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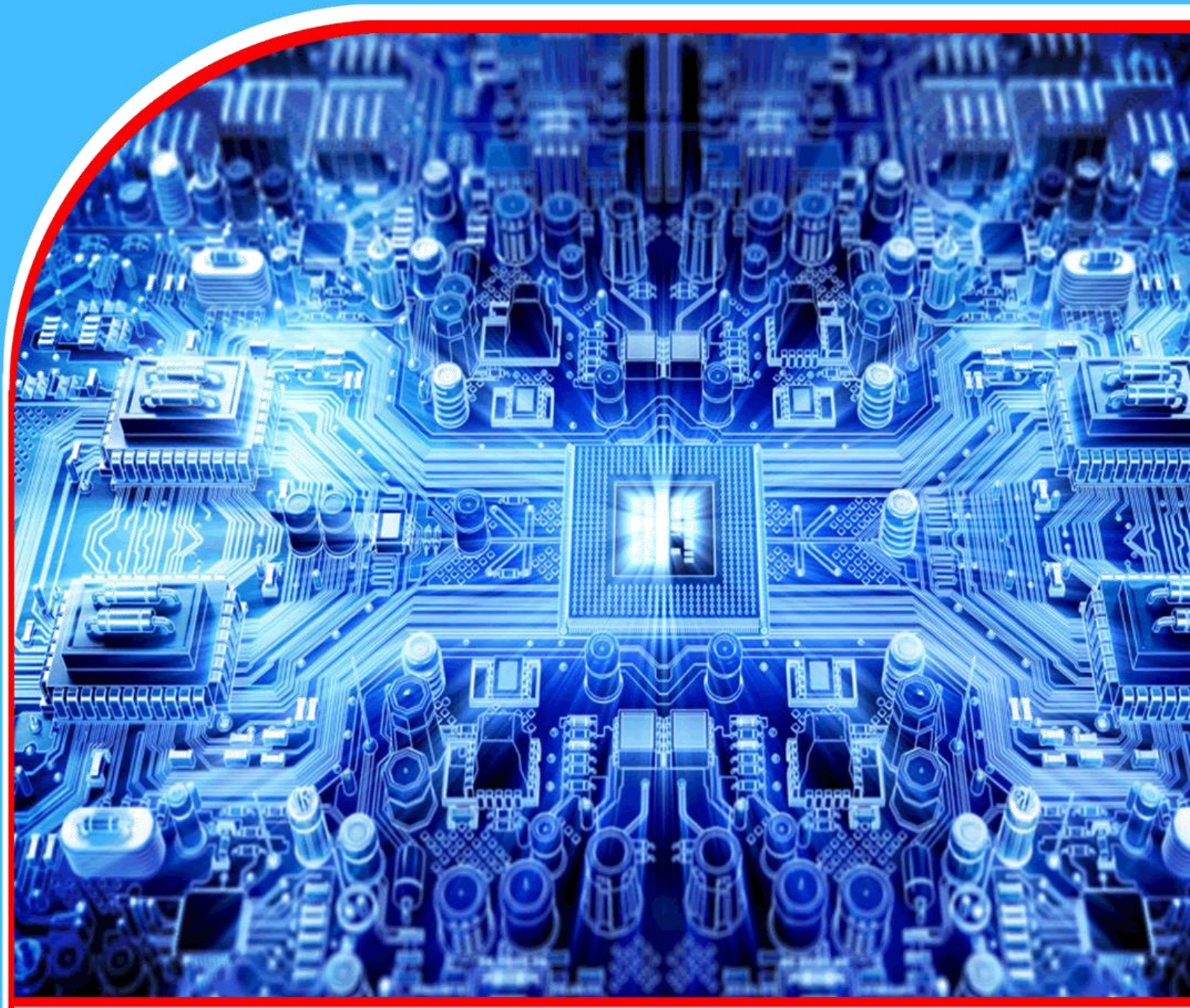

KNOWLEDGE BASED SYSTEM DESIGN FOR DIAGNOSIS OF HEPATITIS B VIRUS (HBV) USING GENERALIZED REGRESSION NEURAL NETWORK (GRNN)

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KNOWLEDGE BASED SYSTEM DESIGN FOR DIAGNOSIS OF HEPATITIS B VIRUS (HBV) USING GENERALIZED REGRESSION NEURAL NETWORK (GRNN)

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Abstract

Purpose*:* It is obvious that accurate diagnosis of a disease is one of the serious problems in modern medicine. This paper proposes a knowledge base system design for the diagnosis of Hepatitis B virus (HBV) using Generalized Regression Neural Network (GRNN). The aim is to embed an intelligent system for the diagnosis of Hepatitis B virus using GRNN since HBV is one of the most deadly viral infections that has colossal effect on the health of the people suffering from it and has remained a lasting health problem affecting a significant number of the world's population.

Methodology*:* The data used for this study was obtained from different sources. Primary data was obtained from field through, observations, and scheduled interviews with stakeholders - Medical Doctors Laboratory Technicians, Laboratory Scientists and Patients suffering from the disease. While secondary data was gotten through visits to the libraries, journals, textbooks, articles and conference proceedings.

Results*:* Hepatitis B is one of the most common of all Hepatitis around the world today. The research found out that using the HBV markers that, if AgHBs = positive, AgHBe = positive and anti-VHD = negative then HBV is Positive, if HBsAg = negative, anti-HBc = positive, IgM anti-HBc = positive and anti-HBs = positive then it is at Acute level, if HBsAg = positive, anti-HBc = positive, IgM anti-HBc = negative and anti-HBs = negative then it is Chronic. Finally, if HBeAg = positive then the Liver is inflammed (HBV profile test). Generalized regression Neural Network (GRNN) is the finest suitable Neural Network for Hepatitis B diagnosis which will help in reducing extra time consumption in treatment. Even if there is any number of missing parameters in blood test, the diagnosis will be done by artificial intelligence using generalized regression neural networks.

Unique contribution to theory, practice and policy: This system will help assist the health practitioners and also keep the vulnerable informed, as well the mortality rate and waiting time to see the experts will be reduced by employing the expert system application in this research. The researcher here recommend for further study on HBV drug resistance.

Keywords: *Diagnosis, Hyper-Severity, Knowledge Based System, Generalized Regression Neural Network (GRNN), Hepatitis B Virus (HBV).*

1.0 INTRODUCTION

1.1 Background of the Study

Modern practices in medical treatment make it necessary that patients consult specialists for further diagnosis and treatment. Other medical practitioners may not have adequate expertise or experience in handling certain high-risk diseases. Nonetheless, typical waiting time for treatments may be few days, weeks or even months. Possibly, by the time the patients consult the specialists the diseases may have already spread out. Since the majority of the high-risk disease could only be cured at the early stage, the patients may have to endure for the rest of their life, due to which new approaches with the support of computer technology for the diagnosis of diseases is essential [3].

A major issue in medical diagnosis is the risk stratification, which refers to the sorting of patients based on the severity of disease. This is vital owing to the fact that it can help in reducing the usage of beds, equipment, and other medical resources. In case the clinical problem goes beyond the physician's competence, the solution is to consult a specialist, however in common; expert opinion is either unavailable or not available in a timely fashion. The problem of deducing certain diseases or formulating a treatment has to be solved by them on the basis of more or less specified observations and knowledge. In order to keep more of the relevant information constantly in mind the physicians are encouraged by continued training and recertification procedures [1]. However, it is assured that most of what is known cannot be known by most individuals due to the fundamental limitations of human memory and recall coupled with the growth of knowledge. A good physician employs his knowledge, experience, and talent during a medical procedure to diagnose a disease.

The diagnosis is then determined by taking the total available patients' status into account. The appropriate treatment is prescribed depending on the diagnosis and the entire process might be iterated. The mortality rate and the waiting time to see the specialist could be cut short by employing the computer technology or computer application or software developed by emulating human intelligence which supports the doctors in making decisions without direct consultation with the specialists. It is possible to shortlist the patients with high-risk factors or symptoms or predicted to be highly infected with certain diseases or illness to see the specialist for further treatment [2].

Neural networks are widely applicable to real world problems and thus have already been employed successfully in numerous industries. Neural networks are appropriate for prediction or forecasting requirements like sales forecasting, industrial process control, customer research, data validation, risk management, target marketing and the like since they are capable of efficiently recognizing patterns or trends in data. Besides fields such as identification of speakers in communications; diagnosis of disease; recovery of telecommunications from faulty software; elucidation of multi meaning Chinese words; undersea mine detection; texture analysis; three-dimensional object recognition; handwritten word recognition; and facial recognition extensively make use of Artificial neural network. Artificial Neural Networks (ANNs) is presently a 'hot' research area in medicine and it is believed that they will receive extensive application to biomedical systems in the nearest future. Hepatitis B including chronic liver disease is quite common in the world, which may cause damage to hepatocytes [4].

The severity may range from healthy carrier to decompensate cirrhosis. [2] Stated that the aim is to an embed intelligent system for the diagnosis of the Hepatitis B virus disease, as

Hepatitis is one of the serious diseases which demands expensive treatment and severe side effects can appear very often. The use of computer technology in the fields of medical diagnosis, treatment of illnesses and patient pursuit has highly increased. Despite the fact that these fields, in which the computers are used, have very high complexity and uncertainty and the use of intelligent systems such as fuzzy logic, artificial neural network and genetic algorithm have been developed. Detecting diseases at early stage can enable a patient to have early treatment which can lead to effective control. Identifying the treatment accurately depends on the method that is used in diagnosing the diseases. A Diagnosis Expert System (DExS) can help a great deal in identifying those diseases and describing methods of treatment to be carried out taking into account the user capability in order to deal and interact with expert system easily and clearly [8]. Expert system uses inference rules and plays an important role that will provide certain methods of diagnosis for treatment [2].

This paper is based on Hepatitis B, which is one of the most common of all Hepatitis around the world. Hepatitis B is the inflammation and swelling of the liver due to infection with the hepatitis B virus - HBV. Hepatitis B may be acute or chronic, the acute Hepatitis B lasts less than six months, and it may lead to various infections that affect the liver. The chronic Hepatitis B is at the risk of a lasting liver disease. It continues after and may persist beyond six months. Most of the damages resulting from hepatitis B virus occur because of the way the body responds to the infection, when the body's immune system detects the infection it sends out special cells to fight it off, however, these disease fighting cells can lead to liver inflammation. Hepatitis B is also known as Serum Hepatitis. It has been in existence for over a thousand years [8]. This disease has been recorded to have had a large number of deaths even in developed countries. Individuals infected with chronic HBV stand the risk of developing cirrhosis, leading to hepatic decompensation and hepatocellular carcinoma (HCC). However, most patients with chronic HBV infection do not developed hepatic complications, there is a probability that serious illness can develop during their life time and it is more probable occurring in men.

Hepatitis is the inflammation of the liver, which is commonly known as jaundice [16]. Most people suffering from Hepatitis type B do not have any symptoms [16]. When a person becomes infected with Hepatitis, his/her liver becomes inflamed. The virus destroys the normal tissue and, at the end, only the fibrous worn-out tissues will remain [6]. More than 40% of the human population has been infected with Hepatitis B Virus (HBV) worldwide, giving rise to 240 million chronic HBV carriers and 620,000 HBV-associated deaths annually [11]. Since the detection of Hepatitis B virus as the cause of Hepatitis, many high-sensitive measurement methods have been developed [16]. The breakthroughs recorded in medical sciences have made it difficult to make clear diagnosis decisions about the disease, especially given the inefficacy of the conventional methods and techniques in medical diagnosis.

A comparative analysis of all neural networks proved that generalized regression neural network will be the best suitable network in diagnosis of Hepatitis B. The capability of Generalized Regression Neural Network (GRNN) to get trained faster compared to most other networks and achieving results for even the few missing attributes makes it useful and acceptable for diagnosis process [12]. GRNN is a very useful tool in performing predictions and comparisons of system performance in practice.

2.0 EMPIRICAL REVIEW

2.1 Overview of Hepatitis B Virus (HBV)

The term 'hepatitis' simply means inflammation of the liver. Hepatitis may be caused by a virus or a toxin such as alcohol. Other viruses that can cause injury to liver cells include the hepatitis A and hepatitis C viruses. These viruses are not related to each other or to hepatitis B virus and differ in their structure, the ways they are spread among individuals, the severity of symptoms they can cause, the way they are treated, and the outcome of the infection. Hepatitis B is an infection of the liver caused by the hepatitis B virus (HBV). The major modes of transmission of hepatitis B (sexual transmission, illicit drug use, exposure to infected blood) and the effect of universal vaccination of infants. When a person first gets hepatitis B, they are said to have an 'acute' infection. Most people are able to eliminate the virus and are cured of the infection. Some are not able to clear the virus and have 'chronic' infection with hepatitis B that is usually life-long. The hepatitis B virus is a DNA virus, meaning that its genetic material is made up of deoxyribonucleic acids. It belongs to a family of viruses known as Hepadnaviridae. The virus is primarily found in the liver but is also present in the blood and certain body fluids [5][12].

HBV is classified in the family Hepadnaviridae. It occurs as seven distinct genotypes, designated A to G, but it is controversial as to whether the outcome of the infection is influenced by the genotype [17]. HBV has a double-stranded DNA genome of approximately 3200 base pairs organized into four partially overlapping open reading frames, which encode the envelope, core (precore/core), polymerase and X proteins [6]. The envelope proteins are surface glycoprotein collectively designated as Hepatitis B surface Antigen (HBsAg). In virus-infected liver cells HBsAg is excessively produce in virus infected liver cells and it is secreted into the blood, where it serves as a marker for active infection and infectivity.

Recombinant HBsAg is used for HBV vaccination currently and the antibody development to HBsAg is associated typically with protective immunity [6].

Hepatitis B virus consists of a core particle (central portion) and a surrounding envelope (outer coat). The core is made up of DNA and the core antigen (HBcAg). The envelope contains the surface antigen (HBsAg). These antigens are present in the blood and are markers that are used in the diagnosis and evaluation of patients with suspected viral hepatitis [10]. The hepatitis B virus reproduces in liver cells, but the virus itself is not the direct cause of harm to the liver. Reasonably, the presence of the virus triggers an immune response from the body as the body tries to eradicate the virus and recover from the infection. This immune reaction causes inflammation and may seriously injure liver cells. Therefore, there is a balance between the defending and damaging effects of the immune response to the hepatitis B virus [10].

2.2 Diagnosis of Hepatitis B Virus (HBV)

Infection with hepatitis B is suspected when the medical history and the physical examination reveal risk factors for the infection or symptoms and signs that are suggestive of hepatitis B. Irregularities in the liver tests (blood tests) also can raise suspicion; however, irregular liver tests can result from many conditions that affect the liver [4]. The diagnosis of hepatitis B can be made only with specific hepatitis B virus blood tests. These tests are known as hepatitis 'markers' or 'serology.' Markers found in the blood can approve hepatitis B infection and distinguish acute from chronic infection [4]. These markers are substances produced by the hepatitis B virus (antigens) and antibodies produced by the immune system to combat the

virus. Hepatitis B virus has three antigens for which there are commonly-used tests – the surface antigen (HBsAg), the core antigen (HBcAg) and the e antigen (HBeAg) [4].

A. HBsAg and Anti-HBs

The presence of hepatitis B surface antigen (HBsAg) in the blood indicates that the patient is currently infected with the virus. Anti-HBs provide whole immunity to subsequent hepatitis B viral infection. Also, individuals who are successfully vaccinated against hepatitis B produce anti-HBs in the blood. Patients who fail to clear the virus during an acute period develop chronic hepatitis B. The diagnosis of chronic hepatitis B is made when the HBsAg is present in the blood for at least six months. In chronic hepatitis B, HBsAg can be detected for many years, and anti-HBs do not appear [4].

B. Anti-HBc

In acute hepatitis, a precise class of early antibodies (IgM) appears that is directed alongside the hepatitis B core antigen (anti-HBc IgM). [5] Later, another class of antibody, anti-HBc IgG, develops and continues for life, irrespective whether the individual recovers or develops chronic infection. Only anti-HBc IgM can be used to diagnose an acute hepatitis B infection.

Table 1: The Markers for Hepatitis Diagnosis [4]

Markers	**Values**
AgHBs	Positive
AgHBs	Negative
AgHBe	Positive
AgHBe	Negative
anti - VHD	Positive
anti – VHD	Negative
anti - VHC	Positive
Rule: IF (AgHBs=Positive) AND (AgHBe= positive) AND (anti-VHD= Negative) THEN Hepatitis B.	

C. HBeAg, Anti-HBe, and Pre-Core Mutations

Hepatitis B e antigen (HBeAg) is present when the hepatitis B virus is aggressively increasing, whereas the production of the antibody, anti-HBe, (also called HBeAg seroconversion) shows a more inactive state of the virus and a lower danger of transmission. In some individuals infected with hepatitis B virus, the genetic material for the virus has endured a structural change, called a pre-core mutation [4]. This mutation results in the failure of the hepatitis B virus to produce HBeAg, even though the virus is actively reproducing. This means that even though no HBeAg is detected in the blood of people with the mutation, the hepatitis B virus is still active in these persons and they can infect others [4].

D. Interpretation of Hepatitis B Blood tests

The following table gives the usual interpretation for sets of results from hepatitis B blood (serological) tests.

Table 2: Markers for Hepatitis B Diagnosis [4]

Most Likely Status	Tests	Results
Susceptible, not infected, not immune	HBsAg anti-HBc anti-HBs	Negative Negative Negative
Immune due to natural Infection	HBsAg anti-HBc anti-HBs	Negative Positive Positive
Immune do to hepatitis B Vaccination	HBsAg anti-HBc anti-HBs	Negative Negative Positive
Acutely infected	Acutely infected anti-HBc IgM anti-HBc anti-HBs	Positive Positive Positive Negative
Chronically infected	HBsAg anti-HBc IgM anti-HBc anti-HBs	Positive Positive Negative Negative

2.3 Neural Network Learning and GRNN Architecture

The network touches “learning” through the mathematical process can be disregarded by the final user mainly. This is the way of viewing the network as “gloomy case”. The gloomy case receives a vector with “n” inputs and provides a vector with “m” outputs. The network studies from a sequence of examples that form the training database. See figure 1 below.

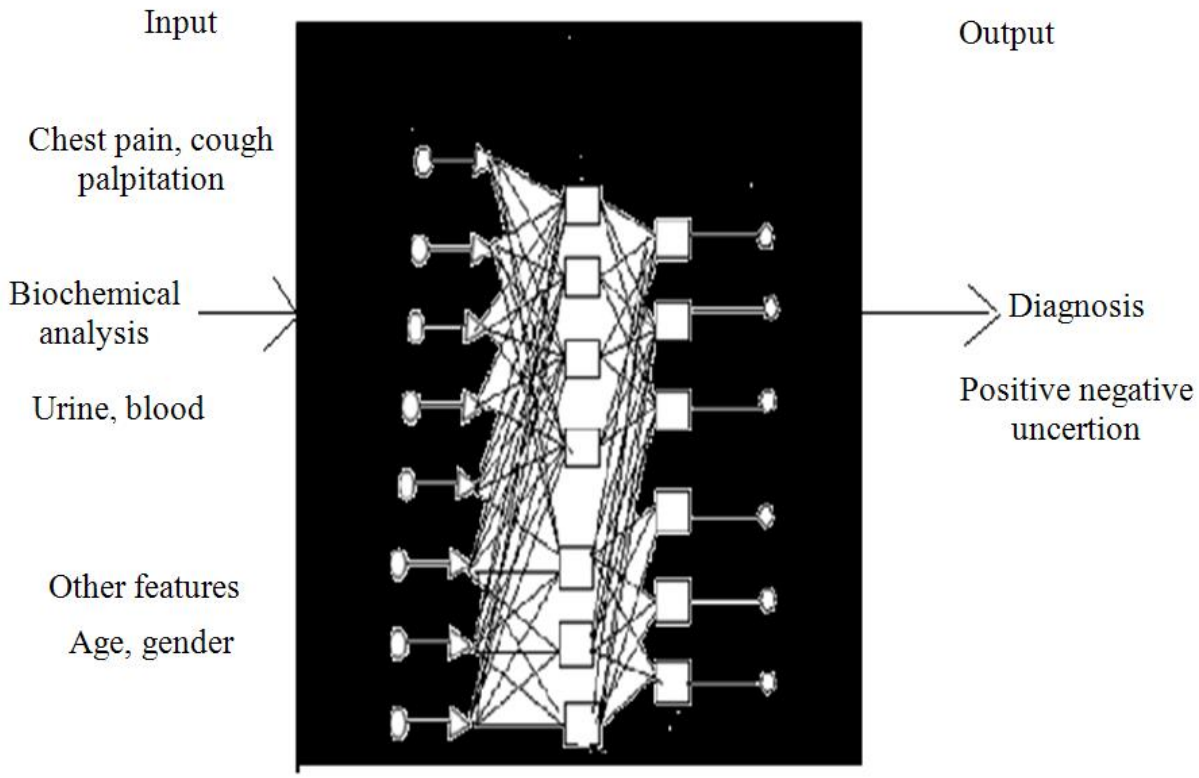

Figure 1: ANNs-based diagnosis using inputs and outputs

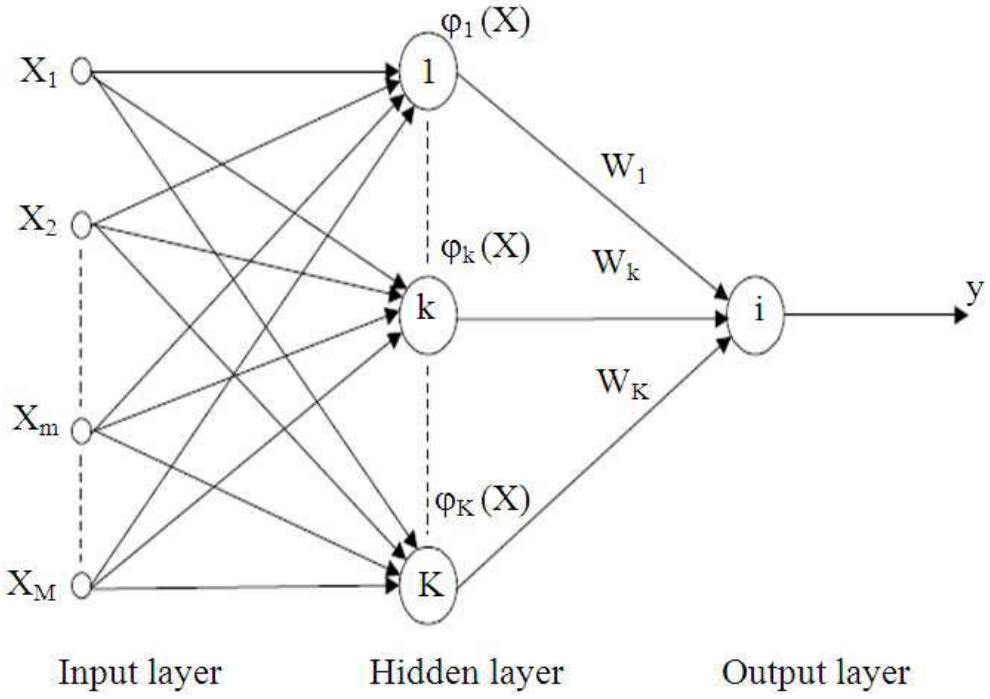

Figure 2: Generalized regression neural network architecture

The generalized regression neural network was originally proposed for system modeling and prediction. It has been used to learn the same problems as the back-propagation network, the

radial basis function network, the probabilistic neural network, and the modular neural network. The network has a relationship to the probabilistic neural network and has sometimes been used in place of it for taxonomy problems.

This network according to [10] has certain features:

i. Firm learning
ii. Good convergence with a large number of training examples
iii. Control of sparse data well
iv. Possible memory control
v. Conceivable computing time issues

GRNN falls into the category of probabilistic neural networks. This neural network like other probabilistic neural networks needs only a fraction of the training samples a back propagation neural network would need. The data available from measurements of an operating system is generally never enough for a back propagation neural network [9]. Therefore the use of a probabilistic neural network is especially advantageous due to its ability to converge to the underlying function of the data with only few training samples existing. The additional knowledge needed to get the fit in a sustaining way is relatively small and can be done without additional input by the user. This makes GRNN a very useful tool to make predictions and comparisons of system performance in practice [10].

3.0 METHODOLOGY

3.1 Method of Data Collection

The data used for this study was obtained from different sources. Primary data was obtained from field through, observations, and scheduled interviews with stakeholders -Medical Doctors Laboratory Technicians, Laboratory Scientists and Patients suffering from the disease. While secondary data was gotten through visits to the libraries, journals, textbooks, articles and conference proceedings.

3.2 Designing the Proposed System

The proposed system is organized as shown in figure 3. It is obvious that database normalization generally yields better results. After normalizing the data, classification method using GRNN is then applied. The design also employed tools such as UML use case diagrams to help capture basic functionalities needed in the new system design.

Finally, a database entity relationship model was designed used to provide a supportive framework for capturing patient information to be fed into the system, which functions as the knowledge base and searches information recursively and matches the patient information with appropriate rules that suit each condition in which case the intelligent system consist of the GRNN which gives accurate result about the status, severity levels of the patients and in furtherance, details the Liver Function Test into four compartments for CHB negative HBs, positive HBs, compensated HBV and decompensated cirrhosis.

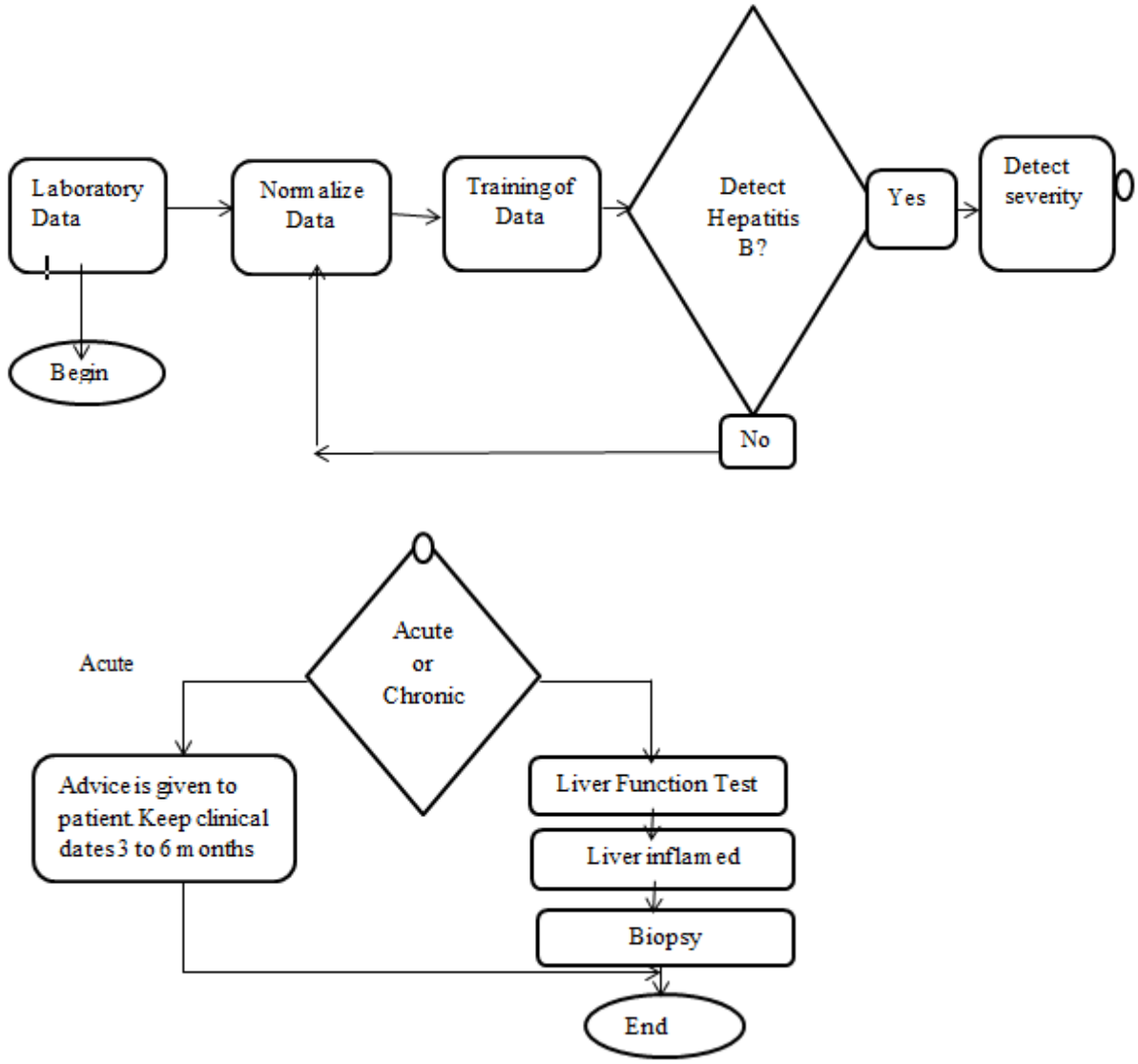

Figure 3: System Design Flowchart

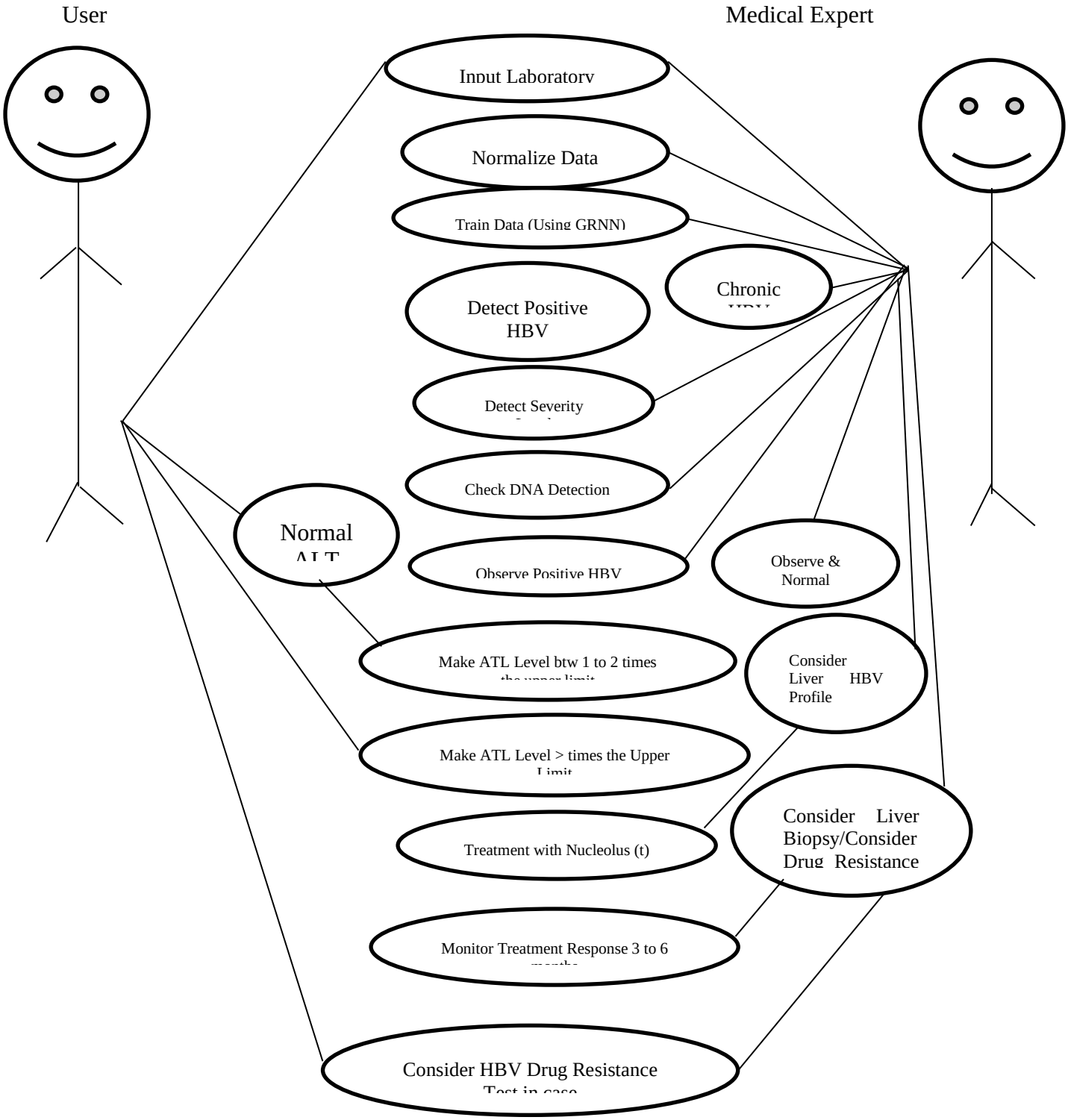

Figure 4(a): System UML Use case Diagram for Chronic HBV (Positive HBc)

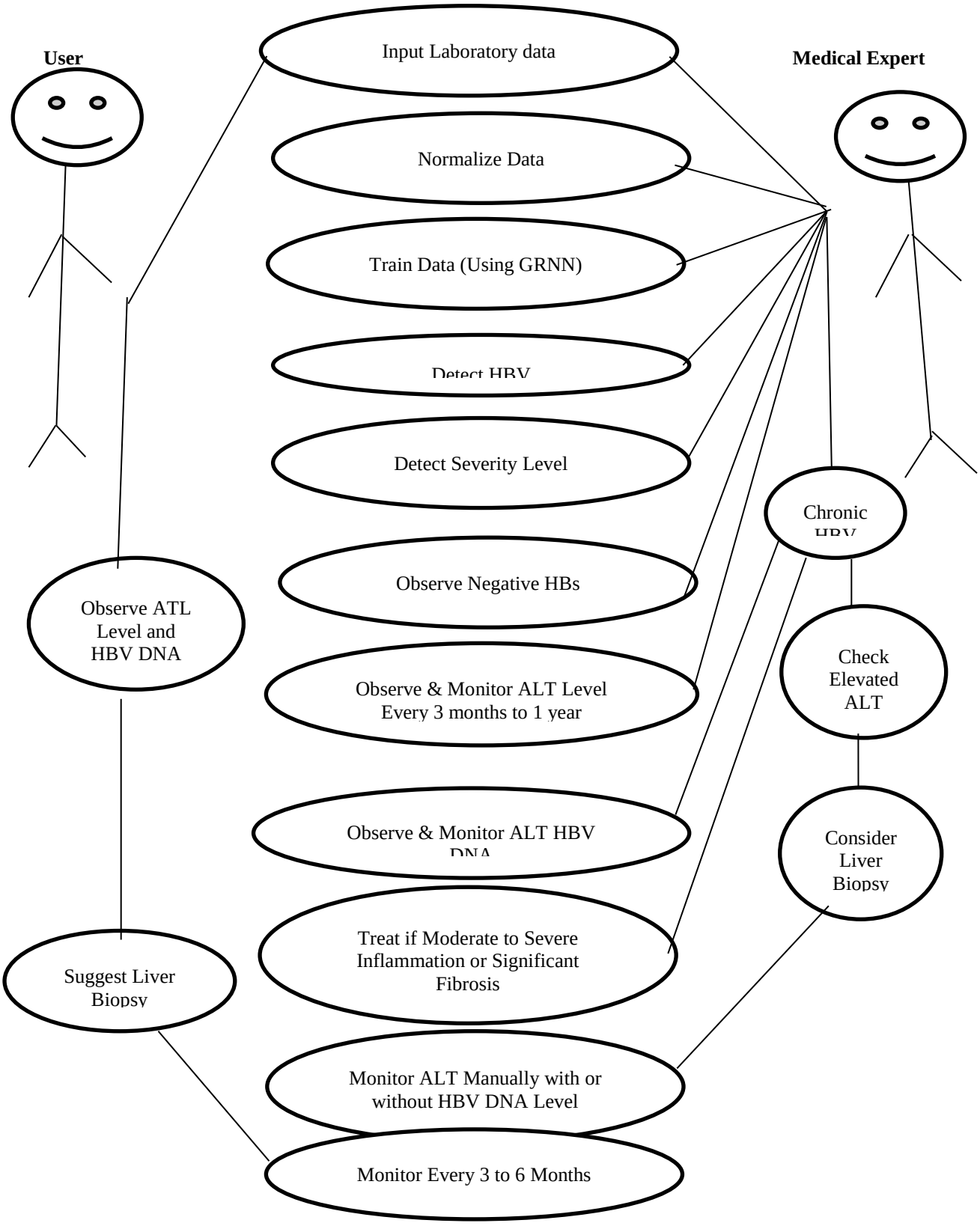

Figure 4(b): System UML Use case Diagram for Chronic HBV (Negative HBs)

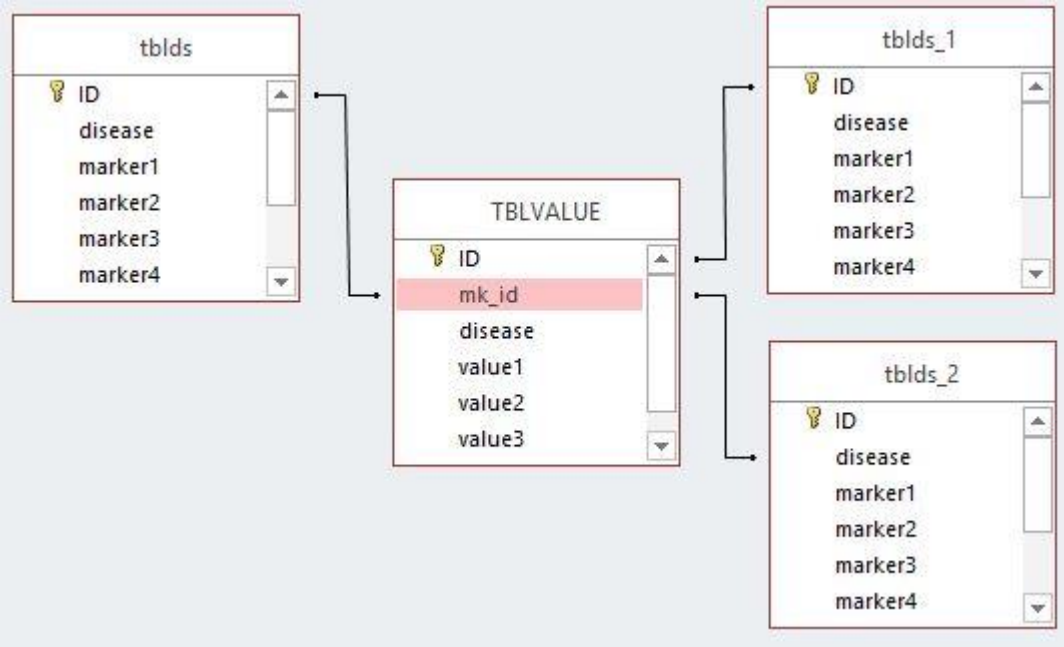

Figure 5: Entity-Relationship (E-R) model for the system

3.3 Algorithm

The data will be established by the neurons in the input layer and transported to first hidden layer neurons through the weighted links. The mathematically processed data and the result are transported to the next layer neurons. Finally the network's output will be produced by the last layer neuron. The hidden layer k-th neuron will process the incoming data Zi by:

Calculating the weighted sum and adding a "bias" term (θ_k) according to Equation (1):

$$net_k = \sum_{i=1}^{m}(Z_i x\, W_i + \theta_k) \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (1)$$

Where $(k = 1,2,3,---,n)$

Transforming the net_k through a suitable mathematical "transfer function"

Result transferred to neurons in the next layer

Various transfer functions are available. However the one which is most commonly used is Equation (2):

$$F(z) = \frac{1}{1+e^{-z}} \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (2)$$

The probability density function used in GRNN is the Normal Distribution. Each training sample, Xj, is used as the mean of a Normal Distribution:

$$Y(x) = \frac{\sum_{i-1}^{n} Yi \exp(-Di2/2\sigma 2)}{\sum_{i-}^{n} Yi \exp(-Di2/2\sigma 2)} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (3)$$

where,

$$Di^2 = (X - Xi)^T (X - Xi)$$

The distance, D_i, between the training sample and the point of prediction, is used as a measure of how well each training sample can represent the position of prediction, X. If the

Distance, D_i, between the training sample and the point of prediction is small, exp $(-D_i^2/\sigma^2)$, becomes big. For $D_i = 0$, exp $(-D_i^2/2\sigma^2)$ becomes one and the point of evaluation is represented best by this training sample.

3.4 System Specification

System specification is a system information utility that produces a specification of a system's hardware and software to meet certain requirements to produce a system design.

3.4.1 Hardware Requirements

The hardware required for the implementation of the program includes:

i. Memory (RAM) 6143MB
ii. CPU speed 2416. MHz
iii. CPU Info Intel®, Core(TM)2 Quad CPU @ 2.40GHz
iv. Printer: HP LaserJet Series

3.4.2 Software Requirements

The applications software that will be developed cannot work without the support of some other categories of software called the system software. Such system software includes:

i. Windows 7 professional edition 32bits/64bits
ii. VB. Net
iii. Avast anti-virus

3.4 System Pseudocode

```
BEGIN
        load marker
        load value
       select case sensitivity
                        case value1
                                if sensitivity.select, then
                                        maxvalue =1 (value1)
                                        maxmarker.value=valueselected
   if AgHBs=positive and AgHBe=positive and anti_VHD=negative
    then Hepatitis B
            end if
   if HBsAg=positive and anti-HBc=positive and IgM anti-HBc=positive and anti-HBs=negative
then Acute
            end if
        if HBsAg=positive and anti-HBc=positive and IgM anti-HBc=negative and anti-HBs=negative
then Chronic (CHB)
```

```
            end if
if HBeAg= positive for CHB
            then liver is affected
            Querry = SELECT* (symptoms) FROM symptomstable WHERE
casevalue1.selected
                        if querry.result.found = true then
                                print diagnosis
                        end if
                End select
POSTIVE HBs for CHB
if positive HBs,
then
normal ATL level
            observe and monitor ATL level
                    if ATL level between 1 to 2 times upper limit then


consider liver HBV
                                consider HBV drug resistance test treatment
                    with nucleolus (t)
                                monitor treatment response every 3 to 6 months
                                    if resistance to nucleolus (t)
                                            then order HBV drug resistance test


        ELSE IF negative HBs then
END IF
NEGATIVE HBs for CHB
ELSIF negative HBs then


END IF
    normal ATL level, HBV DNA
                    observe and monitor ATL level quarterly (in a year) then
                            consider monitoring HBV DNA quarterly using HBV
                                    detection and quantification
END IF
        if normal ATL then
```

monitor ATL manually **with or without** HBV DNA **level**
if elevated ATL **then**
order HBV DNAC 2.00 **then**
consider liver biopsy
and observe **and** monitor ATL **and** HBV DNA
HBV DNA **then,**
suggest liver biopsy
treat()

end if

if moderate **to** severe inflammation **or** significant fibrosis **then,**
monitor **every** 3 **to** 6 months

END IF

4.0 RESULTS

The diagnosis of the disease for individual patients is done on basis of the markers. Figures 6 to 9 shows a few sample results.

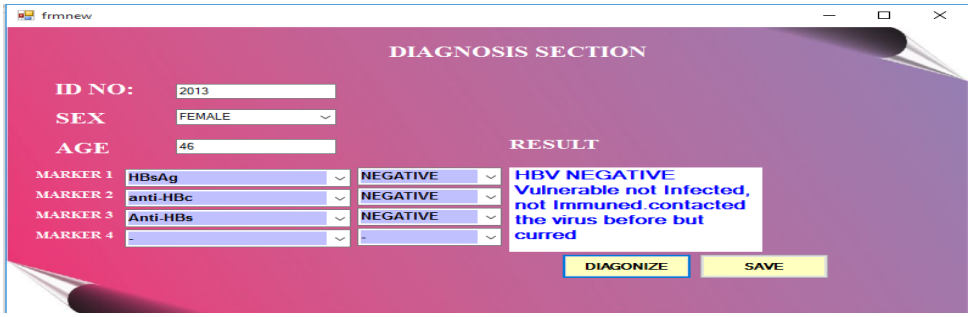

Figure 6: Patient with HBV Negative

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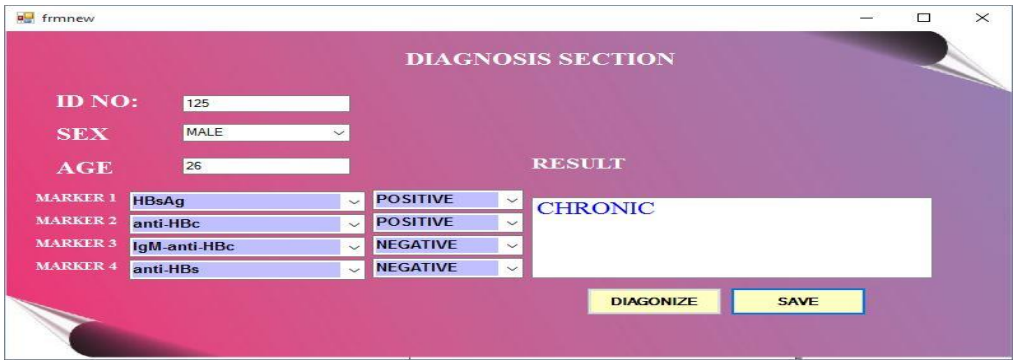

Figure 7: Patient with Acute infection

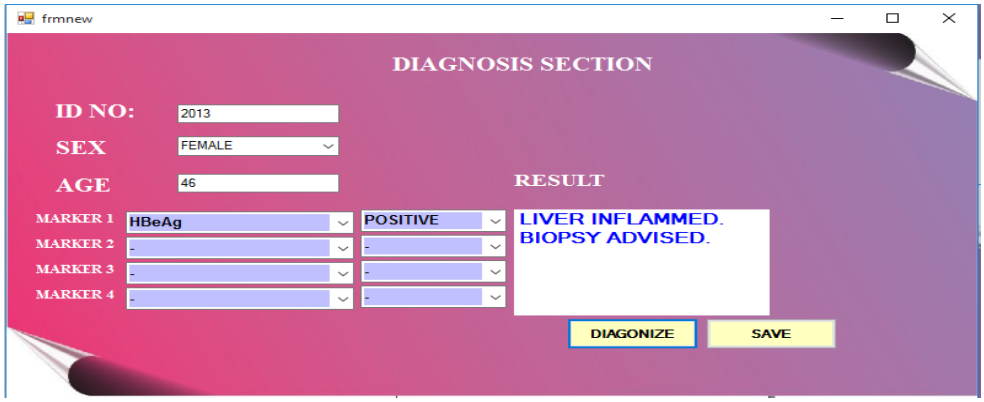

Figure 8: Patient with Chronic infection and defined by the continued presence of HBsAg in the blood for a period more than six (6) months

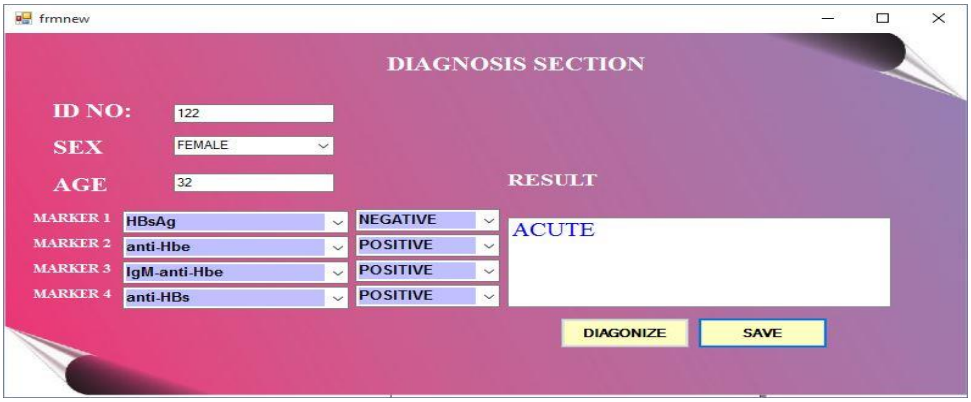

Figure 9: Patient with Liver Inflamed

5.0 CONCLUSION

Hepatitis B is one of the most common of all Hepatitis around the world today. The research found out that using the HBV markers that, if AgHBs = positive, AgHBe = positive and anti-VHD = negative then HBV is Positive, if HBsAg = negative, anti-HBc = positive, IgM anti-HBc = positive and anti-HBs = positive then it is at Acute level, if HBsAg = positive, anti-HBc = positive, IgM anti-HBc = negative and anti-HBs = negative then it is Chronic. Finally, if HBeAg = positive then the Liver is inflammed (HBV profile test). Generalized regression Neural Network (GRNN) is the finest suitable Neural Network for Hepatitis B diagnosis which will help in reducing extra time consumption in treatment. Even if there is any number of missing parameters in blood test, the diagnosis will be done by artificial intelligence using generalized regression neural networks. This system will help assist the health practitioners and also keep the vulnerable informed, as well the mortality rate and waiting time to see the experts will be reduced by employing the expert system application in this research. The researcher here recommend for further study on HBV drug resistance.

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