Liver Cancer Risk Quantification through an Artificial Neural Network based on Personal Health Data

by

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Abstract

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Liver cancer is the sixth most common type of cancer worldwide and is the third leading cause of cancer related mortality. Several types of cancer can form in the liver. Hepatocellular carcinoma (HCC) makes up 75%-85% of all primary liver cancers and it is a malignant disease with limited therapeutic options due to its aggressive progression. While the exact cause of liver cancer may not be known, habits/lifestyle may increase the risk of developing the disease. Several risk prediction models for HCC are available for individuals with hepatitis B and C virus infections who are at high risk but not for general population. To address this challenge, an artificial neural network (ANN) was developed, trained, and tested using the health data to predict liver cancer risk. Our results indicate that our ANN can be used to predict liver cancer risk with changes with lifestyle and may provide a novel approach to identify patients at higher risk and can be bene ted from early diagnosis.

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1 INTRODUCTION

1.1 Liver

The liver is an organ only found in vertebrates which detoxifies various metabolites, synthesizes proteins and produces biochemicals necessary for digestion and growth[1]. In humans, it is located in the right upper quadrant of the abdomen, below the diaphragm. The liver has two large sections, called the right and the left lobes. The gallbladder sits under the liver, along with parts of the pancreas and intestines. The liver and these organs work together to digest, absorb, and process food. The liver's main job is to filter the blood coming from the digestive tract, before passing it to the rest of the body. The liver also detoxifies chemicals and metabolizes drugs. As it does so, the liver secretes bile that ends up back in the intestines. The liver also makes proteins important for blood clotting and other functions. The liver stores vitamins as well as minerals such as copper and iron, releasing them if the body needs them. The liver also helps to break down fats in a person's diet. It either stores fats or releases them as energy.

The various functions of the liver are carried out by the liver cells or hepatocytes. The liver is thought to be responsible for up to 500 separate functions, usually in combination with other systems and organ.

1.2 Disease

The liver is a vital organ and supports almost every other organ in the body. Because of its strategic location and multidimensional functions, the liver is also prone to many diseases[2]. The bare area of the liver is a site that is vulnerable to the passing of infection from the abdominal cavity to the thoracic cavity. Liver diseases may be diagnosed by liver function tests-blood tests that can identify various markers. There are more than a hundred different kinds of liver disease. These are some of the most common[3]: Fascioliasis, Hepatitis, Alcoholic liver disease, Fatty liver disease, Cirrhosis, Liver cancer.

1.3 Liver Cancer

Liver cancer, also known as hepatic cancer and primary hepatic cancer, is cancer that starts in the liver[4]. The leading cause of liver cancer is cirrhosis due to hepatitis B, hepatitis C or alcohol [5]. Other cause include aflatoxin, non-alcoholic fatty liver disease and liver flukes [6]. The most common types are hepatocellular carcinoma (HCC), which makes up 80% of cases [6]. HCC is a cancer formed by liver cells, known as hepatocyte, that become malignant. Primary liver cancer is globally the sixth-most frequent cancer (6%) and the second-leading cause of death from cancer (9%) [6]. In 2018, it occurred in 841,000 people and resulted in 782,000 deaths [7].

1.4 Diagnosis

Many imaging modalities are used to aid in the diagnosis of primary liver cancer. For HCC these include medical ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI). When iimaging the liver with ultrasound, a mass greater than 2 cm has more than 95% chance of being HCC. Tumor markers, chemicals sometimes

found in the blood of people with cancer, can be helpful in diagnosing and monitoring the course of liver cancers.

1.5 Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer in adults and is the most common cause of death in people with cirrhosis [8].

It occurs in the setting of chronic liver inflammation and is most closely linked to chronic viral hepatitis infection (hepatitis B or C) or exposure to toxins such as alcohol, aflatoxin or pyrrolizidine alkaloids.

1.6 Risk Factors

HCC mostly occurs in people with cirrhosis of the liver, and so risk factors generally include factors which cause chronic liver disease that may lead to cirrhosis. Still, certain risk factors are much more highly associated with HCC than others. For example, while heavy alcohol consumption is estimated to cause 60–70% of cirrhosis, the vast majority of HCC occurs in cirrhosis attributed to viral hepatitis (although there may be overlap) [9]. Recognized risk factors include: chronic hepatitis B/C, alcohol abuse, aflatoxin, diabetes etc.

The significance of these risk factors varies globally. In regions where hepatitis B infection is endemic, such as southeast China, this is the predominant cause [10]. In populations largely protected by hepatitis B vaccination, such as the United States,

HCC is most often linked to causes of cirrhosis such as chronic hepatitis C, obesity, and alcohol abuse.

1.7 Artificial Neural Network

Artificial neural networks (ANNs), usually simply called neural networks (NNs), are computing systems vaguely inspired by the biological neural network that constitute animal brains[11]. Artificial neural networks are characterized by containing adaptive weights along paths between neurons that can be tuned by a learning algorithm that learns from observed data in order to improve the model. In addition to the learning algorithm itself, one must choose an appropriate cost function.

1.8 Artificial Neural Network in medicine

ANNs are the mathematical algorithms, generated by computers and learn from standard data and capture knowledge contained in data. It is raised the interest of scientific community worldwide in the field of medicine due to its potential for diagnostic and prognostic applications 12,13.

Nowadays, ANNs are widely used for medical applications in various disciplines of medicine especially in cardiology 14. A recent survey of artificial intelligence (AI) applications in health care reported uses in major disease areas such as cancer as a common machine learning technique. This study models a liver cancer risk quantification using a multi-parametrized neural network. We indicate that our ANN can be used to predict liver cancer risks and suggests interventions to modulate liver

cancer risks by changing life style. Such a model may provide clinicians a novel approach to identify patients at higher risk who may benefit from more.

2 METHODS

2.1 Two Data Source

2.1.1 PLCO Dataset

In this study we developed our machine learning models based on the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) dataset. PLCO was a randomized, controlled trial investigating the effectiveness of various screenings for prostate, lung, colorectal, and ovarian cancers. It was a prospective study that enrolled participants from November 1993 through July 2001. Among a total of 795,163 persons interviewed, 478 were diagnosed with liver cancer.

2.1.2 NHIS Dataset

The National Health Interview Survey (NHIS)[15] was established in 1957 to monitor the overall health status of the United States through personal household interviews on a broad range of health topics. Numerous epidemiologic studies have been conducted using NHIS [15,16]. The NHIS datasets of 1997 to 2019 were used in this study. A basic health data of total 671697 persons including 256 liver cancer were acquired from NHIS data. The featured that used as our input include age, smoking habits, diabetics, race, BMI, heart disease, angina, heart attack, other hearth condition, emphysema, asthma, hypertension, drinking habits, another cancer. Many of these inputs such as BMI, diabetes and smoking habits, were selected because they correlate with liver cancer.

2.2 Sample Size Consideration

All the data in the NHIS dataset from 1997 to 2017 and PLCO dataset were used to maximize the power and generalizability of the results. To investigate the performance of ANN on different datasets, three datasets were built:

1. DS1 = PLCO dataset (participants with cases)
2. DS2 = NHIS dataset (participants with cases)

After constructing and randomizing these two datasets, we used a train/validate/test scheme. The ANN was trained on 70% (training dataset) of the data using 10-fold cross-validation, while the remaining 30% was withheld for further testing (testing dataset). Sensitivity, and specificity were calculated for both training and testing datasets.

2.3 Missing Data

Some entries for some respondents were missing because they did not respond, or the question was not applicable. To address these missing data, we used different ideas. Since our variables have no ordinal relationship, the integer encoding won't be able to address the missing data and may result in poor performance or unexpected results. One of the ideas which used was one-hot encoding, which removes the integer encoded variables and a new binary variable will be added for each unique integer value [17]. Another method that tested was throwing away any individuals with missing data.

2.4 Artificial Neural Network (ANN)

ANN has been used to investigate other cancer types, such as lung cancer [18], prostate cancer [19], endometrial cancer [20], colorectal cancer [21], and pancreatic cancer [22]. Our results indicated that in general, ANN achieves the best performance as compared to other algorithms in terms of sensitivity, specificity, and AUC. Therefore, we used ANN in the present work. A schematic of an ANN model is shown in Figure 1. Our ANN had, in addition to the input and output layers, three hidden layers (each consisting of 12, 13 and 14 neurons respectively). The input features (between 0 to 1) and output (0 or 1) were split into 70/30 for training and testing datasets. Within the training dataset, 10-fold stratified cross validation was used to evaluate the performance of models trained on the different datasets. Once the best model was chosen, we trained it on the full training dataset and then evaluated it on the test dataset. We ran the training for 8000 iterations.

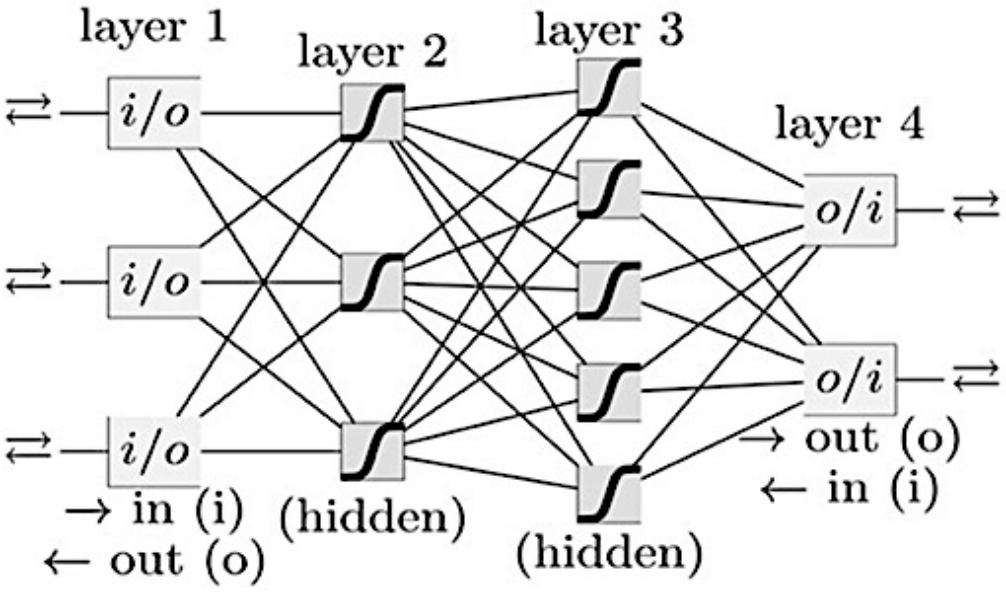

Figure 1. A schematic of an ANN. Each box and line represent a neuron and a weight, respectively. The number of weights grows rapidly with the number of neurons [22].

2.5 Model Performance Evaluation

The models trained on different datasets. Different hidden layers and neuron numbers were tested. Once the best model was selected, its performance on both the training and testing datasets was evaluated.

2.6 Data Analysis

Given the binary outcome, we developed our prediction model using the logistic activation function. The model was developed, and all analyses were performed using an in-house Matlab code. We used an in-house Matlab code to minimize fitting error of (or "train") our 3-layered ANN.

To evaluate the performance of our ANN, we parametrically plotted the sensitivity (i.e. fraction of high-risk persons) and specificity (i.e. fraction of low risk persons who are tested negative) as a function of the risk-score threshold to produce a ROC plot. We created an analogous plot with the positive predictive value (PPV) and negative predictive value (NPV).

3 RESULTS

3.1 Model Selection

The performance of the model was assessed by calculating the AUC of the plots for all two datasets (i.e., DS1, and DS2). We tested different hidden layers, and number of runs to find the best performance. The AUC of all these tests are summarized in Table 1-4.

Yr_cutoff	Hidden layer #	Size of layer	AUC_final
1	2	12,12	0.56 & 0.58
2	2	12,12	0.51 & 0.57
3	2	12,12	0.50 & 0.45
4	2	12,12	0.75 & 0.70

Table 1. AUC for 2 hidden layers and different year cutoff.

Yr_Cutoff	Hidden Layer	Size of Layer	AUC_final
3	3	12,13,14	0.80 & 0.81
3	3	13,14,15	0.75 & 0.79
3	3	14,14,14	0.71 & 0.67
3	3	14,15,16	0.69 & 0.67
3	3	16,16,16	0.71 & 0.72

Table 2. AUC for 3 hidden layers and different year cutoff.

Yr_Cutoff	Hidden Layer #	Size of Layer	AUC_final
1	3	12,12,12	0.81 & 0.73
2	3	12,12,12	0.76 & 0.71
3	3	12,12,12	0.78 & 0.79

Table 3. AUC for 3 hidden layers and different run numbers.

Yr_Cutoff	Hidden Layer #	Size of Layer	AUC_final
3	4	12,12,12,12	0.43 & 0.50
4	4	12,12,12,12	0.67 & 0.66

Table 4. AUC for 3 hidden layers and different year cutoff.

For DS1, the AUC of the ROC plot is 0.74 for the training sets, and 0.75 for the testing sets (Figure 5), while for DS2, these values are 0.80 for training and 0.81 for testing. The best performance of the model was observed for DS2 (Figure 6). The AUC of the ROC plots for different tests for both training and testing datasets are shown in Figures 2-4.

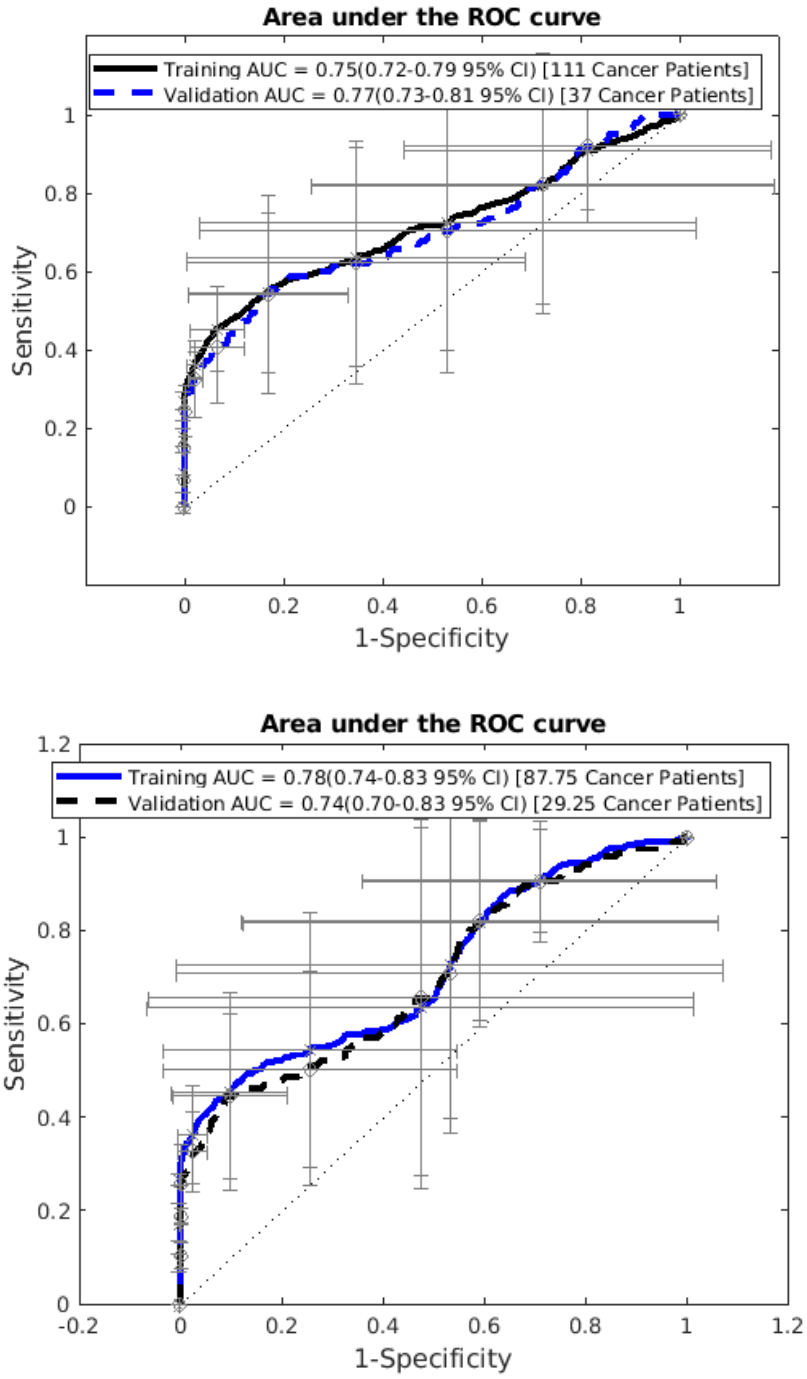

Figure 2. Receiver operating characteristic (ROC) plots for the training and testing for 3 hidden layers.

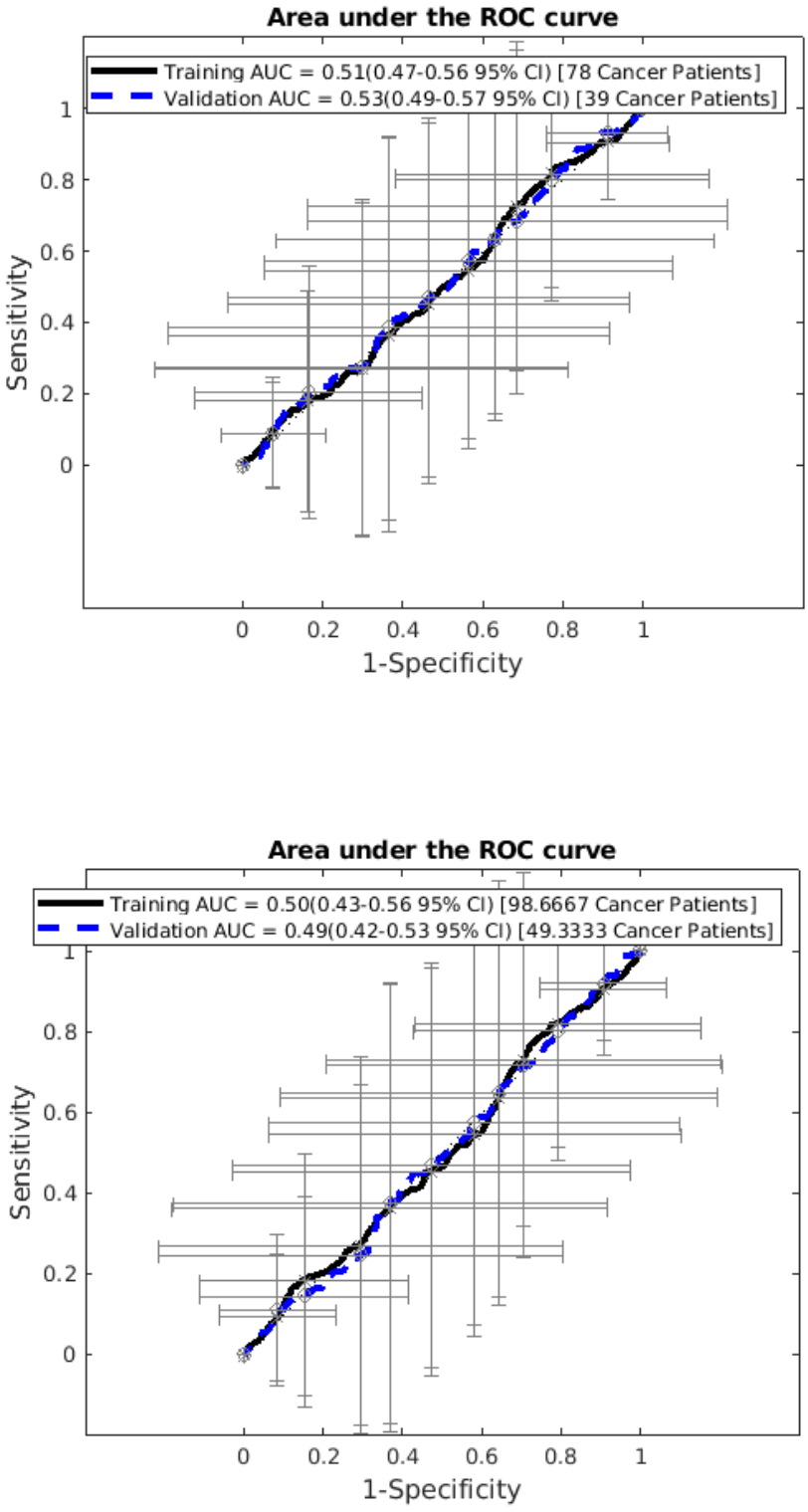

Figure 3. Receiver operating characteristic (ROC) plots for the training and testing for 2 hidden layers.

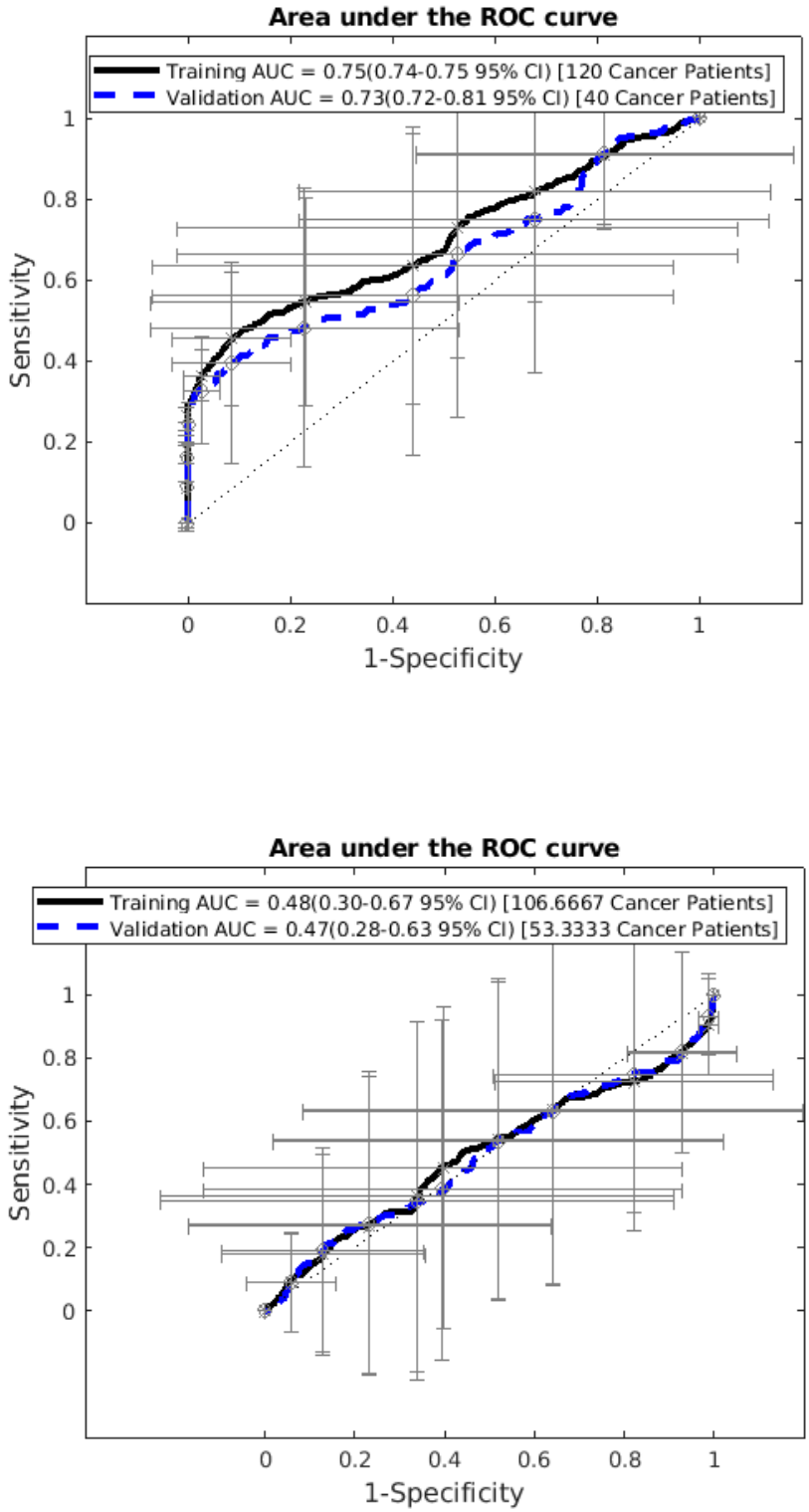

Figure 4. Receiver operating characteristic (ROC) plots for the training and testing for 4 hidden layers.

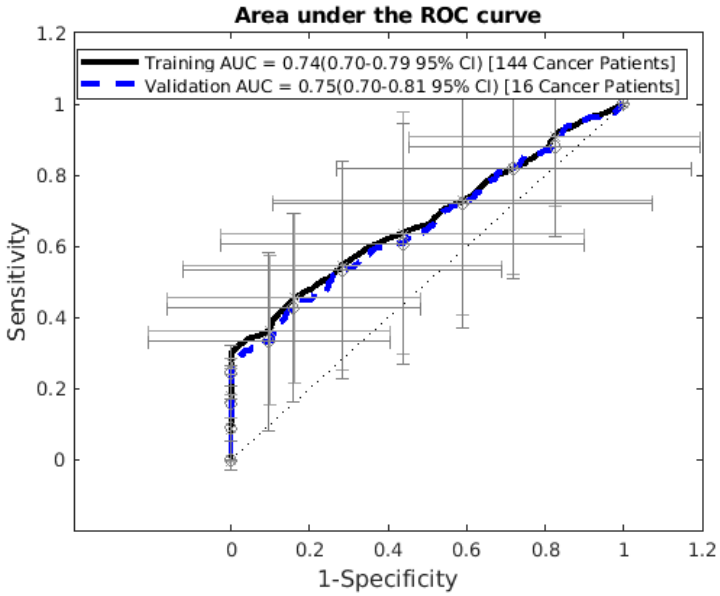

Figure 5. Receiver operating characteristic (ROC) plots for the training and testing of DS1.

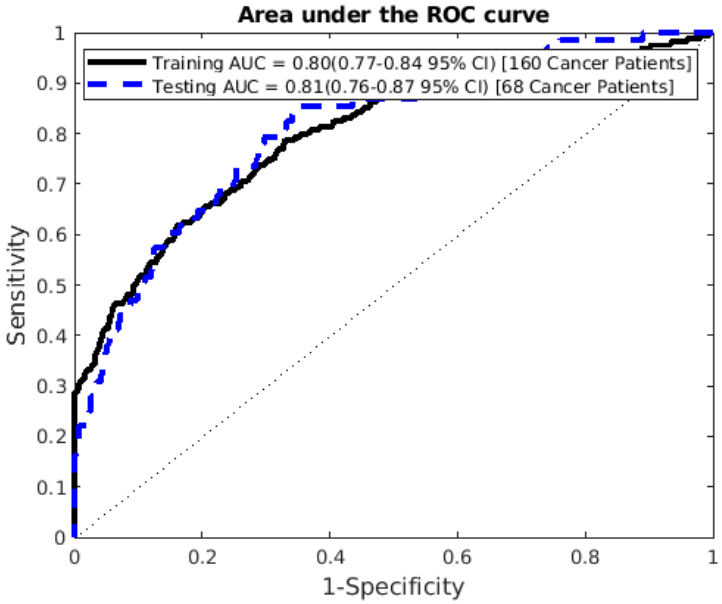

Figure 6. Receiver operating characteristic (ROC) plots for the training and testing of DS2.

3.2 Final Model Performance

we train our model on the full training dataset and evaluated it on the testing dataset. The sensitivity and specificity for both training and testing are plotted as functions of the threshold risk to study their trends (see Figure 7). Selecting the threshold risk that maximizes the sum of the sensitivity and specificity, we get specific values plotted in Figure 8. The positive predictive value (PPV) and negative predictive value (NPV) are plotted as a function of threshold value shown in Figure 9.

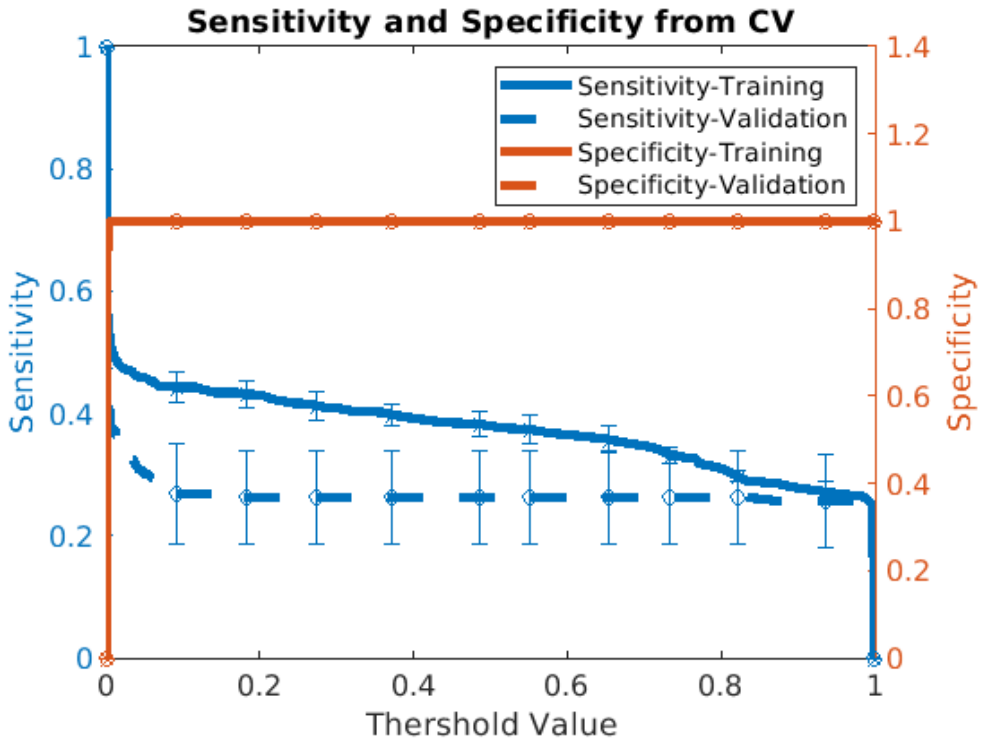

Figure 7. Sensitivity and specificity.

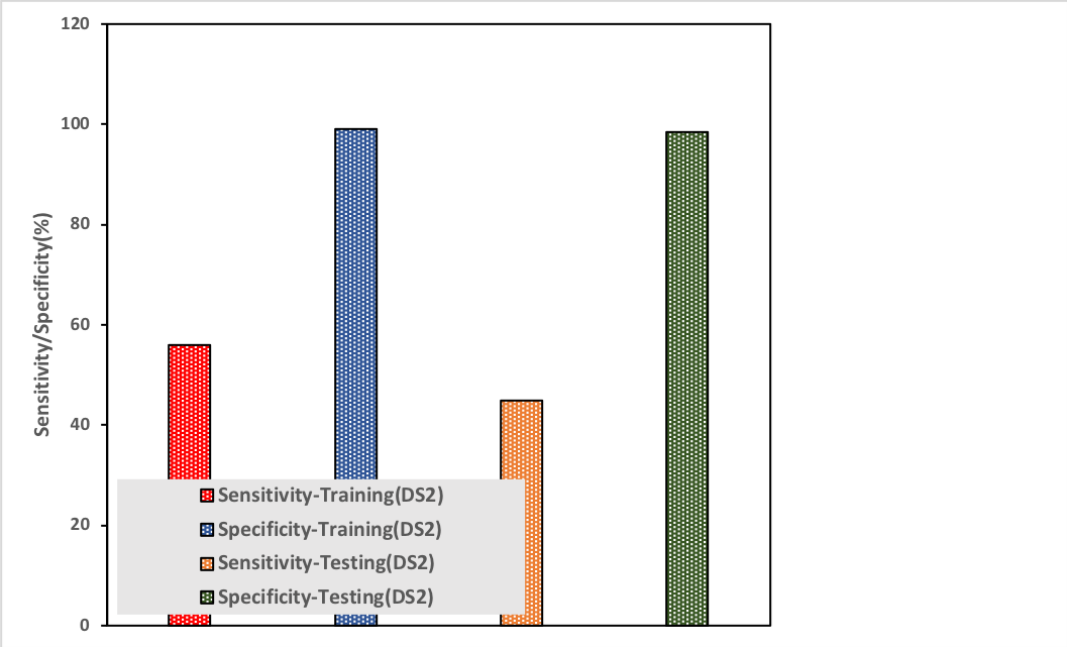

Figure 8. Representation of sensitivity and specificity values for DS2.

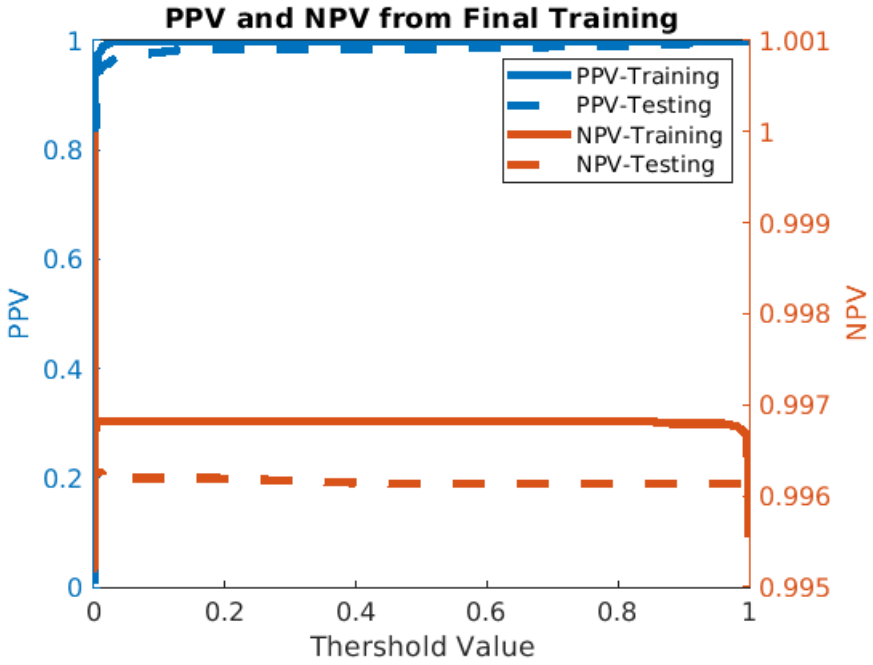

Figure 9. Positive predictive value (PPV) and negative predictive value (NPV) for training dataset.

3.3 Risk Stratification

A risk strati cation scheme was tested to demonstrate the potential application of our ANN model in the clinic. The scheme was designed to divide the population into three categories: low, medium, and high risk. These boundaries were conservatively selected using the training dataset, such that no more than 1% of respondents without cancer and with cancer would be categorized as high and low risk, respectively. However, the medium-high risk boundary could be selected to stratify more respondents with cancer in the high-risk category in case of low cost and/or potential harms in screening non-cancerous respondents. With these boundaries selected from the training data, the strati cation scheme is then applied to the testing dataset to demonstrate the potential clinical application of the model. Per this risk strati cation scheme, high-risk individuals could be screened immediately[22]. The medium-risk and low-risk individuals could receive their standard regular and less frequent screenings, respectively.

Running through the DS2 dataset, the outputs of the ANN were categorized as low-, medium- and high- risk. The categorized fraction of the respondents with and without liver varied at different risk levels. Risk strati cation results for the testing datasets were summarized in Table 5.

Table 5. Risk stratification on the test set

	# Low Risk	%Low Risk	#Medium Risk	% Medium Risk	# High Risk	% High Risk
Cancer	18	10.16	64.60	116	25.24	45
Non-Cancer	27.78	13058	70.44	331073	1.78	8366

The designed ANN recognizes the risks for the applicants. To make an accurate prediction with ANN, it is necessary to train the network with examples which are evenly distributed over the range of application for each input parameter as was mentioned earlier. For this reason, amongst high risk group, 3 different risk factors were selected from the dataset (DS2). Persons who were obese (BMI > 0.30) selected. Current smokers and heavy drinkers (drinks > 100 days/year) were selected. 13 heavy drinkers' people were selected, and their status changed to light drinkers. Amongst these people, 46% (6 people) were shifted from high risk group to medium risk group (see Figure 10). The smoking status was changed for 24 people from current smoker to non-smoker in the input features of ANN and the variation in their risks was studied. Likewise, 54% (13 people) were shifted from high risk group to medium risk group (see Figure 11).

Moreover, the ANN was also trained on a dataset that included BMI with and without HEP. The results can be found in Figure 12.

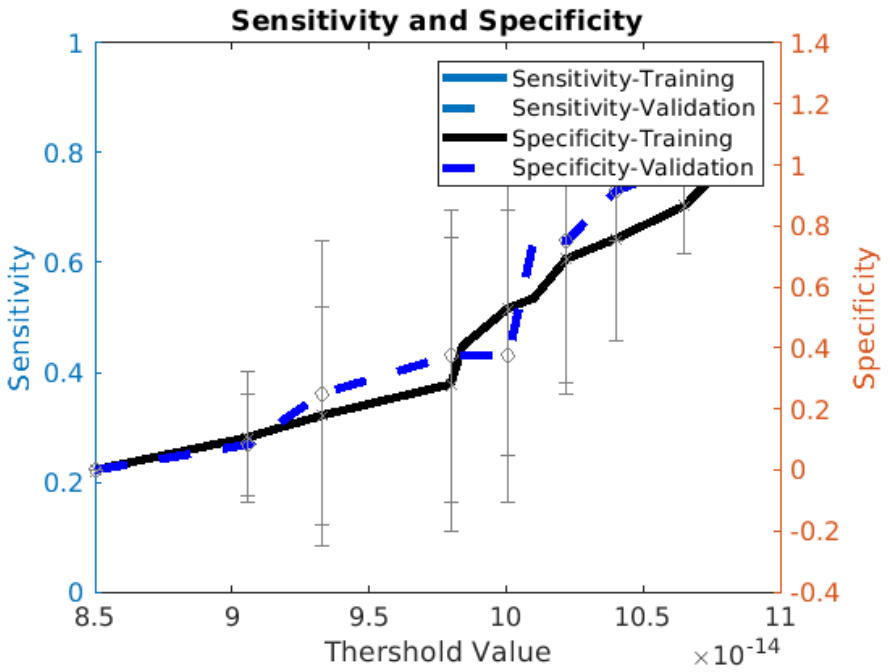

Figure 10. Sensitivity for a people who their heavy drinking status change to light drinking habit.

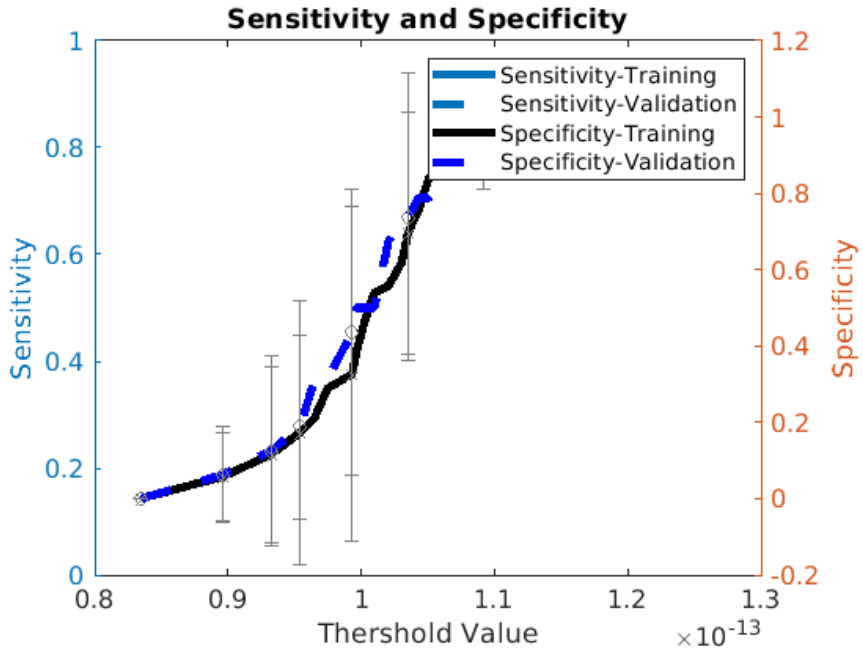

Figure 11. Sensitivity for a people who their smoking status change to non-smoking status.

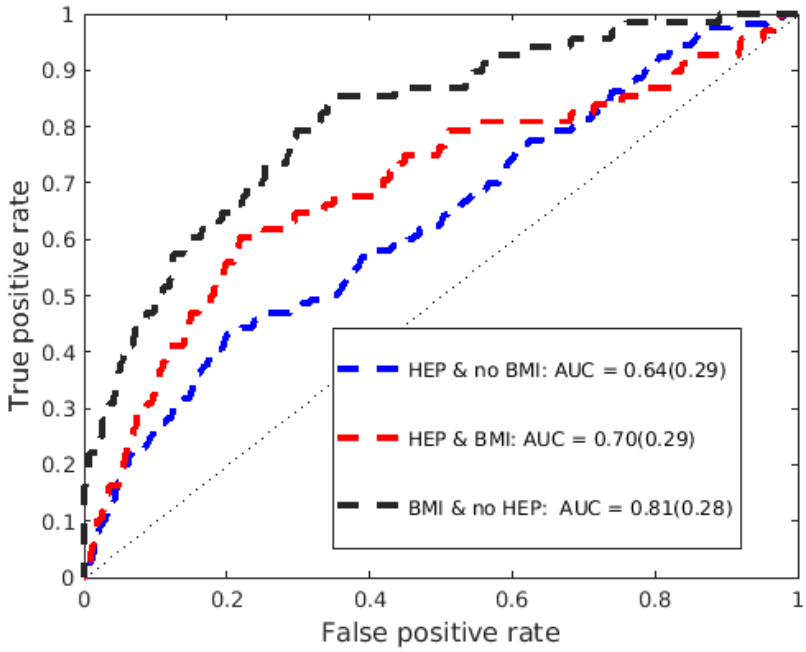

Figure 12. Receiver operating characteristic (ROC) plots with and without HEP.

4 DISCUSSION

In this study, risk of liver cancer is predicted based on basic personal health data (NHIS) using a multi-parameterized ANN model. The model performance was evaluated by training and testing dataset to determine its optimum performance. The best performance of the model was observed with an AUC of 0.80 [CI 0.77-0.84 ±1 standard deviation (SD)] and 0.81 (CI 0.76-0.87 ±1 SD) for training and testing, respectively (Figure 5). With our NPV value from the testing dataset being 99.55%, when our model predicts someone does not have cancer it is only wrong 0.45% of the time. For our testing dataset our PPV value is 0.11%. The group our ANN flags as having cancer is enriched more than 8-fold over the general population.

According to American Cancer Society, currently testing the blood for a substance called alpha-fetoprotein (AFP), which may be produced by cancer cells, or having imaging tests like an ultrasound, computed tomography (CT or CAT) scan, or magnetic resonance imaging (MRI) are the most promising modalities for HCC screening. Note that HCC surveillance has also been shown to be cost effective [23]. It has been found that HCC screening using either biannual AFP and annual abdominal US or triple phase computed tomography (CT) were cost effective compared to no surveillance, with cost effectiveness ratio less than $50000 quality-adjusted life year [24,25]. adding that each of these techniques has its advantages and limitations in screening for HCC, but these techniques are often applied after the appearance of symptoms, which may be fatally

too late in most cases. Moreover, American cancer society states that it is often hard to find liver cancer early because signs and symptoms often do not appear until it is in its later stages. Small liver tumors are hard to detect on a physical exam because most of the liver is covered by the right rib cage. By the time a tumor can be felt, it might already be quite large. However, our ANN is focused on the early prediction and strati cation of HCC risk before symptoms appear by considering the lifestyle. We stress that only personal health data (the type that is readily available in the electronic medical record (EMR) system) was used to reach this level of sensitivity and specificity.

By October 2015, several risk prediction models of HCC were developed in chronic hepatitis B (CHB) cohorts, of which, three studies named the GAG-HCC score (Guide with Age, Gender, HBV DNA, Core Promoter Mutations and Cirrhosis-HCC) [26], CU-HCC score [27] and LSM-HCC score [28] were from Hong Kong, China. The are some common limitations in these risk prediction models. In the cohorts of Korea and Hong Kong, China, the patients recruited in hospital-based studies were more likely to have active disease. Because of that the rate of HCC in training cohort is higher than that in patients with CHB infection only. However, more patients with chronic HBV would belong to the low-risk category in the primary care setting, and this would further increase the negative predictive value of the model for external validation [29]. Another limitation is that in the studies, all patients were from East Asians and risk factors for HCC may be different in other ethnic groups where fewer patients acquire HBV perinatally. The models needed to be independently validated before generalization [29].

Moreover, most available risk prediction models for HCC were limited to individuals at elevated risk who were carrying HBV. And it was useful to estimate risk based not only on hepatitis virus infection status, but also on prevalent and modifiable lifestyle-

related factors [29]. So simple and easy-to-administer risk prediction model which is based on commonly available data in general population would be also of great value. To our knowledge, detailed clinical data could be readily available for the high-risk individuals but much less available for those at average or unknown risk. Besides the factors included in prediction models for high-risk population, body mass index (BMI), physical activity, diabetes, smoking, alcohol consumption, coffee consumption, and other environmental factors should be considered in the risk prediction models for average-risk subjects in different populations. Our ANN model works well on the basis of commonly available data in the EMR and it is based on survey data representative of the general population. The previous studies are based on either one or more clinical conditions or smaller sample sizes. This model can be integrated into an EMR system or be available on websites and portable devices, such as mobile phones and tablets. This will be very helpful for the clinicians to calculate the PC risk of their patients immediately after entering their data.

5 LIMITATION & FUTURE WORK

In this work, we used an ANN to stratify an individual's risk of liver cancer as a means of assisting screening recommendations. This application is limited to use by professionals. In contrast, a comparatively-large portion of population can self-report their life habits such as smoking, exercise, drinking, and other personal health data. This makes it inappropriate for use as a diagnostic tool, but able to mass implemented.

A future aim can be to implement this system of risk prediction in a software-application (an "app") that a smartphone can run. The user application will answer NHIS survey questions and immediately receive the scoring of the risk for liver.

6 CONCLUSION

This study is using ANN to simulate the variation of cancer risk with changes in habits/life style. We reported an ANN that can be used to predict liver cancer with a AUC of 0.81 based solely on personal health data. Compared to current screening techniques, this ANN is non-invasive, cost-effective, and easy to implement with readily available personal health data. The results indicate that the use of a ANN based on personal health information can be used for simulating the cancer risk with varying lifestyle.

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