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<th>First Author/year</th>
<th>Species</th>
<th>Experimental set up in brief</th>
<th>Main findings</th>
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<tbody>
<tr>
<td>Lee 2009</td>
<td>Male C57BL/6 mice</td>
<td>Development of a murine model of liver injury with AKI</td>
<td>Demonstrated that liver IR is associated with reproducible acute liver dysfunction and histological evidence of inflammatory change in the kidney</td>
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<tr>
<td>Rahman 2017</td>
<td>Human</td>
<td>Single centre retrospective study of 116 consecutive patients undergoing OLT</td>
<td>50% of patients developed AKI post operatively, hepatic ischaemia reperfusion injury was single most important factor predicting post-operative AKI.</td>
</tr>
<tr>
<td>Jochmans 2017</td>
<td>Human</td>
<td>Prospective cohort study evaluating risk factors for AKI in 80 OLT recipients</td>
<td>ALT at 6 hours post transplantation was only independent risk factor for AKI</td>
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<tr>
<td>Thongprayoon 2019</td>
<td>Human</td>
<td>Meta-analysis of incidence and impacts of post OLT AKI</td>
<td>Pooled estimated incidence of AKI was 40.7%, AKI requiring RRT 7.7%.</td>
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<tr>
<td>Authors</td>
<td>Year</td>
<td>Type</td>
<td>Description</td>
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<tr>
<td>Bezinover</td>
<td>2011</td>
<td>Human</td>
<td>Graft flush and blood samples obtained from patients undergoing liver transplantation and analysed for cytokine release. TNF-α, IL-1β, IL-2 and IL-8 increased in flush blood compared to radial artery samples.</td>
</tr>
<tr>
<td>Pulitano</td>
<td>2018</td>
<td>Human</td>
<td>Evaluation of 23 genes in reperfusion graft biopsies from patients undergoing liver transplantation and serum levels of cytokines. Comparison of gene expression with development of AKI. Fold changes in expression of ET-1, IL-18 and TNF-α strongly predictive of AKI. Combination of serum ET-1 and IL-18 found to be highly predictive of AKI.</td>
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<tr>
<td>Hetz</td>
<td>2005</td>
<td>Human</td>
<td>Prospective study of patients with normal renal function undergoing first OLT. Plasma ET-1 levels measured before surgery, following graft reperfusion and daily for first 2 postoperative days. Early postoperative reduction in GFR correlated with high postoperative ET-1. Patients with early renal dysfunction did not recover to baseline function.</td>
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<tr>
<td>Llado</td>
<td>2002</td>
<td>Human</td>
<td>Involved patients undergoing liver Patients with reperfusion syndrome had greater</td>
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transplantation, randomised to temporary portocaval shunt or no shunt

Mir122/ HIF-1α

Zhang 2021 Male Sprague-dawley rats
Rat models exposed to IR liver injury (30 minutes total hilar ischaemia, reperfusion for 6 hours), pre-treatment with vehicle, HIF-1α agonist or HIF-1α inhibitor. Supplemental experimental work with BRL-3A (rat normal liver cell line), pre-treatment with hif-1α agonist followed by hypoxia/reperfusion injury.

HIF-1α expression was upregulated in both liver IR injury and H/R injury, HIF-1α expression was associated with a reduced inflammatory response, alleviated oxidative stress and protected liver/hepatocytes from IRI induced cell apoptosis. A2BAR blockade reversed protective effects of HIF-1α over-expression.

Ju 2021 Mice with hepatocyte specific deletion of miR122
Combination of techniques including mouse model of hepatic IR injury in presence of hepatocyte specific deletion of mir122 and human samples from transplant patients including liver

Identification of liver-specific mirna mir122 in human transplant patients. In mouse model HIF-1α found to induce mir122 through repression of PHD1 expression, mir122 over-expression associated with attenuation of...
biopsies, liver injury. Correlation with human setting with identification that elevated mir122 associated with repressed PHD1 in post ischaemic liver biopsies.

**Selten 2017** Human Analysis of mirnas from samples from liver graft preservation fluid, verification of results from pig livers exposed to warm ischaemia Absolute mir122 levels and mir122/mir222 ratios in graft preservation fluid were significantly higher in in grafts from DCD donors, those that developed EAD and serum transaminase levels in first 24 hours. High mir122/mir222 associated with prolonged WIT in pig livers and elevated transaminases post reperfusion.

**Oxidative stress**

**Polat 2006** Wistar albino rats Rats divided into 5 groups: 1) control 2) no pre-treatment 3) desferrioxamine 4) quercetin 5) desferrioxamine and quercetin pre-treatment. Groups 2-5 then exposed to 45 minutes total hepatic

Creatinine and BUN levels increased in groups 2-5. Increased in oxidative stress in group 2 (with reduction in GSH) but decreased in groups 4 and 5. Desferroxamine increased renal GSH
ischaemia and 1 hour reperfusion.
Measurement of renal oxidative stress, overall injury and function

Kadhodaee 2012 Male albino rats 90 minutes partial hepatic ischaemia followed by either 4 hours or 24 hours reperfusion with measurement of renal functional, histological, oxidative stress and inflammatory indices

Evidence of liver injury, renal injury (BUN and histological evidence), increase in markers of renal oxidative stress (all findings more pronounced at 4 hours reperfusion than 24 hours reperfusion)

Lasheen 2019 Adult female Wistar rats Liver IR injury provided by total hepatic ischaemia for 45 minutes followed by 24 hours reperfusion. Rats divided into 4 groups: 1) Sham laparotomy 2) Garlic oil pre-treatment, sham laparotomy 3) liver IR injury 4) garlic oil pre-treatment, liver IR injury.

Downregulation of liver IR injury and AKI following garlic oil pre-treatment. Upregulation of HO-1, PGC1α and Atg7 with garlic pre-treatment indicating increased mitophagy and biogenesis associated with reduction in renal injury

Measurement of liver and renal markers of injury, oxidative stress and
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<th>Year</th>
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<tr>
<td>2015</td>
<td>Human</td>
<td>Retrospective analysis of 998 living donor liver transplantation patients</td>
<td>Early postoperative hypoalbuminemia (marker of oxidative stress) identified to be an independent RF for AKI post LDLT</td>
</tr>
<tr>
<td>2010</td>
<td>Human</td>
<td>Double blind randomised study of 100 patients undergoing OLT. Patients received either NAC or placebo during transplantation process.</td>
<td>NAC did not improve survival, graft function or postoperative renal function. GSH (free radical scavenger) levels highly variable with no difference between the 2 groups</td>
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<tr>
<td>2015</td>
<td>Male</td>
<td>Autologous, orthotopic liver transplantation (AOLT) in absence or presence of 2-aminothoxydiphenylborate (selective Cx32 inhibitor) or propofol. Additional experimental work with NRK-52E kidney tubular cells in culture, subjected to hypoxia-reoxygenation</td>
<td>AOLT associated with significant increase in renal CX32 expression and increased oxidative stress and renal impairment. In cell model, hypoxia-reoxygenation associated with significant cellular injury, attenuated by Cx32 gene knockdown and exacerbated by Cx32 enhancement.</td>
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manipulation of Cx32 expression by either 1) cell culture density 2) pre-treatment with Cx32 inhibitors or enhancer 3) Cx32 gene knock-down

Wu 2020 Human and mouse model with Cx32 knockout assessment of liver tissue and serum samples from patients undergoing OLT. Cx32 induction in human liver samples and mice correlated with injury. Cx32 knockout mice demonstrated less liver injury. Propofol (Cx32 inhibitor) was protective against IR injury

Kupffer cell involvement

Su 2018 Male C57BL/6 mice Necrotic HEK293 cells injected into mice in presence/absence of Kupffer depletion or CXCL1, IL-6 or TNF-α blockade Necrotic cells found to trigger neutrophil mobilisation by CXCL1, with liver snf hepatocytes specifically identified as being the major source of CXCL1. CXCL1 expression by hepatocytes was dependent on Kupffer cell derived TNF-α and NF-κβ signalling.

Chen 2009 huHSP27 OE Comparison of degree of liver injury Huhsp27 OE mice had significant protection
and WT with following IR in WT and huhsp27 OE C57BL/10 and mice with and without Kupffer cell depletion CBA/Ca background following IR in WT and huhsp27 OE mice with and without Kupffer cell depletion against liver injury. Kupffer cell depletion provided significant protection against liver IR in WT mice but not huhsp27 OE mice.

MAP and renal perfusion during transplantation

Kong 2013 Male Sprague-dawley Renal resistive index (RI) and AKI following reperfusion assessed in rats model of syngenic OLT

Intra-renal RI increased during anhepatic phase and decreased following reperfusion. There was no correlation between RI and renal function parameters 30 minutes post reperfusion.

Mizota 2017 Human Retrospective study of patients undergoing living donor LT.

Investigation of relationship between intraoperative haemodynamic parameters and postoperative AKI. Nadir MAP was independently predictive of severe AKI.

Kandil 2017 Human 50 patients randomised to terlipressin infusion intra-operatively and for 5 days post operatively or control group.

Postoperative AKI and NGAL comparable between terlipressin and control groups. MAP maintained in both groups, less fluctuations in
Renal function, peak portal vein blood flow velocity and hepatic artery RI recorded. Measurement of plasma ngal at baseline, 2 and 24 hours post reperfusion.

SVR observed in terlipressin group and lower noradrenaline consumption. No difference in PPV and hepatic artery RI.

**Chae 2017**  
*Human*  
Retrospective review of perioperative factors, including oxygen content, of 334 patients undergoing liver donor LT.  
On multivariate analysis, oxygen content 5 minutes post reperfusion, BMI and furosemide administration independently associated with postoperative AKI.

**Kidney modulation of liver injury**

**Park 2010**  
*Male C57BL/6*  
Lentivirus encoding green fluorescent protein (EGFP) or EGFP-human adenosine A1 receptors (hua1ar)  
EGFP-hua1ar mice were protected against hepatic IR-induced liver and kidney injury. Removal of EGFP-hua1ar injected kidney prior to hepatic IR abolished renal and hepatic protection.

**Park 2009**  
*huHSP27 OE and WT with C57BL/10 and WT mice versus huhsp27 OE mice*  
Comparison of hepatic IR injury and AKI 24 hours post liver IR in huhsp27 OE mice and WT mice.  
Huhsp OE mice were significantly protected against both liver and kidney injury post hepatic IR. Hepatoprotection reduced or abolished when
CBA/Ca background

**IL-18 BP**

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<th>Author</th>
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<th>Results</th>
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<tr>
<td>Gonul 2016</td>
<td>Wistar albino rats</td>
<td>Rats exposed to liver IR injury (pringle manoeuvre) or sham laparotomy following either IL-18BP or no intervention. TNF-α, IL-6, IL-1β, IFN-γ, total oxidant status and oxidative stress index measured in kidney tissue homogenate samples.</td>
<td>Renal total oxidant status, oxidative stress index, IL-18, serum AST, ALT, LDH and creatinine significantly lower in IR+IL-18BP group than IR group.</td>
</tr>
<tr>
<td>Liu 2015</td>
<td>Inbred Lewis rats</td>
<td>Rats subjected to liver transplantation or sham operation. Following 18 hours reperfusion, kidney and blood collected and analysed.</td>
<td>Renal suppression of markers of mitochondrial biogenesis, mitochondrial fission/fusion and enhancement of mitophagy (proteins and mRNa).</td>
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<tr>
<td>Lee 2011</td>
<td>Male C57BL/6</td>
<td>S1P and vehicle given to mice prior to S1P pre-treatment was associated with Renal endothelial injury in mediation of renal injury</td>
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mice hepatic IR injury. Subsequent measurement of renal and hepatic injury attenuation of systemic inflammation and kidney injury without attenuation of liver injury. Effect partially reversed by VPC 23019 (S1P1-R antagonist).

OE: Over-expression; WT: Wild type.