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Original Research Paper

Hematology

REVIEW OF HAEMATOPATHOLOGY IN THE AGE OF ARTIFICIAL INTELLIGENCE-MACHINE LEARNING BETWEEN 2011 AND 2021

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ABSTRACT

Background and Objective: Artificial intelligence has transformed pathology diagnostics over the past decade between January 2011 to December 2021, with new emerging technologies and software promising to transform and enhance haematopathology diagnostics further. More rapid and proficient AI systems appears to be threatening the role of Haematopathologist in the diagnostic process. This systemic review aims to explore the success of artificial intelligence applications in the field of haematopathology and assess whether the role of haematopathologist will indeed prove redundant in the future.

Methods: We performed an extensive search of Pubmed, Medline and National Center for Biotechnology Information (NCBI) at the U.S. National Library of Medicine (NLM) and google scholar databases for artificial intelligence in Haematopathology between January 2011 and December 2021.Reference lists of articles were thereafter reviewed for additional reviews. The results are grouped and discussed according to the world health organization grouping of haematopathology disease. Studies where the AI algorithms were compared to that of specialist pathologist were included as this was the main focus and aim of the review.

Key content and findings: Artificial intelligent applications on peripheral smears, bone marrow aspirate smears, immunohistochemical stains are documented sequentially in the manuscript from the introduction of whole slide imaging applied to peripheral and bone marrow smears for identification of white blood cells to the application of more complex convoluted neural networks for discrimination of lymphoma and leukaemia subtypes and lymphoma grading. All the studies documented in this review have shown favourable outcome for artificial intelligence applications to haematopathology disease.

Conclusion: The above studies have demonstrated that artificial intelligence can be successfully integrated into haematopathology diagnostics. Although all studies were shown to be comparable to the pathologist, there is a requirement for further standardisation and validation studies for optimization of deep learning algorithms. The notion that AI will replace the pathologist is also incorrect. The microscope will not be replaced. Rather, AI integration into pathology is meant *enhance* the accuracy and speed of diagnostic workflows enabling the pathologist to focus on more complex laboratory problems. AI and human pathologists should co- operate, rather than compete.

KEYWORDS : Artificial intelligence, machine learning, deep learning, haematopathology

INTRODUCTION

Artificial intelligence is fast emerging as a transformative force in all fields of medical diagnostics and patient management. Artificial intelligence promises to revolutionize patient management and optimize personalized medicine. Artificial intelligence and machine learning refers to the development and programming of computers and devices which are able to perform human like functions with transformative and enhanced capabilities. Machine learning is an applied field of artificial intelligence in which a large and diverse set of data points is incorporated in computer algorithms for statistical analysis. One type of algorithm commonly used in medical diagnostics is known as deep neural networks or convoluted neural networks which rapidly captures and processes random images to detect patterns and formulate mathematic models for diagnostic algorithms. The interconnected neural networks and processing mimics the human brain neuronal synapses transmitting information in an interconnected web(1).

Deep learning methods utilized in pathological diagnosis include U-Net architecture for semantic segmentation. MVPNet is another type of network used in pathology diagnostics and uses multiple viewing paths for magnification. Convolutional neural networks (CNN) (i.e., Inception, Residual, and Recurrent networks), RAZN (Reinforced Auto-Zoom Net) is also commonly used for pathological diagnostics and uses a policy network to decide whether zooming is required in a given region of interest. Generative adversarial networks (GANs) are deep neural network architectures comprised of two networks (generator and discriminator)(2).

Artificial intelligence has already been applied to radiological imaging and diagnostics without eliminating the requirement for the radiologist input(3).Deep learning algorithms have been developed for oncological diagnosis (squamous cell carcinoma, adenocarcinoma, gastric carcinoma, diabetic retinopathy and melanoma(3).

Whole slide imaging (WSI) imprinting images in a digital matrix has revolutionized pathology diagnostics connecting it to AI systems since almost a decade ago(4). In 2017, the first WSI received FDA approval transforming laboratory work flow (https://www.fda.gov/ newsevents/ newsroom/ press annou ncements/ucm552742.htm). Whole Slide Imaging combined with 5G technology is expected to accelerate the use of WSI in remote diagnosis.Digital image scanners integrated with laboratory IT systems enabled review and reporting of cases by pathologists in an entirely digital workspace reducing the need for manual microscopes. Studies have shown that WSI is non inferior to conventional diagnosis by microscope(5). Digital microscopes such as Nikon Coolscope revolutionized telepathology in remote areas in Southern Africa. Digital microscopy combines ordinary microscopes with digital cameras and network functions which can be connected to laboratory interface systems for remote user control(6).

Phillips received FDA clearance for a pathology solution in April 2019.The device is used for scanning glass pathology slides and review on computer monitors(7). In 2020, the Netherlands-based Laboratory for Pathology East Netherlands Foundation (LabPON) became the first laboratory to transition to Philips Intellisite Pathology Solution instead of a microscope resulting in increase in the speed of logistical workflow and increased throughout.

Telepathology has emerged as a useful tool to facilitate AI technologies. Telepathology uses communication tools for the electronic transmission of digital pathology images to enable remote primary diagnosis, consultations, education and research(8). Telemedicine and remote learning have increased since the start of the COVID 19 pandemic and has proved to be an efficient replacement platform for both low- and high-income countries.

Haematopathology disease by its nature involves complex diagnostic algorithms comprised of diverse diagnostic biomarkers and therefore is the ideal speciality in which deep learning-artificial neural networks and machine learning can be applied. However, due to a proliferation of image analysis software tools and the proficiency of AI applications a debate around replacement of pathologists by computer algorithms has emerged. Indeed, there are studies that show machine learning algorithms provide more accurate and efficient diagnosis than pathologists in a simulated setting(9).

So, how does the haematopathologist facilitate this emerging technology into existing haematopathology practice? Will AI replace microscopes and pathologists? Can computer algorithms transcend pathologists capabilities?(10).

The following review addresses these questions.
We present the following article in accordance with the narrative review reporting checklist

METHODS

We performed an extensive search of Pubmed , Medline (via pubmed), National Center for Biotechnology Information (NCBI) at the U.S. National Library of Medicine (NLM) and google scholar databases for all English articles published on artificial intelligence in Haematopathology between January 2011 and December 2021.The databases searches were supplemented with reference article list reviews. Records were collated in a reference manager software (Endnote™; Version: X7, Clarivate Analytics, New York, NY, USA), and the titles were screened for duplicates. Our review was based on the PRISMA (Preferred Reporting Items for Systemic Reviews and Meta-Analysis) statement.Search terms included 'Artificial intelligence', 'Deep Learning', 'Pathology','Haematopathology' and 'Digital Pathology.The results are grouped and discussed according to the world health organization grouping of haematopathology disease.The search strategy is shown in Table 1.

Inclusion and Exclusion Criteria:

- Search terms restricted to: 'Artificial intelligence', 'Deep Learning', 'Pathology','Haematopathology' and 'Digital Pathology
- Articles in English
- Published between the Period January 2011 and December 2021
- Studies performed on human samples
- Publication types (all included)-articles in scientific journals, letters to editor, book chapters
- Databases used:MEDLINE (via PubMed), Google Scholar and Reference list checks
- Geographical locations: All locations included

Full-text is not available or accessible were excluded. As a result of the paucity of studies in this specialized field, there was a limited number or articles retrieved and therefore limited numbers of articles excluded from this review.

Selection Process:
Articles were selected by two highly trained and experience Haematopathologists. We selected all studies pertaining to artificial intelligence,machine learning,deep learning in the field of Haematopathology. We restrictred our selection to Haematopathology disease only. Both benign and non-benign haematopathology diseases were included. Other Pathological diseases were excluded.We focussed specifically on retrieval of articles which compared AI diagnostics to that of the pathologist. We screened all titles and abstract using the above search terms for relevant articles. Any mismatch at this stage was resolved by discussion. Thereafter the full text was reviewed and analyzed for inclusion in this review.

DISCUSSION

Applications of AI in haematopathology

1. Blood Parameters

Quantitative and Morphological assessment of the peripheral blood count and smear is an integral part of the haematology assessment for both benign and non-benign haematological diseases. Given the variation and combination of blood parameters required to diagnose haematological pathology, AI and machine-deep learning algorithms is the ideal application in this field because it is capable of processing large number of parameters and capable to detecting interactions formulating a 'fingerprint' of the disease entity.Modern blood analysers introduced have aimed to facilitate this manual process by using image analysis software programmes. The Cellavision DM96 was introduced in 2004 with upgrades CellaVision DM1200 in 2009 and CellaVision DM9600 in 2014.These analysers have shown efficacy in detecting complex red cell cytology such as poikilocytosis independent of the pathologist(11). Enhanced image analysis on automated digital microscopy systems using support vector algorithm software allowed more precise identification of lymphoid cells and further characterization of abnormal lymphocytes into HCL,MCL,FL,CLL and blast subclassification(12).Alferez et al was able to achieve 98% accuracy for screening of normal lymphocytes, abnormal lymphoid cells and reactive lymphocytes on 4000 image dataset(13).

Thereafter, convolutional neural networks emerged which enabled large volumes of complex images to be presented to software for training which showed overall more precision in identification of complex white blood cells such as eosinophils, neutrophils, lymphocytes and monocytes.

A recent study evaluated two Smart Blood Analytics (SBA) haematological-predictive models based on two different sets of clinical laboratory blood test results using 8,233 cases and compared to evaluation by haematological and internal medicine specialists. The SBA algorithm includes data acquisition, data filtering, data pre-processing, data modelling and evaluation. The study illustrated that accuracy in diagnosing haematological disease using SBA to be on par with experienced haematology specialists for the following haematological diseases and its prevalence (Table 2).The most common blood parameters and its frequency is shown in Table 3(14).The large dataset used in this study supports the accuracy of the outcome.

2. Bone Marrow Analysis

Bone marrow morphological analysis is an essential component of all haematopathology disease diagnosis. Researchers have developed an algorithm with super-resolution DP images to construct a three dimensional image of BM smears(15).BM cellularity, which has a high rate of observer variation can be assessed using machine learning HALO imaging software(16) and has shown good accuracy compared to pathologist observation. A fully automatic deep learning algorithm was developed for Bone marrow nucleated differentiated count analysis using whole slide imaging and tested on a dataset of 12,426 annotated cells resulting in efficient output and accuracy reaching 0.905(17). The large dataset included in this study supports the accuracy of outcome.

Identification of abnormal lymphocytes remains a challenge to haematopathologist especially in paediatric cases where differentiation between infection or lymphoid malignancy is unclear. Other haematolymphoid malignancies where lymphoid discrimination is essential include diffuse large B-cell lymphoma, chronic lymphocytic leukaemia/small lymphocytic lymphoma, follicular lymphoma, mantle cell lymphoma or even hairy cell leukaemia. Digital pathology methods can assist haematopathologist in such cases where diagnosis is crucial to determine the correct management of patients.To overcome the diagnostic dilemma of abnormal lymphocytes, AI methods were utilized using a specific Machine Learning Algorithm. *The Morphogo machine learning algorithm* was trained to specifically discriminate abnormal lymphocytes from normal lymphocytes using digital imaging analysis. A data set of 15,353 cell images of 347 cases reviewed by pathologists was tested using Morphogo. The positive predictive value for the identification of reactive/normal lymphocytes and abnormal lymphoid cells was 99.04%(18). This algorithm focussed on identification of normal and reactive lymphocytes compared to abnormal lymphocytes.Haematolymphoid tumours are characterized by an arrest of lymphomagenesis at various stages of development and therefore have specific morphological abnormalities of the lymphocytes depending on the stage of mitotic malfunction.Therefore, further studies using AI algoriths to distinguish specific haematolymphoid tumours are required to enable more precise abnormal lymphoid detection.

3. Immunohistochemical Analysis

Deep learning algorithms can be used to distinguish positive and negative immunohistochemical stains in Haematoly mphoid malignancies. Deep learning algorithms have shown good accuracy levels when applied to IHC analytics(19, 20). Ki67 antigen is a nuclear protein biomarker indicating cellular proliferation usually detected by immunohistochemistry. It is a prognostic marker in lymphoid malignancies such as Burkitt's Lymphoma. Studies have shown improved performance and detection of Ki67 using convoluted neural network algorithms versus classical image processing methods(21, 22). AI algorithms can easily be applied in the field of immunohisto chemical detection due to the simple image analysis from immunohistochemistry.

4. Flow Cytometry

Flow cytometry is an essential component for diagnosis of leukaemia and lymphoma. Flow cytometry is a technique for analysing cell populations into clonal versus non clonal populations and can determine tumour subtype and prognosis. Biehl et al used a complex machine learning technique for detection of AML by flow cytometry(23).Machine learning algorithms have also proposed a complex clustering technique to diagnose CLL on flow cytometry with 99.6% accuracy(24).The complexity of Flow Cytometrical diagnosis makes the application of AI in this field both lucrative and complex requiring further studies to optimize algorithms.

5. Acute Myeloid Leukaemia With Recurrent Genomic Abberations

The classification of leukaemia is based on multiple variables including immunophenotypic, flow cytometric, cytogenetic and genetic mutational analysis, in additional to morphological image analysis by the haematopathologist. Machine learning tools which can extract all this information from both peripheral smears and bone marrow aspirates in a single algorithm is ideal for leukemic diagnosis.

Acute Myeloid Leukaemia with recurrent NPM1 gene mutation occurs commonly. In the presence of an additional FLT3-internal tandem duplication, it has an overall favourable outcome. Using a machine learning approach, genomic aberrations in NPM1 mutation was identified in order to risk stratify the disease and develop a scoring system for subclassification based on the number of genomic aberrations present which can predict clinical outcome. This study was successful in demonstrating that machine learning can be used to develop scoring systems for risk stratification(25).

The same group then further developed a machine learning based genomics driven prognostication model for AML with RUNX1-RUNX1T1.Patients were stratified into favourable and poor genetic risks. They showed that this ML model correlates with measurable residual disease (MRD) and clinical outcome in this disease entity. In addition, the study showed that there was a strong correlation between ML derived genetic risk classes and FCM-MRD(multiparametric flow cytometry) where cases that were poor risk were more likely to be MRD positive(25). Both these studies which used AI to risk classify AML using image analysis and genomic aberrations showed good correlations.

6. Acute Promyelocytic Leukaemia

Acute Promyelocytic Leukaemia is a subtype of Myeloid Leukaemia's characterized by the PML-RARA (15;17) translocation. APL can result in fatal coagulation disturbances and is considered a haematological emergency requiring urgent diagnosis and treatment. The typical morphological features are the first clue alerting the pathologist to the presence of this malignancy; however, morphological variations can often be misleading.

A deep learning architecture was designed to train cell-level classification of white blood cells taken from peripheral smears. The model applied recognized APL versus non-APL cells based on location of the Wrights stain chromatin. In non-APL cells, the network focused on cytoplasmic pixels at the edge of the cell where chromatin showed a dispersed pattern whereas in APL cells cytoplasmic pixels were focussed at the centre of the cell where chromatin was more condensed. This morphological difference in APL was intriguing and has not been documented to date. The AI algorithm was tested against 10 practicing academic leukaemia treating haematologists and demonstrated equivalency or better classification performance(26).This study was remarkable as in addition to the successful application of a deep learning algorithm to detect a complex morphological cell abnormality, the algorithm was able to provide further in depth image focus analysis of the chromatin location in the nucleus of the cells to identify the abnormal cells.In this instance AI transcends the morphological diagnosis of the pathologist at the microscope.

7. Acute Lymphoblastic Leukaemia

Acute Lymphoblastic Leukaemia is a common haematolog ical malignancy of clonal B Cells and is prevalent in both children and adults. The diagnosis of ALL is based on peripheral blood smear and bone marrow aspirate morphological assessment by a specialist haematopath ologist. Diagnostic dilemmas often occur especially in paediatric cases because the malignant lymphocytes can mimic non-reactive haematogones in cases with low lymphocyte counts. A deep convoluted neural network (DCNN) was deployed for analysis of ALL tumour cells. The method achieved a 99.50% accuracy for ALL diagnosis and a 96.06% accuracy for classification of ALL into 4 subtypes(27).

Other studies to classify ALL using AL algorithms have also been documented. Residual neural networks (ResNet-50) and VGG-16 and a convoluted neural network was harnessed to classify leukemic cells from microscopic images on a large dataset. The convolute neural network showed optimal accuracy in diagnosing ALL(28).

These studies indicate that there is a requirement for Haematopathologist to apply different deep learning networks for detection of haematological malignancies in order to discover which network works optimally in each given haematological malignancy.

8. Follicular Lymphoma

Digital imaging algorithms have been extensively explored in Follicular Lymphoma due to its complex morphological diagnosis and grading. Follicular lymphoma grading is a based on complex morphological counting of FL cells under high power field microscopy by the pathologist and has high inter-reader variability. Whole slide imaging has improved the diagnosis of follicular lymphoma and reduced the inter observer variability in this lymphoma(29, 30).

A Follicular Lymphoma Grading System (FLAGS), was developed which automatically identifies CD20 stained cells before risk stratifying them. The FLAGS system was used by Haematopathologist and pathology residents to analyse 20 FL slides resulting in acceptable diagnostic performance(31).

9. Diffuse Large B Cell Lymphoma

Diffuse large B-Cell Lymphoma (DLBCL) is a B Cell Lymphoma which is typically classified into 2 major molecular subtypes based on gene expression profiling: The germinal centre B cell -like (GCB) and activated B Cell -like (ABC) cell of origins. The ABC genotype is associated with a poorer prognosis. AI algorithms have been tested and shown efficacy on both morphological and genetic models in DLBCL.

Several groups have used Machine learning algorithms to classify DLBCL into germinal centre and non- germinal centre subtypes using immunohistochemical dat. One group showed a Receiver-Operator Characteristic (ROC) area under the curve of 0.934(33, 34).Gene expression profiling of eight genes in DLBCL was harnessed in a machine learning algorithms and shown to consistently separate DLBCL-NOS into GCB and non-GCB subtypes(35). Artificial intelligence was harnessed to develop a clinical outcome prediction of a 418 RNA-Seq database. The NGS models stratified 30% high risk patients with poor survival as in the training set. The model showed overall reproducible and efficient results for clinical outcome in DLBCL in DLBCL (32).

A highly accurate deep learning platform comprised of multiple convolutional neural networks was developed to differentiate DLBCL versus non-DLBCL based on morpholog ical images from three separate hospitals. Tissue slides were obtained by scanning the entire slide with a scanner. Non DLBCL included reactive lymphocytes and other B cell Lymphomas. Technical variability due to slide preparation and staining was standardised between hospitals in order to obtain a diagnostic rate of almost 100%(36).

10. Lymphoma Progression

Lymphoid neoplasms such as chronic lymphocytic leukaemia and DLBCL can transform to more progressive or accelerated phase of the disease usually corresponding to the acquisition of genetic translocation. Progressive disease known as Richter's transformation can be diagnostically challenging. Using artificial intelligence biomarkers based on morphological features such as nuclear size and intensity, a study showed robust accuracy for diagnosing Richter's transformation (37).

11. Myelodysplasia

Nagata et all demonstrated that deep learning algorithms can distinguish patterns and associations of genetic variants which are relevant for diagnosis and prognosis in myelodysplastic syndrome(38).LIMITATIONS OF AI MACHINE LEARNING FOR HAEMATOPATHOLOGY AND NEED FOR FUTURE RESEARCH:The above studies have shown remarkable sensitivity and specificity of AI in haematopathological diagnosis.These studies have shown a potential for AI to have a more sophisticated performance compared to humans.The capacity of AI algorithms to combine complex variables and large datasets to formulate diagnosis efficiently and rapidly shows promise for haematopathology in the future.However, further studies are required in order to determine whether AI algorithms can be applied to all haematopathology diagnosis, both benign and non -benign conditions.There may be areas in haemato pathology where diagnostic AI replacement may not be suitable.These include complex haematopathology disease such as dysplasia, myelodysplasia and other rare morphological abberrations. Validation and standardization of scanners and staining of slides between laboratories would also need to be addressed. A further challenge is that AI is currently unable to incorporate contextual knowledge into its algorithms.Haematopathologists skill stems from the ability to incorporate past and present clinical history in conjunction with morphological abberrations, molecular and cytogenetic analysis to reach a final diagnosis.This type of diagnosis is hard to quantitate in an algorithm and is based on clinical acumen following years of clinical experience and knowledge.

CONCLUSION

The above studies have demonstrated that artificial intelligence can be successfully integrated into haematopathology diagnostics with good accuracy. Haematopathology diagnosis is acknowledged to harbour significant inter observer variability where misdiagnosis can lead to catastrophic medical errors in treatment. AI has a huge potential to assist pathologists in this regard by reducing these human errors and variations and also identifiying high risk or complex cases requiring consultation and intervention.

However, sensitivity and specificity in AI algorithms will need optimization before it can be fully implemented into diagnostic workflows. Limitations of studies include lack of standardisation and validation which are required for optimization of these deep learning algorithms The range of haematopathology disease explored in AI applications also remains limited.AI algorithms require testing in a vast number of non- benign haematological disease such as Anemia, Thalassaemia, coagulation etc.

The role of haematopathologist going forward is training, validation and optimization of machines to perfect the AI diagnostic algorithms to produce a highly automated laboratory likely dominated by robotics and AI. AI methods will require integration into pathology training programmes. Pathologists need to be familiar with digital image analysis and computer algorithms. Digital Haematopathologist need to work in tandem with AI specialists and data scientists to validate the best deep learning algorithm for each pathological disease entity. Deep learning algorithms would need to be externally validated using images from external hospitals with different scanners and tested for increasing diagnostic performance of clinicians (comparing haematop athologist plus AI vs. haematopathologist alone).

Overall, the role of the new age haematopathologist therefore is:

- To facilitate the migration from physical slide analysis to digital analysis
- To digitize the laboratory workflow and streamline processes to reduce turnaround times
- To connect a multidisciplinary care team for collaboration between clinicians, pathologists and AI specialistsTo facilitate remoted diagnosis using telepathology and telecommunication services such as Skype, WebEx, Zoom, Google Handouts, Spark, or TeamViewer.

- Archiving and tracking clinical data sets for future AI research.
- Development of integrative platforms
- Training of AI platforms for further AI algorithm production

Thus, the notion that AI will replace the pathologist is incorrect. The microscope will not be replaced. Rather, AI integration into pathology is meant enhance the accuracy and speed of diagnostic workflows enabling the pathologist to focus on more complex laboratory problems. AI and human pathologists should co- operate, rather than compete.

Ethical Statements:

"The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved."

Conflicts Of Interest:

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form. The authors have no conflicts of interest to declare."

Table1 : Search strategy (for one database used):

Date of Search	Database	Years searched	Search terms	Number of HITS
15/12/2021	Pubmed (Medline)	January 2011-December 2022	Artificial intelligence, Haematopathology	3
15/12/2021	Pubmed (Medline)	January 2011-December 2022	Deep Learning, Haematopathology	6

Table 2: Haematological

Haematological disease	Prevalence
Other neoplasms of uncertain or unknown behaviour of lymphoid, haematopoietic and related tissue	18.5%
Iron Deficiency Anaemia	14.5%
Purpura and other haemorrhagic conditions	9.0%
Multiple myeloma and malignant plasma cell neoplasms	9.0%
Lymphoid leukaemia	8.5%
Myeloid leukaemia	7.0%
Other diseases of blood and blood-forming organs	6.6%
Myelodysplastic syndromes	5.6%
Other anaemias	2.7%
Polycythaemia vera	2.5%

Table 3: Frequency of blood parameters

Parameter	Relative frequency
Thrombocyte's count	0.99
Lymphocyte count	0.99
Lymphocyte %	0.99
Leukocyte count	0.99
Neutrophils %	0.99
Haematocrit	0.99
Erythrocyte count	0.99
Haemoglobin	0.99
Mean Corpuscular Haemoglobin	0.99
Age	1.00

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