Digestive and Liver Disease 55 (2023) 1455–1461

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Review Article

Artificial Intelligence and liver: Opportunities and barriers

Clara Balsano[a,*], Patrizia Burra[b], Christophe Duvoux[c], Anna Alisi[d], Fabio Piscaglia[e], Alessio Gerussi[f,g], Special Interest Group (SIG) Artificial Intelligence and Liver Disease; Italian Association for the Study of Liver (AISF)[1]

[a] *Department of Life, Health and Environmental Sciences-MESVA, School of Emergency-Urgency Medicine, University of L'Aquila, Piazzale Salvatore Tommasi 1, Coppito, L'Aquila 67100, Italy*
[b] *Multivisceral Transplant Unit Gastroenterology Department of Surgery, Oncology and Gastroenterology, Padua University Hospital, Padua, Italy*
[c] *Department of Hepatology, Medical Liver Transplant Unit, Hospital Henri Mondor AP-HP, University of Paris-Est Créteil (UPEC), France*
[d] *Research Unit of Molecular Genetics of Complex Phenotypes, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy*
[e] *Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy*
[f] *Division of Gastroenterology, Center for Autoimmune Liver Diseases, Department of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy*
[g] *European Reference Network on Hepatological Diseases (ERN RARE-LIVER), Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy*

ARTICLE INFO

Article history:
Received 20 July 2023
Accepted 17 August 2023
Available online 16 September 2023

Keywords:
Artificial Intelligence
Big data
Imaging
Liver disease
Robotic
Transplantation

ABSTRACT

Artificial Intelligence (AI) has recently been shown as an excellent tool for the study of the liver; however, many obstacles still have to be overcome for the digitalization of real-world hepatology. The authors present an overview of the current state of the art on the use of innovative technologies in different areas (big data, translational hepatology, imaging, and transplant setting). In clinical practice, physicians must integrate a vast array of data modalities (medical history, clinical data, laboratory tests, imaging, and pathology slides) to achieve a diagnostic or therapeutic decision. Unfortunately, machine learning and deep learning are still far from really supporting clinicians in 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 new technologies, it is essential to improve clinicians' knowledge about them. To this end, the authors propose that collaborative networks for multidisciplinary approaches will improve the rapid implementation of AI systems for developing disease-customized AI-powered clinical decision support tools. The authors also discuss ethical, educational, and legal challenges that must be overcome to build robust bridges and deploy potentially effective AI in real-world clinical settings.

© 2023 The Author(s). Published by Elsevier Ltd on behalf of Editrice Gastroenterologica Italiana S.r.l. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

1. Introduction

Artificial Intelligence (AI) can not only help improve the diagnosis and treatment of liver diseases but also can play a central role in future liver research. In line with available forecasts, European countries have already started to create artificial neural networks; thus, it is possible to propose that AI will overcome current prejudices and will soon be fully integrated into daily clinical practice. Moreover, translational hepatology is an area that focuses mainly on the study of liver disorders and associated remedies and places particular 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 a large number of open questions that can be better addressed with AI techniques. For example, AI is suggested to (1) predict the future distribution of liver diseases, (2) develop cost-effective solutions for liver disease diagnosis, (3) understand the progression of liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC), (4) determine the most effective treatment for different liver diseases, (5) identify the most effective treatments for slowing the progression of liver cirrhosis to decompensation and HCC, and (6) develop predictive models for effective liver organ allocation and survival outcomes after liver transplantation [1–4].

However, to achieve these goals, several clinical problems have to be solved. Challenges remain in fully implementing AI technologies in clinical practice, including the need to develop robust approaches for structured and unstructured data collection,

* Corresponding author.
E-mail address: clara.balsano@univaq.it (C. Balsano).

[1] See Appendix for list of Special Interest Group (SIG) Artificial Intelligence and Liver Disease; Italian Association for the Study of Liver (AISF).

https://doi.org/10.1016/j.dld.2023.08.048
1590-8658/© 2023 The Author(s). Published by Elsevier Ltd on behalf of Editrice Gastroenterologica Italiana S.r.l. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

sharing, and storage and the need to create guidelines, agreed with researchers with different skills, for producing reliable results through the use of mathematical models. AI can predict a 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 with that of conventional systems and further focusing our effort on carefully designing large prospective trials.

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

To develop trustworthy and practical AI systems in the area of translational hepatology, many issues must be addressed. First, the term 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, translation of the results in clinical practice in terms of individualizing patient management, and sharing of data with a large community of clinicians and researchers.

However, there is a lack of extensive, varied, and high-quality datasets, which are necessary to develop and test AI models. In addition, there is a lack of consistency of medical images in the collection and annotation of medical pictures, posing a problem that may affect how well AI models function across various institutions. Another issue is model explainability, which is essential when dealing with healthcare [6]. In particular, retrospective datasets can be subject 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 recognize why a model is reaching a specific conclusion. To this end, DL is still suboptimal for direct clinical applications until systems to open the blackbox 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 adopting AI in clinical practice.

The need for data that are rich, include ethnic minorities and under-represented populations, and are 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 (General Data Protection Regulation), adopted on April 14, 2016, and became enforceable beginning May 25, 2018. One approach to addressing this challenge is through federated learning, a new data-sharing method, or swarm learning based on blockchain systems, representing 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 centralizing or sharing the underlying data. In other words, they enable 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 trains a model on its own data and shares 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 datasets and business use cases that are seldom achieved in national and international settings, and this is probably the most complex challenge to tackle.

More recently, experts on applications of AI in medicine have called for a paradigm shift of research toward clinical deployment [10]. To date, most studies have focused on training a model on retrospective data and validating 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 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. It will also help data scientists understand the complexities of the medical profession better. The latter will enable them to develop AI systems tailored to the specific needs of physicians (i.e., identifying the ideal biomarker 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. Nevertheless, the digital transition of healthcare requires all experts to rethink the work process and identify where AI can fill the gaps in current diagnostic and therapeutic frameworks. The ideal goal would be not substituting the clinical workforce but rather the assistance to liberate 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 toward the goal of improving outcomes and patients' well-being.

3. Application of AI in diagnostic imaging

As 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, for some years (almost a decade), images of radiology, particularly in the instance of computed tomography (CT) and magnetic resonance imaging (MRI), have become native digital information, providing relative ease to be retrieved and analyzed for computational purposes. Imaging today is more than a picture; it is data. 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, which is the most widely utilized imaging technique as the 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, and has been the most common and most rapidly growing topic of AI in hepatology, as reported in Fig. 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 broader AI. Radiomics consists of extracting a high number of quantitative features from medical images, while AI consists of 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 that one relies on 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 a 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.

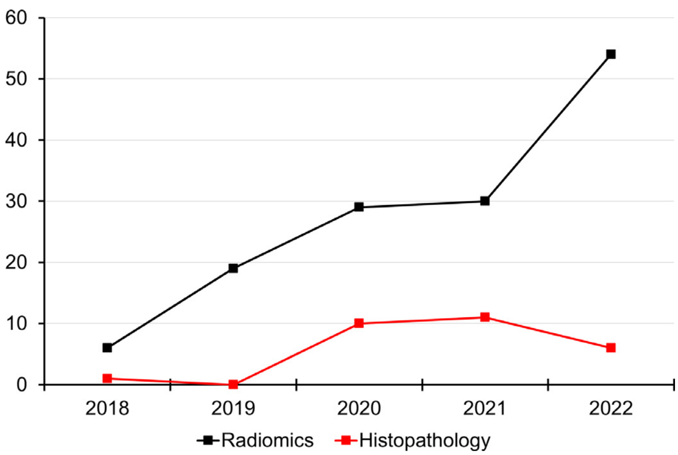

Fig. 1. Studies applying AI in liver histopathology and radiomics in the last 5 years.

Moreover, a very active and promising field of interest is the extraction of radiomic features from MRI to support a 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 significant field of interest and 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 very few laboratories have transitioned to a fully digitalized archive, despite the transition toward 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, glass slides must be scanned for research purposes through a microscopic view and stored in a digital format [11]. To this end, it is worth mentioning that the formats for image acquisitions (e.g., resolution and compression) have not yet been universally standardized in pathology. However, it is conceivable to retrieve stained glass slides 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 multicentric investigations.

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

Currently, AI contributes to boosting the power of diagnostic imaging by providing automate processes of analysis and supporting pathologists or radiologists 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 into the clinical routine of specific referral centers, avoiding the possibility that the correct diagnosis may remain missed even for very long periods.

4. Application of robotics in liver surgery and transplantation

The progress of AI allowed to improve the sensory capabilities of robots and to process information from the environment through the use of various tools (including cameras, microphones, lasers, and contact sensors) as well as processing techniques of sensory information based on DL. Despite this, robotics and AI are two distinct disciplines. The fundamental feature that distinguishes robotics from AI is the presence of the physical apparatus. This aspect poses great challenges in using 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 humans' need for useful machines to assist them in physical work. Today, robotics constitutes an effective technology in surgery and it is widely used in the operating theaters of the most advanced hospitals.

Notably, Giulianotti et al. performed the first donation at the University of Illinois (Chicago) in 2011, and then published the first liver resection using the da Vinci robotic system in 2012 [15]. Since then, the advantages and disadvantages of the robotic approach have been compared to the laparoscopic approach in various fields of liver surgery. The most cited ones are represented by the increased dexterity (thanks to articulated instruments that facilitate delicate dissections, such as near the hepatic hilum, and meticulous and precise sutures), the three-dimensional vision (also magnified and of greater stability), and the filtration of physiological hand tremor [16]. Conversely, laparoscopy shows disadvantages such as the lesser range and radius of movements that can be performed, thus offering worse ergonomics, and a longer learning curve. Moreover, the employment of Firefly fluorescence technology in surgical procedures displayed important advantages. As a matter of fact, such technology enables the acquisition of fluorescent signals together with normal light endoscopic pictures. Overall, this system allows to mantain the fluorescence vision and the use of indocyanine green in order to guide the resection or to perform an intraoperative cholangiography [17].

The interest of applying the robotic platform in liver transplant (LT) field raises from the proven advantages for both the recipient and the donor, especially in case of a 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 compared to open hepatectomy of the donor. In particular, advantages were found for the liver donor (in terms of donor safety and improvement of long-term donor quality of life) and recipient outcomes [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. However, Chen et al. suggested that 15 hepatectomies could be sufficient in the robotic learning curve with respect to the 45 necessaries in the laparoscopic approach [20]. From a series by Broering et al., that performed a comparison with the open approach, blood loss appears to be reduced, as well as the postoperative hospitalization time (since it is basically a laparoscopically assisted surgery). By this way, patients could return to work sooner, with better quality of life and resumption of sexual activity [17]. Furthermore, the multi-input display technology TylePro allows 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 integration of the presurgical data and 2D/3D images as well as the implementation of AI in surgery. Interestingly, the presence of a second console allows undertaking fully tutored teaching courses, with the possibility of constant and precise guidance over the timely interaction and/or intervention by a senior. This aspect is of paramount importance in a surgery field where both the teaching or tutoring and the protection of the donor patient are fundamental. Also, it is possible to practice thanks to dedicated programs (e.g., SimNow DaVinci Intuitive Surgical) enabling the simulation of surgical operations in 3D high definition and virtual reality. Hence, the robot fully satisfies the needs of teaching and learning in surgery.

There are few centers where robotic hepatectomy living donor transplant programs are currently in place. In particular, the largest numbers (thanks also to greater seniority) are in Korea, Taiwan, and South Arabia. As a matter of fact, their growth took advantage from the presence on site of expert surgeons who brought their experience and tutored the transplant surgeons in the first years. In the future this could evolve toward distance teaching courses with remotely connected consoles exploiting the robotic platform with telesurgery. Moreover, centers 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 the first attempts at robotic liver implantation have been published, namely the first experience in 2021 by Lee et al. [19] and the efforts by Suh later in 2022 [21]. The authors highlighted 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 of the suture threads [21]. This same Korean team successfully performed total hepatectomy using 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. In addition, the implementation of AI in surgery might became real, opening a new era in liver transplantation.

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 the risk of dying on the waiting list, to assess donor-to-recipient matching during the 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, postoperative variables, and immunological complications [30]. On the other hand, evaluating the pathology of the donor graft is one of the main issues for forecasting post-LT outcomes. In particular, 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, other morphological patterns, and the staging of liver fibrosis [26,32–34]. Once in use, these algorithms could play a significant role in overall donor liver assessment and in the standardization of the assessment of donor livers.

The efficacy of liver transplantation is also hampered by organ shortage; the number of patients listed for LT exceeds the number of liver grafts available. This imbalance results in a significant proportion of patients who will die or be dropped out of the wait list (WL) while waiting for organ. To counteract the negative impact of organ shortages, 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 the clinical profile of LT candidates have been translated into a consistently 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 with indications to 30%. Liver offering schemes should therefore eagerly be revisited and moved toward precision medicine for refining liver transplantation indications and prioritization in the WL, both in decompensated cirrhosis and HCC [36].

Recent developments in AI have demonstrated the potential to address, at best, the complexity of the liver transplantation process and to increase the accuracy of classical statistical models in improving the prediction of mortality in WL compared to MELD-based systems [37]. In Bertsimas et al.'s study, a state-of-the-art ML-based algorithm termed Optimized Prediction Of Mortality (OPOM) was designed. OPOM was derived from the retrospective analysis of the US Organ Procurement and Transplantation Network (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 scores between 16 and 25. In addition, a higher number of female candidates received transplants when OPOM allocation was utilized.

Recently, a study used a combined approach for addressing the risk of dropout in patients listed for HCC in the OPTN database. Firstly, the authors focused on ML to identify independent predictors of dropout in this population. Then, they designed a Cox-model for dropout of HCC patients integrating six 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 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, and resource allocation and management, AI application in hepatology (and in medicine in general) also involves a series of issues and challenges regarding educational aspects. Indeed, to effectively use this methodology, there are several aspects to consider, even before considering its application on a large scale. This is evident by the fact that, even if AI already provides suited and practical 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 to 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 the medical diagnosis of liver tumors. Artificial vision generally has 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 technology (IT) standards, and interpretation must be built practically from scratch with more challenging technical efforts. As previously reported, this aspect is particularly important when considering other "omics," in which a large amount of data needs to be implemented and interpreted correctly. Therefore, there is a need to prepare the new generations of medical and computer engineering students for this methodological revolution that will see the application of AI in medical problems more and more frequently. This point is essential, considering that these students are fully involved in the AI revolution and, thus, they need to be provided of the necessary scientific tools to "communicate" with each other in a productive manner. To 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 AI applied to medical sciences. In Italy, there are already some examples of this effort: the University of Salerno has already started a master's degree in "Computer Engineering for Digital Medicine," as well as 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 of AI in clinical practice is rapidly increasing, and by 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 medical performance; on the one hand, it can improve the sensitivity of clinical experts, while, on the other hand, it may lower their specificity. Studies showed that AI predictions based on explainable algorithms developed with a transparent model showed substantial benefits in settings such as liver transplantation (*see dedicated section*), antiviral therapy, and chemotherapy or in helping to anticipate strategic decisions to curb the local burden of pandemics such as COVID-19 [40–43]. On the other hand, the potential benefits of AI using ML systems are hampered by their black-box nature, which poses 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 recommendations 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 physicians and patients into a new triadic doctor–machine–patient relationship [44–48]. This revolution complicates the attribution of responsibility in malpractice lawsuit experts attempting 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].

Although a major aim of AI is to help reduce the risk of potential medical errors, paradoxically, an overreliance on AI systems could become dangerous, particularly when clinicians do not have the sufficient technological knowledge to understand the proper functioning of AI systems and their limits and safety (*see dedicated section*). Problems arise 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 faultless.

Experts extensively discussed the possibility of giving the AI systems a legal personhood so that they would become directly responsible for their own decisions and actions. However, if AI systems are 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 interaction. Thus, the basic concept is that errors can derive from human behavior but also from malfunctioning of technologies, even though they are supposed to be "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, giving 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 always conflict when dealing with the most advanced knowledge and technology, AI liability issues when applied to healthcare assistance remain open. Accordingly, introducing AI systems in clinical practice prompts 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 mitigating 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 requires 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 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 proving their medical utility and economic value and in developing strategies for their wider applications. New liability frameworks and collaborative networks for multidisciplinary guidelines will facilitate the rapid implementation of AI systems for developing disease-customized AI-powered clinical decision support tools.

Conflict of interest

The research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding

This research received no external funding.

Appendix

List of Special Interest Group (SIG) Artificial Intelligence and Liver Disease; Italian Association for the Study of Liver (AISF)

Maurizia Rossana Brunetto[h], Ferruccio Bonino[i], Roberto Montalti[j], Silvia Campanile[j], Marcello Persico[k], Domenico Alvaro[l], Silvano Jr. Santini[t], Pietro Invernizzi[u, v], Marco Carbone[u, v], Mario Masarone[k], Albino Eccher[m], Bruno Siciliano[n], Mario Vento[o], Fanny Ficuciello[n], Federico Cabitza[p, q], Simone Penasa[r], Piergiorgio Donatelli[s]

[h]Department of Clinical and Experimental Medicine, Department of Medical Specialties, Hepatology Unit, Reference Centre of the Tuscany Region for Chronic Liver Disease and Cancer, University of Pisa, University Hospital of Pisa, Pisa, Italy

[i]Institute of Biostructure and Bioimaging, National Research Council, Naples, Italy

[j]Department of Clinical Medicine and Surgery, Division of Minimally Invasive and Robotic HPB Surgery and Transplantation Service, University of Naples “Federico II”, Naples, Italy

[k]Internal Medicine and Hepatology Division, Department of Medicine and Surgery “Scuola Medica Salernitana”, Salerno, Italy

[l]Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy

[m]Department of Pathology and Diagnostics, University and Hospital Trust of Verona, Verona, Italy

[n]Department of Electrical Engineering and Information Technology, University of Naples Federico II, Naples, IT, Italy

[o]Department of Information Engineering, Electrical Engineering and Applied Mathematics (DIEM) University of Salerno, Salerno, Italy

[p]Department of Computer Science, Systems and Communication, University of Milano-Bicocca, Milan, Italy

[q]IRCCS Istituto Ortopedico Galeazzi, Milan, Italy

[r]Department Faculty of Law, University of Trento, Trento, Italy

[s]Department of Philosophy, Sapienza University of Rome, Rome, Italy

[t]Department of Life, Health and Environmental Sciences-MESVA, School of Emergency-Urgency Medicine, University of L'Aquila, Piazzale Salvatore Tommasi 1, Coppito, L'Aquila 67100, Italy

[u]Division of Gastroenterology, Center for Autoimmune Liver Diseases, Department of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy

[v]European Reference Network on Hepatological Diseases (ERN RARE-LIVER), Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy

References

[1] Balsano C, Alisi A, Brunetto MR, Invernizzi P, Burra P, Piscaglia F, et al. The application of artificial intelligence in hepatology: a systematic review. Dig Liver Dis 2022;54:299–308. doi:10.1016/j.dld.2021.06.011.

[2] Cabitza F, Campagner A, Balsano C. Bridging the “last mile” gap between AI implementation and operation: “data awareness” that matters. Ann Transl Med 2020;8:501 –501. doi:10.21037/atm.2020.03.63.

[3] Wong GLH, Yuen PC, Ma AJ, Chan AWH, Leung HHW, Wong VWS. Artificial Intelligence in prediction of non-alcoholic fatty liver disease and fibrosis. J Gastroenterol Hepatol 2021;36:543–50. doi:10.1111/jgh.15385.

[4] Nam D, Chapiro J, Paradis V, Seraphin TP, Kather JN. Artificial Intelligence in liver diseases: improving diagnostics, prognostics and response prediction. JHEP Rep 2022;4:100443. doi:10.1016/j.jhepr.2022.100443.

[5] Athreya AP, Lazaridis KN. Discovery and opportunities with integrative analytics using multiple-omics data. Hepatology 2021;74:1081–7. doi:10.1002/hep.31733.

[6] Kundu S. AI in medicine must be explainable. Nat Med 2021;27:1328. doi:10.1038/s41591-021-01461-z.

[7] Obermeyer Z, Powers B, Vogeli C, Mullainathan S. Dissecting racial bias in an algorithm used to manage the health of populations. Science 2019;366:447–53 (80-). doi:10.1126/science.aax2342.

[8] Gunning D, Stefik M, Choi J, Miller T, Stumpf S, Yang GZ. XAI-explainable Artificial Intelligence. Sci Robot 2019;4:4–6. doi:10.1126/scirobotics.aay7120.

[9] Warnat-Herresthal S, Schultze H, Shastry KL, Manamohan S, Mukherjee S, Garg V, et al. Swarm learning for decentralized and confidential clinical machine learning. Nature 2021;594:265–70. doi:10.1038/s41586-021-03583-3.

[10] Rajpurkar P, Chen E, Banerjee O, Topol EJ. AI in health and medicine. Nat Med 2022;28:31–8. doi:10.1038/s41591-021-01614-0.

[11] Gerussi A, Verda D, Bernasconi DP, Carbone M, Komori A, Abe M, et al. Machine learning in primary biliary cholangitis: a novel approach for risk stratification. Liver Int 2022;42:615–27. doi:10.1111/liv.15141.

[12] Cristoferi L, Porta M, Bernasconi DP, Leonardi F, Gerussi A, Mulinacci G, et al. A quantitative MRCP-derived score for medium-term outcome prediction in primary sclerosing cholangitis. Dig Liver Dis 2023;55:373–80. doi:10.1016/j.dld.2022.10.015.

[13] Tovoli F, Renzulli M, Negrini G, Brocchi S, Ferrarini A, Andreone A, et al. Inter-operator variability and source of errors in tumour response assessment for hepatocellular carcinoma treated with sorafenib. Eur Radiol 2018;28:3611–20. doi:10.1007/s00330-018-5393-3.

[14] Gerussi A, Scaravaglio M, Cristoferi L, Verda D, Milani C, De Bernardi E, et al. Artificial Intelligence for precision medicine in autoimmune liver disease. Front Immunol 2022;13:1–17. doi:10.3389/fimmu.2022.966329.

[15] Giulianotti PC, Tzvetanov I, Jeon H, Bianco F, Spaggiari M, Oberholzer J, et al. Robot-assisted right lobe donor hepatectomy. Transpl Int 2012;25:1–5. doi:10.1111/j.1432-2277.2011.01373.x.

[16] Jang EJ, Kim KW, Kang SH. Early experience of pure robotic right hepatectomy for liver donors in a small-volume center. J Soc Laparoendosc Surg 2022;26. doi:10.4293/jsls.2022.00063.

[17] Broering DC, Elsheikh Y, Alnemary Y, Zidan A, Elsarawy A, Saleh Y, Alabbad S, Sturdevant M, Wu YM, Troisi RI. Robotic versus open right lobe donor hepatectomy for adult living donor liver transplantation: a propensity score-matched analysis. Liver Transpl Nov 2020;26(11):1455–64 Epub 2020 Oct 7. doi:10.1002/lt.25820.

[18] Cherqui D, Ciria R, Kwon CHD, et al. Expert consensus guidelines on minimally invasive donor hepatectomy for living donor liver transplantation from innovation to implementation: a joint initiative from the International Laparoscopic Liver Society (ILLS) and the Asian-Pacific Hepato-Pancreato-Biliary Association (A-PHPBA). Ann Surg 2021;273(1):96–108. doi:10.1097/SLA.0000000000004475.

[19] Lee KW, Hong SK, Suh KS, Kim HS, Ahn SW, Yoon KC, et al. One hundred fifteen cases of pure laparoscopic living donor right hepatectomy at a single center. Transplantation 2018;102:1878–84. doi:10.1097/TP.0000000000002229.

[20] Chen PD, Wu CY, Hu RH, Chen CN, Yuan RH, Liang JT, et al. Robotic major hepatectomy: is there a learning curve? Surgery 2017;161:642–9 (United States). doi:10.1016/j.surg.2016.09.025.

[21] Suh KS, Hong SK, Lee S, Hong SY, Suh S, Han ES, et al. Purely laparoscopic explant hepatectomy and hybrid laparoscopic/robotic graft implantation in living donor liver transplantation. Br J Surg 2022;109:162–4. doi:10.1093/bjs/znab322.

[22] Lee KW, Choi Y, Lee S, Hong SY, Suh S, Han ES, Hong SK, Yang SM, Yi NJ, Suh KS. Total robot-assisted recipient's surgery in living donor liver transplantation: first step towards the future. J Hepatobiliary Pancreat Sci 2023 Mar 3. doi:10.1002/jhbp.1327.

[23] Hearn J, Ross HJ, Mueller B, Fan CP, Crowdy E, Duhamel J, et al. Neural networks for prognostication of patients with heart failure. Circ Heart Fail 2018;11:e005193. doi:10.1161/CIRCHEARTFAILURE.118.005193.

[24] Ferrarese A, Sartori G, Orrù G, Frigo AC, Pelizzaro F, Burra P, et al. Machine learning in liver transplantation: a tool for some unsolved questions? Transpl Int 2021;34:398–411. doi:10.1111/tri.13818.

[25] Portmann B., Wight D.G.D. Pathology of liver transplantation (excluding rejection). In: Calne R.Y., editor. Liver transplantation: the Cambridge/King's College Hospital experience. London: Grune & Stratton; 1987. p. 437 Portmann B.W.D. Pathology of liver transplantation (excluding rejection). In: Calne R., ed. Liver Transplantation: The Cambridge - King's College Hospital. 1983.

[26] Cima L, Brunelli M, Parwani A, Girolami I, Ciangherotti A, Riva G, Novelli L, Vanzo F, Sorio A, Cirielli V, Barbareschi M, D'Errico A, Scarpa A, Bovo C, Fraggetta F, Pantanowitz LEA. Validation of remote digital frozen sections for cancer and transplant intraoperative services. J Pathol Inform 2018;9:34.

[27] Watt KDS, Pedersen RA, Kremers WK, Heimbach JK, Charlton MR. Evolution of causes and risk factors for mortality post-liver transplant: results of the NIDDK long-term follow-up study. Am J Transplant 2010;10:1420–7. doi:10.1111/j.1600-6143.2010.03126.x.

[28] Burra P, Shalaby S, Zanetto A. Long-term care of transplant recipients: De novo neoplasms after liver transplantation. Curr Opin Organ Transplant 2018;23:187–95. doi:10.1097/MOT.0000000000000499.

[29] Taborelli M, Piselli P, Ettorre GM, Baccarani U, Burra P, Lauro A, et al. Survival after the diagnosis of de novo malignancy in liver transplant recipients. Int J Cancer 2019;144:232–9. doi:10.1002/ijc.31782.

[30] Khosravi B, Pourahmad S, Bahreini A, Nikeghbalian S, Mehrdad G. Five years survival of patients after liver transplantation and its effective factors by neural network and cox poroportional hazard regression models. Hepat Mon 2015;15:1–7. doi:10.5812/hepatmon.25164.

[31] Markin RS, Wisecarver JL, Radio SJ, Stratta RJ, Langnas AN, Hirst KSBJ. Frozen section evaluation of donor livers before transplantation. Transplantation 1993;56:1403–9.
[32] Eccher A, Neil D, Ciangherotti A, Cima L, Boschiero L, Martignoni G, et al. Digital reporting of whole-slide images is safe and suitable for assessing organ quality in preimplantation renal biopsies. Hum Pathol 2016;47:115–20. doi:10.1016/j.humpath.2015.09.012.
[33] Teramoto T, Shinohara T, Takiyama A. Computer-aided classification of hepatocellular ballooning in liver biopsies from patients with NASH using persistent homology. Comput Methods Programs Biomed 2020;195:105614. doi:10.1016/j.cmpb.2020.105614.
[34] Pérez-Sanz F, Riquelme-Pérez M, Martínez-Barba E, La P-MJ, Nicolás AS, Carpes-Ruiz M, et al. Efficiency of machine learning algorithms for the determination of macrovesicular steatosis in frozen sections stained with sudan to evaluate the quality of the graft in liver transplantation. Sensors 2021;21:1–15. doi:10.3390/s21061993.
[35] Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464–70. doi:10.1053/jhep.2001.22172.
[36] Burra P, Giannini EG, Caraceni P, Ginanni Corradini S, Rendina M, Volpes R, et al. Specific issues concerning the management of patients on the waiting list and after liver transplantation. Liver Int 2018;38:1338–62. doi:10.1111/liv.13755.
[37] Bertsimas D, Kung J, Trichakis N, Wang Y, Hirose R, Vagefi PA. Development and validation of an optimized prediction of mortality for candidates awaiting liver transplantation. Am J Transplant 2019. doi:10.1111/ajt.15172.
[38] Kwong AJ, Ebel NH, Kim WR, Lake JR, Smith JM, Schladt DP, et al. OPTN/SRTR 2020 annual data report: liver. Am J Transplant 2022;22:204–309. doi:10.1111/ajt.16978.
[39] Jassar S, Adams SJ, Zarzeczny A, Burbridge BE. The future of Artificial Intelligence in medicine: medical-legal considerations for health leaders. Healthc Manag Forum 2022;35:185–9. doi:10.1177/08404704221082069.
[40] Brunetto MR, Colombatto P, Bonino F. Bio-mathematical models of viral dynamics to tailor antiviral therapy in chronic viral hepatitis. World J Gastroenterol 2009;15:531–7. doi:10.3748/wjg.15.531.
[41] Iannazzo S, Colombatto P, Ricco G, Oliveri F, Bonino F, Brunetto MR. A cost-effectiveness model to personalize antiviral therapy in naive patients with genotype 1 chronic hepatitis C. Dig Liver Dis 2015;47:249–54. doi:10.1016/j.dld.2014.12.008.
[42] Colombatto P, Demirtas CO, Ricco G, Civitano L, Boraschi P, Scalise P, et al. Modeling hepatocellular carcinoma cells dynamics by serological and imaging biomarkers to explain the different responses to sorafenib and regorafenib. Cancers 2021;13 (Basel). doi:10.3390/cancers13092064.
[43] Damone A, Vainieri M, Brunetto MR, Bonino F, Nuti SCG. Decision-making algorithm and predictive model to assess the impact of infectious disease epidemics on the healthcare system: the COVID-19 case study in Italy. IEEE J Biomed Heal Inf 2022;26:3661–72. doi:10.1109/JBHI.2022.3174470.
[44] Tozzo P, Angiola F, Gabbin A, Politi C, Caenazzo L. The difficult role of Artificial Intelligence in medical liability: to err is not only human. Clin Ter 2021;172:527–8. doi:10.7417/CT.2021.2372.
[45] Vearrier L, Derse AR, Basford JB, Larkin GLMJ. Artificial Intelligence in emergency medicine: benefits, risks, and recommendations. J Emerg Med 2022;62:492–9. doi:10.1016/j.jemermed.2022.01.001.
[46] Maliha G, Gerke S, Cohen IG, Parikh RB. Artificial Intelligence and liability in medicine: balancing safety and innovation. Milbank Q 2021;99:629–47. doi:10.1111/1468-0009.12504.
[47] Debono M, Ghobadi C, Rostami-Hodjegan A, Huatan H, Campbell MJ, Newell-Price J, et al. Modified-release hydrocortisone to provide circadian cortisol profiles. J Clin Endocrinol Metab 2009. doi:10.1210/jc.2008-2380.
[48] Gerke S, Minssen T, Cohen G. Ethical and legal challenges of Artificial Intelligence-driven healthcare. Artificial Intelligence in Healthcare 2020:295–336. doi:10.1016/B978-0-12-818438-7.00012-5.
[49] Price WN II, Gerke S, Cohen IG. Potential liability for physicians using Artificial Intelligence. JAMA 2019;322:1765–6. doi:10.1001/jama.2019.15064.
[50] Smith H, Fotheringham K. Artificial Intelligence in clinical decision-making: rethinking liability. Med Law Int 2020;20:131–54. doi:10.1177/0968533220945766.
[51] Larson DB, Magnus DC, Lungren MP, Shah NH, Langlotz CP. Ethics of using and sharing clinical imaging data for Artificial Intelligence: a proposed framework. Radiology 2020;295:675–82. doi:10.1148/radiol.2020192536.
[52] Kaissis GA, Makowski MR, Rückert D, Braren RF. Secure, privacy-preserving and federated machine learning in medical imaging. Nat Mach Intell 2020;2:305–11. doi:10.1038/s42256-020-0186-1.
[53] Vyas DA, Eisenstein LG, Jones DS. Hidden in plain sight — reconsidering the use of race correction in clinical algorithms. N Engl J Med 2020;383:874–82. doi:10.1056/nejmms2004740.
[54] Larrazabal AJ, Nieto N, Peterson V, Milone DH, Ferrante E. Gender imbalance in medical imaging datasets produces biased classifiers for computer-aided diagnosis. Proc Natl Acad Sci USA 2020;117:12592–4. doi:10.1073/pnas.1919012117.
[55] Mirbabaie M, Hofeditz L, Frick NRJ, Stieglitz S. Artificial Intelligence in hospitals: providing a status quo of ethical considerations in academia to guide future research. AI Soc 2022;37:1361–82. doi:10.1007/s00146-021-01239-4.