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How will artificial intelligence affect diagnosis and treatment of liver disease?

1. Introduction

Recent years have seen a dramatic increase in computational capacity and the volume of data stored which has fuelled progress in machine learning methodology. Increasing attention is turning towards the use of artificial intelligence (AI) in healthcare; AI is facilitating the diagnosis of several conditions, from atrial fibrillation to stroke, and the treatment of others, such as depression and anxiety. Hepatology could see significant change with the introduction of AI but there are important challenges to consider for ensuring successful integration and implementation.

2. What is medical artificial intelligence?

The term 'artificial intelligence' encompasses many techniques, from advanced statistical modelling to 'black box' deep learning algorithms. The area providing the most exciting new applications in healthcare is machine learning (ML), where the *'machine'* is able to *learn* complex and non-linear relationships between variables and outcomes of interest. To do so, self-updating algorithms are fed with large quantities of data, which include variables mapped to outcomes of interest. In doing so, they may elucidate previously unidentified relationships, that traditional statistical methods were unable to detect. ML is also able to analyse types of data not previously amenable to advanced computer-based analysis, such as imaging and text data.

Such techniques have many potential uses in hepatology, from finding new patterns of blood marker variation for predicting or diagnosing liver disease to automating image analysis; from identifying liver regions at risk of irradiation toxicity to using drug structure to predict risk of liver injury. AI could increase diagnostic accuracy, improve decision-making by enhancing predictive capabilities and increase efficiency through automation.

3. AI & new routes of diagnosis

Many liver conditions represent a diagnostic challenge, such as liver cancer which can be difficult to detect at an early stage. One reason is difficulty gaining direct access for visualisation. Commonly preferred modalities of investigation, therefore, are liver function tests (LFTs), ultrasound scans and, when required, biopsies.

LFTs can lack disease-specificity and ultrasound can lack sensitivity and have inter-operator variability. Liver biopsy is the gold standard method of diagnosis for many conditions, such as acute hepatitis and alcohol-related liver disease, however it can cause infection or bleeding and can have sampling errors. In acute or advanced disease, these risks are deemed more permissible due to the imminent need for diagnosis to facilitate treatment. In conditions with a lower risk-benefit, however, the absence of reliable, non-invasive diagnostic tests, can reduce rates of diagnosis. This is true in NAFLD, which is usually asymptomatic but can lead to cirrhosis and HCC. It has thus been a focal point for research, exploring the use of AI to improve diagnosis through enhanced blood test analysis and automated ultrasound analysis.

3.1. Enhanced blood test analysis

AI models can analyse temporal variations of blood test measurements, with other relevant factors such as gender, BMI and genetic profile, to diagnose and predict disease. Numerous models have been developed for diagnosing NAFLD with such data, including Ma et al.'s Bayesian network which obtained an F_1 score of 0.655 [1]. Similar models could be developed for other conditions and may play a role as screening tools, to facilitate earlier treatment. Such analysis may be automated, reducing time doctors spend analysing results and potentially increasing reliability of interpretation. However, we must also guard against over-reliance on such algorithms.

Analysis of key biomarkers using machine learning could also provide deeper insight into the pathophysiology of liver diseases. Ma et al.'s study identified the five strongest predictors of NAFLD as BMI, triglycerides, γGT, ALT and uric acid [1].

3.2. Automation of ultrasound imaging

Use of ultrasound for diagnosis is constrained by technical expertise, equipment availability and inter-operator variability.

Automating analysis of ultrasound imaging may overcome some limitations but is technically challenging.

Fatty liver disease (FLD) is one of the most studied liver conditions for automated ultrasound analysis. It presents a significant challenge as it contains both hypo- and hyper-echogeneic regions. Early approaches using support vector machines (SVMs) showed reasonable accuracy in diagnosis but were computationally expensive. They require the generation of numerous 'support vectors', leading to large matrices of values that the computer must store in its memory and manipulate. Kuppuli et al's single-layer neural network had reduced computational expense and achieved an AUC of 0.92 [2]. More recently, deep learning approaches have shown promise: Byra et al. [3] and Biswas et al. [4] trained CNNs with 97.7% and 100% accuracy, respectively. Other studies have looked at developing similar models for detecting and characterising liver lesions and for staging liver cancers.

However, developing these models usually require manual segmentation or feature extraction, which are time-consuming and require expertise. There may be potential for automatic segmentation using deep learning in future.

4. AI-driven prognostication and treatment

AI could enable more informed treatment decisions by enhancing prediction of outcomes, such as survival following liver transplantation, and risk estimation, such as hepatotoxicity from different treatments.

Present methods are typically reactive rather than predictive. For example, prognostic models in primary biliary sclerosis involve monitoring liver function tests following UDCA therapy [5], which introduces a non-trivial time-delay. New data, including genomic, epigenomic and metabolomics data, has the potential to provide more precise biomarkers which are personalised to individual patients.

4.1. Decision support for liver transplantation

Bertsimas et al. developed a model to predict mortality for candidates awaiting liver transplantation, to enable surgery prioritisation [6]. Using an optimal classification trees approach, they achieved superior AUCs for each risk group compared to existing models and showed a theoretical benefit of 417.96 (17.6%) fewer deaths while waiting for transplantation each year in the United States [6].

AI could also help match donors with recipients. Briceno et al. trained an artificial neural network to predict survival and loss of grafts following transplant [7]. They used 57 different variables, including recipient demographics, diagnosis and comorbidities and donor cause of death. They found AUCs of 0.80 for predicting survival and 0.82 for predicting loss [7], which were significantly higher than existing methods. It is important to use large and international datasets for training such models to prevent overfitting and ensure generalisability.

4.2. Predicting hepatotoxicity

4.2.1. Liver toxicity after radiotherapy

Radiotherapy has become increasingly popular for liver cancers following improvements in targeted delivery. Before such advances, high rates of hepatobiliary toxicity were reported. Stereotactic body radiotherapy (SBRT) is the most advanced method for targeted delivery in common use but toxicity is still observed, particularly in patients with underlying cirrhosis.

Machine learning has the potential to prevent and predict toxicity. It may enable segmentation of tumours and surrounding at-risk organs for guiding delivery. CNN-based liver segmentation has recently shown 95% agreement with manual [8]. One challenge is highly variable tumour appearance in different modalities.

Variables such as phenotypic profiles and baseline liver metabolic function can be used to predict toxicity risk. Ibragimov et al. used a CNN to predict toxicity based on dosing patterns and achieved an AUC of 0.79 [9]. They also found that irradiation of the proximal portal vein has twice the toxicity risk of the left portal vein; an insight which could guide future treatment.

4.2.2. Drug-induced liver injury

Due to its key role in metabolism and its correspondingly large blood supply, the liver is particularly susceptible to drug-induced injury. Predicting which drugs may cause liver injury could aid development of new drugs and clinical trials. In-silico models have been developed which use the chemical structure to classify drugs into liver injury-inducing or not with 72.9% accuracy, 62.8% sensitivity and 79.8% specificity [10].

5. Important considerations

For all AI projects, data security is an important consideration. In healthcare, given the sensitivity of health data, it is even more so. It is important that we respect data protection laws and ensure adequate patient consent. We must proactively identify risks and act with integrity to prevent cases like the Facebook-Cambridge Analytica scandal occurring in healthcare. Public trust is necessary for the development and successful depolyment of such technology.

While AI may demonstrate technical capability for enhanced analysis and predictions, it must also be clinically validated to ensure that efficacy translates to improved real-world outcomes. Integration must also follow careful consider of existing clinical workflows, to facilitate this. Concerns have been raised about the paucity of high-quality, reproducible evidence for some healthcare technologies in use today, and the Theranos scandal is an exemplar of this issue. However, we also want to avoid hindering innovation with excessive regulation and thus an appropriate balance must be found.

There is risk of over-reliance on technology and de-skilling of the workforce. If blood result analysis becomes automated, for example, it is important that we avoid reductions in pathophysiological understanding that impact on our ability to provide care.

6. Conclusion

AI may have the technical capability to support diagnosis, but further development and clinical validation are required before widespread implementation. AI can support treatment decisions by giving accurate predictions of positive and adverse outcomes, facilitating a shift from reactive to proactive management. Developing such tools will likely lead to greater pathophysiological understanding. By facilitating enhanced diagnosis and treatment, AI will support, not replace, doctors, and enable them to harness their experience and human touch in delivering care.

Conflict of interest

Christopher Lovejoy is an employee of Cera Care. Mahiben Maruthappu is an investor and employee of Cera Care. Cera Care is a domiciliary care provider conducting research into how artificial intelligence can be used to improve the care delivered to elderly people living at home.

Ethical approval

Not required. No primary research undertaken, with no involvement of human subjects, human material, or human data.

Consent for publication

No details, images, or videos relating to an individual person contained so no specific consent required.

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Fanconi syndrome due to tenofovir disoproxil fumarate (TDF) after liver transplantation

To the Editor

A 55 year-old man with a previous medical history of hepatitis B virus (HBV) and hepatitis D virus (HDV) infection with decompensated cirrhosis underwent liver transplant (LT) in June 2018. Two weeks after an uneventful liver transplant the patient was taking tacrolimus 9 mg/day, mycophenolate mofetil 360 mg/12 h and prednisone 10 mg/day as part of immunosuppressive therapy, cotrimoxazole 160/800 mg/day, calcium/vitamin D, folic acid 5 mg/day, enalapril 5 mg/day, insulin and TDF 245 mg/day, the latter as a prophylaxis for hepatitis B. Serum creatinine (Cr) and glomerular filtration rate (GFR) at the last outpatient clinic control (July 2018) were 1.03 mg/dl and 81 ml/min, respectively.

In October 2019, four months after LT, laboratory follow-up showed an abnormal renal function (Cr 1.50 mg/dl; GFR 52 ml/min), and the patient referred mild neurological symptoms (tremor, lack of concentration). Due to the suspicion of tacrolimus toxicity the drug was replaced by everolimus (0.75 mg/b.i.d.). Nevertheless, renal function continued to worsen and the patient was finally admitted to our hospital. Laboratory tests showed Cr 1.73 mg/dl and GFR 44 ml/min; 24-h urine showed proteinuria (2.035 g), hyperphosphaturia (1.4 g) glucosuria (14.3 g) and uricosuria (1.1 g). Kidney ultrasound ruled out morphological alterations and renal artery stenosis.

After the later results, highly suggestive of renal tubular damage, the patient was diagnosed with Fanconi syndrome secondary to TDF. TDF was switched to entecavir and the patient was discharged. Three months after discharge renal function had normalized (Cr was 1.2 mg/dl, GFR 62 ml/min) and 24-h urine phosphate and uric acid were also within normal ranges. 24-h urine glucose and protein still remained elevated (2.4 g and 0.179 g per day, respectively), though significantly lower than at hospital admission.

TDF is a nucleotide analogue used since 2001 for treatment of HIV and HBV infection. Renal tubular dysfunction during long-term adefovir or tenofovir therapy in chronic hepatitis B is well known and some patients may develop renal failure, usually mild [1,2]. The degree of association between TDF treatment and changes in markers of renal function/tubular damage vary among studies; discrepancies may result from the use of different definitions and cut-offs for reporting renal toxicity [3].

Fanconi syndrome, an inadequate reabsorption in the proximal renal tubules of the kidney, is caused by various underlying congenital or acquired diseases, and has been associated with drug toxicity. The syndrome has been described in HIV-infected patients who are under TDF, probably due to a combination of TDF toxicity and the use of concomitant antiretroviral drugs. A review of the FDA Adverse Event Reporting System from 2001 to 2006 identified 164 TDF-treated HIV-infected patients with Fanconi syndrome, 83% of which received protease inhibitors [4]. Contrarily, there are very few reported cases of Fanconi syndrome in HBV monoinfected patients treated with tenofovir. In a review article published on 2016 only 8 cases were identified [3] and we only found 5 additional cases of Fanconi syndrome due to TDF in chronic HBV-monoinfected patients [5–9], including a case of early renal injury in a pediatric patient treated for acute hepatitis B [9]. Despite its extremely low incidence, Fanconi syndrome should be suspected in liver transplant patients on TDF with signs of tubular damage. As recommended by the recently published EASL Clinical Guidelines [10], patients treated with TDF should undergo periodical renal monitoring including at least GFR and serum phosphate levels. The concomitant use of nephrotoxic drugs in transplant recipients (i.e. immunosupressants) may be a facilitating factor for TDF toxicity. In such cases, treatment should be immediately changed to tenofovir alafenamide or entecavir.

Conflict of interest

XF has acted as advisor for Gilead and Abbive. JC declares lectures paid by Gilead.

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