A COMBINATION OF STEATOSIS-FIBROSIS INDEX PREDICT MAYOR CARDIOVASCULAR EVENTS IN PLHIV

800

María Luisa Montes[1,2,4], Carmen Busca[1,2,4], Antonio Olveira[1,3], **Jose I. Bernardino[1,2,4]**, Luz Martín-Carbonero[1,2,4], Marta Abadia[1,3], Eulalia Valencia[1,2,4], Rafael Mican[1,2,4], Rocio Montejano[1,2,4], Rosa De Miguel Buckley[1,2,4], Jose R. Arribas[1,2,4], Juan González-García[1,2,4] [1]La Paz University Hospital, Madrid, Spain, [2] HIV Unit [3] Gastroenterology Service, [4]CIBERINFECC

BACKGROUND

- Metabolic dysfunction-Associated Steatosis Liver Disease (**MASLD**) is a highly prevalent condition in people living with HIV (PLHIV). Cardiovascular events, which share multiple pathways or mechanisms with MASLD, seem to depend on the presence of advanced stages of MASLD. MASLD may be even be considered as a target organ cardiovascular lesions.
- Indeed, the underlying insulin resistance and liver fibrosis have demonstrated complex interlinked connections affecting the evolution of cardiovascular damage.
- Despite numerous efforts to adapt and validate the cardiovascular risk scores, they have limitations in predicting major cardiovascular events (MACE) in PLHIV.
- Our objective is to analyze the usefulness of two easy-to-use surrogate biomarkers of hepatic steatosis-insulin resistance and liver fibrosis at cohort entry in predicting MACE in PLHIV with current metabolic abnormalities.

METHODS

- A retrospective cohort study was conducted on PLHIV receiving ART and presenting with current metabolic disorders such as metabolic syndrome, DM2, arterial hypertension, and obesity) and with clinical suspicion of MASLD.
- All Major Adverse Cardiovascular Events (MACE) occurring during the follow-up period were recorded.
- The TyG (Triglyceride-glucose) and FIB-4 indexes were calculated from the blood results obtained at the initial cohort visit.
  - TyG>4.68 was considered as severe hepatic steatosis-insulin resistance risk and high probability of metabolic syndrome development[1].

$$TyG\ index = ln[Fasting\ TG\ (mg/dL)\ x\ FPG\ (mg/dL)]/2$$

  - FIB-4 cut-off values considered for significant fibrosis were adjusted by hepatitis C virus (HCV) coinfection background: >1.3 for non-hepatitis C and >1.45 for HCV coinfected[2].

$$FIB4\ index = \frac{Age\ (years)\ x\ AST\ (UI/L)}{Platelet\ count\ (mm^3)\ x\ \sqrt{ALT\ (UI/L)}}$$

  - A combination of TyG>4.68 and FIB-4>1.3/1.45 was considered a **combined-risk index**.
  - Cox models were developed to evaluate the effect of combined-risk index in the prediction of MACE.

The combination of two "**Easy to calculate and use**" indexes **concerning liver fibrosis and hepatic steatosis-insulin resistance** in the cardiovascular risk scenario might provide a very promising clinical tool for PLHIV.

TABLE 1: Main baseline characteristics of PLHIV a the time of the initial visit in the cohort

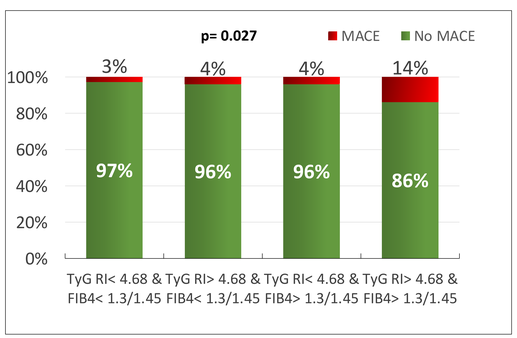
		ALL (N=370)	NO MACE (N=351)	MACE (N=19)	p
Sociodemographic variables					
Cohort entry year [a]	<= 2000	42 (11.4)	42 (12)	0 (0)	
	2001-2005	28 (7.6)	27 (7.7)	1 (5.3)	
	2006-2010	205 (55.4)	189 (53.8)	16 (84.2)	
	2010-2015	66 (17.8)	64 (18.2)	2 (10.5)	
	>= 2016	29 (7.8)	29 (8.3)	0 (0)	0.15
Current age [b] **(years)**		40 (35-45)	40 (34-45)	47 (42-57)	<0.001
Male [a]		297 (80.3)	280 (79.8)	17 (89.5)	0.4
Caucasic [a]		307 (88.2)	289 (87.6)	18 (100)	0.15
HIV related variables					
Nadir CD4+ [b] **(cells/µL)**		203 (87-304)	213 (88-314)	124 (72-208)	0.04
Time of HIV infection [b] **(years)**		6.4 (0.2-14)	6 (0-14)	12 (6-19)	0.03
Age at HIV diagnosis [b]		31 (26-38)	31 (26-37)	32 (25-52)	0.31
Stage CDC C3 [a]		59 (18.4)	50 (16.6)	9 (47.4)	<0.01
Transmission route	MSM [a]	155 (41.9)	151 (43)	4 (21.1)	0.09
	MSW [a]	84 (22.7)	82 (23.4)	2 (10.5)	0.26
	IDU [a]	113 (30.5)	102 (29.1)	11 (57.9)	0.02
	Other [a]	33 (8.9)	9 (8.2)	1 (0.05)	1
HCV coinfection [a]		96 (25.9)	87 (24.8)	9 (47.4)	0.05
Baseline analytical parameters (calculated with two consecutive measurements)					
Time (months) between two measurements [b]		4 (2-6)	4 (2-6)	5 (2-8)	0.44
Naïve at time of analysis [a]		142 (38.5)	137 (39.1)	5 (26.3)	0.34
Platelets (^3) [b]		212 (174-255)	213 (176-256)	190 (165-245)	0.33
Glucose (mg/dL) [b]		93 (87-100)	93 (87-100)	97 (93-107)	0.02
Triglycerides (mg/dL) [b]		139 (97-213)	138 (96-213)	147 (121-224)	0.21
GOT (UI/L) [b]		32 (24-46)	32 (24-46)	37 (23-41)	0.85
GPT (UI/L) [b]		38 (24-67)	38 (24-67)	38 (29-64)	0.94
TyG EH [b]		8.8 (8.4-9.2)	8.7 (8.4-9.2)	9 (8.6-9.4)	0.04
FIB4 [b]		1 (0.7-1.4)	1 (0.7-1.4)	1.3 (1-1.7)	0.02
TyG EH >= 8.38 [a]		278 (75.1)	260 (74.1)	18 (94.7)	0.05
FIB4 >1.3 / >1.45 [a, c]		109 (29.5)	99 (28.2)	10 (52.6)	0.04
Combination of TyG-FIB4 [a] **(combined-risk index)**	Both normal	62 (16.8)	62 (17.7)	0 (0)	
	High TyG/normal FIB-4	199 (53.8)	190 (54.1)	9 (47.4)	
	Normal TyG/High FIB4	30 (8.1)	29 (8.3)	1 (5.3)	
	Both high	**79 (21.4)**	**70 (19.9)**	**9 (47.4)**	**0.02**
Follow-up					
Time of follow-up until CV event [b]		175 (131-191)	178 (135-192)	129 (76-147)	<0.001
Time of follow-up until time of censured [b]		178 (138-191)	178 (135-192)	177 (159-186)	0.98

a) N (%) b) Median (P25-P75) c) FIB4 > 1.3 if HCV-; FIB4 > 1.45 if HCV+ d) N; % (IC 95%)

RESULTS

- We studied 370 subjects with a median follow-up time of 175 (p25-p75 131-191) months. Main baseline characteristics of PLHIV a the time of the initial visit in the cohort are shown in table 1.
- Retrospectively, a total of 19 MACE were registered: 8 myocardial infarction, 6 transient ischemic attack/stroke, and 5 peripheral arterial disease.
- The proportion of subjects with a high risk-combined index was 47.4% in the MACE-population, compared to 19.9% in the non-MACE-population, ($p < 0.05$). We observed that 14% (95% CI: 7%-24%) of MACE occurred within PLHIV who had a high **combined-risk index** at the beginning of their follow-up (Fig. 1).

FIGURE 1: MACE RELATED TO INDEX COMBINATION CATEGORIES



RESULTS

- Kaplan- Meier analysis revealed a significant association between a high combined-risk index at baseline and the incidence of MACE after 10 years of its detection (Fig 2).
- Factors such as age, duration of HIV infection, and abnormal TyG and FIB-4 indexes at baseline were found to be correlated with MACE.
- Cox regression model adjusted* for age, time on HIV infection, nadir CD4+ cells and HCV coinfection, the high **combined-risk index** predicted MACE with a Hazard Ratio (HR) of 2.9 (95% CI: 1.13-7.54; p = 0.03) (Table 2)

FIGURE 2: Kaplan-Meyer analysis

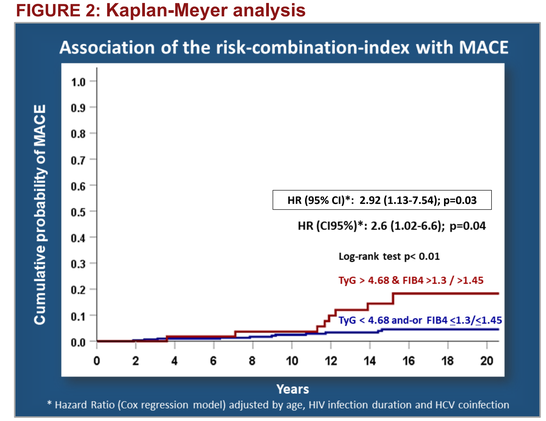


TABLE 2: Cox regression analysis

	Unadjusted		Adjusted*	
	HR (IC95%)	p	HR (IC95%)	p
Age (years)	1.13 (1.08-1.19)	0.000		
Time HIV-infection (years)	1.06 (1-1.13)	0.058		
Nadir CD4+ cells	1 (0.99-1)	0.081		
HCV infection	2 (0.81-4.94)	0.132		
TyG > 4.68	2.01 (0.72-5.57)	0.181		
FIB4 >1.3 / >1.45	2.54 (1.03-6.25)	0.043		
TyG > 4.68 & FIB4 >1.3 / >1.45	**3.78 (1.52-9.4)**	**0.004**	**2.9 (1.13-7.64)**	**0.03**

CONCLUSIONS

- The combined interpretation of TyG and FIB-4 indexes, serving as surrogate markers of hepatic steatosis-insulin resistance and a proxy for liver fibrosis, appears to hold predictive value for MACE in PLHIV.
- Based on our findings, we recommend the routine use of the **combined-risk index** in the care of PLHIV with metabolic disorders. These biomarkers could contribute to a more comprehensive assessment of cardiovascular risk and aid in the early identification of individuals who may be at a higher risk of major cardiovascular events.

[1]Fernando Guerrero-Romero et al. J Clin Endocrinol Metab, 2010 Jul;95(7):3347-51. doi: 10.1210/jc.2010-0288. Epub 2010 May 19.
[2]EASL CPG. J Hepatol. 2021 Sep;75(3):659-689. doi: 10.1016/j.jhep.2021.05.025.Epub 2021 Jun 21.

ADDITIONAL KEY INFORMATION Author contact: mluisa.montes@salud.madrid.org