Predictive biomarkers of treatment toxicity in geriatric oncology

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Predictive biomarkers of toxicity in oncogeriatric patients

NUTRITION Albumin	**INFLAMMATION** CRP, LDH
BLOOD CELLs Hb, Lympho	**KIDNEY** Creatinine clearance

Picard, 2015; Falandry, 2013; Retornaz, 2020, Extermann, 2012; Hurria, 2011; Frelaut, 2023.

Predictive biomarkers of toxicity in oncogeriatric patients

NUTRITION

INFLAMMATION

What about the liver ?

Hb, Lympho

Creatinine clearance

Picard, 2015; Falandry, 2013; Retornaz, 2020, Extermann, 2012; Hurria, 2011; Frelaut, 2023.

Why should we consider the liver in oncogeriatric patients ?

1. Aging is a major risk factor for liver diseases

North America
24.1%
In T2DM (US)
51.8%

Europe
23.7%
In T2DM
68.0%

Middle East
31.8%
In T2DM
67.3%

Asia
27.4%
In T2DM
52.0–57.9%

South America
30.5%
In T2DM
56.8%

Africa
13.5%
In T2DM
30.4%

Worldwide prevalence of NAFLD is 25%

Worldwide prevalence of NAFLD among people with T2DM is 55.5%

Prevalence of NASH in general population is between 1.5–6.5%
Prevalence of NASH among T2DM is 37.3% (24.7-50.0%)

Younossi ZM. *J Hepatol*. 2019.   NAFLD, Nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis
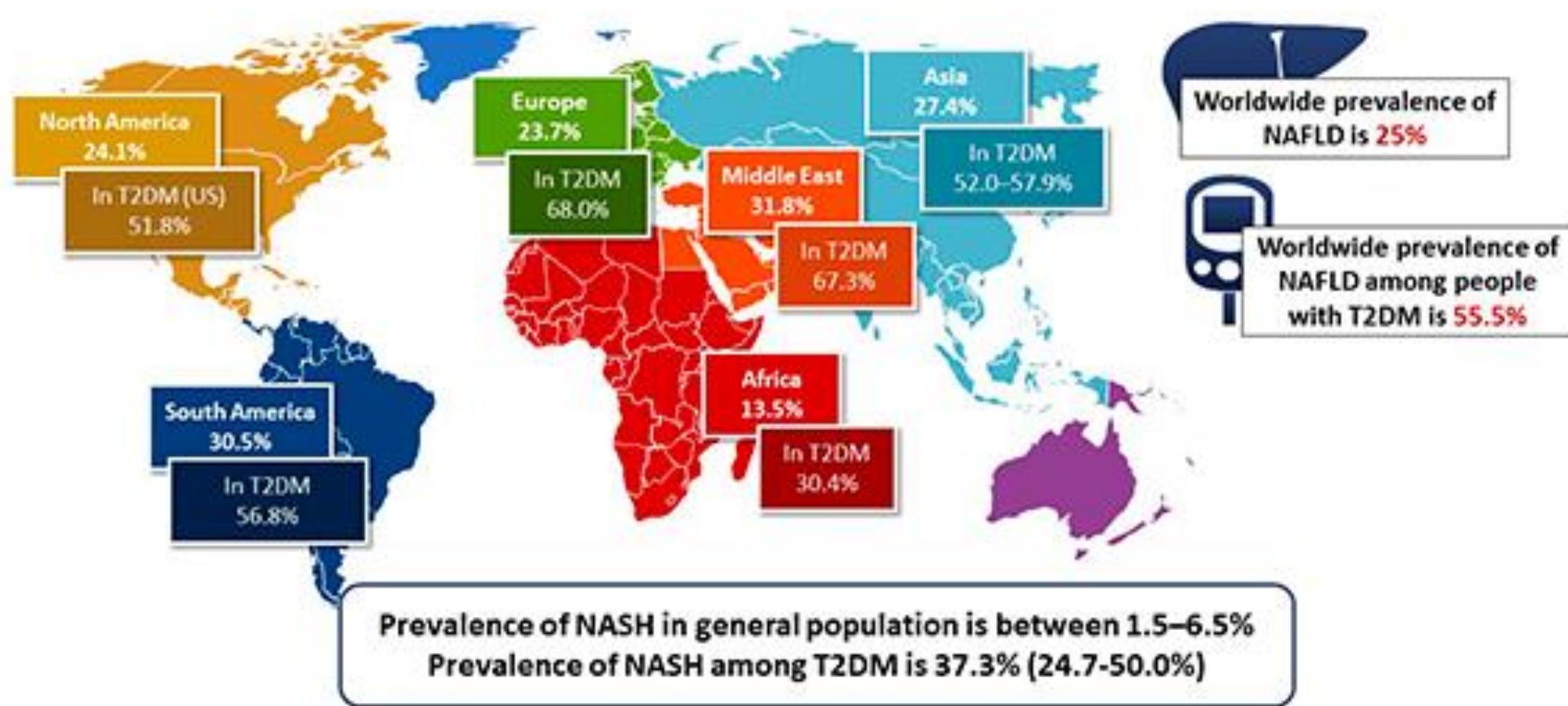
Why should we consider the liver in oncogeriatric patients ?

1. <u>Aging is a major risk factor for liver diseases</u>

2. <u>The liver is altered during aging</u>

↓ size (20 to 40%)

↓ transaminases levels → normal rang of ALT ?

↓ portal flow

↓ Hepatic metabolism → ↓ drug clearance

↓ regeneration capacity → ↓ capacity to regenerate after an acute stress

Elkrief et al, 2016; Guido et al 2016, Wanless et al 1990, Nakunama et al, 1990; Barge et al 2016

Why should we consider the liver in oncogeriatric patients ?

1. <u>Aging is a major risk factor for liver diseases</u>

2. <u>The liver is altered during aging</u>

3. <u>Oncologic treatments and liver toxicity</u>

Oxaliplatin (sinusoidal obstruction syndrome)

Imatinib (hepatic necrosis)

Gemtuzumab (sinusoidal obstruction syndrome)

Immune checkpoint inhibitors (autoimmune hepatitis)

… → drug induced liver injury

Loriot, 2008; Belli, 2018; De Martin, 2020

What kind of liver markers should we use?

Biomarkers

Monomarkers
ALT, Bilirubin...

Scores
FIB-4, ALBI-score, Fibrotest...

Morphological markers

Elastometry (Fibroscan) *No data available*

CT Scan : *In progress (ELCAPA-Liver CT Scan)*
Liver size (correlated with liver function)
Liver nodularity (Sartoris, 2018)
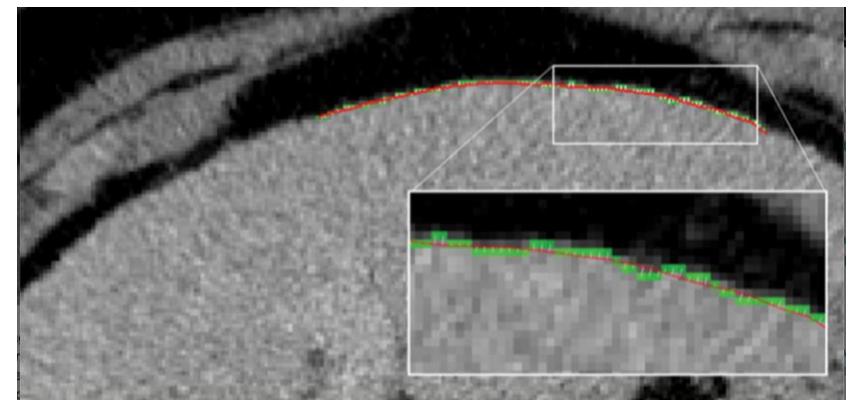
What kind of liver markers should we use?

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$$\text{FIB}-4\ \text{index}= \frac{Age\ (\text{years}) \times \text{AST}\ (\text{UI/L})}{\text{Platelet count(G/L)} \times \sqrt{\text{ALT (UI/L)}}}$$

ALBI-score =

(log10 bilirubine [μmol/L] x 0.66) + (albumine [g/L] x -0.085)

Morphological markers

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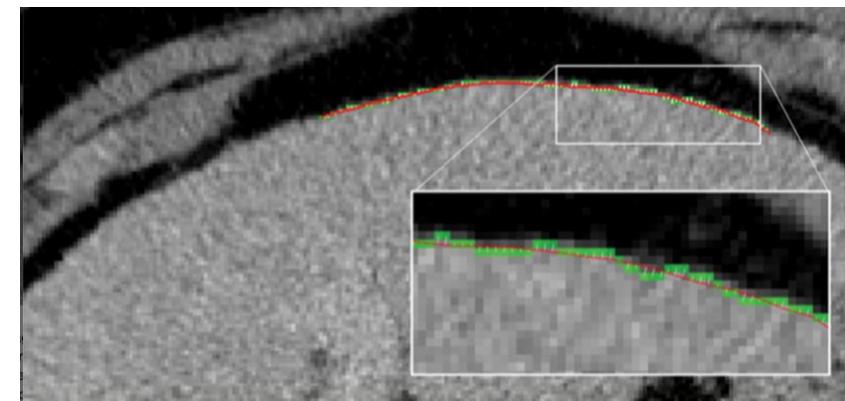
Liver biomarkers and treatment toxicity in general oncology

- ALT alone : not predictive

- AST/ALT (de Ritis index) : Associated to mortality. Not toxicity

- Bilirubin : Mortality only

- Scores (FIB-4, ALBI-score): OS, PFS in liver cancer (HCC and metastasis), but also other type of cancer and treatments

Immune checkpoint inhibitors (ICIs) in non-small cell lung cancer
Matsukane, 2021

Urothelial carcinoma patients treated with pembrolizumab
Kawashima, 2021
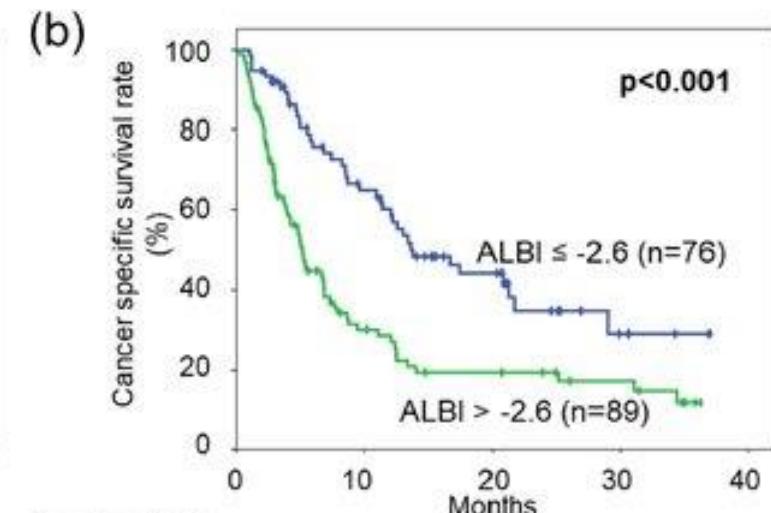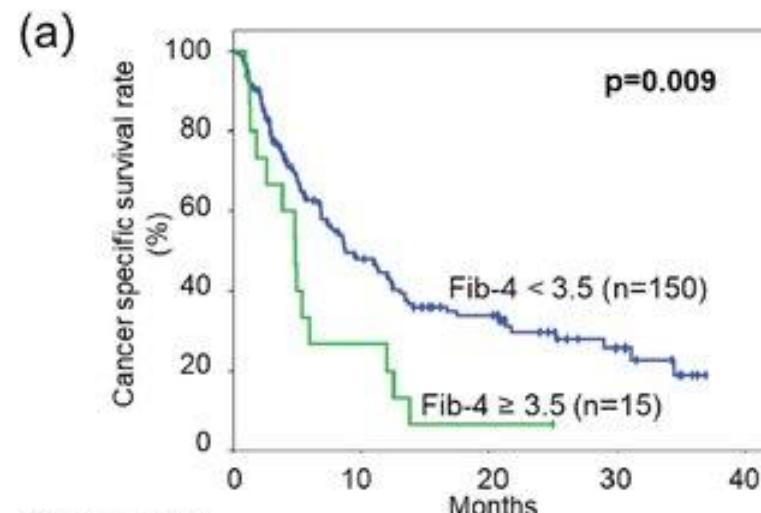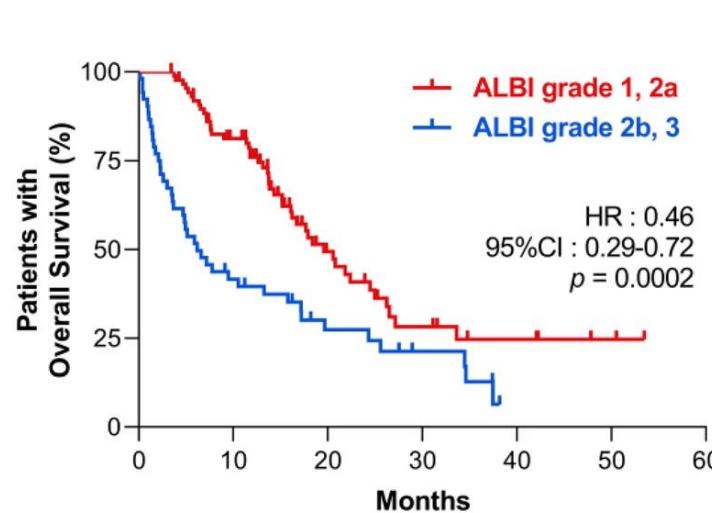
Liver biomarkers and toxicity in older patients with cancer: ELCAPA-LIVER
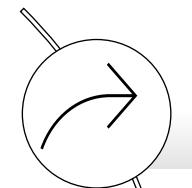
Prospective

ELCAPA cohort
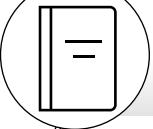
Multicentric (n = 8)
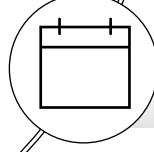
Sept. 2015 to march 2019

Inclusion criteria

Patients 70 yo or older

Solid cancer or hematological malignancy

Geriatric evaluation

Before a new treatment *(chemotherapy, targeted therapy or immunotherapy)*

Available liver biomarkers

Exclusion criteria

Known liver diseases

Liver biomarkers and toxicity in older patients with cancer: ELCAPA-LIVER

FIBROSIS-4 INDEX (FIB-4)

$$\frac{Age\ (years) \times AST\ (UI/L)}{Platelet\ count(G/L) \times \sqrt{ALT\ (UI/L)}}$$
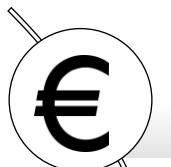
€ Simple and low cost

Only score validated in geriatric patients

Low risk (2) or high risk (2.67) of fibrosis

Predictive of overall mortality in general population

Predictive of overall mortality and dependance in geriatric population

EASL, J Hepatol, 2021; Unalp Arida A et al, 2017; McPherson et al, 2017; De Vincentis A et al, 2019; Kim D et al, 2013

ELCAPA-LIVER: Flow chart

Patients eligible for the ELCAPA-LIVER study
N = 1175

Excluded (**N = 186**)

N = **24 :** chronic liver diseases
N = **160 :** missing data for FIB4 estimation
N = **2** : Lost of follow-up

Patients included in the ELCAPA-LIVER study
N = 989

6-month mortality
N = 989

Cancer treatments grade III/IV toxicity
N = 601 (735 lines)

Unpublished data

ELCAPA-LIVER: Patients characteristics

- median age: 81 years (IQR: 77-84); female: 59%

- main cancer sites:

    digestive 29%, gynecological 28%, urinary tract 14% and lung 12%

- metastatic diseases: 63%, liver metastasis: 35%

- body Masse Index < 22: 29%

- diabetes mellitius: 19%

FIB 4		
<2	2-2,67	>2.67
N = 601	N= 172	N = 216

Unpublished data

ELCAPA-LIVER: FIB-4 and overall mortality

Multivariate analysis

Variables		aHR (CI 95%)	p-value
Cancer site			
	Digestive cancer	Ref	0.014
	Gynecological cancer	0.58 (0.36-1.94)	
	Urinary tract cancer	0.90 (0.58-1.41)	
	Lung cancer	1.44 (0.90-2.17)	
	Other cancer	0.94 (0.58-1.53)	
Metastasis (N=908)		2.94 (1.92-4.51)	<0.0001
Chronic heart failure (N=976)		1.84 (1.12-3.02)	0.017
CRP (N=781)		1.08 (1.05-1.10)	<0.0001
FIB-4 score	<2	Ref	0.028
	>2 & < 2.67	0.95 (0.63-1.45)	
	> 2.67	1.55 (1.10-2.20)	0.013

Mean follow up : 28 mois

22% of deceased patient at 6 month (n=226)

aHR = 1.55 (1.09-2.19) *p =0.013*

*

FIB-4 <2   FIB-4 2-2.67
FIB-4 >2.67
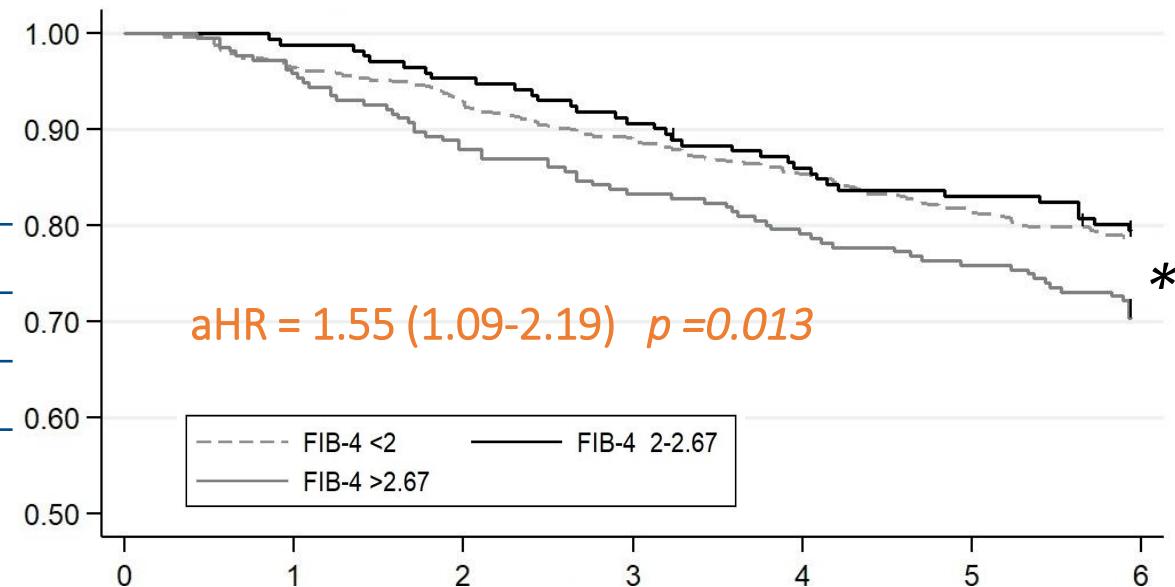
Unpublished data

ELCAPA-LIVER: FIB-4 and treatment toxicity

Treatment duration: 3.8 month (IQR 2.1-5.9)

Chemotherapy : 85%, **Targeted therapy**: 9.7%, **Immunotherapy** : 4.7%

First line: 48.5%

	All cohorte	FIB-4 < 2 (N=356)	FIB-4 2- 2.67 (N=105)	FIB-4 > 2.67 (N=140)	p
Toxicities grade III/IV (N=601)	355 (59.1%)	202 (56.7)	66 (62.9)	87 (62.1)	0.37
Hematological toxicities grade III/IV (N=550)	**123 (22.4%)**	**54 (16.9)**	**26 (26.8)**	**43 (32.3)**	**0.001**
Non hematological toxicities (N=545)	293 (53.8%)	176 (54.3)	53 (57.6)	64 (49.6)	0.48

Unpublished data

ELCAPA-LIVER: FIB-4 and hematological toxicities

Univariate analysis

	Toxicités III/IV	ORa (CI 95%)	p
Age	79 (75-84)	0.96 (0.93-0.99)	0.046
Pulmonary CD.	3 (2.5)	0.26 (0.08-0.85)	0.026
Place of treat.			
HDJ	82 (67.2)	1(ref)	
Domicile	30 (24.6)	2.13 (1.28-3.53)	0.006
Hospitalisation	10 (8.2)	0.75 (0.37-1.54)	
Hemoglobin	9.6 (8.1-10.7)	0.58 (0.50-0.68)	<0.0001
Platelets	243 (182-313)	0.98 (0.96-0.99)	0.038
FIB-4 index	2.1 (1.35-3.36)	1.03 (1.00-1.06)	0.097
<2	54 (43.9)	Ref	Ref
2-2.67	26 (21.1)	1.80 (1.06-3.08)	0.031
> 2.67	43 (35.0)	2.35 (1.48-3.75)	<0.001

Multivariate analysis

Variables		aOR (CI 95%)	p-value
Chronic pulmonary disease (N=544)		**0.32 (0.09-1.11)**	**0.073**
Baseline Hemoglobin (N= 540)		**0.59 (0.51-0.69)**	**<0.0001**
FIB-4 score	**<2**	**Ref**	**0.024**
	>2 & < 2.67	**1.75 (0.98-3.09)**	
	> 2.67	**1.92 (1.15-3.22)**	

FIB-4 isolated variables
Not significant (platelets)

Unpublished data

LIVER biomarkers in geriatric oncology

$$\text{FIB}-4 \text{ index} = \frac{Age \text{ (years)} \times \text{AST (UI/L)}}{\text{Platelet count(G/L)} \times \sqrt{\text{ALT (UI/L)}}}$$

Commonly used in general oncology
No specific study in oncogeriatry

Associated to overall mortality only
(ELCAPA-Liver)
Lot of missing data (ELCAPA-LIVER)
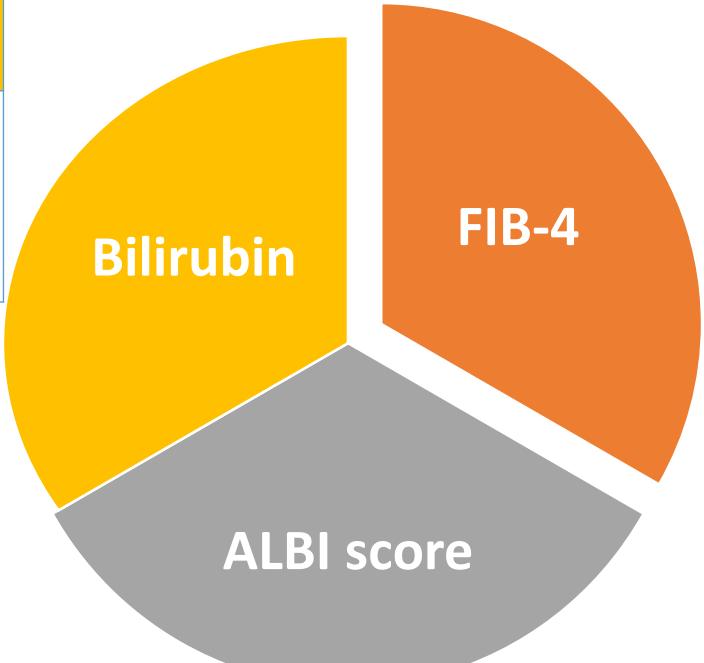
Fibrosis biomarker
Predictive of mortality in oncology

No study in oncogeriatry

Associated to overall mortality
And hematological toxicities
(ELCAPA-LIVER)

Bilirubin

FIB-4

ALBI score

ALBI-score =

(log10 bilirubine [µmol/L] x 0.66)
+ (albumine [g/L] x -0.085)

Predicitive of overall mortality in oncology
Albumin dependant
No study in oncogeriatry

Associated to overall mortality only (ELCAPA-LIVER)
Lot of missing data (ELCAPA-LIVER)

Litterature

ELCAPA LIVER

Retornaz F et al, Oncol, 2020
De Vincentis A et al, Dig Liv Dis, 2019
McPherson et al, AJG, 2017
Ong KL et al, NHANES, 2014

Take home message
Biomarkers and toxicities in geriatric oncology

- Nutrition biomarkers = most consistant in the litterature

- Hematological, inflammation, kidney = frequently used

- Liver diseases = underestimated and underdiagnosed in geriatric population

- Liver biomarkers = predictive of mortality and hematological toxicities

- FIB-4 score > 2.67 → ⚠️ Liver evaluation before a new cancer treatment +++

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