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Artificial intelligence and liver transplantation; literature review

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ABSTRACT

Liver transplantation is the last life-saving solution for patients with end stage liver disease. The discrepancy between waiting list and available organs has led to the appearance of extended donation criteria and the development of several scores (Child-Pugh score, MELD score, DRI score, SOFT score), in order to find the most suitable donor-recipient match. But none of these scores can predict survival after transplantation. Artificial Intelligence (AI) has recently been shown as an excellent tool for the study of the liver and comes in this aid with its various methods (random forest, artificial neural networks, decision tree, Bayesian networks, and support vector machine). *Materials and Methods.* By reviewing the literature (mostly retrospective multicenter studies), we aimed to establish if the AI is a proper or even a more accurate method of predicting posttransplant survival, in comparison with the existing linear statistical models. *Results.* Machine learning showed better results than several current scoring systems that use either isolated donor/recipient scores or combined donor/recipient factors. The advantages of this model are its capacity for analyzing both linear and nonlinear relationships between features and outcomes, its robustness of overfitting by design, and built-in insights into feature importance aiding model explainability. Nevertheless, machine learning has its limitations because it requires large amounts of data, which can be difficult to obtain, it also requires high levels of technical skill, can be difficult to engineer and it's expensive. *Conclusion.* AI may have significant potential in aiding clinical decision-making during liver transplantation, including donor-recipient matching.

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Introduction

Artificial intelligence (AI) refers to the simulation of human intelligence in machines that are designed to think and learn in ways similar to humans. These machines, often referred to as intelligent agents, are capable of performing tasks that typically require human intelligence. The key aspects of AI are: learning, reasoning, perception, natural language processing and autonomous operation [1].

AI can be divided into: machine learning (ML), deep learning (DL), neural networks (NN) and natural language processing (NLP).

Since its discovery, AI is being used in healthcare, finance, transportation, retail and entertainment. AI is revolutionizing liver transplantation by enhancing the evaluation, planning, and post-operative management of transplant procedures [1-3]. If we talk about pre-transplant evaluation, AI can analyze vast amounts of data from both

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recipients and donors and find the best matches. AI cand also predict posttransplant survival and can corelate the factors that contribute to positive outcomes.

Also, by studying the liver imaging (CT or MRI scans), AI can properly evaluate the graft structure, the anatomical variations, the remaining liver volume (especially in living donors) and can prevent potential complications [2-4].

AI has an important role in surgical planning, also. By analyzing all the data, AI helps the surgeon preview virtually the possible complications after surgery, the appropriate approach, the unexpected intraoperative complications. More than that, the surgeon can have real-time guidance in the operating room or robotic assistance [5].

Regarding post-transplant care, AI can provide real-time monitoring, can evaluate patients' vital signs and health metrics, detecting early graft reject, sepsis or liver failure. Furthermore, ML algorithms adjust treatment plans based on how different patients metabolize drugs, the response to therapy and individual risk of rejection. In addition, ML can help develop new drug therapies, by analyzing biological data, adherence to treatment, adverse reactions, drug interactions, body interactions and thereby improving the outcomes [6].

Although AI can be very useful and very rapid, we must take into consideration the ethical implications and ask ourselves who will be responsible in case of medical error, AI or the doctor?

This review of the literature aimed to identify the role of AI in liver transplantation. We searched retrospective studies and key words like "artificial intelligence", "liver transplantation", "liver", "posttransplant survival", "random forest", "artificial neural networks", "decision tree", "Bayesian networks", "support vector machine", on PubMed Central, NCBI, Embase, MedLine, Web of Science, Elsevier, Google Scholar, Cochrane Library. We reviewed over 100 articles, written in English, articles written in other languages being excluded.

Discussions

The role of AI in pre-transplant phase

Neural networks (NNs) are considered a form of ML and consist of a single (shallow) or multiple (deep) hidden layers between input and output, each containing artificial neurons, or nodes, which allow a better interpretation of non-linear relationships.

In LT, AI is used with considerable outcomes for organ allocation, D-R matching, post-LT survival or graft failure.

Nagai et al. created a NN to predict 90-day LT waitlist mortality, using the UNOS database from 2002 to 2021 from which patients who were transplanted within 90 days of listing were excluded. The study concluded that NN algorithm outperformed MELD and MELD-Na scores, with an AUROC (area under the receiver-operating characteristic curve) of 0.936 vs. 0.860 [1,2].

Using pre-transplant donor and recipient data, AI can predict with higher accuracy short and long-term survival [3].

AI and graft assessment

There are two types of grafts. The first one is TLG (transplantable liver graft) which means a liver graft accepted by telephone, that also passed the "in situ" evaluation. The second one is NTLG (non-transplantable liver graft) which means a liver graft accepted by telephone, but then discarded after "in situ" evaluation.

Spain reported that 13.1% of the potential liver grafts are discarded initially and 27.6% after an "in situ" assessment. In present times, the two most frequent reasons for discarding a liver are hepatic steatosis and the macroscopic aspect of the graft [4].

A study published in 2023, on a total of 350 liver grafts (123 NTLG, 227 TLG), donor brain death (DBD) only, aimed to demonstrate the use of AI in predicting if a graft is suitable for use or not.

They compared the data used in liver donation protocol (LDP-a document filled by the surgeon regarding every organ that he evaluates) with those procured by the ML algorithms and concluded that AI is more accurate in predicting the TLG grafts rather than the NTLG [5].

Moccia et al. provided an algorithm that evaluates graft steatosis. They compared smartphone images of 20 accepted graft vs 20 discarded grafts investigating the intensity-based features (INT), histogram of local binary pattern (HLBPriu2) and blood-sample features (Blo), then using a mathematical formula (HLBPriu2 + INT + Blo) obtained a sensitivity, specificity and accuracy of 95%, 81% and 88% [6].

AI and donor-recipient matching

A very important manner in liver transplantation is donor-recipient matching (D-R). The improvement in surgical procedures, diagnosis, postoperative complications management and the development of liver preservation machines had led to increasing graft and recipient-survival rates (>95% at 1 year) and long-term survival rates. Nevertheless, the biggest problem remains the discrepancy between candidates and donor pool [7].

Today, AI applications in hepatology are commonly used in diagnostic imaging and image-guided surgery [8].

Prioritization on the waiting list is based nowadays on MELD score. In order to optimize the allocation system and reduce the mortality on the waiting list, Bertsimas et al. invented a model using classification trees called OPOM (Optimized Prediction of Mortality). They've used a dataset from 2002 to 2016 and found a reduction of mortality by 418 deaths per year, in comparison with MELD score [9].

Unfortunately, whatever score system we use, we cannot predict which patient on the waiting list has the highest probability of death or which one has the highest probability of post-transplant success.

Scores like BAR (balance of risk) and SOFT (survival outcome following liver transplantation) are being most likely used in clinical decision-making process [10,11]. SOFT score integrates 13 donor factors, 4 recipient factors and 1 logistic factor and predicts a 3-month mortality post-transplantation.

BAR score on the other hand predicts 90-day morbidity with an AUROC>0.7 and can also discover the unfavorable D-R matches. However, none of those scores can identify the D-R match with the best outcome, because they are not able to adequately balance waitlist mortality with post-transplant graft and patient survival [12].

Any clinical decision has an objective and a subjective component. Machine learning algorithms are able to handle large amount of data in short time and offer an objective point of view in the matter, that's why they can be a reliable alternative to the linear models [13]. But, in order to obtain valid results, ML must include a ruled-based system for allocation criteria.

Ayllón et al. were the first to create a D-R allocation model, the MADRE model. They've studied 2003 liver transplants using 57 variables and established a 90.79% probability of graft survival and a 71.42% probability of graft loss, outperforming the traditional prioritization scores [14].

Most recently, Guijo-Rubio et al. used ANN networks using the UNOS dataset to predict graft survival and graft loss at 3 months and 1,2, 5 years. The results were similar to those obtained by traditional models; the authors concluded that each ANN should be used in the specific trained population and they should gather huge amounts of data in order to give valid results [15].

In other words, the predictability of an AI model depends on the quantity and quality of the database. ANNs for D–R matching can only be applied in very homogeneous databases that follow similar rules for the prioritization and inclusion criteria. Therefore, for the moment, ANNs can only assist the matching decision [16].

AI and recipient comorbidities

A study from Spain, published in 2023, aimed to analyze the predictive value of candidate comorbidities in graft survival within the first year post-LT, comparing traditional and AI algorithms [17,18].

They used 3 groups of variables: donor data (age, sex, cause of death, donation after cardiac death, donation after brain death), recipient data (age, sex, weight, height, systemic comorbidities, cardiopulmonary comorbidities, infectious comorbidities, surgical comorbidities, oncological comorbidities) and transplant data (time on the waiting list, cold ischemia time, patient death, survival time, liver graft function) [19,20].

The variables with the most predictive power were age (recipient and donor) and 3 comorbidities (antiplatelet and/or anticoagulant treatment-78.4%, previous immunosuppression-69.6%, portal vein thrombosis-66.3%). The model showed a significant C statistic of 0.745 [17].

AI and postoperative sepsis

The risk factors associated with infection after liver transplantation include a high MELD-score, re-transplantation, advanced age of the recipient, history of blood transfusion, dialysis, and a long ICU (intensive care unit) stay [18].

A retrospective study published in 2021 by Kamaleswaran and al. about the use of AI in predicting early sepsis (Sepsis-3 definition) after liver transplantation analyzed a cohort of 5.748 patients over 36 months, between January 2017 and January 2020 [19]. They divided the dataset into two groups: the first group included all non-transplanted patients who were admitted to the ICU at least 31 days prior to admission, and the second group included all patients who underwent transplantation [20].

They analyzed with several ML algorithms the systolic blood pressure (SBP), diastolic blood pressure (DBP), the respiratory rate (RR), mean femoral artery blood pressure (MAP) and oxygen saturation and concluded that SBP, DBP along with changes in respiratory rate, were the most predictive factors, that were present at least 12 hours before a clinical manifestation appeared [20-22].

AI and transplant oncology

The most common treated disease in transplant oncology is hepatocarcinoma (HCC), followed by hilar cholangiocarcinoma and colorectal metastases [21,22].

There are several early prediction models in the literature. First of them is the Milan criteria which finds the HCC patients in whom the tumor is small enough to allow good outcomes after transplantation. It includes one lesion ≤ 5 cm or 3 lesions each measuring <3 cm, no vascular invasion, no metastases. In that seminal study, the 5-year survival in patients transplanted within the Milan criteria was 70%, which was equivalent to liver transplantation for other indications [22]. Another model is MORAL (Model of Recurrence After Liver Transplantation) which identifies pre-liver transplantation (pre-MORAL) (neutrophil-lymphocyte ratio-NLR ≥5, alfa-fetoprotein-AFP>200, tumor size >3 cm) and post-liver transplantation (post-MORAL) (grade 4 HCC, vascular invasion present, tumor size>3 cm, tumor number>3) predictors. Both of these scores outperformed the Milan criteria at predicting recurrence with c-statistics of 0.82, 0.87 compared with 0.63 [23].

The AFP score developed in France, managed to identify a group of patients that, although didn't fit the Milan criteria, could have a good outcome after liver transplantation [24].

The Metroticket 2.0 model combined the AFP values, tumor size, tumor number and had a 0.721 accuracy on 5 years survival after liver transplantation, outperforming as well the Milan criteria [25].

Using noninvasive variables collected from 250 patients, Halazun et al. came up with an artificial neural network (ANN) that outperformed the linear model in predicting tumor grade and microvascular invasion. Also, they've developed a system to predict post-transplant recurrence and obtained an AUC of 0.768, outperforming the models mentioned above [26].

AI and volumetry

Short donor pool and cultural barriers has led to alternatives for LT, one of them being the living donor. For that to happen and to have a favorable outcome, donor liver volumetry (LV) and anatomical study is imperative if we want to secure graft volume, liver resection, donor safety, appropriate graft-recipient weight ratio [27]. Nowadays the gold standard in volumetry is represented by manual liver volumetry (MLV) using CT and MRI scans on portal venous phase and cholangio-sequences respectively, but the method has some limitations like cost, subjectivity, time-consuming or variability, with a percentage of error of 2%-20% [28,29]. The utility of AI in this manner is thought to increase accuracy, efficiency, safety, speed and lower the cost [30].

In order to achieve an optimal post-LT outcome, the donor must be carefully evaluated and he must be offered postoperative security. Thus, a future liver remnant (FLR) of 30-35% is required and a graft recipient weight ratio of 0.8 to 3-3.5, in order to avoid "small for size" or "large for size" syndromes [31]. Another problem that appears in this case is the actual graft weight (AGW). It is considered that the density of the liver equals the density of water, therefor AGW represents faithfully the graft volume [32,33]. Some errors may thus appear because MLV is not able to exclude the liver blood volume as demonstrated by Tongyoo et al. [34].

Therefore, semi-automated and automated image processing models have been imagined in order to outcome these boundaries [35]. Goja et al. discovered that semiautomated models can better measure the real right lobe graft and that left lobe is often underestimated because the surgeons' plane of transection is 1 cm to the right of the falciform ligament, whereas the radiologist plane is in the middle of the ligament [36].

A group of scientists from Korean Republic imagined an automated model named Dr. Liver through which they evaluated the right lobe donor graft (RLDG) compared with MLV. Their findings were: better correlation with AGW (0.98 vs 0.92), an absolute difference percentage (%AD) significantly lower for the model 3.1%±2.8% vs 10.2%±7.5% (a %AD >10% can cause small for size syndrome) and also the time was shorter for the automated model, 7.3±1.4 min vs 37.9±7.0 min [37].

Post-transplant

Several studies used ANNs with different data types to predict graft failure within the first 3- or 12-months post-LT. They used longitudinal clinical and laboratory data collected up to 2 weeks after transplant and achieved an AUROC of 0.90-0.96 [36,37]. Another study used NN algorithms with recipient and donor variables to predict graft failure within 30 days post-LT and achieved an AUROC of 0.818 [38].

Although the short-term LT recipients' outcomes have been improved, long-term outcomes beyond 1 year remain suboptimal because of the complications associated with immunosuppression and comorbidities. Several studies using ANNs and NNs have shown AUROC of 0.81-0.96 in predicting HCC recurrence, acute kidney injury (AKI), major cardiac events, high risk of new-onset diabetes post-LT, biliary complications, the risk of graft vs host disease [39-41].

AI and improving the expenses

Total costs for a liver transplant procedure range between 80,000 and 120,000 €, depending on the ET (Eurotransplant) country and region. Therefor the postoperative course of the patient has a crucial impact on healthcare expenses [42,43].

According to eurotransplant.gov, in 2019, within the ET region, 13.985 patients were listed for transplant. Out of these patients, 1.417 underwent LT. Due to donor pool shortage, 383 potential liver transplant candidates died while on the waiting list.

A model of improving allocation and reducing the waiting on the transplant list is required.

In this aid a large Spanish multicenter trial used AI for donor-recipient matching and demonstrated superiority over currently used allocation strategies, especially in terms of graft survival, 90.79% survival and 71.42% graft-loss [43-46]. The results were also validated on a study performed by King's College Hospital [44].

Achieving better outcomes in liver transplantation implies a lower economic investment compared with dysfunctional grafts. Better D-R matching leads to better outcomes which leads to lower costs on long term and, in the end, to obtaining individual and social benefits [41].

AI and ethics

Although AI showed its benefits in medical area, when we speak about organ allocation the first question that pops up is an ethical one: who should receive a life-saving resource?

Nowadays, even if humans decide the organ allocation, policies are transparent and publicly available [44].

United States (US) came up with a pilot program for allocation, that ranks the candidates based on cumulative weight of specific factors (waiting list survival, post-LT survival, biological factors, patient access, placement efficiency) [45]. The benefits are yet to be obtained.

A pilot study performed in 2023 in United Kingdom (UK) analyzed the public opinion on using AI in organ allocation. The 172 UK laypeople recruited, median age 35-44, found AI acceptable in organ allocation (69.2%) and will still donate if AI allocated their organ (72.7%). They valued the accuracy, impartiality and consistency of AI, although they were concerned about the healthcare dehumanization. The main characteristics to be prioritize were: greater urgency, survival likelihood, life years gained, younger age, future medication compliance, quality of life, lower future and previous alcohol use [46].

From an ethical point of view, there are three barriers to overcome. The first is the “black box issue,” this lack of transparency can be problematic in medical contexts where understanding the rationale behind decisions is important. The second is privacy and data security. The patient must understand the benefits and risks and must be informed about how their data will be used in AI systems and should consent to its use. And last but not least problem is finding the proper answer to the following question: Who is responsible if the model fails? [47-57].

Benefits of AI

AI can analyze large datasets to match donors and recipients more accurately based on multiple criteria such as tissue compatibility, blood type, and genetic markers, improving the chances of transplant success.

AI models enhance the accuracy of imaging techniques like CT and MRI scans, providing detailed assessments of liver anatomy and volume. Also, AI can create detailed 3D models of the liver, aiding surgeons in planning the surgery by visualizing the organ's structure and potential complications.

AI can analyze biological data to accelerate the discovery of new drugs and therapies, can identify suitable candidates for clinical trials and predict potential outcomes, streamlining the development of new treatments [49-54].

Limitations of AI

The quality of the data output from machine-learning systems depends on the quality of the data input. Objective data is thus favored over subjective data, which is inherently prone to bias and carries the potential of diminishing data output [48,56].

Integrating AI tools into existing clinical workflows can be challenging and may require significant changes to how healthcare professionals operate. Healthcare professionals need training to effectively use AI tools, and there may be resistance to adopting new technologies.

The use of AI in healthcare raises ethical questions about decision-making, patient consent, as well as the transparency of AI algorithms.

Over-reliance on AI could lead to reduced human expertise and skills in critical areas of liver transplantation [57].

Conclusions

Artificial intelligence represents a broad and rapidly advancing field that encompasses various technologies and applications aimed at creating machines capable of performing tasks that require human intelligence. Its potential benefits are vast, but it also possesses significant challenges and ethical questions that society must address as the technology continues to evolve.

The integration of AI in liver transplantation is transforming the field by improving accuracy, efficiency, and outcomes at every stage of the process. From pre-transplant evaluation to post-operative care, AI provides valuable insights and support, helping to ensure the success of liver transplants and enhancing patient care. As technology continues to advance, the role of AI in liver transplantation is expected to grow, offering even more innovative solutions to complex medical challenges.

The main limitation of the development of this technology is the lack of data. AI needs large databases to serve as a source of information in order to develop new models of data analysis and interpretation and to improve the existing ones.

Physicians in the field of transplant oncology can become actively involved in applying machine learning through working with data scientists to collect meaningful clinical data (e.g. patient clinicopathologic information, tissue samples, and appropriately protocolled images).

Maybe the most difficult thing in resolving a problem with the help of AI is selecting the most appropriate classifier.

AI has the potential to significantly enhance liver transplantation, improving outcomes and efficiency. However, it also brings forth ethical challenges that must be carefully navigated. Addressing issues of bias, transparency, accountability, privacy, and equitable access is crucial to ensure that AI is used responsibly and ethically in liver transplantation.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. Informed consent was obtained from all subjects involved in the study.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

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