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Advances in Organ Transplantation and The Role of Artificial Intelligence in Enhancing Transplant Pathology: Review

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Abstract

Background: Organ transplantation is a critical medical intervention for individuals with end-stage organ failure, yet the disparity between the demand for and supply of donor organs remains a significant challenge. Traditional diagnostic methods in transplant pathology often suffer from variability and subjectivity, which can lead to suboptimal patient outcomes. Recent advancements in artificial intelligence (AI) offer promising solutions to enhance diagnostic precision and efficiency.

Methods: This review examines peer-reviewed literature from databases such as Web of Science and PubMed, focusing on the application of deep learning-based AI techniques in transplant pathology up until June 2023. We analyze AI's impact on various transplant organs, including heart, lung, kidney, and liver, emphasizing its role in diagnosing transplant-related diseases and improving organ allocation processes.

Results: The integration of AI in transplant pathology has demonstrated significant improvements in diagnostic accuracy. For instance, AI models have achieved a high area under the curve (AUC) values in detecting cardiac allograft rejection and differentiating between rejection grades in kidney biopsies. Furthermore, AI-enhanced digital pathology tools have shown the potential to reduce inter-reader variability among pathologists and facilitate remote consultations.

Conclusion: The incorporation of AI into transplant pathology represents a transformative advancement in the field, promising to enhance diagnostic processes, optimize immunosuppressive therapy, and ultimately improve patient outcomes. However, challenges such as dataset variability and the need for multi-institutional validation remain. Continued research and development of robust AI models are essential for realizing their full potential in clinical practice.

Keywords: organ transplantation, artificial intelligence, transplant pathology, diagnostic accuracy, immunosuppressive therapy.

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1. Introduction

The Centers for Disease Control and Prevention (CDC) identifies the liver, kidneys, lungs, pancreas, intestines, and heart as the most frequently transplanted organs in the USA. Despite about 100,000 individuals awaiting organ transplants daily, the availability of organs remains constrained. Approximately 14,000 dead organ donors are available, each contributing an average of 3.5 organs, but live donors provide just 6,000 organs annually. In the standard of care for organ transplantation, both donors and recipients receive a pre-transplant evaluation of histocompatibility, pathology, and clinical history. Upon identifying a matched couple, the organ transplantation will commence and thereafter undergo monitoring. Post-transplant monitoring includes the study of electronic medical records (EMR), evaluation of blood and bodily fluids for organ function, and the development of donor-specific antibodies, as well as routine biopsies in cases of suspected rejection [1].

Recent breakthroughs in deep learning-based artificial intelligence have transformed digital pathology by facilitating the creation of AI-enhanced diagnostic models for the analysis of digitized glass slides of biopsy specimens. AI-enhanced digital pathology can significantly aid transplant pathology by diminishing inter-reader variability among pathologists, facilitating teleconsultation for pre-and post-transplant evaluations, offering second opinions, and assessing various morphological parameters along with their spatial relationships. Numerous AI models have been created over the years to evaluate transplant-associated diseases of the heart, lung, kidney, and liver [2-5]. Transplant pathology is a specific domain where AI-enhanced digital pathology tools may assist pathologists in improving decision-making and minimizing diagnostic variability. Besides advancements in transplant pathology, AI has been used in organ allocation and donor-recipient matching, transplant oncology, and immunosuppressive treatment [6-11].

Despite the remarkable achievements of AI models in synthesizing information from diverse data sources (such as histopathological reports, laboratory test results, radiological characteristics, and patient demographics), this review concentrates on the AI-enhanced analysis of whole-slide images (WSIs), which is fundamental to diagnosis and prognosis in transplant pathology. This study aims to elucidate the improvements of AI in the diagnosis and prognosis of transplant-associated heart, lung, liver, and kidney diseases. Additionally, we provide insights on the future direction of AI-assisted methodologies in transplant pathology. Figure 1 illustrates a flowchart of AI-assisted transplant pathology. A web-based paradigm for transplant pathology is proposed in Akkus et al. [12]

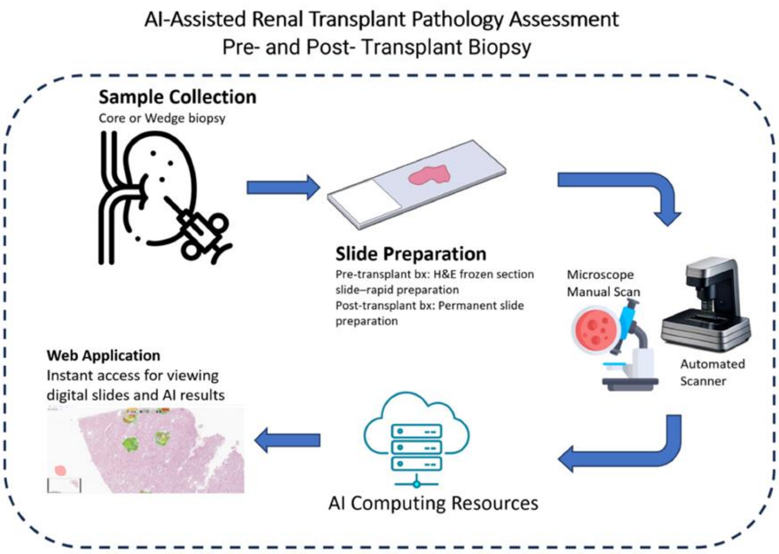

Figure 1. A representation of an AI-enhanced kidney transplant pathology process.

2. Methods

We conducted a comprehensive review of the literature using the Web of Science and PubMed databases. We included peer-reviewed journal articles and conference proceedings concerning the use of deep learning-based artificial intelligence to transplant pathology prior to June 2023.

3. Advancements in Artificial Intelligence in Transplant Heart Pathology

Cardiac allograft rejection is a significant issue in heart transplantation, partly because of the restricted supply of donor organs. While endomyocardial biopsy with histopathology grading is the standard procedure for diagnosing cardiac allograft rejection, significant inter- and intra-observer variability among pathologists can lead to inappropriate administration of immunosuppressive medications, unnecessary follow-up biopsies, and compromised transplant outcomes [12].

To far, four research have examined the use of artificial intelligence in evaluating cardiac transplant rejection and predicting survival. Giuste et al. [13] investigated synthetic picture synthesis to enhance the risk assessment of infrequent pediatric heart transplant rejection. They used advanced and motivational Generative Adversarial Networks (GANs) to produce high-resolution synthetic pictures with rejection indicators, which enhanced the efficacy of their allograft rejection classifier model. Notwithstanding their constrained dataset of merely 12 non-rejection and 12 rejection slides, their methodology markedly enhanced the efficacy of their allograft rejection classifier model, attaining an area under the receiver operating curve (AUC) of 98.84% for image tile-based rejection detection and 95.56% for biopsy rejection prediction at the whole slide image (WSI) level.

Peyster et al. [2] introduced an automated whole slide imaging analysis pipeline using handcrafted feature extraction and selection for the histological grading of cardiac transplant rejection. Their research group included 2,472 biopsy slides from three prominent US transplant hospitals. Their model's performance was analogous to the agreement among pathologists (65.9% vs 60.7%). This work, although not fulfilling our inclusion requirements, is referenced for comparison with deep learning-based AI models. A weakness of this research is that the ground truth diagnostic label was derived from the computerized grading of a single tissue segment, while pathologists evaluate many slide sections microscopically to get a consensus final grade. Subsequently, Lipkova et al. [14] released a work using deep learning to evaluate cardiac transplant rejection from whole slide images of endomyocardial biopsies. Their model exhibited allograft rejection with a remarkable AUC of 0.962, representing a substantial improvement over the research conducted by Peyster et al. [2], which used manually constructed features and a traditional machine-learning methodology.

The AUC for distinguishing between low and high-grade rejection was reported as 0.83. They used a pre-trained CNN model to extract features from picture patches inside their pipeline, subsequently fine-tuning three fully connected layers, while a distinct classifier was developed to assess the rejection grade. The model was trained on 80% of 1690 internal WSI image datasets and verified using two external datasets: 1717 WSI slides from 585 patients in Turkey and 123 WSI slides from 123 patients in Switzerland. Finally, Glass et al. [15] optimized a pre-trained VGG model to forecast myocyte injury in acute cellular rejection (ACR) of cardiac transplants. The authors annotated 19,617 areas, including 10,855 regions of ACR, 5,002 of healing damage, and 3,760 of normal tissue from 200 H&E slides, and reported a validation accuracy of 94%.

4. Advancements in Artificial Intelligence in Lung Transplant Pathology

Notwithstanding advancements in immunosuppressive therapies and pharmacological agents, one-third of lung transplant recipients encounter at least one instance of treated acute rejection within the first year post-transplantation, as reported by the International Society of Heart and Lung Transplantation registry [16-20]. Conversely, statistics from the Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients reveal a reduced incidence of under one-fifth in the first year [21]. Gholamzadeh et al. [22] conducted a comprehensive systematic study of conventional machine-learning approaches aimed at enhancing lung transplantation results and mitigating complications. We concentrated only on research of deep learning-based AI in our evaluation and directed readers to their publications for more information.

Davis et al. [3] conducted significant research on the detection of acute cellular rejection (ACR) in lung transplant biopsies with artificial intelligence. Board-certified lung transplant pathologists provided 3349 annotations, including 2580 patches of normal tissue and 769 lesions indicative of A1/A2 rejection. The training set included 614 A1/A2 lesions and 2064 areas of normal tissue. The validation set included 155 A1/A2 lesions and 156 normal areas to assess the efficacy of their AI model. Their AI model successfully differentiated the vascular component of ACR from normal alveolated lung tissue with a validation accuracy of 95%. During our investigation, we discovered a singular work concerning lung transplant pathology using AI and another study addressing donor-recipient matching with AI [23]. Davis et al. [3] reported encouraging findings in the identification of ACR, associated with chronic lung allograft rejection, in lung transplant recipients. The primary constraint of their study is the absence of multi-institutional validation testing.

5. Advancements in Artificial Intelligence in Renal Transplant Pathology

Kidney transplantation is the most often performed solid organ transplant globally. As reported by the United Network of Organ Sharing (UNOS), over 25,000 kidney transplants were conducted in the USA in 2022, representing a 3.4% increase compared to 2021 [24]. Despite the increasing demand for kidney transplantation, the pathology sector is seeing a reduction in the available manpower. According to the Organ Procurement and Transplantation Network (OPTN), there are 88,629 individuals in the United States awaiting a kidney transplant as of July 23, 2023 [25]. According to transplants performed from 2008 to 2015, the five-year post-transplant survival rates for men and females are 85.85% and 88.2%, respectively [26]. Despite its novelty in this domain, the use of AI might be advantageous in several aspects, including enhancing the matching process between donors and patients, evaluating the histology of kidney biopsies, and directing the treatment and care of transplant recipients. The predominant kidney biopsy grading methods are Remuzzi, Banff, Leuven, and the Maryland Aggregate Pathology Index (MAPI) [27-34].

Hermsen et al. [31] used a UNet architectural CNN model for the multiclass segmentation of digitized kidney biopsy tissue sections stained with periodic acid-Schiff (PAS). The model underwent training on 40 whole slide images (WSIs) and was verified using 10 WSIs from its home institution and 10 WSIs from an external university. In a separate investigation, Hermsen et al. [32] trained a UNet model to evaluate inflammatory and chronic characteristics in kidney transplant samples. Kers et al. [33] examined the efficacy of several CNN topologies in predicting transplant rejection. The research used retrospective multicenter data, including 5844 digital whole-slide pictures of kidney transplant biopsies collected from 1948 individuals. A three-fold cross-validation method was used, and an external dataset including 101 whole slide images was deployed for assessment. This research is limited by its focus on Western European institutions, the absence of ethnicity data owing to legal constraints, the lack of specific baseline features, and limited staining variability.

Smith et al. [4] used a binary thresholding technique and trained a UNet model for glomeruli segmentation to evaluate interstitial inflammation from CD45-stained digital slides. The research included 60 samples from 53 individuals and identified a robust association between the automated inflammatory grading and the Banff scoring system. The drawbacks of this work include an emphasis on pixel counting instead of cell counting, possible intricacies in the use of a deep learning methodology, and a retrospective design that offers low statistical power [35-37]. Wilbur et al. [38] trained an adapted version of the AlexNet CNN network to detect glomeruli in renal biopsies using four stains (H&E, trichrome, silver, and PAS) from various institutions. The research included 71 biopsies, divided into training/validation (n = 52) and testing (n = 19) groups. The authors underscored the significance of varied datasets for creating generalizable AI models. The model's sensitivity varied from 90% to 93% for the intra-institutional dataset, compared to 77% for the inter-institutional dataset. Moreover, several review articles addressing AI in kidney transplantation and the evaluation of renal transplant prognosis by traditional machine learning methodologies are accessible for interested readers in the supplementary resources [27,39-43].

6. Advancements in Artificial Intelligence in Liver Transplant Pathology

Similar to other organ transplants, Liver Transplantation (LT) is an essential intervention for individuals with end-stage liver disease. Recent breakthroughs in surgical methods, greater administration of immunosuppressive medications, and a deeper knowledge of post-transplant morbidities have resulted in a substantial rise in liver transplantation surgeries. The increase in demand has therefore caused a shortage of organ donors, leading to a significant waiting list for liver transplant candidates [44]. Despite the imbalance between organ supply and demand, more than one-third of donor livers are rejected owing to the potential for early allograft dysfunction (EAD), as shown by histopathologic abnormalities [45]. The management of LT is intricate, and the existing methodologies are inadequate for clinical decision-making. A data-driven LT may be beneficial in both pre- and post-LT contexts [46-48]. This study domain is relatively new; however, several investigations have already been undertaken. Narayan et al. [49] conducted a study on the use of AI in forecasting donor liver allograft steatosis and early post-transplantation graft failure. They created a Computer Vision AI platform (CVAI) to evaluate donor liver steatosis and assessed its predictive power for early allograft dysfunction (EAD) in comparison to pathologist steatosis scores. The research included liver biopsy slide data from 2014 to 2019, including 25,494 pictures derived from 90 liver biopsies. The findings revealed that the CVAI platform had marginally superior calibration scores compared to pathologist steatosis scores. Their research was primarily constrained by a restricted sample of donor liver from a single institution and the existence of selection bias in the assessment of relation with EAD.

Yu et al. [50] developed a Multiple Up-sampling and Spatial Attention guided UNet model (MUSA-UNet) to delineate hepatic portal tract areas in liver whole slide images (WSI) that are associated with the stage of liver fibrosis. The dataset included 53 whole slide images (WSIs), with 30 allocated for training and 23 for testing. Their model MUSA-UNet achieved an average precision of 0.94, recall of 0.85, F1 score of 0.89, accuracy of 0.89, and Jaccard Index of 0.80. The primary drawback of their work is the need for a more heterogeneous training dataset that includes stain variations and annotations from several pathologists across various institutions.

Lu et al. [5] introduced an enhanced deep learning classifier (MobileNetV2_HCC_class) capable of predicting the recurrence of hepatocellular carcinoma (HCC) after liver transplantation. Their research included 1,118 patients, with 642 allocated for training, 144 for testing, and 302 for validation. The hazard ratio derived from the classifier in the LT set was 3.44 (95% CI 2.01–5.87, $p < 0.001$) and 2.55 (95% CI 1.64–3.99, $p < 0.001$) after adjusting for known prognostic variables.

Sun et al. [51] created a deep learning model based on the pre-trained VGG16 architecture [20] to quantify the percentage of steatosis in frozen sections of donor liver biopsies. Their approach produced a probability map correlating an input WSI with the resultant percentage of steatosis. Their study dataset consisted of 96 whole slide images (WSIs), with 30 slides designated for training and 66 for testing. In the testing phase, their AI model exhibited a significant correlation coefficient (r) of 0.85 and an intraclass correlation coefficient (ICC) of 0.85, both above the performance of the on-service pathologist ($r = 0.74$ and ICC = 0.72).

7. Discussion

This paper delineates the recent achievements in AI-assisted transplant pathology, particularly emphasizing the use of whole slide imaging (WSI). As we enter the new age of digital pathology with the promised capabilities of AI technology, there exists a substantial chance to transform several facets of solid organ transplantation. These developments have the potential to improve organ procurement procedures, optimize the adaptive management of immunosuppressive medications, and promote graft and patient survival via efficient post-transplant monitoring. Significantly, several deep learning-based AI applications have arisen, addressing distinct transplant organs for the accurate evaluation of histopathology in tissue samples. Most of these suggested AI models have been trained mostly on limited datasets and need external validation. To guarantee strong and accurate results, it is essential to possess well-trained and well-verified AI models that evaluate the histology of transplant organ samples. Such AI models will provide the field with vital insights into the decision-making process about organ rejection or acceptance, perhaps forecast adverse outcomes, and drastically diminish postoperative problems. This advancement aims to improve patient care and outcomes in solid organ transplantation, hence advancing transplant pathology significantly.

The histological assessment of organ biopsies is vital in determining the acceptance or rejection of dead donor organs for transplantation and in post-transplant surveillance when rejection is suspected. The primary concern in the existing practice of pre-transplant histopathology evaluation is insufficient concordance across pathologists [52]. The significant diversity and subjectivity among pathologists present a major challenge in biopsy grading, resulting in poor organ use. The diversity in pre-transplant biopsies is due to the quick embedding and fixation techniques used for analysis, leading to frozen artifacts and producing worse quality slides. In contrast, permanent slides with more intricate preparations are used for post-transplant biopsy assessments. Although histopathological evaluation of transplant organ samples requires specific training and professional consultation, pre-transplant biopsies are sometimes assessed by on-call general pathologists. We assert that the integration of digital pathology and the use of AI and informatics technologies might mitigate the significant diversity and subjectivity among pathologists, provide a secondary virtual expert opinion, and enhance clinical workflow efficiency. Adopting these innovations may establish a new epoch in solid organ transplantation, enhancing diagnostic precision and assisting patients requiring life-saving procedures.

The acquisition of transplant organs mostly depends on contributions from dead or non-related persons. Consequently, immunosuppressive medications are given to patients to enhance long-term tolerance to transplanted organs and avert rejections. Monitoring substantial histopathologic alterations in allografts over time is crucial for evaluating transplant rejection and optimizing immunosuppressive protocols to enhance transplant patient outcomes. The incorporation of AI-enhanced digital pathology and EMR data is beneficial, as it facilitates informed decision-making for customizing customized immunosuppressive treatment protocols, thereby improving the care of transplant patients.

Recent advancements have led to the availability of high-throughput digital pathology slide scanners, which are being integrated into clinical processes. Simultaneously, advancements in computer technology, cloud resources, artificial intelligence techniques, data storage, and network speed have enabled the more efficient processing of extensive volumes of WSI data. Furthermore, the accessibility of portable single-slide scanners facilitates fast onsite assessment of pathology slides, which may be advantageous in organ procurement situations. In pathology departments, digital pathology, automated image analysis of whole slide images (WSI) using artificial intelligence, and web/cloud-based applications have arisen, facilitating immediate access to and sharing of WSI and diagnostic findings. These tools provide prompt access to second viewpoints. The use of AI-assisted digital pathology processes has significant promise for enhancing patient outcomes and maximizing organ usage in transplant pathology. Digital procedures, meanwhile, present issues because to their expensive nature. Moreover, guaranteeing the repeatability and generalizability of AI models necessitates the creation of datasets from many organizations and scanners. Moreover, integrating current AI technologies into healthcare operations at scale while preserving efficiency poses significant challenges. Addressing these problems and integrating AI-assisted digital pathology into transplant pathology will be crucial for improving patient care and organ preservation.

8. Conclusions

AI-enhanced digital pathology has shown potential in improving the histopathological assessment of organ samples, with the capacity to reduce variability and subjectivity among pathologists. Although the use of AI in solid organ transplantation is still in its infancy, researchers are actively investigating its comprehensive potential. It is essential to recognize that certain constraints, as previously mentioned, need thorough examination and resolution prior to the extensive deployment of these AI technologies in clinical processes. From a global perspective, cross-border organ transplantation entails considerable complexities arising from various intricate challenges, including the illicit trafficking of human organs, disparities in legal and regulatory frameworks, cultural and ethical divergences, financial and insurance issues, and travel and visa restrictions. All these criteria must be meticulously considered to guarantee the safety, efficacy, and ethical integrity of the operations.

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التطورات في زراعة الأعضاء ودور الذكاء الاصطناعي في تعزيز علم الأمراض المرتبطة بزراعة الأعضاء: مراجعة

الملخص

الخلفية :تعتبر زراعة الأعضاء تدخلاً طبيًا حيويًا للأفراد الذين يعانون من فشل الأعضاء في المرحلة النهائية، إلا أن الفجوة بين الطلب والعرض على الأعضاء المتبرع بها تظل تحديًا كبيرًا. غالبًا ما تعاني طرق التشخيص التقليدية في علم الأمراض المرتبطة بزراعة الأعضاء من التباين والموضوعية، مما يمكن أن يؤدي إلى نتائج suboptimal للمرضى. توفر التقدمات الأخيرة في الذكاء الاصطناعي (AI) حلولًا واعدة لتعزيز دقة وكفاءة التشخيص.

الطرق :تفحص هذه المراجعة الأدبيات التي خضعت لمراجعة الأقران من قواعد بيانات مثل Web of Science وPubMed، مع التركيز على تطبيق تقنيات الذكاء الاصطناعي القائمة على التعلم العميق في علم الأمراض المرتبطة بزراعة الأعضاء حتى يونيو 2023. نقوم بتحليل تأثير الذكاء الاصطناعي على الأعضاء المزروعة المختلفة، بما في ذلك القلب والرئة والكلى والكبد، مع تسليط الضوء على دوره في تشخيص الأمراض المتعلقة بزراعة الأعضاء وتحسين عمليات تخصيص الأعضاء.

النتائج :أثبت دمج الذكاء الاصطناعي في علم الأمراض المرتبطة بزراعة الأعضاء تحسينات كبيرة في دقة التشخيص. على سبيل المثال، حققت نماذج الذكاء الاصطناعي قيم عالية لمنطقة تحت المنحنى (AUC) في اكتشاف رفض زراعة القلب وتمييز درجات الرفض في خزعات الكلى. علاوة على ذلك، أظهرت أدوات علم الأمراض الرقمية المعزّزة بالذكاء الاصطناعي القدرة على تقليل التباين بين القراء بين علماء الأمراض وتسهيل الاستشارات عن بُعد.

الخاتمة :يمثل دمج الذكاء الاصطناعي في علم الأمراض المرتبطة بزراعة الأعضاء تقدمًا تحويليًا في هذا المجال، حيث يعد بتحسين عمليات التشخيص، وتحسين العلاج المثبط للمناعة، وفي النهاية تحسين نتائج المرضى. ومع ذلك، لا تزال هناك تحديات مثل تباين مجموعات البيانات، والحاجة إلى التحقق المتعدد المؤسسات. يعد البحث والتطوير المستمر لنماذج الذكاء الاصطناعي القوية أمرًا ضروريًا لتحقيق إمكانياتها الكاملة في الممارسة السريرية.

الكلمات المفتاحية :زراعة الأعضاء، الذكاء الاصطناعي، علم الأمراض المرتبطة بزراعة الأعضاء، دقة التشخيص، العلاج المثبط للمناعة.