Background

Liver Transplantation in the United States

Liver transplantation is a life-saving surgery for patients with acute and chronic liver diseases. In the United States, the major disorders that may result in consideration for liver transplantation include acute liver failure, chronic liver disease with advanced cirrhosis, hepatocellular carcinoma (HCC), and liver-based metabolic defects (Figure 1).[1] This review will discuss general information and principles regarding liver transplantation, with a focus on specific information related to liver transplantation for HCV. In the United States in 2017, an estimated 8,082 liver transplants were performed and liver transplants accounted for approximately 23% of all solid organ transplants.[2] From 1988 through 2017 the overall trend shows a steady increase in the number of liver transplants performed in the United States (Figure 2). Advances in the field of transplantation have improved post-transplant survival rates in the United States to 87.7% at 1 year after liver transplantation, 79.9% at 3 years, and 74.3% at 5 years.[3]

Liver Transplantation in Patients with Chronic HCV Infection

For more than a decade, chronic hepatitis C virus (HCV) infection was the most common indication for liver transplantation in the United States, but in 2016 alcoholic liver disease moved ahead of chronic HCV as the most common indication for liver transplantation (Figure 3).[4, 5, 6] Since acute HCV rarely causes liver failure, nearly all transplants related to HCV involve patients with chronic HCV infection who have developed cirrhosis-related complications. Data from 2012-2014 for persons with chronic HCV monoinfection who received a liver transplant in the United States showed that most recipients were male (70.8%) and white (69.1%).[7] During this time period, among the 41,557 persons listed for orthotopic liver transplantation, 21,064 (51.2%) received a liver transplant.[7]
Indications for Liver Transplantation

In 2013, the American Association for the Study of Liver Diseases (AASLD) and the American Society of Transplantation (AST) issued Guidelines for Evaluation for Liver Transplantation in Adults and these guidelines state that "liver transplant is indicated when the limits of medical therapy have been reached". The AASLD/AST guidelines outline four major types of indications for liver transplantation in the United States: (1) acute liver failure, (2) complications of cirrhosis, (3) liver-based metabolic diseases, and (4) systemic complications of chronic liver disease. In addition, there are some rare conditions that can warrant liver transplantation. The following briefly summarizes the major indications for liver transplantation.

Acute Liver Failure

Acute liver failure is defined as the development of encephalopathy (any degree of mental alteration) hepatic and coagulopathy (international ionized ratio [INR] greater than or equal to 1.5) within 26 weeks from the onset of symptoms related to acute hepatitis in patients without preexisting liver disease. Common causes of acute liver failure include acetaminophen overdose, acute viral hepatitis, drug-induced liver injury, mushroom poisoning, autoimmune hepatitis, Wilson's disease, acute ischemic hepatitis (shock liver), and acute fatty liver of pregnancy. Acute HCV infrequently causes acute liver failure. Patients who meet the criteria for acute liver failure should be urgently transferred to a liver transplant center for transplant evaluation and for intensive management of liver failure. Given the rapidity of clinical deterioration, these candidates receive a special listing category (Status 1) to prioritize for deceased donor organs.

Cirrhotic Liver Disease with Complications

Chronic liver diseases that cause cirrhosis are by far the most common indication for liver transplantation in the United States. Alcoholic liver disease and chronic HCV infection are the most common diseases that lead to cirrhosis and liver transplantation. The major cirrhosis-related reasons for transplantation include the development of (1) a decompensating event or condition, such as ascites, hepatic encephalopathy, or variceal hemorrhage, (2) hepatocellular dysfunction with a model for end stage liver disease (MELD) score of 15 or greater, and (3) HCC within transplant criteria. In the United States, HCV infection with cirrhosis is the most common cause of HCC. Although HCC can be cured in some instances with hepatic resection and locoregional therapy, most patients with HCC confined to the liver should be considered for liver transplant. Patients with HCC who meet Milan criteria (solitary HCC lesion less than 5 cm or up to 3 nodules smaller than 3 cm) and have no radiographic evidence of extrahepatic disease, but who are not candidates for surgical resection, are considered liver transplantation candidates, and granted priority for liver transplantation. Certain patients with liver tumor burdens in excess of the Milan criteria may undergo HCC treatment as part of a downstaging protocol in an effort to become eligible as liver transplant candidates.

Metabolic Conditions

Liver transplantation is also considered for those with metabolic diseases, such as non-alcoholic steatosis, familial amyloidosis, Wilson's disease, glycogen storage disease, hemochromatosis, primary hyperoxaluria, and alpha-1 antitrypsin deficiency. Many of these metabolic diseases originate in the liver, but may require liver transplantation because of severe systemic symptoms. Other less common metabolic causes include urea cycle defects, branched-chain amino acid disorders, tyrosinemia, and homozygous familial hypercholesterolemia.

Systemic Complications for Chronic Liver Disease
Two major systemic complications of liver disease that may require liver transplantation are hepatopulmonary syndrome and portopulmonary syndrome.

- **Hepatopulmonary Syndrome**: The hepatopulmonary syndrome is characterized by underlying liver disease and/or portal hypertension that leads to pulmonary microvascular dilatation, pulmonary shunting, and reduced arterial oxygenation.[23,24] Patients with a room air pulse oximetry SPO2 less than 96% at sea level should be further evaluated for hepatopulmonary syndrome by contrast echocardiography or 99m-TC macroaggregated albumin (MAA) lung-brain perfusion scanning. There are no known effective medical treatments for hepatopulmonary syndrome and liver transplantation remains the only approach to reverse this condition, with estimated 5-year survival rates of approximately 75%—a marked improvement over supportive medical therapy alone.[23,25,26,27]

- **Portopulmonary Hypertension**: Portopulmonary hypertension is a severe local hypertensive complication that can result from pulmonary vasoconstriction in patients with cirrhosis and portal hypertension; portopulmonary hypertension can progress to right heart failure and death.[23,28] Liver transplantation is not a first-line option for most patients with portopulmonary hypertension, since moderate to severe portopulmonary hypertension is associated with increased post-transplant mortality, but it can be considered in selected situations, if pulmonary artery pressures have been lowered to less than 35 mm Hg and pulmonary vascular resistance is reduced to less than 400 dyn-sec/cm$^5$ with vasodilator therapy.[29,30]

**Rare Indications**

Other rare conditions for which liver transplantation is considered include fibrolamellar HCC, hepatic epithelioid hemangioendothelioma, hereditary hemorrhagic telangiectasia, hepatoblastoma, neonatal hemochromatosis, metastatic neuroendocrine tumors, erythropoietic protoporphyria, polycystic liver disease, and cholangiocarcinoma.
Timing for Cirrhosis-Related Liver Transplantation

The need for liver transplantation in a person with chronic HCV infection is almost always because of a cirrhosis-related complication. Thus, the following discussion will focus on the timing for liver transplantation in patients who have cirrhosis-related complications. When considering referral for liver transplantation, the natural history of the disease should be compared against the expected survival after transplantation. The use of prognostic scoring systems can assist in this consideration by predicting survival among individuals with cirrhosis. Patients who have an indication for liver transplantation should ideally be referred early in the clinical course rather than late because the transplant evaluation may take weeks to months to complete.

Decompensated Cirrhosis

Decompensated cirrhosis is defined by the occurrence of a complication, such as ascites, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, or hepatorenal syndrome. The development of decompensated cirrhosis negatively influences prognosis.[31] In a natural history study in patients with cirrhosis, more than 90% of the patients who remained compensated were still alive at 5 years, compared with only 50% survival at 5 years among those who experienced a decompensating event.[32] Moreover, once decompensation occurred, 20% died within one year. Similar findings have been repeated in other studies. Accordingly, patients should be referred for transplant evaluation when they experience their first major cirrhosis-related complication, such as ascites, variceal bleeding, or hepatic encephalopathy.[1,6]

Use of Prognostic Scoring Systems

Scoring systems initially designed to predict outcome following portocaval shunt surgery and transjugular intrahepatic portosystemic shunts (TIPS) have been used to predict overall survival in patients with cirrhosis.

- **Model for End-Stage Liver Disease (MELD):** The prognostic MELD has been shown to be a useful tool in predicting short-term survival in patients with chronic liver disease and MELD has become the most important indicator for transplantation. It uses a continuous scale from 6 to 40, based on serum bilirubin, international normalized ratio of prothrombin time (INR), and serum creatinine.[33,34] The modified MELD score was shown to predict mortality for patients on the liver transplant waiting list and was implemented in February 2002, replacing the Child-Turcotte-Pugh score, to prioritize patients for donor allocation in the United States (Figure 4).[35] A similar model, pediatric end-stage liver disease (PELD), is used for pediatric patients.[36] In January 2016, the MELD scoring system for donor allocation in the United States was further modified to incorporate serum sodium, using the MELD-Na equation (see the MELD Calculator Tool); the serum sodium is incorporated in only for patients with a MELD score greater than 11.[37] Based on current guidelines, patients with a MELD score of 15 or greater should be referred to a liver transplant center for evaluation.

- **Child-Turcotte-Pugh (CTP):** The CTP classification (Figure 5) can be used to predict short-term prognosis (Figure 6) in patients awaiting transplantation.[38,39,40] Patients with a CTP score of 7 to 9 (class B) have an estimated 1-year survival of 80%.[41] In the past, a CTP score of 7 or greater was considered a minimal listing criteria for liver transplantation.[42] For the purpose of listing criteria for liver transplantation, the CTP score is no longer used and it has been replace by the MELD score.

Urgent TRANSPLANTATION Referral for Patients with Cirrhosis

Patients with cirrhosis and type 1 hepatorenal syndrome have a median survival of less than 2 weeks and should be urgently referred to a transplant center for an expedited transplant evaluation, as should patients with other evidence for rapid hepatic decompensation.[1,6]
Contraindications for Liver Transplantation

Absolute Contraindications

Candidates for transplant surgery need to be able to survive the surgery and the immediate post-operative period, be compliant with the post-transplant medical regimen, and not have comorbid conditions that could limit graft or patient survival, particularly those that could significantly worsen by the use of immunosuppressive medications. Specific contraindications for liver transplantation vary across transplant centers. The AASLD/AST guidelines list the following as contraindications for liver transplantation:[6]

- MELD Score less than 15
- Severe cardiac or pulmonary disease
- AIDS
- Ongoing alcohol or illicit substance abuse
- Hepatocellular carcinoma with metastatic spread
- Uncontrolled sepsis
- Anatomic abnormality that precludes liver transplantation
- Intrahepatic cholangiocarcinoma
- Extrahepatic malignancy
- Fulminant hepatic failure with sustained intracranial pressure greater than 50 mm Hg or cerebral perfusion pressure less than 40 mm Hg
- Hemangiosarcoma
- Persistent noncompliance
- Lack of adequate social support system

Relative Contraindications

Some of the notable relative contraindications are listed below.[6] Some medical providers have the misperception that chronic hepatitis C or older age are relative contraindications to liver transplantation. Advanced cirrhosis from chronic hepatitis C infection is one of the leading indications for liver transplantation worldwide, accounting for around 40% of the transplants in the United States.[1] Recurrence of hepatitis C infection is universal in the absence of treatment but that does not preclude transplantation. Hepatitis C treatment can be pursued before or after liver transplantation, with timing to be determined based on clinical need. There is no age cutoff for liver transplantation, but older patients have poorer long-term survival due to an increased risk of death from malignancies.

- **Coronary Artery Disease**: Patients with risk factors for coronary artery disease or known history of coronary artery disease require more thorough investigation. Cardiac revascularization may be needed in candidates with significant coronary artery stenosis.
- **Cigarette Smokers**: Individuals who have a history of smoking and especially those who continue to smoke have decreased post-transplant survival due to increased risks of cardiac death and malignancies, including oropharyngeal cancers.
- **Chronic or Recurrent Infections**: Patients with chronic or recurrent infections should be evaluated by a transplant infectious diseases specialist. Patients with HIV should be referred to select transplant centers with expertise in managing the numerous drug interactions between antiretroviral drugs and the immunosuppression regimen. Typically, candidates with HIV will need to have CD4 counts consistently above 100 cells/mm³ and an HIV RNA level anticipated to be completely suppressed by the time of liver transplantation.
- **Extrahepatic Malignancies**: Patients with extrahepatic malignancies are at risk of recurrent disease due to the use of immunosuppression long-term after transplantation. Typically, transplant centers may request a reasonable waiting period after cure of a malignancy (with the exception of non-melanoma skin cancers) before considering
transplantation, although there is no consensus on the optimal window of time needed. Liver transplantation for early-stage perihilar cholangiocarcinoma is done at a few centers under investigational protocols with some success in a highly selected group.

- **Portal Vein Thrombosis**: Although portal venous thrombosis is not uncommon, transplantation may not be a viable option if there is absence of a viable splanchnic venous inflow system, such as a patent large mesenteric or collateral vessel to use.

- **Body Mass Index**: Short- and long-term survival is decreased in patients at extremes of body mass index (less than 18.5 kg/m$^2$ or greater than or equal to 40 kg/m$^2$).

- **Psychiatric Disorders**: Significant psychiatric disorders must be well controlled to optimize compliance after transplantation.

- **Alcohol or Substance Use Disorders**: Patients with a history of alcohol and/or substance use disorders are usually required to have a period of abstinence for consideration of candidacy, and some centers may require counseling and/or attendance in treatment programs for relapse prevention and assurance of compliance with the post-transplant regimen. Patients need to have adequate support from family and/or friends to assist through the evaluation and the perioperative period.
Finding Information About Liver Transplantation Centers

Scientific Registry of Transplant Recipients (SRTR)

The Scientific Registry of Transplant Recipients (SRTR) provides statistical and other analytic support to the Organ Procurement and Transplantation Network (OPTN) and it generates analytic data to support the United States Health and Human Services (HHS) in activities related to solid organ transplantation.[4] The SRTR site includes a function to find and compare transplant programs, as well as information about waiting list number and transplant activity, waiting list mortality rates, transplant number and rates, and survival statistics for all transplant centers. In addition, the site information includes a summary page listing one-year post-transplant survival rates, grading them as “higher than expected”, “as expected”, or “lower than expected” based on risk adjustment models.

Organ Procurement and Transplantation Network (OPTN)

In 1984, the United States Congress enacted the National Organ Transplant Act (NOTA) and established the Organ Procurement and Transplantation Network (OPTN); the purpose of the 1984 act was to create a unified transplant network to be operated by a private, non-profit organization under federal contract. The initial contract for the OPTN was awarded to United Network for Organ Sharing (UNOS) in 1986 and since that time UNOS has administered the OPTN. The OPTN maintains the national patient waiting list, manages transplant policies, and provides support and informational services for patients, all of which can be found on the OPTN website.

United Network for Organ Sharing (UNOS)

The UNOS is a private, non-profit organization located in Richmond, Virginia that works under contract with the federal government to manage the United States organ transplant system, including operation of the Organ Procurement and Transplantation Network (OPTN). Specific UNOS activities include managing the national transplant waiting list, matching donors to recipients, and maintaining a database that includes information for all transplant events that take place in the United States.
Pretransplantation Evaluation

The pretransplantation evaluation is focused on the assessment of operative risks, medical compliance, and comorbid conditions that could affect patient and graft survival, especially in the context of long-term immunosuppressive therapy.\textsuperscript{[1,\textendash}6\textsuperscript{]} The specific evaluation process varies across different transplant centers but typically will include assessments by a transplant hepatologist, a social worker, and a transplant surgeon, in addition to other staff. A multidisciplinary selection committee then reviews the evaluation to determine if the patient is in need of liver transplant listing and is a viable candidate. This committee may make requests for further evaluation or interventions needed before transplant candidacy is accepted. Once approved, patients are listed on the donor organ waiting list based on their ABO blood type, with priority established by the MELD score, either natural or assigned, with the exception of patients with acute liver failure who demand the highest priority as Status 1. Liver transplant candidates should be considered for simultaneous kidney transplantation if they have any of the following: (1) end-stage renal disease, (2) chronic kidney disease with GFR less than 30 mL/min, (3) acute kidney injury with serum creatinine greater than or equal to 2.0 mg/dL and dialysis for more than or equal to 8 weeks, or (4) chronic kidney disease with renal biopsy demonstrating greater than 30\% glomerulosclerosis or greater than 30\% stenosis. The information below summarizes the key elements typically assessed in the transplantation evaluation.

- **Financial Screening**: Obtain medical insurance approval first for transplant evaluation
- **Hepatology Evaluation**: Conduct a thorough history and physical examination, and optimize management of the underlying liver condition
- **Laboratory Testing**: Obtain the following baseline laboratory studies.
  - Hepatic synthetic function, electrolytes, renal function, complete blood counts
  - Viral hepatitis profiles (A,B,C,D)
  - Serologic studies for herpesviruses (cytomegalovirus, Epstein-Barr virus, and herpes simplex virus)
  - Diagnostic tests for HIV infection
  - Screening for nonviral infections (syphilis, toxoplasmosis)
  - Screening for latent tuberculosis (QuantiFERON-TB Gold assay or purified protein derivative skin test)
  - Markers for other causes of liver disease (e.g. ANA, ASMA, AMA, iron studies)
  - Tumor markers (e.g. alpha-fetoprotein)
  - Urinalysis and urine drug screen, 24h urine for creatinine clearance
  - ABO-Rh blood typing
- **Cardiopulmonary Evaluation**: Obtain electrocardiography and echocardiography; if indicated, perform pulmonary function testing, cardiac stress testing, and/or cardiac catheterization.
- **Abdominal Imaging**: Evaluate hepatic artery and portal vein anatomy and screening for hepatocellular carcinoma using dynamic contrast imaging (CT or MRI) or ultrasonography with Doppler. If hepatocellular carcinoma is present, then dynamic contrast imaging (CT or MRI) is needed to assess the size and number of lesions and evaluate for vascular invasion and extrahepatic spread.
- **General Health Assessment**: Obtain chest radiograph, bone density assessment, dental evaluation, vaccinations, esophagogastroduodenoscopy, and age or condition-appropriate cancer screening.
- **Dietician Evaluation**: Assess nutritional status and dietary recommendations.
- **Social Work Evaluation**: Assess psychosocial status and address care support needs.
- **Psychiatry or Psychology Evaluation**: Review history of psychiatric and/or substance use disorders, if present.
- **Anesthesia Evaluation**: Review cardiopulmonary and anesthesia risks and history of complications.
- **Transplant Surgery Evaluation**: Review technical aspects and risks of surgery, and discuss donor options.
- **Infectious Disease Evaluation**: Assess for infections that may require treatment prior to
transplant and guide post-transplant surveillance in the setting of immunosuppression.

- **Financial Counseling**: Develop financial management plans for the surgery and post-transplantation care.
Summary Points

- In the United States, in recent years, approximately 7,000 to 8,000 liver transplantations are performed annually and chronic hepatitis C infection is the second most common indication for transplantation.
- Patients with cirrhosis should be referred for a liver transplant evaluation if any of the following criteria are met: (1) MELD score is greater than or equal to 15, (2) complication due to cirrhosis (e.g. ascites, variceal hemorrhage, or hepatic encephalopathy), or (3) diagnosis of hepatocellular carcinoma within Milan criteria (solitary HCC lesion less than 5 cm or up to 3 nodules each smaller than 3 cm).
- Additional indications for liver transplantation include (1) patients with acute liver failure (INR greater than or equal to 1.5 and hepatic encephalopathy, presenting within 26 weeks from the onset of symptoms, without preexisting liver disease, (2) patients with liver-based metabolic defects with significant systemic manifestations, or (3) systemic complications of chronic liver failure.
- Transplant candidacy is dependent upon the patient’s ability to survive transplant surgery and the immediate post-operative period, the patient’s ability to comply with the post-transplant medical regimen, and the absence of comorbid conditions that could limit graft or patient survival, particularly those that could be worsened by the use of immunosuppression.
- There are multiple contraindications to liver transplantation, and these include absolute and relative contraindications. Certain criteria may vary amongst different transplant centers, but all transplant centers in the United States adhere to OPTN transplant policies.
- Given the time required to complete the transplant evaluation, patients should be referred earlier rather than later in the course of the disease.
Citations


References


Figures

Figure 1 Indications for Liver Transplantation Evaluation

This table shows the major indications for liver transplantation in adults. The most common reason for liver transplantation is cirrhosis from chronic liver disease.


<table>
<thead>
<tr>
<th>Indications for Liver Transplantation</th>
<th>Metabolic Disorders Originating from the Liver</th>
<th>Malignancies</th>
<th>Miscellaneous</th>
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<tbody>
<tr>
<td>Acute Liver Failure</td>
<td>Metabolic Disorders Originating from the Liver</td>
<td>Malignancies</td>
<td>Miscellaneous</td>
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<td>Acute viral hepatitis</td>
<td>Hyperoxaluria</td>
<td>Hepatocellular carcinoma</td>
<td>Polycystic liver disease</td>
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<td>Drug or toxin induced hepatotoxicity</td>
<td>Familial Amyloidosis</td>
<td>Cholangiocarcinoma (limited)</td>
<td>Hereditary hemorrhagic telangiectasia</td>
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<td>Acetaminophen overdose</td>
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<td>Autoimmune hepatitis</td>
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<td>Wilson’s disease</td>
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<td>Hemangioendothelioma</td>
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<td>Cirrhosis from Chronic Liver Disease</td>
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<td>Chronic viral hepatitis</td>
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<td>Wilson’s disease</td>
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<td>Hereditary and neonatal hemochromatosis</td>
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<td>Budd-Chiari syndrome</td>
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<td>Tyrosinemia</td>
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<td>Glycogen storage diseases</td>
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Figure 2 Liver Transplants in United States, 1988-2017

Figure 3 Clinical Characteristics of Adult Liver Transplant Recipients, 2016

Figure 4 Correlation of MELD Score and 3-Month Survival

The cohort of patients in this study included adults (at least 18 years of age) with chronic liver disease who were added to the Organ Procurement Transplantation Network (OPTN) waiting list at a 2A or 2B status. This graphic shows a clear association of MELD score and 3-month survival. Those with a MELD score of 40 or greater had a mortality rate of 71% at 3 months.

Figure 5 Child-Turcotte-Pugh Classification for Severity of Liver Disease

The Child-Turcotte-Pugh (CTP) classification system utilizes two clinical parameters (encephalopathy and ascites) and three laboratory values (bilirubin, albumin, and prothrombin time). Patients are classified as class A, B, or C based on their total points.


<table>
<thead>
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<td>Encephalopathy</td>
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<tr>
<td>Ascites</td>
<td>None</td>
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<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt; 2</td>
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<tr>
<td>Albumin (g/dL)</td>
<td>&gt; 3.5</td>
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<td>Prothrombin time</td>
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<td>Seconds prolonged</td>
<td>&lt;4</td>
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<td>or International normalized ratio</td>
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*Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)

**Class A** = 5 to 6 points

**Class B** = 7 to 9 points

**Class C** = 10 to 15 points
Figure 6 Child-Turcotte-Pugh Score and Mortality at 3 Months

The cohort of patients in this study included adults (at least 18 years of age) with chronic liver disease who were added to the Organ Procurement Transplantation Network (OPTN) waiting list at a 2A or 2B status. Those with higher baseline Child-Turcotte-Pugh scores have a marked increase in risk of death at 3 months than those with lower Child-Turcotte-Pugh scores.