Journal of Digital Health
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Original Research

Artificial intelligence assisted diagnoses of fine-needle aspiration of breast diseases: a single-center experience

Peter Fritz[1*], Raoufi Raoufi[2,9], Peter Dalquen[5], Atiq Sediqi[2,9], Simon Müller[3], Joachim Mollin[4], Steffen Goletz[3], Jürgen Dippon[6], Monika Hubler[3], Tanja Aeppel[3], Bisharah Soudah[3], Haroon Firooz[7], Michael Weinhara[4], Inke Fabian de Barreto[4], Christian Aichmüller[8], Gerhard Stauch[3]

[1] Robert Bosch Hospital, Department of Pathology, 70341, Stuttgart, Germany
[2] Abu Ali Sina Hospital, 1702 Mazar e Sharif, Afghanistan
[3] iPath Telemedicine Network nonprofit company with limited liability (gGmbH) 26603 Aurich, Germany
[4] GOPA Worldwide Consultants, 61348 Bad Homburg, Germany
[5] Institute of Pathology University 4031 Basel, Switzerland
[6] Institute of Stochastic, Faculty of Mathematics, University 70569 Stuttgart, Germany
[7] Firooz Medical Laboratory 3001 Herat, Afghanistan
[8] PAICON GmbH Kurfürsten-Anlage 60 69115 Heidelberg, Germany
[9] Balkh Pathology Laboratory ,1702 Mazar e Sharif, Afghanistan

*Correspondence: peter.fritz2323@arcor.de

Abstract:
Purpose: Since 2010, physicians from Afghanistan have been uploading images of histological and cytological specimens to a telemedicine internet platform (iPath network) for expert evaluation. From this collective work, all cases with fine-needle aspirations (FNA) of mammary gland diseases were extracted and analyzed. The aim of the present retrospective feasibility study is to investigate the utility of artificial intelligence assisted diagnoses in fine-needle aspiration (FNA) of breast diseases.
Material and Methods: A total of 3304 microphotographic images from 438 patients of smears from FNA of the mammary gland were available for this study. Telemedical expert diagnoses from 4 experienced cytopathologists were available in all 438 cases. Their diagnosis (malignant tumor of the mammary gland or benign mammary gland disease) was set as the gold standard. AI analysis was performed using i) clinical context data and ii) two different image recognition methods to determine the probability values for the presence of malignant breast tumor. Youden index and AUC (area under the curve) were used to evaluate test performance.
Results: A score for invasive breast cancer (IBC) calculated from contextual variables agreed with the expert diagnosis (accuracy) in 85.2% and with the two image recognition systems in 78.4% and 65.2%. This simplifies health healthcare management of breast diseases in low income countries as in many patients the less expensive and less time-consuming technique of FNA may replace a histological examination.
Conclusion: Image classification and analysis of context variables can be used to test the validity and plausibility of cytologic diagnoses, especially when cytologic interpretation has to be performed by people who are inexperienced in cytopathology.

Keywords: Breast cytopathology, Artificial intelligence, Fine needle aspiration

Received: Dec.10,2022; Revised: Jan.16,2023; Accepted: Feb.8,2023, Published: Mar.24,2023
Copyright ©2023 Peter Fritz, et al.
DOI: https://doi.org/10.55976/jdh.2202311501-11
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Introduction

Breast cancer is one of the leading causes of mortality and morbidity with somewhat different features in low- and middle-income countries (LMIC) as compared to high income countries [1-6]. In LMCI it is difficult to make a morphologically correct diagnosis following World Health Organization (WHO) recommendations within a reasonable period of time, due to limited means of transportation and a lack of specialist physicians or pathology departments [7]. There are a number of ways to improve the situation through multinational support such as lectures and hands-on assistance in the field. Regular telemedical consultations based on microphotographic images of tissue samples and cytological smears make a particularly important contribution [8,9]. However, experience at institutes in Germany shows that telemedical communication based on such images also requires some practice [10-12].

Cytology offers a way to overcome the technical problems of pathologic diagnosis, such as tissue preparation, paraffin embedding and tissue sectioning to reach an informed diagnosis more quickly. Fine-needle aspiration (FNA) is particularly well suited for this purpose. It is patient-friendly and cost-effective. Sample preparation and processing is less time-consuming and possibly performed directly at the site of cell collection [13,14]. Liquid-based cytology (LBC) would be optimal but requires more expertise and technical support. So only the conventional smear method is used in LMIC. If the cytologic findings are inconclusive, core needle biopsy (CNB) is indicated. Overall, however, CNB is slightly more sensitive, and the specificity of the two methods is the same [13].

In the Department of Pathology at Abu Ali Sina Hospital in Mazar-e Sharif, breast disease has been investigated by FNA for more than 10 years, and the photomicrographs thereof have been uploaded to the iPath-Network web platform developed in Basel [10,11,15]. This platform, accessible to physicians and scientists, enables telemedical consultations and second opinions, especially in the fields of pathology, dermatology, and radiology [12].

With the application of artificial intelligence (AI) methods, a new horizon opens for FNA and those new technologies can compensate partly for the lack of refined diagnostic methods in developing countries. A plethora of new technologies to improve image classification are available [16-25]. Image classification methods trained with neural networks make it possible to determine the probability of the classification of a FNA as either a benign or malignant breast disease [10-13]. In addition, the combination of conventional and computer-assisted methods would provide learning effect for the submitter and an increase in the competence of morphologic diagnosis. Especially in medically underserved countries with a shortage of well-trained cytologists, this approach could be promising [6,13].

To date, these methods have primarily used as whole slide screening for analysis (dynamic telepathology). The present retrospective feasibility study investigates the extent to which analysis of static photomicrographs (JPEG format) from breast FNAs by image classification and analysis of context variables supports the conventionally established diagnosis - or in other words predict the expert diagnosis.

Material and methods

Sample and data

Between 2018 and 2020, FNA was performed in 472 patients with indeterminate breast disease by two physicians (RR, AS) from the above hospital. They examined the smears in Papanicolaou stained and modified hematoxylin and eosin (H&E) stained samples, respectively. Representative photomicrographs of the cytological findings were sent to the iPath platform (Afghanistan group). Based on these images, at least two of the four pathologists (PD, BS, GS, PF, two of them being experienced cytopathologists) involved in the study, including two specialists in cytology made a professional diagnosis according to international standards [7, 26]. All diagnoses were reviewed and discrepancies resolved during daily video conferences in the presence of the physician in charge of pathology at Abu Ali Sina Hospital in Mazar-e Sharif. All individual diagnoses were done independently and used only if a final consensus diagnosis between the four pathologists could be established. In 34 cases (7.2%), a definitive diagnosis could not be made due to poor image quality, low cell count, and/or unclear cytologic findings or lacking consensus between the experts. The remaining 438 cases with evaluable clinical data and images formed the basis for this feasibility study. The expert classifications of these cases were fixed as gold standard. The ground truth (gold standard confirmed by follow-up) was not available. All cases were uploaded on iPath-Network -an open web assisted telemedical system [15] .

Measures of context variables

From each of these 472 case the following features were reported: Age, disease duration, presence of pain, and size, consistency, boundary (smooth/irregular) of the investigated breast mass, skin and nipple changes, and axillary lymph node involvement were included. In addition, the patient was asked whether she was breastfeeding or lactating and whether she had children. Based on these data a score was calculated (IBC score) (for details see Supplement part I and part II) and added to the case data set (see also Supplement part I and part II).The data were either numeric (age, size, duration) or binary (0,1).

Models and data analysis procedures

Note that each of these 472 cases is classified by the expert diagnosis (golden standard) and by the IBC sore and two image classification systems.

The IBC score: Missing data were inserted using an imputation procedure (MICE package in R) [27,28]. A score predicting the diagnosis of invasive breast cancer (IBC) was calculated from the context variables using logistic regression (see Supplement part I for details). A cut-off value of 0.7 was set for this IBC score. Score values above 0.7 were interpreted as indicating malignancy. Missing values were excluded by the MICE package in R [26,27]

Image classification: We used two different approaches for image classification [29-34], both based on neuronal network technology (see Supplement part III and part IV for details). Training set was for both systems different and separated from the 472 test cases. All classified images are of low resolution. For each image a predictor for malignancy (p_malignant or p_max) was given by both classification system. For each study case p_max was calculated and was used for the breast case classification as either benign or malignant. The size of all microphotographs uploaded to the iPath network in JPEG format used in the study was standardized to 224 x 224 pixels. The digital size of an image was <1.5 MB.

Ethical considerations: All patients were informed by their treating physicians (RR, AS, HF) that their cases would be forwarded in anonymized form to an international consortium of experts. Neither name nor date of birth was available to identify patients, and tracing an image or clinical finding to a patient was not possible. The only identification was by iPath number (an 11-element alphanumeric code) and a case number assigned by the submitter that only the attending physician could assign to a patient. Note that approximately 60 % of patients (largely woman) are illiterate. A working ethic commission does not exist in Afghanistan since years. (see also Supplement part V with answers to the reliable *Declaration of Helsinki*).

Working hypothesis: Image classification (even on a low resolution level) and analysis of context variables can predict expert diagnosis better than random guessing. Statistical methods and working hypothesis: AUC (area under curve) and Youden index were used to assess the method reliability [33-36].

Results

Of the 438 test cases, 93 were classified by the experts as malignant and 345 as benign (as a consensus diagnosis). A follow-up for the disease cases was not available due to environmental conditions (wartime, poor state of the health care system). Clinical variables (see following section) were incompletely available. For 34 cases of the original mammary gland registry (7.2%), a definite diagnosis was not established due to poor image quality or lack of a consensus diagnosis. These 34 cases were not included in the study. In average, 7.4 images (median 7.0, standard deviation 3.0) were provided for each patient.

Clinical variables: 11 clinical variables were evaluated (Table 1 and Supplement part II), from which 9 differed significantly (some highly significantly) between benign and malignant breast diseases. Note that even an experienced clinician is overloaded to give a clear statement if faced with the 11 clinical variables. From these data we constricted an IBC score by logistic regression (see supplement part I). Of the variables included (Table 1), age, axillary status, and mobility of mammary gland lesions were found to be significant discriminators in logistic regression. With low efficiency, mobility, painfulness, and consistency of mammary gland change were included in the calculations. A cut-off value of 0.7 was set for the IBC score (see Supplement part I and II). This cut-off value resulted in a sensitivity of 89.3% and a specificity of 84.6%. (Table 2). The difference in IBC score between benign and malignant breast diseases (expert diagnosis as gold standard) is highly significant (for the calculation of the score, see supplement part I).

Accordingly, the significance determined by area under the curve (AUC) and Youden index is high (Table 2). As expected, the significance values of the IBC score calculated for each context variable are highest for axillary lymph node involvement and age (Table 3). Accordingly, analysis of the IBC score predicts expert diagnosis with an accuracy of 85.2%.

Image recognition systems: Each of the 438 cases could be assigned a probability of benign or malignant using the p_max value. The p_max value indicating malignancy correlated highly significantly with expert diagnosis (Table. 2) (P <0.0001). Examples of image classification are given in Figure 1 and Figure 2.

Based on the individual case (Table 3), the accuracy of the diagnosis for image recognition system I is 78.4%. For system II, the accuracy is 65.2%. Accordingly, the two probability values for the test performance (correctness of the system classification) AUC reached moderate values of 0.74 and 0.73 (less than for the IBC score). Both image recognition methods correlated significantly with a low correlation coefficient (r = 0.152, P = 0.003). This situation was taken as an indication that different algorithms underlie the image classification systems.

Combining the results of the two image recognition systems and the context variables, 57 of 93 malignant changes and 304 of 345 benign changes were correctly detected. Taking the results of the three methods together (a case is classified as benign or malignant only if all three systems agree), the specificity is 88.1% and the sensitivity is 61.3% (Table 4).

Table 1. Univariate assignment of study data.

Context Variable	Benign N=345	Malignant N=93	*P* value (t-test or chisq. test)
Characterization of data location, sample size and collection period		Mazar i Sharif N=438 2018-2020	
Age in years			
Mean	27.9	47.7	<0.001
SD	9.8	11.4	
Size of breast lesion (mm)			
Mean	27.7	37.3	<0.001
SD	16.3	19.9	
Months of disease			
Mean	16,2	18.3	0.009
SD	6.9	6.7	
Pain			
yes	163 (47.3)	61 (65.6)	0.003
no	182 (52.7)	32 (34.4)	
Consistency (firm)			
yes	260 (75.3)	75 (85.9)	0.11
no	85 (16.3)	15 (16.1)	
Movable lesion			
yes	177 (51.3)	47 (50.5)	0.99
no	168 (48.7	41 (49.5)	
Regular margin			
yes	143 (41.5)	16 (10.8)	<0.001
no	202 (50.5)	83 (89.3)	
Involvement of the skin			
yes	114 (33.1)	60 (64.5)	<0.001
no	231 (66.9)	33 (35.5)	
Involvement of the axilla			
yes	41 (11.9)	50 (53.8)	<0.001
no	304 (88.1)	43 (46.2)	
Gravidity, preceding birth			
yes	149 (43.2)	20 (21.5)	
no	196 (56.8)	73 (78.5)	0.0002
In lactation			
yes	215 (62.3)	40 (43)	0.001
no	130 (37.7)	53 (57)	

Table 2. Univariate analysis of p_max values of the two image recognition systems and the IBC score of the context variables for the presence of a malignant tumor compared to the expert diagnosis of benign (N = 345) and malignant (N = 93). Sd=standard deviation, p_max= a probability provided by image classification used for classify a breast disease as either malignant or benign

Method	**Benign**	**Malignant**	***p***
Characterization of data			
Location		Mazar i Sharif	
Size		N=438	
Collection period		Year 2018-2020	
P_max	A probability between 0 and 1 for a case to be a benign breast disease or a breast cancer Cut-off=0.38		
Image recognition system I			
Mean (p_max)	0.28	0.36	<<0.001
sd (p_max)		0.08	
	0.09		
Image recognition system II			
Mean (p_max)	0.28	0.39	<<0.001
sd (p_max)	0.16	0.12	
IBC-score	A score value calculated by logistic regression analysis classifying a breast disease as benign or malignant . cut.off=0.7		
IBC score			
Mean	0.53	0.96	<<0.001
sd	0.19	0.24	

Table 3. Analysis of the confusion matrix for the IBC score (analysis of the context variables) and the two image recognition classification systems. PPV= positive predictive value, NPV= negative predictive value, AUC= area under curve

Systems tested for the prediction of malignancy	image recognition system I cut-off = 0.38	Image recognition system II cut-off = 0.38	Analysis of context variables cut-off = 0.7
Characterization data			
Location		Mazar i Sharif	
Size	N = 438		
Collection period	Year 2018-2020		
Sensitivity	51.7	71.1	89.3
Specificity	85.7	61.8	84.6
PPV*	49.5	36.4	61.0
NPV*	86.8	90.5	96.7
Accuracy	78.4	65.2	85.2
Youden index	37.4	38.9	71.9
F1-score	50.6	49.4	72.5
AUC*	0.74	0.73	0.931

*Note that the AUC is independent of the choice of the cut-off.

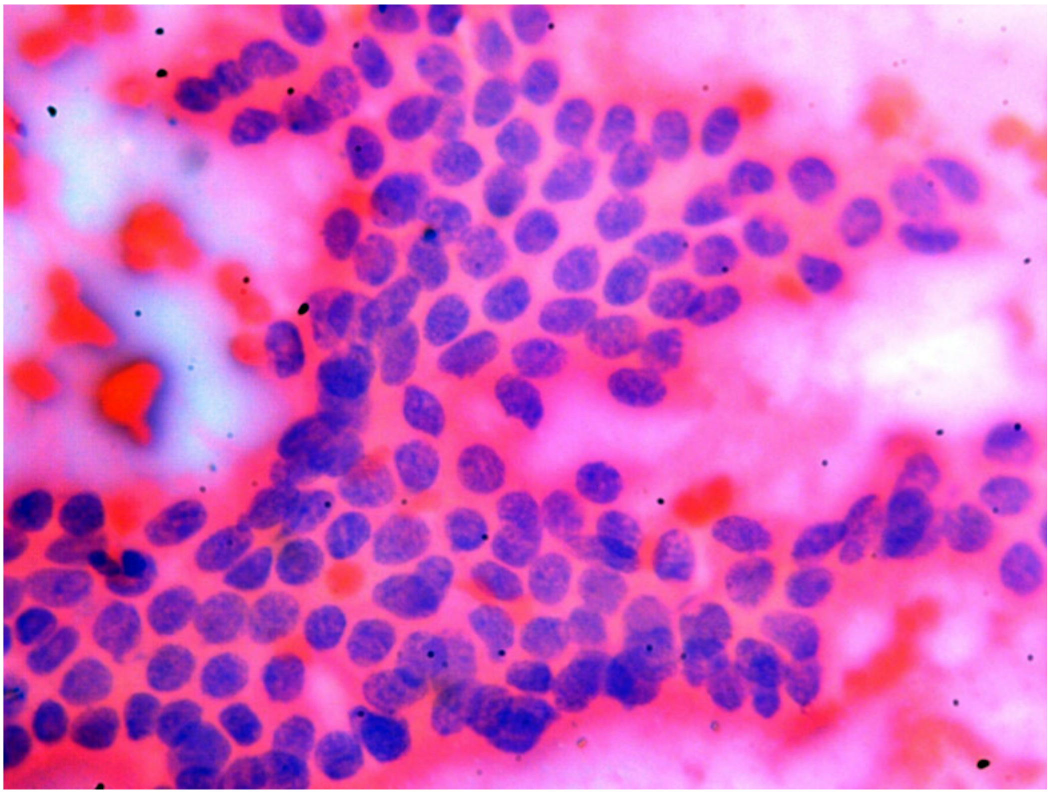

Figure 1. Benign cells from fibroadenoma (primary magnification 400x). iPath-network 1072142, expert diagnosis: fibroadenoma, IBC-Score 0.41. image recognition 0.008 or 0.169 (classification system I respectively II). Note that all score values are below the mean and argue for a benign lesion

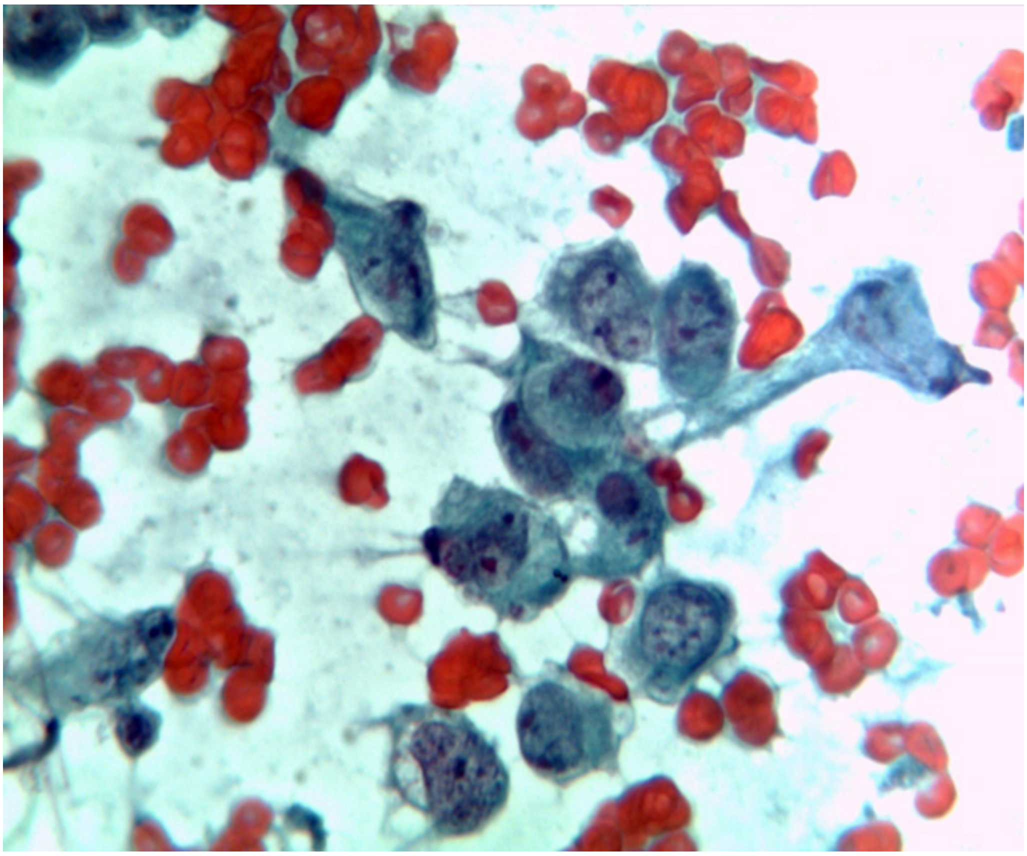

Figure 2. Carcinoma cells (primary magnification 1000x). iPath-network 962973, expert diagnosis: invasive breast cancer, IBC-score 1.088, p_max 0.45 or 0.44 image classification I respectively II. Note that all score values are above the mean and argue for a malignant lesion

Table 4. Concordance between expert diagnosis and the (c9mbined), image classification and analysis of the context variables. How successful expert classification can be predicted by combined AI (arteficial intelligence) methods?

Cytological diagnosis	Image Classification	Context variables	N	Frequency
Characterization data				
Location	Mazar i Sharif			
Size		N=438		
Collection period	Year 2018-2020			
	malignant	malignant	**57**	**61.3**
Malignant	benign	malignant	17	18.3
	malignant	benign	14	15.1
	benign	benign	5	5.3
sensitivity	In 61.3 both AI systems predict correctly the expert diagnosis			
	benign	benign	**304**	**88.1**
benign	malignant	benign	13	3.8
	benign	malignant	26	7.5
	malignant	malignant	2	0.6
	N=345 test cases are benign	moderate to good	specificity 88.1	

Table 5. Present feasibility study

Summary
the expert diagnosis of FNA of breast diseases can be predicted by image classification and analysis of context variable with satisfactory results (AUC area under curve)
low image quality are useable for this prediction
Combining image classification and analysis of context variables makes it possible to support for a final diagnosis even for unexperienced cytopathologists in the majority of cases
Analysis of context variables and image classification may be an essential assistance for unexperienced cytopathologists as shown by our feasability study

Discussion

The present feasibility study shows (Table 5): (1) Analysis of photomicrographs using image recognition methods yielded results consistent with expert diagnoses in a substantial number of cases. This statement holds true for JPEG images acquired with static digital pathology and a pixel matrix below 1.5 MB. However, the test performance points only moderate results in both image classification systems. (2) The two image recognition methods did not differ significantly in their test performance (Table 2 and 3). (3) The performance of the context variables is consistent with the findings of a previous work [37] and has a better test performance compared to the two image recognition methods.

The question arises to what extent the addition of the missing context data may have positively influenced the results. For the experienced clinician, clinical findings in patients who usually come for examination at a late stage already clearly indicate breast carcinoma. At an earlier stage of the disease, when changes in skin, nipple retraction, and enlargement of axillary lymph nodes have not yet occurred, the evidence of carcinoma is less clear. Therefore, the significance of the analysis of contextual variables might be worse than in the present study. However, the present feasibility study clearly shows that the prediction of expert diagnosis is superior to random guessing. This holds true for image classification as analysis of context variables as well as for the combination of both methods.

In an underserved country such as Afghanistan, organizational difficulties of medical practice must also be considered, such as (1) insufficient technical and human resources in the pathology institute, (2) lack of specialized methods such as immunohistochemistry and molecular biology, and (3) lack of reliable follow-up data. Against this background, the use of additional AI-assisted methods gains increasing importance. We hold the opinion that the feasibility of such AI-assisted diagnoses in LMIC is demonstrated by our data.

This leads to the fundamental question, whether the application of AI methods for the analysis of clinical and morphological data is useful at all under these conditions. In our opinion, the answer is yes despite suboptimal results of the present feasibility study. As Table 4 shows, the overall results measured by the classification of a breast tumor as benign or malignant compared with expert judgment (gold standard), are promising despite low sensitivity. If the results of all three systems are consistent, it could be helpful to the inexperienced pathologist in deciding how to proceed clinically. Thus, the lower-performing image recognition methods also appear to be suitable as additional diagnostic tools.

The low correlation coefficient ($r = 0.152$) of the two image classification systems shows that the information gain strongly depends on the algorithms used.The nonoptimal test efficiency and information gain of both systems may be caused by a faulty expert diagnosis. However, this is not very likely due to the high efficiency of the analysis of the context variables. In particular, the consistency of the results of all three systems may be helpful for the cytopathologist who is unexperienced in pathology when deciding on the further clinical course of action. The test performance (Table 3) of all three AI methods (especially of the image classification systems) points to the need of further improvement. Such improvement will be only possible through a close cooperation between mathematicians and pathologists.

Our positive assessment of the use of AI in the assessment of breast tumor FNA is supported by affirmative reports found in the literature with partly better test parameters than in our study [38-48]. Our relatively low AUC for both image recognition systems can be explained by the lower image quality (low pixel count). However, this disadvantage is compensated by the use of 2 independent image classification systems and an additional analysis of context variables. In our opinion, our feasibility study justifies the use of image classification systems and context variables on static images of FNA in breast disease, especially in countries where there are only a few experienced cytopathologists. Further studies are planned with the aim of identifying other prognostic features through image classification of cytologic microphotographic images and analysis of clinical variables, thus reducing the need for core needle biopsies to obtain a definitive diagnosis and therapeutically relevant features of breast carcinoma.

Some inherent disadvantages of the presented study such as the lack of histological counterparts of each study case must be seen under the very difficult conditions of performing this study (war time in Afghanistan, no financial support for the study). A further disadvantage of using context variables may be that the context variables depends on the tumor stage. This valuable argument can be overcome in future by adapting the IBC score with new breast disease register data (no ongoing).

In summary, the data from this feasibility study clearly demonstrate that AI methods can predict and exert supportive diagnosis. From this finding we conclude that AI methods are useful, particularly in underserved countries where they can be used in conjunction with telemedicine guidance to train medical staff and thus improve patient care. Further studies should be done in close collaboration between mathematicians and physicians.

Conclusions

1)Data set with assigned images of breast diseases as basis for training sets should be available as open source images;

2) prospective studies with breast diseases showing the utility of AI-assisted image classification and analysis of context variables should be done in LMIC;

3) beside sophisticated scanning microscopy technology, AI-assisted image classification of low resolution images of breast diseases should be supported.

Acknowledgement

We would like to thank the Evang.- Luth. Church County Office Aurich, director Mr. Holger Dierks for the generous funding.

Statement of Ethics

No Afghan ethic committee is working in Afghanistan and therefore protocol approval was not obtained prior to the initiation of the study. The principles of the Declaration of Helsinki were adhered to as detailed in Supplement part V. Furthermore, the Northwestern and Central Switzerland Ethics Committee confirmed that, while they can not retrospectively approve a project, from their point of view there would be no ethical concerns against the implementation of the research project if it was submitted to them now. All patients were informed by their treating physicians (RR, AS, HF) that their cases would be forwarded in an anonymized form to an international consortium of experts. It was not possible to obtain written informed consent from all patients as many patients were not literate. All non-Afghanistan cases are based on published literature.

Conflict of interest

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

Funding sources

Beside the small funding of the Evang.- Luth. district office Aurich, no funding.

Authors' contributions

F.P.: image classification for training sets, expert diagnosis, data evaluation, manuscript preparation

R.R.: primary diagnosis and patient management in the iPath network

D.P.: image classification and expert diagnosis

S.A.: primary diagnosis and patient management in the

iPath network
M.S.: image classification system II
M.J.: image classification system I
G.S.: data evaluation
D.J.: study concept and supervision
H.M.: data administration
A.T.: expert diagnosis
S.B.: expert diagnosis
F.H.: primary diagnosis and patient management in the iPath network
W.M.: manuscript preparation, data acquisition
F.B.I.: manuscript preparation, image classification II
A.C.: manuscript preparation, study concept, supervision
S.G.: image classification for training sets, expert diagnosis, data evaluation, study concept

Data availability statement

All data can be requested from the correspondence author and will be send as a csv. data base.

Supplementary material

The supplementary material of this research is available at https://file.luminescience.cn/JDH-150%20Supplementary%20Material.pdf.

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