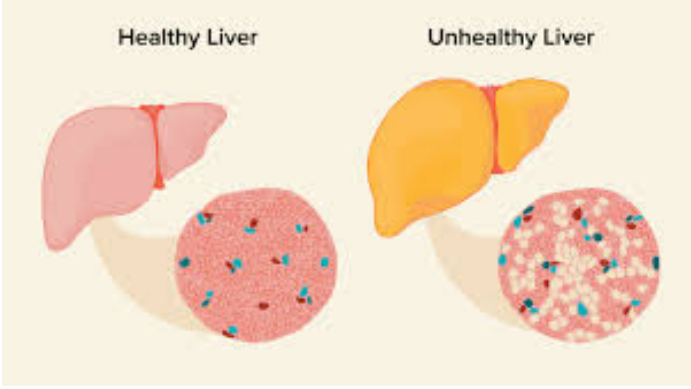
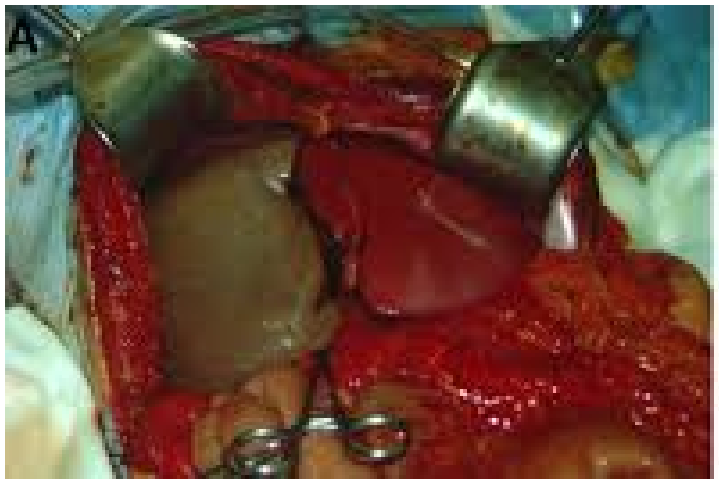
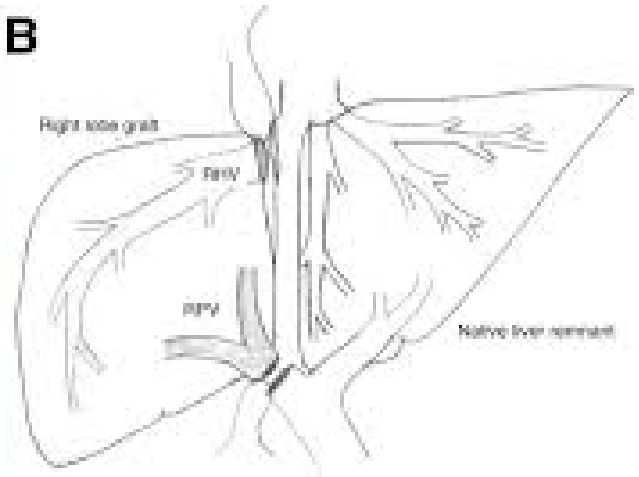
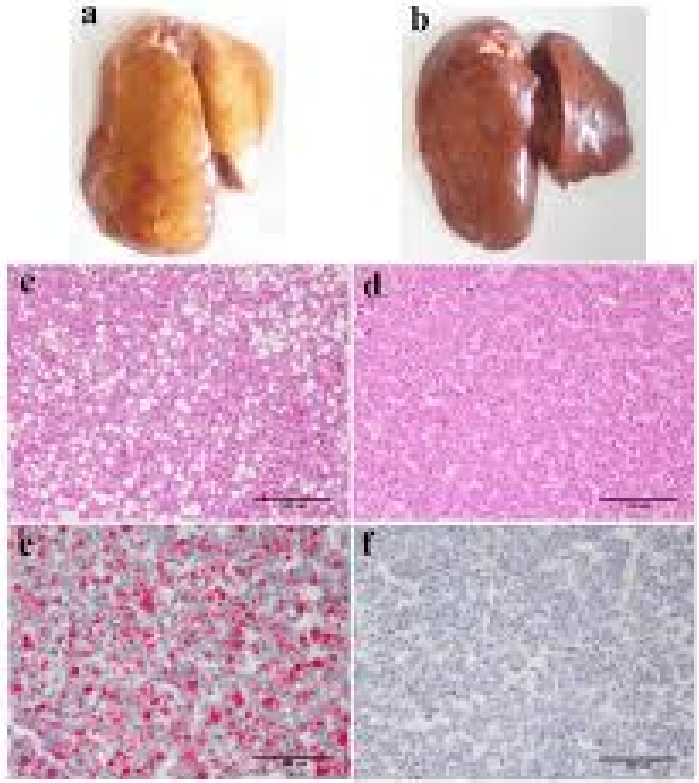


Fatty grafts in Liver Transplant

Dr.Dhanushi Abeynayake





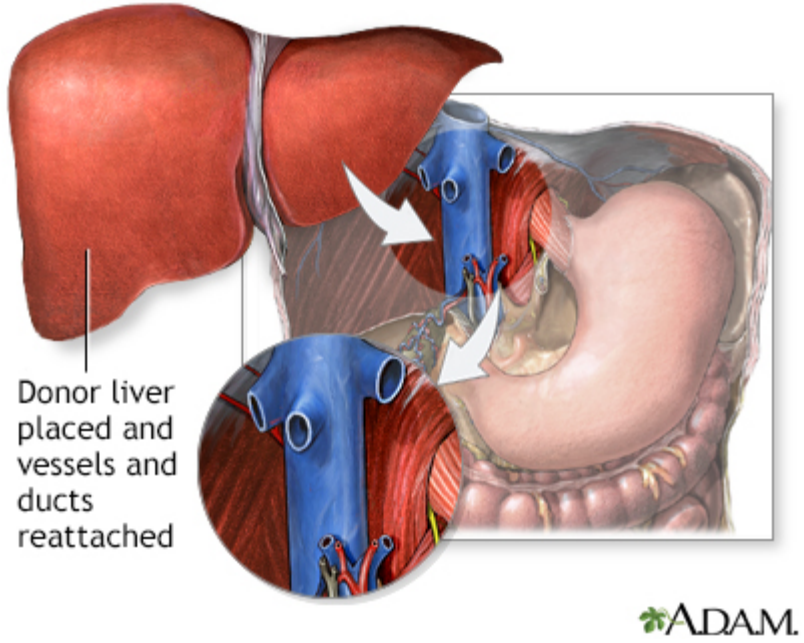


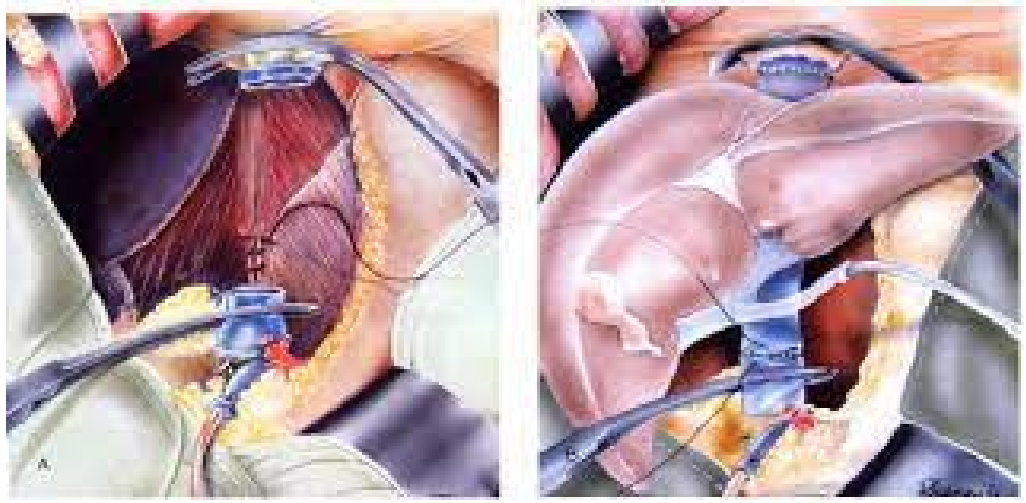
Outline

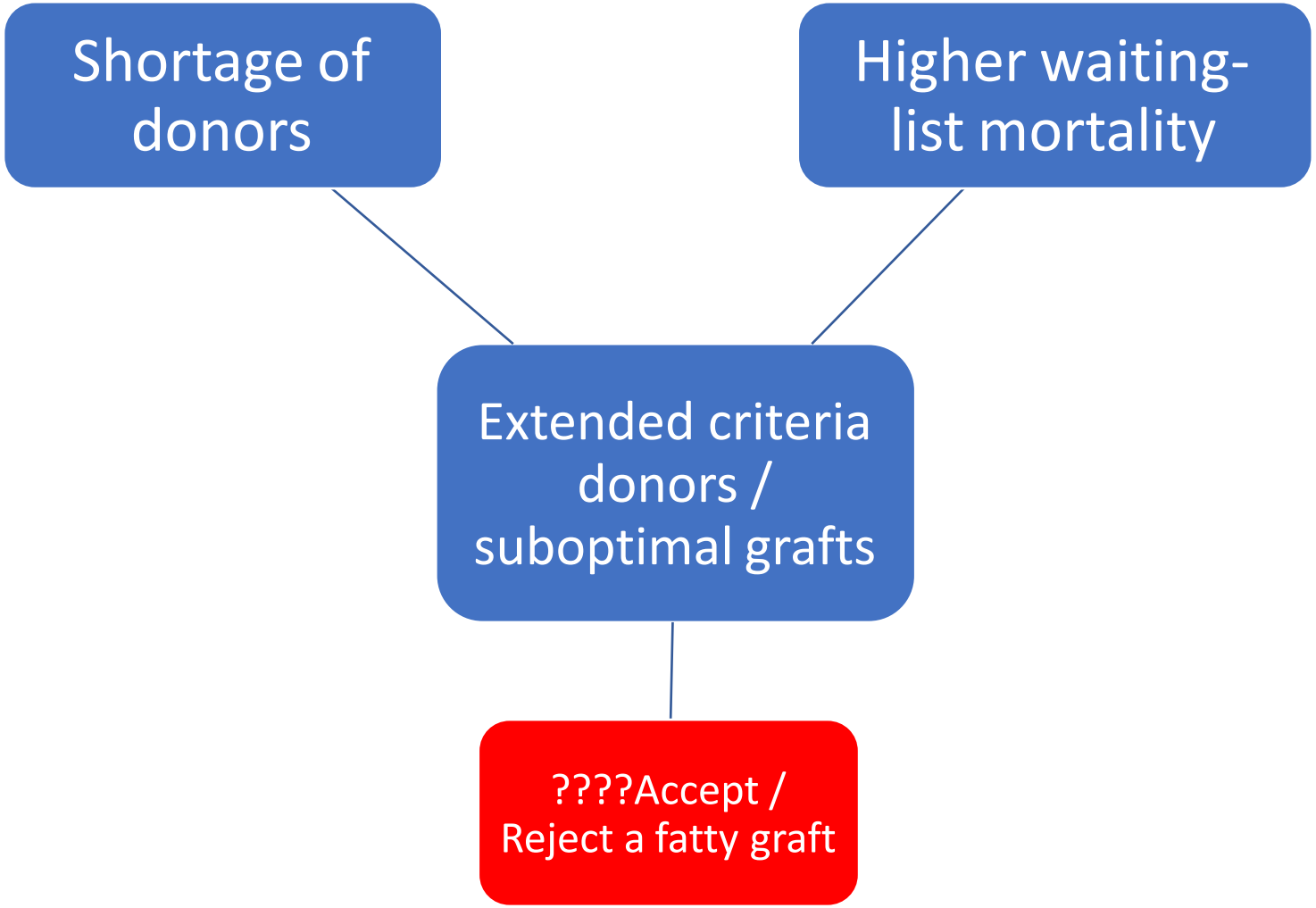
- Current donor status
- Extension of donor criteria
- Heaptic steatosis and outcome of LT
- Evidence
- Assessment of fatty grafts
- Strategies to improve the outcome of LT

Liver transplant

- Ultimate treatment for end-stage liver disease /acute liver failure.






Shortage of donors
Higher waiting-list mortality
Extended criteria donors / suboptimal grafts
????Accept / Reject a fatty graft

Strategies to increase the pool of available liver grafts.

Marginal organs/ Extended criteria

Living donors

Cadaveric split livers

Positive serologies for hepatitis B virus (HBV) or hepatitis C virus (HCV)

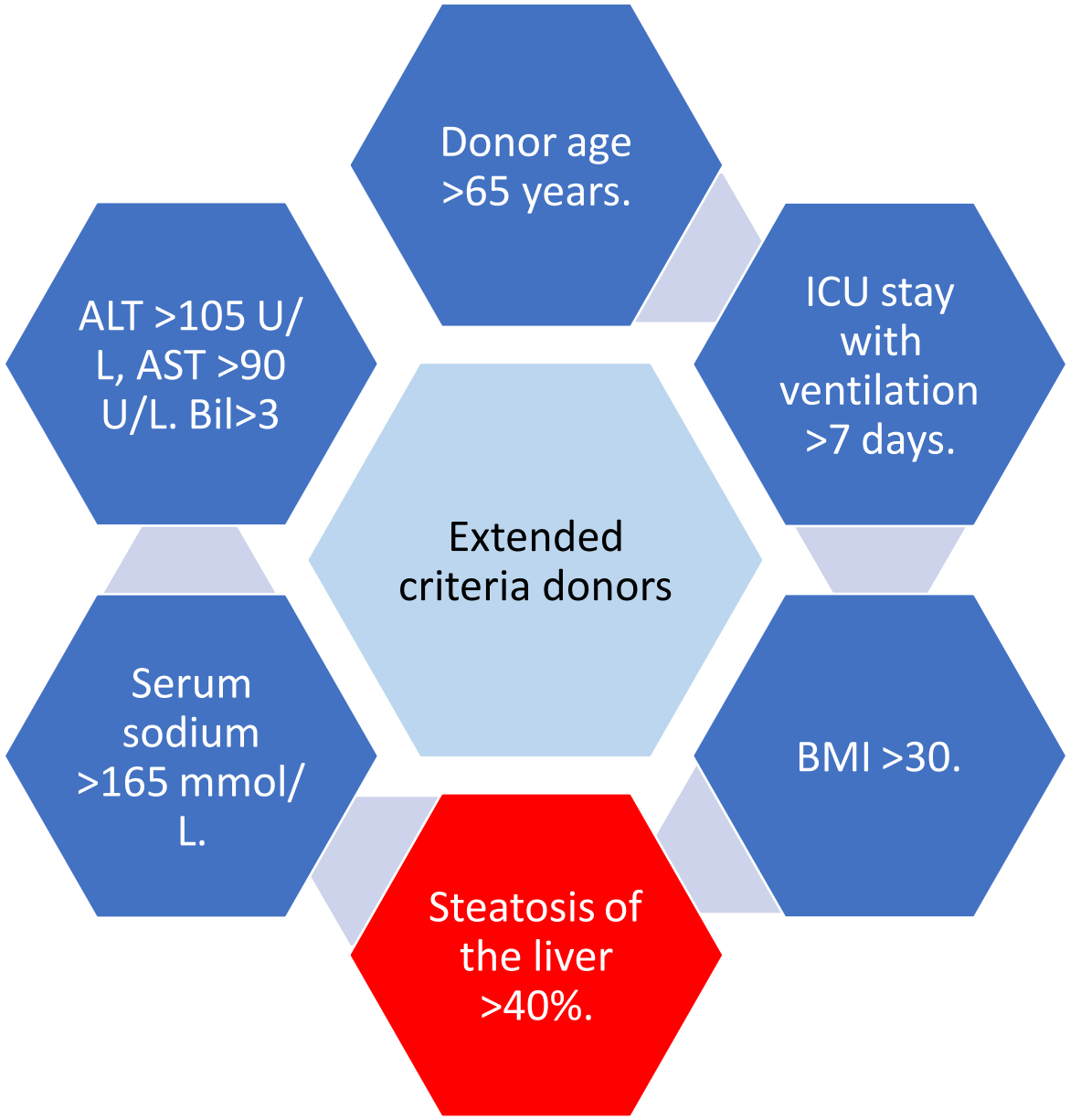
Grafts with a cold ischemia time>12h

Extended criteria donors

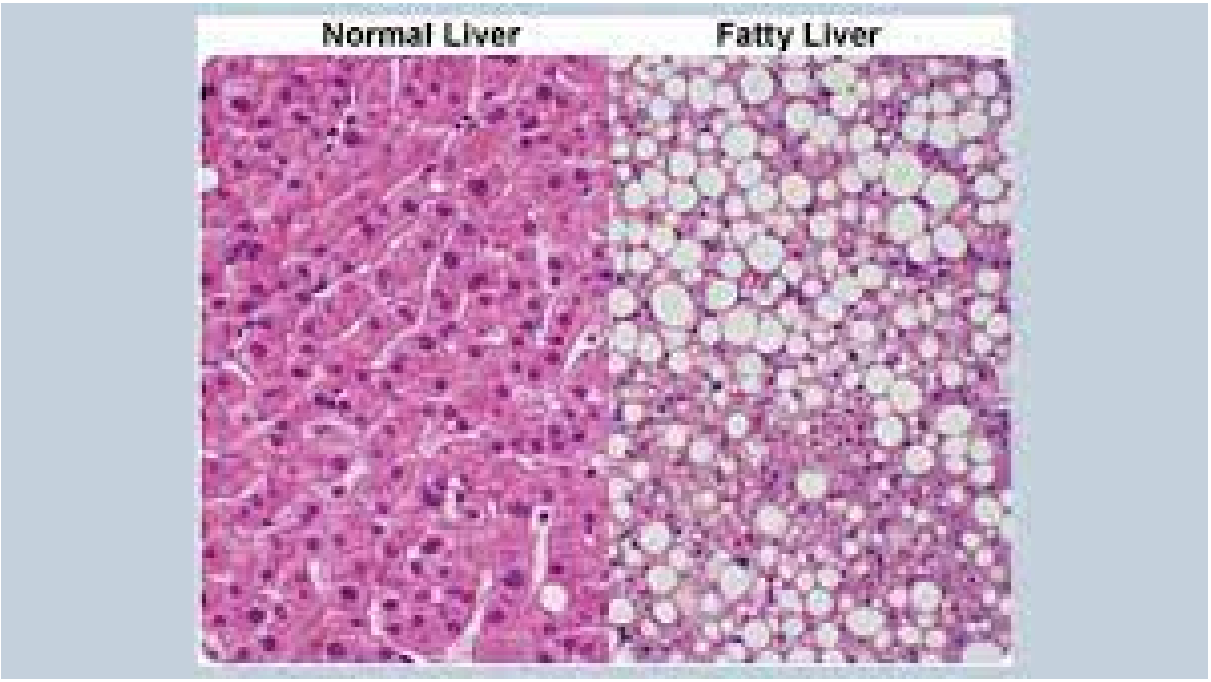
organ with unfavourable characteristics associated with suboptimal post-transplant outcomes

1.poor graft function-- DCDs and the non-DCDs

2.potential for disease transmission.


Donor age >65 years.
ICU stay with ventilation >7 days.
BMI >30.
Steatosis of the liver >40%.
Serum sodium >165 mmol/L.
ALT >105 U/L, AST >90 U/L. Bil>3
Extended criteria donors

Hepatic steatosis



- Mild <30%
- Moderate 30-60%
- Severe >60%

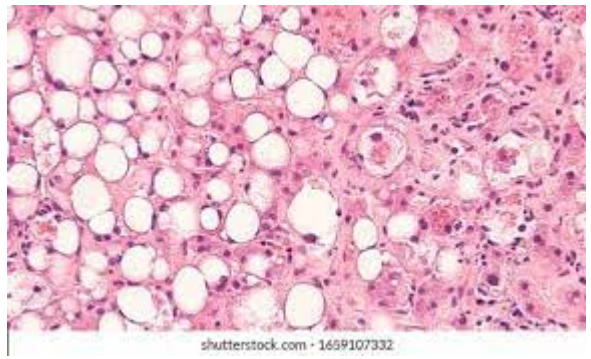
- Quantitatively

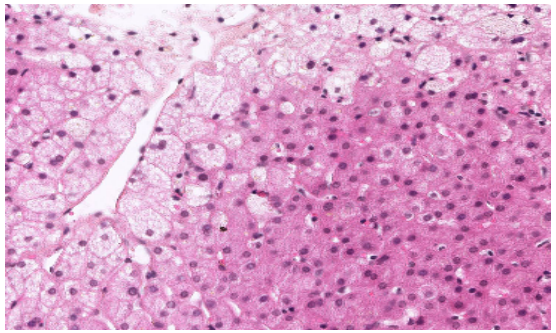
-macrosteatosis- large droplets/ small droplets

-microsteatosis

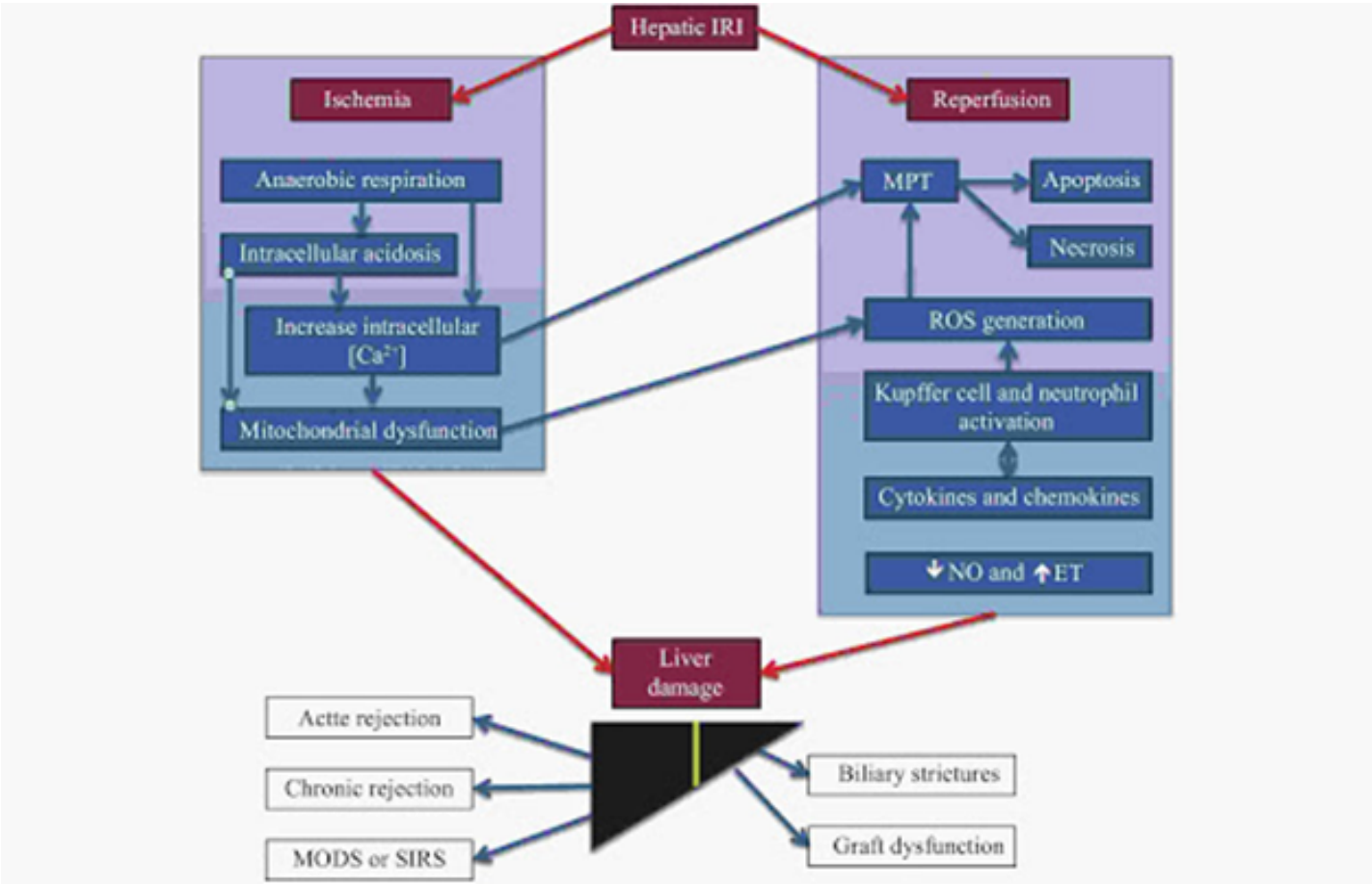
Hepatic steatosis

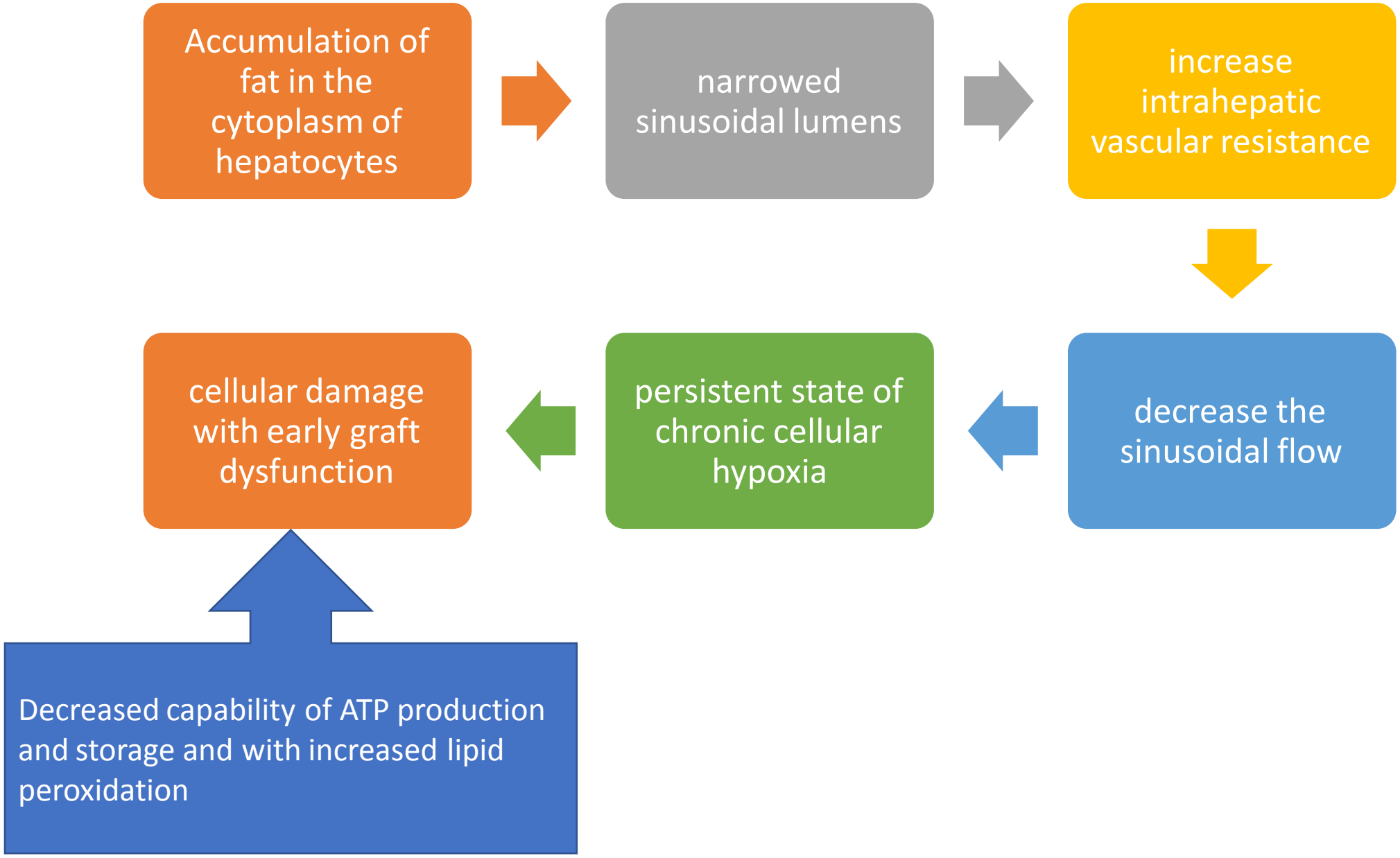
Macrosteatosis	Microsteatosis
• single, bulky fat vacuole in hepatocyte, displacing the nucleus to the edge of the cell • obesity, diabetes, hyperlipidemia, and alcohol abuse. • excessive triglyceride accumulation in the liver	• cytoplasm contains tiny lipid vesicles without nuclear dislocation. • mitochondrial disruption following acute viral, toxin- or drug-induced injury, sepsis, and in some metabolic disorders • most often MaS and MiS present simultaneously



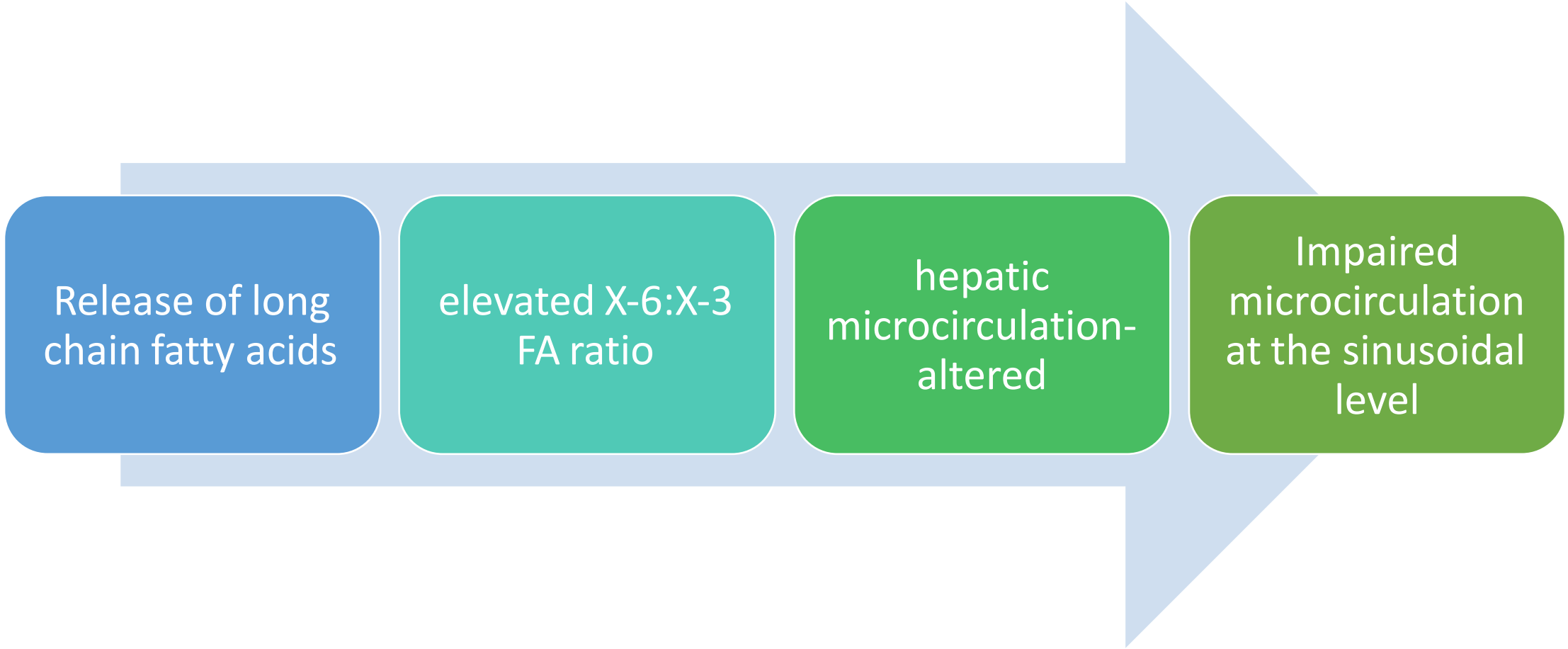


Reperfusion injury in the steatotic liver graft




Accumulation of fat in the cytoplasm of hepatocytes
narrowed sinusoidal lumens
increase intrahepatic vascular resistance
decrease the sinusoidal flow
persistent state of chronic cellular hypoxia
cellular damage with early graft dysfunction
Decreased capability of ATP production and storage and with increased lipid peroxidation

Moderate to severe macrosteatosis is an independent risk factor for the development of biliary complications after LT

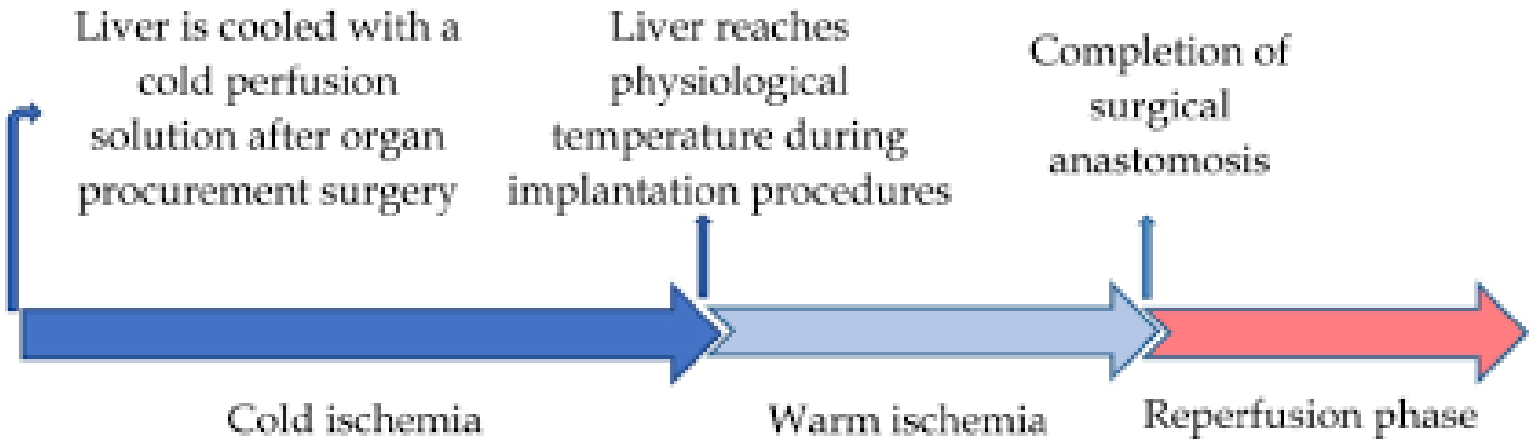


Lung damage

- Increased release of TNF alfa due to Kupffer cell dysfunction

- However, Westerkamp et al. observed
- favorable outcomes by minimizing the effects of I/R injury using a strict policy to keep the CIT as short as possible

-CIT>7 hours, the peak AST in severely steatotic grafts was much higher than that in the controls



Primary graft dysfunction 38.7%

- Related to ischemia reperfusion injury

-early allograft dysfunction (EAD)

- primary non function (PNF) (0.9%-8.5%)

Main definitions of early allograft dysfunction

Author	Definition
Olthoff et al	At least one of the following parameters: bilirubin ≥10mg/dL on day 7; INR ≥1.6 on day 7; ALT or AST >2,000IU/L up to day 7
Ploeg et al	AST >2,000IU/L, TP >16 seconds and ammonia >50µmol/L from day 2 to day 7
Nanashima et al	AST or ALT >1,500IU/L in 2 consecutive tests within the first 72 hours
Dhillon et al	[(ALT+AST)/2] >986IU/L on day 2

Primary non function-

early retransplantation /progression to death

Author	Definition
Ploeg et al.	Liver function inconsistent with life; need for retransplantation or progression to death within seven days of surgery
Nanashima et al	AST or ALT >1,500IU/L in 2 consecutive tests within the first 72 hours, requiring retransplantation or progressing to recipient death
Dhillon et al	[(ALT+AST)/2] >986IU/L on day 2, requiring retransplantation or progressing to recipient death up to day 7
Broering et al	Need for retransplantation up to day 10 or death due to graft nonfunction
Máthé et al	AST or ALT >1,500IU/L in 2 consecutive tests within the first 72 hours, leading to retransplantation or recipient death
Kremers et al	ALT >2,500IU/L, blood glucose levels 2.5 or bile flow

Risk factors for primary graft dysfunction

Donor	Surgical procedure	Receipient
Steatosis- macro ≥30%	Hot ischemia time >40 minutes >45 minutes	Young recipients (tend to receive organs from expanded criteria donors)
Expanded criteria donors	Cold ischemia time >10 hours	
Age >49 years >65 years		

Recent Evidence

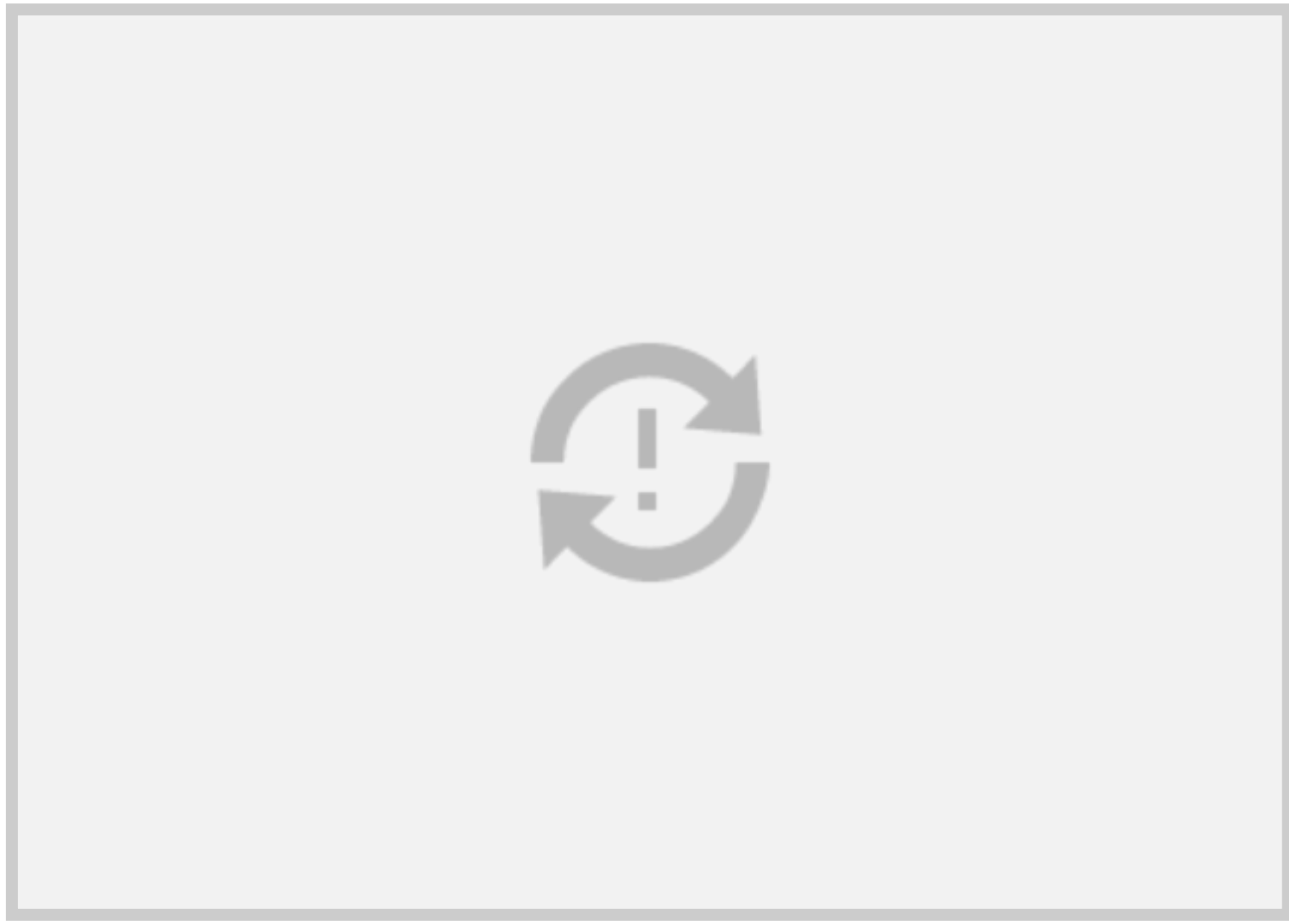
Impact on early post-transplant outcome

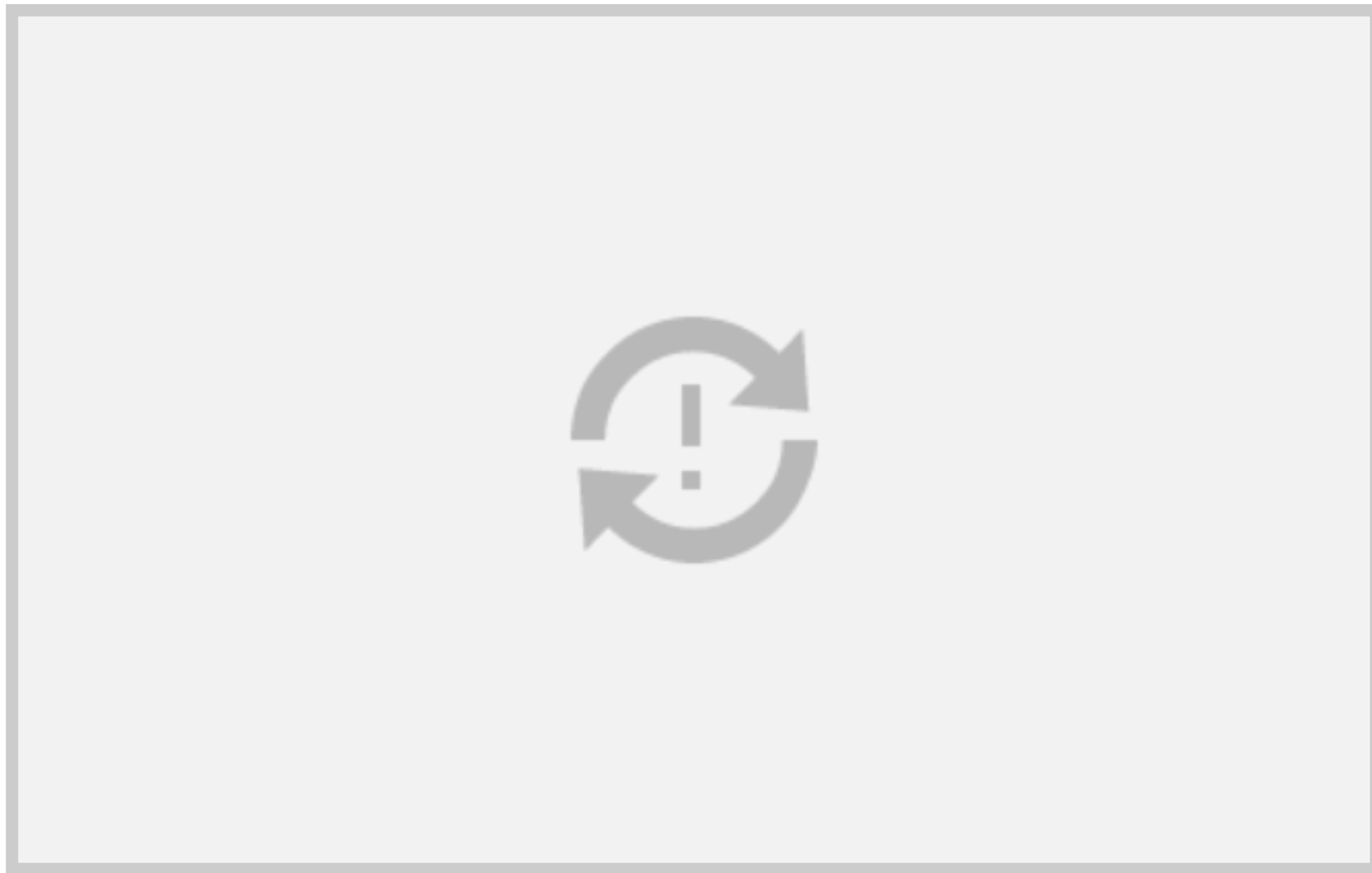
- Accumulating evidence

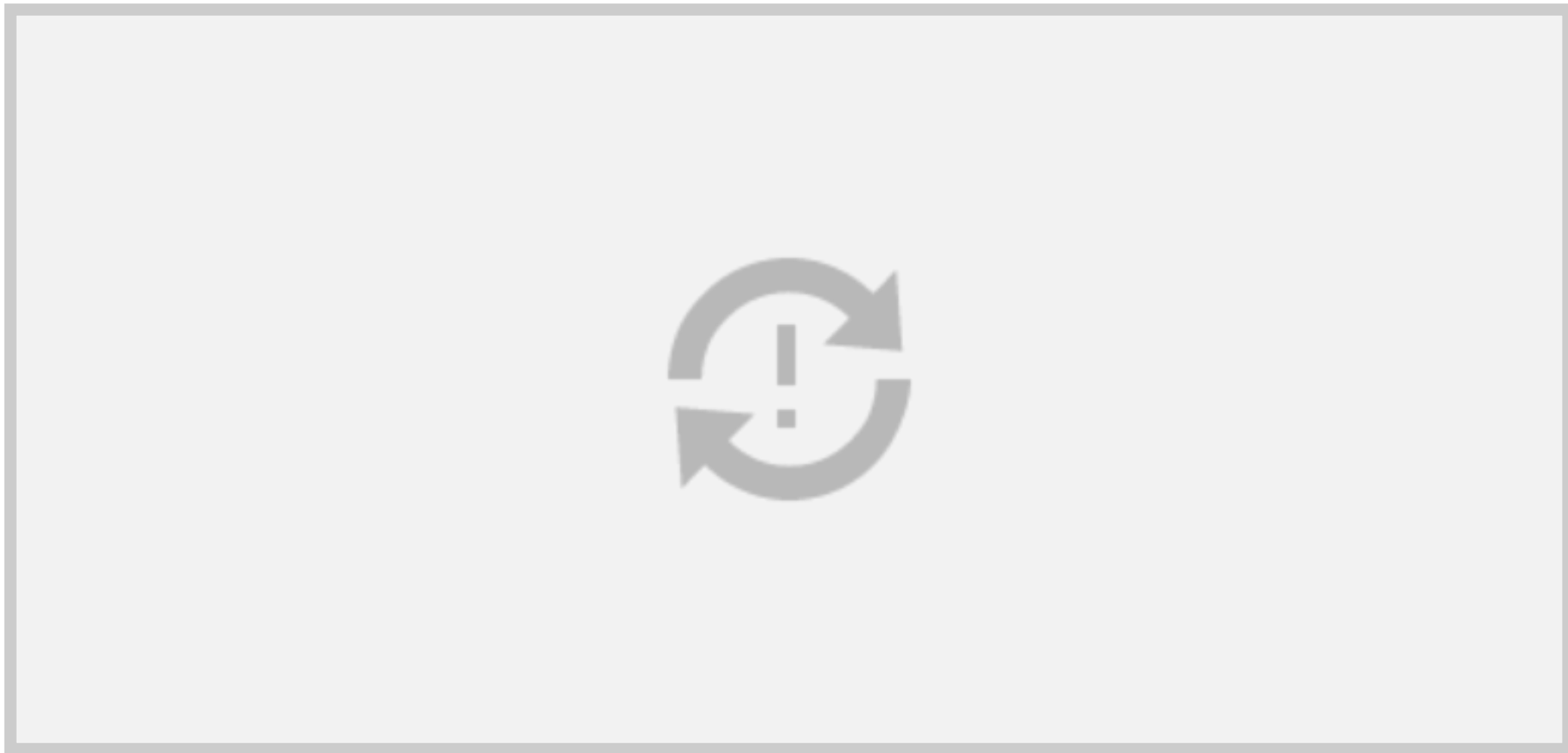
  -**steatosis in liver grafts increases complications after LT**

  -prolonged ICU stay, hospital stay, the incidence of primary graft dysfunction or non-function, and cost

- Studies have been inconsistent regarding the relevance of the higher degree of steatosis (>30%) or type of fat
- For example, the primary non function rates range between 0% and 75% in moderate graft steatosis (30–60%) after LT







The most recent and largest study - USA

- 5051 liver transplanted patients

- **> 30%** of macrosteatosis -**independent risk factor** for lower one year graft survival
- **Cold ischemia >11 h** with **lower degrees of macrosteatosis** -increased risk of graft dysfunction

- >30% MaS may be successfully used, if other donor risk factors are eliminated(e.g.donor age<40,cold ischaemia time< 5h, no donation after cardiac death)

Steatotic grafts - only to candidates in relatively good clinical condition but higher need of LT (e.g., cirrhotic patients with HCC having MELD <25

Avoid in fulminant liver failure or re-transplantation

Caution must be taken in using low quality organs for less urgent patients -since they could eventually wait longer for a better organ

Appropriate balance between donor age, graft MaS, graft ischemia time, and also recipient MELD - decisive

Meta analysis

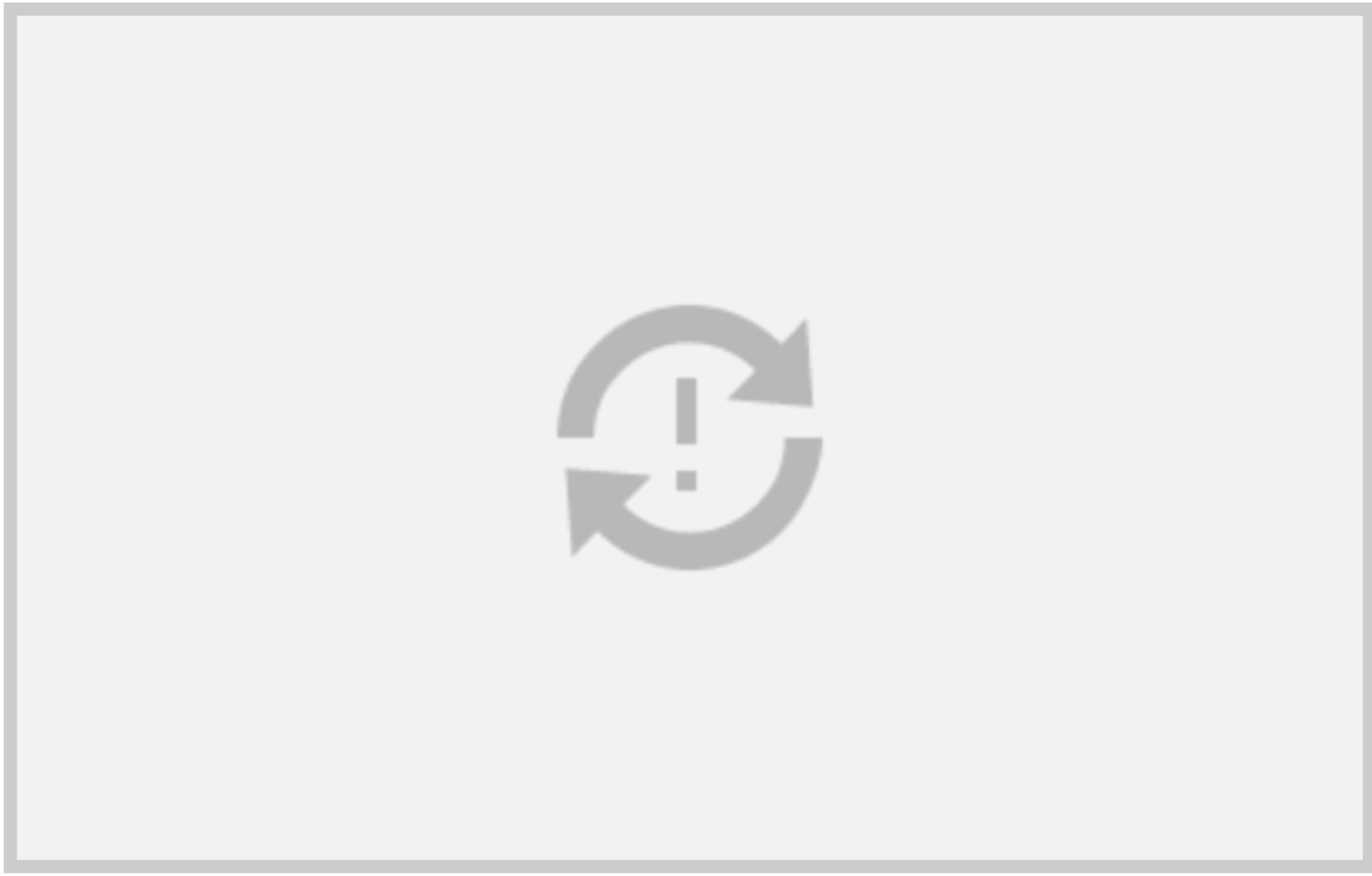
Outcomes concerned

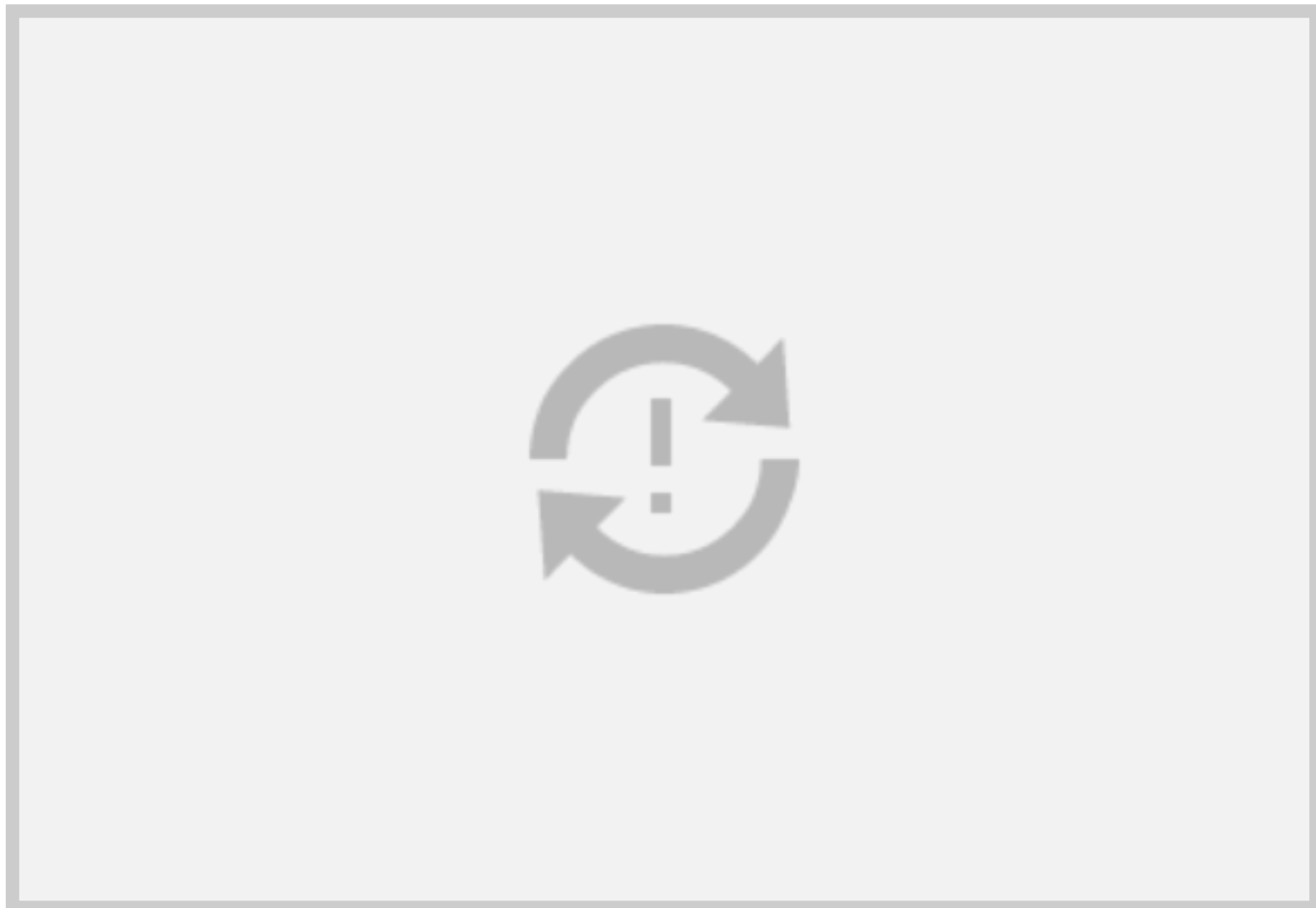
- **primary nonfunction** (PNF) rate -need for urgent re transplantation when a graft never demonstrated any evidence of initial function following transplantation in the absence of any vascular complication

- **early graft dysfunction** (EAD) rate- (1) bilirubin 170 mmol/L on D7; (2) international normalized ratio (INR) 1.6 on D 7; (3) aminotransferase level >2000 IU/ml from day 1 to day 7 after LT

- **Graft survival rate**

- **Patient survival rate.**





Primary non function rates

Early graft dysfunction rates

Graft survival rates

- A possible explanation for the different outcomes

- advanced donor age
- graft donation after cardiac death
- prolonged donor warm ischaemia time (DWIT)
- prolonged cold ischemia time (CIT).

European study

- 20 -severe steatosis
- median degree of total liver steatosis - 90%
- matched control group -recipient age, BMI, MELD score, and cold ischemia time.
- The steatotic group -significantly **higher rate of PDF**
- **ICU and hospital stay - not significantly different**
- proportion of patients with long-term ICU (21 days)and hospital (40 days) stay was significantly higher for patients with a severely steatotic graft.
- **Sixty-day mortality, 3-year patient survival rate –comparable**

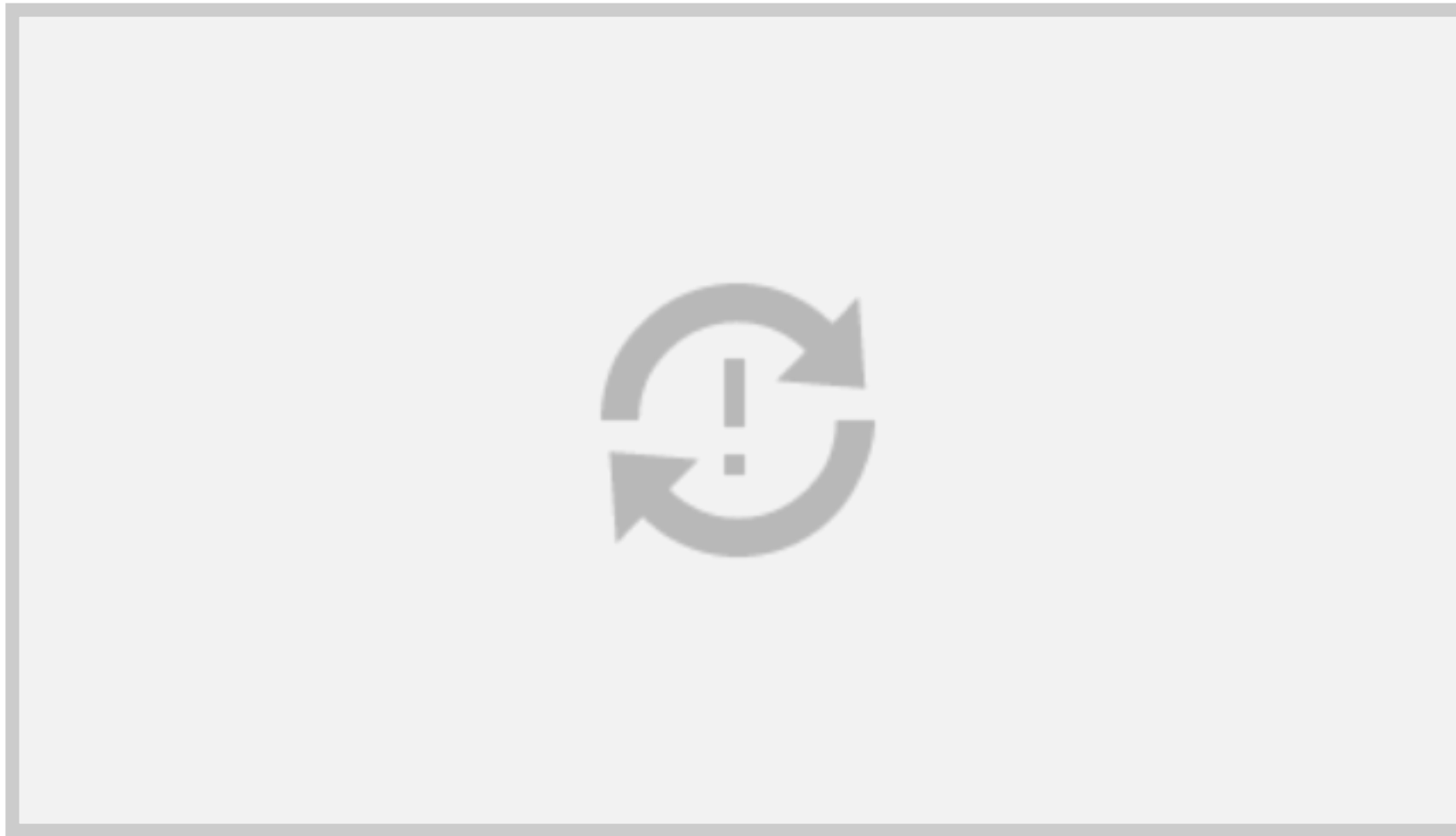
- Postoperative histologic assessment -steatosis decreased significantly

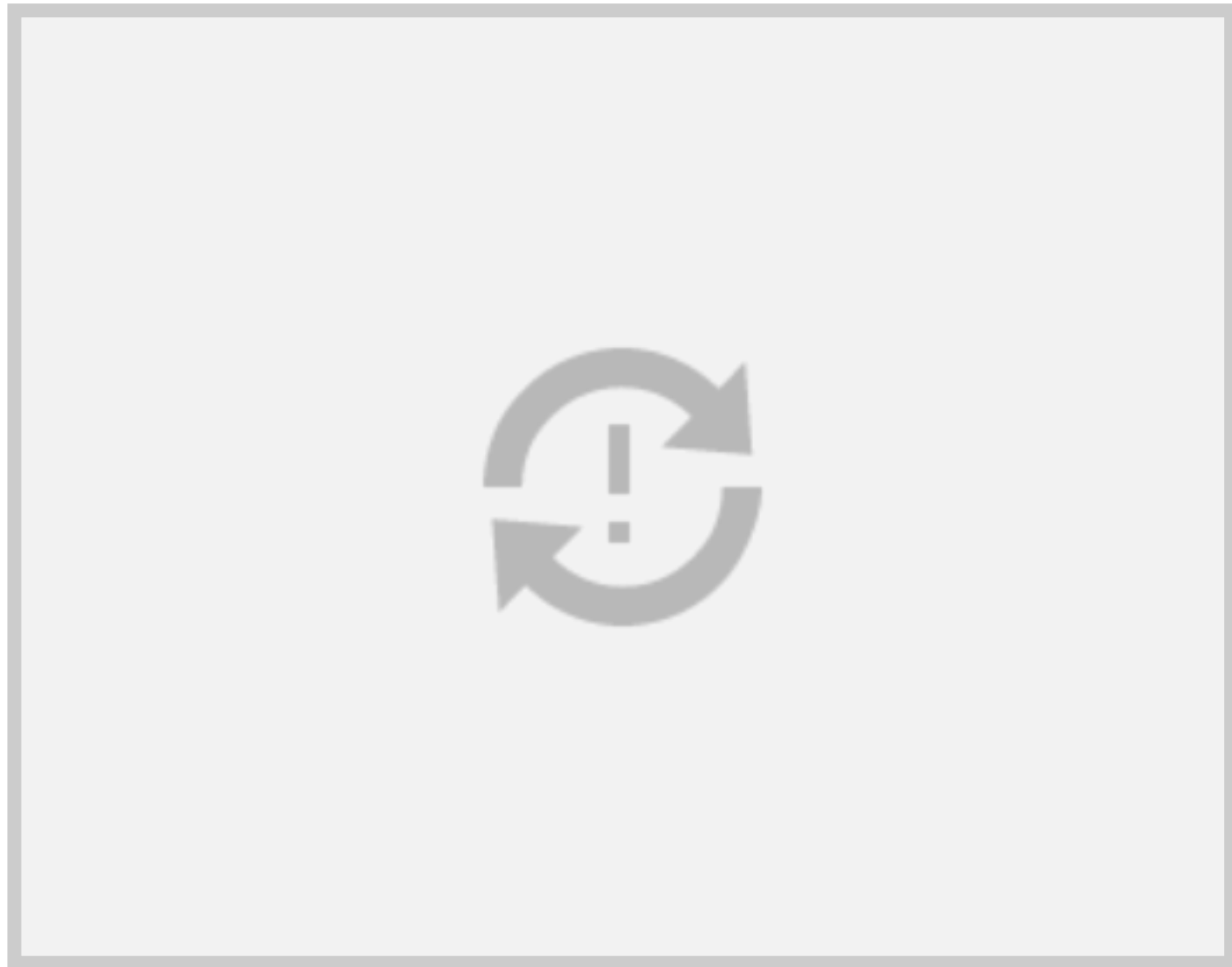
- However….
- **severely steatotic liver grafts** were matched to emergency candidates -**fulminant liver failure or to HCC**

-relatively preserved liver function -**MELD <24**

Study in Chile

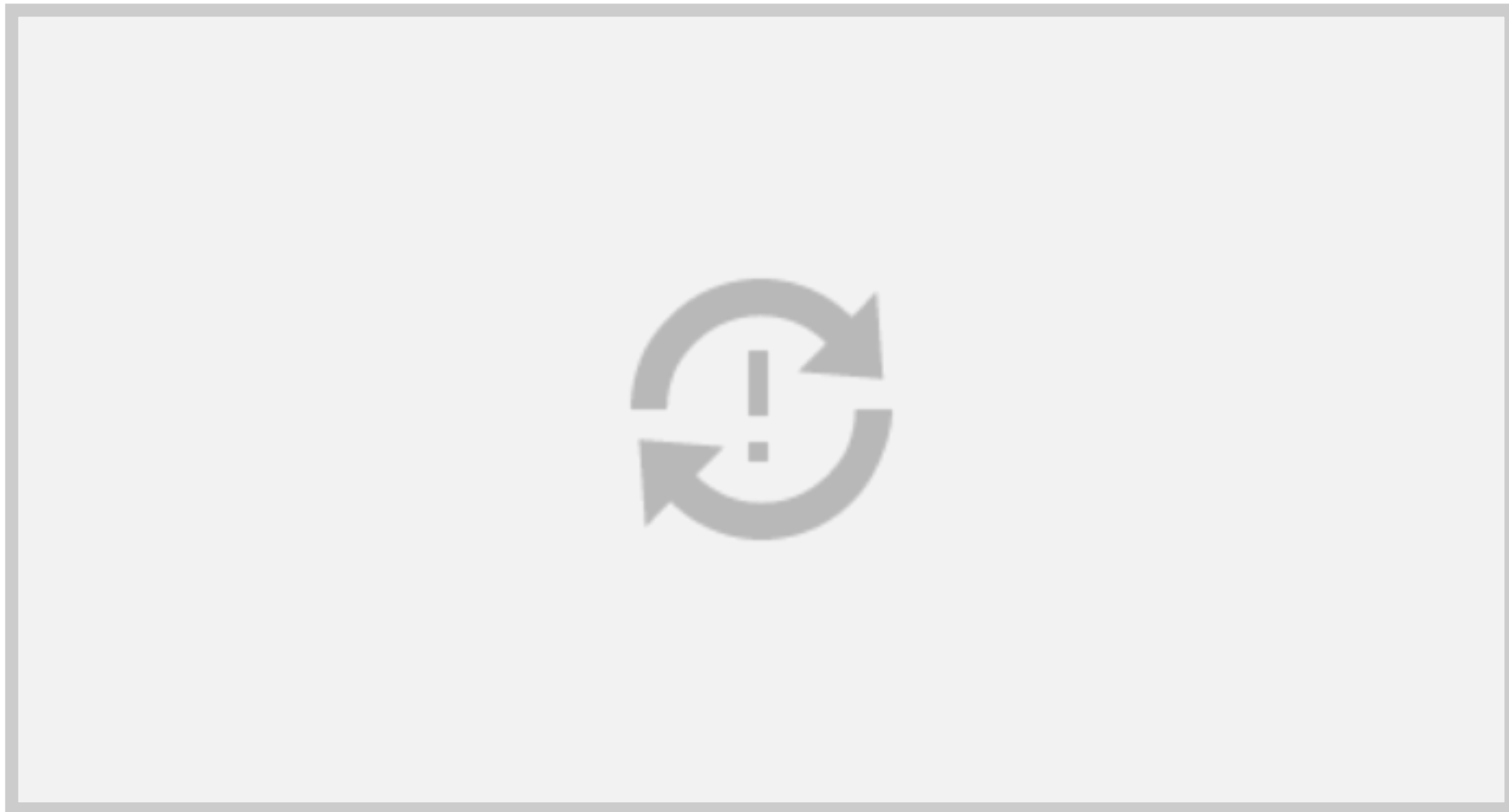
- 58 samples
- Bench biopsy





- Increased risk of **poor initial function**

- **Lower 3-year-survival rate** among patients receiving grafts with **macrosteatosis** compared to patients who received microesteatosis or non-steatotic grafts.



The issue of using **Microvesiculars (MiS) or Macrovesiculars (MaS)** fatty livers remains **controversial**.

steatotic grafts was associated with a **lower survival** rate than the rate with normal allografts.

No significant differences in patient survival when comparing using **mild, moderate or severe steatotic allografts**.

Impact of graft steatosis on long-term outcome after LT

Dramatic decrease in fatty infiltration shortly after LT

Factors that negatively affect this reversal of steatosis

-donor age (>50 years) and prolonged cold ischemia time (>12 h)

- Corresponding to the fat changes in transplanted liver grafts, the presence of moderate to severe MaS before LT did not affect long-term organ survival

Italian study

Transplanting livers with **moderate to severe MaS** is an independent risk factor for the development of **biliary complications** after LT

-impaired microcirculation at the sinusoidal level

- Steatosis in the liver graft -?negative prognostic factor for HCV recurrence

Assessment of fatty liver grafts

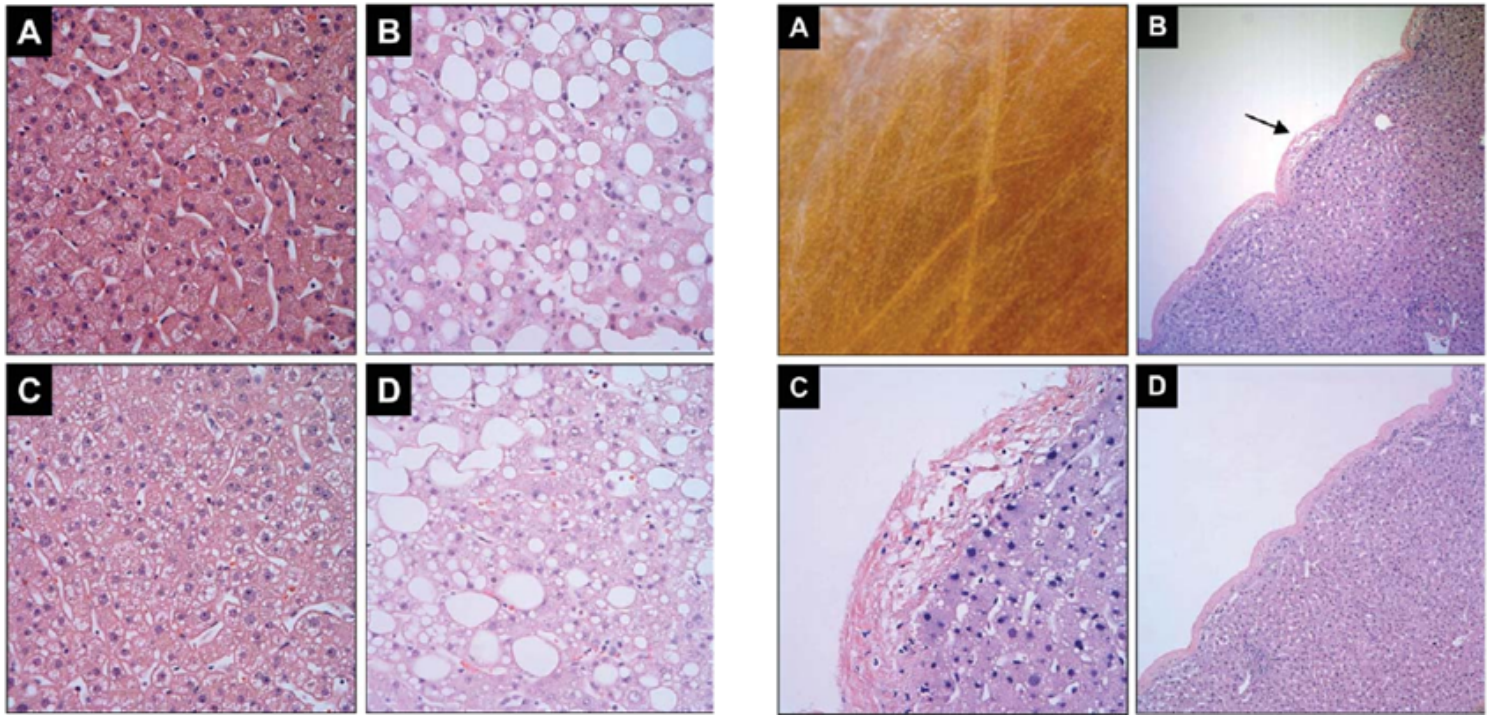
An initial evaluation- visual inspection and palpation- during procurement

-color and texture of the graft –depends on experience of the explanting surgeon- subjective.

Parenchymal texture criteria

- yellowness (normal, mild, moderate, or severe),
- firmness (too soft, normal,mild, moderate, or severe),
- round liver edges (present or absent)
- scratch marks (present or absent).
- ?Livers displaying faint scratch lines on the liver capsule are frequently associated with favorable outcomes

- **Yellowness** and **round edges**, the **absence of scratch marks** was associated with ld-MaS and was less influenced by sd-MaS



German study

-preoperative **ultrasound nor macroscopic evaluation not reliable** in steatosis evaluation

-CT or MRI better

-The gold standard –histology

Use of histology in accepting a graft

European survey

-liver biopsy at the time of procurement - rarely performed

-Only **23%** of liver transplant recipients in the United Network for Organ Sharing (UNOS) had a **liver donor biopsy recorded.**

- **Half** of the transplant surgeons in the UK **never integrate a liver biopsy** into their decision making process

- 38% of surgeons in the UK and 47% in the US -histological examination of the graft
- -when steatosis is suspected at the time of procurement

Limitations of histology

-variability in interpretation

-Staining techniques

-Sample size errors -focal steatosis, hypersteatosis, or hepatic fatty sparing

Addition of a second biopsy from the opposite hepatic lobe - more accurate

H&E-stained frozen biopsy -overestimates MiS but underestimates MaS

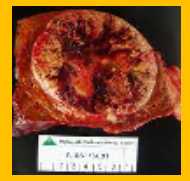
Alternative methods with higher sensitivity - Sudan-III, toluidine blue, and oil red O staining

Strategies to improve outcome after transplantation of steatotic livers

Minimize other risk factors-cold and warm ischemia time must be shortened as much as possible.

Allocate steatotic organs to patients with
lower Model for End-Stage Liver Disease (MELD) scores or
hepatocellular carcinoma or ?ALF

Critically ill recipients with high MELD scores may not tolerate initial graft dysfunction and postoperative complications.



HCC/ALF patients may not have time to wait for a better liver

Place for the liver biopsy

- liver biopsy to precisely assess whether the liver is suitable for grafting
- moderate or severe alcohol consumption
- BMI greater than 25
- donor age of over 40
- DM/metabolic syndrome
- donors without these risk factors- as steatosis may be underdiagnosed by USS

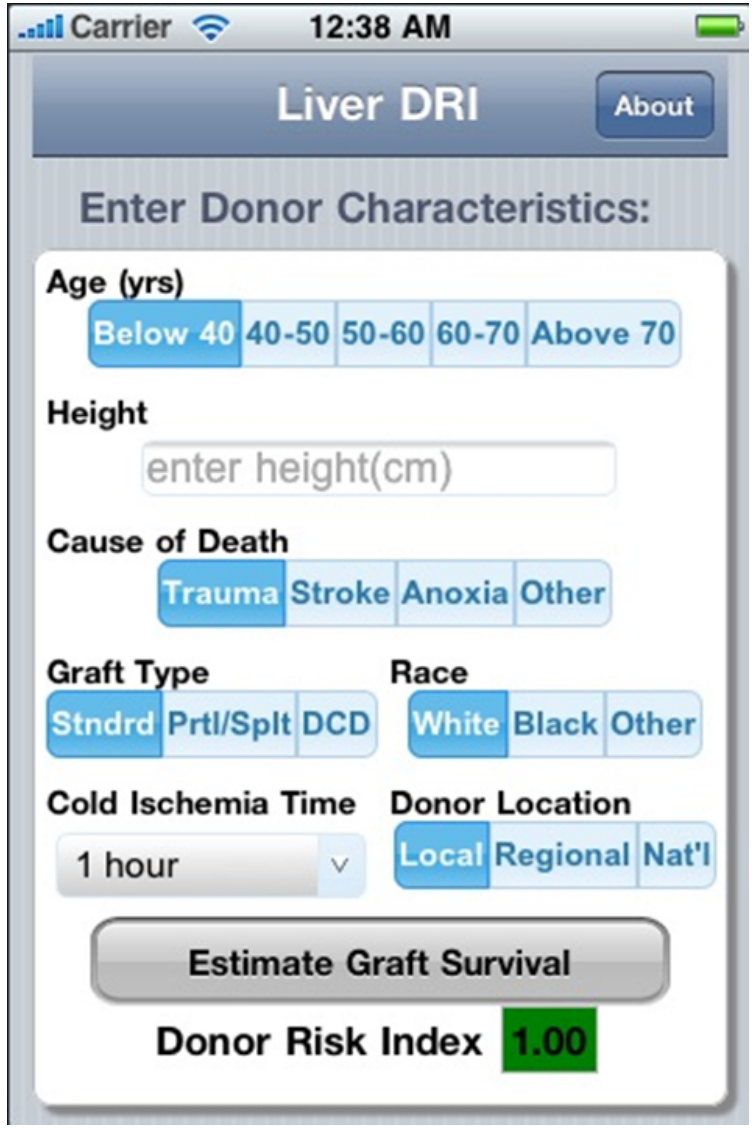
Risk scores to be considered to quantify the risk of graft failure of ECD donors

Donor risk index (DRI)

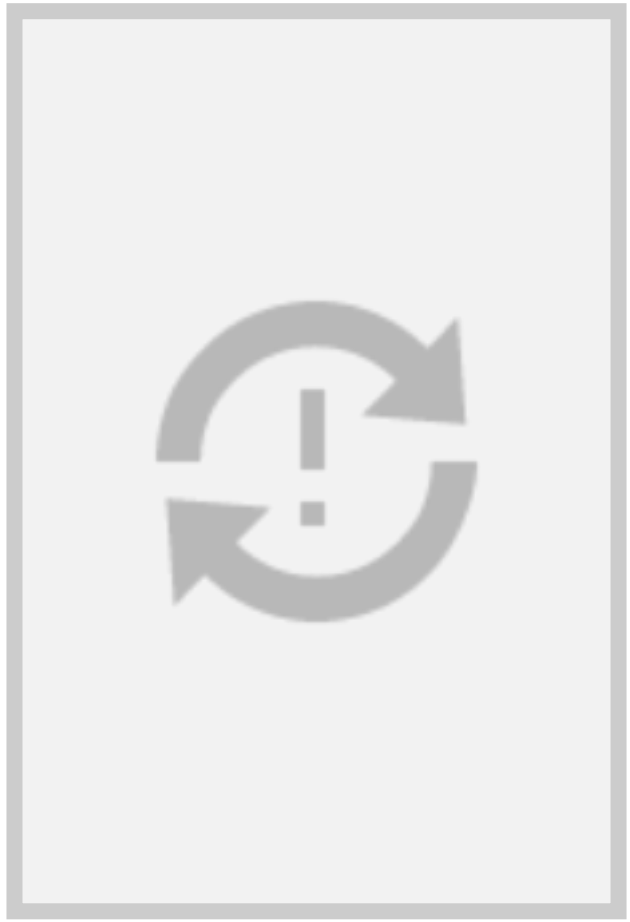
Balance of Risk score (BAR score)

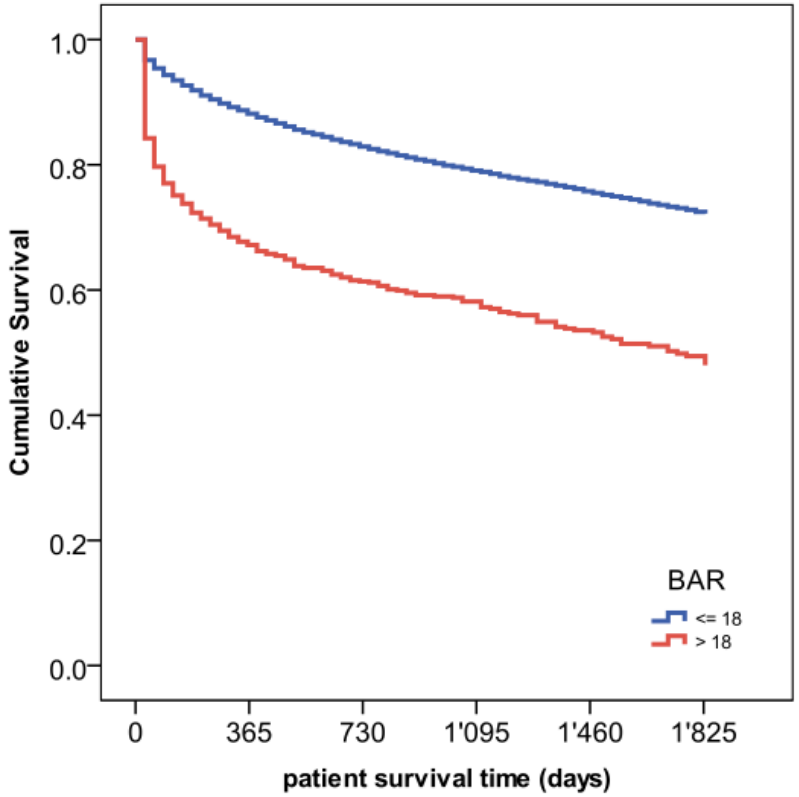
Scores to predict graft survival

- Donor risk index



Balance of Risk score (BAR score)





- Extended-Criteria-Donor-Score (ECD-score)

-1 point each for donor age >55 years, donor hospital stay >5 days, cold ischemic time >10 h and warm ischemic time >40 min.

D-MELD-Score

-lab MELD-Score with the donor age (labMELD x donor age)

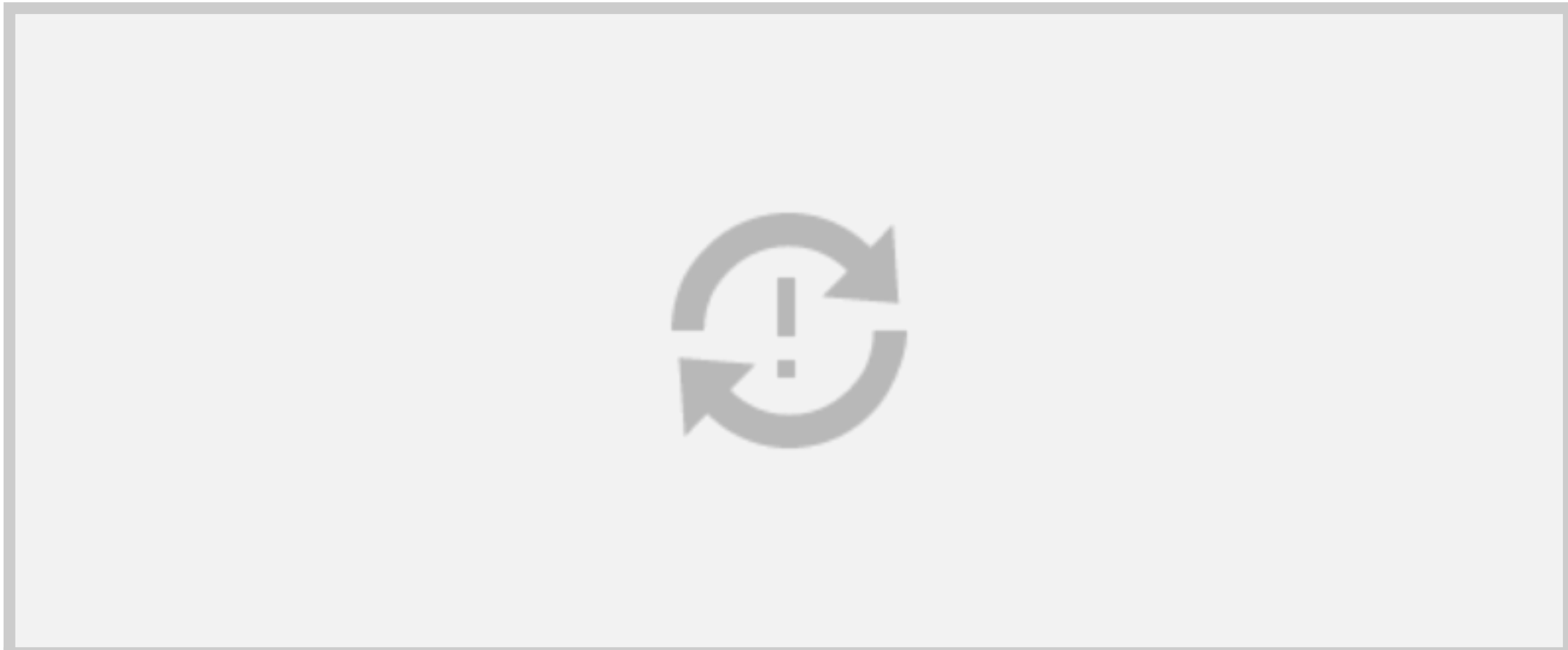
Low-grade macrosteatotic grafts 5-year graft survival rate of > 60% with BAR 18 -comparable to non-steatotic grafts

Microsteatotic or macrosteatotic liver grafts can be used safely up to BAR score of 18 or less

>30% macrosteatotis should be used with risk adjustment - up to BAR score of 9 or less.

Microvescicular steatosis does not preclude the use of grafts.

Antioxidant therapy in LT



Preventing activation of the inflammatory cascade

The new preservation concepts -in situ warm oxygenated perfusion before harvest (normothermic concept)
Hypothermic machine perfusion after organ procurement and transport to the transplantation center (hypothermic concept)
Wide application of perfusion system in marginal grafts such as severe steatotic livers -need long-term data after LT.
May allow in the near future to assess moderately and severely steatotic grafts prior to implantation
May allow further expansion of the donor pool

Hypothermic oxygenated machine perfusion (HOPE)

- Aiming at reconditioning poor quality ECD allografts
- reduce the incidence of biliary complications, mitochondrial damage and level of cellular energy status.
- hypothermic oxygenated organ perfusion is performed
- shortly before the actual implantation
- extracorporeal organ perfusion system with full oxygen saturation over the portal vein

In a Peripheral Hospital within the ET network

In the Transplant Center

Organ Donation and Transport to the Transplant Center

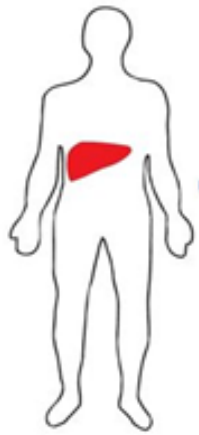
Back table HOPE vs. CCS

HOPE, Liver Assist ® Device

****PROTECTIVE RESPONSE****
-Mitochondrial
-Endothelial
-Parenchymal
-Subcellular pathways

Organ reconditioning

Donor



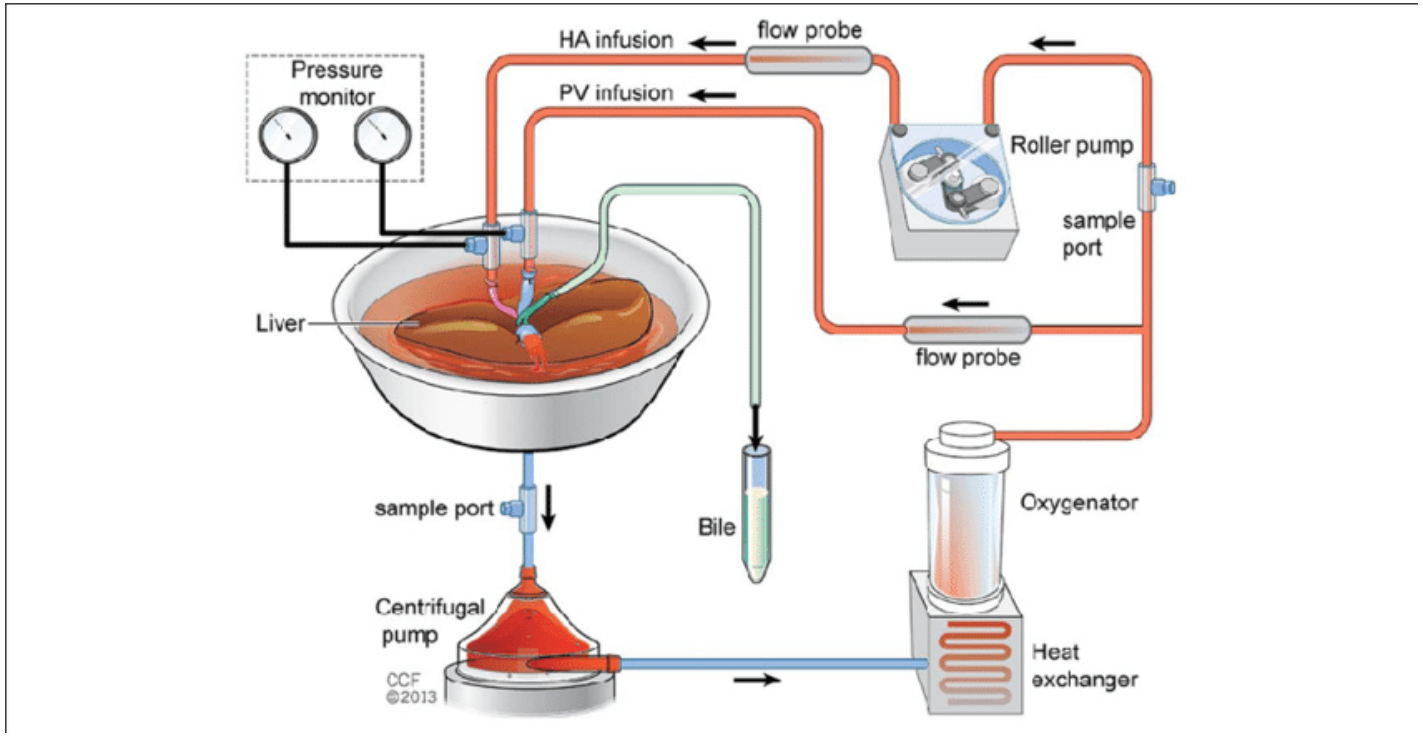
Transport using cold storage

Implantation following CCS
-Exhausted ATP storage
-Extensive ROS burst Following reperfusion
-Mitochondrial damage
-Apoptosis

Conventional cold storage

Normothermic Machine Perfusion (NMP)

- method of organ preservation, provides oxygen and nutrition during preservation and allows aerobic metabolism
- reducing IRI



Living donor LT

- hepatic steatosis-regarded as a contraindication
- However, regeneration ability of the fatty liver is controversially discussed
- Consider graft volume and donor age.
- In cases with no other risk factors, a steatosis degree up to 15% appears acceptable.

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Questions??

THANK YOU!!!!