Original Article

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# Fibrosis-4 index predicts mortality in HIV/HCV co-infected patients receiving combination antiretroviral therapy in rural China

**Xiaochen Chen[1,§], Xing Liu[1,§], Renhai Tang[2], Runhua Ye[2], Yuecheng Yang[2], Shitang Yao[2], Jibao Wang[2], Yingying Ding[1], Song Duan[2,*], Na He[1,3,*]**

[1] *Department of Epidemiology, School of Public Health, and the Key Laboratory of Public Health Safety of Ministry of Education, Fudan University, Shanghai, China;*
[2] *Dehong Prefecture Center for Disease Control and Prevention, Mangshi, Yunnan, China;*
[3] *Key Laboratory of Health Technology Assessment of Ministry of Health, Fudan University, Shanghai, China.*

**Summary** **End-stage liver disease (ESLD) is among leading causes of death for people living with HIV and HCV. Little is known how liver fibrosis score predicts mortality in HIV/HCV co-infected population under combination antiretroviral therapy (cART). A retrospective cohort study of 691 HIV/HCV co-infected patients receiving cART in Yunnan, China from 2005 to 2016 was carried out to explore the association between Fibrosis-4 index (FIB-4) and all-cause mortality. Cox proportional hazard models were used to estimate the hazard ratios (HRs) for FIB-4 and covariates. After a median follow-up of 4.8 years with a total follow-up time of 3,696 person-years (PY), 131 deaths occurred and the all-cause mortality was 3.5 per 100 PY. The mortality was 2.9 (95% CI: 2.3-3.5)/100 PY for the FIB-4 ≤ 3.25 group and 5.8 (4.2-7.4)/100 PY for the FIB-4 > 3.25 group at baseline. People with FIB-4 changed from mild to advanced group showed HR of 1.81 (95% CI: 1.01-3.25) for death, and with FIB-4 sustaining advanced showed HR of 3.11 (1.75-5.54), both compared to those with FIB-4 remained mild, while lower risk of death was observed among married people (HR = 0.63, 95% CI: 0.41-0.99) compared to unmarried, among those with most recent $CD4^+$ T cell counts between 200 and 350 cells/μL (0.50, 0.30-0.86) and > 350 cells/μL (0.25, 0.15-0.41) compared to CD4 under 200 cells/μL. Advanced and progressive liver fibrosis is a strong predictor of all-cause mortality in HIV/HCV co-infected patients under cART in China.**

***Keywords:*** HIV/HCV co-infection, liver fibrosis, FIB-4, mortality

## 1. Introduction

With the widespread use of combination antiretroviral therapy (cART), people infected with human immunodeficiency virus (HIV) have a longer lifespan (*1*) and non-HIV related diseases are the major burden and causes of death currently. In particular, on the basis of fibrosis, end-stage liver diseases are becoming more prominent in HIV-infected patients (*2-4*), accounting for 14-18% of deaths (*5*). Liver fibrosis refers to the excessive deposition of diffuse extracellular matrix and fibrotic lesions in the liver, which is a kind of injury repair responses after chronic hepatic injury. If not treated in time, liver fibrosis may develop into decompensated cirrhosis, and patients would suffer from various consequences including cirrhosis and hepatocellular carcinoma (HCC) (*6*).

Liver fibrosis can be induced by hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol, long-term use of antiviral drugs, etc, and the process is accelerated by HIV infection (*7,8*). In China, especially in rural

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[§]These authors contributed equally to this work.

**Address correspondence to:*
Dr. Song Duan, Dehong Prefecture Center for Disease Control and Prevention, Mangshi, Yunnan 678400, China.
E-mail: dhduansong@sina.com

Dr. Na He, Department of Epidemiology, School of Public Health, Fudan University, Shanghai 20032, China.
E-mail: nhe@fudan.edu.cn, or nhe@shmu.edu.cn

Yunnan, these risk factors are highly prevalent among HIV-infected patients (*9,10*). The prevalence was 77.7% for HCV infection and 15.5% for HIV/HCV co-infection among injecting drug users (IDU) in Yunnan province (*11*). And the prevalence of alcohol use was 65% among HIV patients (*12*). Such high prevalence and co-existence of risk factors bring heavy burden of liver disease to this population. However, how the progression of liver fibrosis affects mortality in HIV-infected people has not been examined.

Severity assessment of liver disease, such as the degree of liver fibrosis, is important for disease progression and treatment guidance for patients with hepatitis C (*13*). Though liver biopsy is the gold standard, the invasive method may cause some complications, has higher cost, and is difficult to be performed repeatedly for assessing liver fibrosis in community (*14,15*). In light of these limitations, many noninvasive indicators have been developed to assessed the severity of liver fibrosis. FIB-4 is calculated by routinely used biochemical data, *i.e.* alanine transaminase (ALT), aspartate aminotransferase (AST), platelet count and age (*16*), and is an internationally recognized well-established noninvasive indicator for the degree of liver fibrosis (*17-19*). Increased FIB-4 has been shown to be associated with increased mortality in general population (*20*), people with liver diseases (*16,21,22*) and patients with HIV/HCV coinfection in western countries (*23*). We conducted this cohort study to examine the utility of liver fibrosis index in predicting mortality among HIV/HCV co-infected patients in the era of cART in Chinese population.

## 2. Materials and Methods

### 2.1. *Study design and subject*

We conducted a retrospective cohort study of HIV/HCV co-infected patients who were under cART in Dehong Prefecture, Yunnan Province, China, a region bordering Myanmar which has high HIV endemic (*24,25*). The observational study period was from the date of cART initiation (*i.e.* baseline) to 31 March 2016 for all patients. The inclusion criteria for the study participants were as following: *i*) age ≥ 18 years at cART initiation; *ii*) cART initiation no later than 31 March 2015 to ensure that each participants had received cART for at least one year; *iii*) tested positive for serum anti-HCV antibody; *iv*) no evidence of hepatitis B virus infection; *v*) had available biochemical data to calculate FIB-4 (*i.e.* ALT, AST, platelet count); *vi*) had at least one follow-up visit. By March 2016, 1,017 HIV/HCV co-infected patients had been reported (*8*). Of them, 204 had not initiated cART, 44 were tested positive for hepatitis B surface antigen, 22 did not have biochemical data available at baseline and 56 did not have biochemical data followed-up. Thus, a total of 691 HIV/HCV co-infected patients under cART were included in the analysis. This study was approved by the Institutional Review Board (IRB) of Chinese National Center for AIDS/STD Control and Prevention and the IRB of Fudan University. Written informed consent was obtained from all study participants.

### 2.2. *Data collection*

Epidemiologic data and laboratory measurements were obtained from the Comprehensive Response Information Management System (CRIMS), which is a web-based national database for real-time collection and maintenance of information for HIV infected people in China (*26*). Demographic characteristics including age, gender, ethnicity, level of education and marital status at initiation of cART were collected. HIV-related data including date of cART initiation, $CD4^+$ T cell counts, HIV viral load, ALT, AST, platelet count at both baseline and follow-up were also collected.

FIB-4 score was calculated by the following formula: AST (IU/L) × age (years)/platelet count ($10^9$/L) × $ALT^{1/2}$ (IU/L) (*16*). And the FIB-4 score was further categorized into two classes: FIB-4 ≤ 3.25 indicating no or mild liver fibrosis, and FIB-4 > 3.25 indicating advanced liver fibrosis (*27*). Accordingly, changes in FIB-4 classes were categorized into four groups: G1, sustaining mild fibrosis (FIB-4 remaining ≤ 3.25) ; G2, change from mild to advanced fibrosis (FIB-4 ≤ 3.25 at baseline, and > 3.25 in most recent follow-up); G3, change from advanced to mild fibrosis (FIB-4 > 3.25 at baseline, and ≤ 3.25 in most recent follow-up); G4, sustaining advanced fibrosis (FIB-4 remaining > 3.25).

### 2.3. *Definition of outcome*

The main outcome was all-cause mortality. Dates of death were obtained from CRIMS. All participants were followed until the occurrence of death, loss to follow-up, or end of this observation (March 31, 2016), whichever came first.

### 2.4. *Statistical analysis*

Categorical variables were expressed as number and percentage. Continuous variables were presented as median and interquartile range (IQR). $\chi^2$ test was conducted to compare distribution of categorical variables while Mann-Whitney u test or Kruskal Wallis test was conducted to compare continuous variables. The overall mortality, mortalities by FIB-4 classes and by epidemiologic characteristics were calculated as the number of deaths divided by person-years (PY) of follow-up. Univariate Cox proportional hazard models were used to estimate the hazard ratios (HRs) for FIB-4 score and other epidemiologic and clinical variables. In multivariate Cox proportional hazard model, variables

**Table 1. Baseline characteristics of HIV/HCV co-infected participants and FIB-4 distributions**

| Characteristics | Total No. (%)[a] | Fib4 ≤ 3.25 No. (%)[b] | Fib4 > 3.25 No. (%)[b] | *P*[c] |
|---|---|---|---|---|
| Age (years) | | | | < 0.001 |
| Median (IQR) | 35 (31-40) | 35 (31-39) | 39 (35-44) | < 0.001 |
| 19 - 29 | 124 (17.9) | 111 (89.5) | 13 (10.5) | |
| 30 - 39 | 384 (55.6) | 309 (80.5) | 75 (19.5) | |
| 40 - 49 | 168 (24.3) | 110 (65.5) | 58 (34.5) | |
| ≥ 50 | 15 (2.2) | 5 (33.3) | 10 (66.7) | |
| Gender | | | | 0.623 |
| male | 674 (97.5) | 521 (77.3) | 153 (22.7) | |
| female | 17 (2.5) | 14 (82.4) | 3 (17.6) | |
| Ethnicity | | | | 0.999 |
| Han | 311 (45.0) | 241 (77.5) | 70 (22.5) | |
| Dai | 131 (19.0) | 101 (77.1) | 30 (22.9) | |
| Jingpo | 223 (32.3) | 173 (77.6) | 50 (22.4) | |
| Others | 26 (3.8) | 20 (76.9) | 6 (23.1) | |
| Education (years) | | | | 0.025 |
| 0 ~ 6 | 344 (49.8) | 254 (73.8) | 90 (26.2) | |
| 7 ~ | 347 (50.2) | 281 (81.0) | 66 (19.0) | |
| Marital status | | | | 0.046 |
| unmarried | 261 (37.8) | 215 (82.4) | 46 (17.6) | |
| married | 353 (51.1) | 261 (73.9) | 92 (26.1) | |
| Divorced/widowed | 77 (11.1) | 59 (76.6) | 18 (23.4) | |
| HIV transmission route | | | | 0.383 |
| IDU | 632 (91.5) | 492 (77.8) | 140 (22.2) | |
| Others | 59 (8.5) | 43 (72.9) | 16 (27.1) | |
| Baseline $CD4^+$ T cell counts(cells/μL) | | | | 0.004 |
| Median(IQR) | 269 (181-378) | 277 (184-405) | 242 (166-321) | 0.001 |
| < 200 | 210 (30.4) | 151 (71.9) | 128 (28.1) | |
| 200 - 350 | 283 (41.0) | 214 (75.6) | 69 (24.4) | |
| > 350 | 191 (27.6) | 163 (85.3) | 28 (14.7) | |
| ARV regimen type, % | | | | 0.001 |
| NVP (*vs*. EFV/RTV) | 302 (44.1) | 232 (76.8) | 70 (23.2) | |
| TDF (*vs*. AZT/d4T/DDI) | 251 (36.6) | 210 (83.7) | 41 (16.3) | |
| Others | 132 (19.3) | 88 (66.7) | 45 (33.3) | |

[a]proportion in column; [b]proportion in row; [c]in bold: $p < 0.05$ (Mann-Whitney *U* test)

of age, gender, ethnicity, level of education, marital status, baseline and most recent $CD4^+$ T cell counts in addition to FIB-4 measures were included, either by "forced-entry" or *p*-value < 0.05 at univariate analysis. Kaplan-Meier survival curves were constructed for each category of changes in FIB-4 class and log-rank test was used for comparisons. Statistical significance was defined as $p < 0.05$. Statistical analyses were performed using SPSS version 22.0 and R version 3.3.2.

## 3. Results

### 3.1. *Patients characteristics*

A total of 691 HIV/HCV co-infected patients were included in the study. The socio-demographic and HIV infection related characteristics were summarized in Table 1. The median age was 35 years old (IQR, 31-40 years). 97.5% were male. 45.0% were Han, the major ethnicity in China, whereas 32.3% were Jingpo and 19.0% were Dai, which are the two major ethnic minority groups in the study area. The majority (91.5%) of the study patients infected with HIV *via* injecting drug use (IDU). The median $CD4^+$ T cell counts was 269 cells/μL (IQR, 181-378 cells/μL) at baseline, and 71.% were less than 200 cells/μL. All patients had initiated cART for HIV, while no one had received treatment for HCV such as ribavirin.

### 3.2. *FIB-4 index and change*

At baseline, the median FIB-4 score was 1.78 (IQR, 1.19-3.00). 22.6% of the participants had FIB-4 > 3.25, indicating advanced liver fibrosis. Participants with FIB-4 > 3.25 tended to be older, had lower education, lower baseline $CD4^+$ T cell counts, and had ARV regime without NVP or TDF. In contrast, having FIB-4 > 3.25 did not differ significantly by gender, ethnicity or HIV transmission route.

The distribution of FIB-4 and its change by characteristics of HIV/HCV co-infected participants after follow-up were shown in Table 2. 479 (69.3%) had the recent FIB-4 score remained in the mild class, 56 (8.1%) changed from mild to advanced class, 91 (13.2%) changed from advanced to mild class and 65 (9.4%) remained in advanced class. Patients with older age, being male, divorced/widowed, had lower baseline or most recent $CD4^+$ T cell counts had higher possibility of sustaining advanced liver fibrosis ($p < 0.05$). While gender, ethnicity, HIV transmission route and most

**Table 2. FIB-4 changes by demographic and clinical characteristics of HIV/ HCV co-infected participants**

| Characteristics | Changes in FIB-4, number and proportion (%) | | | | $P^a$ |
|---|---|---|---|---|---|
| | G1 Sustaining mild | G2 Mild to advanced | G3 Advanced to mild | G4 Sustaining advanced | |
| Age (years) | | | | | < 0.001 |
| Median(IQR) | 35 (30-39) | 37 (33-41) | 38 (34-44) | 40 (36-44) | < 0.001 |
| 19 - 29 | 103 (83.1) | 8 (6.5) | 11 (8.9) | 2 (1.6) | |
| 30 - 39 | 279 (72.7) | 30 (7.8) | 45 (11.7) | 30 (7.8) | |
| 40 - 49 | 94 (56.0) | 16 (9.5) | 29 (17.3) | 29 (17.3) | |
| ≥ 50 | 4 (26.7) | 1 (6.7) | 6 (40.0) | 4 (26.7) | |
| Gender | | | | | 0.056 |
| male | 466 (69.1) | 55 (8.2) | 89 (13.2) | 64 (9.5) | |
| female | 14 (82.4) | 0 (0.0) | 2 (11.8) | 1 (5.9) | |
| Ethnicity | | | | | 0.574 |
| Han | 213 (68.5) | 28 (9.0) | 40 (12.9) | 30 (9.6) | |
| Dai | 89 (67.9) | 12 (9.2) | 15 (11.5) | 15 (11.5) | |
| Jingpo | 159 (71.3) | 14 (6.3) | 30 (13.5) | 20 (9.0) | |
| Others | 19 (73.1) | 1 (3.8) | 6 (23.1) | 0 (0.0) | |
| Education (years) | | | | | 0.028 |
| 0 ~ 6 | 223 (64.8) | 31 (9.0) | 57 (16.6) | 33 (9.6) | |
| 7 ~ | 257 (74.1) | 24 (6.9) | 34 (9.8) | 32 (9.2) | |
| Marital status | | | | | < 0.001 |
| unmarried | 204 (78.2) | 11 (4.2) | 26 (10.0) | 20 (7.7) | |
| married | 225 (63.7) | 36 (10.2) | 59 (16.7) | 33 (9.3) | |
| Divorced/widowed | 51 (66.2) | 8 (10.4) | 6 (7.8) | 12 (15.6) | |
| HIV transmission route | | | | | 0.704 |
| IDU | 441 (69.8) | 51 (8.1) | 83 (13.1) | 57 (9.0) | |
| Others | 39 (66.1) | 4 (6.8) | 8 (13.6) | 8 (13.6) | |
| ARV regimen type, % | | | | | < 0.001 |
| NVP (*vs*. EFV/RTV) | 202 (66.9) | 30 (9.9) | 43 (14.2) | 27 (8.9) | |
| TDF (*vs*. AZT/d4T/DDI) | 195 (77.7) | 15 (6.0) | 29 (11.6) | 12 (18.5) | |
| Others | 79 (59.8) | 9 (6.8) | 18 (13.6) | 26 (19.7) | |
| Baseline $CD4^+$ T cell counts (cells/μL) | | | | | 0.009 |
| Median(IQR) | 281 (188-416) | 239 (159-329) | 233 (163-328) | 262 (179-303) | 0.003 |
| < 200 | 131 (62.4) | 20 (9.5) | 39 (18.6) | 20 (9.5) | |
| 200 - 350 | 190 (67.1) | 24 (8.5) | 35 (12.4) | 34 (12.0) | |
| > 350 | 153 (80.1) | 10 (5.2) | 17 (8.9) | 11 (5.8) | |
| Last $CD4^+$ T cell counts (cells/μL) | | | | | 0.034 |
| Median (IQR) | 523 (347-685) | 494 (365-659) | 388 (277-556) | 409 (257-598) | < 0.001 |
| < 200 | 40 (61.5) | 4 (6.2) | 11 (16.9) | 10 (15.4) | |
| 200 - 350 | 78 (61.9) | 9 (7.1) | 24 (19.0) | 15 (11.9) | |
| > 350 | 345 (72.5) | 42 (8.8) | 54 (11.3) | 35 (7.4) | |
| Last HIV RNA ($n$ = 612) | | | | | 0.146 |
| < 400 | 353 (68.9) | 38 (7.4) | 73 (14.3) | 48 (9.4) | |
| ≥ 400 | 71 (71.0) | 13 (13.0) | 10 (10.0) | 6 (6.0) | |

[a]in bold: $p < 0.05$ (Kruskal - Wallis test).

recent HIV RNA did not show significant association with FIB-4 change.

### 3.3. *Cumulative all-cause mortality based on FIB-4 index*

The median follow-up time was 4.8 years (IQR, 3.3-7.6 years), corresponding to 3,696 person-years for the 691 participants. During follow-up, 131 had died and the all-cause mortality was 3.5 per 100 PY (95% CI: 2.9-4.1). The cumulative mortality increased as the FIB-4 score increased both at baseline and at follow-up. The mortality was 2.9/100 PY (95% CI: 2.3-3.5) in the FIB-4 ≤ 3.25 group and 5.8/100 PY (95% CI: 4.2-7.4) in the FIB-4 > 3.25 group at baseline. The cumulative mortality also differed by FIB-4 change: of the four groups, *i.e.*, G1 (sustaining mild), G2 (changed from mild to advanced), G3 (changed from advanced to mild) and G4 (sustaining advanced), the mortalities were 2.7 (95% CI: 2.1-3.4), 4.3 (2.2-6.4), 4.1 (2.4-5.8) and 8.6 (5.5-11.8) per 100 PY, respectively (Table 3). Log-rank test showed significant difference in survival among the four FIB-4 changing groups (Figure 1).

### 3.4. *Cumulative mortality and associated factors*

In simple Cox proportional hazard regression model, the hazard for death was positively associated with older age, baseline FIB-4 >3.25, most recent FIB-4 > 3.25, in sustaining advanced fibrosis group (G4), most recent $CD4^+$ T cell counts < 200 cells/μL and most recent HIV RNA > 400 copies/mL. In the multiple regression

**Table 3. Cox proportional hazard models for mortality of HIV/HCV co-infected participants**

| Age (years) | Total No. (%) | No. Deaths | Follow-up in person years | Mortality (/100 PY) | *cHR*[a] (95% CI) | *p* | *aHR*[b] (95% CI) | *p* |
|---|---|---|---|---|---|---|---|---|
| 19-29 | 124 (17.9) | 16 | 744.7 | 2.1 | 1.00 | | 1.00 | |
| 30-39 | 384 (55.6) | 65 | 2,107.9 | 3.1 | 1.42 (0.81-2.51) | 0.259 | 1.65 (0.90-3.00) | 0.104 |
| 40-49 | 168 (24.3) | 45 | 771.2 | 5.8 | 2.64 (1.45-4.82) | 0.002 | 2.60 (1.32-5.14) | 0.006 |
| ≥ 50 | 15 (2.2) | 5 | 72.3 | 6.9 | 3.33 (1.21-9.17) | 0.020 | 2.32 (0.74-7.26) | 0.149 |
| As continuous | | | | | | | 1.03 (0.99-1.06) | 0.099 |
| Gender | | | | | | | | |
| male | 674 (97.5) | 130 | 3,607.8 | 3.6 | 1.00 | | 1.00 | |
| female | 17 (2.5) | 1 | 88.2 | 1.1 | 0.31 (0.04-2.24) | 0.248 | 0.78 (0.10-5.80) | 0.805 |
| Ethnicity | | | | | | | | |
| Han | 311 (45.0) | 62 | 1,746.0 | 3.6 | 1.00 | | 1.00 | |
| Dai | 131 (19.0) | 22 | 637.0 | 3.5 | 1.01 (0.62-1.65) | 0.965 | 0.99 (0.56-1.77) | 0.979 |
| Jingpo | 223 (32.3) | 41 | 1,187.0 | 3.5 | 0.98 (0.66-1.45) | 0.918 | 0.80 (0.49-1.31) | 0.376 |
| Others | 26 (3.8) | 6 | 126.0 | 4.8 | 1.38 (0.60-3.20) | 0.450 | 1.32 (0.55-3.17) | 0.535 |
| Education (years) | | | | | | | | |
| 0~6 | 344 (49.8) | 73 | 1,763.4 | 4.01 | 1.00 | | 1.00 | |
| 7~ | 347 (50.2) | 58 | 1,932.6 | 3.00 | 0.71 (0.50-1.00) | 0.051 | 0.86 (0.56-1.33) | 0.508 |
| Marital status | | | | | | | | |
| unmarried | 261 (37.8) | 52 | 1,406.3 | 3.7 | 1.00 | | 1.00 | |
| married | 353 (51.1) | 62 | 1,899.3 | 3.3 | 0.88 (0.61-1.28) | 0.504 | 0.63 (0.41-0.99) | 0.043 |
| Divorced/widowed | 77 (11.1) | 17 | 390.4 | 4.4 | 1.21 (0.70-2.10) | 0.489 | 0.65 (0.34-1.25) | 0.202 |
| HIV transmission route | | | | | | | | |
| IDU | 632 (91.5) | 84 | 3410.0 | 2.5 | 1.00 | | | |
| Others | 59 (8.5) | 47 | 286.0 | 16.4 | 0.70 (0.33-1.50) | 0.352 | | |
| Baseline counts $CD4^+$ T cell(cells/μL) | | | | | | | | |
| < 200 | 210 (30.7) | 49 | 1,269.9 | 3.9 | 1.00 | | | |
| 200-350 | 283 (41.4) | 65 | 1,712.8 | 3.8 | 0.99 (0.68-1.43) | 0.935 | | |
| > 350 | 191 (27.9) | 17 | 684.2 | 2.5 | 0.75 (0.42-1.32) | 0.318 | | |
| As continuous | | | | | 0.999 (0.998-1.001) | 0.312 | 1.00 (0.99-1.01) | 0.313 |
| Last $CD4^+$ T cell counts (cells/μL) | | | | | | | | |
| < 200 | 65 (9.7) | 27 | 313.0 | 8.6 | 1.00 | | 1.00 | |
| 200-350 | 126 (18.9) | 32 | 673.5 | 4.8 | 0.54 (0.33-0.91) | 0.019 | 0.50 (0.30-0.86) | 0.012 |
| > 350 | 476 (71.4) | 57 | 2,654.0 | | 0.24 (0.15-0.38) | < 0.001 | 0.25 (0.15-0.41) | < 0.001 |
| As continuous | | | | 2.1 | 0.998 (0.997-0.999) | < 0.001 | | |
| Baseline FIB-4 | | | | | | | | |
| ≤ 3.25 | 535 (77.4) | 84 | 2,885.3 | 2.9 | 1.00 | | | |
| > 3.25 | 156 (22.6) | 47 | 810.7 | 5.8 | 1.99 (1.39-2.85) | < 0.001 | | |
| As continuous | | | | | 1.01 (0.99-1.02) | 0.439 | 0.99 (0.96-1.01) | 0.354 |
| Last FIB-4 | | | | | | | | |
| ≤ 3.25 | 571 (82.6) | 90 | 3,055.5 | 2.9 | 1.00 | | | |
| > 3.25 | 120 (17.4) | 41 | 640.5 | 6.4 | 2.15 (1.49-3.11) | < 0.001 | | |
| FIB-4 change (Baseline - Last) | | | | | | | | |
| G1 | 480 (69.5) | 69 | 2,545.8 | 2.7 | 1.00 | | 1.00 | |
| G2 | 55 (8.0) | 15 | 356.5 | 4.2 | 1.52 (0.87-2.66) | 0.144 | 1.81 (1.01-3.25) | 0.047 |
| G3 | 91 (13.2) | 21 | 509.7 | 4.1 | 1.48 (0.91-2.40) | 0.112 | 1.59 (0.92-2.77) | 0.097 |
| G4 | 65 (9.4) | 26 | 301.0 | 8.6 | 3.24 (2.06-5.10) | < 0.001 | 3.11 (1.75-5.54) | < 0.001 |
| Last HIV RNA ($n$ = 612, copies/mL) | | | | | | | | |
| < 400 | 512 (83.7) | 75 | 2,952.0 | 2.5 | 1.00 | | | |
| ≥ 400 | 100 (16.3) | 25 | 537.2 | 4.7 | 1.71 (1.07-2.72) | 0.024 | | |

[a]*cHR*, crude hazard ratio; [b]*aHR*, adjusted hazard ratio, adjusted for age, gender, ethnicity, education, marital status, baseline $CD4^+$ T cell counts, baseline FIB-4, last $CD4^+$ T cell counts, FIB-4 changes. [c]in bold: $p < 0.05$.

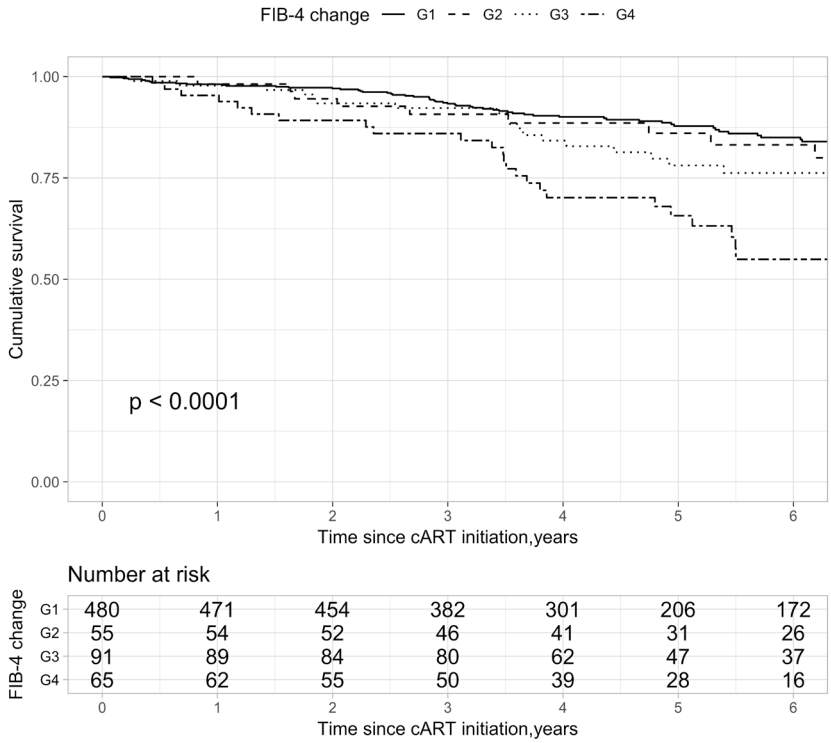


**Figure1. Kaplan-Meier survival curves in patients based on the FIB-4 changes.** The cumulative mortality differed significantly among the different groups of FIB-4 changes ($p < 0.0001$, log-rank test). G1, solid line, sustaining mild; G2, dashed line, mild- to- advanced; G3, dotted line, advanced-to-mild; G4, two dash line, sustaining advanced.

model, higher risk of death was associated with age at 40-49 years old (adjusted HR: 2.60, 95% CI: 1.32-5.14), FIB-4 changed from mild to advanced group (1.81, 1.01-3.25) and FIB-4 sustaining advanced (3.11, 1.75-5.54) compared to FIB-4 remained mild. While lower risk of death was observed among married people (0.63, 0.41 - 0.99), among those with most recent $CD4^+$ T cell counts 200-350 cells/μL (0.50, 0.30 - 0.86) and > 350 cells/μL (0.25, 0.15-0.41). In particular, baseline FIB-4 > 3.25 remained an independent predictor of increased all-cause mortality when adjusted by age, gender, ethnicity, education, marital status and most recent $CD4^+$ T cell counts (1.63, 1.12- 2.38, data not shown in table).

## 4. Discussion

To the best of our knowledge, the present study is the first to report FIB-4 index as a predictor of all-cause mortality in HIV/HCV co-infected Chinese in the cART era. It suggests with epidemiologic evidence that the index constructed from routinely used laboratory measurements in clinical settings could be applied in prognosis for patients with HIV and HCV.

Noninvasive methods of measuring biomarkers of liver fibrosis alternative to liver biopsy is an important issue in various research fields. Studies found that single biomarker such as serum hyaluronan and biomarkers combined such as Fibro Test had shown prognostic values in patients with chronic hepatitis C (*28,29*). Among the combined indexes, FIB-4 score had advantages that it comprises of routinely used biochemical measurements, and shows superiority in accuracy to other markers of fibrosis (*30*). And FIB-4 was also found to be a successful predictor in distinguishing mild and advanced fibroses in HIV/HCV co-infected patients (*31*).

In the present study, both baseline FIB-4 higher than 3.25, indicating advanced liver fibrosis, and FIB-4 progressing from mild to advanced fibrosis during follow-up were found to be independent predictors for all-cause mortality among HIV/HCV co-infected participants under cART. This observation is consistent with studies conducted in the western countries (*31-33*). One large scale cohort conducted in Italy followed up 3,475 HIV patients with or without HCV reported that FIB-4 at cART initiation and its change independently predicted liver related death (*34*). Our study adds to the knowledge that FIB-4 also has predictive value in Chinese population with high prevalence of HIV/HCV infection, alcohol consumption, at the same time receiving cART.

Meanwhile, the most recent $CD4^+$ T cell counts as the marker for immune suppression status predicted mortality in univariate and multiple regression models and the observation was consistent with previous research (*35*). Although most recent HIV RNA greater than 400 copies/mL was also a risk factor for increased

mortality in univariate model, considering that $CD4^+$ T cell counts is highly correlated with HIV viral load, and is more frequently tested for HIV patients, $CD4^+$ T cell counts were included in the multiple regression model. The increase in CD4 was shown to be protective against death, and we suggest to include both FIB-4 and CD4 in risk stratification for HIV/HCV patients.

This study has some limitations. First, this study was a retrospective study based on HIV/HCV infection, information on other factors which might had affected the progression of liver fibrosis, such as alcohol consumption, were not collected. Further studies are needed to control potential confounding brought by alcohol consumption and some other important factors. Second, the causes of death cannot be specified and collected in this study. Thus, all analyses were conducted toward all-cause mortality, and the association between liver fibrosis and liver-related deaths had not been explored.

In conclusion, the FIB-4 index as a marker for liver fibrosis is shown to be a predictor for all-cause mortality in HIV/HCV co-infected patients under cART. FIB-4 may help in risk stratification and in estimating risk of death in clinical settings.

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**References**

1. World Health Organization. Global hepatitis report 2017. *https://apps.who.int/iris/bitstream/handle/10665/255016/9789241565455-eng.pdf?sequence=1.* (accessed April, 2017)
2. Weber R, Sabin CA, Friis-MøllerN, *et al*. Liver-related deaths in persons infected with the human immunodeficiency virus: The D:A:D study. Arch Intern Med. 2006; 166:1632-1641.
3. Peters MG. End-stage liver disease in HIV disease. Top HIV Med. 2009; 17:124-128.
4. Graham CS, Baden LR, Yu E, Mrus JM, Carnie J, Heeren T, Koziel MJ. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: A meta-analysis. Clin Infect Dis. 2001; 33:562-569.
5. Price JC, Thio CL. Liver disease in the HIV-infected individual. Clin Gastroenterol Hepatol. 2010; 8:1002-1012.
6. Ismail MH, Pinzani M. Reversal of liver fibrosis. Saudi J Gastroenterol. 2009; 15:72-79.
7. Jain MK, Seremba E, Bhore R, Dao D, Joshi R, Attar N, Yuan HJ, Lee WM. Change in fibrosis score as a predictor of mortality among HIV-infected patients with viral hepatitis. AIDS Patient Care STDS. 2012; 26:73-80.
8. Ding Y, Duan S, Ye R, Yang Y, Yao S, Wang J, Cao D, Liu X, Lu L, Jia M. More improvement than progression of liver fibrosis following antiretroviral therapy in a longitudinal cohort of HIV-infected patients with or without HBV and HCV co-infections. J Viral Hepat. 2017; 24:412-420.
9. Zhang F, Zhu H, Wu Y, Dou Z, Zhang Y, Kleinman N, Bulterys M, Wu Z, Ma Y, Zhao D. HIV, hepatitis B virus, and hepatitis C virus co-infection in patients in the China National Free Antiretroviral Treatment Program, 2010-12: A retrospective observational cohort study. Lancet Infect Dis. 2014; 14:1065-1072.
10. Wei Q, Lin H, Ding Y, Liu X, Wu Q, Shen W, Gao M, He N. Liver fibrosis after antiretroviral therapy in a longitudinal cohort of sexually infected HIV patients in eastern China. Biosci Trends. 2017; 11:274-281.
11. Zhou YH, Yao ZH, Liu FL, Li H, Jiang L, Zhu JW, Zheng YT. High Prevalence of HIV, HCV, HBV and Co-Infection and Associated Risk Factors among Injecting Drug Users in Yunnan Province, China. PloS One. 2012; 7:e42937.
12. Luo XF, Duan S, Duan QX, Pu YC, Yang YC, Ding YY, Gao MY, He N. Alcohol use and subsequent sex among HIV-infected patients in an ethnic minority area of Yunnan province, China. PloS One. 2013; 8:e61660.
13. Peters MG, Bacchetti P, Boylan R, French AL, Tien PC, Plankey MW, Glesby MJ, Augenbraun M, Golub ET, Karim R, Parkes J, Rosenberg W. Enhanced liver fibrosis marker as a noninvasive predictor of mortality in HIV/hepatitis C virus-coinfected women from a multicenter study of women with or at risk for HIV. AIDS. 2016; 30:723-729.
14. Gebo KA, Herlong HF, Torbenson MS, Jenckes MW, Chander G, Ghanem KG, El-Kamary SS, Sulkowski M, Bass EB, Tm JHUEBPC. Role of liver biopsy in management of chronic hepatitis C: A systematic review. Hepatology. 2002; 36:S161-S172.
15. Bravo AA, Sheth SG, Chopra S. Liver biopsy. New Engl J Med. 2001; 344:495-500.
16. Tada T, Kumada T, Toyoda H, Kiriyama S, Tanikawa M, Hisanaga Y, Kanamori A, Kitabatake S, Yama T, Tanaka J. Long-term prognosis of patients with chronic hepatitis C who did not receive interferon-based therapy: Causes of death and analysis based on the FIB-4 index. J Gastroenterol. 2016; 51:380-389.
17. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, Sulkowski MS, Torriani FJ, Dieterich DT, Thomas DL. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology. 2006; 43:1317-1325.
18. Vallet-Pichard A, Mallet V, Nalpas B, Verkarre V, Nalpas A, Dhalluin-Venier V, Fontaine H, Pol S. FIB-4: An inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. Hepatology. 2007; 46:32-36.
19. Shah AG, Lydecker A, Murray K, Tetri BN, Contos MJ, Sanyal AJ; Nash Clinical Research Network. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2009; 7:1104-1112.
20. Unalp-Arida A, Ruhl CE. Liver fibrosis scores predict liver disease mortality in the United States population. Hepatology. 2017; 66:84-95.
21. Backus LI, Belperio PS, Shahoumian TA, Mole LA. Impact of sustained virologic response with direct-acting antiviral treatment on mortality in patients with advanced

liver disease. Hepatology. 2017. doi: 10.1002/hep.29408.
22. Vergniol J, Boursier J, Coutzac C, Bertrais S, Foucher J, Angel C, Chermak F, Hubert IF, Merrouche W, Oberti F, de Ledinghen V, Cales P. Evolution of noninvasive tests of liver fibrosis is associated with prognosis in patients with chronic hepatitis C. Hepatology. 2014; 60:65-76.
23. Castellares C, Barreiro P, Martin-Carbonero L, Labarga P, Vispo ME, Casado R, Galindo L, Garcia-Gasco P, Garcia-Samaniego J, Soriano V. Liver cirrhosis in HIV-infected patients: Prevalence, aetiology and clinical outcome. J Viral Hepat. 2008; 15:165-172.
24. He N, Duan S, Ding Y, Rou K, Mcgoogan JM, Jia M, Yang Y, Wang J, Montaner JS, Wu Z. Antiretroviral therapy reduces HIV transmission in discordant couples in rural Yunnan, China. Plos One. 2013; 8:e77981.
25. Jia Y, Sun J, Fan L, Song D, Tian S, Yang Y, Jia M, Lu L, Sun X, Zhang S. Estimates of HIV prevalence in a highly endemic area of China: Dehong Prefecture, Yunnan Province. Int J Epidemiol. 2008; 37:1287-1296.
26. Mao Y, Wu ZY, Poundstone K, Wang CH, Qin QQ, Ma Y, Ma W. Development of a unified web-based national HIV/AIDS information system in China. Int J Epidemiol. 2010; 39:ii79-ii89.
27. Vergniol J, Foucher J, Terrebonne E, Bernard PH, le Bail B, Merrouche W, Couzigou P, de Ledinghen V. Noninvasive tests for fibrosis and liver stiffness predict 5-year outcomes of patients with chronic hepatitis C. Gastroenterology. 2011; 140:1970-79, 1979. e1-3.
28. Guéchot J, Serfaty L, Bonnand AM, Chazouillères O, Poupon RE, Poupon R. Prognostic value of serum hyaluronan in patients with compensated HCV cirrhosis. J Hepatol. 2000; 32:447-452.
29. Ngo Y, Munteanu M, Messous D, Charlotte F, Imbertbismut F, Thabut D, Lebray P, Thibault V, Benhamou Y, Moussalli J. A prospective analysis of the prognostic value of biomarkers (FibroTest) in patients with chronic hepatitis C. Clin Chem.. 2006; 52:1887-1896.
30. Poynard T, Ngo Y, Perazzo H, Munteanu M, Lebray P, Moussalli J, Thabut D, Benhamou Y, Ratziu V. Prognostic value of liver fibrosis biomarkers: A meta-analysis. Gastroenterol Hepatol (N Y). 2011; 7:445-454.
31. Jain MK, Seremba E, Bhore R, Dao D, Joshi R, Attar N, Yuan HJ, Lee WM. Change in fibrosis score as a predictor of mortality among HIV-infected patients with viral hepatitis. AIDS Patient Care STDS. 2012; 26:73-80.
32. Campa A, Martinez SS, Sherman KE, Greer JP, Li Y, Garcia S, Stewart T, Ibrahimou B, Williams OD, Baum MK. Cocaine use and liver disease are associated with all-cause mortality in the miami adult studies in HIV (MASH) Cohort. J Drug Abuse. 2016; 2. pii: 27.
33. Berenguer J, Zamora FX, Aldamiz-Echevarria T, *et al*. Comparison of the prognostic value of liver biopsy and FIB-4 index in patients coinfected with HIV and hepatitis C virus. Clin Infect Dis. 2015; 60:950-958.
34. Mussini C, Lorenzini P, Puoti M, Lichtner M, Lapadula G, Di Giambenedetto S, Antinori A, Madeddu G, Cozzi-Lepri A, Monforte AD, De Luca A, Grp IFS. Prognostic value of the Fibrosis-4 index in human immunodeficiency virus type-1 infected patients initiating antiretroviral therapy with or without hepatitis C virus. PloS One. 2015; 10:e0140877.
35. Achhra AC, Amin J, Law MG, Emery S, Gerstoft J, Gordin FM, Vjecha MJ, Neaton JD, Cooper DA, Grp IS, Grp ES, Grp SS. Immunodeficiency and the risk of serious clinical endpoints in a well studied cohort of treated HIV-infected patients. AIDS. 2010; 24:1877-1886.

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