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Deep learning model for detection of hypoalbuminemia using electrocardiography

Short title: Artificial intelligence for hypoalbuminemia

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Abstract

Background: Albumin has a pivotal role in the homeostasis of osmotic pressure and is associated with cardiovascular, nephrotic, hepatic, and nutritional diseases. The detection of hypoalbuminemia is a cornerstone for diagnosis of hidden diseases and patient deterioration. We developed and validated a deep-learning-based model (DLM) for detection of hypoalbuminemia using electrocardiography (ECG).

Methods: This historical cohort study included data from consecutive patients from two hospitals. The patient data in one hospital were divided into development (82,499 ECGs from 54,248 patients) and internal validation (20,664 ECGs from 20,664 patients) datasets, whereas the patient data in the other hospital were included in only an external validation (37,421 ECGs from 37,421 patients) dataset. An DLM was developed using a 12-lead ECG signal, age, and sex from the development dataset. The endpoint was hypoalbuminemia, defined by serum albumin concentration below 3.5 g/dL.

Results: During the internal and external validations, the areas under the receiver operating characteristic curve of the DLM for the detection of hypoalbuminemia were 0.887 (0.877–0.897) and 0.888 (0.880–0.896), respectively. Among the 27,400 individuals without hypoalbuminemia at the initial laboratory exam, those identified by the DLM as higher-risk patients had a significantly larger change in developing hypoalbuminemia than those in the low-risk group (7.09% vs. 1.01%, $p < 0.001$) during 24 months. The sensitivity map showed that the DLM focused on the T wave and QRS complex for the detection of hypoalbuminemia.

Conclusions: The DLM exhibited a high accuracy for hypoalbuminemia detection and prediction using 12-, 6-, and single-lead ECGs.

Keywords: Electrocardiography; Albumins; Deep Learning; Artificial Intelligence

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Introduction

As albumin provides 80% of the total colloid osmotic pressure of plasma and 50% of protein content, it has a pivotal role in the maintenance of homeostasis.[1] Se rum albumin transports several different fat-soluble hormones and drugs and serves as a plasma buffer, maintaining physiological pH levels, and antioxidant, involved in the scavenging of oxygen free radicals.[2,3] Hypoalbuminemia is common in numerous diseases, including liver cirrhosis, malnutrition, nephrotic syndrome, heart failure, and s epsis.[4,5] The evaluation of the albumin level is a cornerstone for diagnosis and proper treatment. The monitoring of the albumin level is crucial for patients who have diseases that impair the retention and excretion of fluid, such as heart failure and liver cirrhosis, and patients who take medications transported by albumin, such as diuretics.[6–8]

As the symptom of hypoalbuminemia is nonspecific, it is challenging to diagnose it with only the medical history and physical examinations until the condition is uncompensated and complications occur.[9] The gold standard for diagnosing hypoalbuminemia is a laboratory examination to measure the concentration of albumin. However, the laboratory tests are invasive, costly, and require specialized equipment and infrastructure, such as trained medical staff for sampling blood and hematology analysis devices for assessment with biochemical reagents. Detecting hypoalbuminemia in daily life is important to monitor the health status and detect deteriorating events. However, the evaluation using a laboratory exam could not be used for this purpose. Moreover, laboratory tests are too expensive to use in low-income countries for screening hypoalbuminemia.

Albumin represents a circulating endogenous reservoir of nitric oxide (NO) and acts as a donor for NO, which has diverse cardiovascular effects.[10] Albumin is associated with right ventricular free wall longitudinal strain and development and prognosis of cardiovascular diseases, which can be correlated with electrocardiography (ECG).[11–16]

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However, it is not simple to provide diagnostic tools using such subtle ECG changes based on conventional statistical methods. Recent studies have shown that deep learning models using ECG could detect diverse diseases, including anemia, valvular heart disease, heart failure, myocardial infarction, and electrolyte imbalances.[17–25] In this study, we developed and validated a deep-learning-based model (DLM) to detect hypoalbuminemia using ECG.

Methods

Study design and population

We carried out a retrospective multi-center diagnostic study in which a DLM was developed using ECGs, and then internally and externally validated. We excluded individuals with missing demographic, electrocardiographic, and albumin laboratory exam information. Data from the Sejong General Hospital (SGH) were used for the development and internal validation. In the SGH, we identified patients with at least one standard digital 10-s 12-lead ECG acquired in the supine position within the study period (October 1, 2016 to August 31, 2020) and at least one laboratory exam for albumin within 30 min after the index ECG. The individuals who visited the general health checkup, outpatient department, and emergency department and were admitted to SGH were the study population for the development and internal validation datasets. As shown in Supplementary material 1, patients who underwent a follow-up albumin laboratory examination after an initial evaluation were assigned t o an internal validation dataset. Patients who had not underwent follow-up laboratory exam were assigned to a development dataset used to develop the DLM. Subsequently , we evaluated the accuracy of the DLM using the internal validation dataset. Data from Mediplex Sejong Hospital (MSH) were used for an external validation. We identified the patients who were admitted to MSH during the study period (March 1, 2017 to August 31, 2020) and who had at least one ECG and one albumin laboratory exam within 30 min after

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the index ECG. As the purpose of the validation data was to assess the accuracy of the DLM, we used only one ECG from each patient for the internal and external validation datasets, the time-closest to the albumin laboratory exam in the study period.

This study was approved by the institutional review boards of SGH and MSH. Clinical data, including digitally stored ECGs, albumin laboratory exam values, age, and sex, were obtained from both hospitals. Both institutional review boards waived the need for informed consent because of the retrospective nature of the study using fully anonymized ECG and health data and minimal harm.

Procedures

The predictor variables were ECG, age, and sex. Digitally stored 12-lead ECG data, 5000 numbers for each lead, were recorded over 10 s (500 Hz). We removed 1-s intervals at both beginning and end of each ECG because of the more artifacts than in other parts. Thus, the length of each ECG was 8 s (4000 numbers). We created a dataset using the entire 12-lead ECG data. We also used partial datasets from the 12-lead ECG data, such as six-limb-lead and single-lead datasets (lead I). We selected the sets of leads because the data can easily be recorded by wearable and pad devices in contact with the hands and legs. Consequently, when we developed and validated the DLM using 12-lead ECGs, we used a dataset of two-dimensional (2D) data of 12 × 4000 numbers. When we developed and validated an algorithm using six-lead ECGs, we used datasets of 6 × 4000 numbers, while for the single-lead ECGs, we used datasets of 1 × 4000 numbers. The endpoint of this research was hypoalbuminemia, defined by serum albumin concentration < 3.5 g/dL.

As shown in Supplementary material 2, the DLM was developed using several hidden layers of neurons to learn complex hierarchical nonlinear representations from the data. A residual block with five stages included two convolution layers, two batch normalizations, one max-pooling, and one dropout layer (repeated), as shown in Supplementary material 2. We used

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1 × 4 max-pooling layers between blocks 1 and 4 and 2 × 4 max-pooling layers between blocks 4 and 5. The last convolutional layer of the residual block was connected to a flattened layer, which was fully connected to a one-dimensional (1D) layer composed of 128 nodes. The input layer of epidemiology data (age and sex) was concatenated with the 1D layer. Two fully connected 1D layers were connected to the output node, which was composed of one node. The output node used a softmax function as an activation function because the output of the softmax function was between 0 and 1. The architecture of the DLM was evaluated and verified using a grid search. We developed an additional DLM using six-limb-lead and single-lead ECGs.

Statistical analysis

Continuous variables are presented as mean values (standard deviations (SDs)) and compared using the unpaired Student's *t*-test or Mann–Whitney *U* test. Categorical variables are expressed as frequencies and percentages and compared using the χ^2 test. At each input (ECG) of validation data, the DLM calculated the possibility of a primary endpoint in the range of 0 (non-hypoalbuminemia) to 1 (hypoalbuminemia). To verify the DLM performance, we compared the probability calculated by the DLM with the presence of a hypoalbuminemia in the internal and external validation datasets. To this end, we used the area under the receiver operating characteristic curve (AUC). We applied the cutoff point to the internal and external validation data to calculate the sensitivity, specificity, positive predictive value, and negative predictive value, which were confirmed at the operating point by Youden J statistics in the development data.[26] The 95% confidence intervals (CIs) were used for all measures of diagnostic performances, except for AUC. The CIs for AUC were determined based on the Sun–Su optimization of the De-long method using the pROC package in R (The R Foundation for Statistical Computing, Vienna, Austria). A significant difference in patient characteristics was defined by two-sided $p < 0.001$. Statistical analyses were carried out using the R software, version 3.4. In addition, we used the PyTorch's open-

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source software library as the backend and Python (version 3.6) for the analysis.

Visualization of the developed XDM for interpretation

To understand the developed model and compare it to existing medical knowledge, it was necessary to identify a region that had a significant effect on the decision of the developed DLM. We employed a sensitivity map using a saliency method.[27,28] The map was computed using the first-order gradients of the classifier probabilities with respect to the input signals. If the probability of the classifier was sensitive to a specific region of the signal, the region would be considered significant in the model. In other words, we verified the region of the ECG that was associated with hypoalbuminemia using a sensitivity map. We used a gradient class activation map as a sensitivity map and guided the gradient back-propagation method. We verified the variable importance values of ECG features, age, and sex in logistic regression, random forest, and deep learning using the deviance difference, mean decreased Gini, and relative importance based on the Garson's algorithm, respectively.[29]

Verification of the DLM performance to predict the hypoalbuminemia by a subgroup analysis

We hypothesized that the ECGs would display subtle abnormal patterns in the pre-hypoalbuminemia phase and that the developed DLM would classify certain cases as abnormal, yielding a false positive (a study subject classified as having hypoalbuminemia but considered as non-hypoalbuminemia) as the initial result. We carried out a subgroup analysis of patients who underwent follow-up laboratory examinations in the internal and external validation datasets. The difference in data between the initial and follow-up echocardiography data was over 14 d. Among those patients, we verified the development of hypoalbuminemia in patients who were initially considered non-hypoalbuminemia patients, whose serum albumin concentration was 3.5 g/dL or higher. The DLM data were categorized

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into high- and low-risk groups based on the risk score using cutoff values, which were determined using the Youden's J statistic with the development dataset.[26] We used the Kaplan–Meier method to analyze the hypoalbuminemia development over 24 months.

Results

The eligible population included 74,919 and 37,426 patients from SGH and MSH, respectively. We excluded 7 and 5 patients from SGH and MSH, respectively, because of missing clinical information (age and sex), laboratory albumin information, or ECG data (Supplementary material 1). The study included a total of 112,333 patients, of whom 3,812 had hypoalbuminemia. The DLM was developed using a development dataset of 82,499 ECGs of 54,248 patients from SGH. The performance of the algorithm was then verified using 20,664 ECGs of 20,664 patients from SGH in the internal validation dataset and 37,421 ECGs of 37,421 patients from MSH in the external validation dataset. In the case of hypoalbuminemia, the ECG had a prolonged QRS duration, rightward T-wave axis, and tachycardia (Table 1).

During the internal and external validations, the AUCs of the DLM for detecting hypoalbuminemia as the endpoint using 12-lead ECGs were 0.887 (95% confidence interval, 0.877–0.897) and 0.888 (0.880–0.896), respectively (Figure 1). The AUCs of the DLM for detecting hypoalbuminemia using six-lead ECGs during the internal and external validations were 0.871 (0.859–0.882) and 0.880 (0.871–0.889), respectively. The AUCs of the DLM using single-lead ECGs during the internal and external validations were 0.854 (0.842–0.867) and 0.879 (0.870–0.887), respectively (Figure 1).

The DLM described the important ECG region for hypoalbuminemia detection. As shown in Figure 2, the DLM focused on the QRS complex and T wave for the detection of hypoalbuminemia. As shown in Supplementary material 3, the variable importance diffe

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red for each machine learning model. The random forest used the T-wave axis, while the DLM used the QT interval as an important predictive variable.

Our study comprised 28,482 patients (20,664 and 7,818 patients in the internal and external validation datasets, respectively) with follow-up laboratory results. Among them, 27,400 patients were normal (non-hypoalbuminemia) at the initial laboratory examination. We carried out a subgroup analysis of hypoalbuminemia development after the initial laboratory examination for the 27,400 patients, of whom 869 developed hypoalbuminemia within 24 months. The high-risk group of the DLM exhibited a significantly higher hazard (Figure 3) and higher development rate of hypoalbuminemia than those of the low-risk group (7.09% vs. 1.01%, $p < 0.001$).

Discussion

We developed and validated the DLM based on an ensemble network for hypoalbuminemia detection using 12-, six-, and single-lead ECGs and demonstrated a reasonable performance. Subsequently, we visualized our DLM to determine the regions and characteristics of the ECG that were used for hypoalbuminemia detection and verified the important variable for the decision in diverse statistical methods, such as logistic regression, random forest, and DLM. We carried out a subgroup analysis for non-hypoalbuminemia (normal) patients at the initial laboratory examination. The DLM could predict the development of hypoalbuminemia. To the best of our knowledge, this study is the first that develops a DLM for detection and prediction of hypoalbuminemia using ECG and demonstrates interpretable patterns of decision making using the DLM.

The development of a reliable tool for detection and prediction of hypoalbuminemia is the cornerstone for the monitoring of the albumin status and early management to prevent an irreversible disease progression.[6–8] Hypoalbuminemia is also associated with the

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nutritional status of patients. As one of the pathophysiologies of hypoalbuminemia is associated with an increase in capillary permeability and altered kinetics of serum albumin in inflammatory states, hypoalbuminemia is a reflection of the extent of physiologic stress from disease- and trauma-related inflammations.[30] Hypoalbuminemia is associated with liver diseases, kidney diseases, and malnutrition or malabsorption based on albumin synthesis, loss, and intake, respectively.[4,5] Therefore, the detection of hypoalbuminemia is important to not only monitor nutritional and homeostasis general conditions, but also early-diagnose other diverse diseases using hypoalbuminemia as a surrogate factor and detect deterioration of the patient.[11–16]

Although laboratory tests for albumin are diagnostic tests for hypoalbuminemia, they require blood sampling and infrastructure for a blood analysis. Therefore, the detection of hypoalbuminemia based on laboratory tests could not be used in daily life and low-income countries. As stated above, albumin is an endogenous reservoir of NO and acts as a donor for NO.[10]The cardioprotective roles of NO include regulation of blood pressure and vascular tone, inhibition of platelet aggregation and leukocyte adhesion, and prevention of smooth muscle cell proliferation. Reduced bioavailability of NO is considered one of the central factors common in endothelial dysfunction. The underlying pathology for most cardiovascular diseases is atherosclerosis, which is associated with endothelial dysfunction.[10] The albumin level has been significantly negatively correlated with right ventricular free wall longitudinal strain.[11] Albumin is a strong prognostic factor for cardiovascular diseases. As the albumin level affects diverse cardiovascular statuses, we hypothesized that we could detect hypoalbuminemia based on ECG.[11–16]

The most important aspect of deep learning is its ability to extract features and develop an algorithm using various types of data, such as images, 2D data, and waveforms.[31] Attia et al. and our study group developed a DLM to screen for heart failure, arrhythmia, valvular

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heart disease, left ventricular hypertrophy, electrolyte imbalance, and anemia.[17–25] Deep learning is criticized for its unreliable outcomes because of the low transparency of the process, so-called black box. Therefore, we used a sensitivity map to describe the abnormal findings that affected the decision of the DLM for the detection of RI and description of the variable importance of ECG features. Using this method, we verified the ECG region and features associated with hypoalbuminemia. Conventional methods are based on hypotheses of researchers. For deep learning methods, such as the DLM and sensitivity mapping in this study, the findings are not based on previous medical knowledge of humans, but on data. Therefore, we could provide new knowledge only by the data, without human prejudice. Deep learning could discover the complex hierarchical nonlinear representation that could not be discovered using conventional statistical methods, such as logistic regression. In this study, we verified the important ECG region for the detection of hypoalbuminemia from waveform data. We verified that hypoalbuminemia could be detected and predicted using ECG based on the DLM. The sensitivity map and variable importance information showed that QRS complex, T wave, QT interval, and PR interval were correlated with the detection of hypoalbuminemia. These findings are in agreement with the results of previous studies. Heaf et al. and Madias et al. showed that the amplitude of the QRS complex was associated with albumin levels.[32,33] Toma et al. and Wu et al. showed that prolonged QT intervals and T accentuated deceleration of the T wave correlated with hypoalbuminemia.[13,34]

In this study, the DLM could predict the development of hypoalbuminemia. The DLM may detect structural and physiological changes that affect the vulnerability of hypoalbuminemia. These findings suggest that the DLM could be used to not only diagnose hypoalbuminemia but also screen patients who have characteristics of hypoalbuminemia risk. The reliable performances of the six- and single-lead ECG-based DLMs indicate that hypoalbuminemia could be screened with both conventional 12-lead ECG and life-type or

wearable ECG device or simple monitoring device. Using this algorithm, developing countries with limited medical resources could be screened with simple devices. In developed countries, patients could be monitored using diverse life-type devices and could be alerted regarding disease progression in daily life.

This study has several limitations. First, we validated the DLM using retrospective da ta. However, it is necessary to validate the DLM with prospective studies and data from daily life. Studies related to the clinical significance of the new technology are required for applicat ion in clinical practice. In our next study, we will verify the DLM performance and significan ce with a prospective study in daily clinical practice. Second, this study was carried out only i n two hospitals in Korea. Hence, it is necessary to validate the DLM with patients in other co untries. Third, the decision process of the algorithm must be further investigated based on deep learning. For example, additional experiments must be performed to understand the d eep learning process and determine the characteristics of the QRS complex that affect the DLM's decision. This will be investigated in our next study.

Conclusion

The DLM exhibited high performances and accuracy in the detection of hypoalbuminemia using ECG and successfully predicted the development of hypoalbuminemia.

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Author contributions: YJL, YYJ and SYL performed data analysis and verified the clinical coding. MSJ, YHC, HJS, and JHB contributed to the study idea and design as well as data collection, performed data analysis, and contributed to subsequent drafts. KHK, JP, and BHO contributed to data collection and revised the manuscript. JK is the principal investigator and contributed to the study idea and design, data analysis, verified the clinical coding, and contributed to subsequent drafts.

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Table 1 Baseline characteristics

Characteristic	Development and internal validation dataset (Hospital A) n=78,171			External validation dataset (Hospital B) n=37,190			*p*
	Non-hypoalbuminemia	Hypoalbuminemia	*p*	Non-hypoalbuminemia	Hypoalbuminemia	*p*	*p*
Study population, n (%)	72,422	2,490		36,099	1,322		0.071
Age, yr, mean (SD)	58.81 (17.20)	72.61 (14.68)	<0.001	53.16 (17.22)	71.74 (14.77)	<0.001	<0.001
Male, n, (%)	38,321 (52.9)	1247 (50.1)	0.006	17,642 (48.9)	654 (49.5)	0.689	<0.001
Heart rate, bpm (%)	72.55 (18.60)	87.92 (24.79)	<0.001	72.05 (16.62)	87.38 (22.58)	<0.001	0.262
PR interval, ms, mean (SD)	170.89 (30.14)	169.47 (36.68)	0.041	166.01 (26.55)	165.00 (32.53)	0.206	<0.001
QRS duration, ms, mean (SD)	96.60 (17.98)	98.24 (22.66)	<0.001	94.46 (14.78)	95.25 (20.04)	0.060	<0.001
QT interval, ms, mean (SD)	404.64 (42.26)	394.76 (59.75)	<0.001	399.98 (38.29)	389.83 (53.60)	<0.001	<0.001
QTc, ms, mean (SD)	437.63 (33.69)	465.31 (43.17)	<0.001	432.24 (31.07)	460.25 (38.60)	<0.001	<0.001
P axis, mean (SD)	43.49 (30.10)	44.49 (38.42)	0.170	44.30 (27.47)	42.47 (32.18)	0.027	<0.001
R axis, mean (SD)	39.51 (44.47)	35.31 (55.51)	<0.001	41.52 (39.16)	29.88 (48.38)	<0.001	<0.001
T axis, mean (SD)	44.77 (47.94)	66.89 (74.53)	<0.001	38.81 (35.91)	56.87 (63.75)	<0.001	<0.001
Albumin, mean (SD)	4.48 (0.36)	3.02 (0.38)	<0.001	4.30 (0.30)	3.01 (0.41)	<0.001	<0.001

Figure legends

Figure 1 Performances of deep learning based model for detecting hypoalbuminemia

Legend: AUC denote area under the receiver operating characteristic curve, CI confidence interval, DLM deep learning based model, ECG electrocardiography, NPV negative predictive value, PPV positive predictive value, SEN sensitivity, and SPE specificity.

Figure 2 Sensitivity map of deep learning based model for detecting hypoalbuminemia

Legend: none

Figure 3 Cumulative hazard of developing hypoalbuminemia in patients with an initially normal

Legend: none

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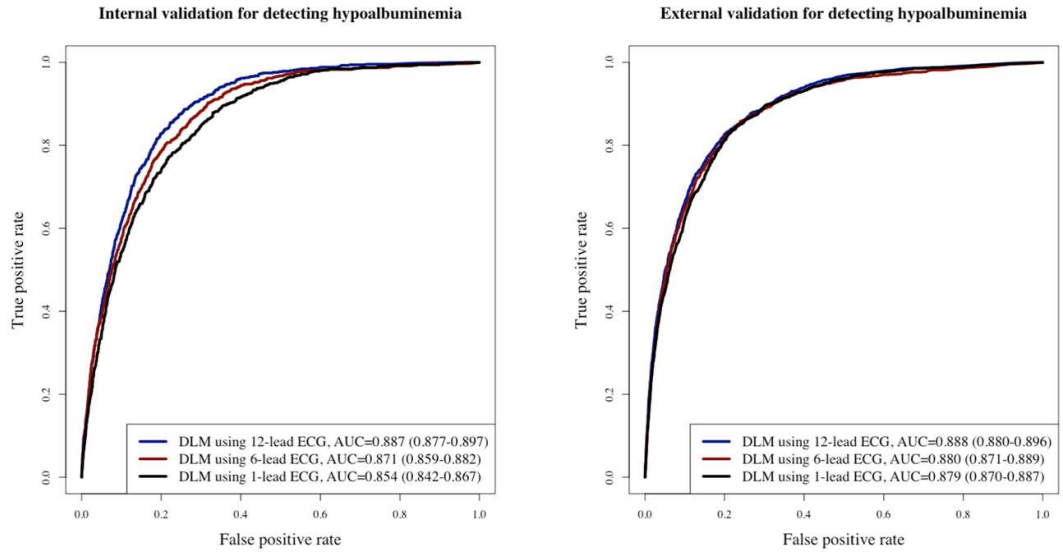
Figure 1 **Performances of deep learning based model for detecting hypoalbuminemia**



	Internal validation					External validation				
	AUC(95%CI)	SEN(95%CI)	SPE(95%CI)	PPV(95%CI)	NPV(95%CI)	AUC(95%CI)	SEN(95%CI)	SPE(95%CI)	PPV(95%CI)	NPV(95%CI)
DLM using 12-lead ECG	0.887 (0.877-0.897)	0.855 (0.829-0.881)	0.777 (0.771-0.783)	0.120 (0.111-0.129)	0.993 (0.992-0.995)	0.888 (0.880-0.896)	0.828 (0.807-0.848)	0.799 (0.795-0.803)	0.131 (0.124-0.138)	0.992 (0.991-0.993)
DLM using 6-lead ECG	0.871 (0.859-0.882)	0.807 (0.778-0.836)	0.785 (0.779-0.791)	0.118 (0.109-0.127)	0.991 (0.990-0.993)	0.880 (0.871-0.889)	0.824 (0.803-0.844)	0.795 (0.791-0.799)	0.128 (0.121-0.136)	0.992 (0.991-0.993)
DLM using single-lead ECG	0.854 (0.842-0.867)	0.782 (0.751-0.812)	0.772 (0.766-0.778)	0.109 (0.100-0.117)	0.990 (0.988-0.992)	0.879 (0.870-0.887)	0.836 (0.816-0.856)	0.782 (0.778-0.786)	0.123 (0.116-0.130)	0.992 (0.991-0.993)

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Figure 2 Sensitivity map of deep learning based model for detecting hypoalbuminemia

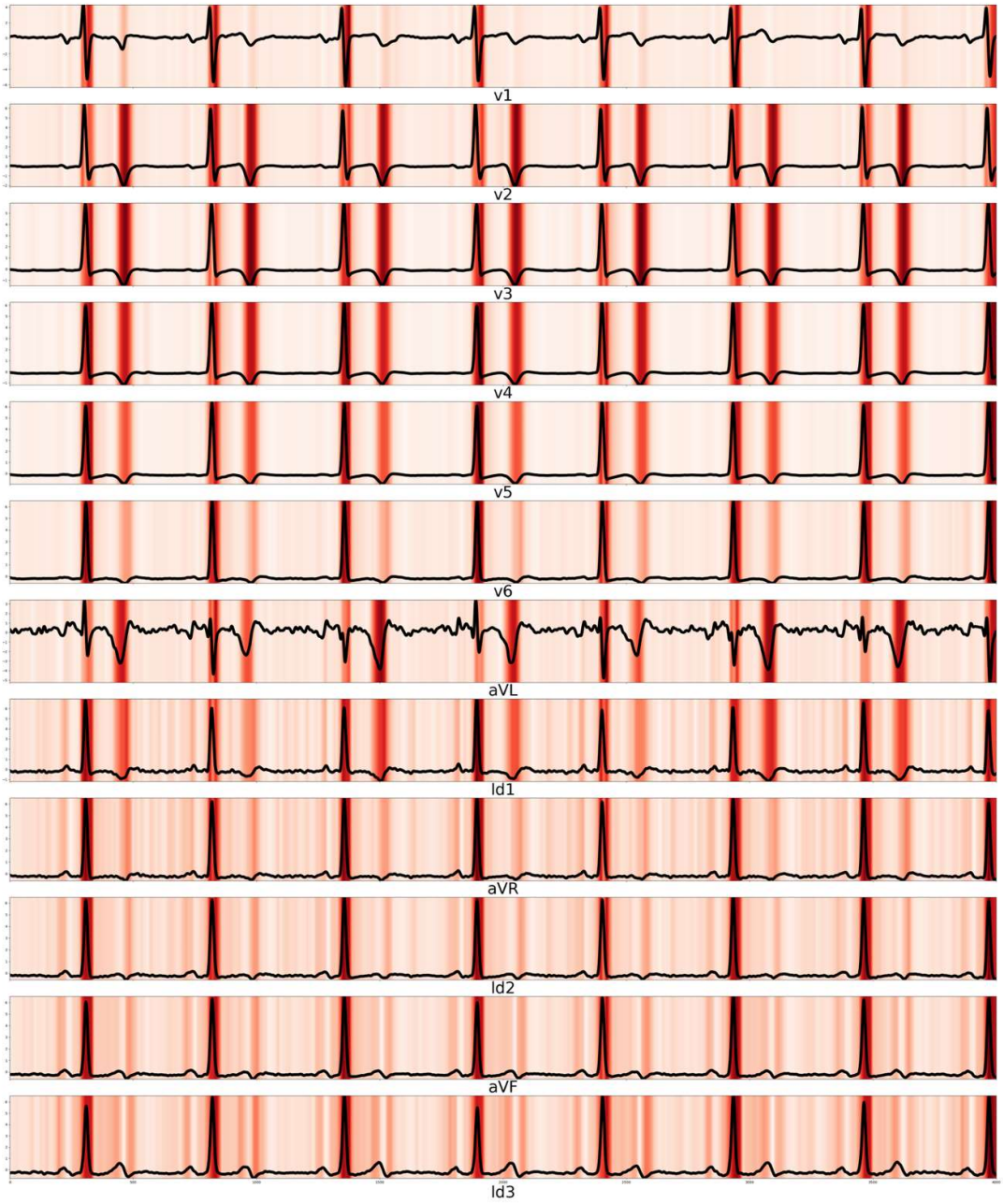

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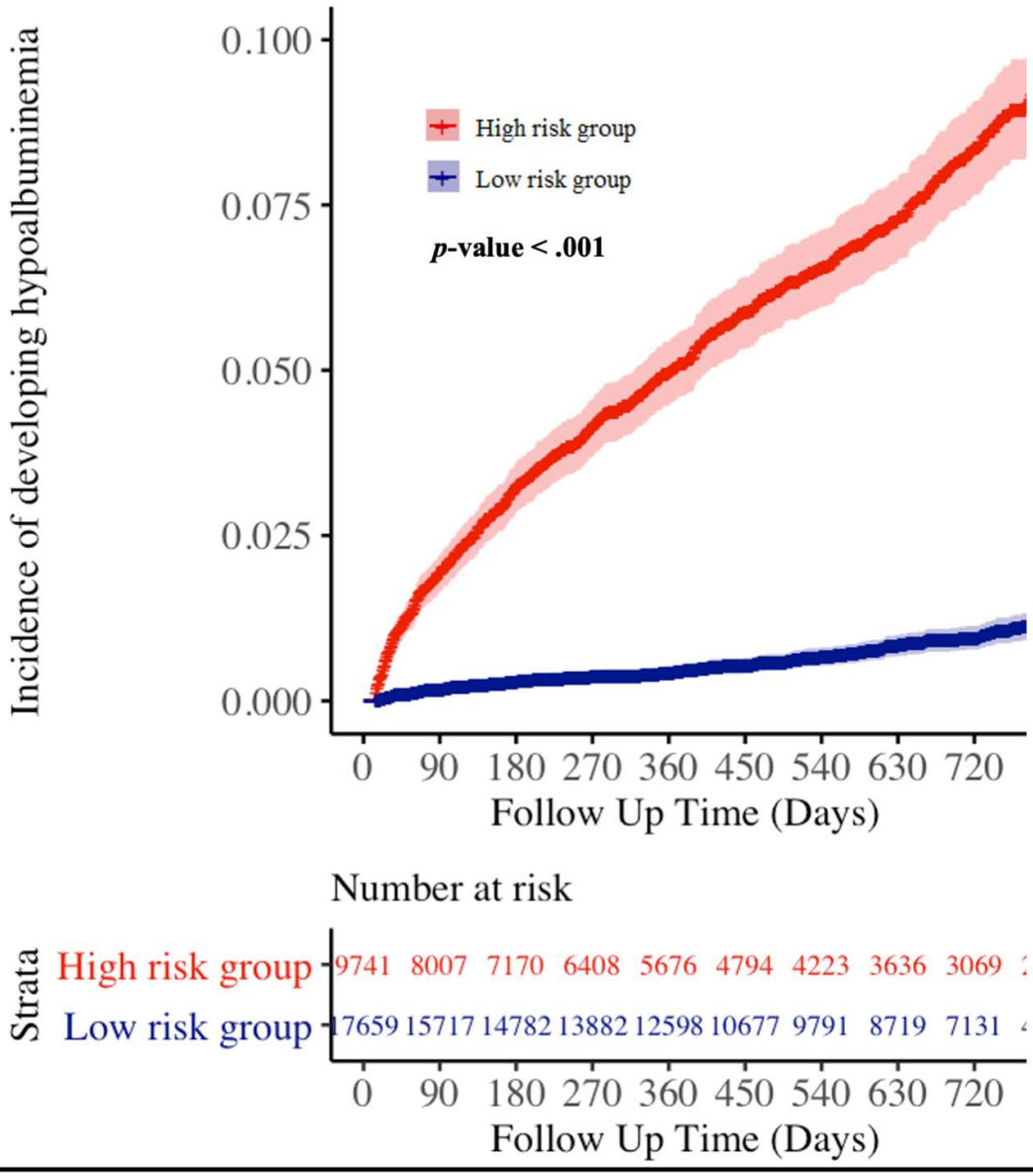
Figure 3 Cumulative hazard of developing hypoalbuminemia in patients with an initially normal



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