NAFLD and Liver Transplantation

Zobair M Younossi MD, MPH, FACP, FAASLD, AGAF, FACG
President, Inova Medicine Services, Inova Health System
Chairman, Clinical Research, Inova Health System
Chairman and Professor of Medicine, Inova Fairfax Hospital,
Falls Church, Virginia, United States

Research funding and/or consultant: Gilead Sciences, Intercept, BMS, NovoNordisk, Viking, Tems, Siemens, Shionogi, Abbvie, Merck, Abbott, Axcella and Novartis.

<table>
<thead>
<tr>
<th>Region</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>24.1%</td>
</tr>
<tr>
<td>Europe</td>
<td>23.7%</td>
</tr>
<tr>
<td>Asia</td>
<td>27.4%</td>
</tr>
<tr>
<td>Middle East</td>
<td>31.8%</td>
</tr>
<tr>
<td>South America</td>
<td>30.5%</td>
</tr>
<tr>
<td>Africa</td>
<td>13.5%</td>
</tr>
</tbody>
</table>

The worldwide prevalence of NAFLD is 25%

- Prevalence of NASH in general population is between 1.5–6.5%
- Prevalence of NASH among T2DM is 37.3% (24.7-50.0%)
- Prevalence NAFLD in children is 7-10% (highest South America and lowest in Africa)
- Prevalence is higher in Hispanic boys and increases with higher BMI
- The prevalence of NAFLD in the US increased 2.7 fold from the late 1980’s to 2010
**Natural History of NAFLD and NASH**

- **The most common cause of death**

- **Normal**
- **Non-NASH 70-93%**
- **NASH (7-30%)**
  - **NASH with fibrosis**
  - **NASH with advanced fibrosis**
  - **1-3% per year**
  - **0.002-0.04% per year**
  - **Cirrhotic HCC**
  - **Non-cirrhotic HCC**

**Fibrolysis**

**Fibrogenesis**

**Non-linear Progression**

**Time**

**HCC, hepatocellular carcinoma.**


---

**Clinical Burden of NAFLD and NASH**

**NASH Denotes Progressive Disease**

**Components of MS Predicts Mortality-NHANES III**

**HCC and NAFLD- SEER 2004–2009**

**Changes in CLD NHANES 1988-1994 and 1999-2016**

**Changes in CLD Mortality National Center for Health Statistics Mortality data**

**Future Clinical Burden of NAFLD 2015-2030**

**Incident liver-related deaths**

**Incident decompenesated cirrhosis**

**Incident HCC**

Global Clinical Burden of NAFLD

**Trends in Incidence Rates (GBD 2012-2017)**

<table>
<thead>
<tr>
<th>Region</th>
<th>Liver Cancer</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>8.7%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Australia</td>
<td>9.8%</td>
<td>3.4%</td>
</tr>
<tr>
<td>High-income Asia-Pacific</td>
<td>6.9%</td>
<td>2.8%</td>
</tr>
<tr>
<td>High-income North America</td>
<td>7.6%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Southern Latin America</td>
<td>6.4%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Western Europe</td>
<td>6.7%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Americas</td>
<td>7.7%</td>
<td>3.2%</td>
</tr>
<tr>
<td>China</td>
<td>6.4%</td>
<td>3.3%</td>
</tr>
<tr>
<td>European Africa</td>
<td>6.6%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>7.1%</td>
<td>3.3%</td>
</tr>
</tbody>
</table>

**Trends in Mortality Rates (GBD 2012-2017)**

<table>
<thead>
<tr>
<th>Region</th>
<th>Liver Cancer</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>3.1%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Australia</td>
<td>3.2%</td>
<td>1.8%</td>
</tr>
<tr>
<td>High-income Asia-Pacific</td>
<td>3.0%</td>
<td>1.5%</td>
</tr>
<tr>
<td>High-income North America</td>
<td>3.2%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Southern Latin America</td>
<td>2.9%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Western Europe</td>
<td>3.2%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Americas</td>
<td>3.3%</td>
<td>1.8%</td>
</tr>
<tr>
<td>China</td>
<td>3.0%</td>
<td>1.6%</td>
</tr>
<tr>
<td>European Africa</td>
<td>3.1%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>3.4%</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

**Liver Cancer**

**Cirrhosis**

Non-Liver Related Outcomes of NAFLD

**NAFLD is Part of A Multisystem Disorder**

- Vascular disease
- Chronic kidney disease
- Osteoarthritis
- Diabetes
- Gallstone disease
- Obstructive sleep apnea
- Polycystic ovary syndrome

**CV Deaths**

- 38.3%
- 30%
- 16%
- 38%
- 12.7%

**Malignancy**

<table>
<thead>
<tr>
<th>Site</th>
<th>Fold increase*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>4.0</td>
</tr>
<tr>
<td>Stomach</td>
<td>3.5</td>
</tr>
<tr>
<td>Pancreas</td>
<td>2.7</td>
</tr>
<tr>
<td>Lung</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Symptoms and PROs in NAFLD and NASH

- Highest rate of Fatigue in real world setting was observed in NASH/NAFLD
- Patients with biopsy-proven NASH (N=1669)
- Prevalence of clinically significant fatigue 31%
- Clinically significant pruritus in 27%
- Pruritus and fatigue had negative impact on PROs

Economic Burden of NASH

- Economic burden of NASH
  - Markov models (prevalence and incidence)
  - In the U.S., there are 688 thousand cases of advanced NASH
  - Lifetime direct costs of all NASH will be $222.6 billion
  - Lifetime direct costs of the advanced NASH population will be $95.4 billion.

NAFLD Pathophysiology
Promoters of NASH and Fibrosis Progression

DAMPs, danger-associated molecular patterns; ECM, extracellular matrix; IL-1β, interleukin-1 beta; PAMPs, pathogen-associated molecular patterns; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor beta; TNF, tumor necrosis factor; TNF-β, tumor necrosis factor-beta.


Histologic Features and Outcomes in NASH

- NAFLD liver biopsy (NAS, Brunt, Original NAFLD, and ZG Criteria) and mortality data (N=209)
- During 146 months FU, 31% of patients died with 9% LRM

- Fibrosis stage, but no other histologic features of steatohepatitis, were independently associated with overall mortality and liver-related mortality

Systematic search of 5 studies of adult NAFLD cohort (N=1495) studies with mortality data and biopsy stage (0–4)

Hagstrom H et al, J Hepatology 2017;67:1265-1273
Non-Invasive Tests for the Spectrum of NAFLD

- Normal Liver
- Steatosis (NAFL)
- Steatohepatitis (NASH)
- Fibrosis & Cirrhosis

**“Wet” Biomarkers**
- Fatty Liver Index (FLI)
- CK-18 NIS4

**“Dry” (Imaging) Biomarkers**
- Ultrasound
- FibroScan™ (CAP)
- MR-PDFF
- MR Liver MultiScan™
- FibroScan™ (VCTE)
- MR Elastography

Non-Invasive Tests for Fibrosis in NAFLD

- **FIB-4 Index:**
  - Originally developed to predict advanced fibrosis in HIV/HCV coinfection
  - Subsequently studied in 541 patients with NAFLD (AUROC 0.80)

- **APRI:**
  - Meta-analysis of 40 studies
  - The lower the APRI score (less than 0.5), the greater the negative predictive value (and ability to rule out cirrhosis) and the higher the value (greater than 1.5) the greater the positive predictive value (and ability to rule in cirrhosis).

- **NAFLD Fibrosis Score (NFS):**
  - 733 NAFLD: 480 derivation; 253 validation
  - Multivariate analysis (Age, hyperglycemia, BMI, platelet count, albumin, AST/ALT ratio) are independent predictors of advanced fibrosis

**FIB-4 Cutoff Value**

- Cutoff Value: 2
- Stage:
  - <1.45: F0-F2
  - 1.45 to 3.25: Indeterminate
  - >3.25: F3-F4

**APRI:**

- The lower the APRI score (<0.5), the greater the NPV (and ability to rule out cirrhosis) and the higher the value (>1.5) the greater the PPV (and ability to rule in cirrhosis)

**NFS Cutoff Value**

- Cutoff Value: 1
- Stage:
  - <1.455: F0-F2
  - 1.455 to 0.676: Indeterminate
  - >0.676: F3-F4
Components

- Procollagen III N-terminal peptide (PIIINP)
- Hyaluronic acid (HA)
- Tissue inhibitor of metalloproteinase 1 (TIMP1)

The Enhanced Liver Fibrosis Test (ELF)

- Patients with NASH and bridging fibrosis (n=219) or compensated cirrhosis (n=258) enrolled in two Phase 2b SIM studies were used to show that ELF can predict progression to cirrhosis and development of liver-related clinical events.
- Optimal threshold of baseline ELF: 9.76 (sensitivity 77%, specificity 66%)

Serum Biomarker for Fibrosis in NAFLD

Radiologic Tests To Measure Liver Stiffness
Sequential Tests for Advanced Fibrosis in NASH

Meta-Analysis of NTs to Distinguish Simple Steatosis From NASH

- In 122 studies, 219 blood markers (single markers and scoring systems) were evaluated
- In meta-analysis, no test reliably differentiated simple steatosis from NASH with a high level of pooled sensitivity and specificity

  - Study of baseline data from STELLAR trials (N = 3202) to diagnose F3/F4 fibrosis
  - Single tests (either NFS, FIB-4, ELF, or FibroScan) led to up to 50% indeterminate results
  - Sequential tests (FIB-4, then ELF or FibroScan) led to up to 24% indeterminate results

<table>
<thead>
<tr>
<th>Outcome With Sequential Tests, % (95% CI)</th>
<th>FIB-4, then ELF (N = 3180)</th>
<th>FIB-4, then FS (N = 3141)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of F3/F4</td>
<td>71</td>
<td>71</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>69 (67 to 71)</td>
<td>77 (75 to 78)</td>
</tr>
<tr>
<td>Specificity</td>
<td>92 (90 to 94)</td>
<td>89 (87 to 91)</td>
</tr>
<tr>
<td>PPV</td>
<td>96 (94 to 97)</td>
<td>95 (93 to 96)</td>
</tr>
<tr>
<td>NPV</td>
<td>55 (53 to 58)</td>
<td>60 (58 to 63)</td>
</tr>
<tr>
<td>Misclassified</td>
<td>24 (23 to 26)</td>
<td>20 (18 to 21)</td>
</tr>
</tbody>
</table>

Anstee. Hepatology. 2019;70:1521

An Algorithm for Risk Stratification in NAFLD

1. History of chronic elevation of AST or ALT (1.5-times ULN in the past 6 months) or
2. History of fatty liver by any radiologic modality (US, CT, MRI) or liver biopsy (any historical test will be sufficient)
3. T2DM with one additional component of metabolic syndrome (BMI>29.9 or Dyslipidemia treated with meds or Hypertension treated with meds) or
4. Non-diabetics with 3 other components of MS (BMI>29.9, Dyslipidemia treated with meds and Hypertension treated with meds)

- For those with elevated AST and ALT for at least 6 months- other causes of liver disease should be excluded
- For those without previous imaging, an US should be performed

FIB-4<1.3
- Follow up by primary care
- Strict life style modification for CV risk

FIB-4>1.3
- Link to Care for Further Assessment
  - TE
  - Serum biomarkers (ELF available)

TE<8 kPa Low Risk
- Strict life style modification
- Consider liver biopsy
- Clinical trials and future medical treatment
Lifestyle Interventions to Manage NAFLD and NASH

Diet and exercise counseling are recommended for patients with NAFLD

- Decreasing caloric intake by ≥30% improves IR and hepatic fat
- Mediterranean diet improves steatosis
- Low-carbohydrate diet improves liver fat metabolism
- Coffee (caffeinated, filtered) ≥ 3 cups/day decreases NAFLD mortality
- Reduction or elimination of alcohol consumption

Physical activity ≥150 min/week decreases serum aminotransferases
- Moderate exercise ≥5 times/week is associated with greatest benefit for long-term NAFLD prevention and improvement
- Losing ≥5% of body weight improves HS
- Losing ≥7% of body weight improves NAS
- Losing ≥10% of body weight improves all features of NASH

>10% weight loss is hard to achieve and hard to maintain


Current and Future Treatment for NASH

- PPAR-y (pioglitazone)
- PPARα/δ agonist
- mTOT
- GLP1RA
- GLP1–GIP–glucagon
- Fatty acid–bile acid conjugates
- FXR agonist
- FGF19
- FGF21
- ACC1 and FASN FGF21
- THRβ agonist
- Integrin inhibitors
- CCR2–CCR5 antagonist
- VAP1 inhibitor

ACC1, acetyl-CoA carboxylase 1; ASK1, Apoptosis signal-regulating kinase 1; FASIN, fatty acid synthase; FGF19, fibroblast growth factor; FXR, farnesoid X receptor; GIP, gastric inhibitory peptide; GLP1, glucagon-like peptide 1 receptor agonist; mTOT, mitochondrial target of thiazolidinedione; THRβ, thyroid receptor beta; VAP1, vascular adhesion protein 1.

Liver Transplantation for NASH: Transplant Candidates 2002 to 2019 SRTR data (N=168,441)

Liver Transplantation for NASH: Survival of Liver Transplant Recipients

- United Network for Organ Sharing and Organ Procurement and Transplantation (UNOS/OPTN) 2003–2014 database
- On MVA, NASH had significantly higher post-transplant survival compared to patients with HCV (HR 0.75; 95% CI 0.71–0.79; P=.001)
- ALD also had significantly better post-transplant survival compared to HCV patients (HR 0.80; 95% CI 0.76–0.84; P=.001).
- Patients with underlying diabetes had significantly lower post-transplant survival (diabetes = HR 1.30; 95% CI 1.25–1.36; P=.001).
- Concurrent diagnosis of HCC was also associated with significantly lower posttransplant outcomes (HR 1.25; 95% CI 1.19–1.32; P=.001).

Liver Transplantation for NASH: Transplant Candidates and Recipients (European Data)

- European Liver Transplant Registry database (January 2002 and December 2016) (N= 68,950)
- Overall, 4.0% were transplanted for NASH – an increase from 1.2% in 2002 to 8.4% in 2016.
- A greater proportion of patients transplanted for NASH (39.1%) had hepatocellular carcinoma (HCC) than non-NASH patients (28.9%, p<0.001).
- NASH was not significantly associated with survival of patients (hazard ratio [HR] 1.02, p=0.713) or grafts (HR 0.99; p=0.815) after accounting for available recipient and donor variables.
- Increasing recipient age (61–65 years: HR 2.07, p<0.001; >65: HR 1.72, p=0.017), elevated model for end-stage liver disease score (>23: HR 1.48, p = 0.048) and low (<18.5 kg/m²:HR 4.29, p = 0.048) or high (>40 kg/m²: HR 1.96, p = 0.012) recipient body mass index independently predicted death in patients transplanted for NASH without HCC.
### Long-term outcomes after LT for NASH

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country, Period</th>
<th>Population, sample size</th>
<th>MELD score</th>
<th>Patient survival, %</th>
<th>Leading cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malik, 2009</td>
<td>US single center 1997–2008</td>
<td>NASH = 98</td>
<td>17</td>
<td>79%</td>
<td>74%</td>
</tr>
<tr>
<td>Yalamanchili 2019</td>
<td>US single center 1986–2004</td>
<td>NASH = 18, CC = 239</td>
<td>-</td>
<td>85%</td>
<td>-</td>
</tr>
<tr>
<td>Bhagat 2009</td>
<td>US single center 1997–2007</td>
<td>NASH = 71</td>
<td>-</td>
<td>82%</td>
<td>79%</td>
</tr>
<tr>
<td>Barritt, 2011</td>
<td>US single center 2004–2007</td>
<td>NASH = 21</td>
<td>23</td>
<td>76%</td>
<td>76%</td>
</tr>
<tr>
<td>Houlihan, 2011</td>
<td>Israel, single center 2000–2008</td>
<td>NASH = 48</td>
<td>15</td>
<td>88%</td>
<td>-</td>
</tr>
<tr>
<td>Charlton, 2011</td>
<td>US, SRTR registry 2001–2009</td>
<td>NASH = 1840</td>
<td>-</td>
<td>84%</td>
<td>76%</td>
</tr>
<tr>
<td>Agopian, 2012</td>
<td>US single center 2002–2011</td>
<td>NASH = 144</td>
<td>33</td>
<td>84%</td>
<td>75%</td>
</tr>
<tr>
<td>Wagner, 2012</td>
<td>US single center 1993–2010</td>
<td>NASH = 115</td>
<td>24</td>
<td>81%</td>
<td>73%</td>
</tr>
<tr>
<td>Kennedy 2012</td>
<td>US single center 1999–2009</td>
<td>NASH = 129</td>
<td>23</td>
<td>90%</td>
<td>88%</td>
</tr>
<tr>
<td>Afzali, 2012</td>
<td>US, UNOS 1997–2010</td>
<td>NASH = 1810; CC = 3843</td>
<td>21</td>
<td>87%</td>
<td>81%</td>
</tr>
</tbody>
</table>

© 2020 AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

### NAFLD Post Liver Transplantation: Recurrent, de novo NAFLD and advanced fibrosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Population, N</th>
<th>Time after LT</th>
<th>NAFLD</th>
<th>NASH</th>
<th>Fibrosis</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kontos 2001</td>
<td>NASH&amp;CC N = 27</td>
<td>1 year</td>
<td>52%</td>
<td>11%</td>
<td>SF3: 4%</td>
<td>Risk of allograft steatosis of 1 year 100%</td>
</tr>
<tr>
<td>Charlton 2001</td>
<td>NASH N = 15</td>
<td>1 year</td>
<td>60%</td>
<td>33%</td>
<td>SF2: 33%</td>
<td>Risk of de novo NASH development was 16%</td>
</tr>
<tr>
<td>Ong 2001</td>
<td>CC N = 51</td>
<td>2 years</td>
<td>25.4%</td>
<td>16%</td>
<td>SF3: 3.4%</td>
<td>Risk of de novo NASH development was 16%</td>
</tr>
<tr>
<td>Seo 2007</td>
<td>Non-NALFD CLD N = 88</td>
<td>2 years</td>
<td>18%</td>
<td>9%</td>
<td>-</td>
<td>Increase of 50% in 100% associated with post-LT NASH</td>
</tr>
<tr>
<td>Bhagat 2009</td>
<td>NASH N = 84</td>
<td>&gt;6 months</td>
<td>-</td>
<td>33%</td>
<td>-</td>
<td>Growth fraction of end-stage liver disease: 100%</td>
</tr>
<tr>
<td>Malik 2009</td>
<td>NASH N = 96</td>
<td>5 years</td>
<td>-</td>
<td>25%</td>
<td>-</td>
<td>Growth fraction of end-stage liver disease: 100%</td>
</tr>
<tr>
<td>Yalamanchili 2010</td>
<td>NASH &amp; CC N = 257</td>
<td>5 years</td>
<td>31%</td>
<td>4%</td>
<td>SF3: 5/6% 10% at 10 yrs</td>
<td>Advanced fibrosis more frequent at 10 yrs</td>
</tr>
<tr>
<td>Dumortier 2010</td>
<td>Non-NALFD CLD N = 421</td>
<td>&gt;6 months</td>
<td>31%</td>
<td>5.3%</td>
<td>SF3: 2.25%</td>
<td>Risk of allograft steatosis of 1 year 100%</td>
</tr>
<tr>
<td>Duseja 2011</td>
<td>NASH or CC N = 88</td>
<td>1 year</td>
<td>39%</td>
<td>28%</td>
<td>SF2: 9%</td>
<td>Risk of allograft steatosis of 1 year 100%</td>
</tr>
<tr>
<td>El Attache 2012</td>
<td>NASH/CC N = 83</td>
<td>1.5 years</td>
<td>-</td>
<td>24%</td>
<td>SF3: 3.8%</td>
<td>Risk of allograft steatosis of 1 year 100%</td>
</tr>
<tr>
<td>Kim 2014</td>
<td>Non-NALFD CLD N = 156</td>
<td>&gt;1 year</td>
<td>27.1%</td>
<td>6.7%</td>
<td>SF2: 4.4%</td>
<td>Risk of allograft steatosis of 1 year 100%</td>
</tr>
</tbody>
</table>

© 2020 AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

### Over 1-2 years:
- 20-60% recurrence of NAFLD Post-LT
- 5-33% recurrence of NASH
- 4% of advanced fibrosis
The prevalence of comorbidities in adult liver transplant recipients (SRTR 1987 to June 2013)

- Consistent with the changes in US population, LT recipients are becoming older, more commonly male and sicker
- Average MELD score increased slightly.
- Rates of nearly all chronic conditions increased
- What contributes to post-LT metabolic profile?
- Given the epidemic of obesity and T2DM, these rates are also higher in LT recipients
- How about meds?

Factors Contributing to Post LT Metabolic Profile

<table>
<thead>
<tr>
<th>CST</th>
<th>Calcineurin inhibitors</th>
<th>mTOR inhibitors (sirolimus, everolimus)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TAC</td>
<td>CSA</td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>New Onset DM</td>
<td>+++</td>
<td>**</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>HTN</td>
<td>+</td>
<td>**</td>
</tr>
</tbody>
</table>


Clinical Issues in Patients with NASH and LT

- **CV and CKD Risks:**
  - Liver transplant candidates with NASH are at high risk of developing CV events before and after LT
  - Accumulation of CV risk factors should be carefully assessed by transplant team (cardiologists and anesthesiologists)
  - Patients with Child A/B NASH cirrhosis and CV comorbidities can be considered for management of dyslipidemia and CV risk
  - NASH is an independent risk factor for pre and post-LT renal dysfunction; appropriate screening and management of kidney disease is highly recommended in this patient population

- **Management of Metabolic Comorbidities:**
  - A multidisciplinary approach is recommended to establish a risk minimization plan
  - Appropriate screening for hypertension, diabetes, and dyslipidemia is recommended in NASH-patients considered for LT and medical optimization is strongly recommended
  - Post-LT moderate exercise is recommended with the dual objective of losing weight and improving muscle mass

(NASH is an independent risk factor for pre and post-LT renal dysfunction; appropriate screening and management of kidney disease is highly recommended in this patient population)

Modified from Tsochatzis E et al. Transplantation 2019;103: 45–56)

NAFLD and Liver Transplantation

**Summary**

- NASH is becoming the most common cause of liver disease in the United and possibly the world
- NASH has significant clinical, economic and quality of life burden
- NASH is the second common indication for LT in the US and the top indication among women
- NASH can recur post LT
- Post LT outcomes for NASH are similar to other etiologies
- Given close associations with metabolic risk factors, CV risk, CKD risk and other metabolic abnormalities, there is a need for assessment and aggressive management both pre-LT and post-LT