Mesa redonda 2:

Receptores de alto riesgo: ¿Podemos hacerlo mejor?

Obesidad y NASH (EHGNA) **en el trasplante hepático**

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Editorial

JOURNAL
OF HEPATOLOGY

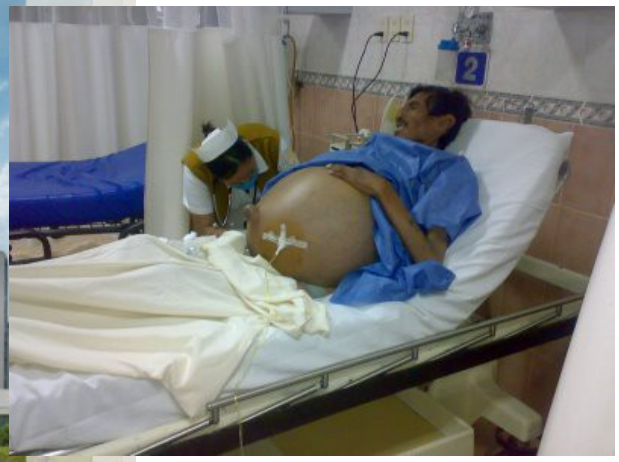
«The times they are a'changin'» – Positioning the European Association for the Study of the Liver in the changing landscape of hepatology

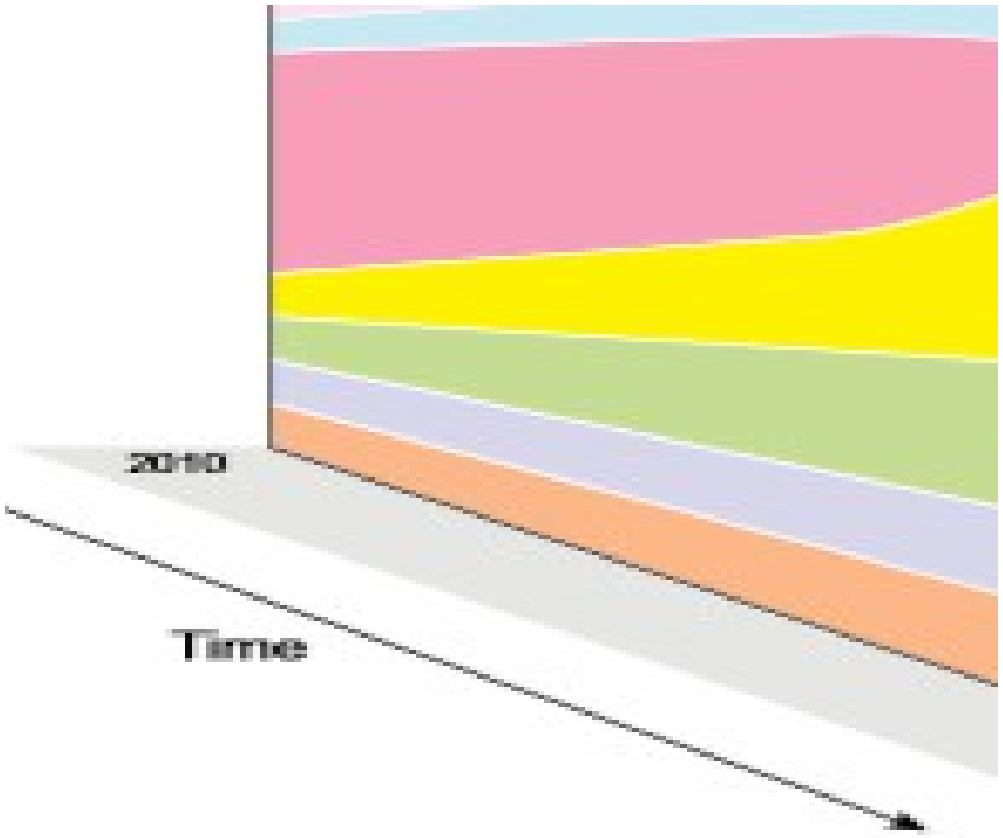
Tom H. Karlsen[1,*], Frank Tacke[2]

The Times They

Bob Dylan

Come gather 'roun

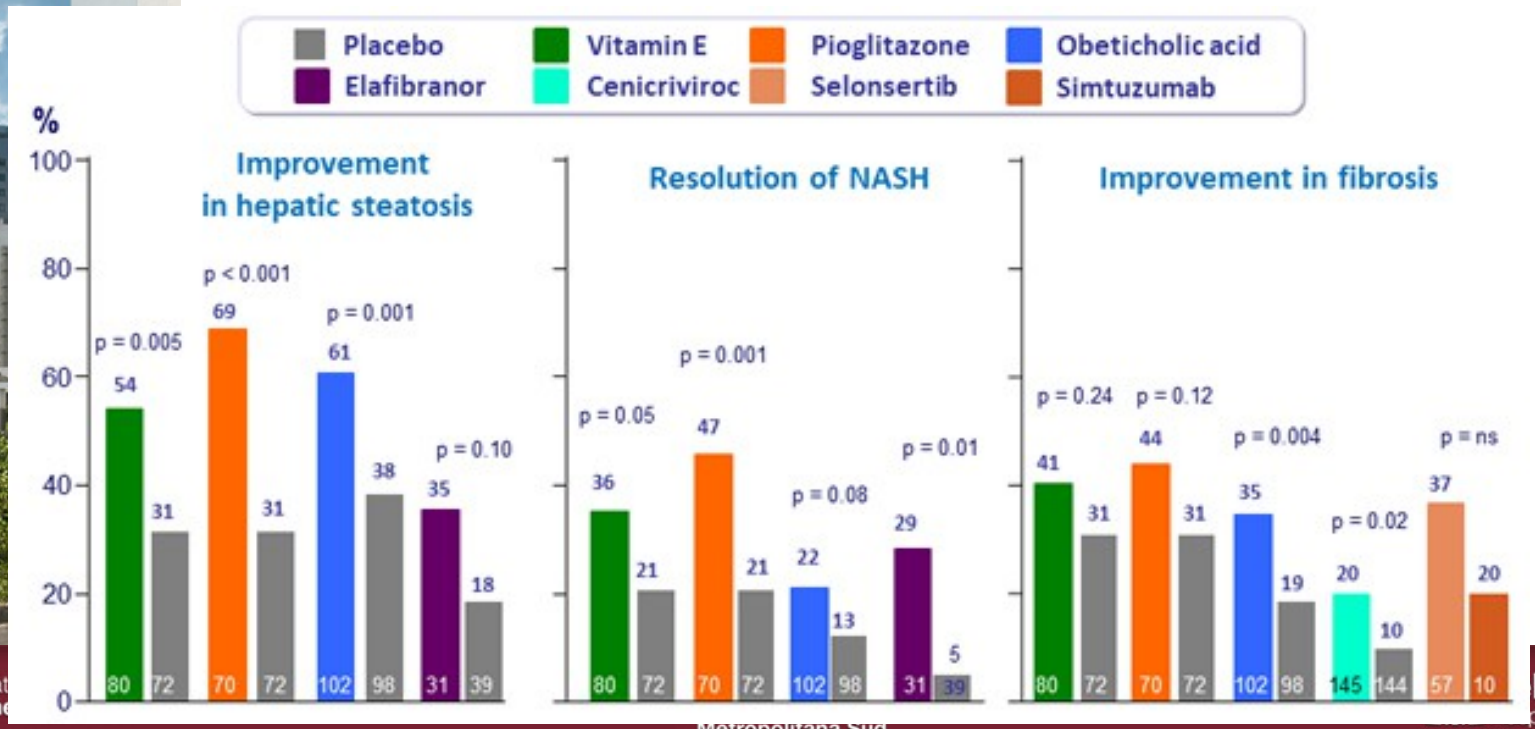




. Schematic representation of
ch. The figure is based on subject
tions shown are not built on und
. HBV, hepatitis B virus; HCC, hepa

Karlsen TH et al. J Hepatol 2018.

	Insulin resistance	Cell stress apoptosis	Inflammation	Fibrogenic remodeling
	Insulin resistance modifiers	Cell stress modifiers	Anti-inflammatory agents	Anti-fibrotic agents
Exemples of drugs in development	PPAR FXR agonist (obeticholic acid, GS-9674) GLP-1 FABAC FGF-21 (BMS-986036) Thyroxine analog	Vitamin E ASK-1 inhibitor (selonsertib) PPAR-γ agonsit FXR agonist Dual PPAR-/δ agonist FGF-21 FGF-19-like agent	CCR2-CCR5 antagonist Vitamin E ASK-1 inhibitor PPAR-γ agonsit FXR agonist Dual PPAR-/δ agonist Galectin 3 FGF-21 FGF-19-like agent	CCR2-CCR5 antagonist ASK-1 inhibitor PPAR-γ agonsit FXR agonist Dual PPAR-/δ agonist Lysyl oxidase-like 2 inhibitor Galectin 3 FGF-21 FGF-19-like agent



SD METABÓLICO

TRASPLANTE HEPÁTICO

OBESIDAD

NAFLD

CIRUGÍA BARIÁTRICA

NASH

EHGNA

Enfermedad hepatica crónica más prevalente en el mundo.

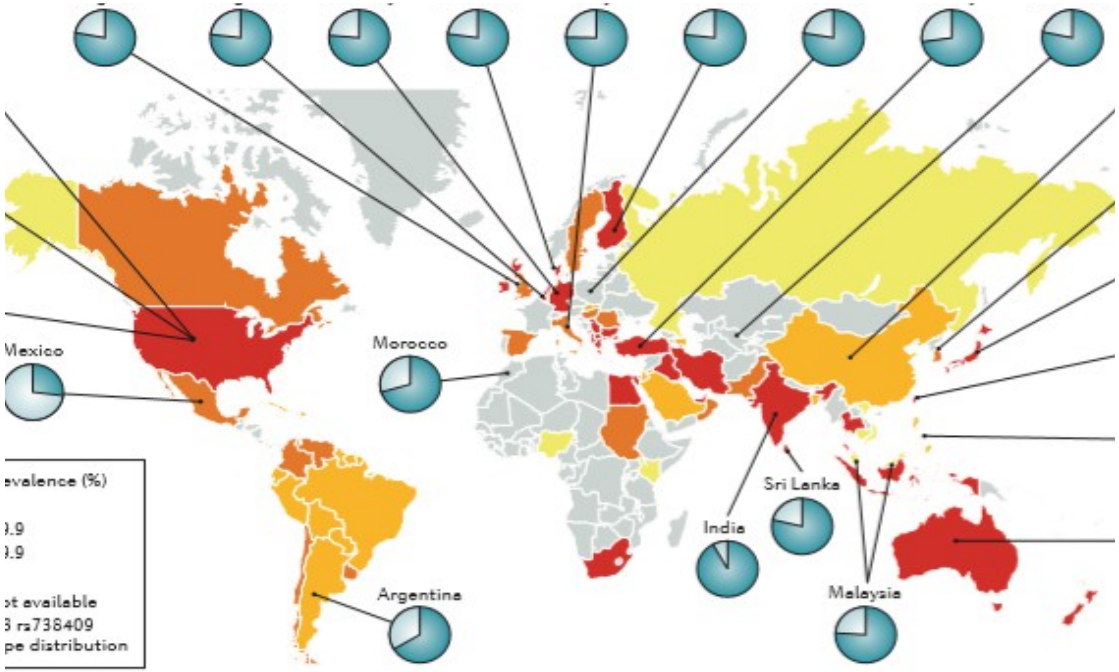
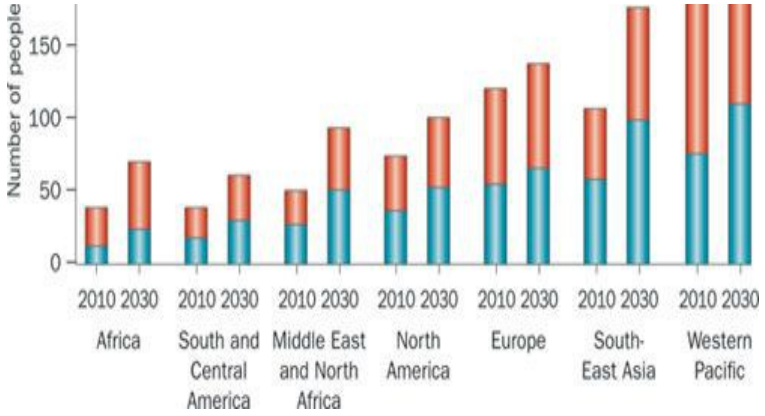


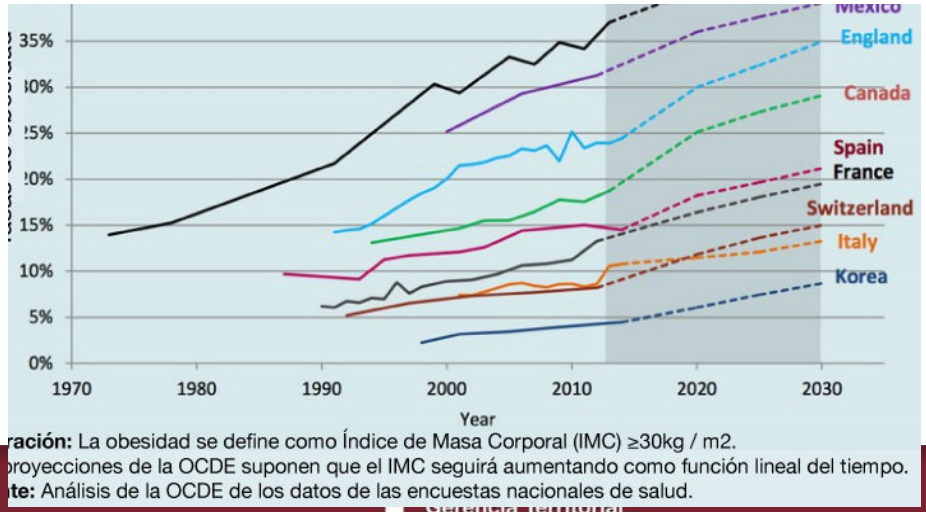
Figure 1 | **Worldwide estimated prevalence of NAFLD and distribution of *PNPLA3* genotypes.** *PNPLA3* is

EEUU	30-46 %
Europa	25-30 %
España	25 %

Younosii Z, et al. Gast & Hepatol 2018.
Augustin S, et al.Medicina Clínica. 201

Prevalencia de obesidad/DM





ración: La obesidad se define como Índice de Masa Corporal (IMC) ≥30kg / m2.
proyecciones de la OCDE suponen que el IMC seguirá aumentando como función lineal del tiempo.
te: Análisis de la OCDE de los datos de las encuestas nacionales de salud.

1. NASH Y SD METABÓLICO CAUSA DE CIRROSIS/HC
2.
3. NASH COMO INDICACION DE TH
4.
5. SD METABÓLICO POSTH Y RECIDIVA EHGNA
6.
7. IMPORTANCIA DE NASH EN LOS DONANTES
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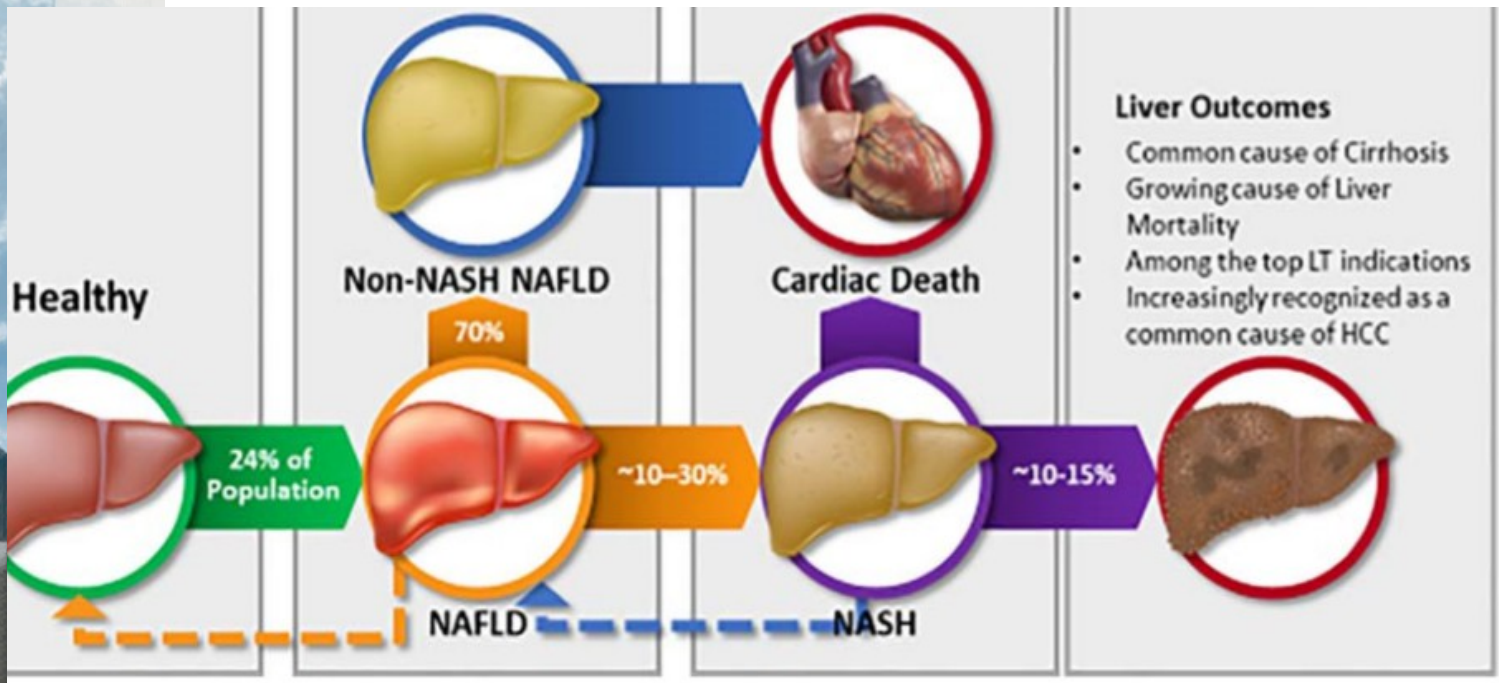
NASH y sd metabólico causa de cirrhosis/HCC



of the natural history of NAFLD and NASH.

Younossi ZM, et al. ClinLivDis,2018

NASH y sd metabólico causa de cirrhosis/HCC

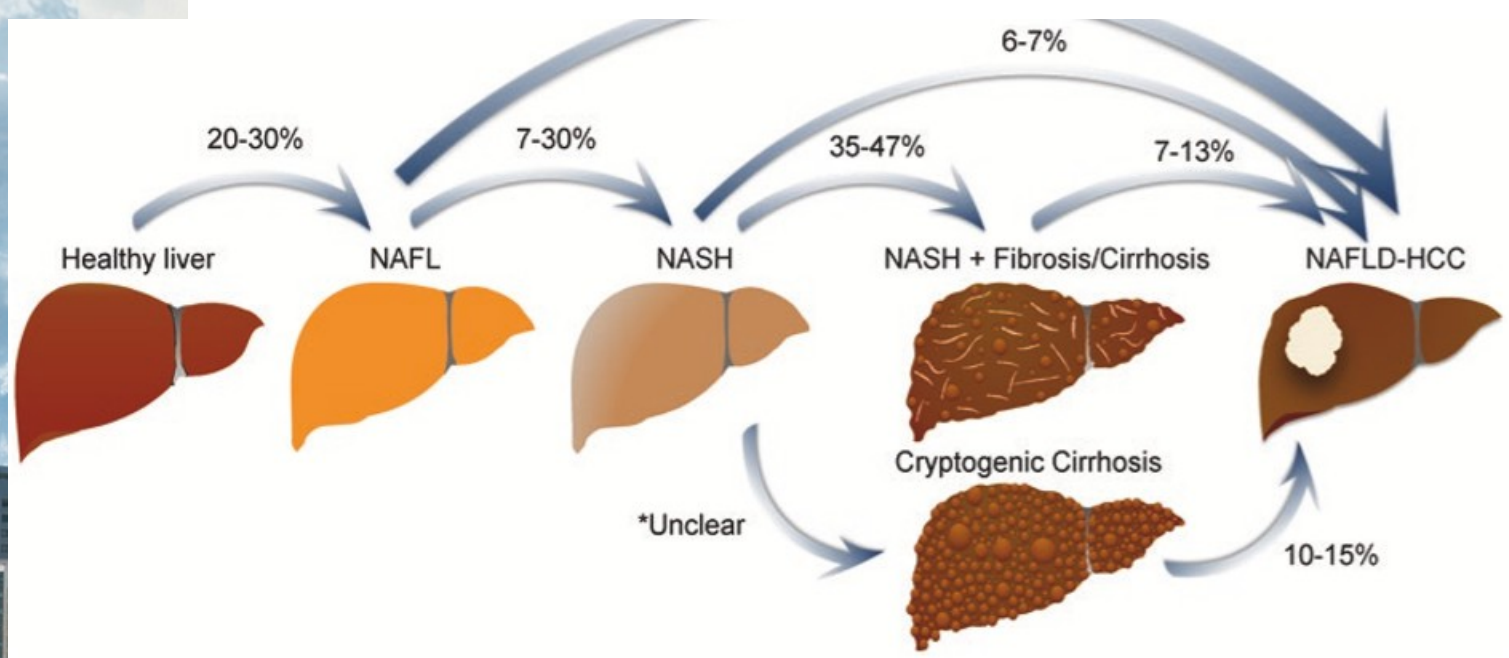


Fig. 2.1 The natural history of non-alcoholic fatty liver disease (NAFLD)
Although NASH accounts for up to half of cryptogenic cirrhosis cases, the proportion of NASH-cirrhosis patients misclassified as cryptogenic cirrhosis is not known

NAFL non-alcoholic fatty liver or simple steatosis, *NASH* non-alcoholic steatohepatitis, *NAFLD-HCC* non-alcoholic fatty liver disease-associated hepatocellular carcinoma
Figure courtesy of Dr. Weiqi Xu, Institute of Digestive Disease, The Chinese University of Hong Kong, Hong Kong

Liu K, et al. Adv, exp Med, 2018.

NASH y sd metabólico causa de cirrhosis/HCC

ABLE 4.

pact of the confounding factors on HCC incidence in those studies which only included patients without prior history of HC

hors	Years	HCC screening	Tools for HCC screening	Frequency of HCC screening	Follow-up time	New HCC	HCC incidence (%)	Rate of HCC-relat mortality (%)
ms et al[25]	2005	No	—		8.3 y	2	—	
yal et al[26]	2006	Yes (according to years)*	US plus AFP	6-12 mo	10 y	10	6.71 at 10 y	1.31
edt et al[27]	2006	No	—		13.7 y	3	—	2.8
uji et al[28]	2009	Yes	AFP and US	4 mo	3.4 y	7	11.3 at 5 y	34.2% at 5 y
himoto et al[29]	2009	Yes	AFP and US	4 mo	3.4 y	11	7.6 at 5 y	10.2
ramura et al[30]	2009	Yes	US	6 mo	5.6 y	16	0.25	—
ha et al[25]	2010	Yes	CT scan and AFP	6 mo	2.7 y	25	12.8	—
la et al[8]	2011	Yes	According clinical guidelines		NA	18	6.8	1.21%
n XY[9]	2012				NA	169	—	
rade et al[21]	2016	NA	—		< 1 y			
ot et al[23]	2017	Yes	US	6 mo	5.4 y	12	15	—
et al[28]	2017	NA	—		10 y	106	2.3	

Incidencia HCC

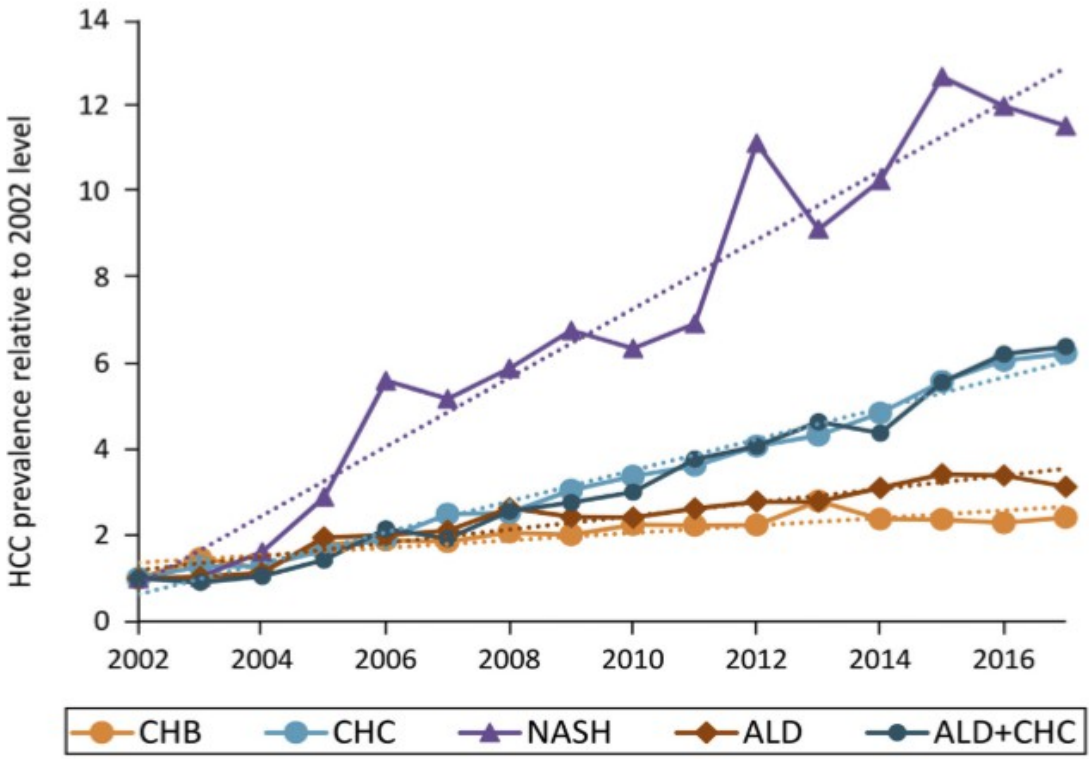
NAFLD con cirrosis 6.7-15 % a 5-10 a

NAFLD sin cirrhosis 2.7 % a 10 años

Reig M, et al. Transplantation 2019

NASH y sd metabólico causa de cirrhosis/HCC

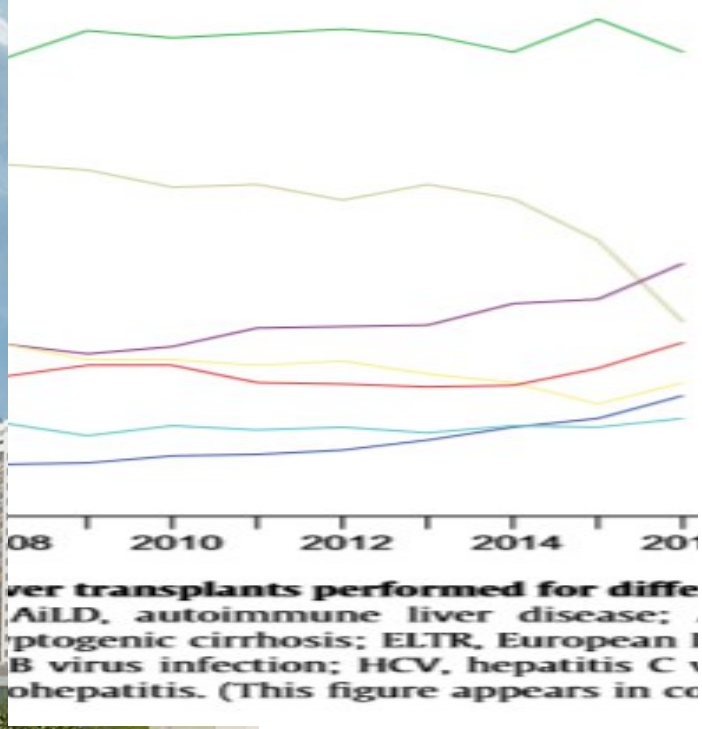
SRTR
6-22 % (global)
X 11 NASH



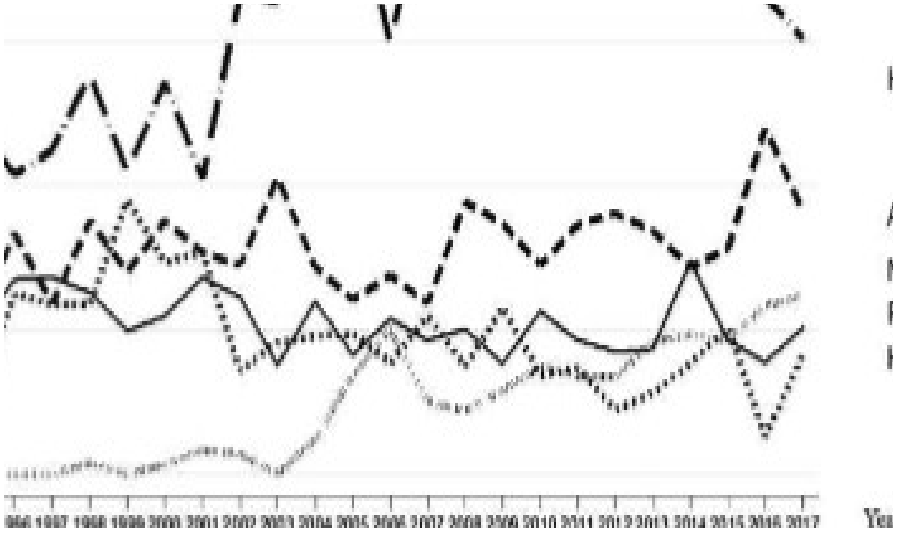
ure 1. Prevalence of C in waitlisted candi-es by etiology relative that in 2002. *Dotted* s represent linear ds.

Younossi Z, et al. ClinGastrHepatol 201

NASH como indicación de TH



NASH
1,2% de casos en 2002
8,4% de casos en 2016



Calzadilla-Bertot, el al. LT 2019.
Haldar D, et al. JHepatol 2019

NASH como indicación de TH
Resultados

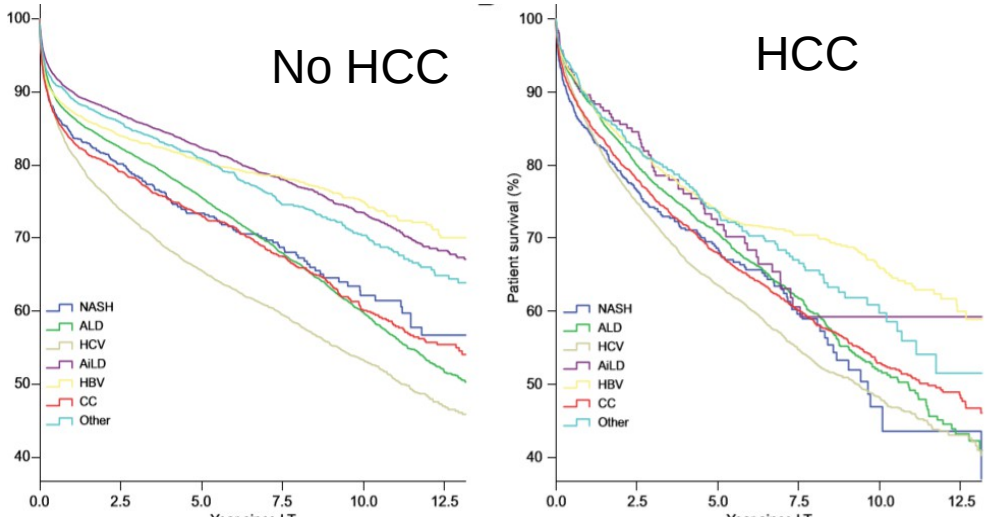
Supervivencia comparable NASH vs no NASH*

Mejor supervivencia que TH por VHC*

Riesgo recidiva NASH

Aumento de mortalidad por eventos CV

Recidiva HCC x2



Shingal A, et al. Transplant Int 2015.Wang X, et al. ClinGastroenterolHepatol, 2
Wong RJ, et al. Clin Transpl 2014.Mathur A, et al. HBP 2013.

NASH como indicación de TH
Resultados

Author, year	Country, Period	Population, sample size	Mean MELD score	Patient survival, %			Leading cause of death
				1 yr	3 yr	5 yr	
Malik, 2009	US single center 1997-2008	NASH = 98	17	79%	74%	72%	Infections: 57% CV: 21%
Yalamanchili, 2010	US single center 1986-2004	NASH = 18, CC = 239	-	85%	-	71%*	CV: 21% Malignancies: 18% Infections: 15%
Bhagat, 2009	US single center 1997-2007	NASH = 71	-	82%	79%	75%	Infections: 53% CV: 26%
Barritt, 2011	US single center 2004-2007	NASH = 21	23	76%	76%	-	Infections: 20% CV: 20%
Houlihan, 2011	Israel, single center 2000-2008	NASH = 48	15	88%	-	82%	CV events, sepsis
Park, 2011	US single center 1998-2008	NASH = 9	13	78%	-	-	n.r.
Charlton, 2011	US, SRTR registry 2001-2009	NASH = 1840	-	84%	78%		No accurate information on causes of death or graft loss
Agopian 2012	US single center 2002-2011	NASH = 144	33	84%	75%	70%	n.r.
Reddy, 2012	US single center 2000-2010	NASH-HCC (LT) = 20	9	-	83%	-	Liver failure. Similar overall survival in patients with NASH and HCV/ ALD-related HCC
Van Wagner 2012	US single center 1993-2010	NASH = 115	24	81%	73%	60%	Infections: 11% CV events: 9%
Kennedy 2012	US single center 1999-2009	NASH = 129	23	90%	88%	85%	Infections: 38% CV events: 19%
Afzali 2012*	US, UNOS data-base 1997-2010	NASH = 1810; CC = 3843.	21	87%	81%	75%*	Primary cause of death missing or unknown in 25% of the cases. CV events: 19%

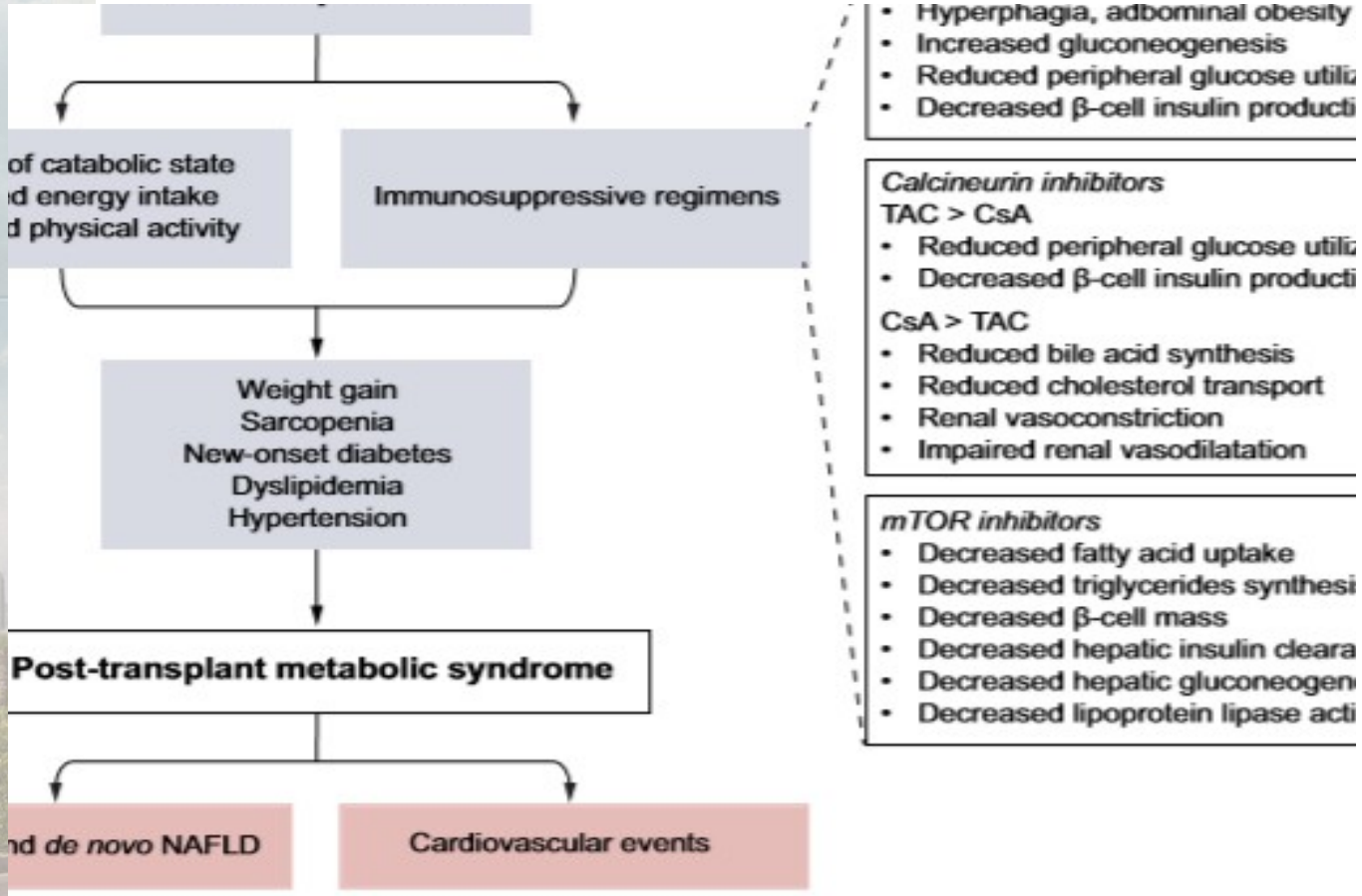
*NASH and CC combined.

ALD, alcoholic liver disease; CC, cryptogenic cirrhosis; CV, cardiovascular; HBV, hepatitis B; HCV, hepatitis C; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; UNOS, United Network for organ sharing; SRTR, Scientific Registry for Transplant Recipients.

Pais R, JHepatol2016.

Sd metabólico posTH y recidiva NASH

30 % TH por NASH presentaran recidiva
30 % TH por otras indicaciones NAFLD- 5 % NASH a 40 meses posTH



Pais R. JHepatol,2016

Sd metabólico posTH y recidiva NASH

NASH and CC N = 27	1 year	52%	11%	≥F3: 4%	Time-dependent risk of allograft steatosis: at 5 y of assessable patients developed fatty liver. Rec developed later than fatty liver alone. Cumulative steroids correlated with time to NAFLD developr
NASH N = 15	1 year	60%	33%	≥F2: 33%	Cirrhosis developed in 12.5% of patients. 1 patie re-transplantation for graft failure after 27 month
CC N = 51	2 years	25.4%	16%	≥F3: 4%	Bridging fibrosis occurred in patients with post L
Non-NAFLD CLD N = 68	2 years	18%	9%	-	Increase of BMI of >10% was associated with p
NASH N = 64	>6 months	-	33%	-	No cirrhosis or re-transplantation because of rec disease. 24% of patients developed graft failure
NASH N = 98	5 years	-	25%	-	Recurrent NASH did not adversely affect surviva in NASH group were re-transplanted within 60 d
NASH and CC N = 257	5 years	31% (45% in NASH cirrhosis; 23% in CC)	4%	≥F3: 5% at 5 years; 10% at 10 years	Advanced fibrosis was more frequent among tho LT NASH (31%) than simple steatosis (6%)
Non-NAFLD CLD N = 421	>6 months	31%	5.3%	≥F3: 2.25%	Most of the patients (52%) had grade 1 steatosis evolution of NAFLD during follow-up was: regres stability (22%), progression (30%). PTMS and li steatosis were independent predictors of *de nov*
NASH or CC N = 88	1 year	39%	28%	≥F2: 9%	Only 9% of recurrent NAFLD had NAS ≥5. NAFL was associated with increased risk for CV diseas correlated with post-transplant BMI, post LT TG corticosteroids dose at 6 month.
NASH and CC N = 83	1.5 years	-	24%	≥F3: 3.6%	The recurrence rate was significantly higher amo with PTMS (34% *vs.* 13% in patients without MS were re-transplanted secondary to graft failure fr recurrence.
Non-NAFLD CLD N = 156	>1 year	27.1%	6.7%	F2: 4.4%	Obesity and donor graft steatosis were indepen for post LT NAFLD.

*de novo NAFLD; **NAFLD includes NASH; #% of patients with the outcome.
tion; PTMS, post-transplant metabolic syndrome.

País R. J Hepatol,201

PAPEL DE LA CIRUGIA BARIÁTRICA

¿Cual es el mejor momento para plantear cirugía bariátrica?

¿Cual es la mejor técnica en este tipo de pacientes?

PAPEL DE LA CIRUGIA BARIÁTRIC

OBJETIVOS

1. Evitar la necesidad de TH en pacientes con EHGNA (mejoría fibrosis)

2. Posibilitar el TH en pacientes obesos

3. Disminuir la morbi-mortalidad posTH

4. Diminuir el sd metabólico posTH

    4.a.Disminuir mortalidad CV

    4.b.Disminuir recidiva EHGNA

Trasplante hepático en pacientes con obesidad

Nair, 2002: Mayor fallo primario, mayor mortalidad por eventos CV.

Dick,2009: IMC > 40, factor de riesgo de mortalidad (RR1.7).

Orci,2012 (SRTR): No influencia en supervivencia.

Hakeem,2013: Mayor morbilidad (infección, estancia).
No influencia en supervivencia.
Bambha,2015: peor bajo IMC (<18) que alto.

Perez-Protro, 2016: No influencia en supervivencia. (mayor sd metabólico)

Beckmann,2019 (meta-análisis): IMC> 30 peor sup paciente e injerto

Consenso SETH 2015: Obesidad no contraindicación absoluta "pero require evaluación exhaustiva".

Consenso OCATT 2019; IMC > 35 Contraindicación "relativa"

¿Cual es la mejor técnica en este tipo de pacientes?

GASTRECTOMIA VERTICAL

Técnica utilizada en 80 % de los casos descritos

Ventajas:

Técnica restrictiva (Evita malabsorción y possible efecto en IS)

Evitas anastomosis intestinales, menor tiempo quirúrgico

Menos complicaciones (importante en pacs ya con alto rieso quir)

Mantiene acceso a via biliar

Inconvenientes:

Complicaciones tardías (Ref ujo 47%; def ciencias vitaminas.)

Posible recuperación de peso posterior

¿Cual es el mejor momento para plantear cirugía bariátrica?

PRETH

References	N	BS Approach	Follow-up (# months)	Complication (%)	Complication Type	%EWL (Time Point)	Comorbidities (% of Patients)
Pre-LT							
Takata et al.[39] (2008)	6	SG	3-18	30%	Hepatic encephalopathy, bleeding	24%-73% (9 months)	Improved or resolved in 100% patients
Safwan et al.[42] (2017)	11	RYGB SG Jejunoileal bypass		Not available	Not available	Not available	Not available
Lin et al.[38] (2013)	20	SG	6-48	25.0%	Renal insufficiency, liver insufficiency, gastric staple line leak, bleeding, wound infection	56% (6 months) 65% (1 year)	Not available
Shimizu et al.[37]	23	RYGB	18 patients with 12-month	34.8%	RYGB-gastrojejunal anastomotic leak,	68% (37 months)	Hypertension 88.9%

Sharpton et al.LT 2019

N= 32 IMC > 40 o IMC> 35 + comorb

Contraindicación: Child > 9, MELD >20, INR>2.5, ascites y/o encefalopatia

TODOS gastrectomia vertical LAP

No reIQ; no mortalidad. 3 complics (3 %)

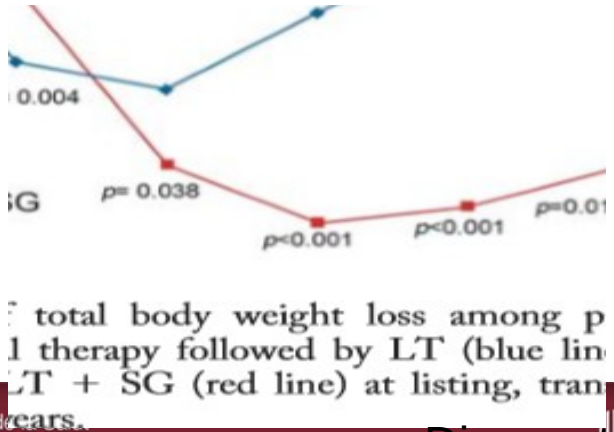
28 (88 %) candidatos a TH (7 sacados de lista por mejoría)

Diwan et al. LT 2018.

¿Cual es el mejor momento para plantear cirugía bariátrica?

SIMULTANEO

Zamora-Valdés et al. Hepatology 2018
N= 29 IMC > 40 o IMC> 35 + comorb
TODOS gastrectomia vertical
Morbilidad 44.8 %,
Mortalidad 2 (1 rec HCC, 1 disfunción)



Diwan et al. LT 2018.

¿Cual es el mejor momento para plantear cirugía bariátrica?

POS

(2007) Tichansky et al.[35] (2005)	1	RYGB	4	None	Not available	BMI 57 → 43 kg/m^2	Hypertension T2DM
Lin et al.[51] (2013)	9	SG	3-36	33.3%	Hernia repair recurrence, bile leak, dysphagia requiring conversion to Roux-en-Y esophagojejunostomy	38% (3 months) 65% (12 months)	Not reported
Khoraki et al.[52] (2016)	5	SG	13-79	40%	Portal vein thrombosis, bleeding	46% (12 months) 43% (24 months)	T2DM (100%)
Osseis et al.[53] (2018)	6	SG	13-101	16.7%	Gastric staple line leak leading to death	76% (24 months)	Hypertension (50%) Obstructive sleep apnea (67%)
Al-Nowaylati et al.[54] (2013)	7	RYGB	55.4	42.9%	Reversal of RYGB secondary to malnutrition, wound infection, hernia, 2 deaths	BMI 44 → 26 kg/m^2 (59 months)	T2DM Hyperlipidemia
Tsamalaidze et al.[55] (2018)	12	SG	25.3	33.3%	Malnutrition requiring g-tube and dilatations, late drain removal	50% (12 months)	T2DM (44%)* Hypertension (27%)* Hyperlipidemia (43%)*

Morris et al. LT 2019 (in press)

N= 15 IMC > 40 o IMC> 35 + comorb

TODOS gastrectomia vertical

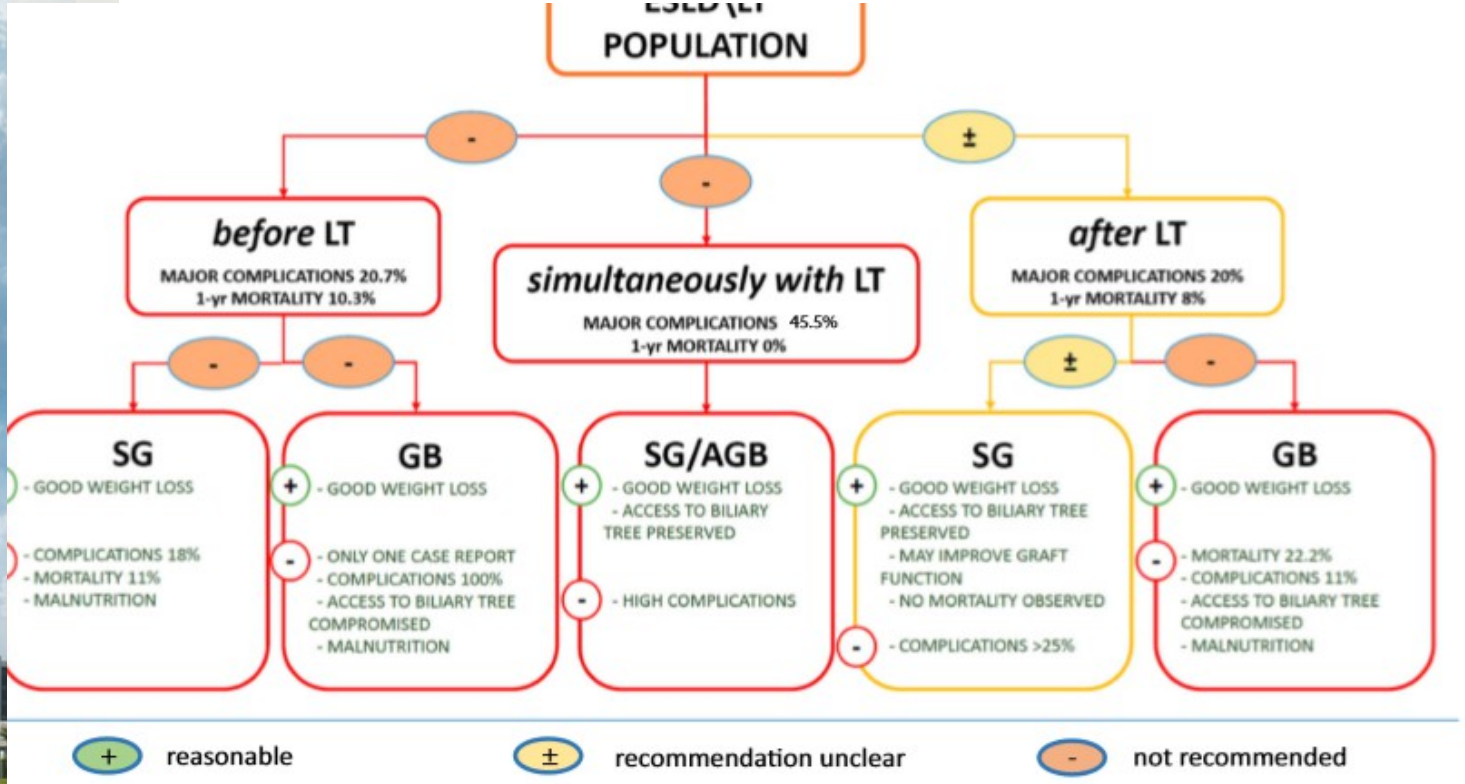
Morbilidad 10 %,

Mortalidad 0

IMC 40-35, Dism req Insulina

Diwan et al. LT 2018.

¿Cual es el mejor momento para plantear cirugía bariátrica?



1 Suggestions for bariatric surgery in organ transplantation

Dziodzio T et al. ObesSurg 2017

¿Cual es el mejor momento para plantear cirugía bariátrica?

PRETH

Ventajas:

Posible mejoría algunos pacientes (control sd metabólico/NASH)

Evitar complicaciones cirugía simultanea (corticoides)

Evitar pérdida de peso rápida posTH y posibles dif cultades control IS

Inconvenientes:

Sólo posible en pacientes Child A, MELD bajo

Caso clínico-HUB

Varón 54 a Cirrosis VHC+ NASH
Encefalopatia/PBE/ascites refractaria Child B, MELD: 25
SAOS/DM insulinodep/HTA (3 fármacos)
Peso: 132 (IMC: 39)
THO Oct 2014 (tec Piggy-back + GV)
Duración. 485 min, 4 CH.
Estancia: 28 dias (sepsis catéter, bacteriemia, SDRA,anasarca)
No reingresos. Control sd metabólico. Vivo a 58 meses.

Pre-intervención	3 m	12 m	24 m
126	76	65	78
37,7	22,7	19,4	23,3
	39,6	48,4	38
7,6	7,4	8,6	8,9
5,4	4,9	6,2	6,5
23	35	43	43
1,27	0,32	0,26	0,25
0,58	0,20	0,33	0,23
118	12	15	16
1,86	3,56	3,52	3,27
0,61	2,47	0,86	1,02
ISCI 135 UI/día Exenatida 10 µg/12 h Doxazosina 4 mg/día Furosemida 40 mg/día	No No	No No	Glargina 12 UI/día Amlodipino 10 mg/día

Obesidad y NASH en el trasplante hepático

CONCLUSIONES

Obesidad y NASH en el trasplante hepático

Estar preparados para el aumento de esta nueva indicación

Establecer protocolos de manejo de obesidad, sd metabólico y riesgo

Control del riesgo de recidiva HCC

Revaloración del manejo de la obesidad Pre/Pos

Definir tipo y momento de cirugía bariátrica

MUCHAS GRACIAS