Predict the Risk of Dyslipidemia via Deep Neural Networks for Survival Data

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Abstract

Background: Dyslipidemia is an important risk factor for coronary artery disease and stroke. Early detection and prevention of dyslipidemia can markedly alter cardiovascular morbidity and mortality. Cox proportional hazard model has been commonly employed for survival datasets to construct the prediction model. Recently, the data-driven learning algorithm began to be used to analyze right-censored survival data. However, there is no attempt to use deep neural networks in dyslipidemia prediction. The objective of this study is to predict the risk of dyslipidemia via deep neural networks for survival data.

Methods: The study cohort was based on the routine health check-up data from 6,328 participants aged 19 to 90 years and free of dyslipidemia at baseline. A deep neural network (DNN) was used to develop risk models for predicting dyslipidemia. Cox Proportional Hazards (Cox) and Random Survival Forests (RSF) were applied in comparison with the DNN model. As metric of performance, we use the time-dependent concordance index (C^{td}-index).

Results: The C^{td}-index of the prediction models by using DNN was 0.802. The DNN model performed significantly better than Cox and RSF model (C^{td}-index: 0.735 and 0.770, respectively). The improvement of DNN over the competing methods was statistically significant. Moreover, DNN provides performance gain on time intervals compared to conventional survival models.

Conclusions: DNN is a promising method in learning the estimated distribution of survival time and event while capturing the right-censored nature inherent in survival data. DNN achieves large and statistically significant performance improvements over previous intuitive regression model and state-of-the-art data-mining methods.

Key Words: dyslipidemia, risk prediction, deep neural network, survival analysis

New & Noteworthy:

- This study applies a DNN based learning algorithm, to develop a risk prediction model for dyslipidemia based on routine check-up data.
- DNN provides performance improvements measured by the C-index score over the COX regression model and RSF in dyslipidemia prediction.
- The DNN model may provide a feasible and accurate approach for identifying the high-risk population among undiagnosed dyslipidemia subjects based on their routine check-up data.

1. Background

Dyslipidemia is the metabolic abnormality of lipoprotein in the human body, mainly including the increase of total cholesterol and low-density lipoprotein cholesterol, triglyceride, and decreased high-density lipoprotein cholesterol, etc [1]. Unhealthy lifestyles, such as high cholesterol diet, an inactive lifestyle, and smoking, are particularly high-risk factors in developing dyslipidemia. In China, the prevalence of dyslipidemia is rapidly increasing. One recent study has illustrated that the incidence density of dyslipidemia in China is as high as 101/1000, and 121/1000 for men and 69/1000 for women, respectively [2]. Dyslipidemia is also a major risk factor for cardiovascular diseases (CVD), a serious threat to people’s health, especially in developing countries. The study shows that CVD mortality increased by 41% between 1990 and 2013, mainly due to low and lower-middle-income countries [3]. Moreover, the burden of dyslipidemia and CVD is now growing faster than our ability to combat. Considering the increased burden caused by dyslipidemia, it is of great significance to manage the disease by early predicting, detecting, and dealing with risk factors [4,5,6].

Traditionally, predictive models were used as the public health responses to disease control. Statistical models and epidemiological models have been commonly employed to construct the predictions. In terms of the methods and statistics of identifying and predicting risk factors, Cox proportional hazard model (CPH) has been widely used. CPH relates the log of the hazard ratio to a linear function of the predictors [7], making it easy to model cause-specific hazards [8]. However, CPH has some limitations. For example, the validity of its results will be affected by factors such as modeling and proportional risk assumption [5]. And CPH has been proven to have a high variance if the model is greatly complex [8]. In order to deal with a variety of potential results, it is necessary to apply appropriate methods to consider and manage competing risks [9]. Furthermore, dyslipidemia possibly also lead to some complications such as atherosclerosis, coronary heart disease (CHD), peripheral artery disease (PAD), stroke, and others, which may delay or mask the symptoms of dyslipidemia [1], making it more difficult to use CPH for accurate prediction. Consequently, it is crucial to use a high prediction capacity method in a complex situation.

Random Survival Forests (RSF) is a nonparametric algorithm, which has been developed to surmount the unsolvable problems of the Cox and other classical models. RSF can cope with plenty of covariates and the correlation between the response and the predictors [6,10]. In addition, RSF can also be applied to select or rank variables, making it to achieve successful risk predictions for several diseases [3]. Meanwhile, to improve the accuracy of disease prediction for survival data, Deep Neural Networks (DNN) have been applied in the field of precise prevention, which is some of the most prominent non-linear algorithms [11]. Recently, it has been suggested that DNN could be a good model for biological networks due to some near-human performance [12].

However, these models' performance differs significantly depending on the assumptions and values of parameters they employ. In addition, some of these models also tend to simplify the complex biological and social processes in which real diseases involve. For these reasons, it is best not to depend on a specific projection coming from a single model. Using multiple models and updating approaches can help diminish some of the limitations inherent in modeling. Recently, a data-driven learning algorithm began to be used to analyze spatial-temporal data. However, there is no attempt to use DNN to predict dyslipidemia. Therefore, the goal of this study is to apply the DNN prediction model to predict the risk of dyslipidemia. To observe the performance gain of our model, we also compare the predictive power of the DNN model with CPH and RSF.

2. Materials and Methods

2.1. Subjects

We conducted a prospective cohort study of 6,328 participants who received routine health check-up at Shandong Provincial Qianfoshan Hospital. These participants met the following criteria: (1) aged between 19 and 90 years; (2) received their first check-ups between 2010 and 2015; (3) received at least three health checks during the 5-year follow-up; (4) individuals who had been diagnosed as having dyslipidemia, diabetes, cardiovascular disease, hepatosis, renal dysfunction, or hypothyroidism at baseline were excluded. The study was approved by the Institutional Review Board of Shandong Provincial Qianfoshan Hospital. The study was conducted in accordance with the principles of the Declaration of Helsinki. The written informed consent was obtained from all eligible participants.

2.2. Outcome and predictor variables

The prediction outcome of this study was the probability of developing dyslipidemia. We defined dyslipidemia according to the 2016 Chinese guidelines for the management of dyslipidemia in adults [13]. Dyslipidemia was defined as having triglycerides (TG) ≥ 2.3mmol/L, and/or low-density lipoprotein cholesterol (LDL-C) ≥ 4.1 mmol/L, and/or total cholesterol (TC) ≥ 6.2 mmol/L, and/or high-density lipoprotein cholesterol (HDL-C) ≤ 1.0 mmol/L.

We employed the predictor variable set collected from the anthropometric and laboratory tests. These predictor variables are closely related to the risk of developing dyslipidemia and can be available in the clinical practice, facilitating the deployment of the model. The anthropometric variables included height, weight, BMI, systolic blood pressure (SBP), and diastolic blood pressure (DBP). In terms of laboratory biomarkers, peripheral blood samples were collected after an overnight fast for measuring the following variables: absolute lymphocyte count (ALC), alanine transaminase (ALT), absolute monocytes count (AMC), aspartate transaminase (ASTblood urea nitrogen (BUN), blood uric acid (BUA), fasting blood-glucose (FBG), gamma-glutamyl transpeptidase (GGT), neutrophil granulocyte (GRA), hematocrit (HCT), highdensity lipoprotein cholesterol (HDL-C), hemoglobin (HGB), low-density lipoprotein cholesterol (LDL-C), mean corpuscular hemoglobin (MCH), mean platelet volume (MPV), platelet large cell ratio (P-LCR), red blood cell count (RBC), serum creatinine (SCr), total cholesterol (TC), triglycerides (TG), and white blood count (WBC).

2.3. Prediction Models

2.3.1. Cox proportional hazard model

Cox proportional hazards model (CPH) is the most widely-used statistical model in the medical setting for investigating the association between the survival time of patients and one or more predictor variables [14]. It has been commonly used in a cohort study to identify the risk factors and construct the prediction model using time-to-event data [15]. However, CPH subjects to restriction about the underlying stochastic process, which assumes the hazard rate are constant and the log of the hazard rate is a linear function of covariates. CPH suffers from high variance when the model is complicated, and nonlinear effects exist.

2.3.2. Random Survival Forest

Random survival forest (RSF) is a data-driven learning algorithm that can automatically deal with the nonlinear effects and interactions among the predictors. Similar to the random forests (RF) [16], RSF uses bootstrap method to randomly select samples from the dataset to construct survival tree models and uses 37% out-of-bag data from each sample to calculate model accuracy [10]. While difference between RSF and RF lies in that response variable in RSF is a survival time, implicating that the data might be censored. In addition, RSF and RF differs in that RSF splits the data at the node with the criterion that maximizes the survival difference. Therefore, RSF is specifically suitable for right-censored data to build prediction model to study the complicated relationship between various predictors and response. It can be used for event-specific selection of risk factors in a nonparametric way with no restrictive assumption; thus, it is suitable to reduce the data dimension of highly correlated biomarker data that are linked with event time of interest [17]. RSF has been applied to identify risk factors for several diseases. An RSF is a collection of randomly grown survival trees, which are generally grown very deeply with many terminal nodes. By using random feature selection at each node, each tree is grown using an independent bootstrap sample of the learning data. The splitting rules are either event-specific or combine event-specific splitting rules across the events [17,18].

2.3.3. Deep Neural Network

The problem of survival analysis has also received substantial recent attention in the deep learning literature. Recently, several works applied deep neural networks (DNNs) to learn complex representations of risk and capture the time-dependent influence of covariates on survival. The current study applied a DNN model, called DeepHit and developed by Lee et al., [19] to learn the estimated distribution of survival time and event while capturing the right-censored nature inherent in survival data. This DNN model makes no assumptions about the underlying stochastic process, making it possible to smoothly learn the nonlinear relationship between the variables and the disease risks.

We treated participants' survival time as discrete and the time frame as finite. The time set was $T = \{0, \ldots, T_{max}\}$ for a maximum time horizon T_{max}. We assumed that exactly one event eventually occurs for each participant and considered one event of interest. The current DNN model employed a network architecture that consists of multiple fully-connected layers and a softmax layer as the output layer. The model was trained by using a loss function that exploits both survival times and relative risks [19]. Figure 1 showed the architecture of the current DNN model.

(Figure 1 insert here)

2.4. Analysis

We assessed the baseline characteristics of participants with and without incident dyslipidemia by using a t-test for continuous variables and a chi-square test for categorical variables. The DNN model was used to develop risk models for predicting dyslipidemia. CPH and RSF models were applied in comparison with the DNN model. To evaluate the prediction performance of the three models, we randomly separated the data into training set (80%) and testing set (20%). As our metric of performance, we use the time-dependent concordance index (C^{td}-index) [20]. The concordance index measures the extent to which the ordering of survival times of pairs agrees with the ordering of their predicted risk, which is a widely-used metric for evaluating the performance of survival models [21].

3. Results

3.1. Descriptive statistics

The baseline characteristics of the study cohort by gender were summarized in Table 1. A total of 2219 dyslipidemia participants were included in this study. Male participants (41.9%) were more likely to develop dyslipidemia than females (21.49%). The mean age of males and females was 45.2 and 41.4, respectively. There were no significant differences in TC, MPV, and P-LCR between the males and females. Except for these three variables, the differences of remaining variables between the patient groups were statistically significant.

(Table 1 insert here)

Kaplan-Meier survival estimates comparing males and females were visualized in Figure 2. We observed a significant difference between male and female participants, with higher survival probabilities for females than males over time. Therefore, the prediction models were respectively constructed by males and females.

(Figure 2 insert here)

3.2. Risk model with Cox

Table 2 shows the results of the Cox prediction model for dyslipidemia based on full-samples. The significant variables included age, BMI, BUN, GGT, GRA, HDL-C, LDL-C, TC, P-LCR, and TG. Except for HDL-C and P-LCR, other significant variables are positive factors in predicting dyslipidemia. BUA was a non-predictive variable in predicting dyslipidemia.

(Table 2 insert here)

We further conducted the Cox prediction model for males and females in Figure 3, respectively. For males, the most predictive variables included HDL-C, TG, TC, and LDL-C. Four variables were found to be irrelevant for predicting dyslipidemia in males, including WBC, P-LCR, AMC, ALC. For females, LDL-C, ALC, GRA, and TG are the most influential factors in predicting dyslipidemia.

(Figure 3 insert here)

3.3. Comparisons of the performance in Cox, RSF, and DNN models

Table 3 compared the prediction performance of Cox, RSF, and DNN models using C^{td}-index values based on testing set and also by gender over time. The C^{td}-index of the DNN model at the 25th percentile survival time was 0.802. The DNN model performed significantly better than Cox and RSF model (C^{td}-index: 0.735 and 0.770, respectively). Similarly, at the 50th and 75th percentile survival time, the DNN model showed higher predictive power than Cox and RSF models. Comparing the prediction performance of these models by gender, we also found DNN model achieved the highest performance than Cox and RSF models. In addition, our results showed that the DNN model significantly provided a better prediction of dyslipidemia for females than males.

(Table 3 insert here)

Figure 4 visualized the predictive power of Cox, RSF, and DNN models over time based on testing set. Compared to Cox models and RSF, the DNN model shows a significantly higher performance over time. We further visualized the performance of the three models. For males, RSF exhibited a very similar predictive power with the Cox model, whereas our DNN model still largely outperformed the Cox and RSF. For females, at the beginning of the prediction time, no significant differences were observed in performance between Cox and RSF, while with the time evolved, RSF showed a performance improvement over Cox. DNN model always outperformed the Cox and RSF.

(Figure 4 insert here)

In sum, DNN showed the highest predictive power and provided performance improvements in dyslipidemia prediction over Cox and RSF in this study.

4. Discussion

This study aimed to apply a DNN based learning algorithm, DeepHit, to develop a more accurate risk prediction model for dyslipidemia. Several common predictors were extracted from the routine health check-up data to construct the prediction model. Our results showed that DNN fitted our data well and provided performance improvements measured by C-index score over the intuitive regression model and state-of-the-art data-mining methods in dyslipidemia prediction.

We compared the predictive power of DNN with CPH and RSF and found DNN was a superior model in dyslipidemia prediction. The improved accuracy on dyslipidemia prediction of the DeepHit model could be attributed to its flexible processing ability, which can smoothly learn the nonlinear relationship between the variables and the disease risks [19]. The Cox regression model [14] follows a strict assumption that the underlying relationship between variables and the hazard rate is a linear function. However, the prevalence of dyslipidemia is rather complicated and beyond the applicable conditions of the Cox Model, which might significantly limit the accuracy of its predictive power. Although RSF [17] is a data-driven algorithm that can automatically learn the underlying patterns between the covariates and the risk events, it has a limited predictive capacity, particularly in the presence of many covariates. Thus, our DeepHit model, which makes no assumptions about the underlying stochastic process, can provide a more accurate prediction of dyslipidemia events.

Our findings on the performance improvement of DNN in dyslipidemia prediction were consistent with existing literature, illustrating that DNN models were powerful techniques for disease prediction. For example, Zhao and Feng [22] found that the DNN model better performed than existing methods, such as a standard CPH and Cox-nnet model, in predicting the development and progression of cardiovascular disease among older populations. Lee et al. [23] presented a new DNN model for overcoming the major disadvantages of the CPH in predicting non-small cell lung cancer patients' recurrence probabilities after surgery; results demonstrated that semi-unsupervised binned-time survival analysis (su-DeepBTS) model exhibited the best performance with a concordance index(C-index) of 0.7306 and an area under the curve (AUC) of 0.7677, better than supervised binned-time survival analysis (s-DeepBTS) and CPH (C-index of 0.7048 and 0.7126 and AUCs of 0.7390 and 0.7420 respectively). For better predicting the progression from mild cognitive impairment(MCI) to Alzheimer's disease(AD), Sebastian Pölsterl et al. [24] proposed a wide and deep neural network model that fused information of anatomical shape and tabular clinical data from survival analysis. Their study indicated that this model was superior to a baseline neural network on shapes and a linear model on common clinical biomarkers, which both enhanced clinical variables and improved prediction performance.

DeepHit was developed in the late 2018 as a new deep learning approach to survival analysis. Although DeepHit exhibited high predictive power over previous intuitive regression model and state-of-the-art data-mining methods, up to present few studies have applied it to disease risk prediction. Except for two studies applying it to predict breast cancer [19] and cystic fibrosis [25], no applications has been developed to predict dyslipidemia risks. Therefore, to the best of our knowledge, this was the first application of the DNN model in predicting dyslipidemia based on the routine check-up data. We specifically confirmed that DNN was a useful tool in dyslipidemia risk prediction. In addition, given the high predictive power of DNN compared to other existing models, our research contributes to the current literature by indicating that nonlinear relationships between predictors and survival times are crucial for assessing the risk of dyslipidemia. Predictive models based on a linear assumption may limit the accuracy of their predictions and hinder practitioners' ability to precisely evaluate the dyslipidemia risks of their patients. Thus, practically, our DNN predictive model provides a feasible and accurate approach for identifying the high-risk population among undiagnosed dyslipidemia subjects based on their routine check-up data. Given the rapidly increasing prevalence of dyslipidemia in China [26], identifying the individual risk of dyslipidemia carries significant implications for early intervention strategies. In addition, dyslipidemia is an essential risk factor for a variety of diseases, such as cardiovascular disease, heart disease, and stroke [27,28]. The policy intervention plans against the prevalence of dyslipidemia will undoubtedly reduce the risk of those chronic diseases among the Chinese population.

Despite these strengths, our research has some limitations. Firstly, our samples consist of patients from large medical institutions with high socioeconomic status, limiting the robustness of the model. It thus should be cautious about generalizing our findings to other groups with distinct geographic and socioeconomic features. Further validation utilizing other data sources, particularly a nationally representative dataset, could make the predictive power of the DNN model in dyslipidemia more accurate. Secondly, we excluded the patients who had already had dyslipidemia at the baseline, which might lead us to underestimate the actual survival time. Finally, our predicators of dyslipidemia were all from the routine check-up. Further work could consider possible environmental variables and other genetic-related factors.

5.Conclusion

In conclusion, our research confirms that DNN approaches are powerful tools to identify subjects with a high risk of dyslipidemia. In addition, our DNN significantly outperformed the other two models in predicting dyslipidemia for survival data. Based on our research, a more precise assessment can be performed in the health populations with DNN to guide the early classification of risks and thus effectively lower the incidence of dyslipidemia and other-related disease.

Authors’ contributions

Conception and design: Hailun Lian, Xiaoshuai Zhang, Xiao Li, Fang Tang

Data analysis and interpretation: Hailun Lian, Dongzuo Liang, Lei Tao, Yuhan Chen, Meixi Yi，Da Zheng

Manuscript writing: Hailun Lian, Dongzuo Liang, Lei Tao, Xiaoshuai Zhang, Xiao Li, Yuhan Chen, Meixi Yi, Fang Tang, Da zheng

Final approval of manuscript: Hailun Lian, Fang Tang, Xiaoshuai Zhang, Xiao Li, Fang Tang

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Statement on conflicts of interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled“Predict the Risk of Dyslipidemia via Deep Neural Networks for Survival Data”.

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Beijing Physical Examination Center. The study was conducted in accordance with the principles of the Declaration of Helsinki. The written informed consent was obtained from all eligible participants.

Availability of data and materials

The data used in this study is provided by Shandong Provincial Qianfoshan hospital. We have obtained the right to use the data through application. If anyone wants to obtain data from this study, they can contact Fang Tang (Contact information: Center for Big Data Research in Health and Medicine, The First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital, Jingshi Road 16766, 250014, Jinan, China. E-mail: tangfangsdu@gmail.com)

Consent for publication

Not applicable

Summary points

What was already known on the topic:

- Early detection and prevention of dyslipidemia can markedly alter cardiovascular morbidity and mortality.
- Cox proportional hazard model (CPH) and Random Survival Forests (RSF) are two common tools to construct the predictive model for dyslipidemia.

- The existing models usually have poor performance in dyslipidemia prediction as they strictly follow basic assumptions and values of parameters.

What this study added to our knowledge:

- This study applies a DNN based learning algorithm, DeepHit, to develop a risk prediction model for dyslipidemia based on routine check-up data.
- DNN provides performance improvements measured by the C-index score over the COX regression model and RSF in dyslipidemia prediction.
- The DNN model may provide a feasible and accurate approach for identifying the high-risk population among undiagnosed dyslipidemia subjects based on their routine check-up data.

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Table 1 Baseline Characteristics by Gender

Variables	**Male**	**Female**	**P-value**
Dyslipidemia	1628(41.90%)	591(24.19%)	<0.001
Age	45.221(±14.414)	41.357(±12.53)	<0.001
ALC	2.245(±0.586)	2.081(±0.528)	<0.001
BUN	5.42(±1.202)	4.585(±1.095)	<0.001
AMC	0.352(±0.111)	0.304(±0.094)	<0.001
TC	4.704(±0.683)	4.7(±0.699)	0.814
HDL-C	1.561(±0.299)	1.791(±0.327)	<0.001
ALT	23.613(±17.556)	16.368(±16.167)	<0.001
AST	21.221(±9.166)	18.868(±7.814)	<0.001
RBC	4.993(±0.357)	4.413(±0.309)	<0.001
HCT	0.449(±0.027)	0.392(±0.027)	<0.001
SCr	76.593(±10.769)	56.355(±8.47)	<0.001
BUA	351.888(±70.862)	257.086(±53.686)	<0.001
MCH	30.771(±1.447)	29.589(±2.193)	<0.001
MPV	10.464(±0.794)	10.47(±0.807)	0.791
FBG	5.23(±0.627)	4.999(±0.481)	<0.001
HGB	153.379(±9.864)	130.336(±10.848)	<0.001
GRA	3.35(±1.074)	3.2(±1.093)	<0.001
TG	1.081(±0.341)	0.879(±0.334)	<0.001
LDL-C	2.648(±0.525)	2.427(±0.583)	<0.001
WBC	6.123(±1.427)	5.723(±1.394)	<0.001
P-LCR	28.487(±6.617)	28.464(±6.708)	0.896
GGT	28.595(±22.144)	15.883(±14.402)	<0.001
SBP	129.361(±17.22)	118.84(±17.119)	<0.001
DBP	82.267(±11.004)	73.586(±10.048)	<0.001
BMI	24.589(±3.105)	22.25(±3.063)	<0.001

Table 2 Cox Proportional Hazard Model for Predicting Dyslipidemia

Variables	Coe	Z statistic	P-value	HR	Lower	Upper
Age	0.004	2.080	0.038	1.004	1.000	1.007
BMI	0.023	2.758	0.006	1.023	1.007	1.040
BUA	0.001	1.477	0.140	1.001	1.000	1.001
BUN	0.037	1.812	0.070	1.038	0.997	1.081
GGT	0.004	3.859	0.000	1.004	1.002	1.006
GRA	0.047	2.039	0.041	1.048	1.002	1.096
HDL-C	-1.437	-9.686	<0.00001	0.238	0.178	0.318
LDL-C	0.519	3.995	<0.0001	1.681	1.303	2.169
P-LCR	-0.006	-1.711	0.087	0.994	0.987	1.001
TC	0.571	5.462	<0.00001	1.769	1.442	2.171
TG	0.642	7.656	<0.00001	1.901	1.613	2.241

Table 3 C^{td}-index for Prediction Model with Cox, RSF and DNN Model

Models	25%	50%	75%
Full testing set			
Cox	0.735	0.735	0.732
RSF	0.770	0.768	0.766
DeepHit	0.802	0.798	0.794
Testing set of male			
Cox	0.733	0.727	0.726
RSF	0.744	0.738	0.737
DeepHit	0.831	0.804	0.809
Testing set of female			
Cox	0.771	0.786	0.780
RSF	0.812	0.818	0.807
DeepHit	0.851	0.849	0.834

Figure Legend

Figure 1 The architecture of the DNN model

Figure 2 Kaplan-Meier survival estimates comparing male with female participants

Figure 3 Cox Proportional Hazard Model for Predicting Dyslipidemia in Male (A) and Female (B)

Figure 4 Comparison of Ctd-index performance in Cox, RSF and DNN Models based on full testing set (A); by the male (B) and female (C)

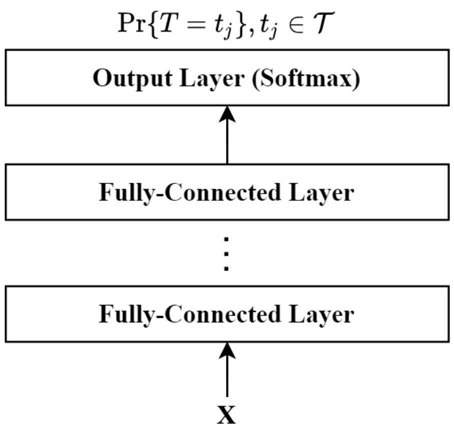


Figure 1 The architecture of the DNN model

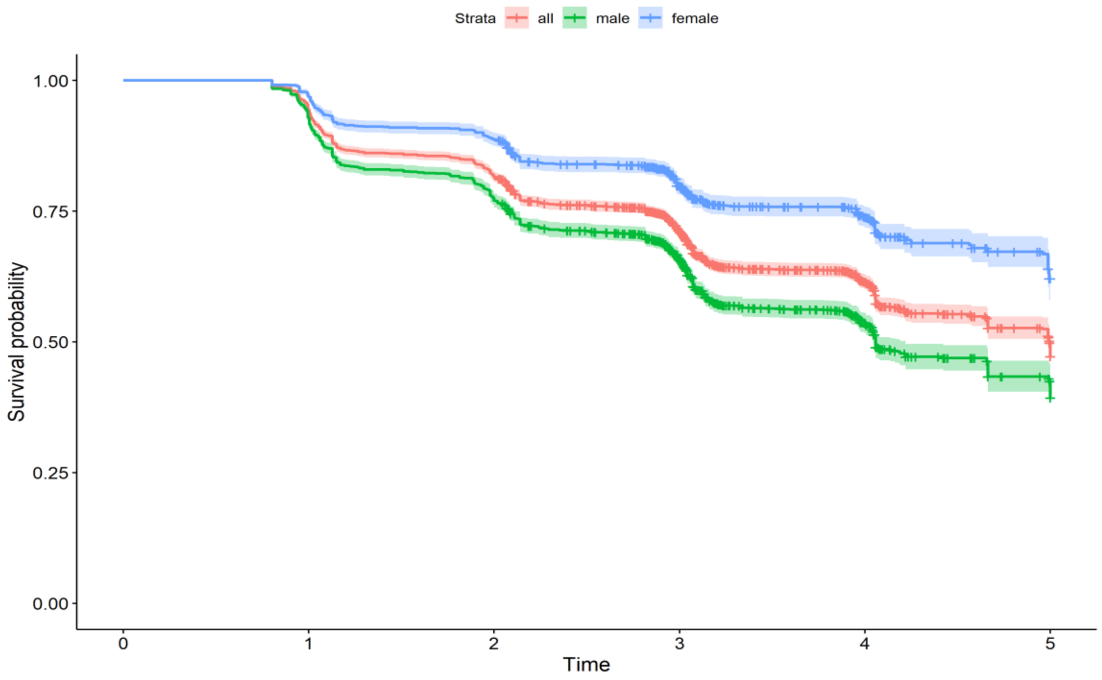
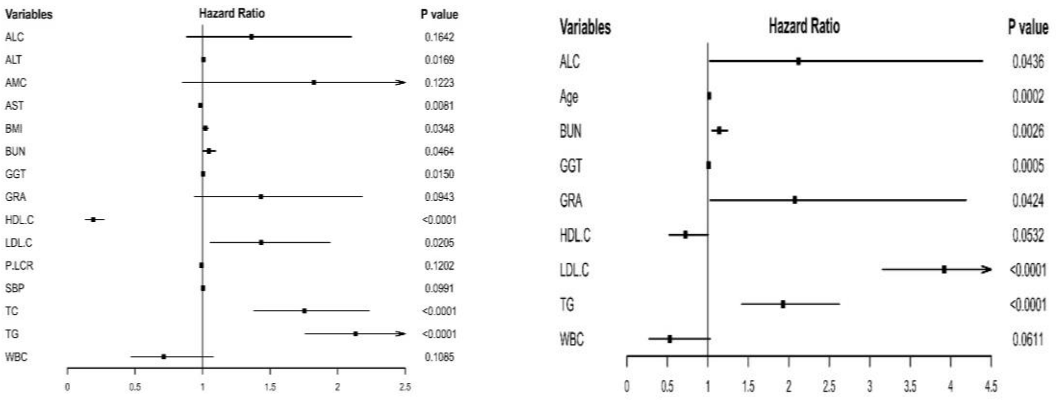


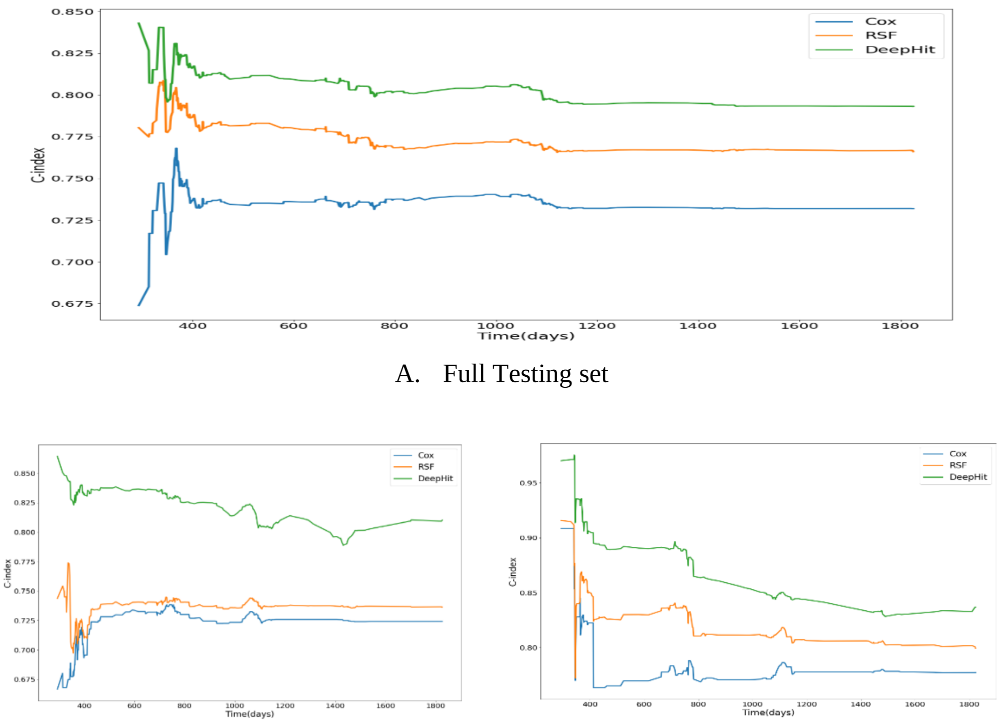
Figure 2 Kaplan-Meier survival estimates comparing male with female participants



A. Male

B. Female

Figure 3 Cox Proportional Hazard Model for Predicting Dyslipidemia in Male (A) and Female (B)



A. Full Testing set

B. Testing set of male

C. Testing set of female

Figure 4 Comparison of C^{td}-index performance in Cox, RSF and DNN Models based on full testing set (A); by the male (B) and female (C)