HCV-Positive ESKD Patient: Isolated Kidney versus Combined Kidney-Liver Transplantation?

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Hepatologist Perspective

- HCV Cirrhosis
- Advanced Liver cirrhosis
- Hepatocellular Carcinoma
- KDIGO
- Simultaneous Liver Kidney Transplant
- VS
- Liver transplant first then kidney later if needed
Nephrologist Perspective

Simultaneous Liver Kidney Transplant

Vs

Kidney transplant only
Liver may recover with HCV Rx
Liver Transplant later if complication

Needs a Kidney Transplant
Agenda

• Issues with Simultaneous Liver Kidney transplantation vs single organ transplantation – which is better?

• What are the guidelines?

• What’s the evidence?

• Implementing the evidence.
Issues with simultaneous liver kidney transplantation vs single organ transplantation (medical therapy/sequential transplant)? – which is better?

- Patient Survival
- Graft Survival
- Quality of Life vs cost-effectiveness
- Equipoise
- Justice (transplant futility)
Which is better? What are the considerations?

HCV Cirrhosis → Advanced Liver cirrhosis → High perioperative risk and mortality

High risk of liver failure and complication => liver related mortality

Poor quality of life from liver decompensation -? Justice

ESKD → Kidney Transplant

Transplant Futility

KDIGO
HCV Cirrhosis

Moderate Liver cirrhosis

Kidney Transplant

ESKD

HCV Rx with SVR will improve liver function. Don’t need LTx

LTx can be performed later if liver worsened or HCC

Can our crystal ball accurately predict whose liver will improve, stabilize or worsen?
The case for SLKT- liver needs the kidney

- Model for End-Stage Liver Disease (MELD) includes Creatinine – increased % of CKD and ESKD in liver transplant patients.
- Post Liver Transplant, 2% to 5% per year will require RRT after transplantation.
- Renal failure/ RRT after orthotopic liver transplantation (OLT) is an important risk factor for poor overall survival.
- pre-OLT renal dysfunction is predictive of post-OLT renal failure which is predictive of graft and patient survival post LTx.

Charlton Liver Transpl 2009
Al Riyami Transplantation. 2008
Nadim Am J Transplant. 2012
Outcomes of LTx patients with ESKD Canadian Experience

LTx requiring RRT post transplant was 1.43x more likely to die over 20 years of observation.

Mean Survival of LTx with and without RRT is 7.5 to 4.8 years

The median time between initiation of chronic dialysis and death was 1.5 years.

Riyami et al. Transplantation 2008
Patient survival

Riyami et al. Transplantation 2008

KDIGO

Kidney Transplant
LTx + Kidney Transplant
Matched RRT
LTx on RRT
Survival Benefit of Simultaneous Liver-Kidney Transplant over Liver Transplant Alone for Recipients with Pre-Transplant Renal Dysfunction

A propensity score matched study comparing 1884 SLK recipients with 31,882 LTA recipients showed SLKT is associated with a 3.7 month expected gain in survival time during 0–5 years post-transplant compared to LTx

KDRI was ≤1.1 (KDPI equivalence ~60%-65%)

Sharma Liver Transpl. 2016
Disadvantage of sequential KTx after LTx

• Patients wait-listed for kidney transplantation after nonrenal organ transplantation have worse outcomes compared to patients waiting for kidney transplant alone (KTA)

Proceedings of Consensus Conference on Simultaneous Liver Kidney Transplantation (SLK)

A consensus conference sponsored by the American Society of Transplant Surgeons (ASTS), American Society of Transplantation (AST), United Network for Organ Sharing (UNOS) and American Society of Nephrology (ASN) convened to examine simultaneous liver-kidney transplantation (SLKT).

automatic approval for:

(i) End-stage renal disease with cirrhosis and symptomatic portal hypertension or hepatic vein wedge pressure gradient $\geq 10$ mm Hg

(ii) Liver failure and CKD with GFR $\leq 30$ mL/min

(iii) AKI or hepatorenal syndrome with creatinine $\geq 2.0$ mg/dL and dialysis $\geq 8$ weeks

(iv) Liver failure and CKD and biopsy demonstrating $> 30\%$ glomerulosclerosis or $30\%$ fibrosis.

Good quality renal graft (favourable KDRI) were preferentially diverted to SLKT
# UNOS guidelines for SLKT safety net

## Table 2. Current UNOS criteria for simultaneous liver kidney transplantation including “safety net”

<table>
<thead>
<tr>
<th>Confirmation of diagnosis needed:</th>
<th>Required documentation in patient’s medical record and report in UNOS computer system:</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD, defined as either measured or calculated GFR ≤60 mL/min for &gt;90 consecutive days</td>
<td>At least one of the following:</td>
</tr>
<tr>
<td></td>
<td>• Maintenance dialysis</td>
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<tr>
<td></td>
<td>• Most recent measured or calculated creatinine clearance or GFR ≤30 mL/min at the time of registration</td>
</tr>
<tr>
<td></td>
<td>• Measured or calculated creatinine clearance or GFR ≤30 mL/min on a date after registration on kidney wait list</td>
</tr>
<tr>
<td>Sustained AKI</td>
<td>At least one of the following or combination of both of the following for the preceding 6 weeks:</td>
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<tr>
<td></td>
<td>• On dialysis at least once every 7 days</td>
</tr>
<tr>
<td></td>
<td>• Measured or calculated creatinine clearance or GFR ≤25 mL/min at least once every 7 days</td>
</tr>
<tr>
<td></td>
<td>• If eligibility is not confirmed once every 7 days for the previous 6 weeks, then the candidate is not eligible to receive liver and a kidney from the same donor</td>
</tr>
<tr>
<td>Metabolic disorders</td>
<td>At least one of the following diagnoses:</td>
</tr>
<tr>
<td></td>
<td>• Hyperoxaluria</td>
</tr>
<tr>
<td></td>
<td>• Atypical HUS due to factor H or factor I mutation</td>
</tr>
<tr>
<td></td>
<td>• Familial nonneuropathic systemic amyloidosis</td>
</tr>
<tr>
<td></td>
<td>• Methylmalonic aciduria</td>
</tr>
<tr>
<td>“Safety Net”: Additional priority will apply to all LTA recipients as well as SLK recipients who experienced immediate and permanent non-function of the transplanted kidney who are on kidney waiting list after becoming dialysis-dependent or having a GFR ≤20 mL/min between 60 and 365 days following liver transplantation</td>
<td>• Confirmation at least once every 30 days that the eligibility criteria continue to be met</td>
</tr>
<tr>
<td></td>
<td>• Once the program confirms eligibility criteria for three consecutive 30-day periods after the initial qualifying date, the candidate will remain eligible for safety net priority indefinitely</td>
</tr>
</tbody>
</table>

Does not apply to KDPI<20%

https://optn.transplant.hrsa.gov/media/1240/05_slk_allocation.pdf
Does kidney transplant benefit from the liver graft?

KDIGO
Kidney graft survival is inferior among SLKT relative to KTx

In 1998 SLK transplants with matching KTA transplants. Five-year kidney graft (64% [SLK] vs 75% [KTA], P < 0.001) and patient survivals (66% [SLK] vs 81% [KTA], P < 0.001). SLKT was taking kidney grafts from non liver ESKD on waiting list.

Choudhury. Transplantation 2017
Does kidney transplant benefit from the liver graft?

When does the nephrologist need to worry about the liver becoming a factor in the morbidity and mortality of kidney transplant?
Predicting the liver reserve—how good are we?
Predicting the liver reserve- how good are we?
# 30 Day Mortality Risk of surgery in cirrhotics

<table>
<thead>
<tr>
<th>CPS</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open Abd surgery</td>
<td>10</td>
<td>30</td>
<td>80</td>
<td>Mansour Srg 1997</td>
</tr>
<tr>
<td>Open Abd Surgery</td>
<td>10</td>
<td>17</td>
<td>63</td>
<td>Neeff, J Gas Srg 2011</td>
</tr>
<tr>
<td>Lap Abdominal Srg</td>
<td>2</td>
<td>12</td>
<td>12</td>
<td>Telem CGH 2010</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MELD</th>
<th>&lt;8-10</th>
<th>10-15</th>
<th>&gt;15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open Abd surgery</td>
<td>6</td>
<td>30</td>
<td>50</td>
</tr>
</tbody>
</table>

- Can proceed
- With caution
- Contraindicate
Assessing the liver function/ reserve/ prognosis

1. Cirrhosis vs Non cirrhosis

2018 KDIGO Hepatitis C in CKD Guideline
Evaluation of liver disease.
All HCV-infected patients with kidney failure
a. should undergo a noninvasive biochemical and/or morphological
evaluation to stage liver fibrosis
b. When biochemical and morphological evaluations yield discordant
results or when liver comorbidities are suspected, liver biopsy is
suggested
c. determine the role and timing of antiviral therapies
Executive summary of the 2018 KDIGO Hepatitis C in CKD Guideline: welcoming advances in evaluation and management

Michel Jadoul\textsuperscript{1}, Marina C. Berenguer\textsuperscript{2,3,4}, Wahid Doss\textsuperscript{5}, Fabrizio Fabrizi\textsuperscript{6}, Jacques Izopet\textsuperscript{7,8}

1.3: Liver testing in patients with CKD and HCV infection

1.3.1: We recommend assessing HCV-infected patients with CKD for liver fibrosis (1A).
1.3.2: We recommend an initial noninvasive evaluation of liver fibrosis (1B).
1.3.3: When the cause of liver disease is uncertain or noninvasive testing results are discordant, consider liver biopsy (Not Graded).
Assessing Liver Fibrosis in HCV Renal Patients

Non-invasive Tests

Non-imaging

FibroTest/FibroMeter, APRI-AST/Plt Ratio Index, Forns, or FIB-4 index

Morphological evaluation

liver stiffness by elastography

TRO significant F3-F4 fibrosis

sensitivity and specificity in CKD on HD is not known

HCV should be treated and with SVR, fibrosis will halt or improve

KDIGO, Kidney Int Suppl. 2018
Assessing the liver function/ reserve/ prognosis

1. Cirrhosis vs Non cirrhosis

2. Refine the cirrhotics
   a. MELD Score
      \[10 \times ((0.957 \times \ln(\text{Creatinine})) + (0.378 \times \ln(\text{Bilirubin})) + (1.12 \times \ln(\text{INR}))) + 6.43\]
      Predict survival
      LTx at MELD score of 12-14

   a. Compensated vs Decompensated
      i. Child Pugh score A vs B/C
      ii. Jaundice, edema, ascites, varices
      iii. SBP, bleeding varices, hepatic encephalopathy, HRS
<table>
<thead>
<tr>
<th>Histological</th>
<th>Clinical</th>
<th>Sub-stage</th>
<th>Hemodynamic (HVPG, mmHg)</th>
<th>Biological</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1-F3</td>
<td>Non-cirrhotic</td>
<td>Stage 1</td>
<td>&gt;6</td>
<td>Fibrogenesis and Angiogenesis</td>
</tr>
<tr>
<td></td>
<td>None (no varices)</td>
<td></td>
<td>&gt;10</td>
<td>Scar and X-linking</td>
</tr>
<tr>
<td></td>
<td>None (varices present)</td>
<td></td>
<td>&gt;12</td>
<td>Thick (acellular) scar and nodules</td>
</tr>
<tr>
<td></td>
<td>()</td>
<td></td>
<td></td>
<td>Insoluble scar</td>
</tr>
</tbody>
</table>

? Point of Reversibility

Garcia Tsao  Hepatology 2010
Predicts Clinical Decompensation in Patients With Compensated Cirrhosis

213 patients with compensated cirrhosis and portal hypertension but without varices. Fu 51 months

Sixty-two (29%) of 213 patients developed decompensation

On multivariate analysis,
1. HVPG (hazard ratio [HR], 1.11; (95% CI], 1.05–1.17)
2. (MELD) (HR, 1.15; 95% CI, 1.03–1.29)
3. Albumin (HR, 0.37; 95% CI, 0.22–0.62).

4. Diagnostic capacity of HVPG was greater than for MELD or Child–Pugh score. Patients with an HVPG <10 mm Hg have a 90% probability of not developing clinical decompensation

Ripoli Gastroenterology 2007
Why don’t we wait for the liver cirrhosis to improve after HCV therapy?

1. Majority of cirrhosis patients show improvement in stage and reduction of clinical decompensation after DAA induced SVR
2. Predicting who will improve

N=104 HCV cirrhosis. PHT>6mmHg
HVPG improved 13.1 +/- 0.77mm Hg to 10.4 +/-0.79 mmHg

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Normalised</th>
<th>Residual CSPHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-9mmHg</td>
<td>63% normalised</td>
<td>0%</td>
</tr>
<tr>
<td>&gt;10mmHg</td>
<td>63% improved</td>
<td>76%</td>
</tr>
</tbody>
</table>

76% will continue to be at risk of liver complications

Can the Liver improve with HCV Rx

- HCV Rx
- Synthetic function
- compensated
- PHT
- decompensated
- Liver Failure
- HCC
- Death
1.3: Liver testing in patients with CKD and HCV infection
1.3.1: We recommend assessing HCV-infected patients with CKD for liver fibrosis (1A).
1.3.2: We recommend an initial noninvasive evaluation of liver fibrosis (1B).
1.3.3: When the cause of liver disease is uncertain or noninvasive testing results are discordant, consider liver biopsy (Not Graded).
1.3.4: We recommend assessment for portal hypertension in CKD patients with suspected advanced fibrosis (F3—4) (1A).
Assessing Portal Hypertension in HCV Renal Patients

• Direct portal pressure
  • Hepatic-vein wedge-pressure gradient of > 10mmHg.

• Surrogate
  • upper endoscopy to look for varices
  • Non-invasive radiological evaluation for portal/splenic varices

Based on the Baveno VI consensus, in compensated cirrhosis
• For those with elastography < 20 kPa and platelet count > 150,000/mm3.
• hypertension is very unlikely (upper endoscopy can be avoided with > 90% reliability)
Executive summary of the 2018 KDIGO Hepatitis C in CKD Guideline: welcoming advances in evaluation and management

Michel Jadoul¹, Marina C. Berenguer²,³,⁴, Wahid Doss⁵, Fabrizio Fabrizi⁶, Jacques Izopet⁷,⁸,

CHAPTER 4: MANAGEMENT OF HCV-INFECTED PATIENTS BEFORE AND AFTER KIDNEY TRANSPLANTATION

4.1: Evaluation and management of kidney transplant candidates regarding HCV infection
   4.1.1: We recommend kidney transplantation as the best therapeutic option for patients with CKD G5, irrespective of presence of HCV infection (1A).
   4.1.2: We suggest that all HCV-infected kidney transplant candidates be evaluated for severity of liver disease and presence of portal hypertension (if indicated) prior to acceptance for kidney transplantation (2D).
   4.1.2.1: We recommend that HCV-infected patients with compensated cirrhosis (without portal hypertension) undergo isolated kidney transplantation (1B).
   4.1.2.2: We recommend referring HCV-infected patients with decompensated cirrhosis for combined liver-kidney transplantation (1B) and deferring HCV treatment until after transplantation (1D).
Outcomes of KTx (alone) in compensated cirrhosis

N=90 HCV+ KTx patients. Transjugular liver biopsy and HVPG<10

Kaplan-Meier curves comparing patient survival after transplantation between patients with cirrhosis (n=9) and without cirrhosis (n=28).

KTx alone may be safe in patients with compensated HCV, cirrhosis, and ESRD with HPVG less than 10 mm Hg.
One- and three-year cumulative graft survival rates censored for death were 94% and 81%, and 95% and 82% for the noncirrhosis and cirrhosis groups, respectively (P=NS).

Clinically compensated patients with cirrhosis may undergo kidney transplantation alone as a safe and viable practice.

Outcome of KTx in cirrhotic vs non cirrhotic (n=131)
San Antonio, Texas

N=131 KTx . 12 with concomitant cirrhosis (HCV=7)

Median Patient survival in cirrhotic = 7.6Y vs 12.9 Y in the non-cirrhotic group.

Median Graft survival in cirrhotic group = 8.1 years vs 12.9 years in non-cirrhotic group (P = 0.052)

Graft survival at 3 years is far below the national average (82%). LTx should be considered in cirrhotics

SLKT- factors that worsen survival

• Sharma et al. showed that there was no survival benefit of CLKT over LT alone, unless the KDRI was ≤1.1 (KDPI equivalence ~60%-65%).

• Renal Graft Quality
  Of 4207 SLK transplants, 6% were from KDPI >85% donors. KDPI >85% recipients had significantly increased mortality (HR=1.83, 95%CI=1.44-2.31) after adjusting for recipient factors.  

  Jay Clin Transplant 2017

• Optimising time of renal transplant in SLKT
  Delayed renal transplant 2-3 days after LTx improved graft and survival outcomes compared to SLKT

  Ekser. Ann Surg 2017
Monitoring of HCV cirrhosis and care of Patients with KTx

Treat HCV with oral DAA for eradication

Monitor Liver Function and reserve
- LFT / MELD / Child Pugh Score
- Presence of ascites
- Falling platelet

Consider OGD for variceal screening

Surveillance for HCC is recommended for advanced fibrosis F3=F4
Conclusion

• Issues with Simultaneous Liver Kidney transplantation vs single organ transplantation –
  • LTx patients with ESKD benefit from SLKT (good kidney graft)
  • KTx patients with ESLD/ PHT benefit from SLKT but graft outcome is inferior to KTx alone

• What are the guidelines?
  • HCV patients with compensated cirrhosis without PHT undergo isolated KTx.
  • HCV patients with decompensated cirrhosis for combined SLKT

• What’s the evidence?
  • KTx transplant In compensated cirrhosis do just as well as non-cirrhosis in era of DAA
  • Patients with PHT may continue to progress and are at risk of poor morbidity/ mortality

• Implementing the evidence
  • Combined Renal/Liver transplant approach to impact access policy, graft selection priority
  • KTx patients with cirrhosis need to be monitored for deterioration and HCC
  • More evidence needed for impact of QOL and research on preserving graft optimisation
Thank You

KDIGO