THE TEXAS HEART INSTITUTE® JOURNAL

Clinical Investigation

A Proposed Genetic Risk Score for Dilated Cardiomyopathy Susceptibility in the Chinese Han Population

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Abstract

Background: Dilated cardiomyopathy (DCM) is one of the most common types of cardiomyopathies. The current study constructs a proposed genetic risk score and assesses its potential as a predictive tool for individual DCM susceptibility.

Methods: A total of 1,000 patients with idiopathic DCM and 828 control participants from the study institution were enrolled. The top 25 up-regulated and down-regulated genes from tandem mass spectrometry analysis of 6 hearts with DCM and 7 control hearts (from a study by Chen et al) were selected for logistic analysis using whole-exome sequencing data. Statistically significant variants were prepared for genetic risk score construction. The predictive power of the genetic risk score and a composite variable for DCM risk were evaluated using receiver operating characteristic curve analysis.

Results: A total of 5 variants associated with DCM susceptibility were identified to develop the genetic risk score. A score of at least 6.4 was more strongly associated with increased risk of DCM (odds ratio, 2.4; $P < .001$) than scores lower than 6.4. Statistical significance remained evident in multivariate analysis after adjusting for traditional risk factors, including age, sex, hypertension, diabetes, and smoking status (odds ratio, 2.54; $P < .001$). Individuals with a score of at least 6.4 exhibited a decrease in left ventricular ejection fraction and an increase in left ventricular end-diastolic diameter compared with individuals with a score lower than 6.4 ($P < .001$). Stratification by age, sex, history of hypertension, diabetes, and smoking status did not substantially affect the association between genetic risk score and the risk of DCM. The discriminant power of the genetic risk score is excellent, with a C statistic of 0.72.

Conclusion: The genetic risk score, which consists of 5 variants, could effectively identify individuals at high risk of DCM in the study population and aid in the implementation of early prevention strategies in clinical practice.

Keywords: Cardiomyopathy, dilated; genetic risk score; prediction algorithms; risk

Introduction

Dilated cardiomyopathy (DCM) is a condition characterized by left ventricular dilation and impaired contractile function that could not be exclusively attributed to coronary arterial injury or abnormal loading condition, with a prevalence of up to 1 in 2,500 in the general population.[1] As the third-most common

Citation: Lan J, Wang L, Qiu G, Wang S, Yang C, Ran M, Li H, Li S. A proposed genetic risk score for dilated cardiomyopathy susceptibility in the Chinese Han population. *Tex Heart Inst J*. 2025;52(1):e248525. doi:10.14503/THIJ-24-8525
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cause of heart failure, DCM is associated with a poor overall prognosis, with a high risk of mortality.[2] Dilated cardiomyopathy can be attributed to genetic and nongenetic causes.[3] When it has a genetic cause, DCM is characterized as a genetically heterogeneous disease with a complex etiology.[4] Previous reports have suggested that inflammation, autoimmune diseases, toxic and metabolic damage, and heredity might participate in the process of DCM.[5-7]

Numerous genetic studies on DCM have been conducted. These studies have identified more than 100 genes that are associated with the DCM phenotype, most of which encode proteins related to the sarcomere, cytoskeleton, sarcolemma, nucleus, and nuclear lamina.[8] Many common genetic variants in DCM-related genes have been found to be associated with susceptibility to and the prognosis of DCM.[4,8,9] For instance, Shen et al[4] found that the rs237028 variant in the *TAB2* gene was associated with DCM susceptibility and prognosis in the Chinese population. In a cohort study involving 341 patients with DCM and 381 control patients, the variants rs17083838 and rs7992670 in the *CDK8* gene were shown to be related to the risk of and prognosis for DCM.[9] In addition, the rs243865-C allele in the *MMP2* gene was found to be correlated with an increased susceptibility to and mortality risk from DCM.[8] These studies, however, primarily focused on individual variants, most of which had modest or small effects on predicting susceptibility to DCM. It is therefore crucial to develop a DCM-related genetic risk score and assess the cumulative effects of multiple genetic loci on susceptibility to DCM.

The cytoskeleton plays a crucial role in maintaining cell structure and integrity.[10] A substantial body of evidence has demonstrated the major involvement of cytoskeletal and cytoskeletal-related proteins in the pathogenesis of DCM.[11-14] In a study conducted by Chen et al,[15] mass spectrometry was used to analyze 34 human hearts, revealing that the up-regulation and stabilization of the cytoskeleton were the prominent features of end-stage heart failure in humans. This study compared the proteomic profiles of DCM and normal hearts; importantly, it showed that the top 25 up-regulated and down-regulated proteins were associated with the cytoskeleton.[15]

Given the importance of cytoskeletal and cytoskeletal-related proteins in DCM, the current study aimed to construct a genetic risk score for susceptibility to DCM by using the differentially expressed genes from Chen et al[15] and the current study's whole-exome sequencing (WES) data.

Key Points

- The authors of this study developed a proposed genetic risk score consisting of 5 variants for the risk of DCM.
- A genetic risk score of at least 6.4 was strongly associated with increased risk of DCM (OR, 2.40 [95% CI, 1.99-2.90], $P < .001$) compared with a score lower than 6.4.
- The composite variable, which combines the genetic risk score with age, sex, history of hypertension, diabetes, and smoking status, could substantially improve the score's predictive ability for DCM risk.

Abbreviations

DCM, dilated cardiomyopathy
LVEDD, left ventricular end-diastolic diameter
LVEF, left ventricular ejection fraction
OR, odds ratio
ROC, receiver operating characteristic
WES, whole-exome sequencing

Supplementary Materials

For supplemental materials, please see the online version of this article.

Patients and Methods

Study Participants

This study enrolled 1,000 patients with idiopathic DCM and 828 control participants from the Cardiology Division of Tongji Hospital in Wuhan, China, between March 2013 and June 2020. These patients were diagnosed with DCM according to the modified version of standardized diagnostic criteria for DCM.[16] Individuals with a history of cardiac valve disease, coronary heart disease, hypertension, tachyarrhythmia, congenital heart disease, pericardial disease, acute viral myocarditis, heavy alcohol intake, skeletal myopathies, systemic diseases of a putative autoimmune origin, diabetes, and nutrition disorders were excluded from the study. Control participants had no history of cardiac disease or cardiac dysfunction. Echocardiography was performed on all participants to assess their heart function. This study adhered to the principles outlined in the Declaration of Helsinki and was approved by the Review Board of Tongji Hospital. Informed consent was obtained from all patients.

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Whole-Exome Sequencing

Genomic DNA was extracted from the peripheral blood leukocytes using the FastPure Cell/Tissue DNA Isolation Mini Kit (Vazyme International LLC) and the commercially available TIANamp Genomic DNA Kit (Tiangen Biotech [Beijing] Co, Ltd). The experimental workflow, sample preparation, and sequencing were performed according to the protocol. All genomic DNA samples were of high quality and assessed through spectrophotometric and electrophoretic analyses. Initially, genomic DNA was fragmented into 300 base pair fragments using an ultrasonicator (Covaris, LLC). Subsequently, the SureSelectXT Human All Exon V6 kit (Agilent Technologies) was employed to prepare the library, capture the target regions, repair and purify fragment ends, and ligate the adapters. These fragments were then amplified using Herculase II Fusion DNA Polymerases (Agilent Technologies). Paired-end sequencing with a read length of 300 base pairs was conducted on the amplicons using an Illumina HiSeq X Ten Sequencing System (Illumina, Inc), following the standard Illumina protocol.

Gene Selection

Chen et al[15] conducted tandem mass spectrometry analysis of 6 hearts with DCM and 7 control hearts. The related data are available in the ProteomeXchange Consortium through the PRIDE partner repository with the dataset identifier PXD008934. In this study, the top 25 up-regulated and down-regulated genes between DCM and controls were found to be associated with the cytoskeleton and were therefore selected for further analysis.

Genetic Risk Score

Common genetic variants with minor allele frequency greater than 0.05 in the selected genes were extracted from the current study's WES data. Logistic regression analysis was conducted to assess the effect of these common variants on DCM risk. Variants in strong linkage disequilibrium with each other ($r^2 > 0.9$) were analyzed using the WES data, and 1 single variant was chosen as the tagged variant for the construction of the genetic risk score. Genotypes with higher susceptibility to DCM were assigned a weighted score of 1 multiplied by the odds ratio (OR), while the rest were given a weighted score of 1. The weighted scores from the selected variants were then summed for each patient and employed to predict their individual risk of developing DCM.

Statistical Analysis

Data analyses were conducted with SPSS, version 26.0, statistical software (IBM Corp). Distribution of normality was tested using the Shapiro-Wilk test. Abnormally distributed quantitative data were presented as median (IQR), normally distributed quantitative data were presented as mean (SD), and categorical variables were presented as numbers (percentages). Differences between groups were assessed using appropriate statistical tests, including the χ^2 test, independent-sample *t* test, or the Mann-Whitney *U* test. Linkage disequilibrium was calculated using Haploview, version 4.1 (Broad Institute). Logistic regression was used to assess the association of common variants and genetic risk score with the susceptibility to DCM. Adjusted variables included age, sex, hypertension, diabetes, and smoking status. All comparisons were 2 sided, and a significance level of $P < .05$ was considered statistically significant.

Results

Baseline Characteristics of the DCM and Control Groups

The baseline characteristics of patients with DCM and control participants are presented in Table I. There were no statistically significant differences in age and sex between the patients with DCM and control participants. Patients with DCM had statistically lower systolic blood pressure, diastolic blood pressure, left ventricular ejection fraction (LVEF), total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol than did the control participants ($P < .05$). Conversely, the level of left ventricular end-diastolic diameter (LVEDD) and the proportion of individuals with hypertension, diabetes, β-blocker use, and smoking were much higher in the DCM group than in the control group ($P < .05$).

Associations of Variants in Selected Genes With Susceptibility to DCM

Based on the results of Chen et al,[15] the top 25 up-regulated and down-regulated genes between patients with DCM and control participants are displayed in Supplemental Table I. Analysis of WES data revealed a total of 1 and 7 common variants within the selected genes associated with DCM risk in dominant and recessive models, respectively (Supplemental Tables II and III). Because rs10160013, rs3740002, and rs3740003

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TABLE I. Baseline Characteristics of the Study Population

Characteristic	Population with DCM (n = 1,000)	Control population (n = 828)	*P* value
Sex, No. (%)			.64
Male	744 (74.4)	608 (73.4)	
Female	256 (25.6)	220 (26.6)	
Age, mean (SD), y	56.9 (14.2)	57.6 (9.9)	.23
Systolic blood pressure, mean (SD), mm Hg	128.5 (40.6)	137.4 (25.6)	<.001
Diastolic blood pressure, mean (SD), mm Hg	80.7 (17.2)	82.6 (12.6)	.006
LVEF, mean (SD), %	34.9 (12.7)	63.6 (7.5)	<.001
LVEDD, mean (SD), mm	63.9 (9.1)	44.7 (5.9)	<.001
Hypertension, No. (%)	391 (39.1)	201 (24.3)	<.001
Diabetes, No. (%)	174 (17.4)	0	<.001
Current smoking status, No. (%)	546 (54.6)	292 (35.3)	<.001
β-blocker use, No. (%)	737 (73.7)	0	<.001
Total cholesterol, mean (SD), mg/dL	148 (40)	182 (37)	<.001
Triglycerides, median (IQR), mg/dL	97 (71-142)	115 (80-150)	<.001
High-density lipoprotein cholesterol, mean (SD), mg/dL	37 (14)	53 (13)	<.001
Low-density lipoprotein cholesterol, mean (SD), mg/dL	93 (33)	102 (30)	<.001

DCM, dilated cardiomyopathy; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction.

P < .05 was considered statistically significant.

SI conversion factor: To convert from mm Hg to kPa, multiply by 0.133. To convert from mg/dL to mmol/L for cholesterol types, multiply by 0.0259. To convert from mg/dL to mmol/L for triglycerides, multiply by 0.0113.

exhibited strong linkage disequilibrium with each other ($r^2 > 0.9$), rs10160013 was selected as the representative variant for further genetic risk score development. Although rs1799852 showed statistical significance in both the dominant and the recessive models, it was regarded as a dominant model because it had a smaller *P* value and a higher OR. Finally, 1 variant in the dominant model and 4 variants in the recessive model were identified for the development of the genetic risk score.

Genetic Risk Score Construction

To evaluate the cumulative effects of the 5 variants on a patient's susceptibility to DCM, a genetic risk score for each individual was calculated (Supplemental Table IV). The score ranged from 5.0 to 8.2, with a mean value of 6.6. According to the maximum Youden Index criterion and receiver operating characteristic (ROC) curve analysis, the optimal cutoff value for the genetic risk score to stratify patients into 2 groups was determined to be 6.4 (ie, <6.4 and ≥6.4). As shown in Table II, individuals with a score of at least 6.4 displayed elevated LVEDD and a higher proportion of diabetes, β-blocker use, and DCM compared with individuals with a score below 6.4. Conversely, the group with scores of 6.4 or higher exhibited substantially lower systolic blood pressure, LVEF, total cholesterol, and high-density lipoprotein cholesterol (*P* < .05). Logistic regression analysis further revealed a strong association between higher genetic risk score and an increased risk of DCM (OR, 2.40 [95% CI, 1.99-2.90]; *P* < .001) (Table III). This statistical significance remained evident in multivariate analysis after adjusting for traditional risk factors, including age, sex,

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TABLE II. Baseline Characteristics of Participants, by Genetic Risk Score

Characteristic	<6.4 (n = 1,272)	≥6.4 (n = 556)	*P* value
Sex, No. (%)			.625
Male	945 (74.3)	407 (73.2)	
Female	327 (25.7)	149 (26.8)	
Age, mean (SD), y	57.0 (12.4)	57.8 (12.5)	.256
Systolic blood pressure, mean (SD), mm Hg	133.6 (38.3)	129.9 (25.5)	.037
Diastolic blood pressure, mean (SD), mm Hg	82.0 (15.2)	80.5 (15.6)	.061
LVEF, mean (SD), %	50.7 (17.4)	42.2 (17.3)	<.001
LVEDD, mean (SD), mm	53.0 (11.9)	58.3 (12.5)	<.001
Hypertension, No. (%)	406 (31.9)	186 (33.5)	.519
Diabetes, No. (%)	102 (8.0)	72 (12.9)	<.001
Current smoking, No. (%)	574 (45.1)	264 (47.5)	.352
β-blocker use, No. (%)	463 (36.4)	274 (49.3)	<.001
Total cholesterol, mean (SD) mg/dL	167 (43)	160 (41)	.001
Triglycerides, median (IQR), mg/dL	106 (80-150)	106 (80-150)	.541
High-density lipoprotein cholesterol, mean (SD), mg/dL	46 (16)	42 (14)	<.001
Low-density lipoprotein cholesterol, mean (SD), mg/dL	97 (31)	97 (32)	.886
DCM, No. (%)	599 (47.1)	401 (72.1)	<.001

DCM, dilated cardiomyopathy; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction.

P < .05 was considered statistically significant.

SI conversion factor: To convert from mm Hg to kPa, multiply by 0.133. To convert from mg/dL to mmol/L for cholesterol types, multiply by 0.0259. To convert from mg/dL to mmol/L for triglycerides, multiply by 0.0113.

TABLE III. Logistic Regression Analysis for Groups With Different Genetic Risk Scores

	Score	Odds ratio	95% CI	*P* value
Unadjusted	<6.4	[Reference]	[Reference]	[Reference]
	≥6.4	2.4	1.99-2.90	<.001
Adjusted[a]	<6.4	[Reference]	[Reference]	[Reference]
	≥6.4	2.54	2.07-3.11	<.001

[a] Adjusted variables included age, sex, hypertension, diabetes, and smoking status.

P < .05 was considered statistically significant.

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hypertension, diabetes, and smoking status (OR, 2.54 [95% CI, 2.07-3.11]; $P < .001$).

The study population was subsequently randomly assigned to a training group (914 individuals) or a validation group (914 individuals). Logistic regression analysis demonstrated that the genetic risk score was strongly associated with the risk of DCM in both the training group (OR, 2.15 [95% CI, 1.65-2.81]; $P < .001$) and the validation group (OR, 2.68 [95% CI, 2.04-3.50]; $P < .001$) (Table IV).

In addition, a subgroup analysis was conducted to further evaluate the associations between the genetic risk score and susceptibility to DCM within different clinically relevant subgroups. Figure 1 illustrates that stratification by age, sex, history of hypertension, diabetes, and smoking did not substantially affect the association between a patient's genetic risk score and risk of DCM.

Association Between Genetic Risk Score and Echocardiographic Parameters

Echocardiographic parameters were compared between individuals in different genetic risk score groups. As shown in Figure 2, individuals in the group with scores of 6.4 or higher exhibited a decrease in LVEF and an increase in LVEDD compared with individuals in the group with scores below 6.4 ($P < .001$).

ROC Curve Analysis

Receiver operating characteristic curve analysis was conducted to evaluate and compare the predictive abilities of the genetic risk score and the composite variable (score combined with age, sex, history of hypertension, diabetes, and smoking status) for DCM risk. As shown in Figure 3 and Table V, the average area under the ROC curve for the genetic risk score and for the composite variable were 0.72 (95% CI, 0.70-0.74) and 0.83 (95% CI, 0.81-0.85), respectively. The composite variable exhibited superior predictive power compared with the genetic risk score ($P < .001$). The predictive efficacy of the genetic risk score and the composite variable for DCM were also assessed within the training and validation groups. As illustrated in Table VI, the average area under the ROC curve for the genetic risk score surpassed 0.7 in both groups. The ROC curve for the composite variable exceeded 0.8, as well, indicating a statistically significantly superior predictive capability for DCM compared with the genetic risk score ($P < .001$).

Discussion

The present study continuously recruited 1,000 patients with DCM and 828 control participants. Association analyses were performed to investigate the relationship between the genetic risk score, which consists of 5 variants, and an individual's susceptibility to DCM. Study findings demonstrated that higher genetic risk scores were associated with increased susceptibility to DCM. Individuals with a score of at least 6.4 further exhibited a decrease in LVEF and an increase in LVEDD compared with individuals whose score was less than 6.4. Stratification by age, sex, history of hypertension, diabetes, and smoking status had no statistically significant impact on the association between genetic risk score and an individual's risk of DCM. In addition, the compos-

TABLE IV. Logistic Regression Analysis for Groups With Different Genetic Risk Scores Using Cross-Validations

		Score	Odds ratio	95% CI	*P* value
Training group	Unadjusted	<6.4	[Reference]	[Reference]	[Reference]
		≥6.4	2.15	1.65-2.81	<.001
	Adjusted[a]	<6.4	[Reference]	[Reference]	[Reference]
		≥6.4	2.27	1.71-3.01	<.001
Validation group	Unadjusted	<6.4	[Reference]	[Reference]	[Reference]
		≥6.4	2.68	2.04-3.50	<.001
	Unadjusted	<6.4	[Reference]	[Reference]	[Reference]
		≥6.4	2.68	2.04-3.50	<.001

[a] Adjusted variables included age, sex, hypertension, diabetes, and smoking status.

$P < .05$ was considered statistically significant.

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Characteristics	Patients with DCM, No.	Total participants, No.	OR (95% CI)
Sex			
Male	742	1352	2.48 (1.99-3.09)
Female	258	476	2.18 (1.51-3.15)
Age, y			
<60	516	997	2.38 (1.85-3.07)
≥60	484	831	2.45 (1.85-3.25)
Hypertension			
No	612	1236	2.75 (2.19-3.46)
Yes	388	592	1.93 (1.37-2.72)
Diabetes			
No	913	1653	2.34 (1.92-2.85)
Yes	87	174	3.14 (1.69-5.84)
Smoking			
No	458	990	3.03 (2.34-3.93)
Yes	542	838	1.89 (1.42-2.52)

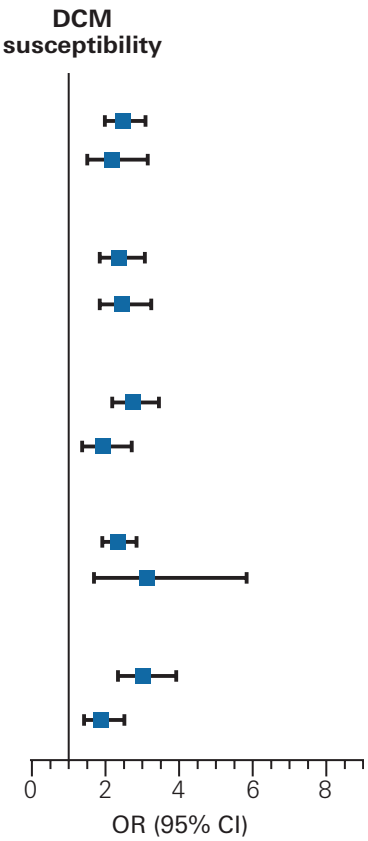

Fig. 1 A forest plot for subgroup analysis indicates that stratification by age, sex, history of hypertension, diabetes, and smoking status did not strongly affect the association between an individual's genetic risk score and risk of DCM.

DCM, dilated cardiomyopathy; OR, odds ratio.

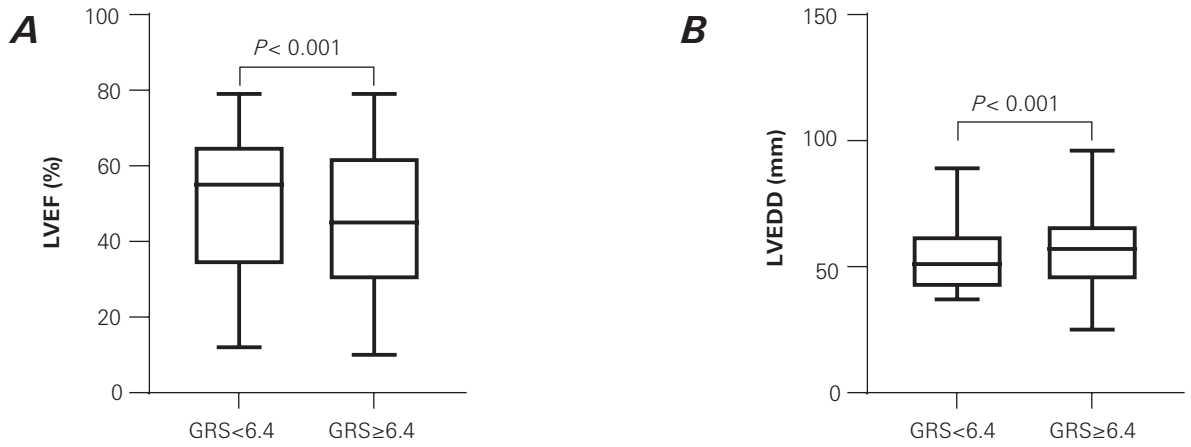

Fig. 2 Comparison of echocardiographic parameters indicates that individuals in the group with genetic risk scores of 6.4 or higher exhibited **(A)** a decrease in LVEF and **(B)** an increase in LVEDD compared with individuals with scores below 6.4 ($P < .001$).

LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction.

$P < .05$ was considered statistically significant.

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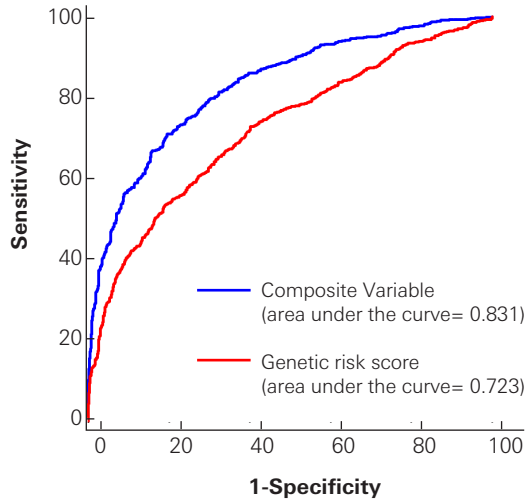

Fig. 3 Receiver operating characteristic curves for dilated cardiomyopathy risk indicate that the composite variable (genetic risk score combined with age, sex, history of hypertension, diabetes, and smoking status) exhibit superior predictive power compared with genetic risk score.

TABLE V. Analysis of the ROC Curve for Predictive Power of DCM Susceptibility

	Area under the curve	SE	95% CI
Genetic risk score	0.72	0.01	0.70-0.74
Composite variable	0.83	0.01	0.81-0.85

DCM, dilated cardiomyopathy; ROC, receiver operating characteristic.

TABLE VI. Analysis of the Receiver Operating Characteristic Curve in the Training and Validation Groups

Dataset	Variable	Area under the curve (95% CI)	Accuracy (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Training group	Genetic risk score	0.71 (0.68-0.74)	0.66 (0.63-0.69)	0.78 (0.74-0.82)	0.56 (0.51-0.60)
	Composite variable	0.83 (0.81-0.86)	0.77 (0.74-0.80)	0.77 (0.73-0.81)	0.77 (0.73-0.81)
Validation group	Genetic risk score	0.73 (0.69-0.76)	0.66 (0.63-0.69)	0.82 (0.78-0.86)	0.53 (0.48-0.57)
	Composite variable	0.83 (0.80-0.86)	0.76 (0.73-0.78)	0.83 (0.79-0.86)	0.69 (0.65-0.74)

ite variable, which combines the genetic risk score with age, sex, history of hypertension, diabetes, and smoking status, could substantially improve the predictive ability for DCM risk.

Dilated cardiomyopathy is a common cause of heart failure and associated with high mortality.[2,3] In recent years, several genetic variants linked to DCM susceptibility have been identified. Most of these risk loci, however, have only modest or small effects on predicting DCM susceptibility, with ORs for DCM risk not exceeding 2.[1,4,17,18] For instance, Shen et al[4] reported an association between rs237028 and DCM susceptibility. Its effect is limited, however, with the OR ranging from 1.42 to 1.73 in different models. In a study involving 488 patients with DCM and 924 control participants, the OR of the risk locus for DCM was only 1.42.[18] A study by Zhang et al[17] found that *LGALS3* gene polymorphisms may be associated with susceptibility to DCM in a Northern Han Chinese population. Their study, however, included only 279 patients with unrelated clinically diagnosed DCM and 363 apparently control participants, which limits the generalization of their results to other populations. The current study's objective was to therefore comprehensively construct a genetic risk score for assessing an individual's risk of DCM.

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First, this study was based on the data from tandem mass spectrometry analysis of 6 hearts with DCM and 7 control hearts as well as on the WES of 1,000 patients with DCM, allowing for a comprehensive assessment of variants associated with the risk for DCM.

Second, this study included a larger population with DCM than did previous investigations.[9,19,20] For example, Shah et al[20] included only 352 patients with DCM and 352 control participants. Another case-control study enrolled 369 control participants and 373 patients with DCM for analysis.[19] The larger sample size in the current study may enhance the reliability of its conclusions and facilitate their generalization to other populations.

Third, the current study's genetic risk score was constructed with a total of 5 variants, which represented the first genetic risk score study of susceptibility to DCM. The genetic risk score in the current study demonstrated excellent risk discrimination, with a C statistic of 0.72. Individuals with a score of at least 6.4 exhibited a 2.4-fold higher risk of DCM compared with individuals with a score below 6.4. The prediction ability of the current study's genetic risk score was independent of traditional risk factors. In addition, a higher score was correlated with reduced LVEF and increased LVEDD, underscoring its critical role in predicting DCM. Notably, the composite variable, combining the genetic risk score with other variables, improved the score's discrimination ability, with a C statistic of up to 0.83. This risk stratification for DCM susceptibility can aid in identifying individuals at high risk of DCM and facilitate early prevention strategies.

Limitations

The current study has several limitations. First, it was a single-center study with 1 cohort, which limits the generalizability of its findings. Although the results were statistically significant, further validation of the genetic risk score through larger, multicenter studies is warranted. Second, the current study was of the Chinese population, which may limit the generalizability of the results to individuals from other racial backgrounds. Verification of the results in diverse populations or among different ancestries is essential. Third, the small sample size used for candidate gene selection may have influenced the accuracy of estimating the impact of individual variants on the risk of DCM. Additional validation, however, can be achieved by filtering notable variants located within or near these genes. Fourth, the study did not incorporate family history indices into the traditional risk assessment. Information about the disease and its direct correlations is often ambiguous, potentially due to variations in the quality of medical care provided at different historical time points. Finally, the study did not take into account multiple testing to ensure sufficient variants for genetic risk score construction.

Conclusion

The proposed genetic risk score consisting of 5 variants exhibited a strong association with susceptibility to DCM within the study population. This innovative risk stratification tool has the potential to effectively identify individuals at high risk of DCM and aid in the implementation of early prevention strategies in clinical practice.

Article Information

Published: 16 May 2025

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Author Contributions: All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Jianjun Lan, Lin Wang, Guoyuan Qiu, Shihai Wang, Chao Yang, and Mengnian Ran. The first draft of the manuscript was written by Shiyang Li and Hongyu Li, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflict of Interest Disclosure: None declared.

Funding/Support: This work was supported by the Sichuan Medical Association Program (No. S20020 and S22076).

Statement of Ethics: This study protocol was reviewed and approved by the Review Board of Tongji Hospital, approval number 20200012. Written informed consent was obtained from all adults participating in this study.

Data Availability Statement: The data that support the findings of this study are not publicly available because they contain information that could compromise the privacy of research participants but are available on request from the corresponding author.

Acknowledgments: The authors would like to thank the staff of the Division of Cardiology at Panzhihua Central Hospital for their help in the recruitment of patients with DCM.

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