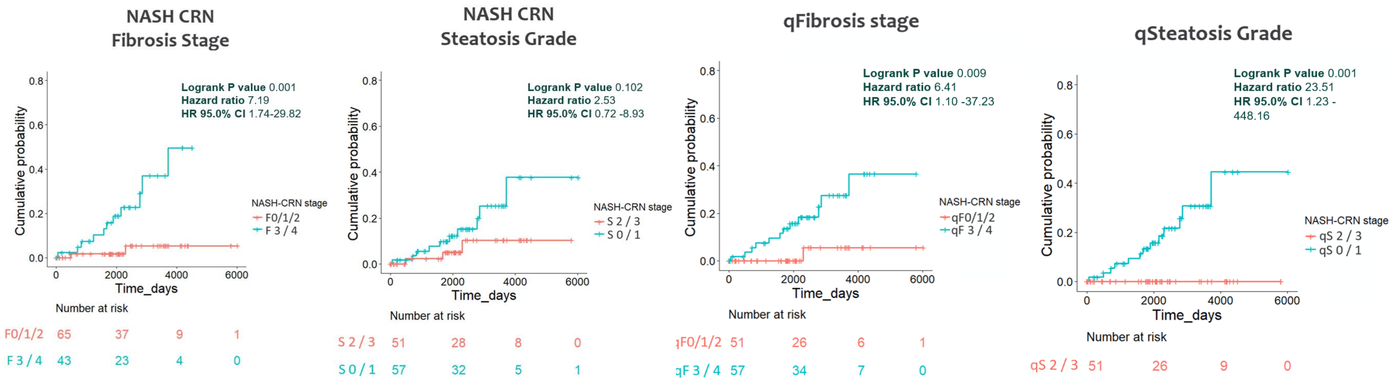

Figure 1: Kaplan-Meier curve of MASLD patients for developing LRE

This is further substantiated by the finding that samples with lower percentages of macrovesicular steatosis had a significantly higher risk of developing LREs compared to samples with more macrovesicular steatosis (18% vs 30%, p = 0.013). In addition, patients with lower zone 2 steatosis had higher risk of LREs (HR 6.86, p=0.001, 95% CI 1.79 - 26.33). Though the difference was not significant, fat distribution was also more azonal in the LRE group (zone 3: 18%, p=0.886; azonal 64%, p=0.901). Ballooning was positively associated with higher risk of LREs (HR 3.20, p=0.042, 95% CI 1.02-10.03).

Table 1: LREs occurring within the cirrhosis population (m=33)

qIBS	LREs
qInflammation grade	**11/33**
0	8/14
1	1/3
2	1/4
3	1/12
qBallooning grade	**11/33**
0	5/9
1	2/12
2	4/12
qSteatosis grade	**11/33**
0	**1/1**
1	**10/23**
2	0/8
3	0/1

Table 2: Percentage of macrovesicular steatosis within cirrhotic patients

Cirrhotic patients (n=33)	Developed LREs (n=11)		No LREs (n=22)		t test p value
	Mean	Standard deviation	Mean	Standard deviation	
Percentage of macrovesicular steatosis (%)	18	12	30	12	**0.013**

Conclusions

Lower steatosis and inflammation grades in cirrhosis correlate with the occurrence of LREs and reiterates the natural history of MASLD - as fibrosis progresses, steatosis regresses. On histology, steatosis was less likely to be macrovesicular and more likely to be azonal in distribution. Our findings open up exciting new areas for validation with larger cohorts and exploration of the process of steatosis fluxes and how it reflects the underlying pathogenesis of MASLD progression to decompensation and LREs.

References

[1]Liu F, Goh GB, Tiniakos D, et al. qFIBS: An Automated Technique for Quantitative Evaluation of Fibrosis, Inflammation, Ballooning, and Steatosis in Patients With Non-alcoholic Steatohepatitis. *Hepatology*. 2020;71(6):1953-1966. doi:10.1002/hep.30986