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ABOUT COVER

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The primary aim of *Artificial Intelligence in Gastroenterology* (*AIG*, *Artif Intell Gastroenterol*) is to provide scholars and readers from various fields of artificial intelligence in gastroenterology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

AIG mainly publishes articles reporting research results obtained in the field of artificial intelligence in gastroenterology and covering a wide range of topics, including artificial intelligence in gastrointestinal cancer, liver cancer, pancreatic cancer, hepatitis B, hepatitis C, nonalcoholic fatty liver disease, inflammatory bowel disease, irritable bowel syndrome, and *Helicobacter pylori* infection.

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MINIREVIEWS

Role of artificial intelligence in Barrett's esophagus

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Abstract

The application of artificial intelligence (AI) in gastrointestinal endoscopy has gained significant traction over the last decade. One of the more recent applications of AI in this field includes the detection of dysplasia and cancer in Barrett's esophagus (BE). AI using deep learning methods has shown promise as an adjunct to the endoscopist in detecting dysplasia and cancer. Apart from visual detection and diagnosis, AI may also aid in reducing the considerable interobserver variability in identifying and distinguishing dysplasia on whole slide images from digitized BE histology slides. This review aims to provide a comprehensive summary of the key studies thus far as well as providing an insight into the future role of AI in Barrett's esophagus.

Key Words: Artificial intelligence; Barrett's esophagus; Dysplasia; Cancer

Core Tip: Barrett's esophagus is a significant precursor to esophageal adenocarcinoma. Detection of dysplasia or neoplastic changes in Barrett's esophagus can often be difficult as endoscopic changes can be subtle. Artificial intelligence has the potential to aid endoscopist in detecting such lesions endoscopically and also reduce the interobserver variability in detecting dysplasia in Barrett's esophagus histologically.

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INTRODUCTION

"Artificial Intelligence" (AI) is a generic term used to denote the ability of a computer program to learn and solve problems autonomously[1]. AI uses input data to learn with the intention of refining the ability to process new data samples that are not part of the original set of training data. This process of "machine learning" (ML) uses mathematical algorithms to capture structure and patterns in large data sets, often in a way that allows the learned function to be applied to new data. Machine learning can be supervised or unsupervised depending on whether the algorithms were trained with known patterns or unknown patterns respectively[2]. Deep learning is a subtype of machine learning in which a convolutional neural network (CNN) receives input (*e.g.*, endoscopic images), learns specific patterns (*e.g.*, mucosal surface/vascular pattern) and processes this information through the multi-layered network to produce an output (*e.g.*, presence or absence of neoplasia). This form of deep learning algorithm is the main driver for the rapidly advancing role of computer-aided diagnosis (CAD) in detection and characterization of lesions during endoscopy[3].

The greatest impact of AI in gastrointestinal (GI) endoscopy has been made in the area of colonic polyp and adenoma detection[4]. Several clinical studies and meta-analyses have shown the potential and at times, the superiority of AI in colonic adenoma detection rate compared to the endoscopist[5-8]. The crux of AI research in GI endoscopy has focused primarily on three domains which include detection, classification and delineation of lesions or disease entities[9]. There is an increasing amount of research in all three domains with regards to the application of AI in BE.

BARRETT'S ESOPHAGUS

Barrett's esophagus (BE) is defined as a change in the squamous lining of the distal esophagus to metaplastic columnar epithelium with goblet cells[10]. This is typically associated with chronic gastroesophageal reflux disease (GERD) with as much as 12% of patients with GERD symptoms harboring BE[11]. While there are variances in how BE is defined between different guidelines[12-14], there is definitive data that it is a precursor that increases the risk of esophageal adenocarcinoma (EAC)[15]. Hence early detection of dysplasia within BE is crucial to institute definitive treatment where possible and prevent further progression into neoplasia. However, this remains a challenge as endoscopic changes indicating dysplasia or early neoplasia can be subtle and be easily missed[16]. Even when there is no visible dysplasia and biopsies are done as per the Seattle protocol, sampling error can lead to areas of concern being missed[17]. The endoscopic diagnosis of BE dysplasia is generally a two-step process of primary detection in overview, followed by detailed inspection of these visible abnormalities for characterization[18]. This process relies on the individual experience of the endoscopist, which might further introduce variations and bias, leading to misjudgment and potentially delay in diagnosis and treatment.

Initially there was great interest in image enhancement technologies to overcome these challenges but to date only virtual and dye based chromoendoscopy have met the parameters outlined in American Society for Gastrointestinal Endoscopy's (ASGE) Preservation and Incorporation of Valuable Endoscopic Innovations (PIVI). Specific to BE imaging [19], PIVI recommends that imaging technology with targeted biopsies should have a per-patient sensitivity of 90% or greater and a specificity of 80% or higher to allow reduction in the number of biopsies.

AI has since emerged as a promising adjunct on this front. AI uses various ML algorithms including CNN to identify and process real time endoscopic data to overcome the inherent limitations of an endoscopist.

AIM OF REVIEW

This review will provide a comprehensive summary of the present evidence, recent research advances and future perspectives regarding the utility of AI in BE endoscopy. AI may overcome the human limitations related to poor intra- and inter-observer agreement, a burden that affects many aspects of medical imaging and endoscopy. If a CAD system was to be trained to distinguish between neoplastic and non-neoplastic BE macroscopically on endoscopy and microscopically on histology with almost-perfection, it seems logical these limitations can be overcomed and better tailored medical management can be rendered.

METHODS AND LITERATURE SEARCH

A comprehensive electronic literature search was performed in the PubMed, MEDLINE and EMBASE databases from inception to the 1st September 2022 using the following key search terms "artificial intelligence" OR "AI" OR "convolutional neural network" OR "deep learning" OR "computer-aided detection" OR "computer-aided diagnosis" AND "Barrett's esophagus." The search was limited to human studies.

Titles and abstracts were screened to exclude studies that did not address the purpose of this review article. The titles of all the identified studies were screened by two reviewers (TNCH and RR) to exclude studies not related to the study topic. The full texts of the screened studies were then assessed for inclusion. Review articles and letters to the editor were excluded. Studies that used other endoscopic techniques such as volumetric laser endomicroscopy were also excluded. Any disagreements were resolved through discussion with senior author LJW until consensus was achieved.

Eligible studies including 12 meta-analyses which reported the use of AI in Barrett's endoscopy and histopathology were included in the review. The analysis flow chart of the included studies is shown in Figure 1.

EXISTING DATA ON THE UTILITY OF AI IN BARRETT'S ESOPHAGUS

Identification and classification of Barrett's esophagus

Pan *et al*[20] developed a DL algorithm using 443 endoscopic images from 187 patients to automatically identify and segment the gastroesophageal junction and squamous-columnar junction of BE. The performance of this automated segmentation algorithm demonstrated satisfactory agreement with expert annotations as measured by intersection over union. This study demonstrates the potential of DL in automating the identification and the classification of BE according to the Prague C&M classification[21] while reducing the inter-observer variability.

DETECTION OF DYSPLASIA AND ADENOCARCINOMA

Following successful identification and classification of BE, the subsequent detection of dysplasia or EAC can be clinically challenging, particularly for non-experts[22]. Further differentiation between non-dysplasia, low-grade dysplasia, high-grade dysplasia and EAC can be subjective and difficult when a focal lesion has been detected. Ebigbo *et al*[23] managed to demonstrate that a CAD system using deep learning of still images [248 high-definition white light images and 74 narrow band images (NBI)] from two databases, was able to diagnose EAC with sensitivity of 97% and 92% as well as specificity of 88% and 100% for white light images (WLI) in both databases respectively. Additionally, the CAD system was able to achieve sensitivity of 94% and specificity of 80% for NBI images. This study demonstrated that a CNN algorithm was able to accurately identify EAC in still endoscopic images, all validated by expert pathologists, at a sufficiently high sensitivity and specificity to meet the PIVI standards mentioned previously.

Due to the limitations of using still endoscopic images, further steps were taken to validate the AI system in real-time by assessing captured endoscopic images taken by an expert BE endoscopist to differentiate between EAC and normal BE with a sensitivity and specificity of 83.7% and 100% respectively with an overall accuracy of 89.9%[24].

Concurrently, de Groof *et al*[25] conducted a pilot study to develop a CAD system using white light endoscopic images from 60 patients to delineate between BE neoplasm and non-dysplastic BE. One endoscopic image from each patient was included in the CAD system with per-image analysis demonstrating sensitivity of 95%, specificity of 85% and diagnostic accuracy of 91.7%. The CAD system was not only able to delineate a BE neoplastic lesion but also able to indicate the most abnormal area within that delineation to obtain a targeted biopsy. Additionally, it took an average of 1.051 s for the algorithm to analyze an endoscopic image and subsequently produce its lesion delineation, signaling the potential to be used in a real-time, automated setting.

The same group of investigators went on further to develop a deep-learning CAD system for primary detection of neoplasia in patients with BE using a CNN model. The system was initially pretrained with a large dataset of 494364 Labeled endoscopic images from multiple locations of the GI tract using a supervised learning approach. The system was then subsequently trained with BE-specific endoscopic images containing a total of 1544 images of BE neoplasia and non-dysplastic BE before being validated using two separate external datasets. The CAD system managed to classify images as containing neoplasms or non-dysplastic BE with 89% accuracy, 90% sensitivity and 88% specificity. Performance was also benchmarked against 53 general endoscopists with a wide range of experience. When compared to the endoscopists, the CAD system managed to achieve higher diagnostic accuracy of 88% *vs* 73%, sensitivity of 93% *vs* 72% and specificity of 83% *vs* 74%[26]. Apart from the large databases used to develop and validate the CNN based algorithm, the computational speed per image analysis was 0.24 s which was a significant improvement from their previous CAD system, paving the way for the incorporation of the CAD system during live endoscopic procedures to help delineate BE neoplastic lesions.

For further validation, the CAD system was tested during live endoscopic procedures in 10 patients with non-dysplastic BE and 10 patients with confirmed BE neoplasia. White light endoscopic images were obtained at every 2 cm level of the Barrett's segment and analyzed by the CAD system. The per-level analysis was 90% accurate with a 91% sensitivity and 89% specificity[27], highlighting the comparable diagnostic performance of the CAD system in both real-time and "offline" settings.

Another study also utilized image databases to develop an AI algorithm using 132 high-definition white light endoscopic images from 46 lesions of histologically confirmed Barrett's neoplasia and 119 images on non-dysplastic Barrett's from 20 patients. The images were used for training, validation and testing of a CNN algorithm to detect Barrett's neoplasia with a sensitivity of 93%, specificity of 78% and accuracy of 83%[28].

The utility of AI in CAD of BE neoplasia was further highlighted in another pilot study, in which Hashimoto *et al*[29] developed a CNN algorithm using 916 images of histology-proven early BE neoplasia containing high-grade dysplasia or T1 stage adenocarcinoma and 919 control images of BE without high-grade dysplasia. The trained CNN algorithm managed to correctly detect early neoplasia in a total of 458 test images with sensitivity of 96.4%, specificity of 94.2% and accuracy of 95.4%.

With the widespread use of image enhanced endoscopy like NBI in routine endoscopic practice for further lesion characterization, it is only natural that a deep learning algorithm would be developed to interpret NBI images and to aid in the diagnosis of BE neoplasia. A study was conducted using a trained CAD system to interpret 183 NBI zoom images

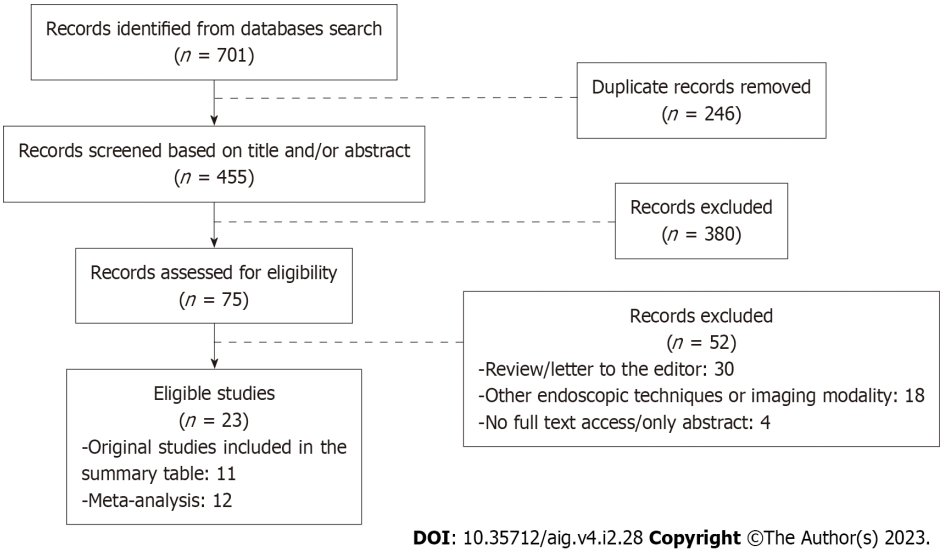

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Figure 1 Identification of studies *via* databases – analyses flow chart of included studies.

and 157 NBI zoom videos with similar diagnostic accuracy of 84%-85%[30].

As most AI studies were largely image database studies and relatively small in number, a meta-analysis of the studies on the performance of AI in detection and characterization of upper GI neoplasia was performed by Arribas *et al*[34], which included nine studies[22-26,28,31-33] on BE neoplasia detection (total of 12909 images from 1506 patients used for training and a total of 2340 images from 445 patients used for testing). The pooled sensitivity and specificity of BE neoplasia detection was 89% and 88% respectively.

A more recent meta-analysis of twelve studies[22,24-28,30,35-38] was conducted to evaluate the diagnostic performance of AI in detecting BE neoplasia comprising 1361 patients and utilizing 532328 images for training. Pooled sensitivity was 90.3% while pooled specificity was 84.4%. Further subgroup analysis demonstrated that pooled sensitivity and specificity were also similar in six studies that used WLI as the main mode of modality[39]. An interesting observation from the meta-analysis was that there was significant heterogeneity amongst the included studies with I^2 of > 50% but the area under the summary of receiver operating characteristics curve was 0.94 (95%CI: 0.92-0.96). Upon further assessment of these studies, multiple factors such as the definitions of dysplastic Barrett's, the different types of AI algorithm and imaging modality used are very likely to contribute to the heterogeneity of the study outcome. This highlights the importance for further standardization of future study protocols with regards to the definition of BE neoplastic lesions and imaging modality used.

PREDICTION OF SUBMUCOSAL INVASION IN BARRETT'S ESOPHAGUS

Apart from detection and classification of neoplasia in BE, the application of AI has shown promise in predicting submucosal invasion in Barrett's cancer. The identification of submucosal invasion (T1b) in Barrett's cancer is important as it has implications for the choice of treatment. Lesions with suspected submucosal invasion should be treated with endoscopic submucosal dissection (ESD) instead of the conventional endoscopic mucosal resection (EMR). ESD is a viable alternative to surgery and considered curative if the resected specimen fulfills the necessary criteria including submucosal invasion depth < 500 μm, good to moderate differentiation and no lympho-vascular invasion[13,40]. A retrospective, multicenter study was conducted to evaluate the diagnostic performance of a CNN based algorithm using a total of 230 white-light endoscopic still images to discriminate between mucosal (T1a) and submucosal (T1b) Barrett's cancer. The trained AI algorithm was able to predict submucosal invasion and differentiate between T1a and T1b carcinoma with a sensitivity of 77%, specificity of 64% and an accuracy of 71%. The AI algorithm demonstrated comparable performance to five international Barrett's expert endoscopists who evaluated the same set of images[41]. This study brings to light the potential for AI to support the clinical decision-making process with regards to the endoscopic *vs* surgical resection of precancerous lesions by predicting the submucosal invasion in Barrett's cancer.

ARTIFICIAL INTELLIGENCE IN BARRETT'S HISTOPATHOLOGY

Interobserver agreement between pathologists can be variable with regards to interpretation of BE histology, a recognized issue particularly for low grade dysplasia (LGD) and indefinite dysplasia (IND)[42]. A study showed that concordance between pathologists progressively decreased from non-dysplastic BE (79%), high grade dysplasia (71%), LGD (42%) to IND (23%)[43]. Given that a diagnosis of dysplasia has significant implications on surveillance schedule and BE therapy, American College of Gastroenterology recommends confirmation by a second GI pathologist for dysplasia of any grade

detected on biopsy[12].

Attempts have been made to use AI to complement the pathologist and improve interpretation of BE histology. It has been made possible with the rapid advancement in the field of digital pathology and the subsequent incorporation of image analysis using AI. Since the introduction of commercial digital slide scanners, it was possible to digitize glass histology slides into whole-slide images (WSI), to facilitate slide-sharing and clinical discussion, archiving of digitized slides and extraction of histopathological features using deep learning methods for image analysis[44].

A study utilized an attention-based CNN algorithm to analyze BE and esophageal adenocarcinoma using high-resolution WSI and achieved a mean classification accuracy of 83%[45]. Similarly, another study trained and validated a deep learning model using WSI from 542 patients that managed to demonstrate sensitivity and specificity > 90% at the various grades of dysplasia (non-dysplastic BE, LGD and HGD)[46]. In time, we expect more studies and advances in this field that can improve interpretation of BE histology with reproducible reliability.

FUTURE PERSPECTIVES OF ARTIFICIAL INTELLIGENCE IN BARRETT'S ESOPHAGUS

GI endoscopy has seen remarkable progress throughout the last few decades with incremental step-wise progress through incorporation of breakthrough technology and medical device innovation. AI has the potential to push the innovation boundary of GI endoscopy by leveraging on existing and new information as well as vast databases to formulate algorithms, and to support the clinician in identifying and characterizing suspicious lesions. In practice, live upper endoscopic images can be sent locally or remotely to the AI system and be analyzed in real time. Based on the available data and capability, the system will be able to detect suspicious lesions for neoplasia and alert the endoscopists to those lesions either with a screen alert or location box. The endoscopist can then decide on the management of the highlighted lesion based on the characterization provided by the system.

AI can lead to earlier detection of neoplasia in BE, improvement in prognosis and reduction of mortality due to EAC. AI in BE is still in its infancy and there is no long-term data to determine the impact of AI on reduction of EAC incidence and EAC-related mortality[47]. But it is not difficult to envision that early and correct staging of neoplasia will spare the patient from the grueling experience of esophageal surgery and will enable the possibility of minimally invasive endoscopic treatments. Additionally, as described above, the invasion of depth of detected lesions could be characterized with a higher level of confidence, in particular among less experienced endoscopists, in the differentiation between mucosal and submucosal invasion. This has therapeutic consequences in the endoscopic resection approach; EMR *vs* ESD. The studies described were summarized in Table 1.

Table 1 Summary of the original research studies included in the review

Ref.	Study objective	Diagnostic modality	Study type	Real time	Dysplasia inclusion	Test images, *n*	Diagnostic performance
Pan *et al*[20], 2021	BE segment identification	WLI, NBI	Retrospective	No	NA	443	IOU: GEJ 0.56, SCJ 0.82, GEJ+SCJ 0.66
Ebigbo *et al*[23], 2019	BE neoplasia detection	WLI, NBI	Retrospective	No	EAC	MICCAI: 100; Ausburg: 148	Sen 92%, Spec 100%; WLI: Sen 97%, Spec 88%; NBI: Sen 94%, Spec 80%
Ebigbo *et al*[24], 2020	BE neoplasia detection	WLI	Prospective	Yes	EAC	191	Sen 83.7%, Spec 100%
de Groof *et al*[25], 2019	BE neoplasia detection	WLI	Retrospective	No	HGD, EAC	60	Sen 95%, Spec 85%
de Groof *et al*[26], 2020	BE neoplasia detection	WLI	Retrospective	No	HGD, EAC	297; 80; 80	Sen 87.6%, Spec 88.6%; Sen 90%, Spec 87.5%; Sen 92.5%, Spec 82.5%
de Groof *et al*[27], 2020	BE neoplasia detection	WLI	Prospective	Yes	HGD, EAC	144	Sen 91%, Spec 89%
Abdelrahim *et al*[28], 2020	BE neoplasia detection	WLI	Retrospective	No	NA	251	Sen 93%, Spec 78%
Hashimoto *et al*[29], 2020	BE neoplasia detection	WLI, NBI	Retrospective	No	HGD, EAC	458	Sen 96.4%, Spec 94.2%
Struyvenberg *et al*[30], 2021	BE neoplasia detection	NBI	Retrospective	No	HGD, EAC	183 zoom images; 157 zoom videos	Sen 88%, Spec 78%; Sen 85%, Spec 83%
Ebigbo *et al*[41], 2021	BE cancer invasion	WLI	Retrospective	No	EAC (T1a, T2a)	230	Sen 77%, Spec 64%
Tomita *et al*[45],	BE neoplasia	NA	Retrospective	No	LGD, HGD,	123 WSI	Mean accuracy 83%

2019	histology detection	EAC

BE: Barrett's esophagus; WLI: White-light images; NBI: Narrow-band images; LGD: Low grade dysplasia; HGD: High grade dysplasia; EAC: Esophageal adenocarcinoma; IOU: Intersection over union; GEJ: Gastro-esophageal junction; SCJ: Squamo-columnar junction; Sen: Sensitivity; Spec: Specificity; MICCAI: Medical Image Computing and Computer-Assisted Intervention; WSI: Whole-slide images; NA: Not available.

AI has also the potential to reduce inter-observer variability in interpretation of not only endoscopic images but also of high-resolution, digitized histology slides to ascertain presence of dysplasia or EAC, thereby alleviating the burden of having a second pathologist for confirmation. As AI systems develop and assimilate into clinical practice, it becomes imperative that they are tested and validated in real-world settings, in diverse patient populations, with physicians of varying expertise, with different endoscope types and in different practice settings. There has been a proposal by ASGE AI task force to develop a large open-source image library as a resource to validate AI systems and to moderate data variability[48].

It is also conceivable that a trained AI system will also be able to generate an endoscopy report at the end of a session, including automated Prague C&M measurements, measurements of hiatal hernia and so on to be reviewed by the endoscopist for verification. Extending beyond that, AI has the potential, *via* a subtype of deep learning called natural language processing[49,50], to automatically extract and analyze keywords from free-text endoscopic and pathology reports, potentially aiding the physician to diagnose, plan and to recommend the appropriate endoscopic surveillance intervals for patients with BE.

CONCLUSION

AI has made significant progress in diagnostic endoscopy and in the identification of BE pathology using a digital workflow. AI driven systems are likely to become an important tool to detect and to characterize Barrett's esophagus related dysplasia and early adenocarcinoma as they can present as very subtle lesions on endoscopy. Further development and validation are required before AI can be adopted mainstream in the clinical management of BE.

FOOTNOTES

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ORIGINAL ARTICLE

Observational Study

Drug-induced liver injury and COVID-19: Use of artificial intelligence and the updated Roussel Uclaf Causality Assessment Method in clinical practice

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Abstract

BACKGROUND

Liver injury is a relevant condition in coronavirus disease 2019 (COVID-19) inpatients. Pathophysiology varies from direct infection by virus, systemic inflammation or drug-induced adverse reaction (DILI). DILI detection and monitoring is clinically relevant, as it may contribute to poor prognosis, prolonged hospitalization and increase indirect healthcare costs. Artificial Intelligence (AI) applied in data mining of electronic medical records combining abnormal liver tests, keyword searching tools, and risk factors analysis is a relevant opportunity for early DILI detection by automated algorithms.

AIM

To describe DILI cases in COVID-19 inpatients detected from data mining in electronic medical records (EMR) using AI and the updated Roussel Uclaf Causality Assessment Method (RUCAM).

METHODS

The study was conducted in March 2021 in a hospital in southern Brazil. The NoHarm© system uses AI to support decision making in clinical pharmacy. Hospital admissions were 100523 during this period, of which 478 met the inclusion criteria. From these, 290 inpatients were excluded due to alternative causes of liver injury and/or due to not having COVID-19. We manually reviewed the EMR of 188 patients for DILI investigation. Absence of clinical information excluded most eligible patients. The DILI assessment causality was possible *via* the updated RUCAM in 17 patients.

RESULTS

Mean patient age was 53 years (SD ± 18.37; range 22-83), most were male (70%), and admitted to the non-intensive care unit sector (65%). Liver injury pattern was mainly mixed, mean time to normalization of liver markers was 10 d, and mean length of hospitalization was 20.5 d (SD ± 16; range 7-70). Almost all patients recovered from DILI and one patient died of multiple organ failure. There were 31 suspected drugs with the following RUCAM score: Possible (n = 24), probable (n = 5), and unlikely (n = 2). DILI agents in our study were ivermectin, bicalutamide, linezolid, azithromycin, ceftriaxone, amoxicillin-clavulanate, tocilizumab, piperacillin-tazobactam, and albendazole. Lack of essential clinical information excluded most patients. Although rare, DILI is a relevant clinical condition in COVID-19 patients and may contribute to poor prognostics.

CONCLUSION

The incidence of DILI in COVID-19 inpatients is rare and the absence of relevant clinical information on EMR may underestimate DILI rates. Prospects involve creation and validation of alerts for risk factors in all DILI patients based on RUCAM assessment causality, alterations of liver biomarkers and AI and machine learning.

Key Words: Chemical and drug induced liver injury; RUCAM; Artificial intelligence; COVID-19; Liver injury

Core Tip: This is a real-life study that correlated hospital clinical pharmacy data with artificial intelligence (AI) and pharmacovigilance in coronavirus disease 2019 (COVID-19) inpatients. Inpatient screening for liver injury was made with AI and drug-induced liver injury was evaluated with the Roussel Uclaf Causality Assessment Method (RUCAM) algorithm. A total of 17 COVID-19 inpatients were evaluated, there were 31 suspected drugs, RUCAM score: possible (n = 24), probable (n = 5), and unlikely (n = 2). This study contributed to the patient safety and pharmacovigilance database. These results are included in a project of clinical pharmacy using AI tools.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic put global health systems at risk of collapse worldwide, with more than 510270667 globally confirmed cases and 6233526 deaths in the past two years[1]. COVID-19 patients may be asymptomatic or develop severe acute respiratory syndrome (SARS) with mild to severe manifestations. As a multiple organ disease, extrapulmonary clinical features range from gastrointestinal to hematological effects. Critically ill patients or those with comorbidities commonly present venous and arterial thromboembolic events, liver injury, secondary bacterial infections including sepsis or cytokine storm, contributing to a poor prognosis and higher mortality rates[2-4]. Current treatment options can be supportive clinical management to drug use such as oxygen, dexamethasone for systemic inflammation, heparin/enoxaparin in prophylaxis of venous thromboembolism, and antiviral or monoclonal antibody such as remdesivir, baricitinib, tofacitinib, and tocilizumab[1,5].

Liver injury is a relevant condition in COVID-19 inpatients. In 2020, liver enzyme abnormalities were estimated to occur in 14% to 53% of patients[6,7]. The liver injury pattern is mild to moderate hepatocellular injury, considering aspartate aminotransferase (AST)/alanine aminotransferase (ALT) <5× the upper limit of normal (ULN) and cholestatic for Delta/Omicron variants[8,9]. High levels of AST and ALT, gamma-glutamyl transferase, and total bilirubin have been associated with severe COVID-19, intensive care unit (ICU) admission, and prolonged hospital stay[10-12]. Pathophysiology possibilities of liver injury in COVID-19 vary from direct infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), hypoxic changes, systemic inflammation, exacerbation of underlying disease and adverse drug reactions. Drug-induced liver injury (DILI) may be present in COVID-19 patients due to wide exposure to multiple treatments with antipyretic, antibiotics, corticosteroids, immunomodulators, and antiviral drugs[13,14].

DILI is a rare adverse drug reaction (ADR) that can cause acute liver failure and even the need for liver transplantation in the worst cases[15]. The disease is classified as hepatocellular, cholestatic, or mixed[16]. The diagnosis is made by exclusion of other liver pathologies such as cirrhosis, viral hepatitis, auto-immune hepatitis or other chronic liver diseases. In clinical practice, relevant DILI occurs when patients present ALT>5×ULN with jaundice, hepatomegaly, hyperbilirubinemia, or right-upper-quadrant pain. In most DILI cases, withdrawal of suspected drug(s) and supportive therapy are the standard treatment practices[13,15,17]. DILI detection and monitoring is clinically relevant, as it may contribute to poor prognosis, prolonged hospitalization and increase indirect healthcare costs[12,14,15].

The updated Roussel Uclaf Causality Assessment Method (RUCAM) is a causality assessment tool strongly recommended by specialists worldwide to evaluate and correlate liver damage to drug/herb use due to its hepatic specificity[18]. The updated RUCAM was complemented by additional criteria to establish DILI with a high degree of certainty, such as clarification of ambiguous questions related to alcohol use, exclusion of non-drug causes as a checklist of differential diagnosis[16].

DILI causality is scored in RUCAM by seven domains: time to symptoms onset, ALT course, patient's risk factors such as alcoholism and age, concomitant drug use, non-drug causes of liver injury, previous knowledge on the hepatotoxicity of the drug, and response to rechallenge. The individual points range from −3 to +3 and the total possible score ranges from −9 to +14. The interpretation of the final score is as follows: 0 or less indicates that the drug is "excluded" as a cause; 1 to 2 that it is "unlikely"; 3 to 5, "possible"; 6 to 8, "probable"; and greater than 8, "highly probable". Although RUCAM provides an objective scoring system, its use still shows limitations regarding expert interpretation and comorbidities such as COVID-19 itself[13,19]. Lack of good quality evidence-based DILI is a reality in Brazil and its early detection by healthcare professionals is an important challenge[20]. DILI sub notification may be attributed to lack of knowledge on how to properly assess DILI and apply RUCAM.

Recent literature has shown the use of technologies to actively search and assess ADR. Artificial intelligence (AI) algorithm-based applications simulate human decision making based on large datasets and health information patterns [21,22]. In the field of *in vitro* studies, AI that uses prediction models based on the chemical structure of compounds and the exploration of 2D and 3D *in vitro* imaging data have demonstrated interesting results in predicting DILI for novel drugs[23]. In clinical practice, a systematic review demonstrated that AI has been used in COVID-19 for diagnosis, clinical decision making, drug discovery, vaccine development and surveillance and chest images classification[21].

Literature has shown interesting AI tools to detect and analyze COVID-19 patients such as rapid classification of medical images (X-ray) through convolutional neural networks using datasets with positive and negative images of COVID-19 inpatients[24]. Specifically for DILI, AI applied in data mining of EMR combining abnormal liver tests, keyword searching tools, and risk factors analysis is a relevant opportunity for automated algorithms to detect possible DILI cases early[25].

Despite global large-scale vaccination slowing the advance of the COVID-19 pandemic, the disease remains a serious concern, demanding clinical investigation and elucidation. Polypharmacy and off label drugs use in COVID-19 are an alert for DILI screening since they can contribute to poor clinical outcomes. This observational study aims to describe DILI cases in COVID-19 inpatients retrospectively detected using AI from data mining in EMR. We intend to discuss the hepatotoxicity profile of drugs used in COVID-19 detected cases assessed by RUCAM, as well as the current prospects and challenges of applying AI and the updated RUCAM in inpatient evaluation that may contribute to patient safety and pharmacovigilance practices.

MATERIALS AND METHODS

We conducted a descriptive retrospective study investigating alterations in liver markers in patients diagnosed with COVID-19 who were admitted to a reference COVID-19 hospital complex in southern Brazil during March 2021. The hospital complex comprises 7 hospitals with different specialties such as cardiology, pulmonology, neurology, pediatrics, and general care, with emergencies, ICU, and a surgical center. In March, 100523 patients were admitted.

We included all patients aged 18 years or more who had COVID-19 diagnosed by real-time polymerase chain reaction assays, with at least one complete set of ALT, AST, and alkaline phosphatase (ALP) results during their inpatient stay and with at least one normal and one abnormal ALT value. We excluded patients with liver injuries defined by other etiologies such as viral hepatitis, alcoholic hepatitis, hepatocellular carcinoma, autoimmune hepatitis, cytomegalovirus, leptospirosis, Epstein Barr, hemolytic diseases, among other hepatobiliary disorders.

The hospital is associated with the NoHarm©[26], a system that uses AI to support decision making in clinical pharmacy. It currently develops two algorithms to optimize pharmacist validation for prioritizing non-standard prescriptions and identifying critical patients. The system is linked to hospital data and indicates potential prescription errors, increasing quality of care and hospital efficiency. We used this AI platform to automatically screen EMR of inpatients with ALT>3×ULN who were suspected of having DILI. We accessed each patient in this platform to check inclusion/exclusion criteria. Afterwards, a chart with ALT course during hospitalization was presented to guide investigators in which days relevant clinical information should be collected. The ALT>3×ULN was chosen to be a cut off to pre-analyze patients for DILI.

We applied the updated RUCAM to all suspected cases of DILI[27]. Then, two independent reviewers (GL and GXO) separately assessed the likelihood of altered liver tests being related to drug use during hospital stay. In the case of disagreement, a third pharmacist reviewed the suspected DILI case. If there was still no consensus, the case was discussed with a fourth hepatology specialist. The domains evaluated were liver injury pattern, timing of events, rechallenge, risk factors, comedications, alternative causes, hepatotoxicity previously established in the scientific

literature, and response to unintentional rechallenge.

The RUCAM classifies DILI as highly probable (≥ 9), probable (6-8), possible (3-5), unlikely (1-2), or excluded (≤ 0)[16]. Cases scored as highly probable, probable, and possible were considered as DILI. Since this is a retrospective study, not all patients would have the same profile of laboratory tests to rule out other causes of abnormal liver chemistries. The RUCAM is used for DILI diagnosis in individual cases, case series, registries, or epidemiological studies involving any types of drugs, herbal medicines, or dietary supplements. Thus, assessments were only based on information available in EMR. Missed information in EMR may compromise RUCAM scores, decreasing punctuation as well as the likelihood of DILI. Drugs with a well-established pattern of absence of liver toxicity in which they were used at usual doses and treatment times were not included in the RUCAM analysis, unless they were the only drug used and the timeframe of events were highly compatible with DILI. Liver injury pattern is defined by the R (the ratio of ALT and ALP expressed as multiples of the ULN) and corresponds to: (1) Hepatocellular if R≥5, (2) mixed if 2<R<5, and (3) cholestatic if R≤2.

Data were constituted by the patient's profile, symptoms, drugs, laboratory tests, image and biopsy exams, if available, hospitalization time, and outcomes. Due to the small sample, statistical analysis of independent variables (risk factors) of DILI was not performed. However, it did not compromise the purpose of the study which is to describe possible DILI cases and suspected COVID-19 medications. The analysis evaluated DILI causality.

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations checklist was applied to this study to facilitate critical appraisal and interpretation of cross-sectional study results[28]. This study was approved by the Ethics Committee (number 4763390 CAAE 46652521.9.0000.5530).

RESULTS

In total, 100523 patients were admitted into the hospital in March 2021, with 478 inpatients showing at least one ALT result >3×ULN detected by AI. Of these, we excluded 290 inpatients with alternative causes of liver enzyme elevation, and who were not positive for COVID-19. We reviewed 188 EMR. From these, absence of essential clinical information excluded most patients. Figure 1 summarizes patients' inclusion and exclusion criteria. The main missing information was serum transaminases follow-up in 91 patients as the patient was released for outpatient follow-up at the slightest improvement. A total of 34 patients had COVID-19 but the ALT peaks were due to other causes such as sepsis, cardiopulmonary arrest, or hypovolemic shock; 16 patients did not use any suspected drug; and 10 patients used medications before hospital admission with no posology information. Lack of virology tests excluded 20 patients who could possibly have had DILI. Drugs used in those patients were chlorpromazine, azithromycin, ceftriaxone, bicalutamide, and ivermectin (off-label use). All of them are well established common DILI agents. We assessed DILI causality with the updated RUCAM in 17 patients and Table 1 shows the complete RUCAM score.

The mean age of patients was 53 years (SD ± 18.37; range 22-83). Most were male (70%), and admitted to the non-ICU sector (65%). The liver injury pattern was mainly mixed with mean normalization of liver injury within 10 d and mean length of hospitalization was 20.5 days (SD ± 16; range 7-70). Almost all patients recovered from DILI and one patient died of multiple organ failure. There were 31 suspected drugs with 2 medications suspected per inpatient. The RUCAM score distribution was as follows: 24 possible cases, 5 probable, and 2 unlikely. The DILI agents in our study were ivermectin, bicalutamide, linezolid, azithromycin, ceftriaxone, amoxicillin-clavulanate, tocilizumab, piperacillin-tazobactam, and albendazole. Antimicrobials were 77% of the suspected agents, followed by antiparasitic 16%, and antineoplastic and immunomodulating agents 7%.

DISCUSSION

The DILI prevalence was 1.6 to every 10000 inpatients in this study differing from the 9.8% in China[29]. The first review of Brazilian DILI case reports was published in 2019 showing DILI as a rare ADR; however, this is controversial since DILI underreporting is a major concern leading to alarmingly low rates of its suspicion and identification[30]. The DILI prevalence in hospitalized patients tends to be higher than in our study. A prospective study from France reported a DILI prevalence of 6.6 per 1000 per week among hospitalized patients. DILI incidence in Switzerland on hospitalization admission was 0.7% and in Turkey prevalence among inpatients was 3.1%[31]. In Iceland, the crude annual incidence rate of DILI was 19.1 cases per 100000 patients[32]. The discrepancy may be related to the calculation of prevalence since we only entered patients whose causality could be assessed with RUCAM unlike other studies that consider DILI if the patient had all other liver diseases excluded.

Most (77%) of our patients with ALT above 5 times the UNL were mainly men and had mild to moderate DILI. Regarding clinical features, COVID-19 Chinese DILI patients' median age was 61 years, they were mainly men, the mean (SD) hospital stay was 21.49 (11.89) d, and the mean (SD) days for the first acute liver injury was 9.57 (9.38) after admission[29]. These findings corroborate with our study, demonstrating a set of specific clinical features for patients with DILI and COVID-19.

Almost all patients' normalized liver markers showed a time frame from drug suspension to recovery ranging from 2 to 25 d. Our findings were consistent with the scientific literature of DILI for COVID-19 and non-COVID-19, suggesting a moderate severity of liver injury, rarely progressing to severe and spontaneously recovering. Even so, clinically monitoring DILI is recommended since it can contribute to a reserved prognosis and prolong length of hospital stay (LOS)[15,33]. Prolonged LOS is associated with negative patient experience and inpatient complications such as infections and falls[34]. None of the patients received drug treatment specifically for DILI besides clinical monitoring and suspected

Table 1 Characteristics of the coronavirus disease 2019 inpatients with drug-induced liver injury detected by artificial intelligence in March, 2021

Patient ID	Age/sex	ALT peak (U/L)	Hospital sector	Type of liver injury	Suspected drug	Posology/time treatment	RUCAM score	Causality	DILI diagnosis in EMR	Outcomes (timeframe)	Hospital length of stay (d)
1	83/M	388	ICU	Unclassified	Ivermectin	48 mg daily/6 d	3	Possible	No	Recovered (10 d)	18
					Bicalutamide	150 mg daily/8 d	2	Unlikely			
					Linezolid	600 mg 12/12 h/5 d	4	Possible			
					Azithromycin	500 mg daily/5 d	4	Possible			
					Ceftriaxone	2 g 12/12 h/3 d	4	Possible			
2	61/M	269	ICU	Mix	Amoxicillin + Clavulanate	625 mg 8/8 h/3 d	7	Probable	No	Recovered (7 d)	40
					Azithromycin	500 mg daily/7 d	7	Probable			
					Ceftriaxone	1 g 12/12 h/5 d	7	Probable			
3	62/M	307	ICU	Mix	Tocilizumab	800 mg/1 d	1	Unlikely	No	Recovered (12 d)	31
4	67/M	222	Non-ICU	Cholestatic	Azithromycin	500 mg daily/3 d	3	Possible	No	Recovered (25 d)	28
					Ceftriaxone	1 g 12/12 h/4 d	3	Possible			
5	69/F	588	ICU	Cholestatic	Azithromycin	500 mg daily/5 d	4	Possible	No	Death	25
					Ceftriaxone	2 g daily/7 d	4	Possible			
6	78/M	163	Non-ICU	Unclassified	Ceftriaxone	2 g daily/7 d	3	Possible	No	Recovered (23 d)	70
7	55/M	682	Non-ICU	Hepatocellular	Azithromycin	500 mg daily/5 d	3	Possible	No	Recovered (6 d)	8
					Ivermectin	18 mg daily/4 d	4	Possible			
8	50/F	157	Non-ICU	Unclassified	Ivermectin	18 mg daily/5 d	3	Possible	No	Recovered	7
9	49/F	127	ICU	Cholestatic	Azithromycin	500 mg daily/6 d	3	Possible	No	Recovered (2 d)	17
					Ceftriaxone	2 g daily/9 d	3	Possible			
10	57/M	274	Non-ICU	Mix	Azithromycin	500 mg daily/5 d	6	Probable	No	Recovered (4 d)	10
11	22/M	312	Non-ICU	Hepatocellular	Azithromycin	500 mg daily/4 d	4	Possible	No	Recovered	5
					Ceftriaxone	1 g 12/12 h/3 d	4	Possible			
12	33/M	551	Non-ICU	Hepatocellular	Ceftriaxone	1 g 12/12 h/53 d	3	Possible	No	Recovered	8
13	61/F	168	Non-ICU	Mix	Piperacillin + tazobactam	4.5 g 8/8 h/9 d	6	Probable	No	Recovered	21
14	32/M	489	Non-ICU	Cholestatic	Ceftriaxone	2 g daily/5 d	5	Possible	No	Recovered (10 d)	10
15	73/M	160	Non-ICU	Mix	Ceftriaxone	1 g daily/8 d	6	Possible	No	Recovered	15
16	29/F	369	Non-ICU	Mix	Amoxicillin + clavulanate	625 mg 8/8 h/3 d	4	Possible	Yes	Recovered	15
17	33/M	213	ICU	Mix	Azithromycin	500 mg daily/5 d	5	Possible	No	Recovered (10 d)	22

	Piperacillin + tazobactam	4.5 g 8/8 h/10 d	4	Possible
	Ivermectin	18 mg daily/1 d	5	Possible
	Albendazole	400 mg daily/2 d	5	Possible

Outcomes (timeframe): Timeframe between drug suspension and recovery of liver injury. Patients 8, 11, 12, 13, and 15 were discharged for ambulatory care without alanine aminotransferase follow-up. Patient 16: Drug-induced liver injury diagnosis was presented in electronic medical record by physicians; however, the suspected drug was ivermectin used by self-medication prior to hospital stay. DILI: Drug-induced liver injury; EMR: Electronic medical records; RUCAM: Roussel Uclaf causality assessment method; ICU: Intensive care unit.

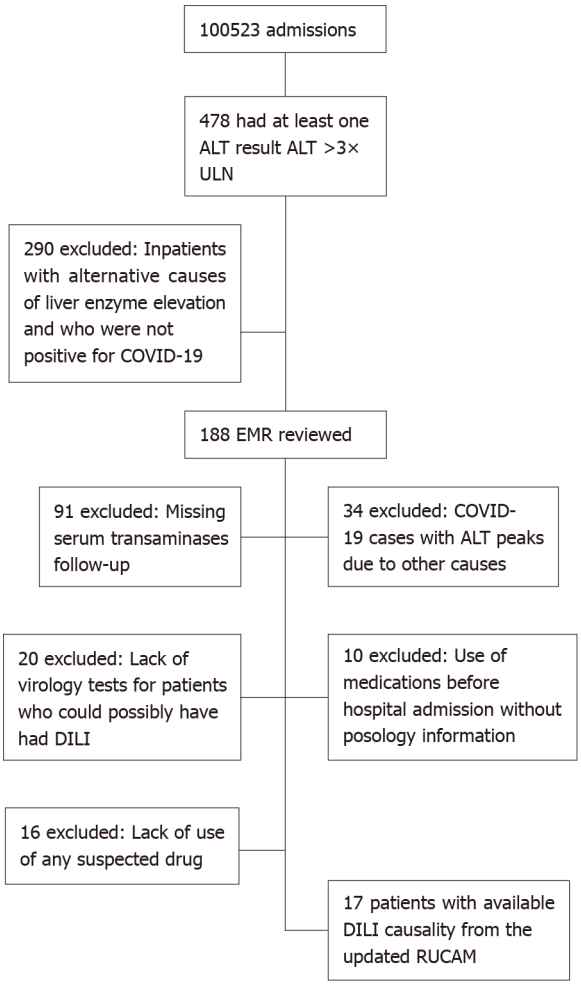

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Figure 1 Patient selection flowchart for drug-induced liver injury assessment. ALT: Alanine aminotransferase; COVID-19: Coronavirus disease 2019; DILI: Drug-induced liver injury; EMR: Electronic medical records; RUCAM: Roussel Uclaf causality assessment method; ULN: Upper limit of normal.

drug suspension.

Serum transaminase elevation presented no determined cause for 171 of our patients and DILI could neither be confirmed nor excluded. This finding suggests that DILI diagnosis remains a challenge due to its multifactorial characteristics and many confounders. Proper diagnosis will depend on the healthcare professional's familiarity with DILI[30]. The fifth RUCAM domain decreases DILI causality if there is no information for any of the following viruses: hepatitis C virus (HCV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis E virus (HEV). In our cases, if virology results were available and negative, drugs scored as "Unlikely" would change to "Possible", suggesting underestimation of DILI prevalence. Medication reconciliation was incomplete for 10 patients, making it infeasible to apply RUCAM. Drugs used before hospital admissions were ivermectin, azithromycin, cefuroxime, hydroxychloroquine, dexamethasone, and prednisone, but posology and duration of treatment were not available in EMR.

Another study evaluating the association between drug treatments and incidence of liver injury and DILI in inpatients with COVID-19 presented the same limitation, since 10% of the suspected cases were excluded due to incomplete EMR [29]. The more incomplete the relevant clinical information, such as the presence of serologies to exclude other possible

causes of liver injury, the less likely it is to assign adequate scores to drugs that may be associated with DILI. Considering this scenario and our findings, quality data on DILI cases assessed by RUCAM in COVID-19 patients are scarce[33].

Literature demonstrates that suspected DILI agents in COVID-19 are mostly antiviral, antibacterial, antifungal drugs, hydroxychloroquine/chloroquine, corticosteroids, and immunotherapy[29]. In a systematic review of 996 DILI cases published in 2020/2021 based on RUCAM as a causality assessment method, antiviral drugs given empirically were mainly responsible for DILI. Liver injury pattern was mainly hepatocellular, differently from our prevalence of mixed pattern. This may be associated with different types of drugs used, as they have diverse DILI pathology mechanisms. Most patients had a positive outcome most likely due to quick cessation of drug treatment, even though DILI was fatal in 19 cases. The ALT and AST peak values were 1.541 U/L and 1.076 U/L, respectively[33]. In contrast, our study showed a maximum ALT of 682 U/L and AST of 556 U/L.

In active search for DILI cases in COVID-19 patients, using lower cutoff points such as ALT one to three times the ULN instead of five times the ULN is preferable, so that no case is missed, since many medicines are used off label and DILI data could demonstrate different hepatotoxicity profiles. Comparison of different liver test thresholds for DILI in hospital patients demonstrate that higher cut-offs, such as ALT levels greater than 5 × the ULN on two consecutive occasions and/or ALP levels greater than 2 × the ULN on two consecutive occasions, as proposed by the DILI Network, are more effective in detecting relevant cases; however, it misses positive cases that were found when the National Medical Products Administration of China, using ALT levels greater than 1 × the ULN on two consecutive occasions or ALT levels greater than 2 × the ULN. In other words, much more labor is required to detect DILI at lower thresholds, despite higher negative predictive values[35]. Automated algorithms to detect DILI using AI may overcome the time-consuming limitation of lower cut-offs, such as when it uses ALT > 3× ULN, as it performs better in sensitivity, a desirable characteristic to detect rare events and avoid missing cases[36]. ALT values 5×> ULN are considered clinically significant, as they will be the best signal allied to symptoms for physicians to consider stop suspected drug treatment[13].

The DILI agents in our study were ivermectin, bicalutamide, linezolid, azithromycin, ceftriaxone, amoxicillin-clavulanate, tocilizumab, piperacillin-tazobactam, and albendazole. The updated Brazilian report of clinical guidelines for inpatient treatment of COVID-19[37] indicates: (1) Anticoagulants: Unfractionated heparin, enoxaparin, or fondaparinux; (2) corticosteroids: Dexamethasone, methylprednisolone, or hydrocortisone; and (3) antimicrobials according to institutional protocols only in the suspected presence of associated bacterial infection. The report demonstrates the lack of evidence for clinical benefit in the hospitalized patient regarding the use of: Azithromycin, chloroquine, colchicine, hydroxychloroquine, ivermectin, and lopinavir/ritonavir. Attention is needed to the irrational use of azithromycin and ivermectin since those drugs have no evidence of clinical benefits in patients with COVID-19 and, as our findings suggest, may even worsen liver injury[38-40].

Antibiotics were the most common agents both in this study and the international literature[17,41]. Ceftriaxone was the main DILI suspected causative agent (10 cases) followed by azithromycin (9 cases). Ceftriaxone is very likely causative of cholestatic injury with minimal symptoms due to crystallization of ceftriaxone in bile present in the gallbladder[42]. Azithromycin is a well-known but rare cause of clinically apparent self-limited cholestatic hepatitis with rapid resolution of symptoms whether the drug is stopped or not[43]. Amoxicillin-clavulanate is the main one of the top-ranking drugs implicated in RUCAM-based DILI cases retrieved from large international medical centers[41]. It causes mostly self-limited cholestatic or mixed idiosyncratic DILI. The onset of injury is a few days to 8 wk after therapy initiation[44,45]. It appeared in only one case probably related to prescription pattern rather than prevalence ratio. Piperacillin-tazobactam rarely causes self-limited cholestatic idiosyncratic DILI[46].

Ivermectin and albendazole are antiparasitic agents used off-label for COVID-19 treatment. Ivermectin presented *in vitro* antiviral effects and a few studies suggested clinical benefits against COVID-19 in the early stages of the pandemic [47]. However, medical centers and governmental organizations such as the Food and Drug Administration and the World Health Organization (WHO) rapidly identified the poor quality data of the publications and ivermectin use was not recommended[48]. The DILI caused by ivermectin and albendazole is extremely rare, with one case report[49]. Ivermectin ADR with COVID-19 reported in the WHO's pharmacovigilance database evidenced a considerable increase (> 50%) in ivermectin related reports since May 2020. Among 53 serious cases, eight cases presented gastrointestinal ADR including one death[50]. Ivermectin is not a potential hepatotoxicity agent; however, in our study, dosages were considerably higher than recommendations leading to causality assessment of "possible" DILI agent.

The COVID-19 patients with DILI presented polypharmacy with acetaminophen, azithromycin, ceftriaxone, dexketoprofen, doxycycline, enoxaparin, hydroxychloroquine, interferon, levofloxacin, lopinavir, metamizole, omeprazole, pantoprazole, piperacillin-tazobactam, remdesivir, ritonavir, and tocilizumab[51]. Domain four of the updated RUCAM [16] regarding concomitant use of drugs lowers scores of a specific drug assessed if the patient is also using another hepatotoxic drug. In the COVID-19 polypharmacy scenario, this is a controversial concern since suspected cases previously scored as "possible" or "probable" would change to high causality association if hepatotoxicity synergism was considered.

It is controversial that the combination of hepatotoxic drugs may increase the risk of DILI. Evidence exists that rifampicin increases the risk of hepatotoxicity when combined with isoniazid for tuberculosis treatment due to a synergistic effect. Anti-tuberculosis treatment combined with non-nucleoside reverse transcriptase inhibitors and protease inhibitors is more likely to cause DILI than both treatments alone[52]. Concomitant administration of drugs metabolized by the liver (*via* CYP450) modulates active metabolites *via* induction, inhibition, or substrate competition and may increase DILI risk[53]. On the other hand, RUCAM decreases an individual medication's score when concomitant hepatotoxic drugs are co-administered, since sufficient evidence regarding synergistic hepatotoxicity of drugs beyond antiretroviral and anti-tuberculostatic is still lacking[16]. We found only one article summarizing possible ADR worsening by drug-drug interactions in COVID-19, which specifically mentioned remdesivir *vs* rifampicin and ribavirin and human immunodeficiency virus antiviral treatment contraindication due to hepatotoxicity[54]. As a result, especially

for COVID-19, cases of DILI could be missed or sub classified after a RUCAM score considering the fourth domain.

Intrinsic DILI is drug dose-dependent, thus the risk of developing liver injury may increase accordingly when the potential safety range of the drug dose is exceeded. In addition, lipophilicity molecules may enter hepatocytes and hepatic metabolism, which hypothetically could increase DILI risk[31]. Alcohol consumption is included in the RUCAM causality assessment scale as a risk factor due to liver metabolization, especially regarding acetaminophen, isoniazid, methotrexate, and halothane[55]. In our study, none of the patients were heavy alcohol consumers excluding this risk factor and probable confounder. The role of pre-existing liver disease on DILI is yet to be completely understood.

There is no consensus if chronic hepatic diseases, such as non-alcoholic fatty liver disease, hepatocellular carcinoma, or viral hepatitis, could worsen DILI severity outcomes[31]. Currently, RUCAM decreases DILI causality if the patient has HAV (type A viral hepatitis), HBV (type B viral hepatitis), HCV (type C viral hepatitis), HEV (type E viral hepatitis), ultrasound alterations of the hepatobiliary tract, acute hypotension (especially cardiac arrest), sepsis, malignant metastatic disease, autoimmune hepatitis, chronic hepatitis, primary biliary cholangitis, sclerosing cholangitis, genetic liver diseases, Cytomegalovirus infection, Epstein-Barr Virus infection, Herpes Simplex Virus infection, and Varicella Zoster Virus infection[16].

Idiosyncratic DILI occurs independently of drug dose, route, duration of treatment, or administration. The RUCAM score increases if patients are 65 years or older, and older age is considered a risk factor. The underlying mechanisms include declination in liver capacity, underlying diseases and alterations in pharmacokinetics features[56]. Data from the WHO Safety Report Database revealed that elderly patients were much more likely to develop cholestatic DILI[32]. Even though gender is not independently associated with DILI, cases are preponderantly in females, especially severe and immune-mediated DILI. Nowadays, literature demonstrates that polymorphisms of genes involved in drug metabolism and transport and human leukocyte antigen are risk factors for DILI.

COVID-19 itself has been associated with transaminase elevation either caused by viral direct damage, hypoxemia, or multisystem inflammatory syndrome. Thus, we suggest reviewing the updated RUCAM's domain number five and adding COVID-19 as an alternative cause of increased ALT/AST. The systematic review of 966 DILI cases in COVID-19 patients also evidenced barriers to properly determine the quantitative contribution of DILI and COVID-19 in abnormal liver tests, suggesting COVID-19 as a DILI confounder[31]. Although we have identified these possible weaknesses in applying the RUCAM to assess DILI in COVID-19 patients, the algorithm remains the best choice to assist health care professionals in the diagnosis and causality assessment of liver injury when alternative causes are excluded[57]. We strongly recommend the prospective use of RUCAM in healthcare services to overcome poor DILI clinical assistance.

The main challenges in the DILI field refer to early detection and diagnosis by healthcare professionals. Using AI and machine learning may be the key to overcoming this scenario. Literature has focused on AI on quantitative structure activity relationship analysis to predict hepatotoxicity substances in drug development with interesting contributions[58, 59]. However, relevant clinical application of AI would consist of machine learning algorithms automatically and prospectively tracing DILI in EMR and patients' hospitals datasets by crosslinking DILI threshold criteria, risk factors, liver injury International Classification of Diseases (ICD-10) codes, liver tests, and data mining[60,61]. In the next step, an alert would be triggered in electronic systems to physicians and clinical pharmacists informing of potential DILI cases for clinical follow-up[62].

Research that used EMR algorithms for DILI screening found low positive predictive values (PPV)[13]. A recent meta-analysis showed that PPV was only 14.6% for machine learning and AI in EMR. Divergences in liver tests reference values and DILI threshold criteria among different studies decrease comparisons and evaluations of sensitivity and specificity [25]. In this study, we used AI to automatically detect COVID-19 patients with abnormal liver markers and compiled data with dashboards to identify key days patients should be investigated. However, the updated RUCAM application was still manually performed. Prospects in our work involves creating and validating signals for pharmacists generated from automated scores for all DILI patients based on RUCAM assessment causality, AI, and machine learning.

This study has the limitations of a retrospective study design. Incomplete case datasets in EMR that could impact different RUCAM scores may underestimate the prevalence of DILI as well as the hepatotoxicity profile of the suspected drug. No statistical analysis was performed due to the small and non-homogenous sample. Therefore, these findings may only suggest associations, propose insight into DILI, and guide further investigations since the results lack external validation. The assessment of DILI and vaccines was not performed as it was out of the study scope.

CONCLUSION

Our study shows that DILI has a rare incidence in COVID-19 inpatients and the absence of relevant clinical information on EMR may underestimate DILI rates. Abnormal liver tests such as ALT and AST are important triggers to detect DILI, but since they lack specificity a complete evaluation of the patient is necessary for a proper diagnosis. The DILI features in COVID-19 inpatients are provided by age, gender, patients, suspected drugs, type of injury, laboratory data, and clinical outcomes and these findings are consistent with DILI literature of non-COVID-19 cases.

The DILI diagnosis is still a challenge due to its multifactorial character and many confounding factors, including COVID-19, and its early detection by health professionals is an important challenge. The updated RUCAM is the standard tool to assess hepatotoxicity and future research must focus on its prospective applicability to improve DILI quality data. The use of AI in clinical pharmacy decision support in conjunction with RUCAM can contribute to patient safety and pharmacovigilance practices, improving clinical outcomes.

ARTICLE HIGHLIGHTS

Research background

Liver injury is a relevant condition in coronavirus disease 2019 (COVID-19) inpatients. Drug-induced liver injury (DILI) may be present in COVID-19 patients due to wide exposure to multiple treatments. Artificial intelligence (AI) applications are interesting tools for early detection of DILI cases in hospitals using electronic medical records.

Research motivation

DILI detection and monitoring is clinically relevant, as DILI may contribute to poor prognosis, prolonged hospitalization and increase indirect healthcare costs.

Research objectives

To demonstrate the use of AI and the updated Roussel Uclaf Causality Assessment Method (RUCAM) to detect DILI cases from data mining in electronic medical records (EMR) of COVID-19 inpatients.

Research methods

The study was conducted in March 2021 in a hospital in southern Brazil. Hospital admissions were 100523 during this period. The NoHarm© system uses AI to support decision making in clinical pharmacy. 478 cases met the inclusion criteria and from these, 290 inpatients were excluded due to alternative causes of liver injury and/or due to not having COVID-19. We manually reviewed the EMR of 188 patients for DILI investigation. Absence of clinical information excluded most eligible patients. The updated RUCAM was applied to all suspected cases of DILI.

Research results

In total, 17 COVID-19 inpatients were evaluated and there were 31 suspected drugs with the following RUCAM score: possible (n = 24), probable (n = 5), and unlikely (n = 2). DILI agents were ivermectin, bicalutamide, linezolid, azithromycin, ceftriaxone, amoxicillin-clavulanate, tocilizumab, piperacillin-tazobactam, and albendazole. Lack of essential clinical information excluded most patients.

Research conclusions

These results are included in a project of clinical pharmacy using AI tools. Future research must focus on the prospective applicability of the updated RUCAM to improve DILI quality data. The use of AI in clinical pharmacy decision support in conjunction with RUCAM can contribute to patient safety and pharmacovigilance practices, improving clinical outcomes.

Research perspectives

These results are included in a project of clinical pharmacy using AI tools. Future research must focus on the prospective applicability of the updated RUCAM to improve DILI quality data. The use of AI in clinical pharmacy decision support in conjunction with RUCAM can contribute to patient safety and pharmacovigilance practices, improving clinical outcomes.

FOOTNOTES

Author contributions: Ortiz GX conceptualization, data curation, formal analysis, and writing the original draft; Ulbrich AHDPS and dos Santos HDP resources, software and reviewing; Becker MW, Lenhart G, and Schwambach KH writing, reviewing, and editing; Blatt CR project administration and reviewing; All authors contributed to the article and approved the submitted version.

Institutional review board statement: The study was reviewed and approved by the Federal University of Health Sciences of Porto Alegre and the Institute of Artificial Intelligence in Healthcare.

Informed consent statement: This is not applicable to the study. The ethical advice is described in the document "Institutional Review Board Approval Form or Document".

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