Lack of prediction of fragility fractures by risk assessment tools in a cohort of people with HIV

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INTRODUCTION

PWH have a higher age-stratified incidence rate of fractures than the general population which are associated with hospitalizations, detrimental quality of life, excess costs, and death.

In PWH, fragility fractures occur at an earlier age, increasing the individual and social impact of these outcomes.

Current European and Spanish national guidelines recommend screening people with HIV (PWH) for bone disease using predictive tools developed for the general population, though data on PWH are scarce.

OBJECTIVE

We assessed the accuracy of FRAX and Qfracture scoring systems to predict the occurrence of fragility fractures in a Spanish national cohort of PWH.

METHODS

- Prospective cohort of 17,671 adults with HIV infection of the AIDS Research Network (CoRIS) in Spain during 2004-2019.
- Exclusion criteria:
  - Individuals <30 years-old,
  - Incomplete data for scores calculation,
  - No data on non-AIDS events and bone fractures during follow-up.
- Censored: first event of **fragility fracture**, lost to follow-up, or death.
- We calculated the 10-year KM survival estimates of fragility fractures during follow-up and computed the 10-year risk of fracture by **FRAX** and **Qfracture** scores at cohort inclusion.
- Discriminatory measures and calibration (observed to expected ratios, O/E) were calculated by quintiles of risk and age.
  - Spanish recommended assessment thresholds (3% and 10% risk of hip and major osteoporotic fractures at 10 years, respectively) were also applied to assess FRAX discrimination and calibration.

RESULTS

Table 1. Baseline characteristic of the population according to the presence of fragility fractures.

	Total population (n=6,080)	No fracture (n=5,967)	Fragility fracture (n=113)	p-value
Age, mean (SD)	41 (9.0)	41.1 (8.8)	50.0 (11.1)	<0.001
Female gender, n (%)	927 (15.2)	899 (15.1)	28 (24.8)	0.004
Alcohol use, n (%)	380 (6.2)	348 (5.8)	32 (28.3)	<0.001
Active smoking, n (%)	2,467 (40.6)	2,409 (40.4)	58 (51.3)	0.019
BMI, median (IQR)	24.2 (22.1, 26.8)	24.2 (22.1, 26.8)	24.1 (22.5, 26.5)	0.750
Prior fragility fracture, n (%)	5 (0.1)	5 (0.1)	0 (0)	0.760
Nadir CD4 cell count, median (IQR)	289 (146, 431)	291 (149, 434)	154 (58, 281)	<0.001
Time of HIV diagnosis [years], median (IQR)	7.1 (3.5, 11.6)	7.1 (3.5, 11.7)	5.9 (2.5, 9.2)	0.004
Ethnicity, n (%)				
White or not stated	5,600 (92.1)	5492 (92.0)	108 (95.6)	0.960
Asian	23 (0.4)	23 (0.4)	0 (0)	
Black	457 (7.5)	452 (7.6)	5 (4.5)	
Cancer history, n (%)	123 (2.1)	117 (2.0)	6 (5.3)	0.012
Chronic kidney disease, n (%)	13 (0.2)	12 (0.2)	1 (0.9)	0.120
Cardiovascular disease, n (%)	176 (2.9)	169 (2.8)	7 (6.2)	0.035
COPD, n (%)	41 (0.7)	40 (0.7)	1 (0.9)	0.780
Chronic liver disease, n (%)	392 (6.4)	369 (6.2)	23 (20.4)	<0.001
Diabetes mellitus, n (%)	94 (1.6)	92 (1.5)	2 (1.8)	0.850
Other endocrine disorders, n (%)	11 (0.2)	9 (0.2)	2 (1.8)	<0.001
Use of immunosuppressors (RA/SLE proxy), n (%)	6 (0.1)	5 (0.1)	1 (0.9)	0.007
Use of glucocorticoids, n (%)	10 (0.2)	10 (0.2)	0 (0.0)	0.660

- During a follow-up time of 42,411.55 person-years, 113 first episodes of fragility fractures were recorded (86 major osteoporotic fractures, 11 hip fractures).

Figure 1. Kaplan-Meier curves for fragility fracture-free probabilities for PWH by gender.

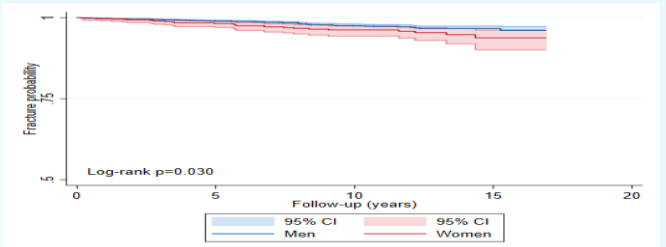

Table 3. Calibration of 10-year observed versus predicted fragility fracture rates, by quintile of predicted risk groups

	Major osteoporotic fractures						Hip fractures			
Quintile	Cut off	Fractures n=86	10-year observed rate [%] (95%CI)	Mean predicted risk (%)	O/E ratio	Cut off	Fractures n=11	10-year observed rate [%] (95%CI)	Mean predicted risk [%]	O/E ratio
FRAX										
1	--	10	1.65 (0.74,3.7)	1.64	1.01	--	0	0	0.10	0
2	1.8	1	0.23 (0.03, 1.64)	1.8	0.13	0.2	2	0.13 (0.02, 0.9)	0.2	0.65
3	1.9	22	3.6 (1.77, 7.28)	2.39	1.51	0.3	0	0	0.3	0
4	2.7	3	1.38 (0.4, 4.71)	2.7	0.51	0.4	3	1.92 (0.53, 6.87)	0.47	4.11
5	2.8	50	19.34 (13.44, 27.37)	4.19	4.62	0.6	6	3.9 (1.61, 9.25)	1.34	2.91
QFracture										
1	--	3	0.52 (0.16, 1.64)	0.36	1.44	--	0	0	0.02	0
2	0.46	6	0.78 (0.18, 3.26)	0.50	1.56	0.03	0	0	0.04	0
3	0.55	13	4.19 (1.94, 8.95)	0.61	6.90	0.05	1	0.13 (0.02, 0.92)	0.06	2.25
4	0.68	11	3.11 (1.45, 6.58)	0.81	3.82	0.07	1	0.68 (0.1, 4.76)	0.10	6.60
5	1.02	53	14.58 (10.15, 20.71)	2.08	7.00	0.15	9	2.79 (1.24, 6.25)	0.54	5.19

- For both tools, observed to expected ratios increased as the risk increased and in almost all age groups.

Table 2. Discriminatory measures of FRAX and QFracture using recommended thresholds and top 10% risk cut-offs for each tool

	Major osteoporotic fracture			Hip fracture		
	FRAX[a]	FRAX[b]	QFracture[c]	FRAX[a]	FRAX[b]	QFracture[c]
AUC	0.53 (0.50-0.55)	0.66 (0.61-0.71)	0.67 (0.62-0.73)	0.54 (0.45-0.63)	0.72 (0.57-0.88)	0.81 (0.68-0.95)
Sensitivity	5.81 (1.91-13)	41.9 (31.3-53)	44.2 (33.5-55.3)	9.09 (0.23-41.3)	54.5 (23.4-83.3)	72.7 (39.0-94.0)
Specificity	99.9 (99.8-100)	90.6 (89.8-91.3)	90.6 (89.9-91.4)	99.5 (99.3-99.7)	90.1 (89.3-90.9)	90.1 (89.4-90.9)
PPV	55.6 (21.2-86.3)	5.99 (4.23-8.2)	6.34 (4.53-8.6)	3.13 (0.08-16.2)	0.99 (0.36-2.14)	1.32 (0.57-2.58)
NPV	98.7 (98.3-98.9)	99.1 (98.8-99.3)	99.1 (98.8-99.4)	99.8 (99.7- 99.9)	99.9 (99.8- 100)	99.9 (99.8-100)

AUC = area under the curve; NPV = negative predictive value; PPV = positive predictive value.
Values are percentages (95% confidence interval).
a Using recommended assessment thresholds for PWH (FRAX scores ≥10 for major osteoporotic fracture and ≥3 for hip fracture).
b Using top 10% risk as thresholds (3.7 for major osteoporotic fracture and 0.6 for hip fracture).
c Using top 10% risk as thresholds (1.6 for major osteoporotic fracture and 0.3 for hip fracture).

Figure 2. Calibration of the observed fragility fracture rates (black, expressed as percentages with 95% confidence interval) versus FRAX (light grey) and Qfracture (dark grey) estimated risks, by age. A) mayor osteoporotic fractures, B) hip fractures.

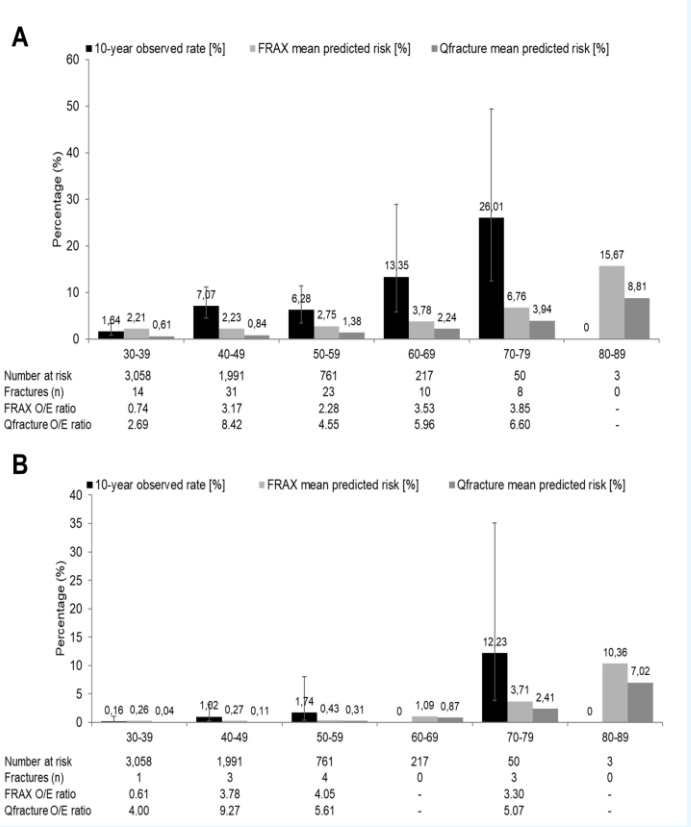

Table 4. Calibration of 10-year observed versus predicted fragility fracture rates using recommended assessment thresholds in PWH

Risk category	Cut-off	Incident cases (%)	10-year observed rate [%] (95% CI)	Mean predicted risk [%]	O/E ratio
Major osteoporotic fractures					
Low	--	81 (94.19)	4.56 (3.33, 6.23)	2.37	1.92
High	10	5 (5.81)	81.48 (44.98, 99.14)	15.0	5.43
Hip fractures					
Low	--	10 (90.91)	0.67 (0.31,1.46)	0.32	2.09
High	3	1 (9.09)	7.69 (1.12, 43.36)	5.94	1.29

- When using the recommended assessment thresholds, less than 6% and 10% of major osteoporotic and hip fractures would have been identified, respectively.

CONCLUSIONS

FRAX and Qfracture displayed similar discriminative capacity in PWH compared with studies in the general population. However, the tools significantly underestimated the risk of fractures in PWH. The recommended assessment thresholds were not able to identify fragility fractures during follow-up. A fracture prediction tool developed for PWH is needed.

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