Validation of the SURFASA score to define steroid responsiveness in patients with acute autoimmune hepatitis

Su Lin[1,2], Andrew Hall[1,3,4], Rahul Kumar[1,5], *Alberto Quaglia[6], *Rajiv Jalan[1, 7]

*Both contributed equally and are joint senior authors.

1 Liver failure Group, Institute for Liver and Digestive Health, Division of Medicine, University College London Medical School, Royal Free Hospital, London, UK

2 Department of Hepatology, Hepatology Research Institute, the First Affiliated Hospital, Fujian Medical University, Fuzhou, Fujian, China, 350001

3 Department of Cellular Pathology, Royal Free Hospital, London, UK

4 Sheila Sherlock Liver Center, Royal Free London NHS Foundation Trust

5 Department of Gastroenterology and Hepatology, Duke-NUS academic Medical Centre, Changi General Hospital, Singapore

6. Department of Cellular Pathology and UCL cancer Institute, Royal Free Hospital, London, UK

7. European Foundation for the Study of Chronic Liver Failure (EFCLIF), Barcelona, Spain.

*Corresponding author: Prof Rajiv Jalan Liver Failure Group, Institute for Liver & Digestive Health, Division of Medicine, University College London UCL, Rowland Hill Street, London, NW3 2PF, United Kingdom Phone: +44 02074332795; E-mail: r.jalan@ucl.ac.uk

Authors' Contributions

Study concept and design: Rajiv Jalan and Alberto Quaglia

Acquisition, cleaning and analysis of data: Su Lin

Histology staining: Andrew Hall

Histopathology review: Alberto Quaglia

Drafting of the manuscript: Su Lin and Rajiv Jalan

Critical revision: Alberto Quaglia and Rahul Kumar

Study supervision: Rajiv Jalan

All authors contributed to the manuscript for important intellectual content and approved the submission.

Competing interests: Rajiv Jalan has research collaborations with Takeda, and Yaqrit, and consults for Yaqrit. Rajiv Jalan is the founder of Yaqrit Limited, which is developing UCL inventions for treatment of patients with cirrhosis. Rajiv Jalan is an inventor of ornithine phenylacetate, which was licensed by UCL to Mallinckrodt. He is also the inventor of Yaq-001, DIALIVE and Yaq-005, the patents for which have been licensed by his University into a UCL spinout company, Yaqrit Ltd.

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Dear editor,

We read with interest the paper of De Martin and colleagues [1], in which they developed a novel scoring system to predict corticosteroid response in patients with severe acute autoimmune hepatitis (AIH). The SURFASA score comprised three parameters, the baseline INR, change in INR over 3-days and change in total bilirubin over 3-days after initiation of steroids. The results showed that for patients with a SURFASA score <–0.9, the chance of steroid response was 75%. On the other hand, if the SURFASA score was greater than 1.75, the risk of dying or being transplanted was greater than 85%.

We validated this novel score in patients with biopsy-proven acute AIH. The study population was derived from the CARNATION cohort, which is a single centre, retrospective-prospective project that aims to explore clinicopathological correlates of patients with acute hepatitis[2]. This study was approved by the London - Hampstead Research Ethics Committee (07/Q0501/50) and was in compliance with the Declaration of Helsinki. Nineteen patients with acute AIH that were admitted between 2010-2019 were included. All received corticosteroids, [prednisolone, median dose of 40mg (IQR 40-60mg)]. Corticosteroids were started a median of 2 (IQR 0-6) days after hospitalisation. The mean age was 50.4 ± 15.6 years; 42% were male. None had hepatic encephalopathy (HE) and only 1 had ascites (5.3%) on admission. Twelve (63%) survived spontaneously (responders) over 3-months and the rest either died or received liver transplantation (non-responders). The baseline patient characteristics are listed in supplementary table 1.

Compared to the non-responders, the responders had significantly lower MELD, MELD-Na, ALF-OF score and SURFASA score. The AUROC of SURFASA for predicting outcome was 0.964, which was higher than those of other models. The pair-wise comparison of AUROC between SURFASA, MELD, MELD-Na and ALF-OF score did not show any significant differences ($p>0.05$ for each paired comparison) (table 1a). Additionally, none of the pathology features identified in the liver biopsy determined response to steroids. (supplementary table 1)

In our cohort, the best cut-off value of SURFASA was -2.35, which was significantly lower than reported in the study by Martin et al. [1] (Table 1b). Based on the published thresholds [1], which were -0.9 and 1.75, the SURFASA score could not discriminate survivors from

non-survivors (Table 1b). When the threshold was lowered to -2.35, the survival rate was 100% in the patients with SURFASA score <=-2.35; 77.8% of those with SURFASA>-2.35 died or received liver transplantation. (Table 1b)

The main difference between this cohort and the patients in which the SURFASA score was derived is that all the patients in the validation cohort had acute AIH [4 had minimal fibrosis (F1)], while in the derivation cohort, there were 31% with moderate fibrosis (F2-3) and 21% had cirrhosis (F4). More patients had HE (derivation: 12% grade I-II, 3% grade III-IV; validation: 0). These differences may account for different thresholds observed, as the presence of HE, and fibrosis grade ≥F3 have been shown to have poorer corticosteroid responsiveness [3]. The different clinical profiles of the two cohorts might partially explain the discrepancy in result.

In conclusion, we agree with De Martin et al. that the SURFASA score is useful in predicting steroid response and patient survival but the traditional scores such as MELD, MELD-Na or ALF-OF perform with similar accuracy. Importantly, our data suggests that the thresholds of the SURFASA score may differ depending on various factors, and that in our cohort of acute AIH with no or minimal underlying fibrosis, the predictive SURFASA score was -2.35. More prospective studies are necessary for further validation.

Table 1 The performance of SURFASA score in acute AIH. (Table 1A) Performance of different liver specific prognostic scores to define patient outcome. Levels of significance: p < 0.001 for all (receiver operator characteristic analysis). (Table 1B) Different thresholds of SURFASA score for predicting outcome. Levels of significance: *p = 0.001; ˆ p > 0.05. (Fisher's exact test).

Table 1A.

	AUROC	Cut-off	Sensitivity 95%CI	Specificity 95%CI	+LR	-LR	P value
SURFASA	0.964	>-2.35	100 (59.0-100).	91.67 (61.5-99.8)	12.0	0.00	0.0016
MELD-Na	0.917	>26.03	87.50 (47.3-99.7)	84.62 (54.6-98.1)	5.69	0.15	<0.0001
MELD	0.893	>23.03	100 (63.1-100)	76.92 (46.2-95.0)	4.33	0.00	<0.0001
ALF-OF	0.821	>2.737	75 (34.9-96.8)	84.62 (54.6-98.)	4.87	0.30	0.0016

Table 1B

Threshold		Survival	Death/transplantation	P value
-2.35*	<=-2.35	10(100%)	0	0.001
	>-2.35	2(22.2%)	7(77.8%)	
-0.9 ˆ	<=-0.9	12(100%)	5(71.2%)	0.123
	>-0.9	0	2(100%)	
1.75 ˆ	<=1.75	12(63.2%)	7(36.8%)	1
	>1.75	0	0	

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Supplementary table 1 baseline characteristics of study population

	Total (n = 19)	Responders (n = 12)	Non-Responders (n = 7)	P value
Age (years)	50.37 ± 15.59	49.58 ± 17.35	51.71 ± 13.19	0.767
Male, n (%)	8 (42.11)	7 (58.33)	1 (14.29)	0.147
HE, n (%)	0	0	0	NA
Ascites, n (%)	1 (5.26)	1 (8.33)	0 (0)	1
MELD	24.53 ± 3.87	22.52 ± 3.01	27.97 ± 2.55	< 0.001
MELD-Na	25.94 ± 3.43	24.19 ± 2.66	28.95 ± 2.36	0.001
ALF-OFs	2.97 ± 0.49	2.80 ± 0.39	3.27 ± 0.51	0.025
Total bilirubin (μmol/L)	332.26 ± 110.96	335.75 ± 100.26	326.29 ± 135.8	0.876
INR	1.99 ± 0.71	1.61 ± 0.57	2.64 ± 0.38	< 0.001
Creatinine (μmol/L)	76.21 ± 46.08	64.33 ± 16.14	96.57 ± 71.61	0.283
ALT (U/L)	925.21 ± 514.52	1042.92 ± 562.65	723.43 ± 372.27	0.156
AST (U/L)	1143.63 ± 617.22	1234 ± 724.7	988.71 ± 368.39	0.343
ALP (U/L)	144.58 ± 31.2	141.08 ± 35.97	150.57 ± 21.95	0.485
Albumin (g/L)	29.68 ± 7.45	31.17 ± 6.29	27.14 ± 9.06	0.325
CRP(mg/L)	16.79 ± 9.01	17.67 ± 9.23	15.29 ± 9.12	0.594
White blood cell ($\times10^9$/L)	9.29 ± 9.98	9.96 ± 12.09	8.16 ± 5.34	0.66
Neutrophil ($\times10^9$/L)	4.63 ± 3.06	4.11 ± 2.54	5.52 ± 3.85	0.409
Lymphocyte ($\times10^9$/L)	1.47 ± 0.92	1.52 ± 1.06	1.4 ± 0.67	0.761
Platelets ($\times10^9$/L)	231.37 ± 123.86	249.75 ± 98.36	199.86 ± 162.65	0.481
SURFASA score	-3.02 ± 1.7	-4.03 ± 1.14	-1.29 ± 0.89	< 0.001
Fibrosis, n (%)				1
F0	10 (71.43)	8 (72.73)	2 (66.67)	
F1	4 (28.57)	3 (27.27)	1 (33.33)	
Hepatocyte preserved, n (%)	12 (85.71)	10 (90.91)	2 (66.67)	0.396
Multilobular necrosis, n (%)	8 (57.14)	5 (45.45)	3 (100)	0.209
Perivenulitis, n (%)	5 (35.71)	5 (45.45)	0 (0)	0.258

Ductular reaction, n (%)	14 (100)	11 (100)	3 (100)	NA
Ductular cholestasis, n (%)	2 (14.29)	1 (9.09)	1 (33.33)	0.396
Acidophilic body n (%)	6 (46.15)	5 (50)	1 (33.33)	1
Canalicular cholestasis, n (%)	4 (30.77)	2 (20)	2 (66.67)	0.203
Lobular inflammation, n (%)	11 (84.62)	8 (80)	3 (100)	1
Portal inflammation, n (%)	13 (92.86)	10 (90.91)	3 (100)	1
Interface inflammation, n (%)	7 (50)	6 (54.55)	1 (33.33)	1
Lymphoid aggregate, n (%)	6 (42.86)	5 (45.45)	1 (33.33)	1
Lymphoid follicle, n (%)	14 (100)	11 (100)	3 (100)	NA
Neutrophil, n (%)	9 (64.29)	6 (54.55)	3 (100)	0.258
Plasma cell, n (%)	11 (78.57)	8 (72.73)	3 (100)	1
Macrophages, n (%)	4 (28.57)	3 (27.27)	1 (33.33)	1
Eosinophil, n (%)	3 (21.43)	1 (9.09)	2 (66.67)	0.093

Continuous variables were expressed as mean ± standard deviation and analysis with Mann-Whitney U-test.

Categorical variables were expressed as percentages and examined with Fisher’s exact test.

Abbreviation: INR, international normalised ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; MELD score, model for end-stage liver disease score; MELD-Na score, end-stage liver disease-sodium score; ALF-OFs, Acute Liver Failure-Organ Failure Score;