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Artificial Intelligence in Gastroenterology

Contents

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EDITORIAL

- 1 Gastrointestinal disorders in children with autism: Could artificial intelligence help?

Al-Biltagi M, Saeed NK, Qaraghuli S

MINIREVIEWS

- 13 Current advancements in application of artificial intelligence in clinical decision-making by gastroenterologists in gastrointestinal bleeding

Maulahela H, Annisa NG

- 21 Artificial intelligence and human liver allocation: Potential benefits and ethical implications

Mucenic M, de Mello Brandão AB, Marroni CA

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AIMS AND SCOPE

The primary aim of *Artificial Intelligence in Gastroenterology* (AIG, *Artif Intell Gastroenterol*) is to provide scholars and readers from various fields of artificial intelligence in gastroenterology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

AIG mainly publishes articles reporting research results obtained in the field of artificial intelligence in gastroenterology and covering a wide range of topics, including artificial intelligence in gastrointestinal cancer, liver cancer, pancreatic cancer, hepatitis B, hepatitis C, nonalcoholic fatty liver disease, inflammatory bowel disease, irritable bowel syndrome, and *Helicobacter pylori* infection.

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Artificial intelligence and human liver allocation: Potential benefits and ethical implications

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Abstract

Since its implementation almost two decades ago, the urgency allocation policy has improved the survival of patients on the waiting list for liver transplantation worldwide. The Model for End-Stage Liver Disease score is widely used to predict waiting list mortality. Due to some limitations related to its use, there is an active investigation to develop other prognostic scores. Liver allocation (LA) entails complex decision-making, and grafts are occasionally not directed to the recipients who are more likely to survive. Prognostic scores have, thus far, failed to predict post-operative survival. Furthermore, the increasing use of marginal donors is associated with worse outcomes. Adequate donor-recipient pairing could help avoid retransplantation or futile procedures and reduce postoperative complications, mortality, hospitalization time, and costs. Artificial intelligence has applications in several medical fields. Machine learning algorithms (MLAs) use large amounts of data to detect unforeseen patterns and complex interactions between variables. Artificial neural networks and decision trees were the most common forms of MLA tested on LA. Some researchers have shown them to be superior for predicting waiting list mortality and graft failure than conventional statistical methods. These promising techniques are increasingly being considered for implementation.

Key Words: Liver transplantation; Liver cirrhosis; Artificial intelligence; Prognosis; Survival; Machine learning

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Core Tip: This review discusses the ethical aspects and current advancements in liver allocation (LA). It summarizes the concept of artificial intelligence and focuses on the latest developments of machine learning algorithms as applied to predicting waiting list mortality and LA. To date, only a few research groups have published works on this field; they also wrote reviews on the subject. Our minireview offers a thorough and impartial view of the topic, and we hope this will alert other potential researchers to this promising field.

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INTRODUCTION

Liver transplantation (LT) is the treatment of choice for patients with terminal liver disease[1]. LT is increasingly performed worldwide; however, organ scarcity remains a significant challenge for transplant teams[2], placing greater weight on the need for efficient liver allocation (LA). Therefore, correct organ allocation is of paramount importance.

An optimal allocation system for LT should balance considerations of equity (equal opportunity to receive the graft), need (to reduce waiting list mortality), utility (maximizing the overall life-years gained), and benefit (optimizing outcomes from each organ transplanted)[3].

Urgency criteria are based on need, prioritizing grafts to the most critically ill patients. Survival without LT is estimated through prognostic models, such as the model for end-stage liver disease (MELD). MELD is a validated score derived solely from laboratory test results (total bilirubin, serum creatinine, and prothrombin time). MELD is simple and accurate, and it predicts the 3-mo mortality of candidates with an area under the receiver operating characteristic curve (AUROC) of 0.83[4]. Since 2002, the MELD score was adopted by the United Network for Organ Sharing (UNOS) to rank waitlisted patients in order of urgency in the United States (US). Several countries followed this organ allocation system (sickest first)[5]. While post-transplant survival for the sickest is lesser than that of patients with better physiological reserves, they are the ones who benefit the most from LT. Patients with a MELD score of 31-34 had a relative life expectancy 43 times higher than those who remained on the list, and patients with a MELD score of 35-40 were 128 times more likely to survive[6]. MELD was further refined after studies showed adding serum sodium concentration to the formula (MELD-Na) improves risk stratification. This system replaced MELD for LA in some countries, such as the USA, Canada, and Brazil[5,7-9]. Godfrey *et al*[10] advised of a possible loss of predictive accuracy of the MELD score over time, reaching an AUROC of only 0.70 in 2015. This may be due to changes in the epidemiology and treatment of liver diseases and increasing age and comorbidities. Despite several valid concerns about the model, it remains the most widely used.

Urgency allocation models have no value in predicting survival after LT[11,12]. Additionally, the donor pool has been expanded in the last two decades. Although the use of marginal livers (*e.g.*, older donors, steatotic livers, and donation after cardiac death) has been necessary in this regard, it increases the risk of graft failure and postoperative complications, adding further complexity to the matter of allocation[13,14]. Living donor liver transplantation is another strategy to expand the donor pool; however, it poses an inherent risk to healthy donors. Its proportion to the total number of LT is small[3].

The MELD score does not reflect mortality risk in compensated patients with hepatocellular carcinoma (HCC). Exception points are granted to candidates with HCC, one of the leading LT indications worldwide. Currently, the prioritization of HCC candidates varies from one country to another, and there is no international consensus on the matter[15]. Due to the excessive advantage conferred by these exception points, there have been some changes in global allocation policies[16-18]. Notwithstanding these revisions, HCC candidates still have increased transplant rates, decreased risk of delisting, and worse post-transplant prognosis[15].

Outcomes after LT depend on both the preoperative condition of the recipient and donor "quality". Utility criteria have been sought to offer grafts to recipients with greater chances of survival, estimating the outcome based on donor and recipient characteristics[3,16]. While this would decrease the odds for older and sicker patients to receive an organ, the overall post-transplant survival could improve. Better selection avoids retransplantation or futile procedures and reduces postoperative morbidity, hospitalization time, and costs. The survival benefit is quantifiable by estimating waiting list survival and post-transplant outcomes. A benefit-based system could balance urgency and utility in allocation decisions. For a benefit-based allocation to be successful, transplant teams would need an accurate model to predict post-transplant survival.

Although the concept of applying donor-related variables to an algorithm had been used before, Feng *et al*[19] devised the term “donor risk index” (DRI), wherein they identified seven donor characteristics that predicted graft failure. Other researchers further investigated this interesting concept, adding cold ischemia time and organ origin (national or regional). However, DRI has not been widely adopted owing to the following main reasons cited by surgical teams: the inaccuracy to predict survival, exclusion of other relevant risk factors, and difficulty of explaining its concept to the recipients[20].

Since neither candidate nor donor factors are predictive of survival following transplantation, scores that include both variables have been described over the previous years. Halldorson *et al*[21] proposed adding donor age to the MELD score, creating the D-MELD, demonstrating a survival disadvantage when combining higher donor age with higher MELD recipients. Schaebel *et al*[22] proposed the balance of risk (BAR) score, which included donor, recipient, and procurement surgery variables. For an estimated 5-year survival, the c-statistic reached an AUROC of 0.63. Rana *et al*[23] developed a complex score named survival outcomes following liver transplantation (SOFT), containing > 100 variables. It reached an AUROC of 0.70 to predict 3-mo survival after LT. In 2018, the United Kingdom introduced allocation rules based on benefit. Each graft is offered nationally to the recipient predicted to have the greatest survival benefit from that specific graft. LA is based on the transplant benefit score (TBS), calculated by 21 and 7 receptor and donor criteria, respectively. TBS reflects the difference in days between expected 5-year post-operative survival and expected 5-year waiting list survival. The model reduced deaths on the waiting list and maximized post-operative life-years[24].

The external validity of these scores is limited by several factors, such as ethnicity, regional differences in the allocation and transplantation procedures, and changes in practice over time. Since the scores are based on logistic regression (LR) models, they depend upon the assumption of independence of each variable and are limited when facing nonlinear variable interactions. Complex donor-related models are considered difficult to implement, and their accuracy can be limited by the large number of variables that impact survival and possible undetected confounding factors. They have not been validated by other researchers or found wide acceptance to date. Moreover, they were not designed for an ideal donor-recipient matching[23,25].

Therefore, transplant teams are faced with a complex decision-making process when having to choose recipients for LA. Objective criteria would exempt the medical staff from difficult decisions and assess whether patients are excessively sick to be transplanted[3,7,26]. “Artificial intelligence” (AI) or machine learning algorithms (MLAs) are under increasingly active investigation for this use[27].

AI

AI is a general term used to describe any application wherein computer systems perform tasks normally associated with human intelligence. It can be a substitute for human subjectivity and limitations[28]. AI encompasses simple automated tasks and increasingly complex fields, such as machine learning, deep learning, and artificial neural networks (ANNs).

In classical programming, the computer is supplied with an algorithm and a dataset to provide an output. Machine learning, in contrast, supplies the computer with data and associated outputs, which it uses to create an algorithm that describes the relationship between the two. These MLAs can detect patterns and improve their analysis over time with further data[29]. MLAs can analyze any number of variables and are not driven (or limited) by hypothesis. This method detects nonlinear patterns within large datasets wherein multiple interactions between variables can occur. MLA can accommodate numerous interdependent variables and improve as more cases are increasingly analyzed[30,31].

Typically, MLA applied to healthcare fall into the category of supervised learning techniques. These algorithms learn the associations between input and labeled outcome data. The following are the basic steps of supervised ML: (1) Acquire a dataset and split it into separate training, validation, and test datasets; (2) use training and validation datasets to create a model that analyzes the association between data and outcomes; and (3) evaluate the model *via* the test dataset to determine how well it predicts outcomes. There are other techniques used, such as unsupervised learning, wherein data are not labeled to find out previously unknown patterns. Semi-supervised learning is particularly useful for datasets that contain both labeled and unlabeled data. Reinforcement learning uses the consequences of their actions to learn to determine the optimal behavior for a given context[29,32].

The decision tree (DT) is a supervised learning technique primarily used for classification tasks (categorical variables). It consists of a hierarchically organized structure of nodes that makes predictions by splitting (branching) the data. Each split can connect to a new root node or attach to a terminal or “leaf” node. A random forest (RF) is an ensemble method that produces multiple DTs[29].

One of the advantages of DTs for healthcare applications is their interpretability. However, each node is determined in isolation without considering the possible impact of future splits. This can fail to capture the dataset’s underlying characteristics. This disadvantage stimulated the development of optimal classification trees (OCTs). This type of DT is formed entirely in a single step, allowing each split to be determined with full knowledge of all other splits[33].

ANN is an MLA inspired by biological neural networks. Each ANN contains nodes (analogous to cell bodies) that communicate with other nodes *via* connections (analogous to axons and dendrites), with multiple layers (an input layer, an output layer, and a hidden layer between them) of connected mathematical functions. ANNs can capture complex nonlinear relationships in data, allowing for sophisticated supervised and unsupervised learning tasks[28,29,32].

Support vector machine (SVM) is another type of MLA. This method organizes data by variable classes in a nonlinear modality, subsequently separating by a hyperplane and forming multidimensional planes in space using these data. It can be used for classification or regression problems[34].

AI APPLIED FOR THE PREDICTION OF MORTALITY IN THE WAITING LIST

MLA has shown promising results for predicting 3-mo mortality on the waiting list. The simulation model was based on OCTs. OCTs were fed with > 1.6 million observations and trained, validated, and tested. The result showed a slightly superior AUROC than MELD-Na for predicting death or unsuitability for LT (0.859 *vs* 0.841). The authors argue that this system would save at least 418 more lives annually in the US[35]. An interesting point in this simulation model compared with MELD was the increased allocation of livers to non-HCC patients and a decreased number of waitlist deaths and removals for both HCC and non-HCC patients. Their results await further validation.

Cucchetti *et al*[36] applied an ANN model to predict the 3-mo mortality of patients awaiting LT in the pre-MELD era. The analysis included only laboratory values (liver biochemical and function tests, creatinine, and hemogram). The participants were randomly divided into training and testing groups in a proportion of 75%-25%. After each of the 10 training sessions, ANN was tested on the remaining individuals who were not selected for training. The most accurate ANN system was tested in a retrospective cohort in another LT center. The performance of ANN in predicting the 3-mo mortality was superior to that of MELD (AUROC, 0.98 *vs* 0.86). Results were similar for the external validation cohort (0.96 and 0.86, respectively).

AI APPLIED FOR LA

Hundreds of variables contribute to multiple decisions made in an organ transplant. For each record, the UNOS database collects > 400 parameters. AI can theoretically improve the outcomes of allocation strategies[30,31]. An optimal outcome would be a decreased number of retransplant procedures, excellent graft and overall survival, and decreasing rate of waiting list mortality.

In a large multicenter Spanish study, Briceño *et al*[37] applied 57 variables (26, 19, 6, and 6 from the recipient, donor, retrieval procedure, and transplant procedure, respectively) for each donor-recipient pair to predict 3-mo graft survival. A total of 1003 liver transplants were analyzed. This sample had been previously described in a pilot study by the same group of researchers[38]. The following were the two models of ANN used: a positive-survival (PS) model to predict the 3-mo graft survival rate after LT and a negative-survival (NS) model to predict the 3-mo graft failure rate. These ANN models are MLAs that simulate a biological neural system. In this study, 90% of the data was used for training and 10% for testing, which was repeated ten times to allow all patterns to participate in both phases. Subsequently, the model that correctly classified the most D-R pairs was chosen. PS methodology was slightly superior to common statistical methods (multiple regression, MR) to predict graft survival (90.8% *vs* 87.7%). NS methodology performed worse for predicting graft loss; however, it was far superior to MR (71.4% *vs* 3.4%). Finally, the AUROC curves were compared with previously reported scores (MELD, D-MELD, DRI, P-SOFT, SOFT, and BAR). In the PS model, ANN had an AUROC of 0.81, significantly higher than that of other conventional statistical methods (which varied from 0.42 to 0.68). In the NS model, NN had an AUROC of 0.82, which was also significantly higher than that of the other scores (which varied from 0.42 to 0.61). Of the previously reported scores, BAR showed the best AUROC results.

Ayllón *et al*[30] applied D-R pairing with ANN on 858 cases in a large-volume LT center (King's College Hospital). They used the same PS and NS models described by Briceño *et al*[37], with some differences in the included variables. AUROCs for PS (0.94) and NS (0.94) 3 mo after LT were significantly more accurate than that of BAR, which is the second-best score (AUROC, 0.84). Furthermore, the researchers performed a 12-mo analysis, and when ANN was used to predict graft survival and loss (0.78 and 0.82, respectively), their results were better than that of the best prediction achieved by other scores (BAR, 0.71).

Lau *et al*[39] applied ML techniques in an Australian single-center study with 180 LTs. A bootstrap sample containing approximately 63% of the cases was used for the training set, and the remaining data were used for testing. This process was repeated 1000 times. RF classifiers and ANN were used on the overall top 15 ranked characteristics to determine the performance as measured by AUROC values. Graft failure (NS) within 30 d was the primary outcome, and NS at 3 mo postoperatively was the secondary outcome. The results were subsequently compared with those of DRI and SOFT scores. The AUROC for the 30-d NS was 0.818 with RF and 0.835 with NN compared with 0.64 and 0.68 with SOFT

Table 1 Overview of original works on artificial intelligence applied to liver allocation

Ref.	Sample size and location	AI model(s)	Outcomes analyzed	Results	Comments
Briceño <i>et al</i> [37], 2014	1003 LT recipients (multicenter in Spain)	ANN with PS and NS model with D-R pairing	3-mo Graft survival (PS); 3-mo Graft failure (NS)	AUROC 0.81 (PS); AUROC 0.82 (NS)	Superior to BAR score (0.68 for PS, 0.61 for NS). Other conventional statistics fared worse
Ayllón <i>et al</i> [30], 2018	858 LT recipients (single-center in England)	ANN (PS and NS) with D-R pairing	3-mo Graft survival (PS); 3-mo Graft failure (NS)	AUROC 0.90 (PS); AUROC 0.90 (NS)	Superior to BAR score (AUROC 0.71). Same model above on a different population (external validation)
Lau <i>et al</i> [39], 2017	180 LT recipients (single-center in Australia)	ANN and RF	30-d and 3-mo Graft failure (NS)	30-d prediction: AUROC 0.82 (RF) AUROC 0.835 (ANN)	Superior to SOFT and DRI scores
Guijo-Rubio <i>et al</i> [40], 2021	20456 LT recipients (5-yr survival) to 37646 LT recipients (3-mo survival) UNOS database	ANN, RF, DT, SVM, MLP	3-mo, 1 yr, 2 yr, 5 yr survival	AUROC up to 0.618 (3-mo), 0.614 (1-yr), 0.611 (2-yr), 0.644 (5-yr)	No superiority compared to conventional statistics (LR was slightly superior)

AI: Artificial intelligence; ANN: Artificial neural network; AUROC: Area under the receiver operating characteristic curve; BAR: Balance of risk; DRI: Donor risk index; DT: Decision tree; D-R: Donor-receptor; MLP: Multilayer perceptron; NS: Negative-survival; LT: Liver transplantation; LR: Logistic regression; PS: Positive-survival; SOFT: Survival outcomes following liver transplantation; SVM: Support vector machines; RF: Random forest; UNOS: United network of organ sharing.

and DRI scores, respectively. The AUROC decreased to 0.715 with RF and 0.56 with NN to predict the 3-mo NS (including 90 cases in the analysis).

Contrastingly, MLA did not prove to be superior to LR for predicting survival after adult LT using donor-recipient matching in a large database[40]. Four different survival endpoints were analyzed using the UNOS database, including 3-mo and 1-, 2-, and 5-year survivals, varying from 37646 transplants in the 3-mo analysis to 20456 transplants in the 5-year analysis. A total of 28 variables were considered, including recipient, donor, and matching variables. Several types of MLA were used, including ANN, RF, DT, and SVM. The researchers suggested that this lack of accuracy of MLA could be ascribed to database limitations. The highest AUROCs were obtained with LR, followed by RF.

Table 1 summarizes the original works on AI applied to LA that were discussed above.

A systematic review of AI for predicting post-transplant survival was performed by Wingfield *et al* [34] Nine publications were included, and articles were considered of good quality overall. ANN and LR were the most common types of MLA and conventional statistical methods, respectively. MLAs were similar or superior to conventional statistics.

CONCLUSION

Although prioritization criteria have successfully reduced mortality in the waiting list, there is room for refinement in mortality prediction and a growing need for improving LA guidelines. Conventional statistical methods have, thus far, failed to provide a useful and widely applicable allocation score. AI can bring meaningful insights to this field. Paradoxically, MLA could help improve the ethics of LA, increasing waitlist and post-transplant survival, preferably with quality-adjusted life-years gained. The results obtained, thus far, are promising; however, we must consider the limitations of AI in medicine. First, its accuracy depends upon the availability of accurate, organized, and thorough datasets. In this regard, the algorithms also depend upon the data used to feed them, and regional particularities can limit their validation. Further, the clinical relevance of the results must be properly evaluated by experts in the field. Moreover, it can be challenging for the lay population to understand and accept LA decisions based on AI analysis. Finally, the health providers must make the final decision, at least while the concepts of ethics and justice rest upon the human mind.

FOOTNOTES

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