



## Risk Factors for Mortality in Liver Transplant Recipients

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### ABSTRACT

Orthotopic liver transplantation (OLT) has become one of the major routine operation and lifesaving procedure for many end-stage hepatic diseases like acute liver failure, hepatoma, Wilson's disease, severe hepatitis, and decompensated liver diseases. The primary reason for morbidity and mortality after OLT is infections. Bacterial infections are the foremost common risk factor for morbidity in liver transplant recipients whereas viral and fungal infections also contribute. Liver transplant recipients with MELD score  $\geq 30$  are a specific subgroup of patients with an individual high- risk profile and they need close monitoring. The other risk factors include immunosuppression before transplantation, underlying condition of the recipient, co-morbidity associated with liver disorder i.e. diabetes, COPD, obesity, renal failure and dialysis, Acute liver failure, prolonged hospital stay and catheters before liver transplantation, ascites & Spontaneous bacterial peritonitis before transplantation. Therefore, a better understanding of these risk factors should be considered and need attention to reduce this risk.

**Keywords:** Liver transplantation, Infection, Bacteria, Viral, Fungal.

### INTRODUCTION

Liver transplantation (LT) or hepatic transplantation is the replacement, either partly or completely, of a diseased liver with a healthy liver from another individual, either from deceased donor or living donor.<sup>1-3</sup> Orthotopic liver transplantation (OLT) has become a routine operation and is the foremost effective life sparing procedure for patients with certain intense and chronic end-stage liver diseases, such as acute liver failure, hepatoma, wilson's disease, severe hepatitis, and decompensated liver diseases. The survival rate for these patients in one year is 90% and five year is 80%. Infection remains the major cause of mortality and morbidity after OLT, i.e. up to 80% of the patients. Most frequent infections are bacterial (70%), followed by viral (20%) and fungal infections (8%).<sup>2-4</sup> Due to immunosuppression, clinical symptoms can be blurred or absent which can be lead to delayed diagnosis. The risk of infection after OLT contribute both donor and recipient factors as well as aspects related to the transplant operation.<sup>2</sup>

In immunosuppressed liver transplant individuals, infections are markedly challenging to investigate because the usual signs and symptoms of infection, such as fever and leukocytosis may be masked or hidden.<sup>4</sup> Because of developments in surgical strategies, and a lessening in homograft rejection, life span after liver transplantation has enhanced over the decades.<sup>3</sup> The survival rate and quality of life of sufferers can improve by understanding the complications. The main cause of morbidity during the first three years after OLT is opportunistic infections.<sup>4-5</sup> During 2008-2009, a total of 6331 liver transplantations were done in US, with a

survival rate of 85% at one year, according to the United Network for Organ Sharing (UNOS).<sup>3</sup>

#### Bacterial infections

The leading reason for infection in liver transplant recipients is the bacterial pathogens. After liver transplantation, the highest occurrence of infections appear during the initial month primarily involve the site of surgery, the intestinal cavity, circulatory system, genitourinary system and the airway tract.<sup>8</sup> Risk factors include surgical procedure, prolonged hospitalization, prior colonization, mechanical ventilation, indwelling vascular and urinary catheterization. etc.<sup>9</sup>

After liver transplantation, virtually any microorganism can cause illness, the most common bacteria was found to be *Enterococcus*, *Staphylococcus aureus*, *Viridans streptococcus* and *Enterobacteriaceae*. Despite the disparity in incidence rates among geographic areas, antimicrobial resistance pattern is found to be in an increasing trend among bacteria.<sup>10</sup>

#### Viral infections

Liver recipients are commonly affected with Hepatitis B or C viruses. If the Hepatitis B virus is present at OLT, there is a higher chance to occur after OLT, often leading to graft failure and recipient death.<sup>6</sup> The prophylactic treatment with anti- HBV immunoglobulins (HBIG) during and after OLT led to a substantial reduction of HBV recurrence<sup>11</sup>. HCV- related disease has become one of the leading OLT indications. In the past hepatitis C virus (HCV) present at OLT, almost universally led to recurrence after OLT, often leading to graft failure and recipient death. Accelerated development of cirrhosis for this patients may occur.<sup>6</sup> Patients transplanted with HBV or HCV can also develop



cholestasis and rapid liver failure within weeks after OLT.<sup>12</sup>

OLT is possible for the HIV patients with the end-stage liver diseases, if the CD4 lymphocyte counts are normal and no resistance to highly active anti-retroviral therapy (HAART) exists.<sup>11</sup> Cytomegalovirus (CMV) infection is discovered to be important threat aspect for fatality in liver transplant recipients. The individuals without CMV disease until they receive a latently infected liver from a CMV- seropositive donor (CMV D+/R- mismatch) are the one who are at highest probability of CMV infection.<sup>13</sup>

### Fungal infections

*Candida* and *Aspergillus* are the most frequent species among fungal infections which affect liver transplant recipients. Other species which causes infection are *Cryptococcus neoformans*, *Histoplasma Capsulatum*, *Coccidioides dermatitidis*, *Sporothrix schenckii*, *Alternaria species*, *Pneumocystis Jirovesii* and *Trichophyton rubrum*.<sup>14</sup> *Candida* species is found to be the most recurrent infection in liver transplant recipients and occurs during first 1-3 months after liver transplantations. The single most common species which is the reason for mortality is *Candida albicans*. The species reported more often from blood cultures is *Candida non-albicans*. Other species reported include *Candida glabrata*, *Candida parapsilosis*, *Candida krusei*, *Candida tropicalis*, *Candida guilliermondii* and *Candida kefyr*.<sup>14-15</sup>

The risk factors for second most common fungal infection after *Candida* species i.e. *Aspergillus* species are renal insufficiency, retransplantation, renal failure, surgical factors, Cytomegalovirus infection, fulminant hepatic failure, prior colonization, microbial factor and prolonged ICU stay. The common species among *Aspergillus* species is *Aspergillus fumigatus*, whereas *Aspergillus niger*, *Aspergillus flavus* and *Aspergillus terreus* are rare. Remarkable reduction in invasive infection from *Aspergillus* species is seen who had treated with antifungal prophylaxis and mortality associated with fungal infections is also reduced.<sup>15</sup>

### Meld score $\geq 30$

The Liver transplant recipients with a MELD score  $\geq 30$  are at high risk of early mortality within the first 3 months after transplantation. A close monitoring and early care should be provided to these patients to prevent poor outcomes in the first days and weeks after transplantation. The MELD score is calculated based on serum creatinine, serum bilirubin and INR value and it has been validated to predict early death of liver transplant recipients.<sup>16</sup>

### Table 1: MELD Score calculation<sup>17</sup>

MELD score =  $10\{0.957 \log(\text{serum creatinine}) + 0.378 \log(\text{total bilirubin}) + 1.12 \log(\text{INR}) + 0.643\}$ .

### Other factors

The other risk factors for mortality in liver transplant recipients are immunosuppression before transplantation, underlying disease condition of the recipient, co-morbidity associated with liver disease i.e, diabetes, COPD, obesity, renal failure and dialysis, Acute liver failure, prolonged hospital stay and catheters before liver transplantation, ascites, hepatic encephalopathy and Spontaneous bacterial peritonitis before transplantation.<sup>2-5</sup>

### CONCLUSION

Opportunistic infections remain the major preventable causes of morbidity and fatality after orthotopic liver transplantation. Bacterial, viral and fungal infection constitutes the risk factor for fatality in liver transplant recipients. Most of the infections occur at the time of intense immunosuppression and during prolonged hospital stay. Prophylactic treatment for the high risk patients should be provided to reduce infections. Better treatment for co-morbid disease should also to be considered. Early diagnosis and prompt treatment is fundamental for the patient survival.

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