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NUTRIM School of Nutrition and Translational Research in Metabolism

Liver resections and liver failure

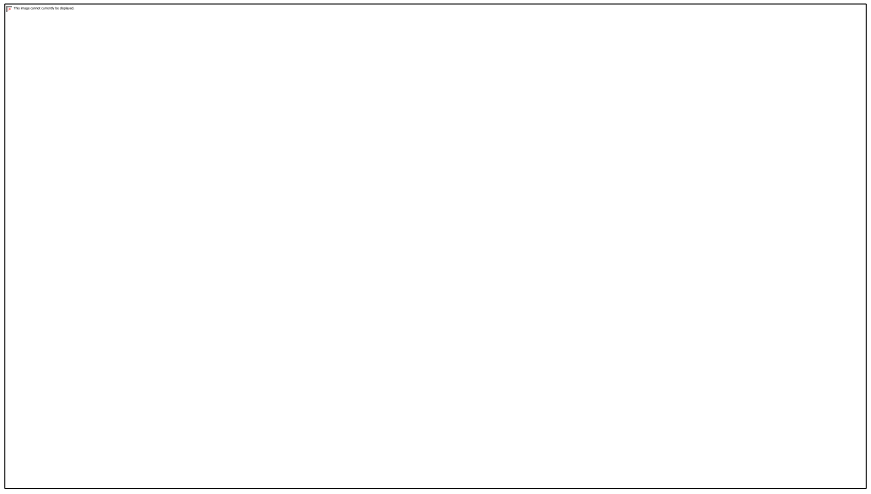
Steven W.M. Olde Damink

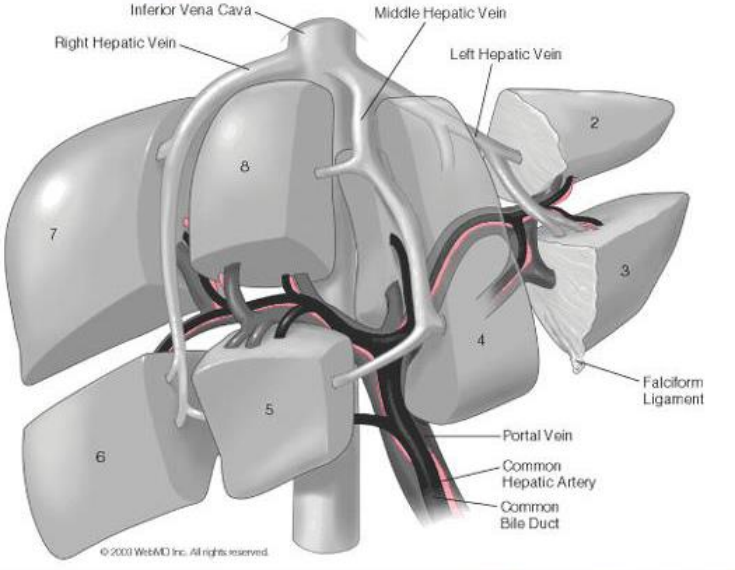
Overview

- Postresectional liver regeneration – in short
- Postresectional liver failure (PLF)
  - Definition
  - Risk factors, Risk-analysis, Pathogenesis
- Prevention
- Current and future therapies

Partial hepatectomy

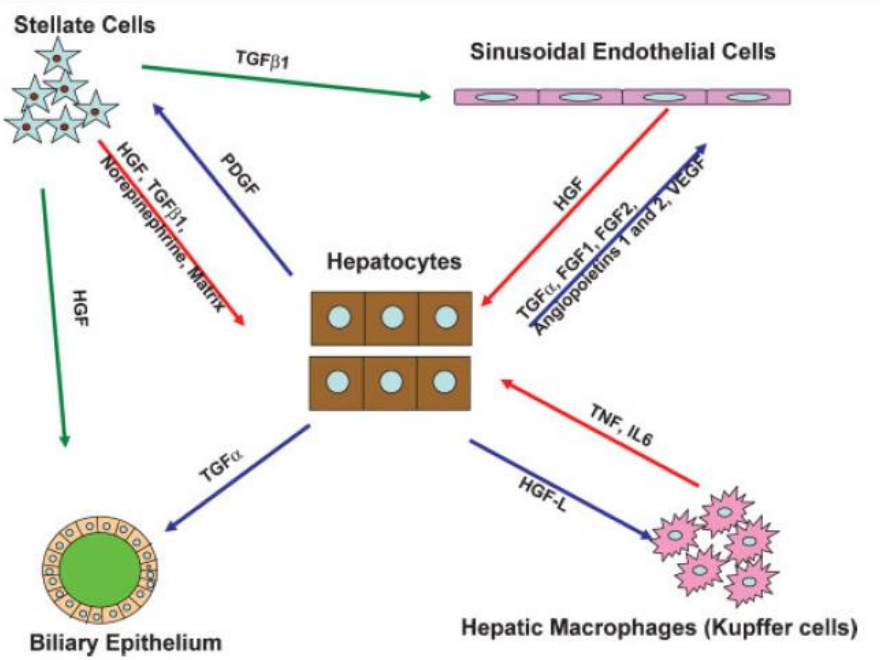
- Preferred curative treatment!
- Malignant lesions (primary & secondary)
- Benign lesions

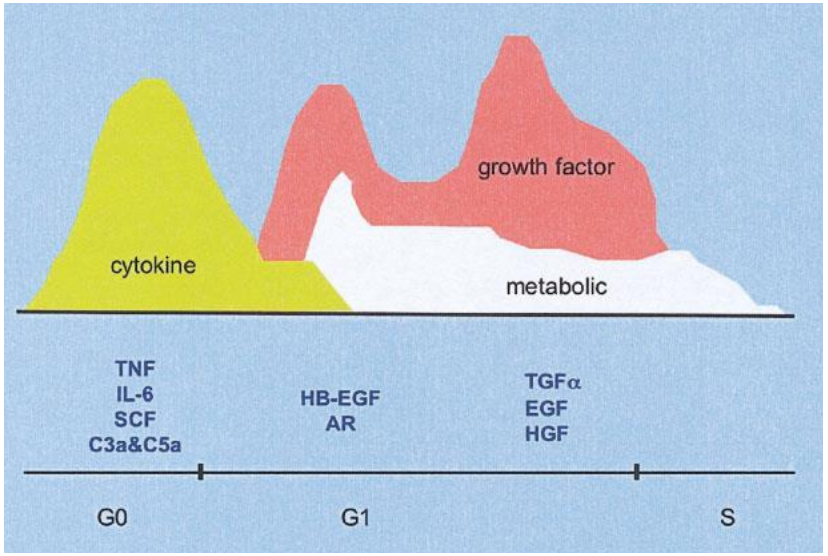




Postresectional liver regeneration

- Liver regeneration starts immediately after resection
- Interplay parenchymal and non-parenchymal cells and driven by multiple signals





Michalopulos, J Cell Physiol 2007
Fausto, Hepatology 2006

Postresectional liver failure (PLF)

Regeneration?

Postoperative result

Quality liver parenchyma

Quantity liver parenchyma

Definition of PLF

- **Based on bilirubin and/or INR and/or other parameters**

- 50-50 criteria
  - Predicts death on ICU on postoperative day 5 when bilirubin >50umol/l and PT <50%
- Peak bilirubin
  - Predicts liver-related death within 90 days after resection when bilirubin level >7.0mg/dL
- Definition of ISGLS
  - Grade A, B, or C based on clinical symptoms and deviation in postoperative course, can predict postoperative mortality
  - Measured on or after postoperative day 5

No consensus

Balzan, 2005
Mullen, 2007
Paugam-Burtz, 2009
Rahbari, Surgery 2011

Definition of PLF

Criterion	**PPV**	**NPV**	**Measure**
"50-50 criteria"	29-54%	97-96%	Postoperative overall mortality on ICU
"Peak bilirubin"	32-40%	97-99%	Liver-related mortality within 90 postoperative days
"ISGLS definition"	21%	97%	Overall postoperative mortality

Balzan, 2005
Mullen, 2007
Paugam-Burtz, 2009
Rahbari, Surgery 2011
Skrzypczyk, Ann Surg 2014

PLF - Incidence

Autor	Year	Patients (n)	Morbidity (%)	PLF (%)	30 day mortality(%)	Overall mortality (%)
Schroeder	2006	587	32	32	8,5	n.a.
Balzan	2005	704	n.a.	3,8	n.a.	3,7
Poon	2004	820	30	3,2	2,7	3,7
Dimick	2004	16582	n.a.	n.a.	7,3	n.a.
Coelho	2004	83	45	7,2	8,4	n.a.
Imamura	2003	915	44	0,1	0	0
Jarnagin	2002	1803	45	5,5	n.a.	3
Alfieri	2001	254	26	4,2	n.a.	3,9
Akashi	2000	96	39	11,4	5,2	10,4
Belghiti	1999	747	22	1,2	n.a.	4,4

Validation of *Peak bilirubin*

- **Multicenter**
  - Maastricht University Medical Center, Maastricht
  - The Royal Free Hospital, London
- Retrospective analysis of patient files, 2005 - 2012
- n = 956

- **Inclusion**
  - All patients undergoing liver resection
  - Independent of quality of background liver

Validation of *Peak bilirubin*

Significant postoperative morbidity

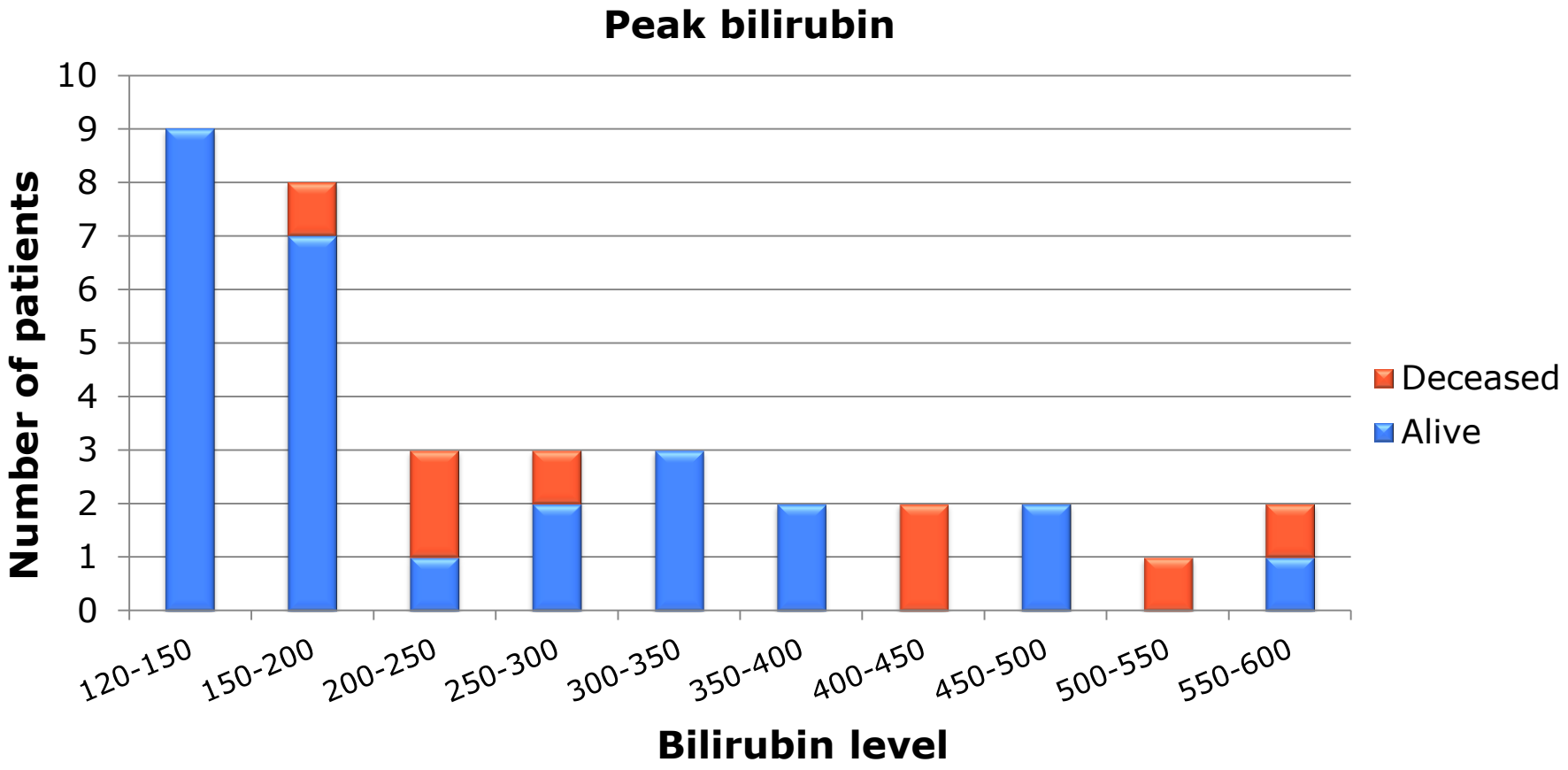
Total n=956	
Sens	14.3%
Spec	100%
PPV	100%
NPV	77.3%

Liver-related 90-day mortality

Total n=956	
Sens	34.8%
Spec	97.1%
PPV	22.9%
NPV	98.4%

Van Mierlo et al HPB 2016 (accepted)

Validation of *Peak bilirubin*



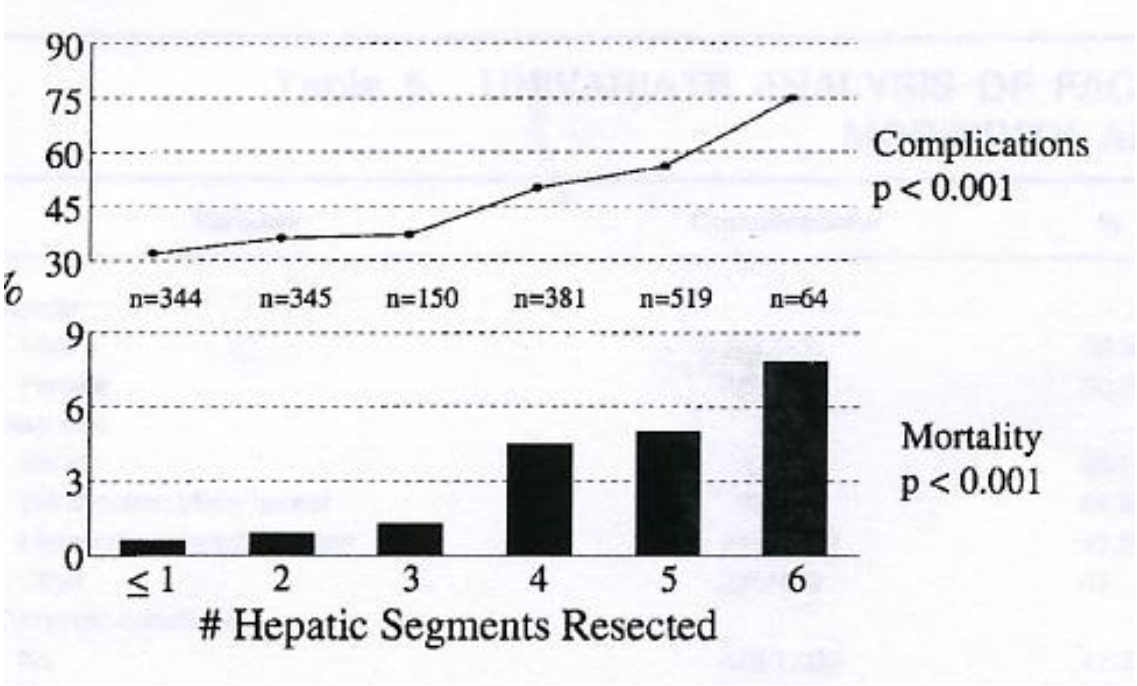
Risk factors for PLF

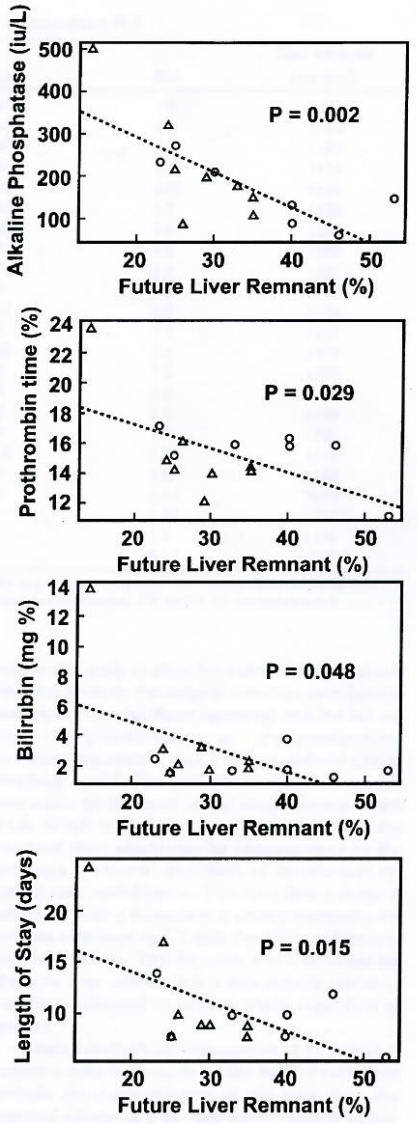
- **Patient factors**
  - Co-morbidity
  - Pre-existent liver disease
  - Age > 65
  - Male sex
- **Peri-operative factors**
  - Excessive intra-operative blood loss or transfusion
  - Added biliary or vascular procedures
  - Long operative time
- **Postoperative factors**
  - Infectious complications
  - Insufficient remnant liver volume

Helling TS, HPB 2006
van den Broek MA, et al, Liv Int 2008
Garcea J Hepatobiliary Surgery 2009
Van Mierlo, J Hepatol 2016

Pathogenesis of PLF - RLV

- **Minimum amount of remnant liver volume (RLV)**
  - RLV 25-30% → normal liver function
  - RLV >40% → impaired liver function





Jarnagin, Ann Surg 2002

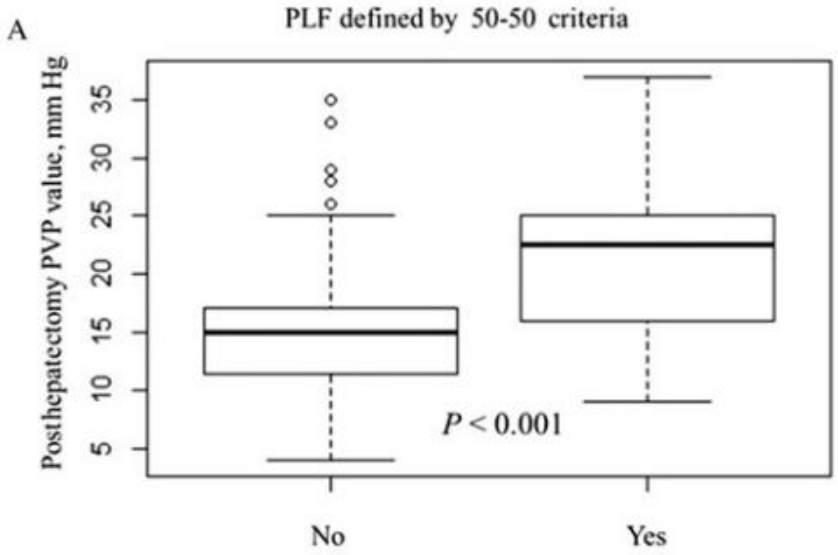
Pathogenesis of PLF - hemodynamics

- **Hepatic haemodynamic imbalance**
  - Adaptive reduction of arterial blood flow through hepatic arterial buffer response
  - Increased portal flow and pressure after major hepatectomy increase the risk for PLF
  - Post-reperfusion portal hypertension in partial liver transplantation → sinusoidal injury and ↓NO

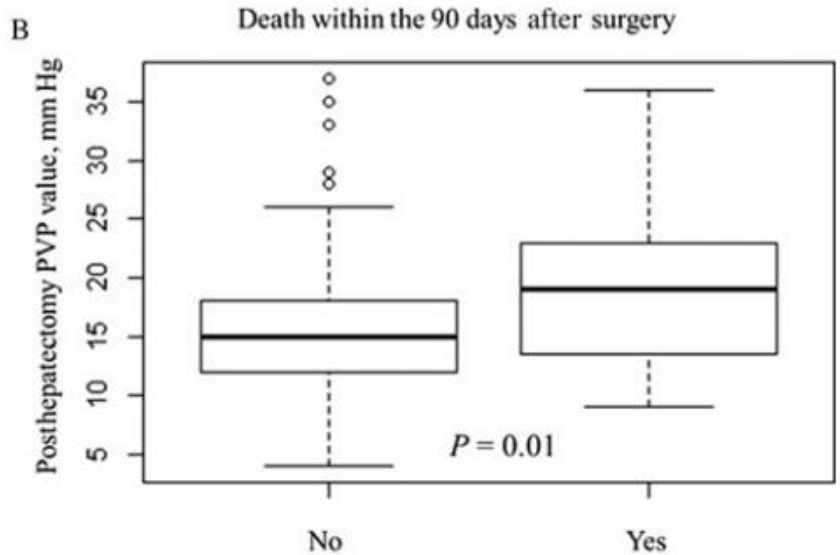
Allard, Ann Surg 2013

Golriz, Clin Res Hepatol Gastroenterol, 2015

Pathogenesis of PLF - hemodynamics



	No	Yes
Mean (±SD)	14.9 (±5)	21.7 (±7)
Median (range)	15 (4–35)	22.5 (9–37)



	No	Yes
Mean (±SD)	15.2 (± 5)	19.6 (±7)
Median (range)	15 (4–37)	19 (9–36)

Allard, Ann Surg 2013

Golriz, Clin Res Hepatol Gastroenterol, 2015

Pathogenesis of PLF – immune response

- **Impaired liver innate immune defense**
  - Cytokine release by activated Kupffer cells hampered after major liver resection
  - Impaired phagocytic activity after major resection
  - Risk of infection increases with the extent of resection → majority of patients with hepatic dysfunction develops infectious complications

Table 2 Hepatic dysfunction and infection following minor, standard, and extended liver resection

	Extent of liver resection		
	Minor (n = 20)	Standard (n = 57)	Extended (n = 27)
Postoperative hepatic dysfunction****			
No	17 (85.0)	9 (15.8)	1 (3.7)
Mild	3 (15.0)	28 (49.1)	11 (40.7)
Moderate	0	15 (26.3)	7 (25.9)
Severe	0	5 (8.8)	8 (29.6)
Infection***	3 (15.0)	14 (24.6)	16 (59.3)

***p = 0.001, ****p < 0.0001 by Pearson χ^2.
Values in parentheses are percentages of patients in each category by extent of liver resection.

Schindl, Gut 2005

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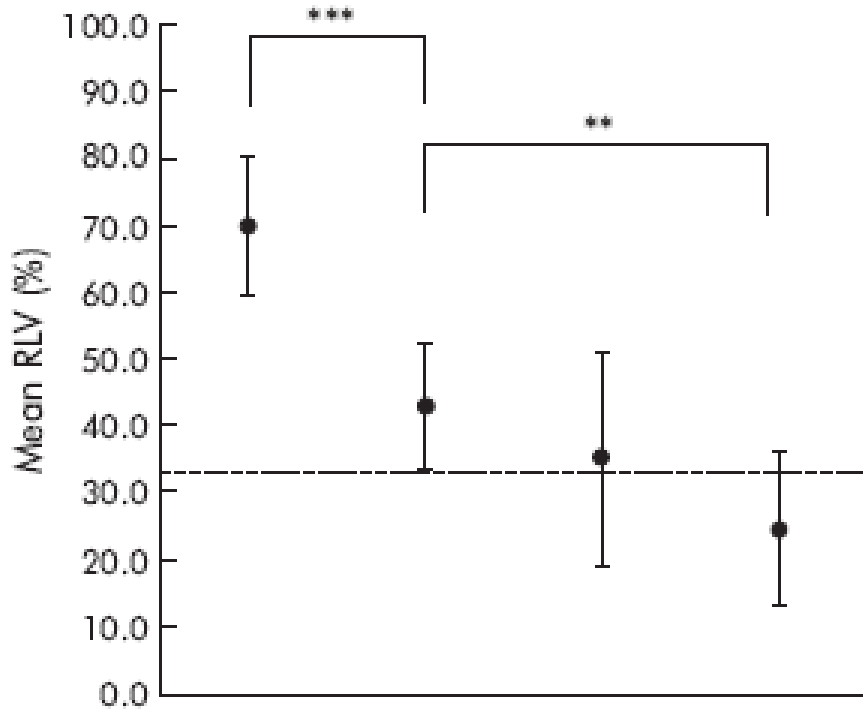


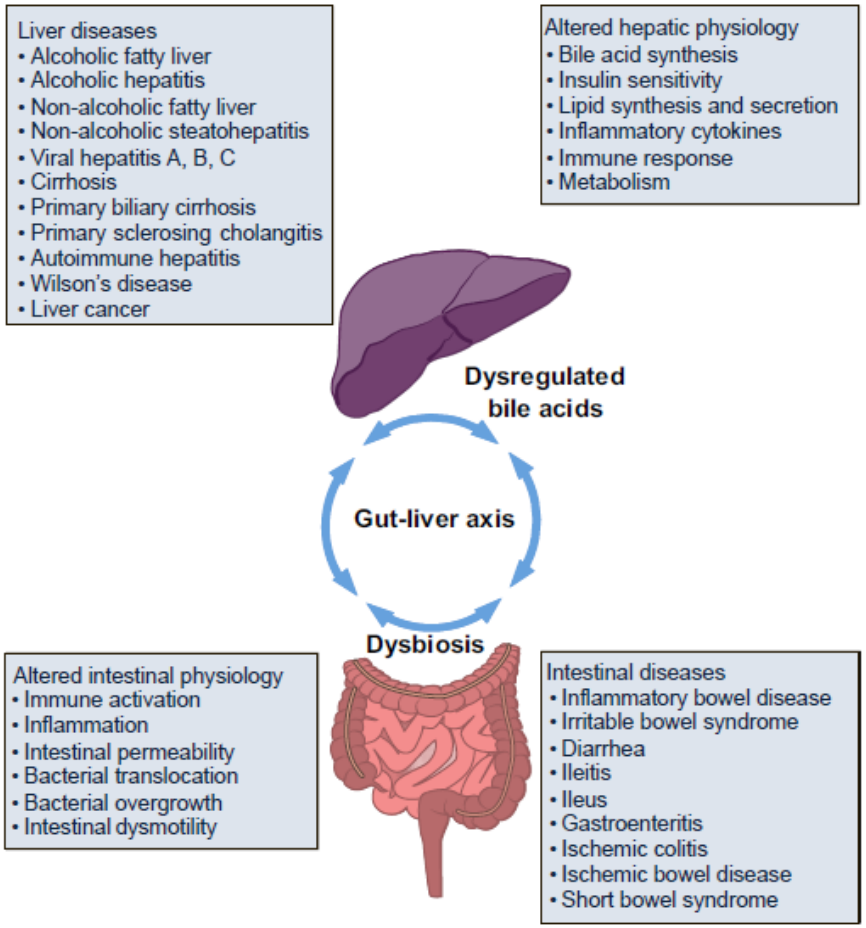
Hepatic dysfunction	No	Mild	Moderate	Severe
n	27	42	22	13
Mean %RLV	69.9	42.9	35.3	24.5
SD	22.6	15.4	15.3	6.0

Figure 3 Mean (SD) relative residual liver volume (%RLV) in patients with no, mild, moderate, and severe hepatic dysfunction following liver resection (one way between group ANOVA; **p=0.005, ***p<0.0001). Reference line indicates 33% RLV.

Schindl, Gut 2005

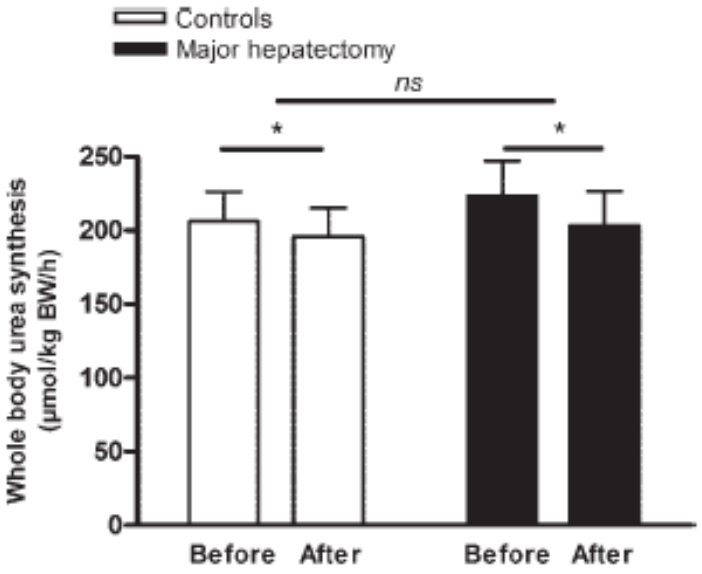
Pathogenesis of PLF – gut microbiome

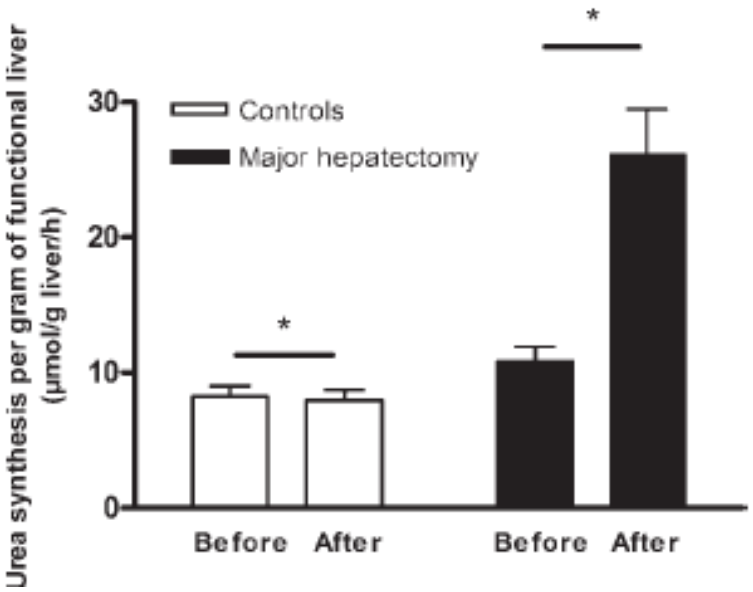
- **Gut microbiome-gut-liver axis**
  - Failure of gut-derived endotoxins to reach the liver → impaired DNA synthesis
  - Excessive levels of endotoxin can impair liver regeneration and cause mortality after extended hepatectomy



Liu, J Hepatol 2015

Pathogenesis of PLF – urea synthesis





Van de Poll et al. AJP 2007

Urea synthesis probably not limited

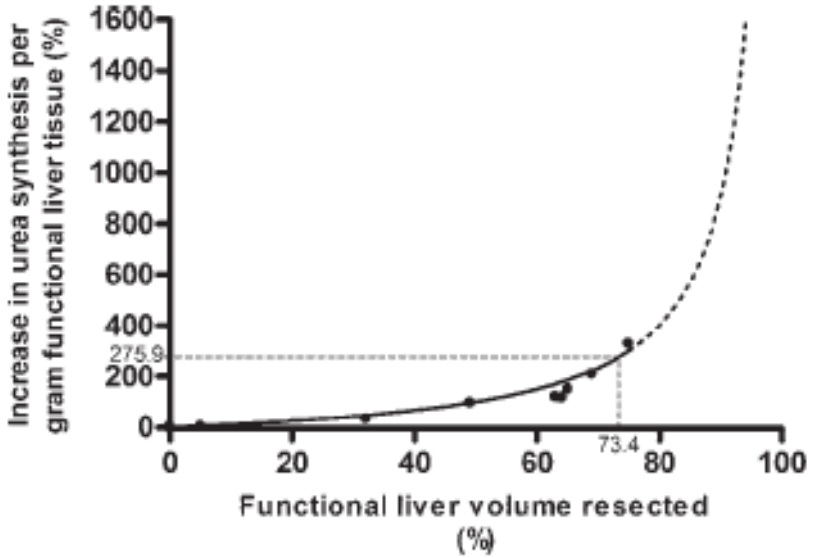
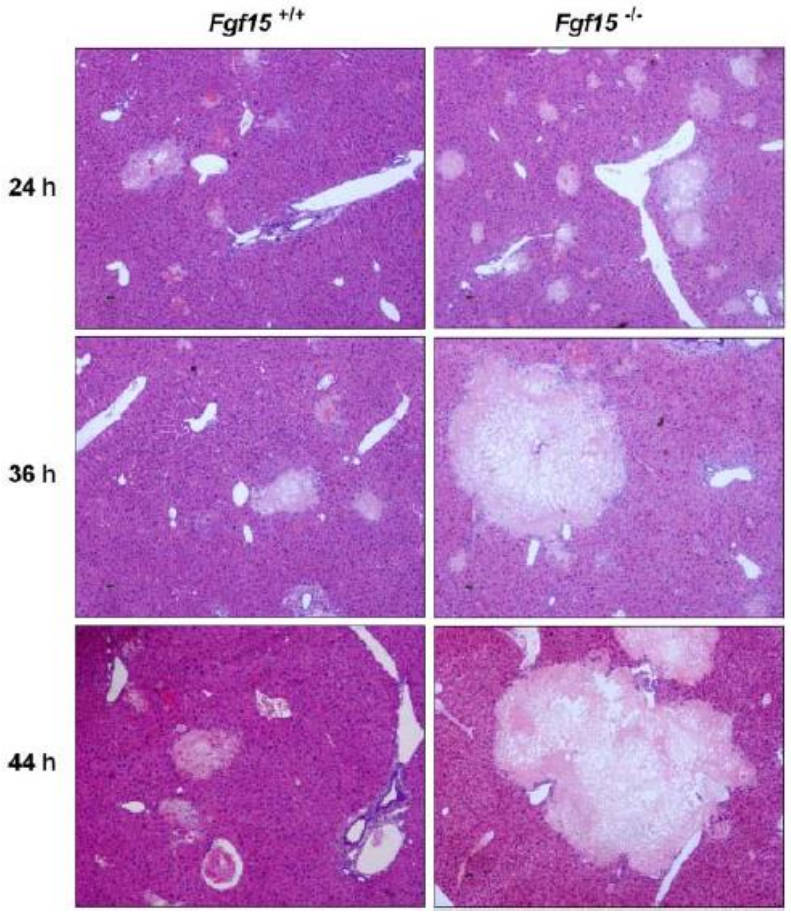


Fig. 7. Increase in urea synthesis/g liver in relation to the resected liver volume. Dots represent individual patients in the present study. From the theoretical prediction line, it can be conceived that beyond 70–80% hepatectomy the demanded functional adaptation increases exponentially, rapidly increasing the risk of liver failure. The value of 74.4% is derived from recent work from our group (25). In that study, a residual functional liver volume of 26.6% or less in patients with a normal liver was found to be predictive of liver insufficiency following hepatectomy. In this case, urea synthesis/g liver has to increase almost 300%.

Van de Poll et al. AJP 2007

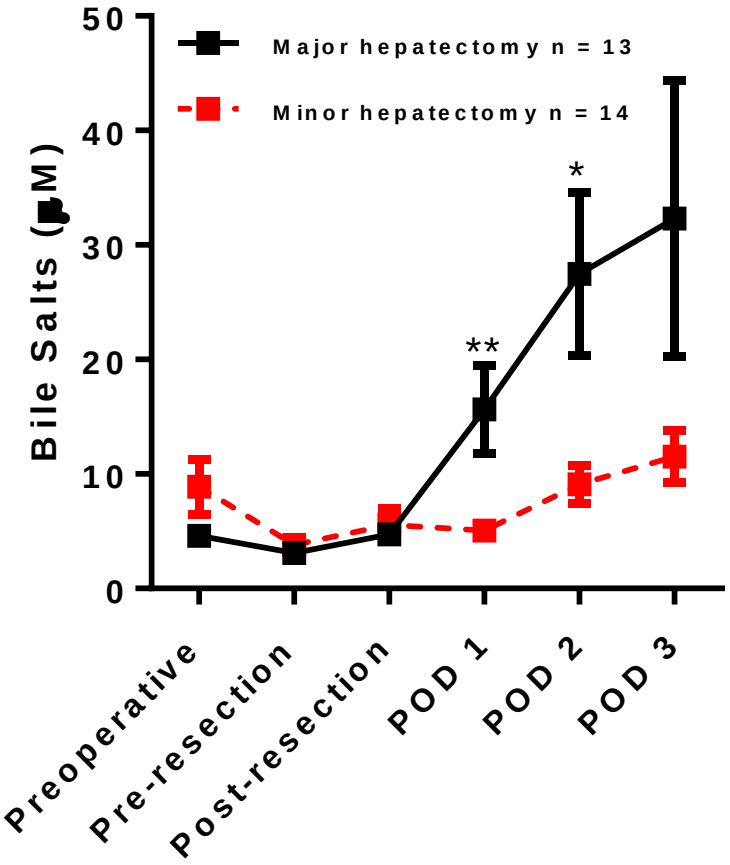
Pathogenesis of PLF – bile salts

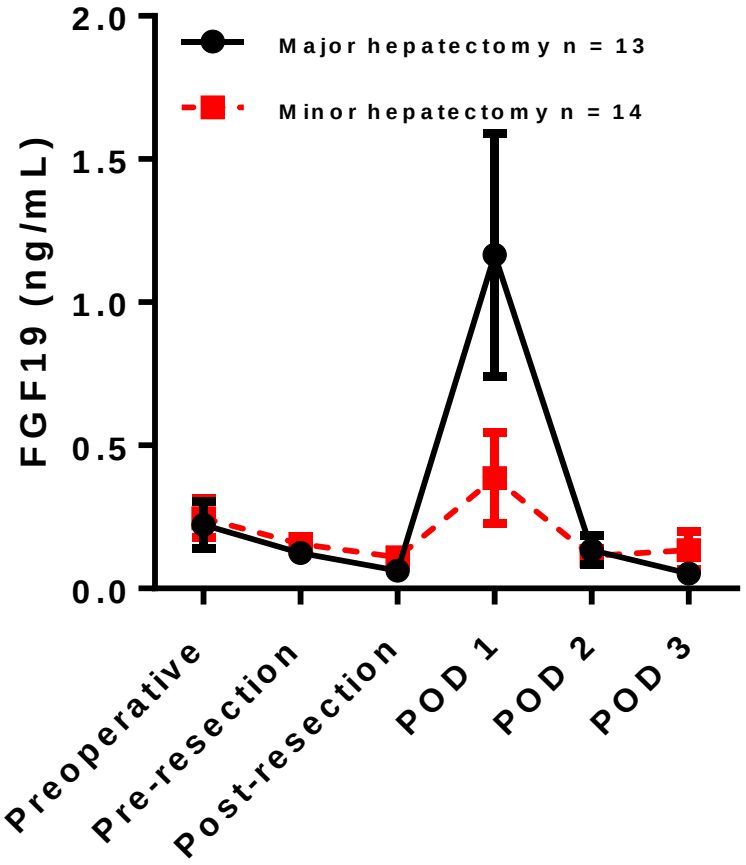
- **Unmet hepatic metabolic demand**
  - Dysfunction of canalicular transporters → hepatic accumulation of bile salts (BS)
  - Stimulation of hepatic nuclear receptors involved in BS homeostasis and fibroblast growth factor 19 (Fgf19) signaling contribute to modulation of BS
  - Disruption leads to accumulation of toxic bile constituents → damaged internal hepatocellular membranes and apoptosis



Uriarte, Gut 2013

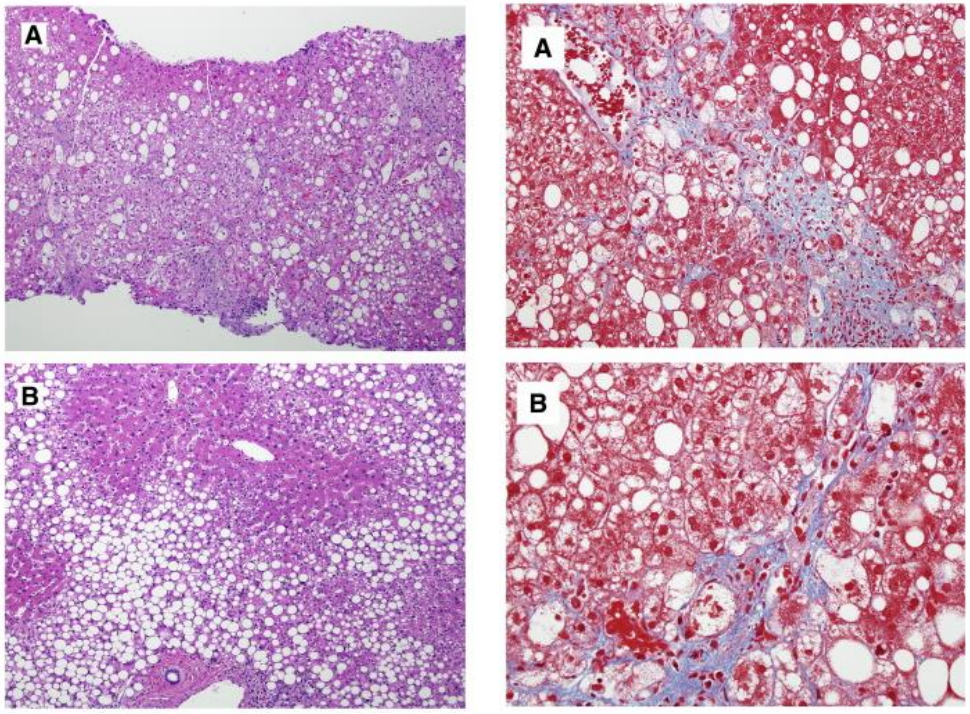
Pathogenesis of PLF – bile salts



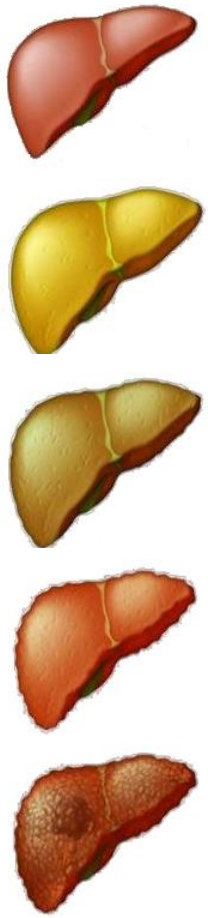


Pathogenesis of PLF – liver disease

- **NAFLD/NASH (CRLM, HCC)**
  - Prevalence: ~20-30% of adults in Western population NAFLD, 3-5% NASH
  - Risk factors for PLF and higher postoperative morbidity & mortality



NASH without and with fibrosis

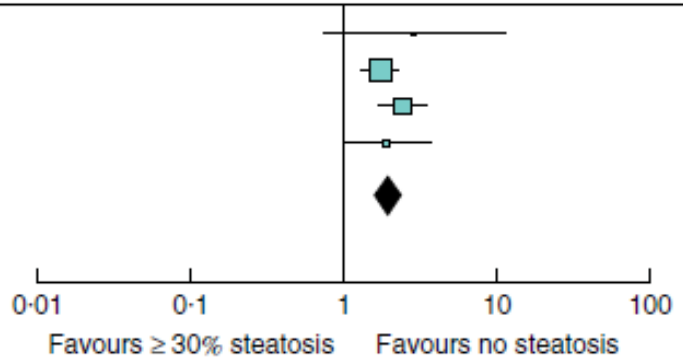


de Meijer, Br J Surg 2010
Vernon, Aliment Pharmacol Ther 2011
Reddy, Hepatology 2012

Pathogenesis of PLF – liver disease

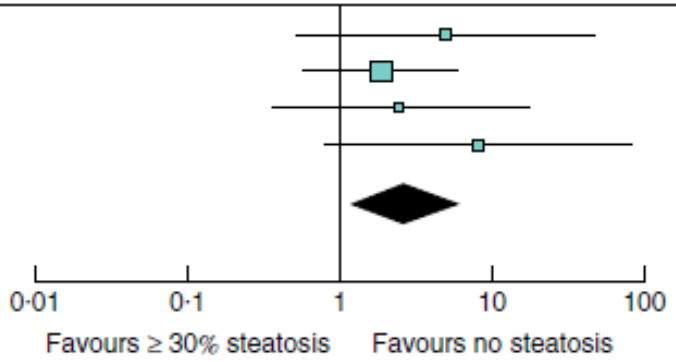
Reference	Complication rate ≥ 30% steatosis	Complication rate No steatosis	Risk ratio	Weight (%)
Behrns *et al.*[21]	2 of 7	7 of 72	2·94 (0·75, 11·52)	2·0
Kooby *et al.*[22]	63 of 102	56 of 160	1·76 (1·36, 2·29)	54·7
Gomez *et al.*[23]	36 of 51	37 of 128	2·44 (1·77, 3·38)	35·3
McCormack *et al.*[24]	7 of 14	15 of 58	1·93 (0·98, 3·82)	8·0
Overall	108 of 174	115 of 418	2·01 (1·66, 2·44)	100·0

Test for heterogeneity: $\chi^2 = 2{\cdot}66$, 3 d.f., $P = 0{\cdot}45$, $I^2 = 0\%$
Test for overall effect: $Z = 7{\cdot}12$, $P < 0{\cdot}001$



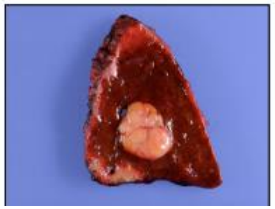
Reference	Mortality rate ≥ 30% steatosis	Mortality rate No steatosis	Risk ratio	Weight (%)
Behrns *et al.*[21]	1 of 7	2 of 72	5·14 (0·53, 49·86)	14·0
Kooby *et al.*[22]	6 of 102	5 of 160	1·88 (0·59, 6·01)	53·5
Gomez *et al.*[23]	2 of 51	2 of 128	2·51 (0·36, 17·34)	19·3
McCormack *et al.*[24]	2 of 14	1 of 58	8·29 (0·81, 85·03)	13·3
Overall	11 of 174	10 of 418	2·79 (1·19, 6·51)	100·0

Test for heterogeneity: $\chi^2 = 1{\cdot}59$, 3 d.f., $P = 0{\cdot}66$, $I^2 = 0\%$
Test for overall effect: $Z = 2{\cdot}37$, $P = 0{\cdot}02$

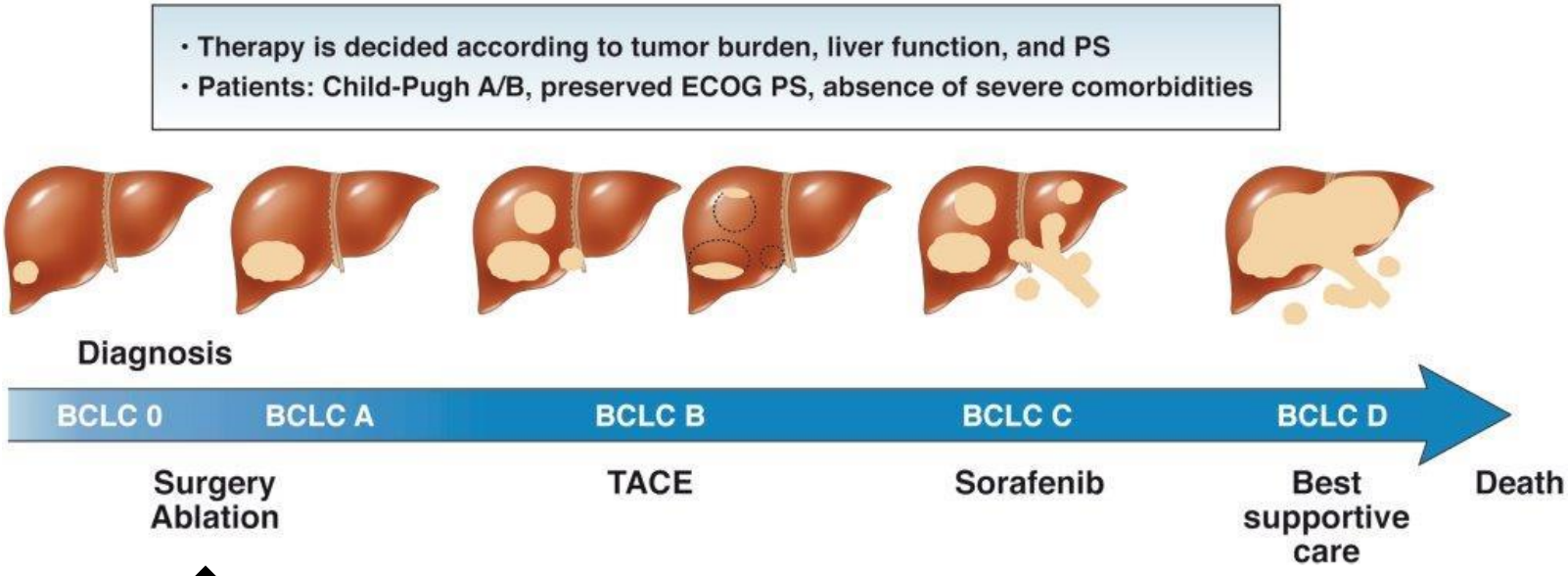


de Meijer, Br J Surg 2010

Pathogenesis of PLF – liver disease



- **Fibrosis and cirrhosis (HCC)**
  - Mostly related to chronic viral hepatitis or by progression of steatosis
  - Mortality rate average (0-5%) due to strict patient selection & hepatic function assessment



de Lope, J Hepatol 2012
Bruix, Gastroenterology 2016

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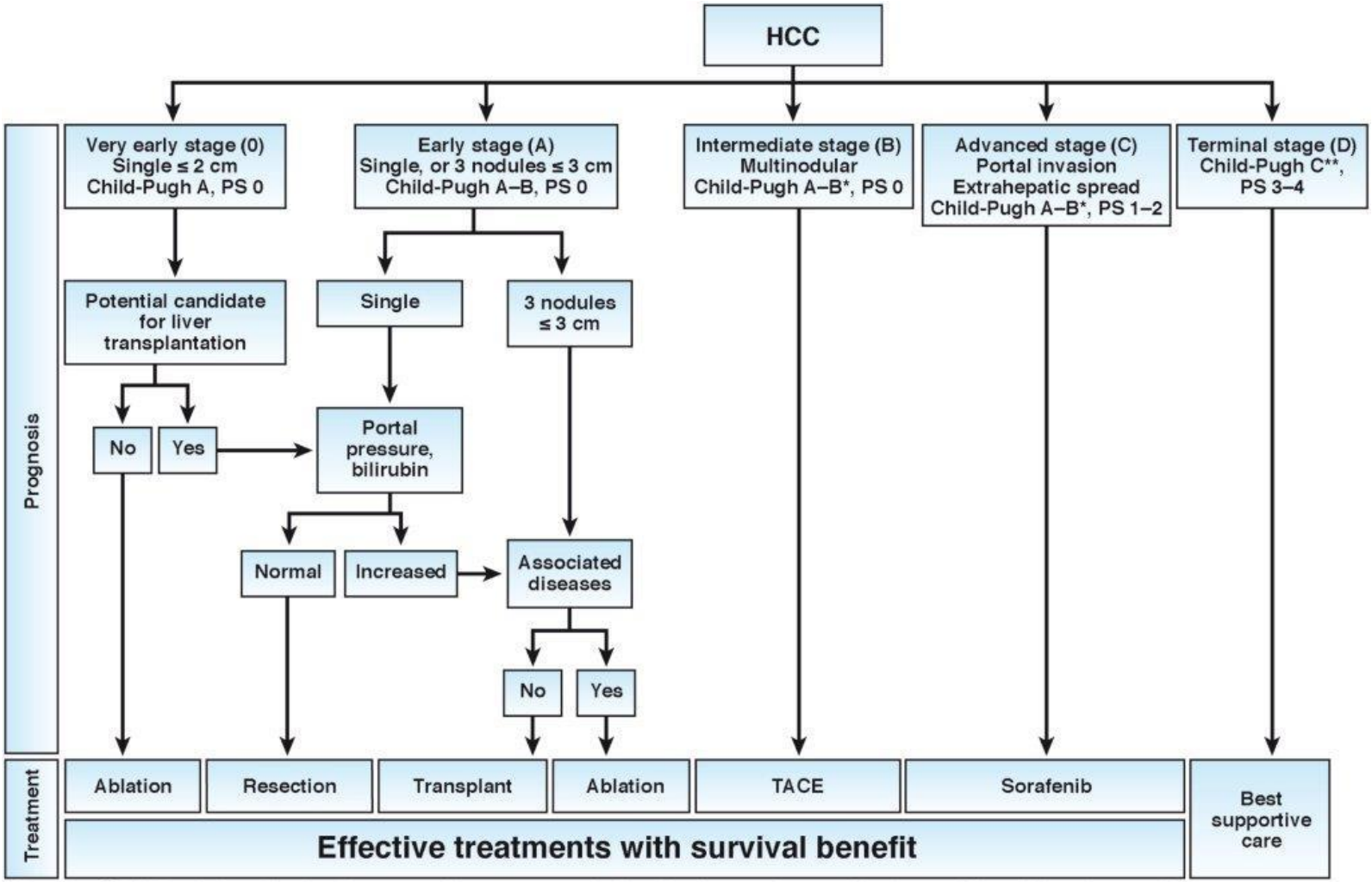


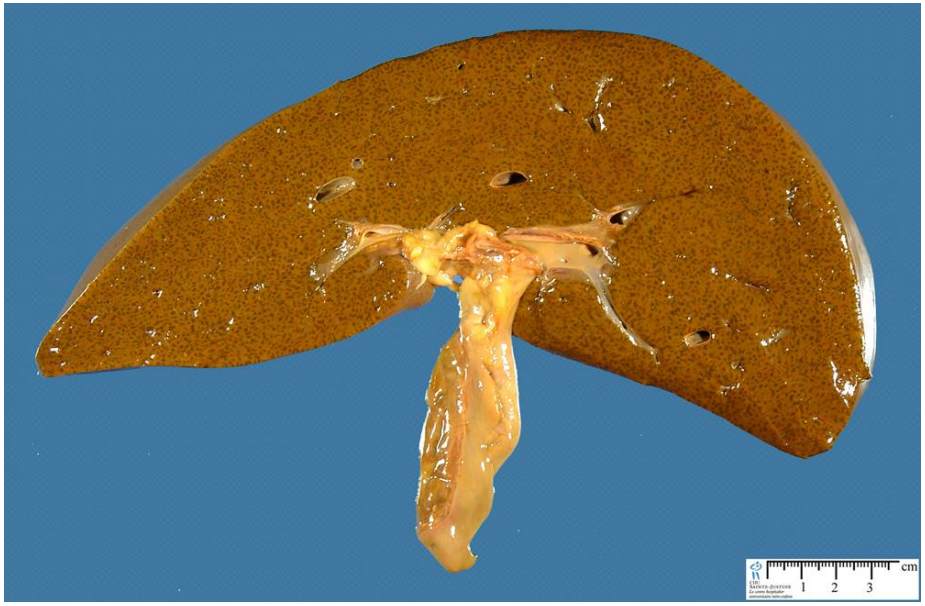
*Note that Child-Pugh classification is not sensitive to accurately identify those patients with advanced liver failure that would deserve liver transplant consideration.

**Patients with end stage cirrhosis due to heavily impaired liver function (Child-Pugh C or earlier stages with predictors of poor prognosis, high MELD score) should be considered for liver transplantation. In them, HCC may become a contraindication if exceeding the enlistment criteria.

Bruix, Gastroenterology 2016

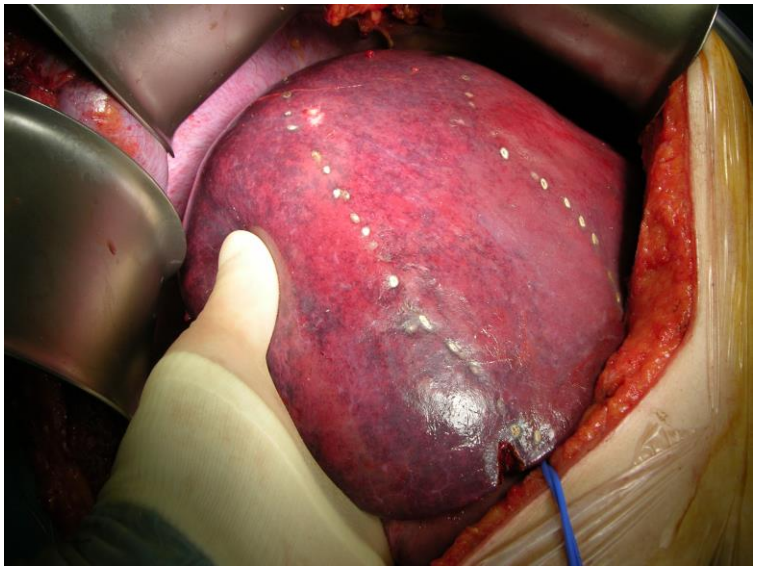
Pathogenesis of PLF – liver disease

- **Cholestasis (iCCA, pCCA)**
  - Resection for pCCA → PLF in 30% and mortality in 8-12% of patients
  - Resection for iCCA → few patients develop PLF and mortality in 1% of patients

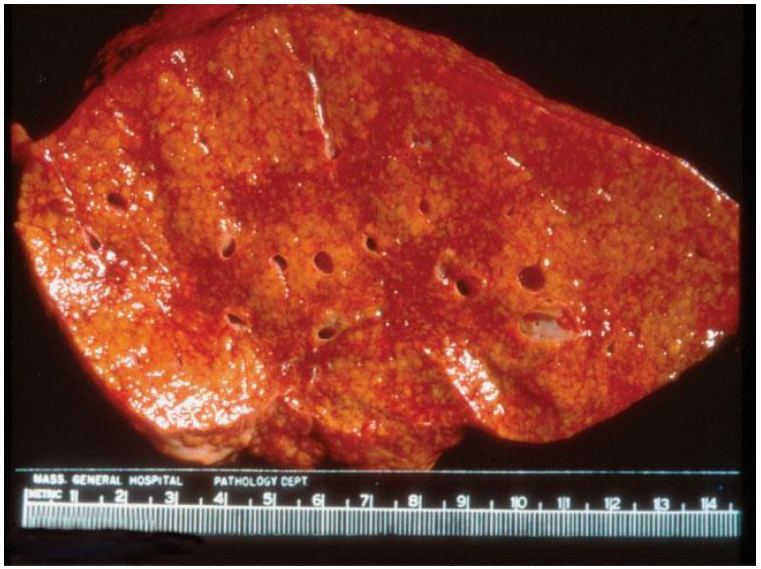


Pathogenesis of PLF – liver disease

- **Chemotherapy-associated liver injury (CALI)**
  - Sinusoidal obstruction syndrome (SOS, Oxaliplatin)
  - Chemotherapy-associated steatohepatitis (CASH, Irinotecan?)
  - Nodular regenerative hyperplasia

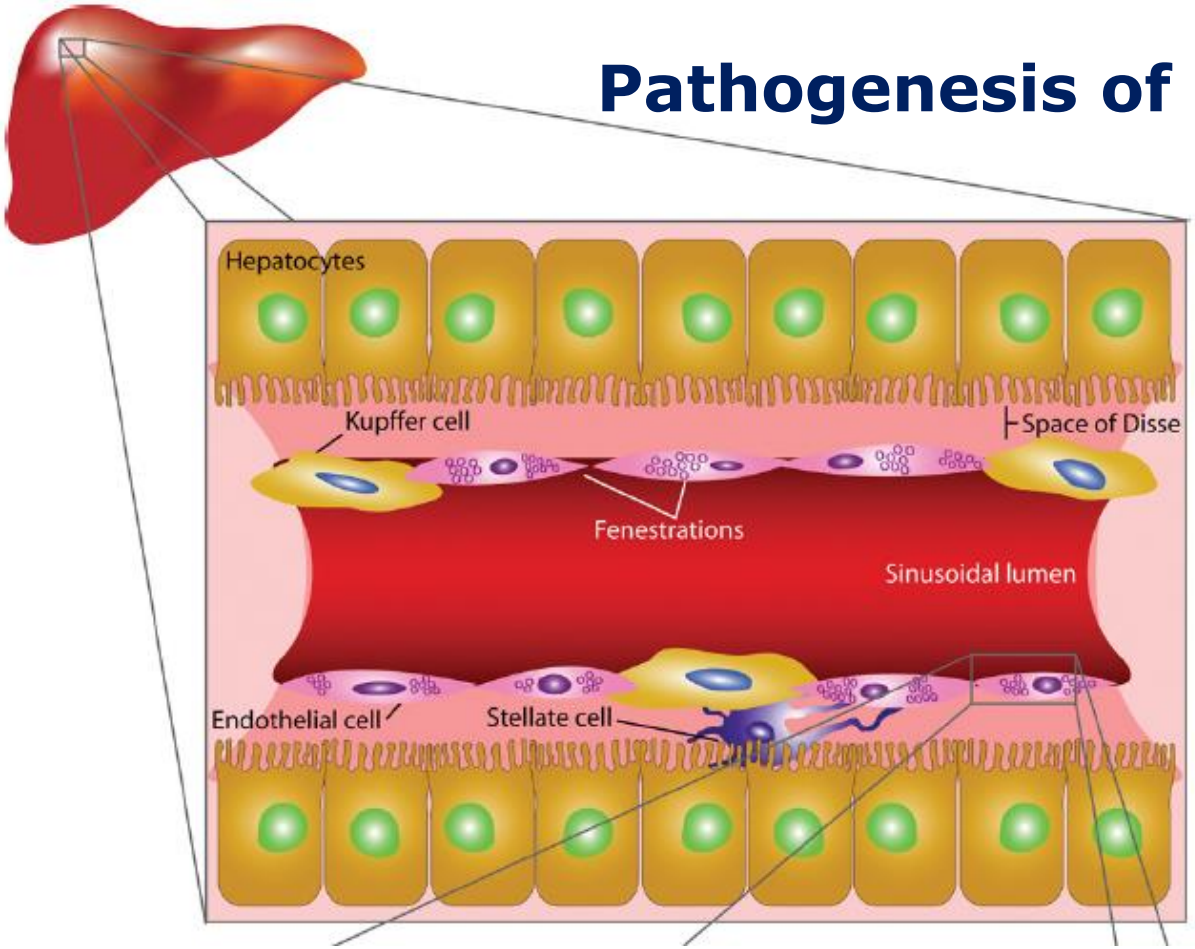


Blue liver
SOS



Fatty "yellow" liver
steatohepatitis

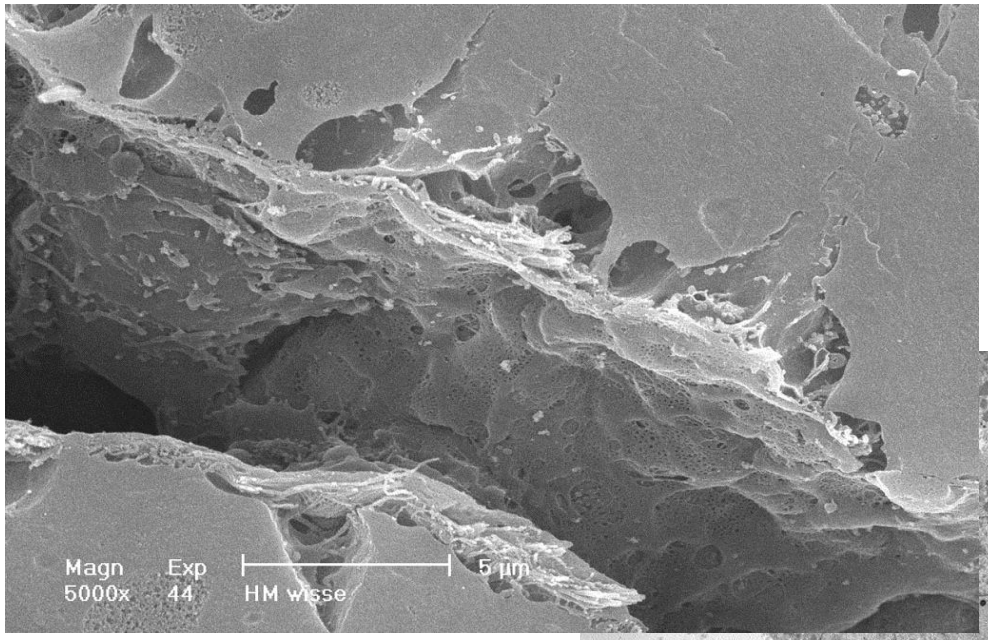
Pathogenesis of PLF – SOS

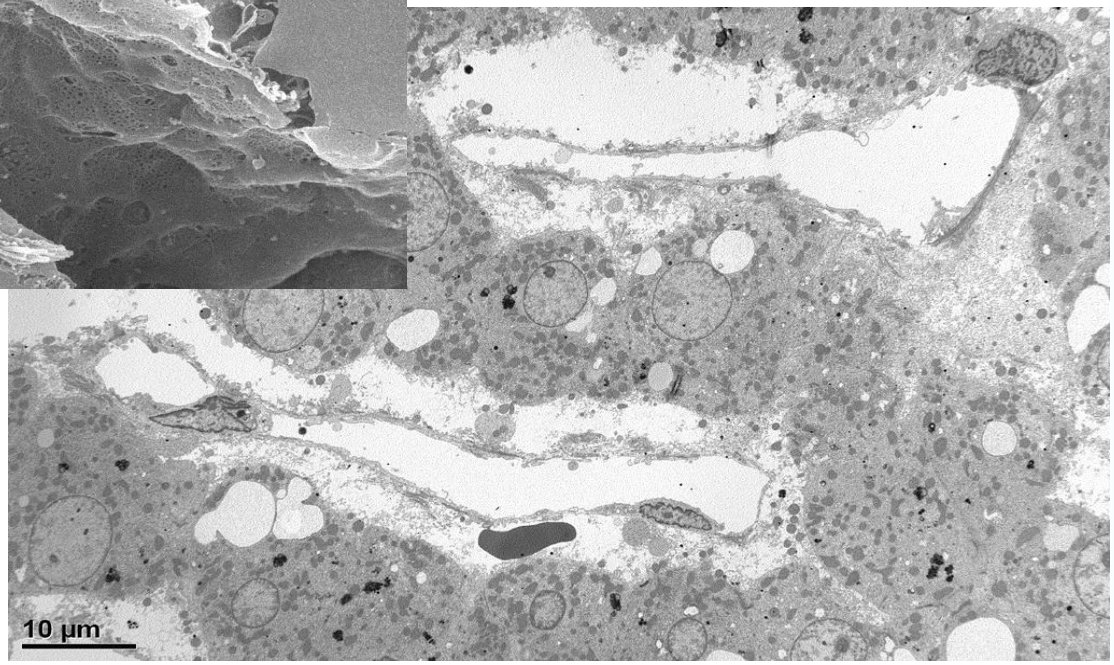


- Injury of sinusoidal endothelium → extravasation of RBCs → venous outflow obstruction → congestion → fibrotic changes

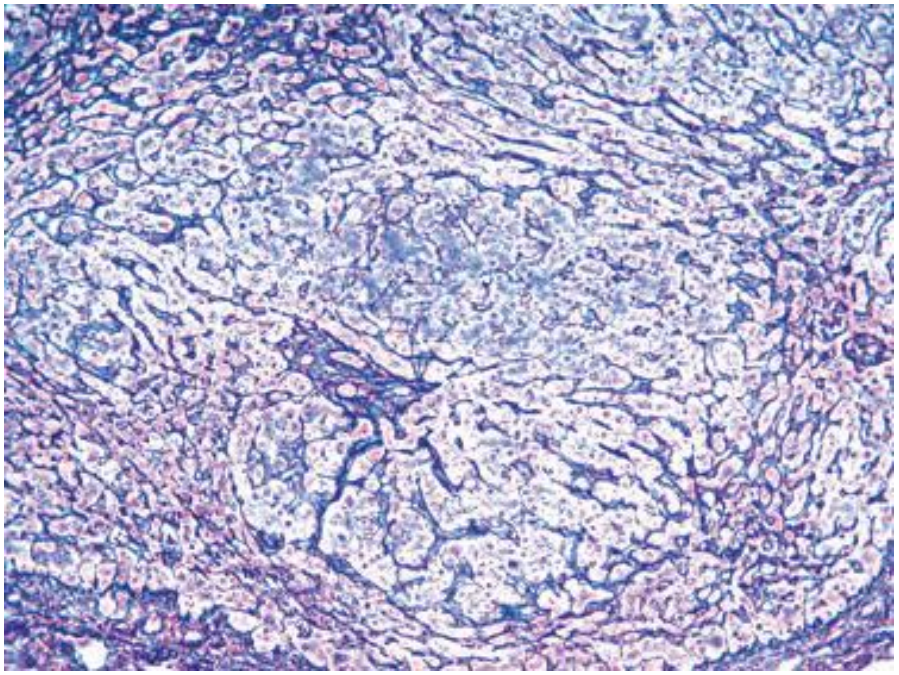
Jacobs, Wisse Am J Path 2010

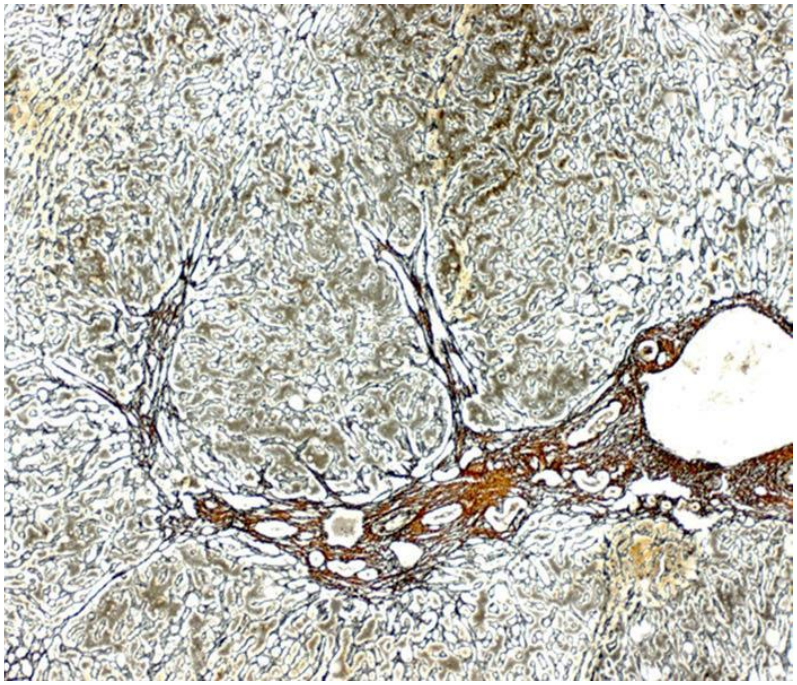
Pathogenesis of PLF – SOS





Nodular regenerative hyperplasia (NRH)





Rubbia-Brandt, Histopathology 2010
Viganò, Ann Surg Oncol 2015

Pathogenesis of PLF – NRH

- Prevalence of NRH increased after oxaliplatin administration (21.4 vs. 8.4 %, p = 0.003)
  - Prevalence reduced by addition of bevacizumab (11.7 vs. 19.8 %; p = 0.020)
- NRH is an independent predictor of PLF (9.2 vs. 2.3%, p= 0.021)
- In patients with grades 2-3 NRH, the rate of PLF was 14.3%
  - 25.0% after major hepatectomy

Most severe liver injury?

Viganò, Ann Surg Oncol 2015

Pathogenesis of PLF – CASH

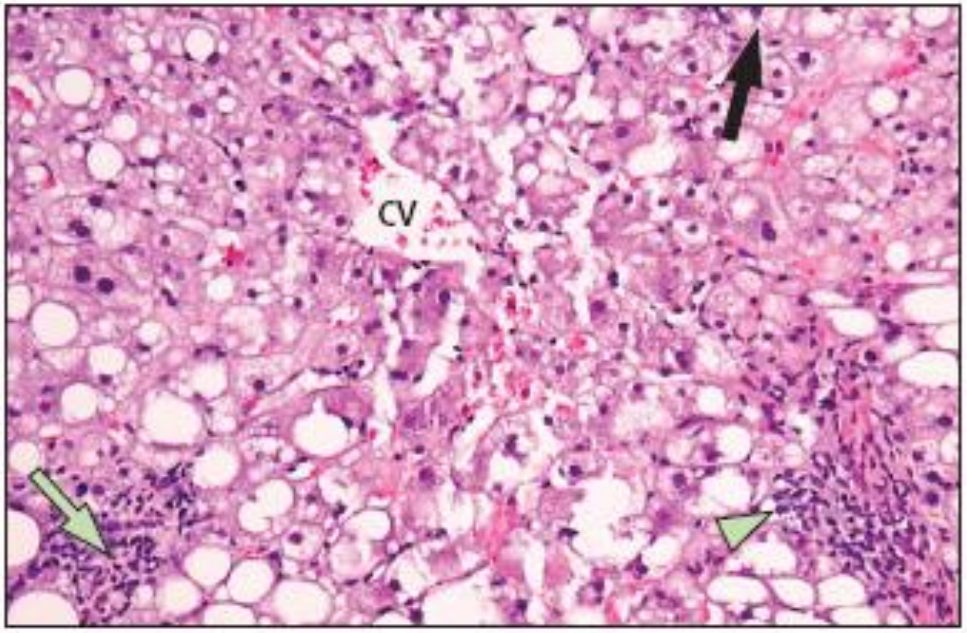
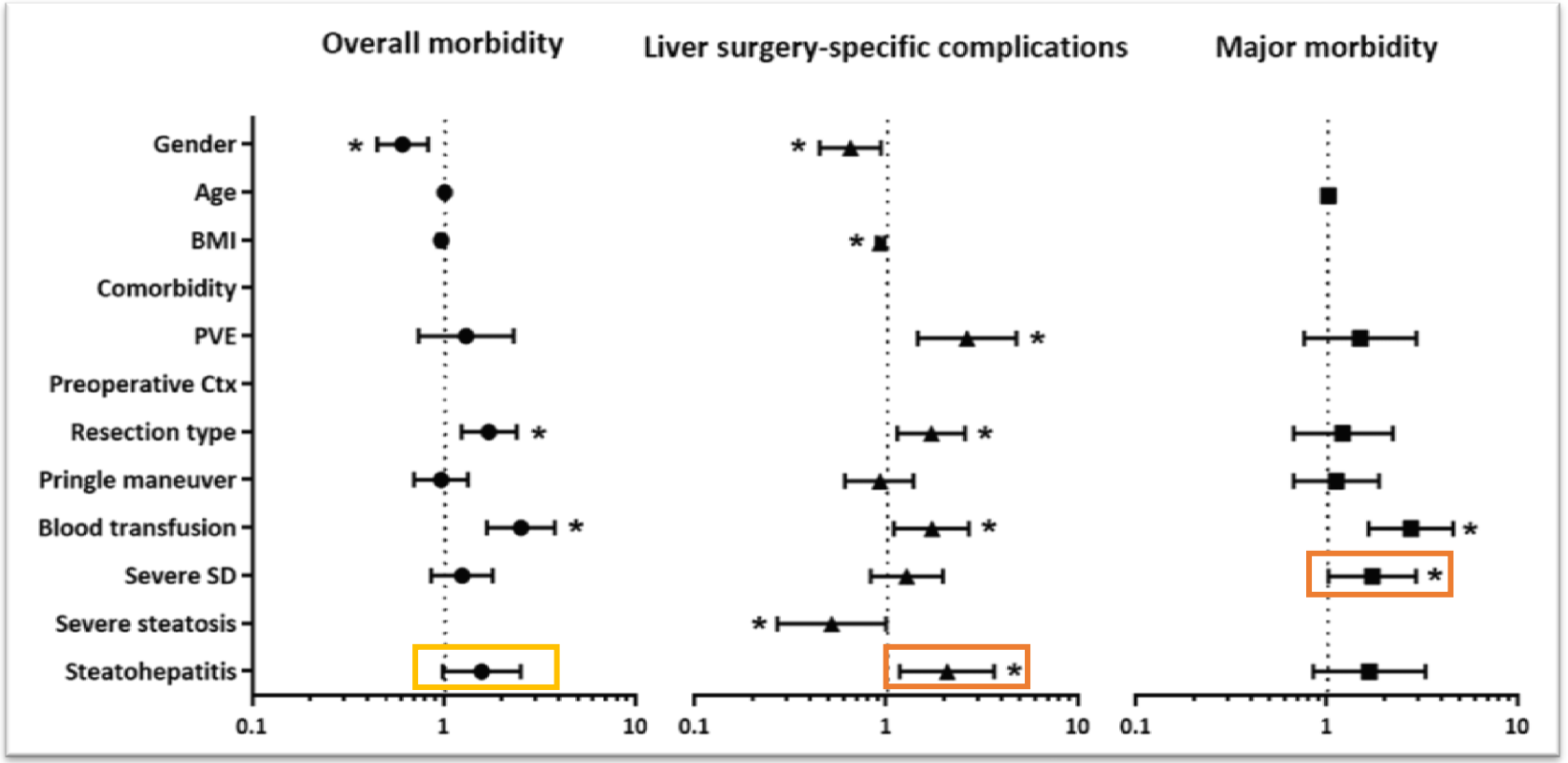


Figure 3: Steatohepatitis
Moderate steatosis (40–50% of hepatocytes), hepatocyte-ballooning degeneration (black arrow), lobular inflammation (green arrow), and portal inflammation (green arrowhead). Kleiner score for non-alcoholic fatty liver disease is 6. CV=central vein. Stained with haematoxylin and eosin, magnification ×200.

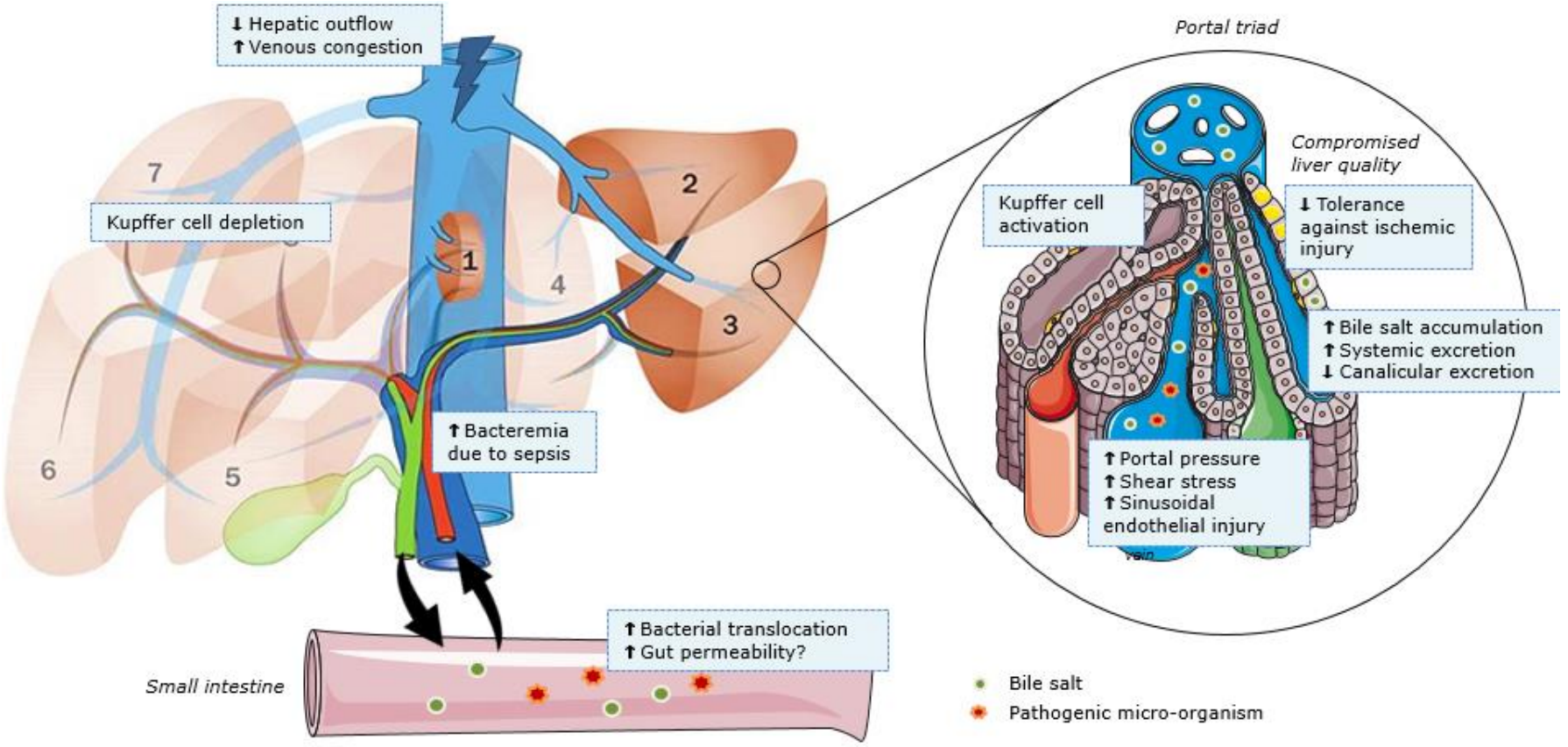
- Excess of fatty acids → oxidation →O2 radicals → second hit → cellular death

Pathogenesis of PLF – CALI



Zhao, in preparation

Overview pathogenesis of PLF



Van Mierlo et al. J Hep 2016

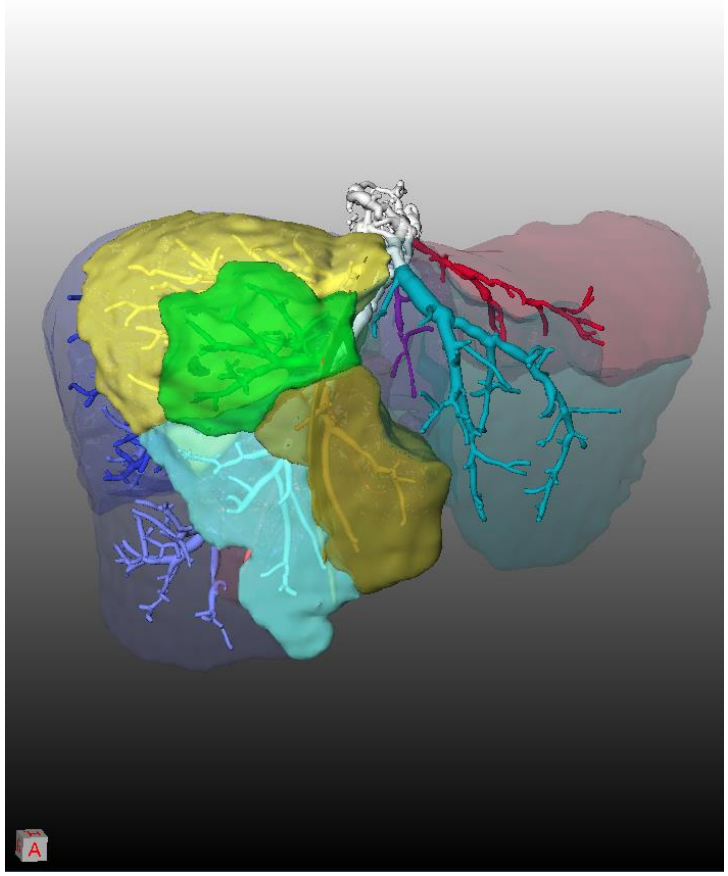
Prevention

- Optimize preoperative liver function
  - Nutrition, fitness, biliary drainage in cholestasis, diet?
- Limit hepatic haemodynamic disbalance
  - Splenectomy and splenic artery ligation → activation hepatic arterial buffer response
- Provide optimal perioperative care
  - Prevent perioperative excessive blood loss, blood transfusion, hepatic manipulation
  - Low CVP (<5cm H20)
  - Pringle-Manoeuvre

Melendez et al. 2002, 2005

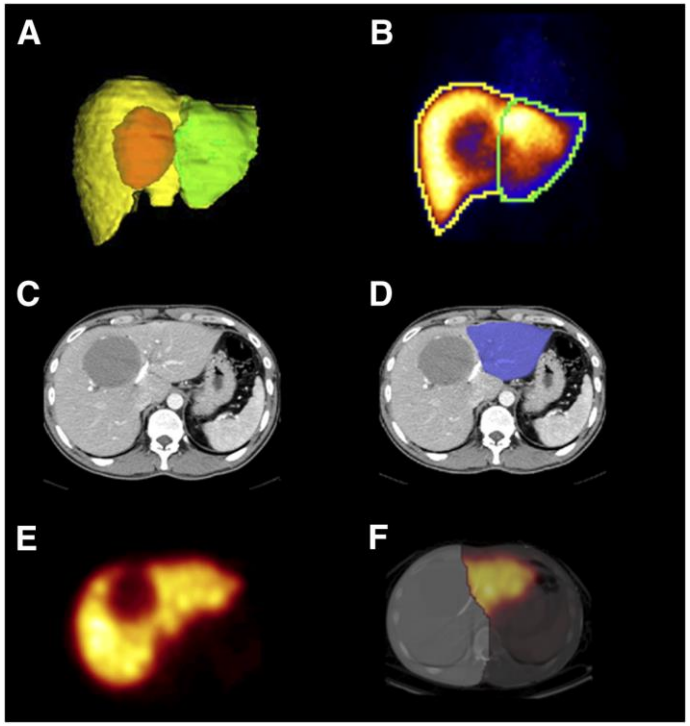
Prevention - volumetry

- 2D volumetry – preoperative 3D modelling



Prevention - functional tests

- Biochemistry
  - Secretory, synthetic and detoxifying funtion (bilirubin, INR, ALT, AST, ammonia, metabolites)
- Breath tests
  - LiMAx
  - ICGR-15
- Imaging
  - ^{99m}Tc-labeled GSA liver scintigraphy
  - ^{99m}Tc-mebrofenin hepatobiliary scintigraphy with SPECT
  - Gladolinium-enhanced MRI



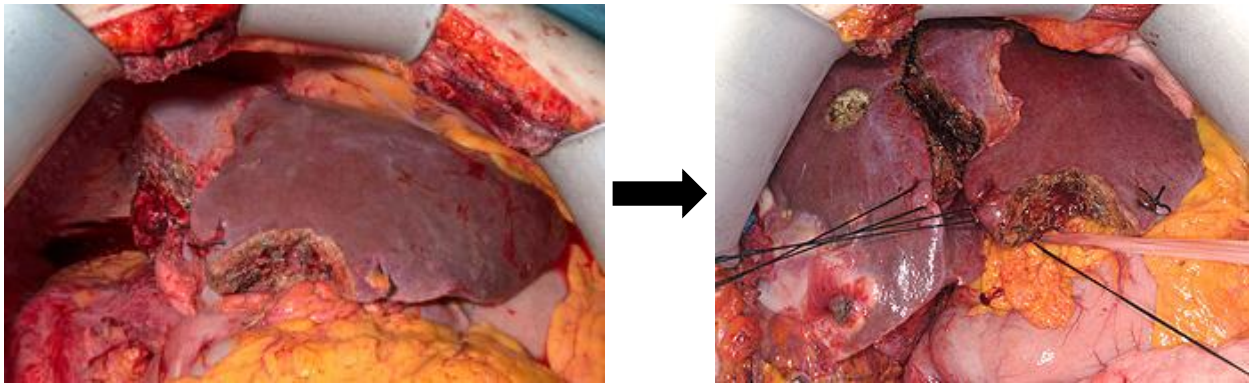
de Graaf, J Nucl Med 2010

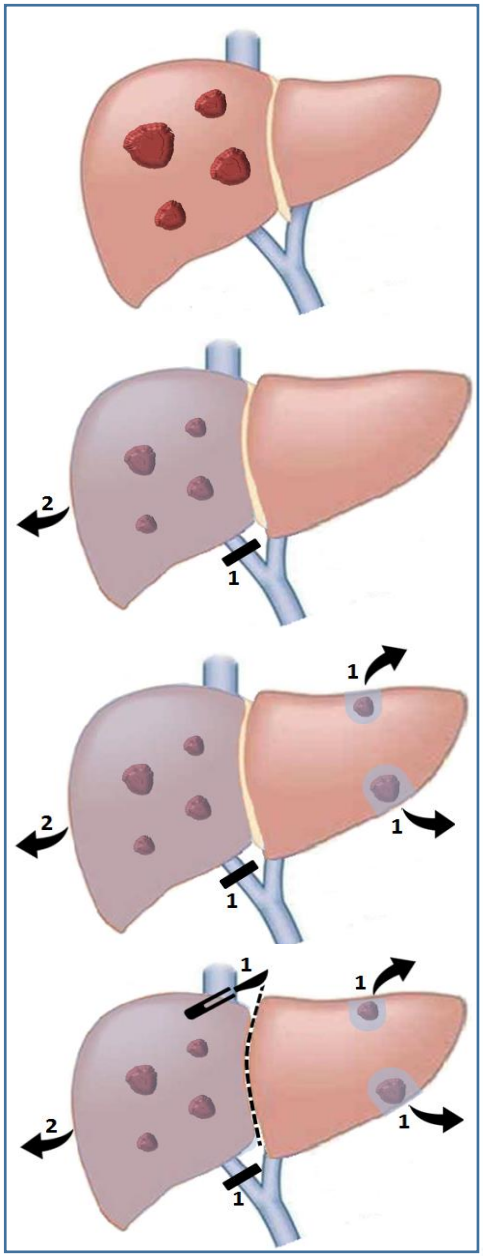
Prevention – liver enlargement

- Enlarge remnant liver volume
  - Portal vein embolization
  - Two-stage hepatectomy
  - ALPPS

1 = tempus 1
2 = tempus 2

ALPPS registry
Severe morbidity: 28%
Mortality: 9%





Current therapies

- Goal-directed therapy

Table 3. Goal-directed therapy in patients suffering from post-resectional liver failure

Circulatory disturbances	CVP 8–12 mmHg
	MAP 65–90 mmHg
	Haematocrit ≥30%
	Pulmonary capillary wedge pressure ≤12–15 mmHg
Renal dysfunction	Urine output ≥0.5 mL/kg/h
Ventilatory dysfunction	Arterial oxygen saturation ≥93%
	Central venous oxygen saturation ≥70%
Hepatic encephalopathy	Improvement to grade ≤2
Coagulopathy	In case of bleeding
	Platelet count ≥50 × 10^9/L
	International standardized ratio ≤1.5
Malnutrition	Enteral energy supply of 2000 kcal/day

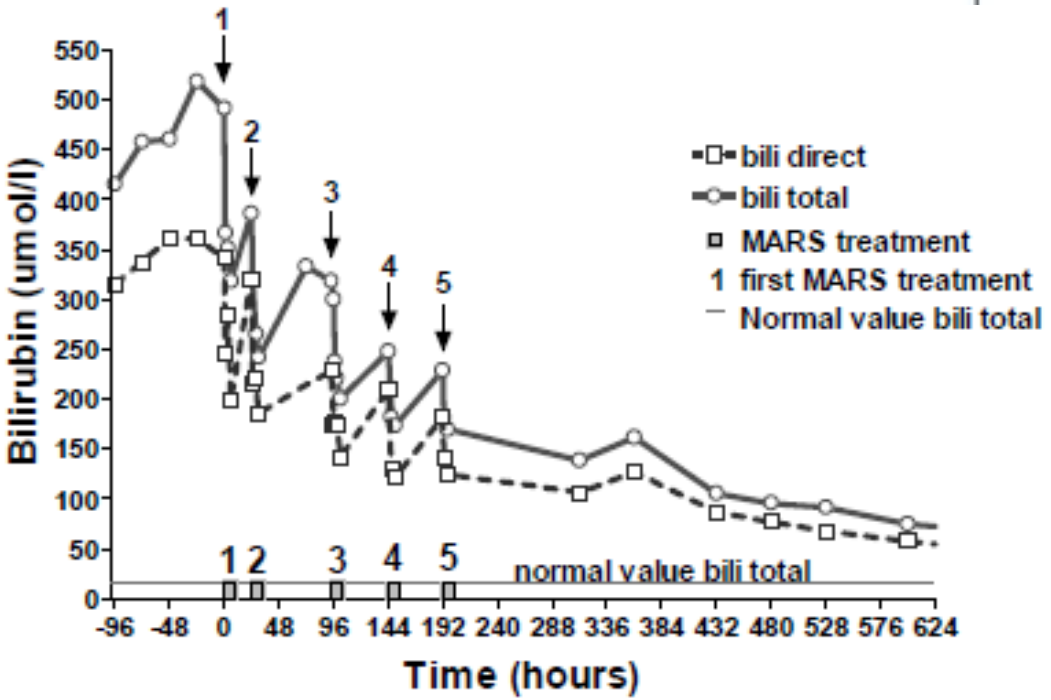
CVP, central venous pressure; MAP, mean arterial pressure.

van den Broek, Liver Int 2008

Current therapies

- **Functional support**
- Molecular absorbent recirculation system (MARS)
- Extracorporeal bio-artificial liver devies (BAL)

- Extracorporeal high-flux hemodialysis with albumin dialysis (Prometheus)
- High-volume plasmapheresis



van de Kerkhove, Liver Int 2003

NUTRIM School of Nutrition and Translational Research in Metabolism

High-volume plasmapheresis

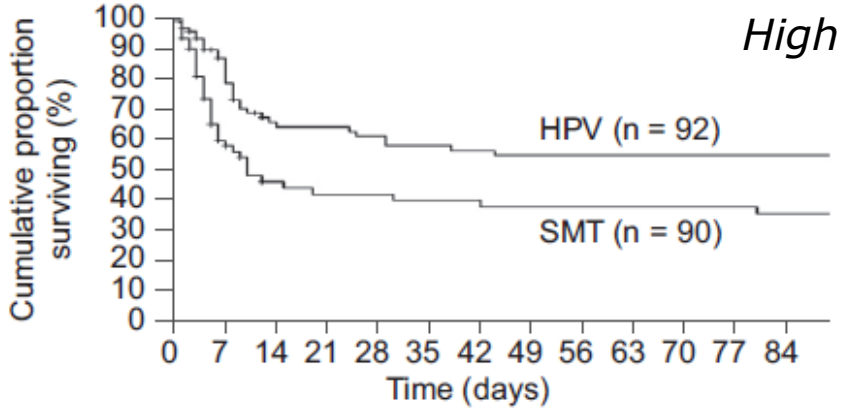


Fig. 1. Main results of the intention-to-treat analysis survival data in the standard medical treated group (SMT) compared to the high-volume plasma exchange (HVP) treated group (LogRank: $p = 0.0058$).

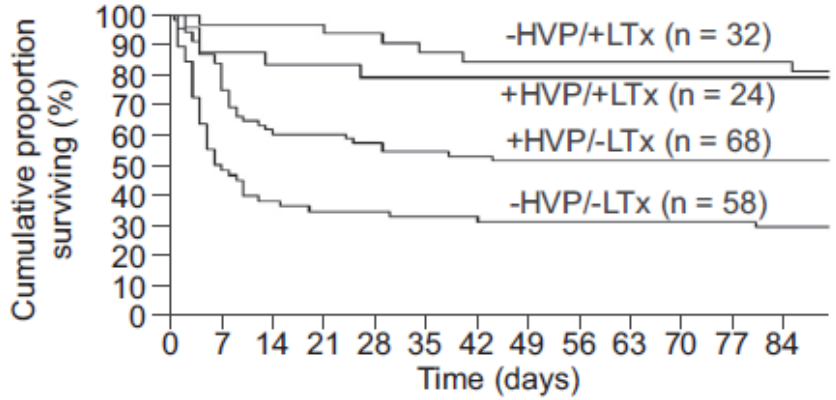


Fig. 2. Survival in the groups, in the two groups receiving SMT (standard medical treated group) with and without emergency transplantation (–HVP +LTx *vs.* +HVP–LTx) and the two group receiving SMT with and without emergency transplantation (–HVP–LTx *vs.* +HVP–LTx) (LogRank: $p = 0.0058$) and Cox proportional hazard: LTx: $p < 0.0001$; HVP: $p = 0.0076$).

Larsen, J Hepatol 2016

Current therapies

- Rescue liver transplantation → Not often performed, however in Norway:

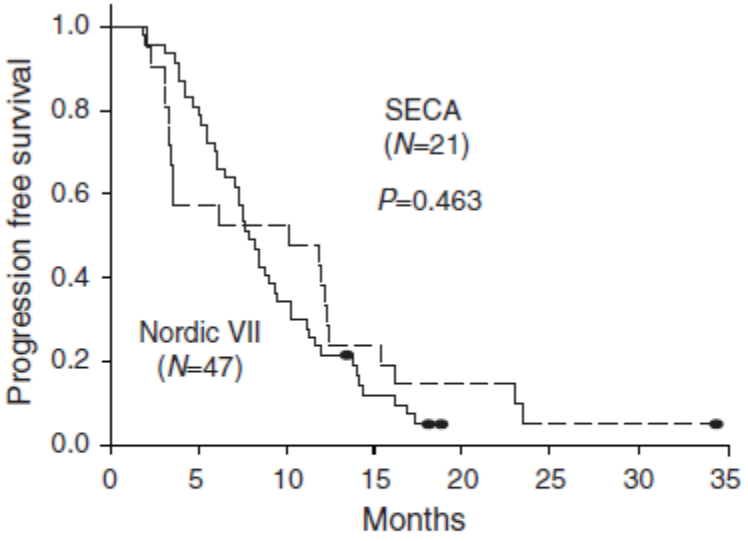


FIGURE 1. PFS for patients included in the liver transplantation group (SECA study, hatched line, n = 21) and the chemotherapy group (NORDIC VII study, solid line, n = 47).

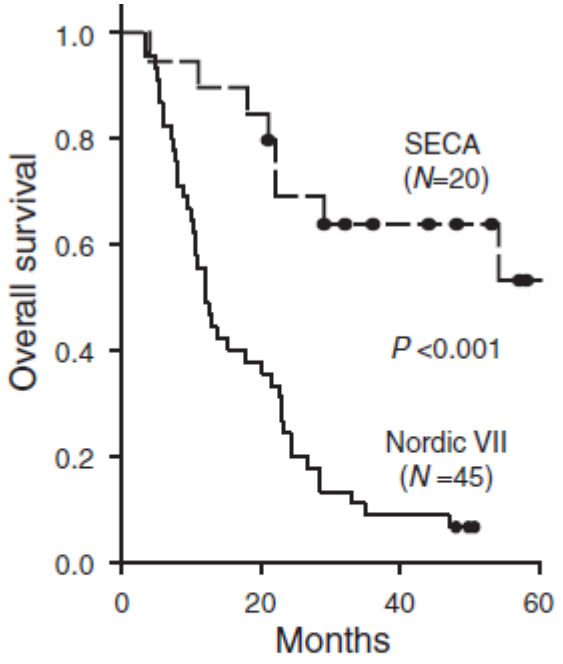
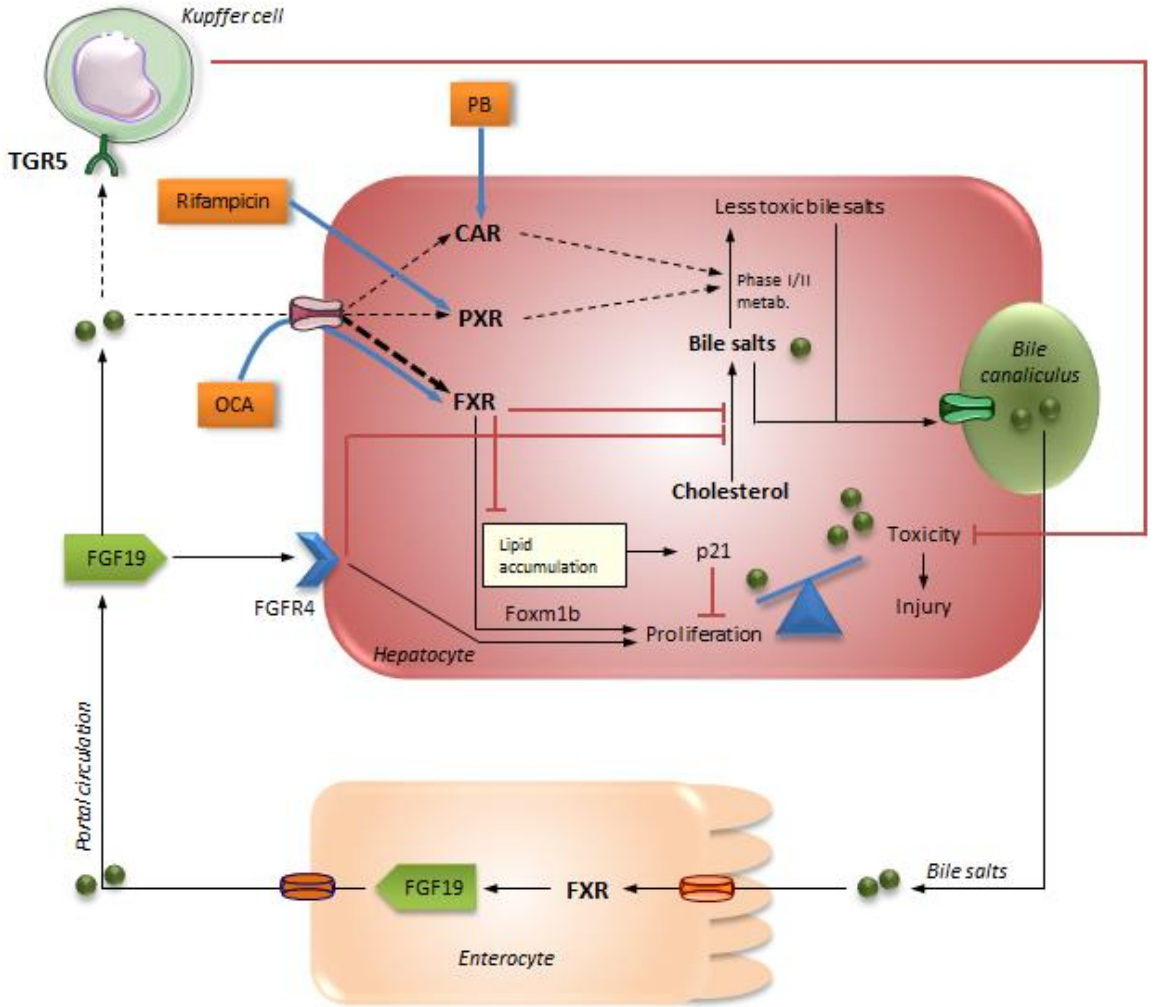


FIGURE 3. Kaplan-Meier OS curve from time of progressive disease for patients included in the liver transplantation group (SECA study, hatched line, n = 20) and the chemotherapy group (NORDIC VII study, solid line, n = 45, 2 patients with similar OS and PFS were excluded from analysis).

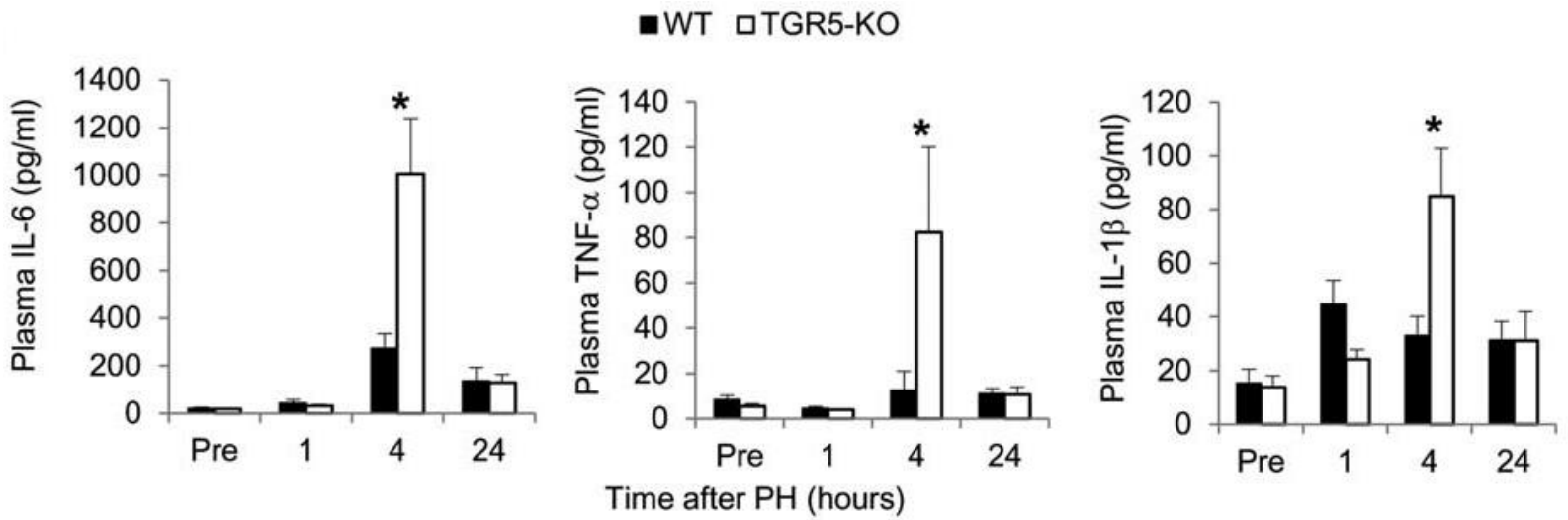
Dueland, Ann Surg 2015

Future therapies



Regenerative medicine – TGR5

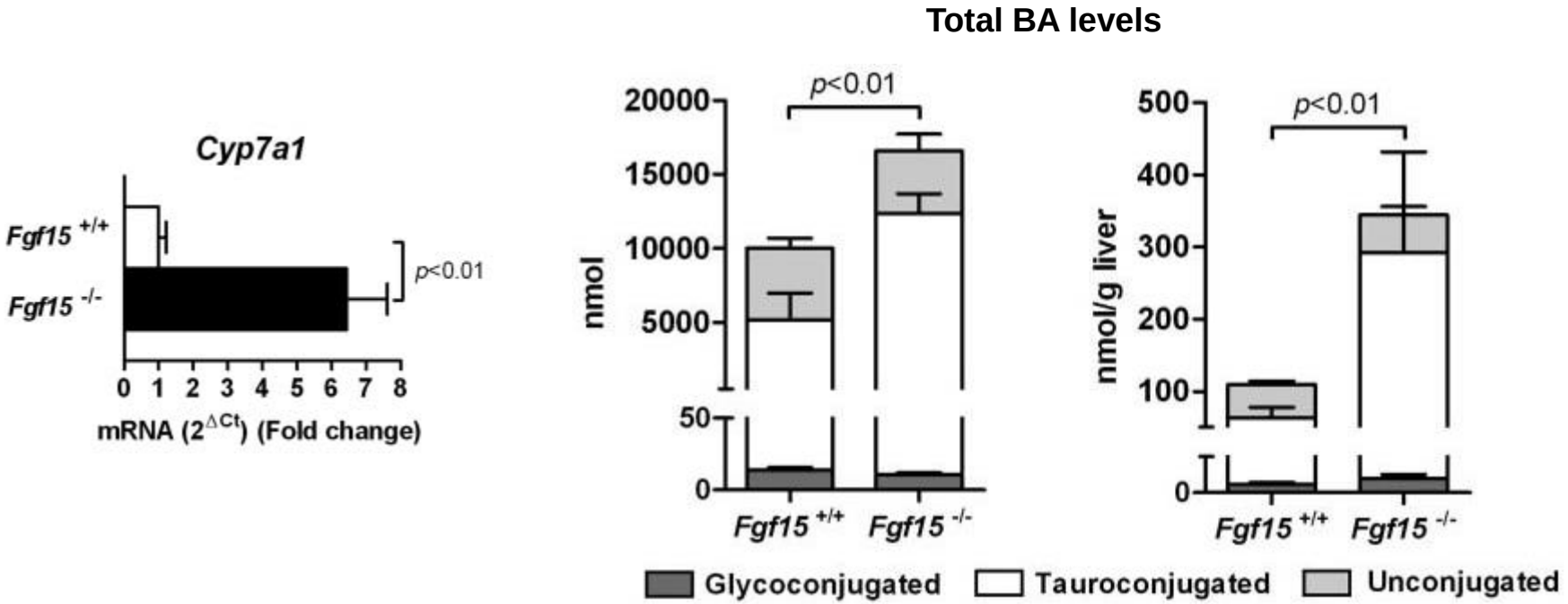
TGR5 protects from bile acid overload during liver regeneration



- *TGR5* KO mice after 2/3 PH → increased inflammation

Pean et al. 2013 Hepatology

Regenerative medicine – Fgf15



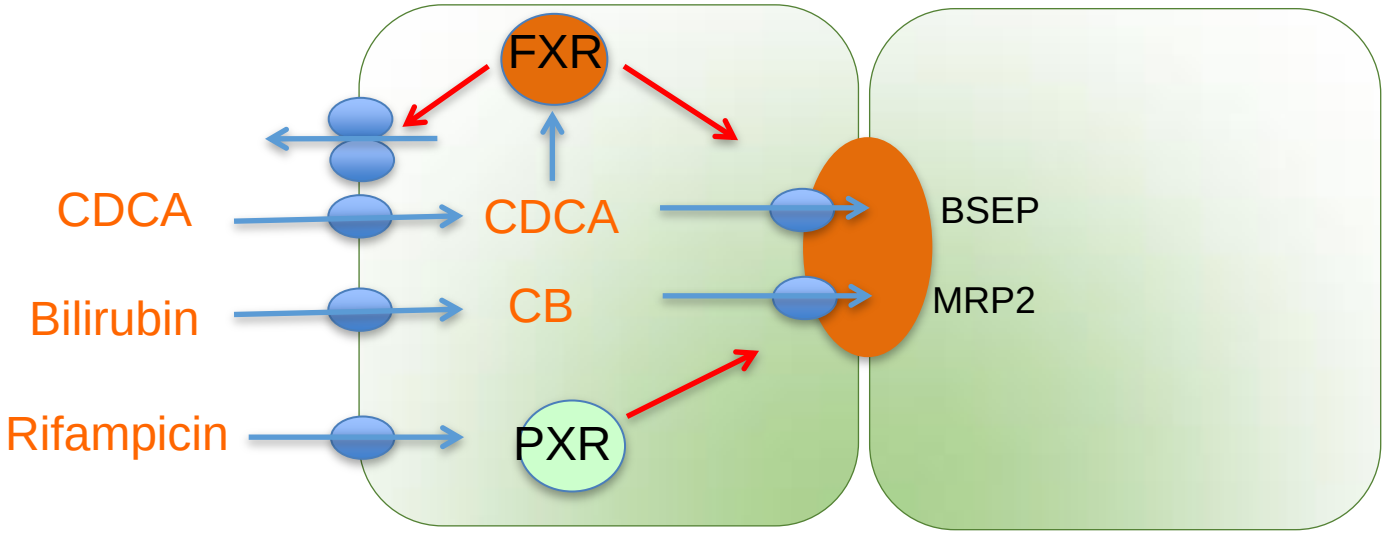
Fgf15 KO mice after 70% PH:

- Increased Cyp7a1
- Increased total and intrahepatic bile acid levels

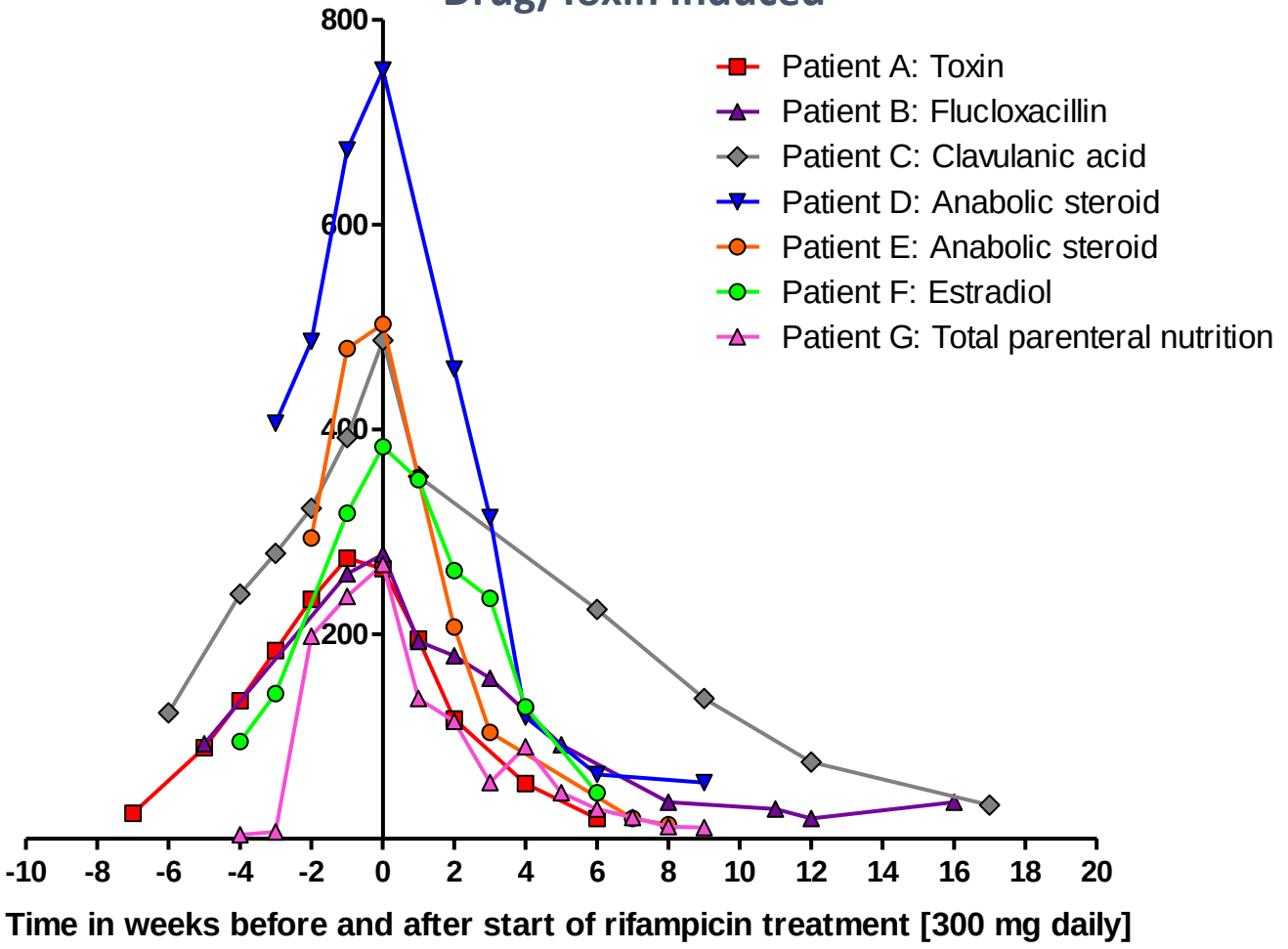
Uriarte et al. 2013 Gut

Regenerative medicine – PXR

- Member of nuclear receptor family
- Activated by bile acids
- Controls hepatic drug detoxification by promoting phase I and II reactions
- Phase III elimination of compounds including bilirubin and bile salts



Severe Persistent Hepatocellular Secretory Failure
Drug/Toxin Induced



van Dijk, Liver Int 2014

Acknowledgements

Maastricht	Kees Dejong	Frank Schaap
	Peter Jansen	Liyanne vd Laarschot
	Kiran Koelfat	**Kim van Mierlo**
	Maartje van den Broek	
UCL, London	Liver Unit	Rajiv Jalan
	Surgery	Max Malago, Dipok Dhar
UCL, Brussels	Liver Unit	Isabelle Leclerq
AMC, Amsterdam	Liver Unit	Ulrich Beuers, Peter Jansen
	Surgery	Thomas van Gulik

Thank you for your attention