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Various Medical Aspects of Liver Transplantation and its Survival Prediction using Machine Learning Techniques

C. G. Raji[1*] and S. S. Vinod Chandra[2]

[1]Manonmaniam Sundaranar University, Tirunelveli – 627012, Tamil Nadu, India; rajicg80@gmail.com
[2]Computer Center, University of Kerala, Thiruvananthapuram – 695034, Kerala, India; vinod@keralauniversity.ac.in

Abstract

Objective: Prognosis models play a significant role in forecasting the patient's survival in Organ transplantation. To review the impact of machine learning methods in predicting the of survival of patients who undergoes Liver Transplantation using a Multilayer Perceptron Artificial Neural Network model with an extensive discussion of all the medical aspects is the key objective of this paper. **Methods/Analysis:** Medical practitioners studied various parameters during pre-transplantation for predicting the survival of a patient. This study considered those parameters and reviewed whether these parameters have any vital part in the survival rate of a patient after Liver Transplantation (LT). This study also compared various scores including Model for End Stage Liver Disease (MELD) score, Emory score and Child score that are used in survival prediction. Currently the medicinal specialists estimate the outcome of LT with MELD score. We employed a detailed learning about the health aspects of LT and various machine learning techniques used in this area. In order to perform the experimentation, the dataset was congregated from the United Network for Organ Sharing transplant database (n = 65534). With the three layer architecture, the model trains the attributes of donors, recipient and transplantation using back propagation algorithm. 10-fold cross validation was applied in each training and test set before training. During the training process, the appropriate donor-recipient pairs were found out and obtained the best liver patient survival in transplantation. **Findings:** We conducted a comprehensive study about LT for the liver patient survival prediction. We proposed a Multilayer Perceptron Artificial Neural Network model to predict the survival rate after LT with 99.74% accuracy using United Network Organ Sharing registry. We also compared the performance of proposed model with existing models and proved that proposed model produced more accuracy than other models. **Novelty/Improvement:** The multilayer perceptron model succeeded clinical scores in terms of high accuracy, sensitivity and specificity. Machine learning techniques show better performance than conservative numerical methods in donor, recipient and transplantation attributes which are used to predict the survival. Due to less expensive and producing reliable solutions with rich datasets, machine learning techniques have been succeeded the conventional statistical methods and medical scoring systems. The proposed model predicts a promising accuracy for the prediction of best survival rates after.

Keywords: Artificial Neural Networks, Liver Transplantation, Machine Learning, Multilayer Perceptron, Post-Liver Transplantation Survival Prediction

1. Introduction

Over last two decades, the area of Liver Transplantation (LT) showed a progressive growth and lot of advances has been made in this field contributing to an improved survival rate for patients who undergo the treatment. A successful LT was accomplished in humans[1]. LT is the crucial restorative cure for patients with end stage liver disease[2]. The recipients are in the waiting lists and the donors in the donor bank. From the donor bank, the liver is allocated to the recipients. Based upon the survey performed, there are three criteria of organ allocation in

* *Author for correspondence*

terms of medical urgency, utility and transplant benefit[3]. Sometimes the patients who are low in the waiting list have been given more priority in the medical urgency-based allocation system[3]. But assessing the patients carefully in accordance with expected post-transplant survival is given priority in the utility based system[3]. Both the survival and waiting list are taken into consideration in transplant benefit allocation scheme[3]. The organs are allocated to the recipients depending upon the Model for End Stage Liver Disease (MELD) score. The medical experts get judgment for LT and forecast the output of transplantation according to the MELD score. MELD score comprises of attributes such as Bilirubin, Creatinine and International Normalized Ratio (INR), Creatinine may differ one to one with the body weight and gender of liver recipient[4]. MELD score follows sickest first principle[4]. According to the MELD score principle, the patients in top position in the waiting list may get highest preference in the allocation of organs in LT[4]. But the machine learning tools determine the allocation of liver organs according to the disease severity of the patient[5]. Also with the help of several machine learning techniques, the doctors can calculate the long term survival of the patients after LT.

1.1 Overview of Liver

Liver is the largest fleshy organ present on the right part of the abdomen[6]. It is separated with two lobes namely right lobe and the left lobe. The functions of liver comprise carbohydrate, lipid, and protein metabolism, the creation of bile acids, the detoxification and flow of lipid soluble compounds, and storage[6]. The liver transmits the waste materials and takes fats all over the body; it also generates cholesterol as well as certain proteins. Accumulation and release of glucose as well as storing of iron for producing hemoglobin are also its major functions. The liver helps in regulating the blood clotting.

2. Liver Transplantation

In the pre transplantation phase, the following factors are taken into account by a doctor.

2.1 Causes of Liver Disease

Liver diseases result in liver failure. Liver failure includes chronic liver failures (liver fails gradually) and acute liver failures (liver fails rapidly). The liver can be damaged because of the overdose of drugs, fat accumulation in liver, hepatitis B and C, alcohol usage and genetic diseases.

2.2 Individual Symptoms

A wide variety of reasons are for the liver failure or damage. It is necessary to discover the issues causing liver failure. The indication of the liver disease includes as cities, bleeding, mental imbalances, jaundice and skin pigmentation.

2.3 Graft Weight

Generally the size of liver is larger in males than females[7]. The weight of the liver is increased in males of age between 41 to 50 years. In the case of females, it is increased in 51 to 60 years. So the liver weight of patients of age more than 50 can be estimated with three parameters such as body weight, age and gender. After that the liver weight starts falling. So in such patients, the liver weight can be estimated using two parameters such as weight and age[7]. The Graft Weight Ratio (GRWR) is defined as the ratio of graft weight of donor to the graft weight of recipient[7].

2.4 Associated Co-morbid Condition

It should be notified whether any additional medical conditions are there along with liver disease. The conditions include hypertension, tuberculosis, asthma, heart disease, stroke, jaundice and kidney diseases. All these disorders need to be identified by the doctor before starting the treatment of liver.

2.5 Previous Abdominal Surgeries and Non-Abdominal Surgeries

Studies have proved that the occurrence of previous abdominal and non-abdominal surgeries affect the danger of mortality in patients who undergone LTs[8,9]. Special consideration need to be taken to those patients prior to the transplantation.

2.6 Drugs Allergy and Associated Liver Tumors

The doctors have to take necessary steps to identify any of the drugs make allergy to the patient. Also it has to find out the associated liver tumors such as HepatoCellular Carcinoma (HCC) is there in the patient.

Table 1. Enzymes and parameters of liver with its functions and normal values

Enzymes and Parameters	Functions	Normal Range of values
Bilirubin	It is a yellowish product seen in blood. When the amount of bilirubin in blood is high, it will result in jaundice. The symptoms of high bilirubin include yellowish eyes, skin and urine.	0.3-1.9 mg/dL
Creatinine	It is formed in kidneys, liver and pancreas. We get it from animal products as well as fish products. After the production of creatinine in the liver, it is passed to the muscles for the storing purpose. The waste products are emitted by the kidneys. The kidneys pass the creatinine through urine.	0.7-1.3 mg/dL
Albumin	It is a type of protein seen in blood. Liver disease results in low level of Albumin. It guards our tissues and acts as defence that combines with the toxic drugs and waste materials that is dangerous to the body.	3.4-5.4 g/dL
HB	HB is hgb which is the major carrier of oxygen in the blood. It is composed of two parts. Heme means iron and globin means protein made up of amino acids. Low level of hgb results in anaemia.	Male ->14-18 g/dL Female ->12-16 g/dL
Platelet Count	Advanced liver diseases can cause decreased platelet count.	Normal range is 150,000 to 400,000 per micro litre
SGPT	SGPT called Alanine transaminase (ALT) is an enzyme supports the development of proteins. It is increased in liver diseases.	0-45 IU/I[33]
SGOT	SGOT called Aspartate aminotransferase (AST) is anenzyme usually found inside liver cells. When a blood test detects high levels of this enzyme in the blood it usually means the liver is injured in some way. However AST can also be released if heart is damaged. In liver disease patients, the level of SGOT in blood will be high.	0-35 IU/I[33]
ALP	ALP, also called Alkaline Phosphatase, is an enzyme produced in liver cells. High level of ALP in blood may be seen in liver or bone diseases.	30-120 IU/I[33]
GGT	GGT, gamma-glutamyltransferase, is formed in most of the body tissues particularly in gallbladder and liver. Bile duct block and liver problems are detected using this test. High levels of GGT may be related to heart problems and hypertension.	0-30 IU/I
Total Protein level	It refers to the presence of albumin and all the other proteins in the blood.	6.3 to 8.4 g/dL
A/G Ratio	A/G ratio test gives knowledge about the amount of albumin with globulin in the body. A/G ratio is found to be altered in liver diseases.	0.8 – 2.0
Globulin	Globulin is a protein which is the transporter of several hormones, antibodies, metals and minerals. The high level of globulin is seen in chronic inflammations, liver problems, rheumatic arthritis, leukaemia etc. The low level is seen in liver problems, malabsorption and kidney diseases. The difference between total protein value and total albumin value is globulin.	2.3-3.5 g/dL
BUN	BUN is Blood Urea Nitrogen. BUN is a waste product generated from the protein metabolism in the liver. The high level of BUN can be caused by problems with kidney, less intake of fluid, bleeding in intestine, high level intake of protein, lack of exercise, heart problems, less production of digestive enzyme produced by pancreas etc.	7-18 mg/dL
Sodium	Sodium is a very important element of the body. Low level of sodium may be due to vomiting and diarrhoea. Insufficient drinking of water or taking more salt, results in high level of sodium.	136-145 mEq/L
Potassium:	Potassium is seen inside the cells of the human body. Low level of potassium affects both the heart and muscles which will result in heart problems and muscle weakness. Potassium levels may be decreased in excessive diarrhoea or vomiting.	3.8-5.2 mEq/L
Calcium	Calcium is the plentiful mineral in the body. It is highly essential for hormonal actions. The vitamin D levels and CO_2 levels are associated with calcium. It is concerned in the contraction of muscles, absorption of proteins, bone metabolism, nerve impulse transmission and clotting of blood.	8.6-10.2 mg/dL

Magnesium	Magnesium is seen in bones, teeth, heart, nerves etc. The patients with low level of magnesium are short tempered, have more anxiety, tenseness, nerviness, sleeplessness, embarrassment etc.	1.9-2.7 mEq/l
HBsAg	HBsAg is Hepatitis B surface antigen. It helps to find out if there is hepatitis B infection in the body.	negative
HBeAg:	HBeAg is Hepatitis B e-Antigen. The Hepatitis B cells produced a viral protein called HBeAg. If it is positive, shows that the person has highly infectivity and contains lot of virus. But if it is negative, shows that the person has low infectivity and contains less level of virus.	negative
Anti-HCV	Anti-HCV is used to find out the presence of HCV in the body. HCV leads to chronic liver diseases & HCC.	10.9
HIV	Organ failure is a significant problem for patients with human immunodeficiency virus (HIV) infection. Organ donors and recipients should be screened for HIV.	negative
AFP	Alpha-fetoprotein is a protein generated in the forming fetus. AFP test is used to find out the presence of cancer cells in liver as well as in other parts of the body, as AFP levels may be increased in liver cancer and some other form of cancer like yolk sac tumour.	<10 ng/ml

2.7 Blood Investigations through Liver Function Tests

Since the liver executes multiple tasks, no particular clinical assessment is appropriate to supply an entire assessment of the liver tasks in every clinical situation[10]. A wide variety of biochemical and laboratory assessments are used to estimate several tasks of the liver and to assess the patients with malicious liver disease[10]. Such assessments are called Liver Function Tests (LFTs). These are used to assess a variety of elements in the blood, set by the liver. There are a lot of LFTs available presently[11].

Mainly there are three reasons to go for a clinical study[11].

- Diagnose the severity of disease.
- Describe prediction and determine disease progression.
- Guide and assess response to treatment.

Through LFTs, all the functions of liver are tested. Presently many of the clinical biochemistry laboratories supply packages of LFTs which includes calculation of serum bilirubin concentrations, alkaline phosphatase and aminotransferase levels and urine analysis[6]. Researchers propose that the measurement of the serum bile acid concentration is also a sensitive indicator of liver disease[10]. The enzymes and parameters along with their reference values used for diagnosis purposes are précised in Table 1.

2.8 Types of LT

The time of liver transplant arrives when the liver becomes diseased or injured so that it cannot function properly. The factors such as hepatitis, cirrhosis, alcoholism and liver cancer injure the liver. For LT, we can transplant liver either from a living donor or a deceased donor. Mainly there are three phases for LT such as hepatectomy, a hepatic phase, and post implantation phase. Hepatectomy phase is the liver removal phase includes division of all the ligaments attached to the liver including common bile duct, hepatic artery, portal vein and hepatic vein. A hepatic phase is the no liver phase. The post transplantation phase is the period after surgery which includes the continuous follow-up by a physician. Generally LT is categorized as[12],

- Reduced size LT
- Split-LT
- Living related LT

2.8.1 Reduced Size LT (RSLT)

Shortage of donor organs leads to one of the major problem in children who are awaiting LT[13]. In RSLT, a small part of the liver from an adult is transferred into a child that has been recognized in many centres[14]. An orthotropic RSLT was performed which gives a fraction of donor weight to that of recipient was 12:1 without any similarity in their age[15]. The transplantation was successful shows a high survival rate. The reduced-size grafts are taken when there are no adult recipients to accept the entire graft[15]. In order to increase the use of entire graft, a different method was used to split up the adult liver into two grafts, the right one to the adult recipient and left one for the child[15]. The use of reduced-size grafts from adults in children was recognized in a number of countries to resolve the scarcity of suitable pediatric donors and a decrease in the mortality rate of children waiting for transplants[15]. RSLT

improves the current donor pool available to the pediatric recipient[15].

2.8.2 Split-LT (SLT)

The scarcity of donor livers in the donor pool is a major issue. A procedure used to split a cadaver liver into two recipients results in split-LT. The recipients may be two adults or one adult and a child. SLT provides an ultimate solution to develop the donor pool for both children and adults[16]. In SLT, graft size is an important factor in both donor as well as recipient[16]. It has been learned from the surgical experience that the donor to recipient weight ratio plays a key role to determine which portion of the graft is suitable for a child[16]. Generally the liver segment 2 and 3 is accommodated to a child when the donor to recipient weight ratio exceeds 5 to 10:1[16]. If the ratio is less, then it is permitted to use left or right lobe of graft. From the clinical study, the left lateral segment is a best fit for most of the children[17]. SLT have been outstanding with major reduce in paediatric wait-list times and wait-list morbidity[18].

2.8.3 Living Related LT (LRLT)

LRLT is performed with living donors. LRLT is also called Living Donor Living Transplantation (LDLT). In this technique, a small part of the liver is replaced from a living person and attached to the recipient body by a liver surgeon[19]. The first successful LDLT have segments 2 and 3 were transferred from a mother to her son was accomplished in 1989[15]. In the Asian regions, there was the availability of liver graft from deceased donors[14]. LD grafts are not subjected to major cold ischemia, and the role of steatosis to the poor performance of the graft should therefore be minimum[20]. Short waiting time, the capacity to adjust the cold ischemic time and an increase in the organ storage are the major merits of LDLT[21]. Morbidity and mortality of the donor are the demerits of LDLT[21]. The most important difficulty in post-transplant morbidity in the recipients of LDLT is seen in surgical complications[22]. Biliary problems (especially biliary leak), vascular problems and accidental re explorations were perceived at advanced frequencies in LDLT recipients[23]. Researchers found that LDLT proposes a suitable chance and long survival to the patients who are in the waiting list with liver disease or HCC that cannot be treated by other procedures[24].

When the liver disease patient approaches a doctor, the following parameters are the preliminary measures the doctors take care of.

2.8.3.1 Age of Donor and Recipient

The age of a donor has been progressively rising above the earlier period. In 1991, 13% of cadaveric donors of liver were over the age of 50[25]; but after 10 years it was raised to 30%[25]. The age of the patient is more important when they go for LT[25,26]. In the early days, if the donor age is greater than 50 years was thought to have poor survival. Later, studies have proved that the donor age is greater than 50 with no additional risk factors will survive more[25,26]. Older donor livers be probable to be smaller and darker-coloured, and may have advanced fibrous thickening of the capsule[25]. Old age donors also have an enhanced rate of steatosis, which may potentiate cold preservation injury[25]. When an older donor is selected, care should be taken because each organ of the old donor should be assessed systematically based on other risk factors particularly steatosis and cold ischemic time[25].

2.8.3.2 Gender

LT with unmatched gender leads to a poor graft survival[27,28]. There is no such difference in the survival rate for a female recipient with a male donor. High survival output results with matched gender LT[28,30]. Generally Creatinine in MELD score is lower in females than the males[28,30]. It results in the poor survival rate with female to male LT. There is no risk of poor survival in male recipient to female donor LT[28,29,32]. These facts are true with adults only and exception cases for children[28,30].

2.8.3.3 Blood Group

For the best results of LT, the blood group of donors and recipient should be compatible[33]. Studies showed that the donors with blood group A can donate to recipients with blood group A and AB[33]. Also it is found that the donors with blood type B can donate to recipients with blood types B and AB. The donors with blood type AB can donate to recipients with blood type AB only[33]. There was a question arise that the donors with blood type O can donate to recipients with blood types A, B, AB and O[33]. It is proved from the studies that it is possible because O is the universal donor[33]. The recipients with blood type O

can receive a liver from blood type O only. But AB group is the universal recipient. The recipients with blood type AB can receive a liver from blood types A, B, AB and O[33]. The recipients with blood type A can receive a liver from blood types A and O[33]. The recipients with blood type B can receive a liver from blood types B and O. So from all these studies it is confirmed that the recipients with AB blood group and donors with O blood groups are well-matched with any other blood type[33].

2.8.3.4 Body Mass Index (BMI)

In order to estimate the survival output of LT, assessment of BMI of both recipient and donor plays a vital role in pre-transplantation[28]. BMI is defined as the fraction of weight of liver patient to the square of the height of liver patient[28,34]. The weight in BMI is stated in kilograms and height in meters[28]. Overweight patients are at a complication in good success rate in LT than non-obese recipients[28,35]. Studies demonstrated the idea of BMI with the classification of patients into 6 groups[28,35–37] as shown in Table 2 .

Table 2. Classification of the liver patients for the illustration of BMI

PATIENT GROUP	STATUS	BMI
Group 1	Underweight	< 20 kg/m^2
Group 2	Non obese	20 – 25 kg/m^2
Group 3	Overweight	25 – 30 kg/m^2
Group 4	Obese	30 – 35 kg/m^2
Group 5	Severely Obese	35 – 40 kg/m^2
Group 6	Morbidly Obese	40 kg/m^2
Compared with normal BMI[29,37,38]		20 - 25 kg/m^2

Throughout the examination with covariate adjusted mortality hazard regression it was found that the patients who were in Group 1 had a 61% better risk of death[28,35]. But there was no variance in mortality for Group3, Group 4, Group 5 and Group 6 when related to the patients in Group 2 considered as normal[28,35]. Recently, researchers described that the morbidities in post transplantation are higher among diabetic obese patients, but these are not the risk factors affecting post-transplant survival[28,38,39]. Clinicians confirmed that BMI is the suitable measure of body fat and obesity alone; hence we should not let this avoid patients from getting liver transplants[40,41].

2.8.3.5 Duration of Liver Disease till Diagnosis

It is necessary to diagnose the liver disease properly before treatment. The doctors need to take the decision for LT may sometimes depend upon the duration of the liver disease. Liver disease can be caused by diseases such as gallstones, high cholesterol or triglycerides, infection (hepatitis), alcohol, blood flow blockage to the liver, and toxins (medications and chemicals). Symptoms of liver disease depend upon the cause may include nausea, vomiting, upper right abdominal pain, and jaundice. Treatment depends upon the cause of the liver disease.

2.8.3.6 Stage and Grade of Liver Tumor

The United Network of Organ Sharing has approved the criteria proposed of single tumor size is less than or equal to 5 cm or up to 3 tumors each are less than or equal to 3 cm in size, and no macro vascular invasion have an excellent outcome for the prediction of HCC [42–44]. Other than Milan, earlier studies proposed three more criteria to find out HCC including the University of California, San Francisco (UCSF) criteria, the Tumour-Node-Metastasis (TNM) criteria and the Pittsburgh modified TNM criteria[43]. The various criteria are listed in Table 3. The size of the tumor can be considered as an autonomous prognosticator of survival in patients suffering resection[43]. Recent study proposed that patients undergoing LT with HCC under the Milan criteria have an excellent outcome[44]. Radiologists introduced various crucial techniques to form the stage of HCC before liver surgery and to sense minute intra-hepatic metastases[43]. Helical Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are the best available technologies, with accuracies estimated around 80%[42,43]. MRI-angiography has better performance than helical CT in detection of HCC nodules between 10 and 20 mm in diameter but both techniques failed to detect nodules smaller than 1 cm[43]. Intra-operative ultrasonography (IOUS) enables the detection of nodules between 0.5 and 1 cm[43]. The criteria endorsed by the European Association for the Study of the Liver define HCC in cirrhotic patients of a nodule at least 2 cm in diameter or a hepatic mass with Alpha-FetoProtein (AFP) levels greater than 400 ng/mL[44].

2.9 Various Scores in LT

For the prediction of LT, various scoring systems are used

by the physicians. The established scoring is based on the resulting sum of a subset of individual variables. Initially the EMORY score was used in the patients who were to undergo Transjugular Intra-hepatic Porto-systemic Shunting[45]. The Child-Turcotte score is the initial version of the Child Score which replaces the Emory score[45]. Later Child proposed Child-Pugh score which is superior to the Child-Turcotte score[45,46]. The Mayo clinic introduced MELD score which replaced Child-Pugh score to estimate the survival of patients who undergo LT[4]. Studies proved that in order to determine the death rate in patients and to evaluate the priority of donors in the waiting list, MELD scale is a valuable score[4].

2.9.1 EMORY Score

The Emory score includes four parameters such as ALT, bilirubin, pre TIPS (Transjugular Intra-hepatic Porto-systemic Shunt) encephalopathy unrelated to bleeding and variceal haemorrhage[9]. The individual risk score of each patient is obtained from the resulting sum of these four parameters. The patients are categorized into three. The resulting sum with 0 point fall under group A, 1 to 3 points fall under Group B and 4 to 5 points fall under category 3. The risk of death is very less for the patients who are in the Group A. Group B patients will survive in moderate level. The risk of death is more for Group C patients.

2.9.2 CHILD Score

2.9.2.1 Child-Turcotte Score

The Emory Score was later replaced by Child-Turcotte score[45]. Child score included two continuous variables and three quantitative variables for the forecasting of survival after LT[45]. Instead of using four parameters in Emory score, Child proposed five parameters including bilirubin, albumin (continuous variables), ascites, Encephalopathy and nutritional status (quantitative variables)[45]. The patients undergoing transplantation is categorized into three namely Group A, Group B and Group C with respect to the resulting sum of these five variables. Group A patients had Biliruibin<34 mol/l, Albumin>35g/l, no Ascites and Encephalopathy and the nutritional status was good. Group B patients had the range of Bilirubin=34 to 51 mol/l, Albumin=30 to 35 g/l, controlled Ascites, minimal Encephalopathy and fair nutritional status. Group C patients had the range of bilirubin>51mol/l, Albumin<30 g/l, Refractory Ascities, Advanced Encephalopathy and poor nutritional status. The score which is the variables sum 5 to 8 fell under Group A, 9 to 11 fell under Group B and 12 to 15 fell under Group C.

2.9.2.2 Child-Pugh Score

Child proposed Child-Pugh score replaced the Child-Turcotte score[45,46]. Child-Pugh score also consists of five parameters including Bilirubin, Albumin, Ascites, Encephalopathy and Prothrombin time (PT). The nutrition status in Turcotte score is replaced by PT in Pugh score. How long the blood to clot is the PT. A PT test can be used to check for bleeding problems. The PT can be expressed as percentage or as time value. Studies have proved that grouping was done with the patients who undergone transplantation. The resulting sum of these five variables shows the outcome of LT. The patients with Bilirubin less than 34 mol/l, Albumin greater than 35 g/l, PT less than 4 and no ascites and encephalopathy came under group A. The patients with Bilirubin 34 to 51 mol/l, Albumin 28 to 35 g/l, PT4 to 6, minimal encephalopathy and controlled Ascites came under Group B. The patients with Bilirubin>51, Albumin<28, Prothrombin time>6, Advanced Encephalopathy, and refractory Ascites came under Group C.

2.9.2.3 MELD Score

The Model for End Stage disease (MELD) score was put forward by Mayo clinic on February 27, 2002 which replaced the Child-Pugh score[4,28]. The MELD score comprises Bilirubin, Creatinine and INR [4,28]. The INR can be stated with the formula[4,28],

$$\text{INR} = \frac{Patient's\ PT}{MNPT} \quad (1)$$

The MNPT is defined as the geometric mean of PT of at least 20 grown up regular subjects of both genders. The MELD score is considered by the formula[4,28],

$$MELD = 9.6 \times log_e(X) + 3.8 \times log_e(Y) + 11.2 \times log_e(INR) + 6.4 \times C \quad (2)$$

Table 3. Listing the criteria of TNM, modified TNM, UCSF and Milan

TNM Criteria	TX Primary tumour cannot be assessed T0 No evidence of primary tumour T1 Solitary, #2 cm, without vascular invasion T2 Solitary, #2 cm, with vascular invasion; multiple, one lobe, #2 cm, without vascular invasion; or solitary, .2 cm, Without vascular invasion. T3 Solitary, .2 cm, with vascular invasion; multiple, one lobe, #2 cm, with vascular invasion; or multiple, one lobe,.2 cm, with/without vascular invasion T4 Multiple, more than one lobe; invasion of major branch of portal or hepatic vein; invasion of adjacent organs other than Gallbladder; or perforation of visceral peritoneum. Stage grouping Stage I T1N0M0 Stage II T2N0M0 Stage IIIA T3N0M0 Stage IIIB T1N1M0; T2N1M0; or T3N1M0 Stage IVA T4, any N, M0 Stage IVB Any T, any N, M1 N: Regional lymph nodes NX Regional lymph nodes cannot be assessed N0 No regional lymph node metastasis N1 Regional lymph node metastasis M: Distant metastasis MX Distant metastasis cannot be assessed M0 No distant metastasis M1 Distant metastasis
Modified TNM Criteria	T0: Tumour not found T1: 1 nodule 1.9 cm T2: 1 nodule 2.0-5.0 cm; 2 or 3 nodules, all 3.0 cm T3: 1 nodule 5.0 cm; 2 or 3 nodules, at least one 3.0 cm T4a: 4 or more nodules, any size T4b: T2, T3, or T4a plus gross intrahepatic portal or hepatic vein involvement as indicated by CT, MRI, or US N1: Regional (portal hepatis) nodes, involved M1: Metastatic disease, including extra hepatic portal or hepatic vein involvement Stage I: T1 Stage II: T2 Stage III: T3 Stage IVA1: T4a Stage IVA2: T4b Stage IVB: Any N1, any M1
UCSF Criteria	1 tumour ≤6.5 cm or ≤3 tumours with the largest tumour diameter ≤4.5 cm and total tumour diameter ≤8 cm.
Milan Criteria	Single tumour ≤5 cm in size or ≤3 tumours each ≤3 cm in size, and no macro vascular invasion.

Where X and Y are the amounts (mg/dl) of Creatinine and Bilirubin respectively and C is given as

$$C = \begin{cases} 0 & \text{if alcoholic or cholestatic liver disease} \\ 1 & \text{otherwise} \end{cases} \quad (3)$$

Arrangement of MELD scores based on the performance is as shown in Table 4.

Table 4. Classification of MELD scores according to the performance

MELD VALUE	RESULTS
MELD <15	Best
MELD 15-25	Good
MELD>25	More complicated
MELD>40	Bad

Doctors prefer more with patients are having MELD<15 to get best survival rate[4,28]. At the same time the doctors are not preferring the patients with MELD>40 because of poor survival rate. The 3-month mortality based on MELD score is shown in Table 5.

Table 5. 3-month mortality based on MELD score

MELD Score	Mortality
40 or more	71.3%
30-39	52.6%
20-29	19.6 %
10-19	6.0 %
<9	1.9 %

3. Surgical Findings

When the medical experts decide for transplantation, the factors such as donor type, graft weight of the donor and GRWR need to consider seriously. There is an urgent requirement to raise the organ donor pool. Hence there are different criteria for donor selection[27].

3.1 Type of Donors

Transplant physicians and candidates have become progressively more aware that donor characteristics significantly affect LT outcomes[32]. In today's desperate environment, the chance for transplantation introduced by each organ of the donor is thoroughly judged by organ procurement organizations and transplant physicians[32]. Feng et al. established a composite score consisting of seven donor characteristics (age, African American race, height, split liver, donation after cardiac death and death from cerebrovascular accident or other causes)[29] known as Donor Risk Index (DRI), to support transplant clinicians with forecasting the risk of graft loss related with a specific liver donor[29].

3.1.1 Deceased Donor (DD)

The deceased persons are the people who have died unexpectedly in case by an accident or brain death. The liver of such people are contributed to others those who are in high need. Such persons are called deceased donors. Currently, the deceased donors in the waiting list for LT are prioritized by medical urgency[12]. After demise, the liver is separated completely from a person and is placed in the recipient. This type of transplantation is deceased donor LT. DDs include both Donors after Brain Death (DBD) and Donors after Cardiac Death (DCD).

3.1.2 Living Donor (LD)

Due to the insufficiency of deceased donors, a portion of the liver has been taken from a person and placed in the recipient. Such donors are called living donors. The liver surgeons take out a portion of the liver from a living donor. The recipient's complete diseased liver is separated and the strong portion of the liver from a LD is placed in the separated section. Both of the livers in donor as well as recipient will develop into complete size within few weeks. This type of LT is also performed from adult donors to the paediatric recipients. The LDLT take care of the number of hepatic veins, number of portal veins, number of bile ducts, number of blood transfusions, Cold Ischemic Time (CIT) and Warm Ischemic Time (WIT) of both donor as well as recipient[47]. If the number of blood transfusions is more, surgery will be complicated. Usually the liver surgeons prefer right lobe for transplantation[48]. It is better to have LT with living donors. Patients undergoing LDLT have to know the possibility and difficulty of complications compared to deceased donor LT[23].

3.1.3 Extended Criteria Donor (ECD)

The scarcity of organs has led centers to elaborate

their measures for the approval of ECDs or marginal donors[25]. The use of Extended Criteria Donors (ECDs) minimizes the scarcity of appropriate donor livers for transplantation[49]. The use of grafts with ECD provides an immediate expansion of the donor pool. But the use of ECD in liver donors increases the risk of primary non-function[49]. The characteristics of ECD are the donor age more than 65 years, Intensive Care Unit (ICU) stay and ventilation support more than 7 days, body mass index (BMI) greater than 30, biopsy proven steatosis greater than 40%, peak serum Natrium greater than 165 mmol/l, Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST) greater than 3 normal, serum total bilirubin greater than 3 mg/dl, positive serology for viral hepatitis (Hepatitis B Virus (HBV) surface antigen HbsAg[49], HBV core antibody antiHB, or Hepatitis C Virus (HCV) antibody-anti HCV positivity), sepsis with positive blood culture, meningitis, history of extra hepatic malignancy, and previous drug abuse[49]. These features have been supposed to increase the risk of initial graft dysfunction, and their combination is thought to be additive on graft injury[49].

3.1.4 Steotatic Liver Donor

The accumulation of fat in the liver results in steotatic (fatty) liver. LT with more than 60% severe steatosis is related with a high risk of primary nonfunction[25,50]. These livers should not be used for organ donation. The results of LT with liver containing less than 30% mild steatosis is similar to those of transplantation performed with non-fatty livers[25,50]. The result of livers with 30 to 60% moderate steatosis is varying, and the use of these livers depends on the existence of additional risk factors[25,50].

3.1.5 Donor with Malignancies

It can be reasonably assumed that the risk of malignancy increases with donor age, and it means that transplanting livers from elderly donors may boost the risk of transmitting defined and undefined malignancies[51]. Independent of the organ transplanted the most frequently transmitted malignancies are usually central nervous system tumours, melanoma, renal cell carcinoma, and lung carcinoma[51]. Liver donors with less severe malignancies such as skin cancer other than melanoma which had been treated years ago and the liver donors with less severe central nervous system tumours may be considered[51]. The donors with metastatic malignancy should be excluded from liver donation[51]. The rules and regulations vary according to different countries[51]. The candidates who received the graft from donors with malignancies should have their immunosuppression adjusted because over immunosuppression reduces immune surveillance that can increase the tumour growth[51].

3.2 Graft Weight of DD

The liver of the deceased donors should match with the recipient. The requirements from the deceased donors will be Donor name, Donor ID, Ethnicity, Height, and Weight, important signs including blood pressure, heart rate and temperature, social history including drug use. History of treatment in hospital including current drug usage, present history of hypotensive episodes, urine output, indications of sepsis, AST, Bilirubin (direct), other laboratory tests within the past 12 hours including ALT, Alkaline Phosphatise, Total Bilirubin, Creatinine, Haemoglobin (hgb), INR or PT if INR is not available and White Blood Cell Count (WBC). The left liver graft and the right liver graft can be use from a donor to a recipient. But the left liver graft from a small donor will not meet the metabolic demands of an adult recipient[52]. The use of a right liver graft without a middle hepatic vein is one of the solutions to this problem[52]. One of the major components of survival after LT is the graft weight matching[53]. The graft weight of deceased donor should match with the graft weight of the recipient. If the graft weight is not matching, it will result in poor survival of LT.

3.3 Graft Recipient Weight Ratio (GRWR)

The LDLT performed to the adult recipients is limited by the sufficiency of graft size[54]. The minimum graft size based on the survival of the recipient should be evaluated by clinical study[54]. Preoperative computed measurement of graft size of a LD is essential[54]. The GRWR (Graft weight of donor/Graft weight of recipient) is considered as a threshold value 0.8.

4. Current Issues

4.1 Organ Availability

The organs are allocated to the recipients from either living donors or deceased donors. The availability of organ is less compared to the patients in the waiting list.

All the organs available cannot be used for transplantation in some times[55]. The allocation of donor organs depends upon the age, organ size or graft weight, disease in donor etc. More number of donors needs to come forward in order to save the life of people in the waiting lists.

4.2 Rules and Regulations

Several procedures have to be done for the allocation of organ in the LT. These procedures take a lot of time to complete. This will result in the morbidity and mortality of patients in the waiting list. The procedures comprise the submission of several original as well as copy of documents essential for transplantation. Steps have to be taken to make these procedures smoother. Thus we can save the life of many people in the waiting list.

4.3 Cost of Treatment

LT course of action is very expensive. The costs include hospitalization charges, laboratory tests, radiological imaging tests, cardiac tests to determine the health of heart, routine cancer screening tests, medicines, psychological evaluation costs, cost of meeting with social workers, counselling charges, surgery room, recovery room, ward and intensive care unit costs, and other fees.

4.4 Multidisciplinary Unit of Treatment

LT is carried out by multidisciplinary team of transplant surgeons, nephrologists, hepatologists, endocrinologists, anaesthetists, a transplant coordinator, an organ donor coordinator, dieticians, intensive care physicians, specialist transplant nurses, transplant coordinators and social workers. All the team members work hard to achieve the best possible survival of the patient. Availability of such highly trained personnel may pose problems.

4.5 Complications Involved in LT

The complications in LT can be classified into short term complications and long run complications. The short term complications include post transplantation technical and medical complications, primary dysfunction, graft rejection and infections[56]. One of the technical complications is arterial complication mainly the hepatic artery thrombosis. The blood containing oxygen enters into the liver from the heart through the hepatic artery. This thrombosis develops mostly in the paediatric population. Ischemia or necrosis results when the thrombosis found at an early stage[56]. But biliary complications occur when it found at the later stage. As per the clinicians report, the timing of occurrence and clinical consequences depends on the treatment of thrombosis. The doctors advise re-transplantation for the patients those who are diagnosed with arterial thrombosis. Another infrequent complication of only 2 to 3% is the portal vein thrombosis. The blood containing nutrients and digestive food particles enter into the liver from the small intestine trough portal vein thrombosis. The problems of LT includes the high risk of infection, rejection, graft failure, biliary tract problems and a higher risk of developing certain conditions, such as diabetes[56]. Leaks and strictures which occur early in the post transplantation have technical causes[56]. Late strictures and obstruction are more likely to be complex and have multiple causes. Doctors found that the occurrence of 20% complication may come with haemorrhage[56]. The factors associated with this complication include pre-existing coagulopathy, significant haemorrhage during surgery and instant poor synthetic function. Haemorrhage is identified within 48 hours after transplantation[17,57].

Another frequent medical complications found in the early post transplantation phase are hemodynamic alterations, and respiratory, renal and neurological complications[56]. The hemodynamic complications include both arterial hypertension mainly due to the effect of immunosuppressive drugs, electrolyte alterations and the presence of intense pain[56]. Electrolytic alterations of sodium, potassium, calcium and magnesium results in cardiac arrhythmia and should be treated quickly[56]. Respiratory complications results in reduced ventilation capacity, the reduction in diaphragm motility and the presence of ascites[56]. The existence of renal dysfunction, peri-operative haemorrhage, vascular clamping with hypotension, the use of nephrotoxic drugs, sepsis, a state of shock, and possibly dysfunction of the graft, results in poor renal action[56]. The patient's neurological state depends upon the surgery and the drugs used[56]. The clinicians divided the rejection into three as hyper acute, acute and chronic. The hyper acute rejection occurs within minute to hours, the acute rejection occurs within days to months and the chronic rejection occurs within days to months[58–60]. The rejection can be treated with the introduction of various high dosages of

immunosuppressive drugs[56]. A serious problem occurs in the poor liver patient survival is the infection[28]. The infection occurs after LT is due the action by bacteria, virus and fungi[56].

The long run complications include chronic renal failure, systemic arterial hypertension, diabetes mellitus, dyslipidemia, obesity, bone or neurological complications and the development of de novo tumours[38]. The chronic rejection can be diagnosed by liver biopsy test. In test, whether any small bile ducts were lost can be detected. Clinical and biochemical cholestasis are the symptoms of chronic rejection[56]. As per the clinical study, the rate of bilirubin greater than 10 mg/dl, re-transplantation is advised[56]. Another frequent complication occur in the liver recipients is the arterial hypertension. It occurs mostly based on tacrolimus (immunosuppressive drug) other than cyclosporine. The overdose of Calcineurin Inhibitors (CNI) and steroid doses results in another complication called Diabetes Mellitus (DM). The CNI usage causes change in insulin synthesis and secretion. The patients with alcoholic cirrhosis or hepatitis C are affected more with Diabetes Mellitus and have to be treated urgently[56,59,61]. Because of the uncontrolled diet, genetic predisposition, de novo diabetic mellitus, post transplantation renal dysfunction, usage of immunosuppressive drugs will result in another complication, dyslipidemia[56]. Controlled diet, reduction in weight, control of DM and the use of pravastatin (HMG-CoA reductase inhibitor drug) includes the treatment of dyslipidemia[56]. Clinicians proved that obesity is a frequent complication found in patients those who undergone transplantation after one year. Uncontrolled intakes of food, usage of various drugs, lack of exercise, pre-transplantation obesity are the reasons for obesity[56,60,61]. The lack of calcium results in another major bone complication called osteopenia[56]. As per the researchers study, 5 to 15% of patients will be affected with de novo tumour after transplantation[56]. The complications can be precisely identified, and remedial methods introduced before they become life threatening[28,62].

5. Survival

The survival depends upon the quality of graft, the availability of donor and disease affecting to the patient. There are two main goals of LT. One is the prolonged survival and the other is the quality of life[63]. With the clinical introduction of cyclosporine and by refining cyclosporine use with the addition of corticosteroids, survival rates after LT have more than doubled[64]. Cyclosporine is effective on its own and is a very powerful immunosuppressive drug[65]. Doctors predict the survival rate of LT depends upon the scoring systems.

5.1 Use of Machine Learning Techniques for Survival Prediction

Machine learning is a type of artificial intelligence to discover patterns in large data sets using the computation of several algorithms and can constantly develop with additional datasets[18]. The data sets are the input to the machine learning algorithm. Prediction is based on predictor variables[18]. It needs to develop a machine learning tool with medical data as input to generate the appropriate outcome including the risk as well as survival rate, in machine learning techniques[66]. The survival rate is the time to the occurrence of the event[67]. The event includes the development of a disease, response to the treatment, alive or death[67]. The outcome of machine learning models can be estimated using methods like Receiver Operating Characteristics (ROC) curves[68] and Cox regression models[22]. Several machine learning techniques are used in transplantation for the optimal allocation of organs in liver and to evaluate the survival in post transplantation[69]. Using machine learning techniques, the donor livers are allocated to the appropriate recipient and predict the best survival of the recipient. In order to predict the survival of LT, various machine learning algorithms can be used which includes neural networks[46], decision trees, support vector machines[70] and random forests[71].

Research studies show that Artificial Neural Networks (ANNs) are informative tools which can solve complications in forecast, optimization, associative memory and pattern matching[72]. Various authors compared ANNs with different statistical techniques and described the practical comparisons, differences, possibility and estimation of neural networks and logistic regression models[73]. Stepwise logistic regression analysis was used to obtain an expression to estimate the probability of liver failure in a patient[74,75]. In order to evaluate the prediction of individual tests and that of the logistic regression models, the ROC curve analysis was performed using software (Labroc1) and SPSS for Windows were used to perform all other calculations[74]. Neural network technique was used with random

sampling and the outcome was measured using ROC curve analysis[75]. A feed forward fully connected neural network was used with a standard back propagation algorithm[76]. After training, the survival of 98% of the patients was correctly predicted[76]. Recurrent neural networks were used to predict liver transplant liver failure based on a time series sequence of medical data with the help of a Back Propagation Through Time (BPTT) algorithm[77]. This model achieved good result in the survival of a patient after transplantation with postoperative history of patient and preoperative risk assessment[77]. Authors from Italy proved that neural networks are better than the MELD score for the prediction of end stage liver disease[78]. For the study, the authors collected data from Liver Transplant Unit, Italy and proved the fact with the help of ROC curves[78]. The authors predicted the liver transplant failure in 30 days with a multilayer perceptron neural network model using back propogation algorithm. For the estimation of output, the authors compared ANNs with logistic regression models. ANNs were used to find the recurrence of HCC after LT[79]. Recently we have noticed from the paper to report the organ allocation scarcity and problem with the survival rate, a Multi-Objective Evolutionary Algorithm (MOEA), was used to train radial basis function neural networks, where accuracy was the measure used to evaluate model performance[69]. This system will help medical experts allocate organs also[69]. Researchers found that ANNs are very helpful in determining the survival rate of children who undergo acute paediatric liver failure[80].

5.2 Survival Prediction using Multilayer Perceptron (MLP) ANNs

Clinical studies show that forecasting the survival of LT is based on MELD score[81]. One of the three parameters in MELD score is creatinine, which changes based on body weight of the liver patient. Female liver patients have lower level creatinine than male liver patients[82]. The lack of new survival prediction techniques forced doctors to depend upon MELD score for the survival prediction. In order to forecast the survival in LT, researchers introduced high accuracy prediction models as ANN[83]. ANN can solve various problems which cannot solve by logistic regression models and conventional statistical methods[84,28]. We proposed a Multilayer Perceptron (MLP) ANN model for predicting the survival of patients[28]. The materials for the learning were collected from United Nations Organ Sharing database which consists of both pre-transplant and post-transplant liver data[28]. It also comprises both gender patient records onwards. We performed the study in adult patients with MELD records. So the Pediatric End Stage Liver Disease(PELD) records and the data beyond MELD comes were filtered off. Through the principal component analysis, we finalized the dataset with 383 records consisting of 27 input attributes and verified using various association rule mining algorithms. We were given the 27 clinical input attributes to the MLP model and binary output from the model is Graft Status (GSTATUS). If the GSTATUS =0 means the graft is survived and GSTATUS =1 shows the graft is not survived[28]. The input attributes in the MLP model were trained using back propagation algorithm[82]. Out of the three layers in the MLP model such as input layer, hidden layer and output layer, the donor-recipient matching was done in the hidden layers. The errors during training could be reduced by correcting the weights and number of hidden layers in order to get a best survival output [28]. The complexity of the model, classification accuracy, training time and the various model performance measures were the features taken in the training phase[28]. In our model, the total number of epochs used is 1500[28]. The classification accuracy was computed in each phase of training and achieved the best survival output[28,84].

On the basis of various performance measures and accuracy, we performed the survival prediction of liver patients after transplantation[28,81]. The model output was obtained on the basis of Mean Absolute Error (MAE), Root Mean Squared Error (RMSE), Relative Absolute Error (RAE), Root Relative Squared Error (RRSE) and kappa using the ROC curves in WEKA software[28,81]. We trained 383 liver patient records and obtained the best survival output after LT successfully[28,83]. The best survival output of LT depends up on the pre transplantation nature of patient, the quality of liver and the problems in surgery[28,86]. The authors could achieve 89.70% accuracy in survival prediction with 91.30% sensitivity and 88.60% specificity[28,88]. They used MLP model for the Benign End stage liver disease patients and compare the performance with MELD and SOFA score with n=360[28,88]to predict the patients' survival. The researchers achieved 91% accuracy with 67.9% sensitivity and 94.8% specificity in 251 patients with cirrhosis[28,78]. The authors could observe

that 96.00% survival accuracy obtained with 80.40% sensitivity, 88.20% specificity[28,89] and in the further model, the survival accuracy is 91.00% with 78.30% sensitivity and 80.60% specificity[28,90]. With 10 folds cross validation, the MLP model was trained and verified. We could perform the LT survival prediction of patients using MLP with 99.74% accuracy and obtained the survival rate in the form of ROC curves[28]. The comparison between the existing models and proposed MLP model is as shown in Table 6. The sensitivity of proposed model is 99.34% and specificity is 100.00%. But with MELD score, the graft survival rate is 79.17% and graft failure rate is 20.83% using the same dataset[28].

Table 6. Comparison of proposed classifier with existing classifiers based on accuracy, sensitivity and specificity

Classifier	Accuracy	Sensitivity	Specificity
Proposed MLP	99.74%	99.34%	100.00%
[88]	89.70%	91.30%	88.60%
[89]	96.00%	80.40%	88.20%
[90]	91.00%	78.30%	80.60%
[78]	91.00%	67.90%	94.80%

6. Conclusion

Several machine learning techniques are introduced in addition to the MELD score to forecast the increased survival after LT. Artificial neural network based techniques are widely used in learning of medical data and predict survival results. The role of machine learning tools in medical field is increasing day to day as the medical data is growing in an exponential rate where the doctors cannot easily identify hidden patterns and useful information occurring in large volume data. One of the key areas is the prediction of suitability and survival rate of organs in transplantation. ANN is a dominant improvement in the area of computers and medicine. In order to do the machine learning operations in engineering, medicine, mathematics, economics, science, geology and many others, the role of ANNs is remarkable. During experimentation, we could observe that only 79.17% survival accuracy with MELD score. But with the training of suitable dataset in the MLP model, we could achieve 99.74% survival accuracy of patients after LT. Sometimes the clinician's and doctor's judgement for the allocation of liver from donor to recipient may be biased can be avoided with the help of ANN. In order to take accurate and precise decisions for the doctors, the machine learning techniques plays a very significant role.

7. Ethical Approval and Consent

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8. Disclosure of Potential Conflicts of Interest

The authors declare that they have no conflict of interest.

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