

THE DEVELOPMENT OF A FUZZY LOGIC SYSTEM USING MATLAB FOR EARLY DETECTION OF HEREDITARY CANCER IN BRCA1/2 NEGATIVE CASES

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ABSTRACT

The purpose of our study is to expedite cancer diagnosis through the development of software for rapid detection of hereditary breast cancer (BC) with negative *BRCA1/2* on MATLAB, utilizing a fuzzy logic system with several variants of genes associated with BC. This system serves as a clinical decision-support tool, assisting in early classification and interpretation of genetic variants by combining clinical and genetic data. Clinical data were obtained from Erciyes University Faculty of Medicine Department of Medical Genetics and Uludağ University Faculty of Medicine Department of Medical Genetics. 488 individuals were studied. Only 90 of them were relevant to our investigation since their *BRCA1/2* genes did not exhibit notable genetic mutations. We examined 16 distinct breast cancer risk factors and focused on mutations related to 18 hereditary BC genes. The collected data were integrated into the developed system, and various membership functions were given varying degrees of possibility, ranging from 0 to 1, depending on their participation in input clusters. After the system was trained on 90 cases and validated on six independent patients, its accuracy was assessed, yielding reliable results. Following the training

phase, outcomes revealed the presence of two pathogenic variants at 0.92 (92%), two benign variants at 0.25 (25%), and two variants of unknown significance at 0.5 (50%). Given the high incidence of breast cancer, early prediction is paramount. Despite the emergence of fuzzy logic systems in medical applications, limited research akin to our study exists. The establishment of this artificial intelligence software holds promise for advancing the early detection of BC in future clinical applications.

Key words: Fuzzy Logic, *BRCA1*, *BRCA2*, breast cancer, MATLAB.

INTRODUCTION

Breast cancer (BC) represents a complex, multifactorial disease predominantly affecting women, with rare occurrences in men [1]. Its etiology often involves genetic alterations impacting genes crucial for cellular growth regulation. These genetic variations lead to uncontrolled cell division and proliferation. Nearly 10% of breast cancer cases are attributed to mutations in high-penetrance genes, including *PALB2*, *TP53*, *ATM*, *CHEK2*, *PTEN*, or *CDH1* [2]. Notably, certain genetic factors, such as mutations in the Breast Cancer Associated Genes (*BRCA1*) and (*BRCA2*), are recognized for their pronounced and definitive roles in breast cancer development. It is posited that germline mutations occurring in the *BRCA1/2* genes are predominantly linked to the majority of hereditary breast cancers. These mutations account for only 28% of familial risk factors. Nonetheless, advancements in high-resolution screening methodologies have led to the identification of novel variations within the *BRCA1/2* genes on a daily basis [3].

Although germline alterations in the *BRCA1* and *BRCA2* genes confer significantly heightened risks for both breast and ovarian cancers, their penetrance remains in-

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completely understood. The risk of the development of BC in *BRCA1/2* carriers by age 70 ranges from 45% to 87%. These variations comprise mutations at 3'/5' splice sites, 3'/5' untranslated regions (UTRs), synonymous mutations, frameshift mutations, nonsense mutations, and missense mutations, within the coding regions [4]. There are about 2,000 mutations in the *BRCA2* coding region. Approximately 55% of these variants have been found only within families [5]. Variants with uncertain significance (VUS) have been assigned to around 1800 SNPs in *BRCA1* and *BRCA2* [6].

Machine learning techniques have been increasingly employed in cancer-related models for survival prediction and prognosis, yielding accurate and reliable approximations [7]. This has spurred interest within the medical imaging community to leverage such techniques to enhance cancer screening accuracy. However, there remains a paucity of studies utilizing machine learning methodologies to personalize cancer risk prediction or to compare the reliability and accuracy of such models with those employed in community practice. Artificial intelligence (AI) aids radiologists in improving breast cancer detection accuracy with minimal recalls. Specifically, AI demonstrates 88.8% sensitivity in brain cancer detection, outperforming radiologists who exhibit 75.3% sensitivity. Notably, when AI assists radiologists, there is a significant 9.5% increase in AI sensitivity, reaching 84.8% [8].

The fuzzy logic model operates on estimations rather than strict, fixed values. Unlike classical Boolean logic, which categorizes objects as either true or false, fuzzy logic allows for classification with values ranging between 0-1 [9]. Fuzzy logic finds broader application in system control due to its enhanced effectiveness and reduced complexity. Despite individual attempts to utilize fuzzy logic for decision-making, as suggested by Sizilio et al. (2012), these approaches prove effective in dealing with imprecise and inaccurate data but may ultimately become more intricate. Accurate evaluation and identification of breast cancer risk are critical to the decision-making process for the best course of follow-up care for suspected cases of breast cancer. Although current technical developments, some clinicians believe that the criteria and procedures used to evaluate the stage of breast cancer healing and thus predict the risk of recurrence are still unclear and subjective. Conversely, previous studies employing fuzzy logic for patient classification aimed to incorporate both classification and algorithm selection based on the fuzzy logic principle of membership degree [9]. In this research, we used MATLAB to create a fuzzy logic system for rapid detection of hereditary breast cancer (BC) with negative *BRCA1/2* mutations. While machine learning models such as Random Forest and XGBoost offer high predictive accuracy, they often function as “black boxes” with limited

transparency in how predictions are made. In clinical genetics, where variant classification has direct implications for patient care, interpretability is critical. Fuzzy logic provides a clear advantage in this context due to its rule-based framework and ability to handle uncertainty. In our system, expert knowledge, particularly the ACMG variant classification criteria [10], was embedded into membership functions. This approach allows clinicians to trace how both genetic and clinical inputs contribute to each classification. The proposed model integrates a wide spectrum of hereditary cancer gene variants and clinical risk factors to classify ambiguous genetic findings and to assess the pathogenicity of genetic variants, particularly variants of uncertain significance (VUS). The system supports early risk estimation and improves clinical decision-making in *BRCA1/2*-negative breast cancer cases where traditional genetic screening offers inconclusive results.

MATERIALS AND METHODS

Study design and data Collection

Patient data for this retrospective study were obtained from the medical genetics departments at Erciyes University Faculty of Medicine and Uludağ University Faculty of Medicine. 90 of the 488 datasets that were analyzed were deemed suitable for analysis due to the absence of significant mutations within *BRCA1/2* genes, the study concentrated on 18 inherited risk factor genes: *CHEK2*, *TP53*, *FAM175A*, *NBN*, *MSH6*, *APC*, *RAD50*, *MSH2*, *ATM*, *CDH1*, *MUTYH*, *PALB2*, *BART1*, *BLM*, *MRE11A*, *PMS2*, *PTEN*, and *BRIP1*. Clinical parameters were categorized into 15 distinct input clusters representing cancer-associated risk factors, such as sex, age, family history, consanguinity, relatedness degree, lymph node, malignancy, location, tumor size, gene, progesterone positivity, estrogen receptor positivity, gene variation, classification, and diagnosis. The fuzzy logic system used the risk factors as input clusters. A membership function was introduced into each input cluster. As a result, each membership function represented different levels of cluster membership. The American College of Medical Genetics and Genomics (ACMG) Guideline was used to classify genetic variants as benign, likely benign, variant with uncertain significance (VUS), likely pathogenic, and pathogenic [10].

Establishing fuzzy logic with clinical data of the patients

Prior to introducing the patient data into the system, the inputs and functions of membership were identified. Consequently, the system ultimately made use of 90 different patient datasets. Still, more data always seems to make the system function better. Accurate and proportionate data are essential for producing accurate findings; otherwise,

the results will be incorrect. Furthermore, the system will produce inaccurate results if data is entered incorrectly.

Creating Fuzzy Logic System on MATLAB

MATLAB or Matrix laboratory is a certified programming language created by MathWorks. It is a multi-paradigm numerical computation software. It enables data drawing, functions, matrix processing, algorithm implementation, and interface with programs written in alternative languages like C, Java, Fortran, and C++ [11]. Recently, MATLAB has been heavily used in many different domains related to image processing. The foundation of developing an artificial intelligence application is fuzzy logic. Fuzzy logic typically leads directly to findings. By providing members in intervals of 0 and 1, it illustrates the differences between items in “fuzzy” sets.

Applications of fuzzy logic have been used in many different fields, and using the fuzzy logic toolbox on a MATLAB program makes them simple to use. Many functions that are available and will be written by the programmer can simplify operations. There are five different windows in MATLAB: current directory, workspace, command history, array editor, and command window. Figure 1 shows how to apply the toolbox’s capabilities to access and use fuzzy modeling and system design for Fuzzy Logic Designer.

Fuzzy Logic Assumption Methods

Mamdani Fuzzy Inference Method (MFIM) was applied in this work [12]. It is utilized to create the load sensor and has two inputs: displacement and the load sensor. The Mamdani Fuzzy technique is a fuzzy logic approach that

can be used to solve any issue and is incredibly easy for individuals to develop [13].

The MFIM model’s five primary steps are shown in Figure 2. To identify the input variable membership degrees between 0 and 1, an initial fuzzification step was created. Utilizing fuzzy logic operations that are dependent on values is the second phase. The third step, termed “fuzzy cluster implementation,” was created to change “or” and “and.” In the fourth stage, the results are collected and represented as output. The final data is assembled in the penultimate step [12].

RESULT

Data collection and study design

Figure 3 illustrates the distribution of tumor sites among 90 female patients. Among the patients, 38% (34 patients) had a tumor on their left breast alone, 29% (26 patients) had a tumor on their right breast, and 7% (six patients) had bilateral tumors. However, 22 % (20 patients) were VUS, 26% (24 patients) of the patient’s tumor locations were not indicated, 20% (18 patients) were lightly pathogenic, 6% (five patients) were classified as pathogenic, and 23% (21 patients) had benign variants within the genes linked to hereditary breast cancer as shown in Figure 4.

Combining the Massive Data

Tables 1 (a, b, and c) present data from randomly selected patients with BRCA1/2 negative breast cancer from the established database.

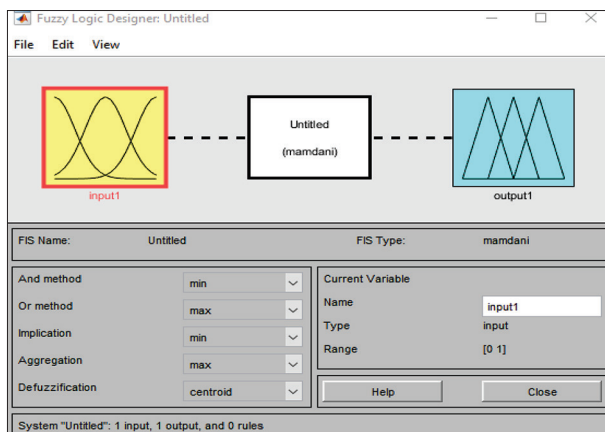


Figure 1. Fuzzy Logic Designer Window

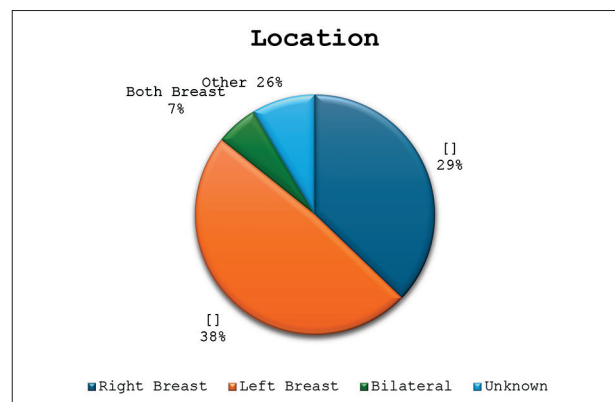


Figure 3. Distribution of the tumor location. 38% (34 patients) had a tumor on their left breast alone, 29% (26 patients) had a tumor on their right breast alone, and 7% (six patients) bilateral.

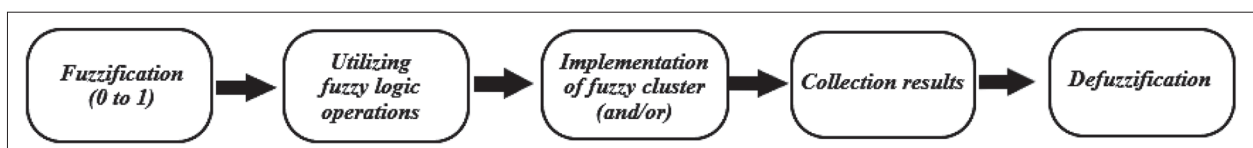


Figure 2. The MFIM model’s five primary steps

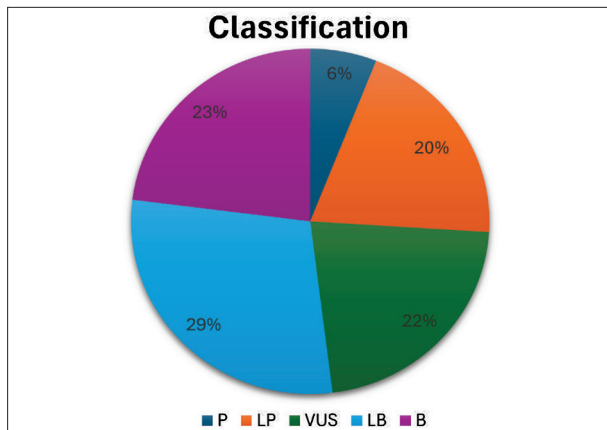


Figure 4. Gene variant distributions according to ACMG categories (P: pathogenic, LP: likely pathogenic, LB: likely benign, B: benign, VUS: variant with unknown significance).

Developing a Fuzzy Logic System Utilizing Patients Data

Figure 5 shows the creation of one output parameter and 14 distinct input parameters during this investigation. Artificial intelligence classifies risk factors into groups based on membership functions, which enables the rating of these elements. For varying patients, membership functions in the input clusters supplied varying degrees of options, ranging from 0 to 1. These values reflect clinical and biological risks. A membership value of 1.0 indicates complete belonging to a category, while 0.5 reflects uncertainty or partial membership. For instance, a value of 1.0 reflects full certainty in assigning a case as ‘pathogenic’, while 0.5 is commonly associated with a variant of uncertain significance (VUS). Table 2 presents the values of the membership functions for each risk factor in each input cluster.

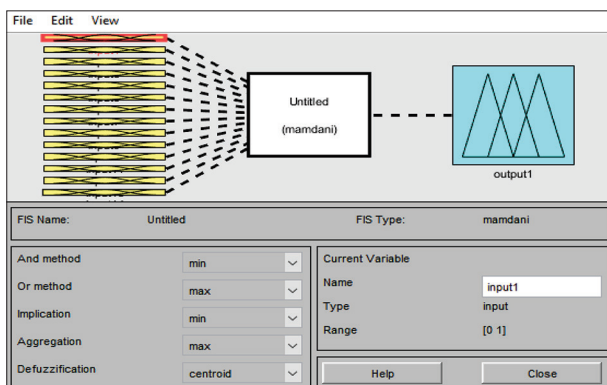


Figure 5. Representation of the fuzzy logic model in MATLAB, showing how 14 clinical input parameters are mapped to a single output classification. The membership functions assign degrees of belonging to each input, with values ranging from 0 to 1.

Table 1.a. The first example of patient data.

Input Parameters	Sample Patient Data
Age	51
Sex	Female
Consanguinity	No
Family History	Yes
Membership Degree	unknown
Tumor Size	10cm
Lymph Node	No
Malignancy	2
Location	Both Breast
Estrogen Receptor	Positive
Progesterone	Positive
Gene Variation	<i>APC</i>
Diagnosis	Positive
Classification	Likely Benign

Table 1.b. The second example of patient data.

Input Parameters	Sample Patient Data
Age	50
Sex	Female
Consanguinity	No
Family History	Yes
Membership Degree	1
Tumor Size	16cm
Lymph Node	No
Malignancy	Unknown
Location	Left Breast
Estrogen Receptor	Positive
Progesterone	Positive
Gene Variation	<i>ATM</i>
Diagnosis	Positive
Classification	VUS

Table 1.c. The third example of patient data.

Input Parameters	Sample Patient Data
Age	62
Sex	Female
Consanguinity	No
Family History	Yes
Membership Degree	1
Tumor Size	20cm
Lymph Node	Unknown
Malignancy	Unknown
Location	Right Breast
Estrogen Receptor	Negative
Progesterone	Negative
Gene Variation	<i>RAD50</i>
Diagnosis	Positive
Classification	Pathogenic

Table 2. Membership function values in each input cluster for each risk factor.

Risk Factors	Membership Functions	Values
Age	<15	0
	16-29	0.25
	30-39	0.5
	40-59	0.75
	>=60	1
Sex	Female	1
	Male	0
Consanguinity	Yes	1
	No	0
Family History	Yes	1
	No	0
Membership Degree	0	0
	1 & 2	0.5
	>=3	1
Tumor Size	0-19cm	0
	20-39cm	0.5
	>=40cm	1
Lymph Node	Yes	1
	No	0
Malignancy	Grade 1	0
	Grade 2	0.5
	Grade 3	1
Location	Other	0.25
	Right Breast	0.5
	Left Breast	0.75
	Both Breast	1
Estrogen Receptor	Positive	1
	Negative	0
Progesterone	Positive	1
	Negative	0
Gene Variation	TP53	0.1
	FAM175	0.15
	RAD50	0.2
	NBN	0.25
	MSH6	0.3
	APC	0.35
	MSH2	0.4
	ATM	0.45
	CDH1	0.5
	MUTY	0.55
	PALB2	0.6
	BLM	0.65
	MRE11A	0.7
	PMS2	0.75
	CHEK2	0.8
	PTEM	0.85
	BART1	0.9
	BRIP	1
Diagnosis	Yes	1
	No	0
Classification input and output	Benign (B)	0
	Likely Benign (LB)	0.25
	VUS	0.5
	Likely Pathogenic (LP)	0.75
	Pathogenic(P)	1

Table 3. Output cluster and Values of Membership.

Membership Functions of Output Classification	Values of Membership Functions
Benign	0
Likely Benign	0.25
VUS (Variant with Unknown Significance)	0.5
Likely Pathogenic	0.75
Pathogenic	1

In the rule section, the dataset comprising information from 90 patients was utilized for training the system, incorporating risk factors within the rule section as depicted in Figure 6. The results were evaluated and accessible during the test phase, as stated in the classification in the output of the last section. The membership functions and values of the output are shown in Table 3.

Fuzzy System verification

The tests of verification were conducted to assess its performance. An interval for classification was established to determine the cancer status of the depicted individual in Figure 7. This figure shows the fuzzy inference system's rule viewer, which visually displays how input parameter combinations influence the final classification output. A value of 1 corresponds to 'Pathogenic', 0.75 to 'Likely pathogenic', 0.5 to 'VUS', 0.25 to 'Likely benign', and 0 to 'Benign', based on ACMG classification criteria.

The experimental cohort consisted of six patients who had not been previously encountered by the system. Each patient presented distinct gene variant classifications: one likely benign, two variants of uncertain significance (VUS), and two pathogenic variants. Table 4 illustrates the dataset of the experimental cohort utilized in the validation study. The method reliably produced a pathogenic likelihood of 0.92 for both tests in first and second BC patients with pathogenic variations in the NBN and RAD50 genes, respectively. This was demonstrated by their equal percentages. The third test used data from a different patient to further confirm the accuracy of the system. Table 9 shows that the algorithm assigned a probability of 0.25 for the likely benign categorization of a BC patient having a likely benign mutation in RAD50. The patients who remained with variants of unknown significance (VUS) in the APC, MSH2, and MSH6 genes were given a VUS probability of 0.5 for every test. Interestingly, our classification table showed that the algorithm could predict potential differences in VUS with accuracy. Overall, the designed fuzzy logic system assigned output values ranging from 0 to 1 for each individual in the test group. The percentage outputs presented in the results were calculated by mapping these

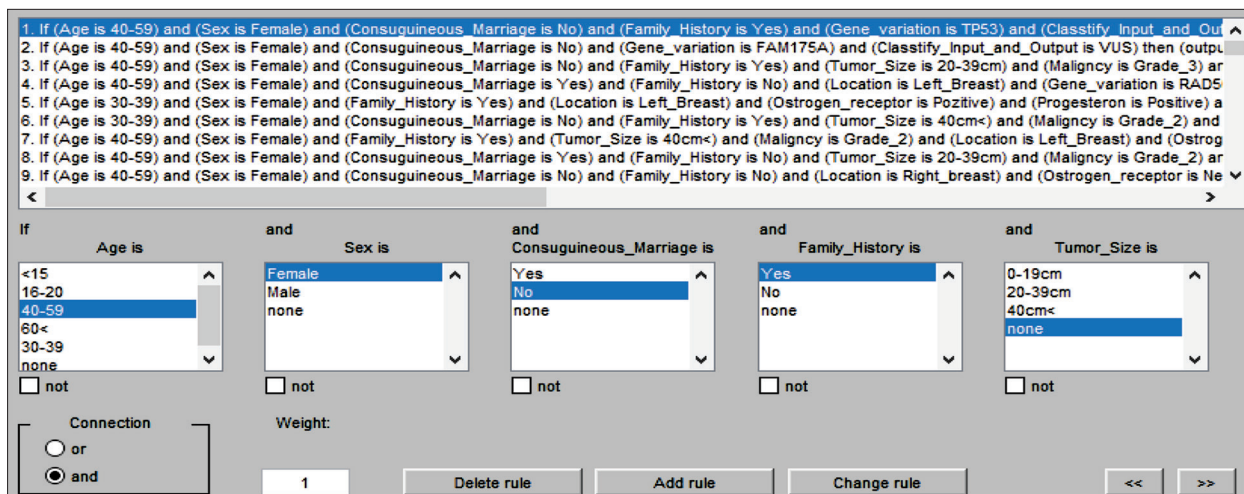


Figure 6. Rules section in the Fuzzy Logic System, utilized data from 90 patients and parameters as input and membership functions within the rule section.

Table 4. System validation results

Risk factors	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age	42	42	34	52	47	49
Sex	Female	Female	Female	Female	Female	Female
Consanguinity	Unknown	No	Unknown	Unknown	Yes	Unknown
Family History	Positive	Positive	Positive	Positive	Negative	Positive
Tumor Size	Unknown	1.9x1.8	3x2.5	2x2	1.2x0.5	3x2x2
Membership Degree	Grade 2	Grade 3	Grade 2	Grade 2	Grade 2	Grade 3
Location	Right Breast	Right Breast	Right Breast	Left Breast	Right Breast	Left Breast
Estrogen receptor	Positive	Positive	Positive	Positive	Positive	Negative
Progesterone	Positive	Negative	Positive	Positive	Positive	Negative
Gene/Gene Variation	Encodes Nibrin <i>NBN</i>	Double Strand Break Repair Protein <i>RAD50</i>	Double Strand Break Repair Protein <i>RAD50</i>	DNA Mismatch Repair Protein <i>MSH6</i>	Adenomatosis Polyposis Coli <i>APC</i>	DNA Mismatch Repair Protein <i>MSH2</i>
Variant	c.1154_1155del	c.2014C>T	c.980G>A	c.663A>C	c.296G>A	c.435T>G
Diagnose	YES	YES	YES	YES	YES	YES
Classification	P	P	LB	LB/CIP	VUS	VUS
Output	P	P	LB	LB/CIP	VUS	VUS
Percentage Of Results	0.92 %92	0.92 %92	0.25 %25	0.5 %50	0.5 %50	0.5 %50

VUS: variant with unknown significance, LB: likely benign, P: pathogenic

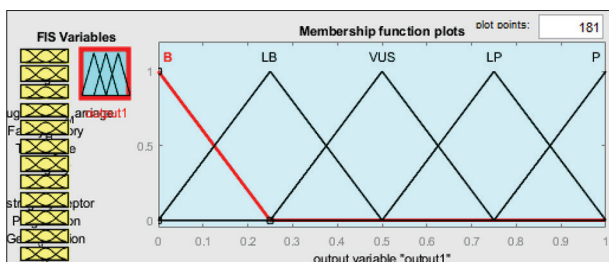


Figure 7. The set of outputs within the fuzzy logic interface on MATLAB, showing classification intervals from 0 to 1. A value of 1 corresponds to 'Pathogenic', 0.75 to 'Likely pathogenic', 0.5 to 'VUS', 0.25 to 'Likely benign', and 0 to 'Benign', based on ACMG classification criteria.

membership values directly to a percentage scale (e.g., a membership value of 0.92 is equivalent to 92% likelihood). Although the system demonstrated consistent results during validation, the small sample size (six patients) limits the generalizability of the findings, and the confidence scores presented here are preliminary. These outcomes should be considered exploratory; future work with a larger and more diverse cohort will expand validation.

DISCUSSION

Precision medicine is being revolutionized by artificial intelligence (AI) techniques such as machine learning and fuzzy logic, which convert large amounts of data into knowledge that can be applied in clinical settings. Because the subject of medicine is inherently ambiguous, fuzzy logic techniques are employed to lessen uncertainty in the field. In medical practice, early diagnosis is critical, which has led to the development of evidence-based computerized diagnostic tools that support doctors in making primary care decisions. These instruments have the potential to save lives and shorten treatment times [14]. Because they decrease the amount of uncertainty in clinical decision-making, fuzzy logic techniques are very helpful in the treatment of diseases like cancer and cardiovascular disorders. Particularly, one of the main causes of cancer-related mortality for women worldwide is heterogeneous breast cancer.

In order to create a scoring system for breast cancer estimation utilizing family history, TNM stage, and BC class as risk variables, the fuzzy logic system was recently employed to predict the mortality of breast cancer [15]. An assessment of breast cancer risk was carried out in a different study by Valarmathi et al. (2012). The staging of lymph nodes, tumors, and metastases was done using the Unity rule and the ID3 algorithm. The fuzzy logic toolbox was used to estimate the intensity range of breast cancer. The factors included diagnosis stages such as TNM, gender, age, diet, location, year, heredity, marital status, disease phase, and therapy [16]. However, according to ACMG guidelines [10], this study concentrated on 18 inherited risk factor genes: *CHEK2*, *TP53*, *FAM175A*, *NBN*, *MSH6*, *APC*, *RAD50*, *MSH2*, *ATM*, *CDH1*, *MUTYH*, *PALB2*, *BART1*, *BLM*, *MRE11A*, *PMS2*, *PTEN*, and *BRIP1*. Data were categorized into 15 distinct input clusters representing cancer-associated risk factors, such as age, sex, family history, consanguinity, relatedness degree, lymph node, malignancy, location, tumor size, gene, progesterone positivity, estrogen receptor positivity, gene variation, classification, and diagnosis. In addition to their genetic variants, which are believed to be connected to the molecular etiology of breast cancer.

Previous studies using a combination of population-based and family-based approaches have illuminated the relationship between breast cancer susceptibility genes and genes involved in DNA repair [17]. The *BRCA1/2* genes are essential for maintaining the integrity of the genome, in part because they are involved in DNA repair mechanisms, control over checkpoints in the biological cycle, and regulation of critical mitotic or cell division stages. As a result, a significant increase in genomic instability is

triggered by the total loss of function in either protein [18]. The *BRCA1/2* genes' clinical significance and complexity are highlighted by the discovery of thousands of unique disease-associated mutations within them. Given the well-established roles and impacts of *BRCA1/2* genes, our study directed attention to alternative hereditary cancer-related genes for early breast cancer prediction utilizing fuzzy logic. Specifically, we concentrated on the intricate interplay of genetic mutation, specifically targeting patients with negative *BRCA1/2*. Among 488 patient datasets, 90 individuals were selected for exhibiting variations in 18 different hereditary cancer genes, excluding *BRCA1* and *BRCA2*. These datasets were utilized to develop the fuzzy logic system. To the best of our knowledge, this study represents a unique endeavor by amalgamating a diverse array of cancer risk factors alongside genetic variants. In the realm of artificial intelligence or fuzzy logic, the inclusion and training of the system with an extensive set of risk factors are paramount for attaining heightened accuracy and thereby fostering consistency in results.

In our work, we classified our outputs as pathogenic, likely pathogenic, likely benign, benign, and VUS using the ACMG variant classification criteria. Another study found that in order to provide a risk prediction for breast cancer, we classified the output clusters as not serious, serious moderate, very serious, and extremely serious [10]. Another investigation concentrated on enhancing early prediction and personalized medicine strategies for *BRCA1* and *BRCA2* positive breast cancer patients through the utilization of a fuzzy logic system [19]. This study incorporated an analysis of 16 distinct risk factors, focusing exclusively on a cohort of 268 patients positive for *BRCA1* and *BRCA2* mutations. In contrast, our study derived results from a dataset comprising 90 patients negative for *BRCA1/2* mutations, afflicted with hereditary breast cancer, and exhibiting genetic variations within 18 different genes. Our investigation revealed a wide range of genetic variations across many genes. Despite these differences, both studies employed a standardized set of five membership functions in the output, including likely Benign, Benign, Likely Pathogenic, Pathogenic, and Variant of Uncertain Significance (VUS).

Six independent test groups were executed to evaluate the efficacy of the designed fuzzy logic system; the groups were not previously integrated into the system. The analysis yielded precise and consistent outcomes across all six new test groups. As a consequence, we may conclude that individuals with hereditary breast cancer who test negative for *BRCA1/2* can benefit from early detection utilizing the data generated by artificial intelligence techniques.

CONCLUSION

Nowadays, artificial intelligence is becoming more prevalent in the health area. With an increase in cancer cases worldwide, novel approaches to therapy must be developed. Risks of human errors will be decreased with the use of artificial intelligence and innovative technologies. This study assumes critical importance as a precursor to future precision medicine endeavors. Our developed model represents a distinctive exemplar of personalized medicine, offering early prediction capabilities for numerous patients at risk of breast cancer. Moreover, its potential for pre-diagnostic application within clinical and hospital settings or under the guidance of healthcare professionals is underscored, considering the potential time-consuming and frustrating diagnostic and treatment processes for both clinicians and patients.

CONFLICT OF INTEREST

The authors do not have any conflicts of interest to declare.

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There is no funding for this study.

DATA AVAILABILITY STATEMENT

The data is available upon request.

AUTHOR CONTRIBUTION

Conceived and designed the analysis: N.S., P.G.V., M.S.B.A., B.D., L.A., S.O.S., M.D., S.G.T., M.C.E.; Collected the data: B.D., L.A.; Contributed data or analysis tools: N.S., P.G.V.; Performed the analysis: N.S., P.G.V.; Wrote the paper: M.S.B.A., M.C.E.; revised the paper: M.D., S.G.T., M.S.B.A., M.C.E.; supervised the project: M.C.E.

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