Heliyon 8 (2023) e12431

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Artificial intelligence applications in pathological diagnosis of gastric cancer

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ARTICLE INFO

Keywords:
Gastric cancer
Pathological diagnosis
Artificial intelligence
Gastroenterology

ABSTRACT

Globally, gastric cancer is the third leading cause of death from tumors. Prevention and individualized treatment are considered to be the best options for reducing the mortality rate of gastric cancer. Artificial intelligence (AI) technology has been widely used in the field of gastric cancer, including diagnosis, prognosis, and image analysis. Eligible papers were identified from PubMed and IEEE up to April 13, 2022. Through the comparison of these articles, the application status of AI technology in the diagnosis of gastric cancer was summarized, including application types, application scenarios, advantages and limitations. This review presents the current state and role of AI in the diagnosis of gastric cancer based on four aspects: 1) accurate sampling from early diagnosis (endoscopy), 2) digital pathological diagnosis, 3) molecules and genes, and 4) clinical big data analysis and prognosis prediction. AI plays a very important role in facilitating the diagnosis of gastric cancer; however, it also has shortcomings such as interpretability. The purpose of this review is to provide assistance to researchers working in this domain.

1. Background

Globally, gastric cancer is the third leading cause of death from tumors [1]; however, the incidence rates vary widely on the basis of regions. Gastric cancer is diagnosed histologically after endoscopic biopsy and staged using computed tomography, endoscopic ultrasound, positron emission computed tomography, and laparoscopy [2]. Endoscopic ultrasound is most beneficial in identifying early gastric cancer (EGC) [3]. Endoscopy and minimally invasive techniques can be used in the treatment of EGC [2]. The literature suggests that the survival rate of patients with EGC is high if they can obtain an accurate early diagnosis and prediction of postoperative complications [4, 5]. Artificial intelligence (AI) technology has been widely used in the field of gastric cancer, including diagnosis, prognosis, and image analysis. The purpose of this review is to provide a general understanding of AI to doctors who are involved in the diagnosis of gastric cancer, clarify the current state and role of AI in such diagnosis, and offer some guidance for research in related fields. Eligible papers were identified from PubMed and IEEE up to April 13, 2022, using the terms “artificial intelligence” and “gastric cancer”. The filtering criteria are shown in Figure 1, duplicates were excluded by reference manager software (Endnote). Through the comparison of these articles, the application status of AI technology in the diagnosis of gastric cancer was summarized, including application types, application scenarios, advantages and limitations. In this review, we have introduced the current status of AI in gastric cancer based on four aspects: 1) accurate sampling from early diagnosis (endoscopy), 2) digital pathological diagnosis, 3) molecules and genes, and 4) clinical big data analysis and prognosis prediction (Figure 2.).

2. Development history of AI

AI, a technical science that studies and develops theoretical methods and applied systems for simulating the functioning and extension of human intelligence, was already mentioned in the 1950s [6]. As a type of machine intelligence, AI has cognitive functions similar to those of human beings, including learning and problem solving [7]. The promise of AI in healthcare is ripe, and AI will reshape medicine broadly in the coming years, improving the experience for clinicians and patients [8].

Machine learning (ML), one of the cores of AI, can automatically build mathematical algorithms based on given data (called training data) and make predictions or decisions without human instructions [9]. Currently, ML methods such as Bayesian networks, linear discriminants, support vector machines (SVMs), and artificial neural networks (ANNs) have been widely used in medical domains, such as radiology, neurology,

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https://doi.org/10.1016/j.heliyon.2022.e12431
Received 24 May 2022; Received in revised form 29 September 2022; Accepted 9 December 2022

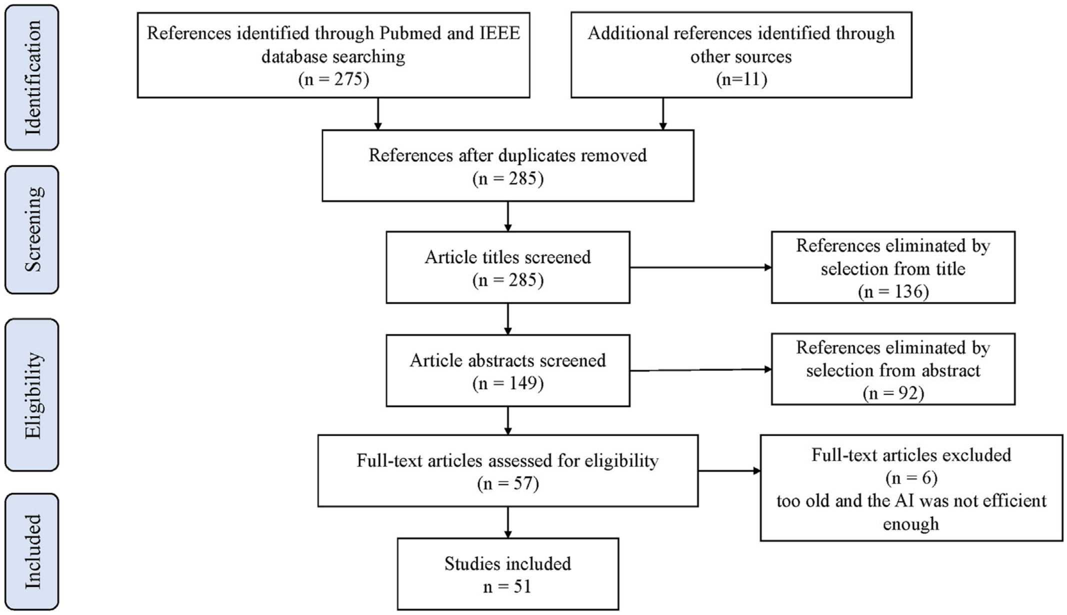

Figure 1. The PRISMA flowchart.

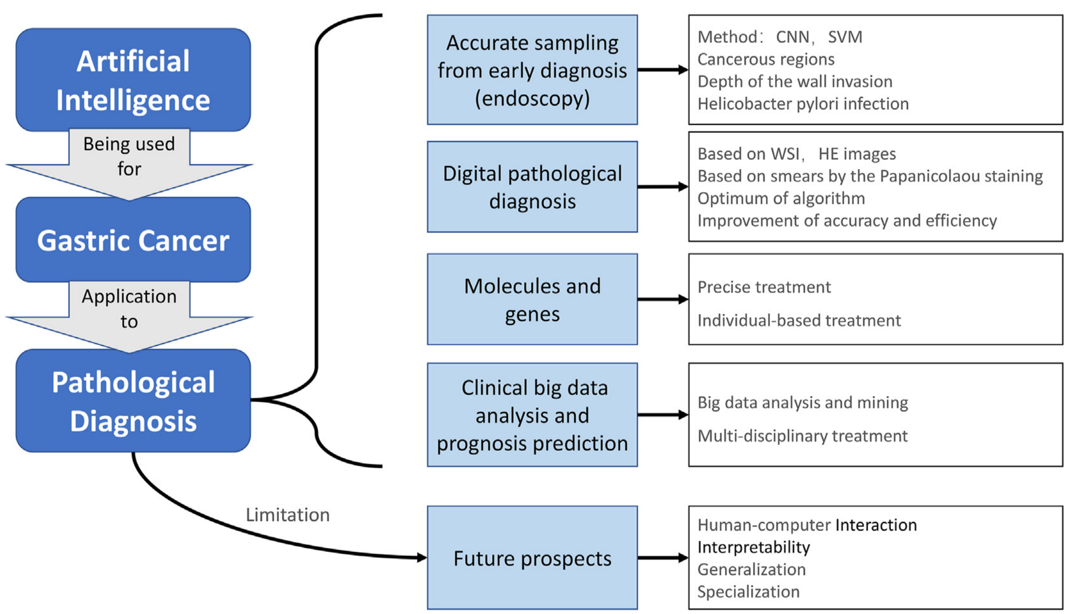

Figure 2. The consort diagram of this manuscript.

orthopedics, pathology, ophthalmology, and gastroenterology [10]. ANNs are ML models that are proposed on the basis of modern neuroscience. They attempt to process information by simulating the processing and memory of the human brain neural network, and have solved many complex problems of pattern recognition, thus resulting in the concept of deep learning (DL) [11].

DL technology has rapidly gained attention as an optimal ML method, and the application of artificial intelligence (AI) in medicine has been enthusiastically explored. DL has been widely used in medicine [12, 13, 14], especially in cancers such as skin cancer [15], breast cancer [16], and gastric cancer [17, 18].

3. Accurate sampling from early diagnosis (endoscopy)

Magnifying endoscopy, which is usually combined with narrow spectrum imaging such as narrow band imaging [19], flexible spectral imaging color enhancement, and blue laser imaging, is a common method for the clinical diagnosis of gastric cancer [20, 21, 22]. However, the clinical personnel who conduct endoscopic diagnostic examinations require considerable professional knowledge and experience. Approximately 10% of upper gastrointestinal cancer cases (including gastric cancer) are not detected through endoscopy [23].

Researchers have attempted to use AI to assist in the endoscopic diagnosis of gastric cancer to address the problem of missed diagnosis by endoscopic doctors due to inexperience or fatigue (Table 1). A convolutional neural network (CNN) is one of the most commonly used AI models and has been used to automatically distinguish between cancerous and noncacerous regions under endoscopy, with accuracy between 86–92.5% [1, 24, 25, 26]. The accuracy of these AI methods is equivalent to or even better than that of experienced endoscopists, which implies that such techniques can provide substantial assistance in decision-making. Furthermore, the sensitivity can be as high as 100% if needed [27], which implies that the detection rate is comparable to that of the most experienced endoscopists. This has important implications for

Table 1. The application of AI in accurate sampling from early diagnosis (endoscopy).

References	Year	Disease	Algorithm	Endoscopic	No. of cases	Results
Kubota et al.	2012	Gastric cancer	Back propagation	Conventional endoscopy	344	Accuracy, 64.7%,
Miyaki et al.	2013	MGC	Logistic regression	Magnifying endoscopy with FICE	46	Accuracy, 85.9%; Sn, 84.8%; Sp, 87.0%
Miyaki et al.	2015	EGC	SVM	Magnifying endoscopy with BLI	100	The SVM output value was significantly different
Shichijo et al.	2017	HP	CNN	Conventional endoscopy	397	Accuracy, 88.9%; Sn, 87.4%; Sp, 87.7%
Itoh et al.	2018	HP	CNN	Conventional endoscopy	139	Sn, 86.7%; Sp, 86.7%
Hirasawa et al.	2018	Gastric cancer	CNN	Conventional endoscopy	77	Sn, 92.2%; Sp, 98.6%
Sakai et al.	2018	EGC	CNN	Conventional endoscopy	9650 images	Accuracy, 87.6%
Kanesaka et al.	2018	EGC	SVM	Conventional endoscopy	207 images	Accuracy, 96.3%; Sn, 98.3%; Sp, 96.7%
Wu et al.	2019	EGC	DCNN	EGD	9151 images	Accuracy, 92.5%; Sn, 94.0%; Sp, 91.0%
Zhu et al.	2019	EGC	CNN	Conventional endoscopy	993 images	Accuracy, 89.16%; Sn, 76.47%; Sp, 95.56%
Wu et al.	2021	EGC	DCNN & DRL	EGD	1050	Accuracy, 84.7%; Sn, 100%; Sp, 84.3%

BLI: blue-laser imaging; CNN: convolution neural network; DCNN: deep convolution neural network; DRL: deep reinforcement learning; EGC: early gastric cancer; EGD: esophagogastroduodenoscopy; FICE: flexible spectral imaging color enhancement; HP: helicobacter pylori; MGC: mucosal gastric cancers; SVM: support vector machine; Sn: sensitivity; Sp: specificity.

the screening of EGC, although more time is required to rule out false-positive cases.

In addition to CNNs, SVM is often used in the AI diagnosis of gastric cancer. An SVM-based analysis system was used to quantitatively identify gastric cancer from images obtained through magnifying endoscopy. The SVM output value for the tumor region was significantly different from that of other regions [28]. The endoscopists could diagnose early gastric cancer with the aid of a computer-aided diagnosis (CAD) system based on SVM, with an accuracy of 96.3%, positive predictive value of 98.3%, sensitivity of 96.7%, and specificity of 95% [29].

The utility of AI in the endoscopic diagnosis of gastric cancer is not only in detection, but also characterization. The computer-aided pattern recognition system [30] and the convolutional neural network computer-aided detection (CNN-CAD) system [31] were used to identify the depth of the wall invasion of gastric cancer and screen patients using endoscopic images. The results showed that the overall accuracy rate of the pattern recognition system was 64.7%, and the diagnostic accuracy was 77.2%, 49.1%, 51.0%, and 55.3% for the T1, T2, T3, and T4 stages, respectively. The accuracy was 68.9% in T1a (mucosal invasion) staging and 63.6% in T1b (submucosal invasion) staging [30]. Comparatively speaking, CNN seems to have an advantage in this respect. The CNN-CAD system showed higher accuracy (89.2%) and specificity (95.6%) than the pattern recognition system when determining the invasion depth of gastric cancer. This result was even significantly superior to that of experienced endoscopists [31].

In addition, chronic gastritis associated with Helicobacter pylori (HP) can cause mucosal atrophy and intestinal metaplasia, both of which could increase the risk of gastric cancer [32]. Therefore, the accurate diagnosis of HP infection is also crucial for the early diagnosis and prevention of gastric cancer. A CNN system capable of recognizing the specific features of gastric endoscopy images was developed to detect HP infection early, thus preventing gastric cancer. The accuracy of these systems was 83.1–87.7% and the maximum sensitivity and specificity were 88.9% and 87.4%, respectively [33, 34]. The accuracy of the CNN-aided system was significantly higher than that of the endoscopists, and it was more efficient. This proved that the AI-assisted diagnosis of HP infection is feasible and expected to promote and improve the early diagnosis of gastric cancer.

However, AI needs to incorporate the decision-making processes of endoscopists, because when they look at the gastric mucosa, they do not just judge by color or shape. In the near future, we should discuss how to shape the interaction between the endoscopist and AI [35].

4. Digital pathological diagnosis

Whole slide imaging (WSI) which digitizes a slide to produce whole slide images on a screen, is a disruptive technology that has led to significant advances in digital pathology diagnosis over the past decade [36]. Based on the WSI, AI has been widely used in digital pathology, such as pathological diagnosis [37], histological classification [38], and histological prediction [39] (Table 2). The area under the curve for the CNN-CAD system in the pathological diagnosis of gastric cancer was 0.89, the sensitivity was 0.778, the specificity was 0.995, the overall accuracy was 0.989, and the positive and negative predictive values were 0.822 and 0.994, respectively. The CNN-CAD system achieved the same classification results as pathologists [37]. For the three-tier classification (positive for carcinoma or suspicion of carcinoma, caution for adenoma or suspicion of a neoplastic lesion, or negative for a neoplastic lesion), the overall concordance rate of the AI image analysis software was 55.6% (1702/3062), and the kappa coefficient was 0.28 (95% confidence interval, 0.26–0.30; fair agreement) [38]. In addition, deep residual learning can predict microsatellite instability directly from hematoxylin-eosin (H&E) histology images without additional genetic or immunohistochemical tests. This approach has the potential to provide broader immunotherapy to patients with gastrointestinal tumors [38]. Other studies have shown that deep learning models of WSIs can not only help pathologists detect diagnoses but also help oncologists explore new prognostic factors, especially those that are difficult to calculate manually [40].

In addition to histological H&E staining images, gastric smears stained by the Papanicolaou technique were also the most important source of training data for AI models of gastric cancer, especially in early research. Karakitsos et al. conducted a series of studies based on gastric smears stained by the Papanicolaou technique. Initially, they collected 23 cases of cancer, 19 of gastritis, and 58 of ulcers, and used morphometry and the backpropagation (BP) algorithm in artificial neural networks (ANNs) to identify benign and malignant gastric lesions with an overall accuracy of 97.3% [41]. Subsequently, they compared the accuracy of two different ANNs, which were based on BP and a learning vector quantizer, for identifying benign and malignant gastric lesions based on nuclear morphological and textural data. They proved that the overall accuracy of both ANNs exceeded 97%, with more than 97% of the benign cells and more than 95% of the malignant cells being properly classified [42]. Next, they investigated the potential value of ANNs for the discrimination of benign lesions from malignant gastric lesions, and the results indicated that the ANNs may offer useful information concerning the potential of malignancy in gastric cells [43].

Algorithms have also been one of the focal points of gastric cancer AI in recent years. Sharma et al. proposed an introductory CNN architecture for two computerized applications, namely, cancer classification based on immunohistochemical response and necrosis detection based on the existence of tumor necrosis in the tissue. This CNN architecture demonstrated favorable results, with an overall classification accuracy of 0.6990 for cancer classification and 0.8144 for necrosis detection [44]. Song et al. detected gastric cancer using a CNN with the DeepLab V3

Table 2. The application of AI in Digital Pathological Diagnosis.

References	Year	Disease	Algorithm	Image type	No. of cases	Results
Karakitsos et al.	1996	Gastric cancer	Back propagation	Papanicolaou	100	Accuracy, 97.3%
Karakitsos et al.	1997	Gastric cancer	BP & LVQ	Papanicolaou	120	Accuracy, >97%
Yoshida et al.	2018	Gastric cancer	MIL	H&E	3062	Overall concordance rate, 55.6%
Wang et al.	2019	Gastric cancer	CNN	H&E	124	Accuracy, 98.9%; Sn, 77.8%; Sp, 99.5%
Kather et al.	2019	MIS of gastric cancer	CNN	H&E	1554	AUC for MSI detection, 0.81
Wang et al.	2021	MLNs of gastric cancer	Deep learning	H&E	1164	Accuracy, 96.9%; Sn, 98.5%; Sp, 96.1%
Ba et al.	2022	Gastric cancer	Deep learning	H&E	110 WSI	Pathologists with DL had higher sensitivity than without. (90.63% vs. 82.75%, P = 0.010)

AUC: area under curve; BP: back propagation; CNN: convolution neural network; H&E: hematoxylin-eosin staining; MIL: multi-instance learning; MLNs: metastatic lymph nodes; MSI: microsatellite instability; WSI: whole slide imaging.

Table 3. The application of AI in genes.

References	Year	Disease	Algorithm	Target of detection	No. of cases	Results
Ishii et al.	2013	Gastric cancer (2 subtypes)	Bayesian network	gene expression profile	46	Accuracy of the classifier, 100%
Yan et al.	2013	Gastric cancer	DM & ML	feature genes	216	Sn, >90%; Sp, >90%

ctDNA: circulating tumor DNA; DM: data mining; ML: machine learning; MRD: molecular residual disease.

architecture and achieved a sensitivity of 99.6% and an average specificity of 80.6% on 3212 WSI real-world test datasets digitized by 3 scanners. Moreover, 1582 WSI samples from two other medical centers were selected to further verify the generalization ability of the algorithm [45]. Qu et al. presented a novel stepwise fine-tuning-based deep learning scheme for gastric pathology image classification. They established new types of target-correlative intermediate datasets to further boost the performance of state-of-the-art deep neural networks and alleviate the insufficiency of well-annotated data. The results congruously demonstrated the feasibility and superiority of the proposed scheme for boosting the classification performance [46].

To be clear, AI cannot replace the breadth and contextual knowledge of pathologists, but only a combination of the two can best represent the advantages of AI. Ai assistance has indeed improved the accuracy and efficiency of pathologists in the diagnosis of gastric cancer. Pathologists, in turn, understand the impact of false positives and false negatives on patients, enabling them to optimize diagnostic points of operation to meet more personalized clinical needs. The aid of AI effectively reduces the workload of pathologists, allowing them to spend more time on difficult cases [47].

4.1. Molecules and genes

Molecular and genetic techniques are increasingly being used in the diagnosis and prognosis of tumors. The identification of patients who are at a high risk of gastric cancer can facilitate early intervention. For example, in treatment-targeted patients with localized gastric cancer, circulating tumor DNA-detected molecular residual disease can identify high-risk patients with recurrence and facilitate intensive research on neoadjuvant therapy to improve survival [48]. More detailed molecular signatures can also be used to tailor treatments to each patient, and the response to targeted therapies can be more effectively predicted to maximize efficacy and avoid overtreatment [49].

AI has been widely used in this domain (Table 3). A classifier can be built to distinguish the gene expression profiles of each subtype of gastric cancer, to guide medical treatment for different subtypes or to predict prognosis [50]. Multiple algorithms can also be integrated to establish a complete and systematic data mining model for identifying biomarkers based on gene expression data, and to identify the biological characteristics of gastric cancer with the gene characteristics obtained from the prediction model [51].

4.2. Clinical big data analysis and prognosis prediction

AI is also often used in clinical big data analysis and prognosis prediction, such as the integration of patient history, clinical nursing data, pathology, and imaging data, which have been used for data analysis and mining (Table 4). Complex cases should be treated in a multidisciplinary manner, combining gastroenterology, radiology, pathology, medicine, surgery, and radiation oncology [3]. In gastric cancer, for example, AI has been used to predict complications after gastrectomy to significantly reduce postoperative mortality and morbidity [5], strengthen early

Table 4. The application of AI in prognosis prediction.

References	Year	Disease	Algorithm	Prognosis prediction	No. of cases	Results
Chien et al.	2008	Gastric cancer	ANN, DT, LR	Post-operative complication	521	ANN was a better technique than DT and LR
Lai et al.	2008	Primary gastric cancer	ANN	Preoperative prediction of tumor staging	121	Accuracy, 81.82%
Jagric et al.	2010	Gastric cancer	LVQNN	Liver metastases after a gastric cancer surgery	213	Sn, 71%; Sp, 96.1%
Liu et al.	2018	EGC	Data mining	Non-invasive screening	618	Accuracy, 77.84%; AI can effectively evaluate the risk of EGC and assist clinicians in improving the diagnosis and screening of EGC.

ANN: artificial neural networks; DT: decision tree; EGC: early gastric cancer; LR: logistic regression; LVQNN: learning vector quantization neural networks.

diagnosis and screening to improve the survival and quality of life of EGC patients [4], predict the preoperative staging of tumors by using clinicopathological datasets and genetic susceptibility tests [52], and predict tumor recurrence in patients with gastric cancer to develop specific treatment and follow-up strategies [53].

5. Conclusion and future prospects

With the rapid development of digital pathology and ML technology, the application of AI in the diagnosis of gastric cancer is becoming increasingly extensive. AI has been used in many cases, including endoscopic diagnosis, identification of the depth of wall invasion, histological diagnosis and classification, gastric smear diagnosis, molecular and genetic, and prognosis prediction. The applications of AI technology in gastric cancer have demonstrated accuracy and diagnostic efficiency that are equivalent to or even superior to those of general pathologists. However, AI will not replace the breadth and contextual knowledge of pathologists; rather, only through their combination may pathologists' accuracy and efficiency in gastric cancer diagnosis be improved.

However, researchers have found that AI technology still has many problems, such as black boxes [54, 55, 56], a lack of high-quality datasets [54], and the generalization of AI models [56]. Future AI research of this kind will likely focus on how to solve these problems.

First, AI algorithms lack a common understanding of their inner workings. The challenge of interpreting and understanding how complex AI models make decisions is one of the major obstacles to the clinical adoption of DL algorithms, also known as the black box problem. DL has defects such as selection bias, overfitting, and spectral bias (class imbalance), which might affect the accuracy. AI algorithms of DL such as CNN models have shown a lack of interpretability, in which graph neural networks (GNN) have an advantage [57]. In the future, GNNs can be expected to have more applications in the diagnosis of gastric cancer. Especially when medical AI models gain new insights beyond current human knowledge, the interpretability of GNN will help researchers master these new insights to better understand the biological mechanisms behind disease.

Furthermore, there are often data issues associated with using AI. For example, there are few high-quality datasets available for training and validation. We can consider the federated learning (FL) method to solve the problem of insufficient data [58]. FL is a multidistributed joint learning technology that can learn among multiple databases and obtain a high-precision system by transferring system parameters from the central database under the premise of limited data sharing. Using federated learning, we can effectively develop accurate weakly supervised deep learning models from distributed data silos without direct data sharing and its associated complexity, while also maintaining differential privacy using random noise generation.

The last important question is the generalization of AI models and medical decision support tools. AI models with a single source of data may not perform well when faced with data from other sources. In addition, to improve generalization, AI models can be trained and verified with datasets from different sources. For complex cases, multidisciplinary data such as gastroenterology, radiology, pathology, internal medicine, surgery, and radiation oncology can also be incorporated into the comprehensive analysis of AI. On the other hand, AI technology is increasingly relying on substantial computing power and massive data support, which are not always accessible to researchers. Under such circumstances, it can be predicted that the specialization of AI technology (single disease or even single subtype) for gastric cancer (even for medicine) may be a feasible option.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Funding statement

Ph.D. Ji Bao was supported by the 1·3·5 Project for Disciplines of Excellence–Clinical Research Incubation Project, West China Hospital, Sichuan University [2020HXFH029], Key R&D (Major Science and Technology Project) Project of Sichuan Science and Technology Department [22ZDYF1406].

Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of interest's statement

The authors declare no competing interests.

Additional information

No additional information is available for this paper.

Acknowledgements

We thank Fei Xiang and Yi-zhe Wang from Chengdu Knowledge Vision Science and Technology Co.,Ltd for commenting of AI technology, especially the architecture of artificial neural network.

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