Title

Artificial Intelligence and Liver: opportunities and barriers

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Abstract

Artificial intelligence (AI) was recently shown to be an excellent tool for the study of the liver however many obstacles have still to be overcome for digitalization of real-world Hepatology.
The authors present an overview of the current state of the art on the use of the innovative technologies on different areas (big data, translational hepatology, imaging, transplant setting). In the clinical practice physicians must integrate a vast array of data modalities (medical history, clinical data, laboratory tests, imaging, pathology slides) to achieve a diagnostic or therapeutic decision. Unfortunately, machine learning and deep learning are still far to really support clinicians in the real life. In fact, the accuracy of any technological support has no value in medicine without the support of clinicians, to make better use of it is essential to improve their knowledge underlying new technologies. To reach the goal, collaborative networks for multidisciplinary approaches will improve the rapid implementation of AI systems for developing disease-customized AI-powered clinical decision support tools. Finally, we discuss ethical, educational and legal challenges that must be overcome in order to build robust bridges and deploy potentially effective AI in real-world clinical settings.

Keywords: Liver disease, Big data, Artificial Intelligence, Imaging, Transplantation, Robotic

1. Introduction

It is easy to see how Artificial Intelligence (AI) will not only help to improve the diagnosis and treatment of liver diseases, but how it will also play a central role in the future liver research. We will experience a profound transformation in medical practice in the near future. In line with available forecasts, European countries have already started to create artificial neural networks, thus it is possible to estimate that AI will overcome current prejudices and soon will be fully integrated into daily clinical practice.

The study of liver disorders and associated remedies is the focus of the medical specialty known as "translational hepatology", which places special emphasis on converting fundamental scientific findings into practical applications to address unsolved questions in a wide spectrum of liver disorders, including viral hepatitis, cirrhosis, and liver cancer.

When correlating historical data with real-world and digital data, there are large number of open questions that can be better addressed with AI techniques. Among these are included: 1. how to predict the future distribution of liver diseases; 2. how to develop cost/effective solutions for liver disease diagnosis; 3. how to predict the progression towards liver fibrosis, cirrhosis and hepatocellular carcinoma (HCC); 4. which is the most effective treatment for the different liver diseases; 5. what the most cost-effective treatments are for slowing the progression of liver cirrhosis to decompensation and HCC; and 6. how to develop predictive models for effective liver organ allocation and survival outcomes after liver transplantation [1–4].

However, to achieve these goals several burning clinical problems have to be solved. Several challenges remain to fully implement AI technologies in clinical practice, including the need to develop robust approaches for structured and unstructured data collection, sharing and storage, and the need to create guidelines, shared with researchers with different skills, for producing reliable results through the use of mathematical models. AI can predict a very large set of clinically relevant features, but now it is time to prove that these approaches work in a clinical setting, by comparing algorithm performance to that of conventional systems, and further to focus our effort in carefully design of large prospective trials.

2. Application of AI for interpreting big data derived from translational hepatology: obstacles to obtain reliable results

To develop trustworthy and practical AI systems in the area of translational hepatology, many issues must be addressed. First of all, the term of big data in hepatology, as well as in other fields, includes a large panel of clinical parameters and analytics provided by omics, which comprises epigenomics, transcriptomics, metabolomics and metagenomics [5]. The future of big data in translational hepatology will involve AI in three main steps: development and implementation of machine learning (ML) and deep learning (DL) approaches that may link multiple analytics by network fusion methods, translate the results in clinical practice in terms of individualizing management of patient, and sharing of data with a large community of clinicians and researchers.

There is a lack of extensive, varied, and high-quality data sets, which are necessary to develop and test AI models: this is one of the major issues. In addition, lack of consistency in the collecting and annotation of medical pictures is another issue that may affect how well AI models function across various institutions. Another issue is model explainability that is essential when dealing with healthcare [6]. Especially retrospective datasets can be subjective to selection bias; ML models can propagate this bias after training on small and poorly representative data [7]. Explainability of the model represents a system that helps the researcher and the end-user of the model to recognize why a model is reaching a specific conclusion. To this end, DL is still sub-optimal for direct clinical applications until systems to open the black-box are employed [8]. Since physicians must have confidence in the precision and dependability of the model's predictions, this can be a significant hurdle to the adoption of AI in clinical practice.

The need for data that are rich, include ethnic minorities, under-represented populations and large in size has fueled collaborations among clinical and research centers. However, the data sharing legislation has progressively changed toward privacy protection, especially in Europe after approval of GDPR, adopted on 14 April 2016 and became enforceable beginning 25 May 2018. One approach to addressing this challenge is through the use of federated learning or a new data sharing method, the swarm learning, based on block-chain systems, represent a promising trade-off between the need for large samples and data protection [9].

Federated learning and swarm learning are ML approaches that allow for the training of models across multiple devices or locations, without the need to centralize or share the underlying data. In other words, it enables the training of a model on a large dataset, without the need to share the data with a central location, thus preserving the privacy and security of the data. However, a federated learning approach would require the participation of multiple institutions to share their data, models and computation power. Each institution would train a model on its own data and share the updates with a central server, where they are aggregated to update a global model. It requires a collaboration level and a consensus on minimum data sets and business use cases that is seldom achieved in national and international settings, and this is probably the hardest challenge to tackle.

More recently, experts of applications of AI in medicine have called for a paradigm shift of research toward clinical deployment [10]. To date, the majority of studies have focused on training a model on retrospective data and validate it in other datasets, without fully addressing how to integrate this model in the stream of clinical practice. A thorough examination and validation of AI models is required, which can be a time- and resource-intensive procedure.

Regulations and guidelines are required to guarantee the moral and safe application of AI in clinical practice. Not less important will be the harmonization of privacy regulations and data protection laws. Finally, it is essential to educate hepatologists, data scientists, and developers of AI systems in order to fully utilize the potential of AI in the field of translational hepatology. This will stop the development of erroneous expectations and enable a more efficient application of AI in the detection and treatment of liver disorders, as well as have data scientists to better understand the complexities of the medical profession. The latter will enable them to develop AI systems that are tailored to the specific needs of physicians (i.e. the identification of the ideal biomarkers patterns associated with the disease and patient data security) and that take into account the consequences of their decisions for the health and well-being of patients. Yet, the digital transition of healthcare requires all experts involved to re-think the work process and identify where AI can fill the gaps of current diagnostic and therapeutic frameworks. The ideal goal would be not the substitution of clinical workforce but rather assistance with the goal of liberating clinicians from repetitive and redundant duties.

It is in the essence of being translational that makes hepatology a discipline that must leverage the most advanced technology to translate basic scientific research into clinical practice and allow for tapping the potential of data towards the goal of improving outcomes and patients' wellbeing.

3. Application of AI in diagnostic imaging

As we outlined above, AI has a clear potential to play a significant role in the field of hepatology, particularly in the areas of imaging analysis to support diagnosis and prognostication of disease courses. In fact, since some years (almost a decade), images of Radiolology, particularly in the instance of computed tomography (CT) and magnetic resonance imaging (MRI), have become a native digital information, providing relative ease to be retrieved and analyzed for computational purposes. Imaging today is more than picture, it is data. Having said this, it must be acknowledged that this is fully true for CT and MRI, which are almost invariably acquired and archived by standardized criteria, while this is not so true for ultrasonography that is the most widely utilized imaging technique as first approach to patients at risk for any liver disease and the most common technique detecting incident liver abnormalities. With this background, it is not surprising that imaging has been the most intense field of application of AI in hepatology, almost invariably requiring a CT or MRI investigation, enabling a prompt availability of retrospective data, have been the most common and most rapidly growing topic of AI in hepatology, as reported in ***Figure 1*** and extensively reviewed by Nam et al. [4]. In particular, when dealing with radiology, a distinction should be made between two approaches: radiomics and the broader AI. Radiomics consists in the extraction of a high number of quantitative features from medical images, while artificial intelligence consists in advanced computational algorithms, potentially, but not exclusively including quantitative features extracted from medical images, that can accurately perform predictions for decision support. AI can be supervised or unsupervised, the difference is one relies labeled data to help predict outcomes, while the other processes unlabeled or raw data. Whatever approach is adopted, AI using radiology images has been addressed so far mainly to aid in reaching more precise and reproducible diagnosis of focal liver lesions, to predict prognosis (i.e. survival or recurrence) in treated or untreated tumors and to estimate histological or molecular characteristics of lesions.

Moreover, a very active and promising field of interest is the extraction of radiomic features from MRI to support more accurate diagnosis, but most importantly to stratify patients for prognosis in rare diseases, such as Primary Biliary Cholangitis or Primary Sclerosing Cholangitis [11,12].

Another very significant field of interest and of potential application of AI is the analysis of histological microscopic slides. The source data in this case are still almost invariably not in a digital format, since only extremely few laboratories have transitioned to a fully digitalized archive, despite the transition towards the whole slide imaging (WSI) technique, which includes the digitalization of the whole histological section via a digital scanner, as soon as the section is stained and thus before microscopic observation, has started. In the instance of not having a whole slide digital imaging approach in place, glass slides must be scanned for research purposes through a microscopic view and stored in a digital format [11]. To this end, it worth to mention that the formats for image acquisitions (e.g. resolution, compression, etc) have not been yet universally standardized in pathology. However, it is conceivable to retrieve stained glass slides or of the paraffin-embedded specimens, to be cut new and stained and subsequently digitally scanned and stored in a new-adopted standardized way. Therefore, both prospective and retrospective studies can be carried out in unremarkable modalities in the instance of multicentric investigations.

Worth to remind that pathological diagnosis, as well as radiological imaging interpretation, is significantly affected by interobserver variability, as we already demonstrated for liver cancer assessment [13], pointing to the benefit of building a reproducible approach by digital tools. These factors contributed to have histopathology as second most common and most growing field of application of AI in hepatology after radiology, as reported in Figure 1 [4].

Currently, AI have already contributed to boost the power of diagnostic imaging by providing automate processes of analysis and to support the pathologist or radiologist for diagnosis and prognostic stratification is extremely important [14]. In fact, the capacity of AI-driven software to propose the possible diagnosis of one or another liver disease, thanks to the recognition of specific features, is already a reality in many applications and might soon be integrated in the clinical routine of specific referral centers avoiding that the correct diagnosis may remain missed even for very long periods of time.

4. Application of robotic in liver surgery and transplantation

The progresses of AI made it possible to improve the sensory capabilities of robots and to process information from the environment, through the use of cameras, microphones, lasers and contact sensors, as well as processing techniques of sensory information based on deep learning. Despite this, Robotics and AI are two distinct disciplines. The fundamental feature that distinguishes robotics from AI is the presence of the physical apparatus which poses great challenges in the use of robots in poorly structured environments where it is difficult to manage interaction for safety and efficiency reasons. The evolution of robotics originated in response to human's need for useful machines to assist them in physical work. Today, robotics constitute an effective technology also in surgery, widely used in the operating theaters of the most advanced hospitals.

In 2011 at the University of Illinois-Chicago Giulianotti performed and then in 2012 published the first liver resection using the da Vinci robotic system for the purpose of donation [15]. Since then, the advantages and disadvantages of the robot compared to the laparoscopic approach have been investigated in various fields of liver surgery, the most cited being the increased dexterity, thanks to articulated instruments that facilitate delicate dissections (such as near the hepatic hilum) and meticulous and precise sutures; three-dimensional vision, but also magnified and of greater stability and filtration of physiological hand tremor [16]. Laparoscopy is defeated due to the lesser range and radius of movements that can be performed, to offer worse ergonomics, and a longer learning curve. Thanks to the Firefly it is not necessary to give up fluorescence vision and the use of indocyanine green to guide the resection or to perform an intraoperative cholangiography [17].

The interest in the robotic platform in the liver transplants field is justified by the desire to exploit the now proven his advantages for both the recipient and the donor, when it comes to living donor hepatectomy. In 2019 the "Expert Consensus Guidelines on Minimally Invasive Donor Hepatectomy for Living Donor Liver Transplantation - From Innovation to Implementation as standard" established the non-inferiority of minimally invasive liver resections for the liver donor in terms of donor safety and recipient outcomes compared to open hepatectomy of the donor, while improving the long-term donor quality of life [18]. The world's largest laparoscopic Mininvasive Donor Hepatectomies (MIDH) series [19] estimates that approximately 60 pure laparoscopic donor hepatectomies are needed in one year to standardize the procedure, but Chen at al. suggest that could be sufficient 15 hepatectomies in the robotic learning curve vs the 45 necessaries in laparoscopic approach, net of comparable results [20]. From a series of Broering et al., compared to the open approach, blood loss appears to be reduced, as well as postoperative hospitalization time (since it is basically a laparoscopically assisted surgery) and patients can return to work sooner, with better quality of life and resumption of sexual activity [17]. Thanks to the Firefly, after the fluorescence activation at the surgeon console, it is not necessary to give up using of indocyanine green to guide the resection, to perform an intraoperative cholangiography or to identify any leaks at the end of the hepatectomy [16]. Not to be overlooked is the possibility, thanks to the TilePro (multi-input display technology), of being able to see the preoperative radiological images, the intraoperative ultrasound and also the three-dimensional reconstructions, whose use was born from liver transplantology, on the same screen as the operating field. In the future we could see an ever-greater autonomy of the robot through the presurgical data and 2D/3D images integration together with the implementation of artificial intelligence in surgery. Interestingly enough, the presence of a second console allows to undertake fully tutored teaching courses, with the possibility of constant and precise guidance over the timely interaction and/or intervention by a senior, in a surgery where both the care for teaching the technique and the protection of the donor patient are fundamental. Also it is possible as weel to exercise thanks to dedicated programs (e.g., SimNow DeVinci Intuitive surgical) with the simulation of surgical operations in 3D high definition and virtual reality; so, the robot fully satisfies the needs of teaching and learning in surgery.

There are few centers where robotic hepatectomy living donor transplants programs are currently in place; the largest numbers, thanks also to greater seniority, are in Korea, Taiwan and South Arabia. Their growth took advantage from the presence on site in the first years of expert surgeons who brought their experience and tutored the transplant surgeons. In the future, thanks to the robotic platform with telesurgery, this could evolve towards distance teaching courses, with remotely connected consoles; center aspiring to embark on a surgery program will be able to receive mentorship without the need for the physical presence of world experts in the field.

In the last two years to go beyond the limits the first attemps robotic liver implantation have been published; from the first experience in 2021 by Lee et al. [19], the tentative continued in 2022 with K. S. Suh [21]. The authors highlight that one of the major limitations of the robot, i.e. the absence of tactile feedback was responsible for the potential graft damage during its manipulation the suture threads [21]. This same Korean team successfully performed total hepatectomy too with the robot [22]. Beyond the implementation of hugely complex gestures in robotics, in the future we will have a robot with the possibility of automation through the integration of presurgical data and 2D/3D images together with the implementation of artificial intelligence in surgery, opening a new Era in LT.

5. Applicability of AI in the transplant setting

The evaluation of liver transplant recipients depends on a complex, multidimensional and nonlinear relationship between variables pertaining to the donor, the recipient, and the surgical procedure. In the setting of liver transplantation ML models have been developed to predict pre-transplant survival and management on the waiting list, including risk of dying on the waiting list, to assess the donor to recipient matching during allocation process and to predict the outcome [23, 24]. Long-term outcome after solid organ transplantation is even more difficult to predict than in the early post-transplant period because it may also be influenced by conditions unrelated to the graft [24–26], such as infections, malignancies, and metabolic or cardiovascular diseases [27–29], together with recipient characteristics, intraoperative variables, post-operative variables and immunological complications [30].

On the other hand, the evaluation of pathology of the donor graft is one of the main issues for forecasting post-LT outcome. In particular, a marked macrovescicular steatosis is associated with early allograft dysfunction, primary nonfunction, and postreperfusion syndrome [25,31].

Several studies have focused on models quantifying steatosis, inflammation, hepatocellular ballooning and other morphological pattern, as well as the staging of liver fibrosis [26,32–34]. Once in use, these algorithms could play a significant role in overall donor liver assessment as well as standardizing the assessment of donor livers and, importantly, will be invaluable for providing standardized data to evaluate with the outcome data.

The efficacy of liver transplantation is also hampered by organ shortage, the number of patients listed for LT exceeding by far the number of liver grafts available. This imbalance results in a significant proportion of patients who will die or be dropped out from the wait list (WL), while waiting for organ. To counteract the negative impact of organ shortage, notably in countries with medium to low organ donation rates, predictive models of mortality have found a major application in the field of LT. The model for end stage liver diseases (MELD) was developed and adopted in the USA 20 years ago [35], offering the highest priority for organ allocation to patients listed with the highest MELD score in an attempt to minimize the risk of death or drop out in the waitlist. Over the last decade, some emerging limitations and epidemiological changes in clinical profile of LT candidates have been translated in a consistent declining precision of MELD, and individual graft allocation is increasingly questioned, since mortality in the WL still averages an unacceptable 15-20% rate, peaking in some countries and indications to 30%. Liver offering schemes should therefore eagerly be revisited and move toward precision medicine for refining liver transplantation indications and prioritization in the WL, both in decompensated cirrhosis and HCC [36].

Recent development in AI demonstrated a potential to address at best the complexity of liver transplantation process and to increase accuracy of classical statistical models in improving prediction of mortality in the WL, compared to MELD-based systems [37]. In the Bertsimas at al. study, a state-of-the-art ML based algorithm termed OPOM was designed. OPOM was derived from the retrospective analysis of the US OPTN database, including decompensated cirrhosis served by MELD, and HCC patients, served by an exception MELD system. OPOM allowed a better description of patients' trajectories, and identification of key root nodes, as specific bilirubin values in patients with low MELD scores (figure available on request). As a result, OPOM outperformed MELD to predict 3-month mortality in the waitlist. Simulation studies suggested that OPOM had the potential for a nationwide reduction in WL mortality by 17.5% (i.e., 418 fewer deaths/year), peaking at 28-

30% in patients with MELD score between 16-25. Also, a higher number of female candidates received transplants when OPOM allocation was utilized.

Recently, addressing the risk of drop-out in patients listed for HCC in the OPTN database, used a combined approach, based 1st on ML to identify independent predictors of drop out in this population and 2nd, designing of a Cox-model for drop-out of HCC patients integrating 6 predictors identified by a random forest model [38]. The predictive model reached a c-index of 0.74 in the validation set. However, the training set was retrospective and did not consider critical predictors as tumor progression in the waitlist or response to therapy.

These exploratory studies demonstrate the potential of AI to refine current predictive models both pre- and post- liver transplantation. According to current guidelines, a careful assessment of AI-based models on external prospective cohorts with simulation studies is mandatory to detect potential dysfunctions before adoption in the real-life.

6. Artificial Intelligence in hepatology, educational aspects

Aside from ethical issues and the undoubtful perspectives of advancement in terms of precision medicine, diagnostic power, decision-making, resources allocation and management, AI application in hepatology (and in medicine in general) also involves a series of issues and challenges on regards of educational aspects. Indeed, to effectively use this methodology, there are several aspects to consider, even before being able to think of its application on a large scale. This is evident by the fact that, even if AI already provide suited and effective approaches for the interpretation of medical data aimed at assisted diagnosis and personalized therapy, more and more in the field of hepatology, the most crucial obstacle of its practical application, is the lack of specific background knowledge of the professional figures involved. In fact, it is emblematic that the most advanced aspect of AI application in hepatology is represented by radiomics, where already available image processing algorithms are adapted and applied to medical diagnosis of liver tumors. Artificial Vision has generally a well-established range of methodological standards that can be relatively easily processed by AI algorithms that already exist for image recognition and have been suitably "adapted" to recognize liver masses. Different is the case of other clinical/laboratory data, where the data collection, database management, information technologie (IT) standards and interpretation must be built practically from scratch with more challenging technical efforts. This aspect, as previously reported, is particularly important when considering other "omics", in which a very large amount of data need to be implemented and interpreted correctly. Therefore, there is the need to prepare the new generations of medical and computer engineering students for this methodological revolution that will see the application of AI in medicine problems more and more frequently. This aspect is particularly important in the perspective that they are involved in the AI revolution, giving them the scientific tools necessary to "communicate" each-other in a productive manner. For this purpose, Universities need to design dedicated courses in existing degree programs to teach the meaning and potential of AI, and to create other degree programs from scratch, with the specific aim of training professionals in artificial intelligence applied to medical sciences. In Italy, there are already some examples of this efforts: the University of Salerno has already started a master's degree in "Computer Engineering for Digital Medicine", as well a specific course in "Artificial intelligence applied to medicine" in the master's degree of Medicine and Surgery.

7. AI and Ethical and Legal Aspects

The integration AI in clinical practice is rapidly increasing and relying on diagnostic and prognostic algorithms clinicians are helped in the decision-making process to generate personalized treatments in many clinical settings [10,39]. However, there is still a debate on how AI assistance may affect the medical performance as on the one hand it can improve the sensitivity of clinical experts while in the other hand it may lower their specificity. Studies showed that AI predictions based on explainable algorithms developed with a transparent model reporting showed substantial benefits in settings as liver transplantation (*see dedicated section*), antiviral therapy and chemotherapy or in helping to anticipate strategic decisions to curb the local burden of pandemics as COVID-19 [40–43]. On the other hand, the potential benefits of AI using ML systems are hampered by their black box nature that pose new important ethical and legal challenges spanning from data quality to medical-legal questions arising from the incorporation of AI into clinical practice [10,39,44]. Because of the uncertainty generated by the lack of scrutiny of the recommendation provided by AI algorithms clinicians will be unable to take appropriate steps to mitigate their concern that algorithm inaccuracy could lead to patient injury and medical liability [44–46].

Substantially AI transforms the traditional therapeutic relationship between physician and patient into a new triadic doctor-machine-patient relationship [44–48]. This revolution complicates the attribution of responsibility in malpractice lawsuits experts attempted to define a new legal framework that considers the AI role in healthcare reducing as much as possible the existing heterogeneity of approaches across countries regarding medical liability [44–46,48,49].

In spite of the fact that a major aim of AI is to help reducing the risk of potential medical errors paradoxically an overreliance on AI systems could become dangerous particularly when clinicians have not sufficient technological knowledge to understand the proper functioning of AI systems, their limits and safety (*see dedicated section*). The problems arises when it is difficult to rely on alternative systems that in parallel could provide information on the reliability of any particular result provided by AI since any AI-helped action will never be fault-free.

Experts discussed extensively the possibility to give the AI systems a legal personhood so that it would become directly responsible for its own decisions and actions. However, if AI systems would be recognized as a legal personhood with an active part in the decision-making process it will be unacceptable to attribute any error to the human factor. The safety of the health care system relies on an organizational framework that warrants the well-functioning of all interdependent components and services: people, technology and their interactions. Thus, the basic concept is that errors can derive from human behavior, but also from malfunctioning of the technologies, even though they are supposed "intelligent". The Committee of Legal Affairs of the European Parliament stated that "AI-systems have neither legal personality nor human conscience, and that their sole task is to serve humanity" (https://commission.europa.eu/system/files/2022-09/1_1_197605_prop_dir_ai_en.pdf)[44]. To date, to give AI a legal personality is considered inadequate because even supposed intelligent technologies are not substantially different from any other non-AI based sophisticated technology already used (https://commission.europa.eu/system/files/2022-09/1_1_197605_prop_dir_ai_en.pdf) [44].

However, since the experts' opinions are always conflicting when dealing with the most advance knowledge and technology AI liability issues when applied to healthcare assistance remain open. Accordingly, the introduction of AI systems in clinical practice prompt to build infrastructures to deal with critical issues such as data, quality, privacy and security and safe data sharing [50–52]. Special attention should be paid to mitigate bias throughout the whole cycle of medical AI, from data collection to after deployment particularly when hurting marginalized groups [53,54]. As predictive models developed by ML algorithms are based on data on which the whole AI system is built, one major target of AI ethics will be to address the biases of AI models associated with the quality and quantity of the data used [55]. Regulation and governance of medical AI needs the implementation of standardized safe AI practices and the establishment of a transparent reporting of the performance of AI systems. This policy will make clinicians less skeptical and more reliant on their AI assisted decision-making without losing control over their own care because of the potentially unexplained AI results.

Finally, since medical doctors are currently held liable when they deviate from the standard of care and patient injury occurs a special concern is accountability, as it is not yet clear whether developers, sellers or healthcare providers should be held accountable if a given AI system makes mistakes even after being clinically validated.

8. Conclusion

In conclusion, to fully exploit all the great potential of AI in healthcare, some crucial technological, educational, and ethical issues need to be addressed. Furthermore, all the societal complexities of AI applications need to be considered in the proof of their medical utility and economic value and the development of strategies for their wider applications. New liability frameworks and collaborative networks for multidisciplinary guidelines will facilitate a rapid implementation of AI systems for developing disease-customized AI-powered clinical decision support tools.

Conflict of interest

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Legend

Figure 1. Studies applying AI in liver histopathology and radiomics in the last 5 years.

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