

GRELL & ENCR

2025 Scientific Meeting Porto, Portugal

27-30 MAY



HEPATOCELULAR CARCINOMA ETIOLOGY IN MADEIRA ISLANDS, PORTUGAL

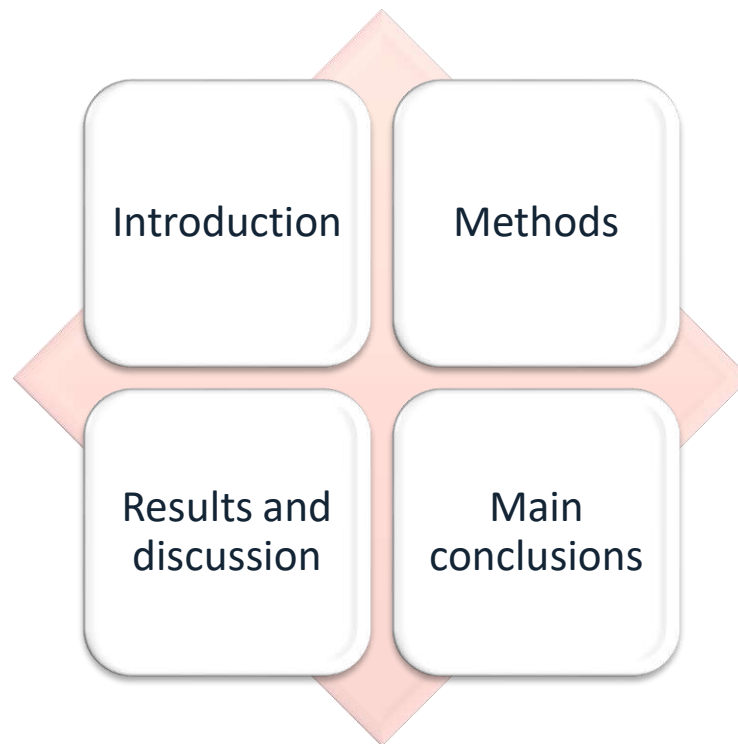
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Overview



Introduction

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GLOBAL CANCER STATISTICS 2022

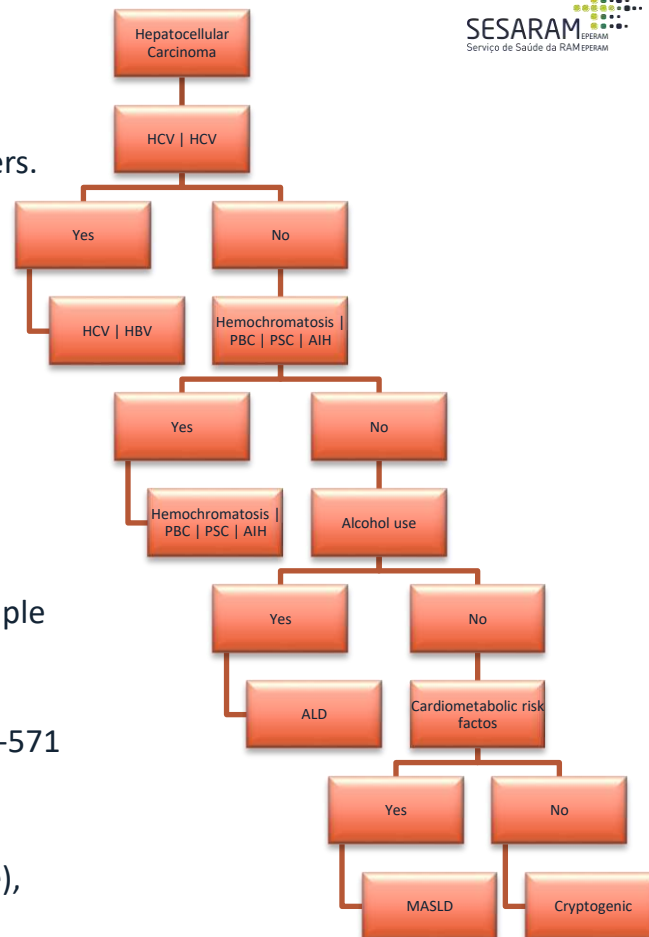
TABLE 1 New cases and deaths for 36 cancers and all cancers combined in 2022.

Cancer site	Incidence			Mortality		
	Rank	New cases	% of all sites	Rank	Deaths	% of all sites
Lung	1	2,480,301	12.4	1	1,817,172	18.7
Female breast	2	2,308,897	11.6	4	665,684	6.9
Colorectum	3	1,926,118	9.6	2	903,859	9.3
Prostate	4	1,466,680	7.3	8	396,792	4.1
Stomach	5	968,350	4.9	5	659,853	6.8
Liver	6	865,269	4.3	3	757,948	7.8
Thyroid	7	821,173	4.1	24	47,485	0.5
Cervix uteri	8	661,021	3.3	9	348,189	3.6
Bladder	9	613,791	3.1	13	220,349	2.3
Non-Hodgkin lymphoma	10	553,010	2.8	11	250,475	2.6
Esophagus	11	510,716	2.6	7	445,129	4.6
Pancreas	12	510,566	2.6	6	467,005	4.8
Leukemia	13	486,777	2.4	10	305,033	3.1

Portugal: 1740 new cases and 1611 deaths in 2022

Madeira islands: liver cancers ranks 10 in incidence

- Hepatocellular carcinoma (HCC) accounts for >75% of liver cancers.
- Unlike most cancers, it occurs in an already damaged organ.
- It is highly lethal, therefore the need of a better understanding.
- HCC is mainly caused by 4 modifiable etiologies
 - ALD – Alcohol
 - HCV – Hepatitis C virus
 - HBV – Hepatitis B virus
 - MASLD – Metabolic dysfunction-associated steatotic liver disease
- Cancer registries do not routinely collect data on these variables
- To classify our HCC population by etiology we followed the example of a few scientific papers on this subject:
 - Beste L, et al. Gastroenterology. 2015. 149(6):1471-1482
 - Pinheiro P, et al. Clin Gastroenterol Hepatol. 2024. 22(3):562-571
 - Welzel T, et al. Am J Gastroenterol. 2013. 108:1314–1321
 - Makarova-Rusher O, et al. Cancer. 2016. 122:1757–1765
- **Main objective:** Distribution of cases by etiology, incidence (rate), and trends of HCC cases in Madeira islands.



Adapted from doi: 10.1053/j.gastro.2015.07.056

Methods

Subjects

- **Madeira residents** diagnosed with **hepatocellular carcinoma** between **2010-2023**.
- HCC only. Morphologies collected: 8000-8010, 8170-8180.

Data

- Platform of the **National Cancer Registry** database (**RON**).
- Etiology **completeness**:
 - Medical reports
 - Serological tests:
 - HCV and HBV: HCV RNA+, anti-HCV (+), anti-HBVC (+), anti-HBVe (+), AgHBVs (+), AgHBVe (+), and an anti-HBVs (-) confirmed a never infected case
 - Diabetes, Dyslipidemia
- Discharge data (ICD-9 and -10 codes) also used to classify HCV and HBV.
- If steatosis was not mentioned and not confirmed by biopsy or image exams, it was considered when the patient had: obesity, diabetes, or dyslipidemia + hypertension.

Software

- **Joinpoint 5.3** for annual percentage trends.

Main sex differences:

- Males are more affected by ALD
- Females are more affected by MASLD

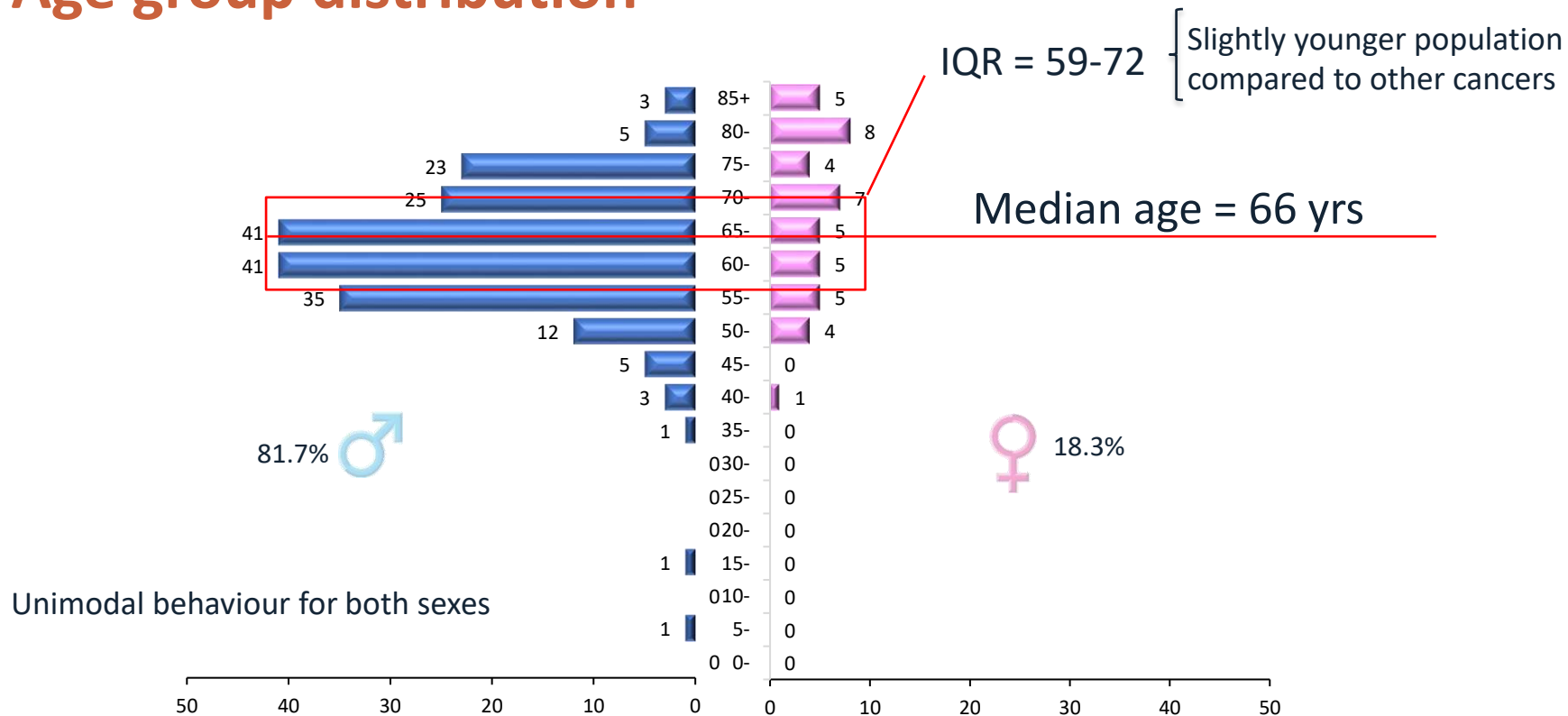
HCC group characteristics

Characteristic	All causes	HCV	HBV	HCV-HBV	ALD	MASLD	Other	Cryptogenic
Total (%)	240 (100%)	20 (8.3%)	31 (12.9%)	17 (7.1%)	120 (50%)	41 (17.1%)	2 (0.8%)	9 (3.8%)
Age (mean; median [IQR])	65.4; 66 (13)	58.8; 58 (9.5)	63.6; 66 (13)	59.9; 61 (5)	65.1; 66 (11)	72.9; 73 (17)	39; 39 (48)	73.8; 81 (9)
Gender								
Male	196 (100%)	15 (7.7%)	24 (12.2%)	16 (8.2%)	116 (59.2%)	18 (9.2%)	2 (1%)	5 (2.6%)
Female	44 (100%)	5 (11.4%)	7 (15.9%)	1 (2.3%)	4 (9.1%)	23 (52.3%)	0 (0%)	4 (9.1%)
Alcohol use	170 (100%)	13 (7.6%)	23 (13.5%)	13 (7.6%)	120 (70.6%)	0 (0%)	1 (0.6%)	0 (0%)
Substance abuse	11 (100%)	4 (36.4%)	0 (0%)	7 (63.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Obesity	68 (100%)	1 (1.5%)	8 (11.8%)	5 (7.4%)	33 (48.5%)	21 (30.9%)	0 (0%)	0 (0%)
Diabetes	110 (100%)	7 (6.4%)	8 (7.3%)	7 (6.4%)	54 (49.1%)	33 (30%)	1 (0.9%)	0 (0%)
Dyslipidemia	127 (100%)	7 (5.5%)	18 (14.2%)	7 (5.5%)	60 (47.2%)	32 (25.2%)	1 (0.8%)	2 (1.6%)
Hypertension	156 (100%)	8 (5.1%)	17 (10.9%)	11 (7.1%)	78 (50%)	38 (24.4%)	1 (0.6%)	3 (1.9%)
Steatosis	55 (100%)	4 (7.3%)	8 (14.5%)	6 (10.9%)	19 (34.5%)	18 (32.7%)	0 (0%)	0 (0%)
Stage								
Stage I	49 (100%)	3 (6.1%)	7 (14.3%)	4 (8.2%)	24 (49%)	9 (18.4%)	1 (2%)	1 (2%)
Stage II	35 (100%)	3 (8.6%)	3 (8.6%)	0 (0%)	22 (62.9%)	5 (14.3%)	0 (0%)	2 (5.7%)
Stage III	94 (100%)	8 (8.5%)	13 (13.8%)	8 (8.5%)	45 (47.9%)	18 (19.1%)	1 (1.1%)	1 (1.1%)
Stage IV	59 (100%)	5 (8.5%)	8 (13.6%)	5 (8.5%)	27 (45.8%)	9 (15.3%)	0 (0%)	5 (8.5%)
Unknown	3 (100%)	1 (33.3%)	0 (0%)	0 (0%)	2 (66.7%)	0 (0%)	0 (0%)	0 (0%)

Non-Portuguese Natality (4.6% of all cases):

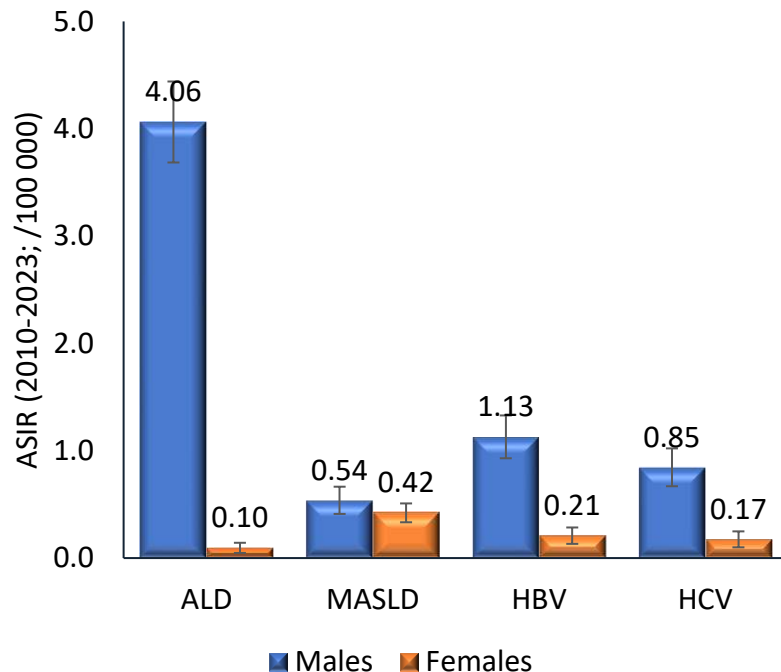
82% had 1 type of viral hepatitis.

Age group distribution



Incidence rate by cause and sex

GBD comparison



Group	No. cases	Rate (/100000; 95% CI)	GBD (PT), 2010-2021
Both sexes	240	3.5±0.2 (3.1-4.0)	4.1-4.9/100 000
HCC – ALD	120	1.8±0.2 (1.5-2.1)	1.6-2.0/ 100 000
HCC – MASLD	41	0.5±0.1 (0.3-0.6)	0.3/ 100 000
HCC – HBV	40	0.6±0.1 (0.4-0.8)	0.6-0.7/ 100 000
HCC – HCV	29	0.5±0.1 (0.3-0.7)	1.4-1.6/ 100 000
Males	196	6.9±0.5 (5.9-7.9)	6.8-8.3/ 100 000
HCC – ALD	116	4.1±0.4 (3.3-4.8)	3.2-4.1/ 100 000
HCC – MASLD	18	0.5±0.1 (0.3-0.8)	0.4/ 100 000
HCC – HBV	32	1.1±0.2 (0.7-1.5)	1.1-1.3/ 100 000
HCC – HCV	23	0.9±0.2 (0.5-1.2)	1.8-2.3/ 100 000
Females	44	0.9±0.1 (0.7-1.2)	1.9-2.0/100 000
HCC – ALD	4*	0.1±0.1 (0-0.2)	0.3-0.4/ 100 000
HCC – MASLD	23	0.4±0.1 (0.3-0.6)	0.2/ 100 000
HCC – HBV	8*	0.2±0.1 (0.1-0.4)	0.2/ 100 000
HCC – HCV	6*	0.2±0.1 (0.0-0.3)	1.0/ 100 000

* Few cases. Read with care!

- Differences mainly includes females and HCV etiology.

Incidence rate by cause and sex

Other studies

Group (US2000)	No. cases	Madeira islands	Florida, US (2010-18) ⁺	California, US (2010-18) [#]
Both sexes	240	5.7/ 100 000		
HCC – ALD	120	2.8/100 000		
HCC – MASLD	41	1.0/100 000		
HCC – HBV	40	0.9/100 000		
HCC – HCV	29	0.7/100 000		
Males	196	10.9/100 000 ↑	8.8/100 000	9.2/100 000
HCC – ALD	116	6.3/100 000 ↑↑	1.3/100 000	1.4/100 000
HCC – MASLD	18	1.2/100 000 ↓	2.2/100 000	2.1/100 000
HCC – HBV	32	1.8/100 000 ↑↑	0.2/100 000	0.3/100 000
HCC – HCV	23	1.2/100 000 ↓↓	4.4/100 000	4.8/100 000
Females	44	1.8/100 000 ↓	2.2/100 000	2.6/100 000
HCC – ALD	4*	0.2/100 000 ≡	0.3/100 000	0.2/100 000
HCC – MASLD	23	0.9/100 000 ≡	0.7/100 000	0.8/100 000
HCC – HBV	8*	0.3/100 000 ↑↑	0.0/100 000	0.0/100 000
HCC – HCV	6*	0.3/100 000 ↓↓	0.9/100 000	1.1/100 000

*Few cases. Read with care!

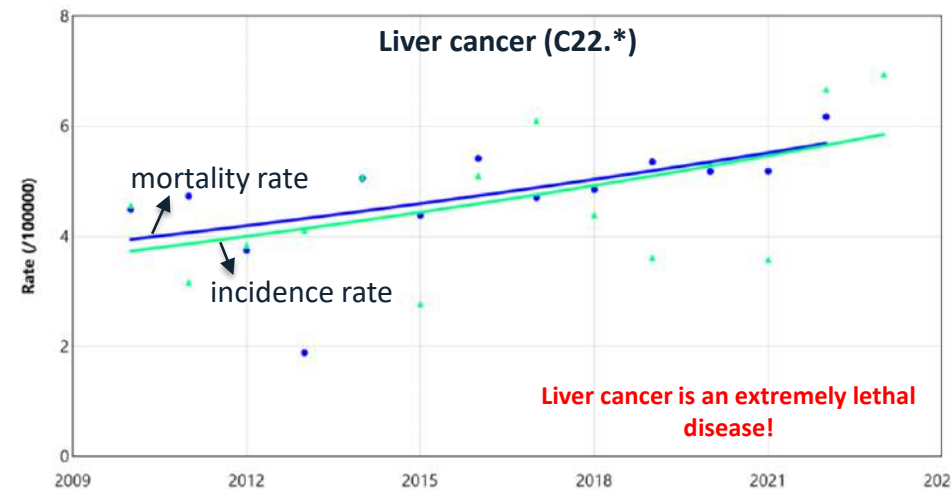
⁺ Whites; doi: 10.1016/j.j.cgh.2023.08.016

[#] Whites; doi: 10.1001/jamanetworkopen.2025.2208

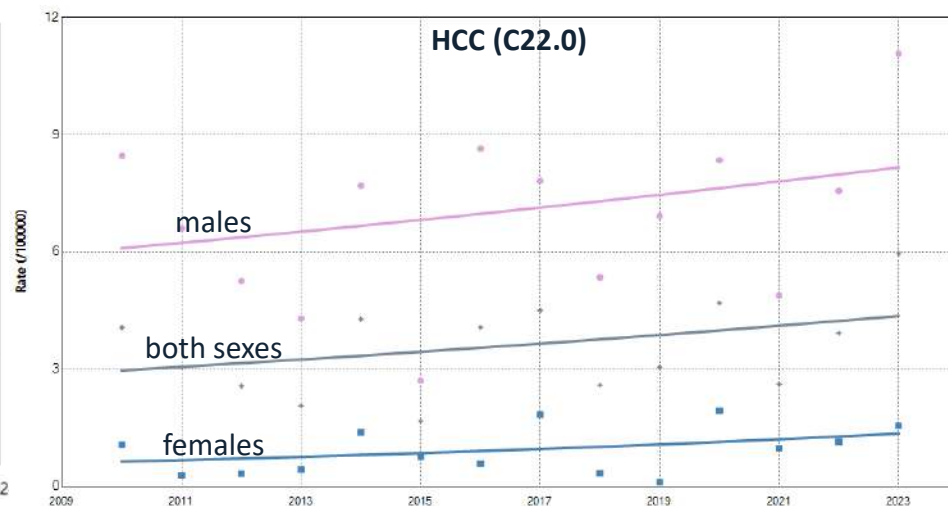
↑ Higher; ↑↑ Much higher (>3x)

↓ Lower; ↓↓ Much lower (<3x)

Incidence and mortality rate trends



Group (C22.*)	Years	AAPC	95% CI	P-value
Incidence (males and females) 2010-2023		3.52	0.05-7.12	.047
Incidence (males)		2.43	-1.05-6.04	.156
Incidence (females)		6.16	-2.55-15.66	.154
Mortality (males and females) 2010-2022		3.10	0.00-6.29	.050
Mortality (males)		0.91	-2.70-4.65	.596
Mortality (females)		7.63	1.50-14.12	.019



Group	Years	AAPC	95% CI	P-value
Incidence (males and females) 2010-2023		3.0	-1.4-7.6	.166
Incidence (males)		2.3	-1.9-6.6	.264
Incidence (females)		6.0	-3.9-16.9	.221

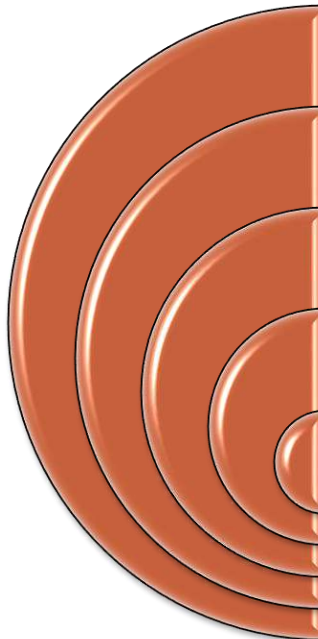
Incidence rate

2010-2023 wASR= 4.7/ 100 000
 Globocan 2022 (PT)= 6.7/ 100 000
 GBD (PT)= 4.1-4.9/100 000

Mortality rate

2010-2022 wASR=4.8/ 100 000
 Globocan 2022 (PT)= 5.8/ 100 000

Conclusions



Alcohol, viral hepatitis, and metabolic conditions are modifiable etiologies.
Attention for alcohol and metabolic comorbidities are needed.
HBV vaccination program (1995) may have contributed for the low values of HBV-related HCC. An HCV screening is ongoing on Madeira (2020).
A program to monitor cirrhotic patients is active on the Autonomous Region of Madeira (RAM).
This study contributes with valuable information on a preventable cancer that is not well understood.

References

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Thank you!

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Annex 1

HCV and HBV ICD-9 and ICD-10 codes

- HCV:
 - **ICD-9:** 070.41 / 070.44 / 070.51 / 070.54 / 070.7 / 070.70 / 070.71 / V0262
 - **ICD-10:** B17.1 / B17.10 / B17.11 / B18.2 / B19.2 / B19.20 / B19.21 / Z22.52
- HBV:
 - **ICD-9:** 070.2 / 070.20 / 070.21 / 070.22 / 070.23 / 070.3 / 070.30 / 070.31 / 070.32 / 070.33 / 070.42 / 070.52 / V02.61
 - **ICD-10:** B16 / B16.0 / B16.1 / B16.2 / B16.9 / B18.0 / B18.1 / B19.1 / B19.10 / B19.11 / Z22.51

Annex 2

Serological tests

1. HCV: HCV RNA+, anti-HCV (+)
2. HBV: anti-HBVC (+), anti-HBVe (+), AgHBVs (+), AgHBVe (+), and an anti-HBVs (-) confirmed a never infected case
3. Diabetes: fasting glucose $2 \times >125\text{mg/dL}$, HbA1c $>6.5\%$
4. Dyslipidemia: total cholesterol $>190\text{mg/dL}$ and/ or triglycerides $>150\text{mg/dL}$

Annex 3

Steatosis classification (when not mentioned on reports)

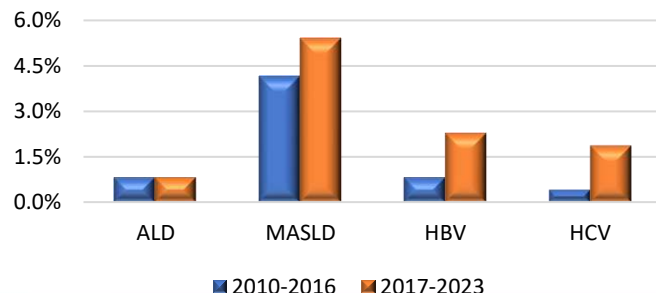
1. Biopsy
2. Image exams (ultrasound, CT scan, MRI)
3. Obesity
 - BMI > 29m², or mentioned on medical reports
4. Diabetes
 - medical reports > diabetes therapeutics > serum tests consistent with diabetes
5. Dyslipidemia + hypertension
 - Dyslipidemia: medical reports > dyslipidemia therapeutics > serum tests consistent with dyslipidemia
 - Hypertension: medical reports > hypertension therapeutics > tests consistent with hypertension > 140/90 mmHg

Annex 4

Distribution of cases by period and sex

Cause	2010-2016			2017-2023			Total
	Female	Male	Total (2010-2016)	Female	Male	Total (2017-2023)	
ALD	2 (11.8%)	50 (64.1%)	52 (54.7%)	2 (7.4%)	66 (55.9%)	68 (46.9%)	120 (50.0%)
MASLD	10 (58.8%)	7 (9.0%)	17 (17.9%)	13 (48.1%)	11 (9.3%)	24 (16.6%)	41 (17.1%)
HBV	2 (2.0%)	10 (10.6%)	12 (12.1%)	5.5 (6.9%)	22 (21.1%)	27.5 (25.5%)	39.5 (34.5%)
HCV	1 (5.9%)	7 (6.4%)	8 (6.3%)	4.5 (14.8%)	16 (8.5%)	20.5 (9.7%)	28.5 (8.3%)
Other							
Autoimmune hepatitis	0 (0%)	1 (1.3%)	1 (1.1%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)
Hemochromatosis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	1 (0.7%)	1 (0.4%)
Cryptogenic	2 (11.8%)	3 (3.8%)	5 (5.3%)	2 (7.4%)	2 (1.7%)	4 (2.8%)	9 (3.8%)
Total	17 (100%)	78 (100%)	95 (100%)	27 (100%)	118 (100%)	145 (100%)	240 (100%)

Females



Males

