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Data Mining Applications in Liver Transplantation: A Review and Extension

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Abstract

Background and Objective: Liver transplantation is an accepted treatment for patients who present with end-stage liver disease. However, LT is restricted due to a lack of suitable donors, and further on this imbalance between supply and demand leads to death for those who are waiting on the waiting list. Specialists use MELD to assign the donor organ to the recipient and predicting the survival of patients after liver transplantation, but this index alone will not be suitable for this task and has some weaknesses. furthermore, other indicators need to be selected so that they can have a more appropriate allocation and better predictive power. The optimal allocation in waiting time and predicting the survival of patients after liver transplantation is a problem that might be answered using data mining techniques. The purpose of the present study is to review and compare the different data mining, machine learning, and deep learning techniques in the articles published in this area.

Method: Using relevant keywords, international databases relevant materials were investigated. After limiting the search strategy and deleting the duplications, the rest of the valid papers were screened by examining the title and abstract. To increase the sensitivity of the searching procedure, reference lists of papers were also examined. Finally, 42 articles related to the subject of research were selected from 1994 to 2020.

Conclusion: By reviewing the literature, we found that artificial neural network (ANN), ensemble models such as random forest (RF) and Gradient boosting machine (GBM) and their combinations among other data mining models, have shown the best results in the allocation problem and forecasting graft survival after LT. And these machine learning models, when in addition to the MELD score, use other features such as age, sex, Body mass index (BMI), Albumin, and several other useful related features, the model has a better performance in predicting graft survival after LT than the prediction only with the MELD score.

Keywords: Liver Transplantation, Data mining, Machine Learning, Ddeep Learning, Neural Network, organ allocation, survival analysis

Background and Objective

Conventionally, Liver Transplantation (LT) is a definitive treatment especially for acute and chronic end-stage liver disease[1]. Although LT is considered an expensive procedure, still many patients undergo this procedure due to its better survival rate compared to other treatments. Meanwhile, the survival rate highly depends upon the quality of the graft, availability of the donor, and the condition of the disease which has affected the patient. LT has two main objectives; the first aim is increasing survival, while the other one is a better quality of life. From the clinical studies point of view, we have observed that the model for end-stage liver disease (MELD) score is normally used for optimal organ allocation[2]. However, sometimes, those who come first in the waiting list, receive the LT first, without considering affecting factors related to the characteristics of the donors and recipients.

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This is while medical experts make judgments on LT and forecast its outcome, according to the MELD score[3]. The MELD score consists of three variables including bilirubin, creatinine, and International Normalized Ratio (INR). The prothrombin time (PT) is replaced by INR in the MELD score[3]. The INR is the PT ratio calculated in terms of the appropriate ISI of the local PT test system. INR can be calculated using the formula [3],

$$\mathrm{INR} = \left(\frac{\text{Patient's PT}}{\mathrm{MNPT}}\right) \qquad (1)$$

The MNPT is the geometric mean of prothrombin time of at least 20 adult normal subjects of both sexes. The MELD score is calculated by the formula [2],

$$\mathrm{MELDScore} = 9.6 \times \log_e(\mathrm{X}) + 3.8 \times \log_e(\mathrm{Y}) + 11.2 \times \log_e(\mathrm{INR}) + 6.4 \times \mathrm{C} \qquad (2)$$

where X and Y are the amounts(mg/dl) of creatinine and bilirubin respectively and C is given as[2],

$$\mathrm{C} = \begin{cases} 0 & \text{if an alcoholic or cholestatic} \\ 1 & \end{cases} \qquad (3)$$

In 2008, Kim et al.[4] demonstrated that the addition of serum sodium concentration to the MELD score (MELD-Na) was superior to MELD alone to predict waitlist mortality, prompting the national implementation of MELD-Na in June 2016.

Despite not achieving uniform acceptance at the time of implementation, MELD quickly demonstrated its benefits, with reductions in waitlist mortality and maintenance of excellent posttransplant survival. However, as quickly as the benefits were appreciated, the downsides of MELD became apparent as well. Primarily, the overemphasis on MELD exception points for candidates with HCC resulting in downgrades in the attribution of MELD exception points for HCC patients in April 2003 and again in January 2004[5]. In addition to the issues surrounding MELD exception points, there appears to be a sex-based inequity in MELD-based allocation. Female candidates awaiting liver transplantation have reduced rates of liver transplantation, and higher rates of waitlist removal and death when compared with male candidates[6]. The latter has been attributed in large part due to an underestimation of renal function in female candidates through the utilization of the serum creatinine component in MELD-based allocation. Indeed, it has been demonstrated that the MELD score underestimated disease severity in women by up to 2.4 points and that MELD-Na exacerbated this disparity. Finally, recent evidence has pointed to disease-based differences in the predictive power of MELD. Godfrey et al.[7] have demonstrated a temporal decline in the predictive ability of 90-day mortality for both MELD and MELD-Na from 2002 to 2016. Associated with this decline was the notable finding that MELD and MELD-Na based mortality predictions were worse for candidates with alcoholic liver disease and nonalcoholic fatty liver disease, both of which are significantly increasing as indications for liver transplantation.

However, even after using the MELD score, patients are undergoing LT might still show a poor prognosis. The low survival rate generally occurs due to the inappropriate selection of parameters and the inappropriate model[8].

The post-transplantation mortality rate can be reduced if an intelligent system is developed. Thus, here we have reviewed the articles published in the field of data mining applications in liver transplantation from 1994 to 2020.

Method

Searching Strategy

International refereed journals were used to find out the published articles from 1994 to 2020. Moreover, search engines like PubMed, Scopus, and IEEE Xplore were searched using relevant keywords. We can see a Flowchart of the search strategy in Fig.1.

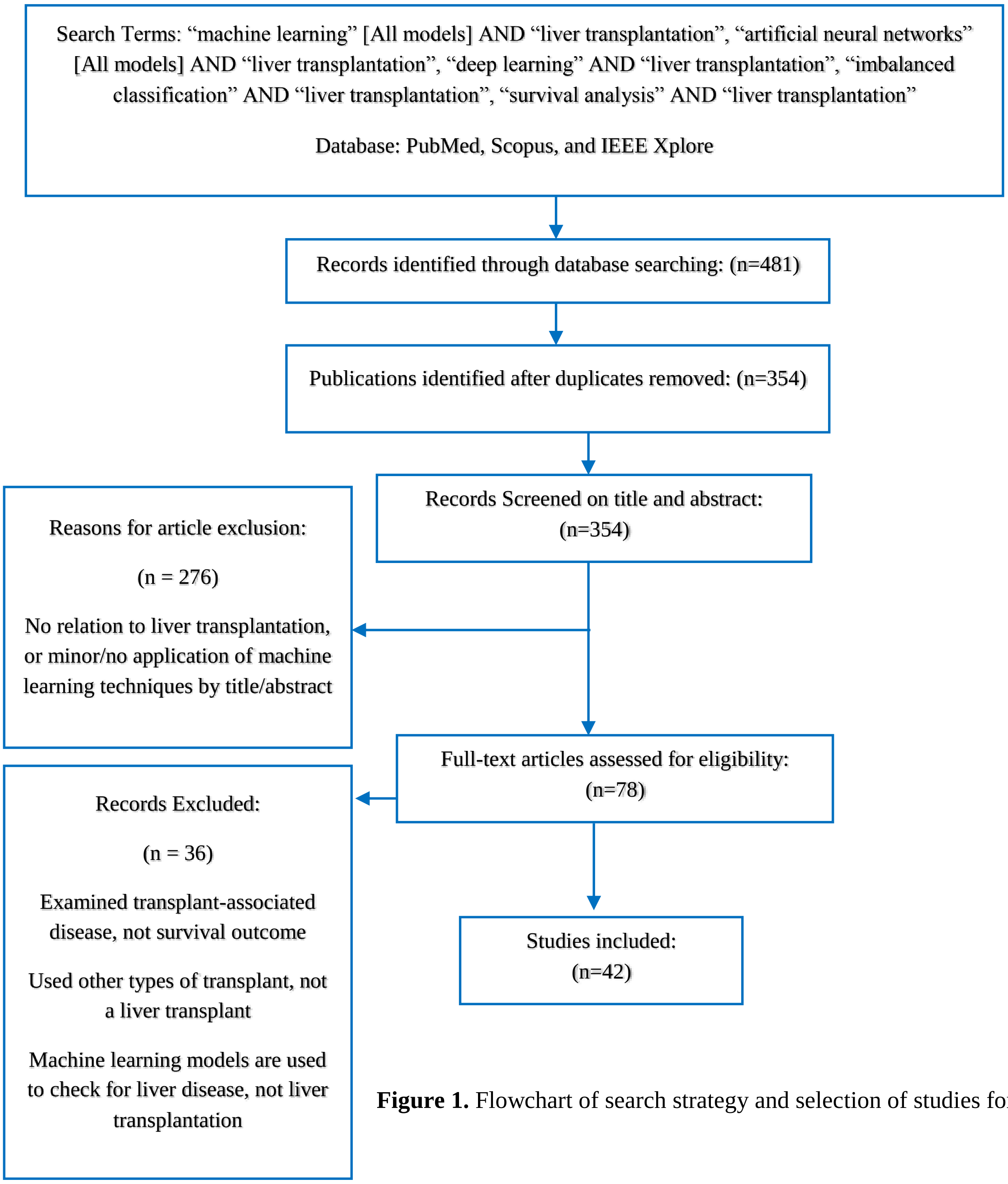

Figure 1. Flowchart of search strategy and selection of studies for inclusion.

Related articles reviewed from 1994 to 2020

The study performed by Doyle et al[1] covered 149 adult patients undergoing LT at Presbyterian University Hospital from January to August 1992. On the latter, researchers developed an expression using stepwise logistic regression to find out the probability of graft failure in LT. They demonstrated their obtained results using the ROC curve. However, the authors failed to demonstrate the accuracy of the prediction of survival after LT due to the lack of large datasets. So the authors opened a challenge to discover a model explaining the nonlinearity among existing variables.

Doyle, et al. [9] presented a feed-forward backpropagation (BP) neural network model to predict the survival rate. The random sampling method was employed considering 10 separate training and test datasets and overall accuracy was represented using ROC curves.

Marsh, et al.[10] provided a survival analysis for HCC after Orthotropic LT for 214 patients. They employed a three-layer ANN model. Finally, they discovered that male patients had a higher risk of HCC recurrence compared to females.

Parmanto, et al.[11] proposed recurrent ANN using Back Propagation and run a time series model of the historical data. To evaluate the accuracy of the prediction, cross-validation was employed.

Hoot and Aronsky[12] used transplant information from the United Network for Organ Sharing database to construct a Bayesian network model to predict 90-day graft survival. The final model incorporated a set of 29 pre-transplant variables, and it achieved performance, as measured by area under the receiver operating characteristic curve, of 0.674 by cross-validation and 0.681 on an independent validation set.

Ioannou[13] presented a comprehensive model that predicts survival rate after LT based on pre-transplant donors and recipient characteristics using cox proportional hazards regression. The model illustrated that change in pre-transplant donor and recipient characteristics have a significant impact on post-transplant survival.

Cuccheti, et al.[14] conducted a study considering 251 patients with cirrhosis moved to LT at the LT unit, at Bologna. They proved that ANN has shown better performance compared to the MELD score.

Cruz-Ramírez, et al.[15] present a generalized radial basis functions (GRBF) neural networks model which might assist medical experts in the donor-recipient allocation problem. These models are obtained by a multi-objective evolutionary algorithm.

Pérez-Ortiz, et al.[16] proposed a novel algorithm for ordinal classification based on combining ensemble techniques and discriminant analysis. The proposal is applied to a real application of liver transplantation, where the objective is to predict survival rates of the graft. When they compared to other state-of-the-art classifiers like AdaBoost, EBC(SVM), or KDLOR, the proposed algorithm is shown to be competitive.

Cruz-Ramírez, et al.[17] described a decision support system for assigning a liver from a donor to a recipient on a waiting list which willing to maximize the probability of belonging to the survival graft class.

Nakayama, et al.[18] developed algorithms for forecasting the prognosis of acute liver failure, to detect the affecting criteria on liver transplantation.

Do Nascimento, et al.[19] examined MELD score and other variables related to long-term mortality using a new model: the Survival Tree analysis.

Zhang, et al.[8] in his paper established a survival model for liver patients with Benign End-Stage Liver Diseases and examined its efficiency with MELD and Sequential Organ Failure Assessment score. They developed an ANN model according to 360 patients which had been gathered between 1999 and 2009.

Pérez-Ortiz, et al.[20] developed a multi-objective and evolutionary algorithm to establish a complete system for donor-recipient assignment in LT.

Cruz-Ramrez et al.[21] proposed a model incorporating Radial Basis Function neural networks using a multi-objective evolutionary algorithm (MPENSGA2) to tackle long computational time for running ANN.

Cruz-Ramírez, et al.[22] used a multi-objective evolutionary algorithm and various techniques to select individuals from the Pareto front to obtain artificial neural network models to aid decision making. Moreover, a combination of two pre-processing methods has been applied to the dataset to offset the existing imbalance. One of them is a resampling method called SMOTE and the other is an outlier deletion method. The best model obtained with these procedures (with AUC = 0.66) gives medical experts a probability of graft survival at 3 months after the operation. This probability can help medical experts to achieve the best possible decision without forgetting the principles of fairness, efficiency, and equity.

Briceño, et al.[23] employed an ANN for donor recipients in LT and compared its performance with well-known scores (MELD, D-MELD, DRI, P-SOFT, SOFT, and BAR) of graft survivals.

Pérez-Ortiz, et al.[24] proposes a novel donor-recipient liver allocation system constructed to predict graft survival after transplantation utilizing a dataset comprised of donor-recipient pairs from different centers (seven Spanish and one UK hospitals). They used the ordinal regression learning paradigm due to the natural ordering in the classes of the problem, via a cascade binary decomposition methodology and the Support Vector Machine methodology. Finally, a simulation of the proposal is included, to visualize its performance in realistic situations. This simulation has shown that there are some determining factors in the characterization of the survival time after transplantation (concerning both donors and recipients) and that the joint use of these sets of information could be, in fact, more useful and beneficial for the survival principle.

Khosravi, et al in paper[25] aimed to model the survival of patients with liver transplant in a wide age range (two years old and above) using ANN and Cox PH regression models to compare the performance of these two methods to predict death due to complications of liver transplantation. The results of this study revealed that ANN was better than the Cox PH regression model to predict survival in patients with liver transplant based on the area under the ROC curve.

Kim, et al.[26] used 2011 liver match-run data to compare classifiers based on logistic regression, support vector machines, boosting, classification and regression trees, and Random Forests. and then because the accept-or-decline module will be embedded in a simulation model, they also developed an evaluation tool for comparing the performance of predictors, which they call sample-path accuracy. The result shows that the Random Forest method resulted in the smallest overall error rate, and boosting techniques had greater accuracy when both sensitivity and specificity were simultaneously considered important.

Raji C.G. and Vinod Chandra S.S.[27] proposed a survival forecasting model to analyze the three-month mortality of patients after LT. They used an ANN model for this purpose.

Dorado-Moreno, et al.[28] performed a proper donor-recipient matching to the survival time of the recipients using an ANN. They combined evolutionary algorithms to optimize corresponding parameters with an over-sampling technique.

Lau, et al.[29] revealed that considering 15 top-ranking donor and recipient variables existing before transplantation the best predictors of outcome were reached using the random forest and ANN.

M. Pérez-Ortiz, et al.[30] proposed a new allocation system that applies machine learning to forecast graft survival after transplantation using a dataset in the UK. The main novelty of the system is that it tackles the imbalanced nature of the dataset by considering semi-supervised learning, analyzing its potentials for obtaining more robust models in LT.

Dorado, et al.[31] overcomes an issue regarding the organ allocation system in LT using machine learning.

C. G. Raji and S. S. Vinod Chandra[32] proposed an efficient and accurate ANN for predicting the long-term survival of liver patients who had undergone LT procedure. To perform the dimensionality reduction of a huge database, the principal component analysis was done and the significant relationship among attributes was identified using several rule mining techniques, such as apriori, Tertius, and treap algorithms. They investigated the survival analysis of 13 years after LT.

Ayllon, et al[33] examine the performance of the ANN-based methodology in a different European health care system.

Andres, et al.[34] presented an original model to forecast individual survival after LT due to Primary Sclerosing Cholangitis. They used a computerized package, called PSSP, patients (n = 2769) who received an LT for PSC from 2002 to 2013; finally, they generated a new model for forecasting survival distributions.

Hence, liver quality evaluation is also a vital step for estimating the success rate of LT. Therefore, in this respect, Qing Lan, et al.[35] constructed a multivariate logistic regression for single liver quality evaluation, and to assess cross-liver quality evaluation, they applied a multi-task learning logistic regression.

Bhat, et al.[36] used machine learning algorithms like the random forest, neural network, Logistic regression, Gradient boosting, and support vector machine to identify key predictors and survival outcomes of new-onset diabetes after transplant (NODAT) in liver transplant (LT) recipients. they found that older, male, and obese recipients are at an especially higher risk of NODAT.

Jarmulski, et al[37] have built models predicting whether a patient will lose an organ after a liver transplant within a specified time horizon. they have used the observations of bilirubin and creatinine in the whole first year after the transplantation to derive predictors, capturing not only their static value but also their variability. their models indeed have a predictive power that proves the value of incorporating variability of biochemical measurements, and it is the first contribution of this paper. As the second contribution, they have identified that full-complexity models such as random forests and gradient boosting lack sufficient interpretability despite having the best predictive power, which is important in medicine. they have found that generalized additive models (GAM) provide the desired interpretability, and their predictive power is closer to the predictions of full-complexity models than to the predictions of simple linear models.

Lee, et al.[38] in their paper demonstrated that a machine learning model with a gradient boosting machine, random forest, and decision tree showed better performance than the traditional logistic regression model to predict acute kidney injury (AKI) after liver transplantation. Among these models, the gradient boosting machine showed the best performance with the highest AUROC.

Liu, et al.[39] proposed a predictive model for the prediction of acute rejection of liver transplantation. they compared several methods, including SVM, ANN, and random forest, and the experimental results indicate that the proposed method is comparative, and provides interpretable results. And they used the CART algorithm in the model since the outcomes could be represented as rule forms, the practitioners can understand how the outcome is induced from data.

Fast and accurate graft hepatic steatosis (HS) assessment is of primary importance for lower liver dysfunction risks after transplantation. Moccia[40] investigated the automatic analysis of liver texture with data mining algorithms to automate the HS process.

Guijo-Rubio, et al. in their paper[41] develop and validate a machine learning (ML) model for predicting survival after liver transplantation based on pre-transplant donor and recipient characteristics. Several methods including proportional-hazards regression models and ML methods such as Gradient Boosting were applied, using 10 donor characteristics, 15 recipient characteristics, and 4 shared variables associated with the donor-recipient pair. To measure the performance of the seven state-of-the-art methodologies, three different evaluation metrics are used, being the concordance index (ipcw) the most suitable for this problem. The results achieved show that, for each measure, a different technique obtains the highest value, performing almost the same, but, if we focus on ipcw, Gradient Boosting outperforms the rest of the methods.

Farzindar and Kashi[42] presented the application of deep learning techniques to develop a modern model for the prediction of graft failure and survival analysis in liver transplant patients. To provide an additional tool to clinical practitioners in the allocation of a scarce resource, they developed a multi-task model to learn the survival function of a donor-recipient pair and hence predict the exact time of failure which outperforms the traditional cox hazard models.

Bertsimas, et al.[43] developed an optimized prediction of mortality (OPOM) utilizing machine-learning optimal classification tree models trained to predict a candidate's 3-month waitlist mortality or removal utilizing the Standard Transplant Analysis and Research (STAR) dataset. The result shows that OPOM delivered a substantially higher AUC across all disease severity groups, and OPOM more accurately and objectively prioritizes candidates for liver transplantation based on disease severity, allowing for a more equitable allocation of livers with a resultant significant number of additional lives saved every year.

Nair, et al in paper[44] proposed a model for prediction of life expectancy after liver transplantation is deployed using the machine learning process. The proposed model uses a moderate amount of 200 data, which are created using all the novelty rule followed by the UNOS. The proposed system uses the Kmeans clustering for efficient clustering of the likely data in between the Donor data and Recipient data. Once they are clustered then they are fed to the Hidden Markov Model to evaluate the Probability matrix data. This is used by the Dumpster Shaffer reasoning to evaluate the proper value count, which is being used by the abstract Fuzzy classification to evaluate the Proper correct prediction of life span.

Ershoff, et al.[45] trained a deep neural network (DNN) to predict 90-day post-transplant mortality using preoperative variables and compared the performance to that of the Survival Outcomes Following Liver Transplantation (SOFT) and Balance of Risk (BAR) scores. they using United Network of Organ Sharing data on adult patients who received a deceased donor liver transplant between 2005 and 2015 (n = 57,544). The DNN was trained using 202 features, and the best DNN's architecture consisted of 5 hidden layers with 110 neurons each. The area under the receiver operating characteristics curve (AUC) of the best DNN model was 0.703 (95% CI: 0.682-0.726) as compared to 0.655 (95% CI: 0.633-0.678) and 0.688 (95% CI: 0.667-0.711) for the BAR score and SOFT score, respectively. they concluded that despite the complexity of DNN, it did not achieve a significantly higher discriminative performance than the SOFT score.

Kong, et al[46] developed a simple scoring system for the preliminary prediction of the postoperative 90-day mortality of adult LT based on preoperative characteristics of LT Recipients. The simple four-factor prediction model includes these four factors: serum creatinine (Cre), age, total bilirubin (TB), and serum albumin (Alb).

Kantidakis, et al. in paper[47] applied ML techniques such as random forests and neural networks to large data of 62294 patients from the United States with 97 predictors selected on clinical/statistical grounds, over more than 600, to predict survival from liver transplantation. the results show that random survival forest slightly better predictive performance than Cox models based on the C-index. and Neural networks show better performance than both Cox models and random survival forest based on the Integrated Brier Score at 10 years.

Liu, et al.[48] used a data-driven approach to devise a predictive model to predict postoperative survival within 30 days based on the patient's preoperative physiological measurement values. they used random forest (RF) to select important features, including clinically used features and new features discovered from physiological measurement values. Moreover, they propose a new imputation method to deal with the problem of missing values and the results show that it outperforms the other alternatives. The experimental results on a real data set indicate that RF outperforms the other alternatives.

A summary of researches published in the literature is given in Table 1.

the abbreviation used in Table 1:

1. LR: Logistic Regression
2. ANN: Artificial Neural Network
3. DT: Decision Tree
4. SVM: Support Vector Machine
5. RF: Random Forest
6. NB: Naive Bayes
7. MOEA: Multi-Objective Evolutionary Learning Algorithm

Table 1. Research Gap Table

				Preprocessing methods		Models used									
ID	First author	Publication year	subject	feature selection methods	imbalance methods	LR	ANN	DT	SVM	RF	Boosting	NB	MOEA	Survival model	other
1	Doyle	1994	forecasting	☐	☐	☒	☐	☐	☐	☐	☐	☐	☐	☐	☐
2	Doyle	1994	forecasting	☐	☐	☐	☒	☐	☐	☐	☐	☐	☐	☐	☐
3	Marsh	1997	forecasting	☒	☐	☐	☒	☐	☐	☐	☒	☐	☐	☐	☐
4	Parmanto	2001	forecasting	☐	☐	☐	☒	☐	☐	☐	☐	☐	☐	☐	☐
5	Hoot	2005	forecasting	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☒
6	Ioannou	2006	forecasting	☒	☐	☐	☐	☐	☐	☐	☐	☐	☐	☒	☐
7	Cucchetti	2007	forecasting	☐	☐	☐	☒	☐	☐	☐	☐	☐	☐	☐	☐
8	CruzRamírez	2011	allocation	☐	☐	☒	☒	☒	☒	☐	☐	☒	☒	☐	☐
9	Pérez-Ortiz	2012	forecasting	☐	☒	☐	☐	☐	☒	☐	☒	☐	☐	☐	☒
10	CruzRamírez	2012	allocation	☐	☐	☐	☐	☐	☐	☐	☐	☐	☒	☐	☐
11	Nakayama	2012	forecasting	☐	☐	☐	☐	☒	☐	☐	☐	☐	☐	☐	☐
12	DoNascimento	2012	forecasting	☐	☐	☐	☐	☒	☐	☐	☐	☐	☐	☐	☐
13	Zhang	2012	forecasting	☒	☐	☐	☒	☐	☐	☐	☐	☐	☐	☐	☐
14	Pérez-Ortiz	2012	forecasting	☐	☐	☒	☒	☒	☒	☐	☐	☐	☒	☐	☒
15	CruzRamirez	2013	forecasting	☐	☐	☒	☒	☒	☒	☐	☐	☐	☒	☐	☒
16	CruzRamírez	2013	allocation	☐	☒	☐	☐	☒	☒	☐	☐	☐	☒	☐	☒
17	Briceño	2014	allocation	☐	☐	☒	☒	☒	☒	☐	☐	☐	☐	☐	☒
18	Pérez-Ortiz	2014	allocation	☐	☐	☐	☐	☐	☒	☐	☐	☐	☐	☐	☒
19	Khosravi	2015	forecasting	☐	☐	☐	☒	☐	☐	☐	☐	☐	☐	☒	☐
20	Kim	2015	allocation	☒	☒	☒	☐	☒	☒	☒	☒	☐	☐	☐	☐
21	Raji	2016	forecasting	☐	☐	☐	☒	☒	☐	☐	☐	☐	☐	☐	☒

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				Preprocessing methods		Models used									
ID	First author	Publication year	subject	feature selection methods	imbalance methods	LR	ANN	DT	SVM	RF	Boosting	NB	MOEA	Survival model	other
22	DoradoMoreno	2016	allocation	☐	☒	☐	☒	☐	☒	☐	☐	☐	☐	☐	☒
23	Lau	2017	allocation	☒	☐	☐	☒	☐	☐	☒	☐	☐	☐	☐	☒
24	Pérez-Ortiz	2017	allocation	☐	☒	☐	☐	☐	☒	☐	☐	☐	☒	☐	☐
25	DoradoMoreno	2017	allocation	☐	☒	☐	☒	☐	☒	☐	☐	☐	☐	☐	☒
26	Raji	2017	forecasting	☐	☐	☐	☒	☐	☐	☐	☐	☐	☐	☐	☒
27	Ayllón	2018	allocation	☐	☐	☐	☐	☐	☐	☐	☐	☐	☒	☐	☒
28	Andres	2018	forecasting	☒	☐	☐	☐	☐	☐	☐	☐	☐	☐	☒	☐
29	Lan	2018	forecasting	☐	☐	☒	☐	☐	☐	☐	☐	☐	☐	☐	☒
30	Bhat	2018	forecasting	☐	☐	☐	☒	☐	☒	☒	☒	☐	☐	☒	☐
31	Jarmulski	2018	forecasting	☐	☒	☒	☐	☐	☐	☒	☒	☐	☐	☐	☒
32	Lee	2018	forecasting	☐	☐	☒	☒	☒	☒	☒	☒	☒	☐	☐	☒
33	Liu	2018	forecasting	☐	☒	☐	☒	☒	☒	☒	☐	☐	☐	☐	☐
34	Moccia	2018	forecasting	☐	☐	☐	☐	☐	☒	☒	☐	☐	☐	☐	☒
35	Guijo-Rubio	2019	forecasting	☐	☐	☐	☐	☐	☒	☐	☒	☐	☐	☒	☐
36	Farzindar	2019	forecasting	☒	☐	☐	☒	☐	☐	☐	☐	☐	☐	☐	☐
37	Bertsimas	2019	forecasting	☐	☐	☐	☐	☒	☐	☐	☐	☐	☐	☐	☐
38	Nair	2019	forecasting	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☒
39	Ershoff	2020	forecasting	☐	☐	☐	☒	☐	☐	☐	☐	☐	☐	☐	☐
40	Kong	2020	forecasting	☒	☐	☒	☒	☐	☐	☐	☐	☐	☐	☐	☐
41	Kantidakis	2020	forecasting	☐	☐	☐	☒	☐	☐	☐	☐	☐	☐	☒	☐
42	Liu	2020	forecasting	☒	☐	☒	☐	☒	☐	☒	☒	☐	☐	☐	☐

Table 2. More information on the research gap table

ID	First author	Publication year	Number of patients studied	Number of features examined	Evaluation model	Model performance
1	Doyle	1994	148	11	Accuracy, areas under receiver-operating characteristic (ROC) curves (AUC)	accuracy: 92.7% AUC: 0.90±0.04
2	Doyle	1994	155	19	AUC	AUC: 0.90
3	Marsh	1997	214	9	AUC	AUC: 0.971±0.034
4	Parmanto	2001	293	16	6-fold cross-validation	90% on the learning set and 78% on the test set
5	Hoot	2005	12,239	29	AUC	0.674 by cross-validation and 0.681 on an independent validation set.
6	Ioannou	2006	20,301	13	Risk scores, Comparison of predicted survival	-
7	Cucchetti	2007	251	10	AUC	AUC = 0.96
8	CruzRamírez	2011	1001	42	C measure, MS metric, AUC, KAP P A metric, Root Mean Square Error (RMSE)	C measure (MPDENN-C): 84.46% MS metric (MPDENN-MS): 45.55% AUC (Naive Bayes): 64.3%
9	Pérez-Ortiz	2012	1001	41	Correct Classification Rate (CCR), Minimum Sensitivity (MS), Average Mean Absolute Error (AMAE), Maximum Mean Absolute Error (MMAE)	CCR (SVM): 81.38 ± 0.15 MS (Ensemble product combiner): 2.55 ± 4.27 AMAE (Ensemble product combiner): 1.374±0.072 MMAE (Ensemble product combiner): 2.527±0.275
10	CruzRamírez	2012	1001	41	Accuracy, Minimum sensitivity (MS), AUC, RMSE, Kappa	Accuracy (MPENSGA2-E (GRBF)): 84.50% MS (MPENSGA2-E (GRBF)): 3.13% AUC (MPENSGA2-E (GRBF)): 0.6529
11	Nakayama	2012	1,022	5	accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV)	Accuracy: 79% PPV: 83% NPV: 75%
12	DoNascimento	2012	529	7	P-values	-
13	Zhang	2012	360	18	Hosmer-Lemeshow test and ROC analysis	AUC (in one-year prediction): 0.91 AUC (in two-year prediction): 0.88

Table 2. More information on the research gap table

ID	First author	Publication year	Number of patients studied	Number of features examined	Evaluation model	Model performance
14	Pérez-Ortiz	2012	114	41	CCR, MS, RMSE, and AUC	MS (MPDENN): 49.65±13.02 AUC (MPDENN): 0.604±0.117
15	CruzRamirez	2013	1003	64	correct classification rate (C), minimum sensitivity (MS), AUC, root mean squared error (RMSE), Kappa	correct classification rate (SLogistic): 88.45 MS (M2-MS): 48.98 ± 5.18 AUC (M2-MS): 0.5659 ± 0.0339 RMSE (Mono-E): 0.3207 ± 0.0048
16	CruzRamírez	2013	1,001	41	correct classification rate (C), minimum sensitivity (MS), AUC	C (SVM): 88:71±0.17 MS (MPDENN-MS): 44.74 ± 8.78 AUC (MPDENN-E): 0.5314± 0.0538
17	Briceño	2014	1003	57	AUC	AUC (NN-MS): 0.8215
18	Pérez-Ortiz	2014	1437	38	Accuracy, Geometric mean of the sensitivities (GMS), Average mean absolute error (AMAE)	Accuracy (ELMOR): 85.11±0.24 GMS (ECOC-CascadeSVM): 7.46±9.47 AMAE (ECOC-CascadeSVM):1.345±0.083
19	Khosravi	2015	1168	37	Accuracy, AUC	Accuracy (ANN and Cox PH): 92.73% AUC (ANN): 86.4% AUC (Cox PH): 80.7%
20	Kim	2015	3,140	376	Error rate, Accuracy, Sensitivity, Specificity, G-metric	Accuracy (LR): 93.17 % G-metric (LR): 44.59 %
21	Raji	2016	383	27	Mean Absolute Error (MAE), RMSE, RAE, Root Relative Squared Error (RRSE)	Accuracy (MLP): 99.74% MAE (MLP): 0.0049 RMSE (MLP): 0.0527
22	DoradoMoreno	2016	1406	38	Accuracy, GMS, Average mean absolute error (AMAE)	Accuracy (ELMOR): 85.21 ± 0.27 GMS (IM-ORNET): 7.47 ± 12.08 AMAE (KDLOR):1.206 ± 0.064
23	Lau	2017	1000	276	AUC	AUC (ANN): 0.835
24	Pérez-Ortiz	2017	822	37	GMS, Accuracy	Accuracy (SVC): 90.15 ± 0.35 GMS (CS-SVC): 55.09 ± 9.10

Table 2. More information on the research gap table

ID	First author	Publication year	Number of patients studied	Number of features examined	Evaluation model	Model performance
25	DoradoMoreno	2017	1406	38	GMS, Average mean absolute error (AMAE), Accuracy	Accuracy (ELMOR): 85.21 ± 0.27 GMS (DIM-ORNET): 14.97 ± 13.17 AMAE (KDLOR): 1.206 ± 0.064
26	Raji	2017	383	27	Accuracy	Accuracy: 99.53%
27	Ayllón	2018	822	55	AUC	AUC: 0.94
28	Andres	2018	2769	30	D-calibration	D-calibration (PSSP model) = (p = 1.0)
29	Lan	2018	1071	6	classification error	testing errors varying from 9% to 36%
30	Bhat	2018	61,677	11	average squared error	average squared error (random forest): 0.1059
31	Jarmulski	2018	1095	2	AUC	AUC (random forest): 0.7421
32	Lee	2018	1211	72	AUC	AUC (gradient boosting): 0.90
33	Liu	2018	525	45	AUC	AUC (SVM(RBF)):0.958
34	Moccia	2018	40	168	sensitivity, specificity, and accuracy	Sensitivity: 95% Specificity: 81% Accuracy: 88%
35	Guijo-Rubio	2019	39,095	29	concordance index (c-index), ipcw, AUC	c-index (Coxnet):0.5906 ± 0.0070 ipcw (Gradient Boosting):0.5751 ± 0.0151 AUC ():0.6079 ± 0.0078
36	Farzindar	2019	59,115 and 87,334	10 and 10	concordance index (c-index)	c-index (for SRTR dataset): 0.82 c-index (for UNOS dataset): 0.57
37	Bertsimas	2019	1 618 966	28	AUC	AUC: 0.859
38	Nair	2019	200	25	Mean absolute Error (MAE)	MAE: 5.2
39	Ershoff	2020	57,544	202	AUC	AUC (DNN model): 0.703
40	Kong	2020	1,495	33	AUC	AUC (ANN): 0.698
41	Kantidakis	2020	62294	97	concordance index (C-index), Integrated Brier Score (IBS)	C-index (RSF): 0.622 IBS (ANN): 0.18
42	Liu	2020	538	17	AUC, specificity	AUC: 0.771 Specificity: 0.815

Table 2 provides more information about the number of patients studied, Number of features examined, Evaluation model, and Model performance (The table shows only the performance of some of the best models.).

Discussions and findings

After reviewing the above-mentioned articles, the following results are discussed:

- After a deep investigation of the works published in the area of data mining models in LT, 42 related papers were found.

- Most of the research in LT areas incorporate the MELD scores for allocation problem. However, to run a comprehensive analysis for the allocation problem multi-criteria decision-making models shall be employed to take other affecting parameters on LT success into consideration.

- The concentration of data mining on LT has been consistently growing during recent years compared to the past two decades.

- Almost 26% and 74% of papers are carried out in allocation problem and forecasting respectively. Moreover, a rare number of publications consider both simultaneously.

- Among the works published in the area of data mining models, artificial neural networks have been employed more than other approaches like SVM and logistic regression.

- In the last 5 years, MOEA models like Memetic Pareto Differential Evolutionary Neural Network (MPDENN) and MPENSGA2 (a multi-objective evolutionary algorithm based on Pareto dominance is used with an improved NSGA2 algorithm) have been rarely used compared to the past two decades.

- In the last 5 years, unlike two decades ago, many Survival models such as Cox proportional hazards regression have been used. And researchers have compared these models with machine learning models.

- In recent years, unlike previous years, ensemble models such as random forest (RF) and Gradient boosting machine (GBM) have become very popular due to the high speed and high accuracy of the model.

- Between 1994 and 2014, in these 20 years, researchers usually used predefined and well-known parameters such as MELD in their articles, but in the last 5 years, researchers have used different feature selection methods to select the top features from many variables. This makes the output of the model more accurate and the model more reliable.
- In most of the researches carried out in the literature, a low number of donors/patients have been considered due to restrictions on donor policy or

other constraints. This might generate a bias during data analysis.

- Most of the data were collected locally in one country (even just in one hospital). This may lead to local results which further cannot be useful for others.

- Reviewing the literature, it is revealed that most of the conducted researches in the past few years used Different techniques to solve the problem of data imbalance. And this problem has been the main focus of many articles in the last 5 years due to its high importance.

- Reviewing the literature, it is revealed that machine learning models that use several other features in addition to the MELD score in their models, such as age, sex, Body mass index (BMI), Albumin, and several other useful related features, the models have a better performance in predicting graft survival after LT than the prediction only with the MELD score. For example, in Article [14] it is shown that the ANN was superior to the MELD scoring system in predicting the 3-month mortality of patients with an end-stage liver disease listed for liver transplantation.

Implications for Extension

According to the aforementioned findings, below some implications for further extensions are presented:

Practical implications:

- **Implications on organizational chart**: Data mining models are associated with strong mathematics and statistical analysis. However, clinicians are mostly involved in medical practice. Therefore, the applications of data mining models in LT requires the cooperation of both clinician and data scientist, to attain the pre-determined objectives. Moreover, this task should be performed regularly to get a chance for further improvements. Here, the success key is to set up a clinical data scientist team to work with the clinician's face to face without any interruptions. Thus, in the organization chart of the hospital, a box for clinical data scientists should be placed. The number of staff and their allocations highly depends on the size of the hospital and the number of patients who are being referred to the LT unit. By this approach, considering the plan –do –check – act (PDCA) cycle further enhancements can be elaborated.

- **Infrastructures**: As data mining models need huge data and their performance requires a large dataset, working with a well-organized database would be essential. Herby, for the hospitals and units where hospital information system (HIS) or medicine 2.0 (medicine on the web) came into routine operation, implementation of data sciences should be easier.

- **Decision support systems**: Likewise, to other interdisciplinary researches, clinical data sciences; due to its inherent, must have done according to a strong infrastructure. Here, the development of an LT decision support system (LTDSS) would be highly valuable where the results obtained from heavy intensive mathematical models might convert into a well-organized decision support system enabling all team members to monitor the LT dashboard and tracks the performance reports as well.

- **LT consortium:** Considering the lack of data in LT due to its inherent, and to obtain the results applicable across the globe, "organizing LT consortium" is recommended. If so, big data can be collected from different countries and data analysis can be elaborated as a whole. The obtained results can be further used globally.

Theoretical extensions:

The following extensions to the theory of data mining models can be further elaborated:

- **Dynamic data mining models**: Most of the researches conducted in literature used static data mining models like Multi-Layer Perceptron (MLP) which are not time-dependent models. However, in data analysis of LT many clinicians may encounter situations, where the affecting parameters may vary over time. For instance, the creatinine may fluctuate due to the bodyweight of the liver recipient and this may lead to a significant change in the MELD score. Therefore, time-dependent neural network models like Hopfield ANN can be made to tackle with this issue or any other inconvenience caused according to static modeling.
- **Hybrid models**: Reviewing the literature, it is revealed that most of the conducted researches used conventional neural networks or SVM. However, as it is now routine in other disciplines, hybrid models have to be examined to enhance the performance of prediction. For instance, ANN and SVM can be first adapted as a constructive algorithm, and then other improvement models like genetic algorithm may be embedded in the current system. This procedure will stop when

the best know results are reached.

- **imbalanced Data:** imbalanced classification has been the focus of many machine learning researchers in the past years, given the hindrance that it usually poses for the learning machine. Reviewing the literature, it is revealed that most of the conducted researches in the past few years used Different techniques like a cost-sensitive approach (i.e. modifying the classification method) and resampling strategy (over-sampling the minority class or under-sampling the majority one) to solve this problem. But these techniques have disadvantages, for example in under-sampling It can discard potentially useful information which could be important for building rule classifiers. And in Over-Sampling It increases the likelihood of overfitting since it replicates the minority class events. To solve these problems, it would be better to use stronger models such as the Adaptive Synthetic Sampling Approach (ADASYN) and KMeans SMOTE or a combination of over-sampling and under-sampling methods.

Conclusion

In this paper, all works published in the area of data mining models in LT are analyzed. The results reveal that mostly neural network models have been employed for both allocation and prediction purposes. Some practical implications are presented from different aspects like an organizational chart, required infrastructure such as HIS, medicine 2.0 as well as organizing an LT consortium for running big data analysis allowing researchers to publish their obtained results globally across the universe. Finally, some theoretical extensions have been made for instance applying dynamic data mining models, as well as examining hybrid models such as neural networks – Genetic algorithm enabling us to reach a better performance.

As most of the research published in the literature incorporated the MELD score for the allocation of donors to the recipients, it’s time to consider other factors affecting LT through a multi-criteria decision-making process. Since this process has some complications for further implementation, the whole process must be created and developed as an LT decision support system which might amend to current HIS or medicine 2.0 as a new module. The latter has to be monitored and further enhanced through feedback given during the development phase.

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