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A Validated Prognostic Score Estimating the Risk of Liver-Related Death Among HIV/HCV Coinfected Individuals

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INTRODUCTION

The arrival of potent and less toxic direct-acting antivirals (DAA) for treatment of HCV infection may see improved outcomes and less toxicity among HIV/HCV coinfected individuals. However, the estimated costs of €30,000-90,000 per treatment will necessitate prioritisation of those at greatest risk of liver-related death (LRD) for therapy.

Development of a simple, widely applicable prognostic score for LRD among HIV/HCV coinfected individuals is essential to predict the future burden of LRD. An accurate prognostic score in this setting will aid comparison of individual risk profiles when prioritising who should be treated with new DAAs for HCV.

METHODS

The LRD risk score was developed using EuroSIDA participants with HIV/HCV coinfection positive for HCV RNA and follow-up after 1/1/2000. Cox proportional hazards regression using the Fine and Gray method for handling competing risks and stepwise variable selection was used to identify factors associated with LRD. Scaled model coefficients were used to create the prognostic score.

Data from the Swiss HIV Cohort Study (SHCS) were used to validate the LRD score on an external population of HIV/HCV coinfected individuals positive for HCV RNA. Sensitivity, specificity and the area under the ROC curve (AUROC) were used to assess the ability of the LRD score to identify those at risk of progression to LRD. Cumulative incidence functions were used to predict the 5-year probability of LRD according to levels of the LRD score.

Calculating the LRD score (Table 1)

- The LRD score is calculated based on an individual's age, CD4 cell count, HBV coinfection status, the minimum duration of HCV infection, liver fibrosis staging and whether they are taking cART.
- Scores associated with each variable are summed to calculate the LRD score. An example of the LRD score calculation is shown in Table 1.

Results (Baseline characteristics – Table 2)

- The EuroSIDA derivation cohort included 158 LRDs and 3627 coinfected individuals with HCV RNA who were mostly male (68.3%) injecting drug users (IDU) (70.8%).
- The external SHCS cohort included 38 LRDs and 1303 coinfected individuals with HCV RNA with a similar proportion of males (66.5%) but fewer IDUs (47.0%).
- The largest differences between the two cohorts were seen for the minimum duration of HCV infection (2.7 vs. 7.1 years) and the proportion with F2/F3 fibrosis (14.4% vs. 6.3%, for EuroSIDA and the SHCS respectively).

Table 1

LRD Score calculation sheet

Variable	Criteria	Score contribution	Score
Age	< 35	0	
	≥ 35	2.5	2.5
CD4 cell count	0 ≤ cells/mm³ < 100	4	
	100 ≤ cells/mm³ < 300	2	
	300 ≤ cells/mm³ < 500	1	1
	500 ≤ cells/mm³	0	
Taking antiretroviral therapy	Yes	0	0
	No	1	
HBV status	HBsAg positive	2	
	HBsAg negative	0	0
Duration of HCV infection	< 2 years	0	
	2 ≤ years < 10	1.5	1.5
	10 ≤ years	2	
Fibrosis staging	F0/F1	0	
	F2/F3	3.5	3.5
	F4	4.5	
Total		=	8.5

LRD score calculation for a 40 year old individual without HBV coinfection, taking cART, a CD4 cell count of 400cells/mm³, estimated minimum duration of HCV infection of 5 years and F3 liver fibrosis

Table 2

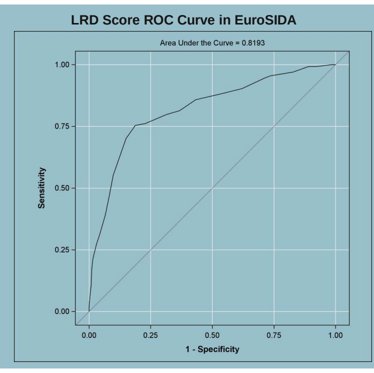
Baseline characteristics

Variable		EuroSIDA	SHCS
HCV RNA positive coinfected individuals (Total PYFU)		3627 (14,576)	1303 (7,742)
Liver-related deaths		158	38
Age	Median (IQR)	37 (31 - 42)	42 (37 – 46)
Male	N (%)	2478 (68.3)	866 (66.5)
Injecting drug user	N (%)	2569 (70.8)	612 (47.0)
MSM	N (%)	299 (8.2)	163 (12.5)
Heterosexual	N (%)	548 (15.1)	216 (16.6)
HBsAg positive	N (%)	227 (6.3)	89 (6.8)
Minimum duration HCV positive (Years)	Median (IQR)	2.7 (0.7 - 6.0)	7.1 (4.0 – 10.3)
Taking cART	N (%)	2338 (64.5)	925 (71.0)
CD4 cell count (cells/mm³)	Median (IQR)	381 (238 - 564)	402 (365 – 588)
Nadir CD4 cell count (cells/mm³)	Median (IQR)	168 (70 - 290)	165 (70 – 282)
Fibrosis staging (N (%))	F0/F1	2768 (76.3)	1086 (83.4)
	F2/F3	523 (14.4)	82 (6.3)
	F4	336 (9.3)	135 (10.4)

SHCS: Swiss HIV cohort study, MSM: Men who have sex with men, cART: Combination antiretroviral therapy, IQR: Interquartile range

Figure 1

LRD Score ROC Curve in EuroSIDA



Results (LRD score performance in EuroSIDA – Figures 1, 2 and Table 3)

- The mean LRD score was significantly higher among those who died of LRD (8.2 (95% CI 7.7 – 8.6) vs. 4.9 (4.8 – 5.0); *P*<0.0001).
- A 1-unit increase in the LRD score was associated with 2.5-fold increased risk of LRD (sub-distribution hazard ratio (sHR): 2.5 (2.2 – 2.8); *P*<0.0001).
- The LRD score achieved an AUROC score of 0.82, substantially higher than prediction based solely on liver fibrosis levels (AUROC=0.72).
- The 5-year probability of LRD increased from 1.4% (0.95 – 2.0) in those at low risk to 5.0% (3.5 – 6.9), 13.2% (9.5 – 17.5) and 21.3% (15.5 – 27.8) in those at medium-low, medium-high and high risk of LRD, respectively (*P*<0.0001 for separation between strata).
- Assuming that DAA therapy will lead to an overall 80% reduction in LRD, the estimated number needed to treat (NNT) to observe 1 fewer LRD is 81 in those at low risk, 23, 9 and 5 in those at medium-low, medium-high and high risk of LRD, respectively.

Results (LRD score performance in the SHCS –Table 3)

- The mean LRD score was significantly higher among those who died of LRD (8.2 (7.3 – 9.2) vs. 5.6 (5.5 – 5.8); *P*<0.0001).
- A 1-unit increase in the LRD score was associated with 2.4-fold increased risk of LRD (sHR: 2.4 (1.9 – 3.2); *P*<0.0001)
- The LRD death score achieved an AUROC score of 0.79 in the validation cohort, similar to that achieved in EuroSIDA, showing impressive replicability.
- In the SHCS, the 5-year probability of LRD increased from 0.9% (0.3 – 2.0) in those at low risk to 2.5% (1.2 – 4.7), 7.4% (3.0 – 14.6) and 13.4% (6.5 – 22.8) in those at medium-low, medium-high and high risk of LRD, respectively (*P*<0.0001 for separation between strata).

CONCLUSIONS

A simple prognostic LRD score calculated from information readily collected at clinical sites can accurately predict progression to LRD among HIV/HCV coinfected individuals, outperforming prediction based solely on fibrosis staging.

The score performed impressively when identifying those at the greatest risk of LRD in the derivation and external cohort. Therefore, the LRD score should be considered for use in the clinical setting when facing tough decisions on who to prioritise for treatment with new HCV treatments.

Figure 2

Probability of LRD by Risk Score in EuroSIDA

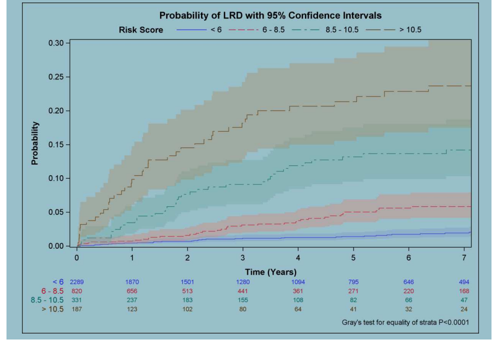


Table 3

Incidence of LRD and number needed to treat to prevent 1 LRD by risk score category

Cohort	Risk Category (Score)	Incidence of LRD /100 PYFU (95% CI)	NNT 50%	NNT 80%
EuroSIDA	Low risk (< 6)	0.38 (0.25 - 0.50)	142	81
	Medium-low risk (6 – 8.5)	1.22 (0.84 - 1.59)	40	23
	Medium-high risk (8.5 – 10.5)	3.66 (2.56 - 4.76)	15	9
	High risk (> 10.5)	6.92 (4.88 - 8.97)	9	5
SHCS	Low risk (< 6)	0.18 (0.05 - 0.30)		
	Medium-low risk (6 – 8.5)	0.49 (0.20 - 0.78)		
	Medium-high risk (8.5 – 10.5)	1.36 (0.42 - 2.30)		
	High risk (> 10.5)	2.76 (1.15 - 4.37)		

PYFU: Person years follow-up; NNT: Number needed to treat; SHCS: Swiss HIV Cohort Study
NNT 50%: Number needed to treat to prevent 1 LRD assuming that treatment results in an average 50% reduction of LRD.NNT shows the number of patients needed to be treated in order to observe 1 less LRD over a 5-year period

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The Swiss HIV Cohort Study

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