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Original Article

Plasma SFRP2 hypermethylation as a diagnostic biomarker for dilated cardiomyopathy detected by methylation-specific PCR

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Abstract: Objective: To investigate the clinical utility of plasma Secreted Frizzled-Related Protein 2 (SFRP2) gene hypermethylation as a non-invasive epigenetic biomarker for diagnosing Dilated cardiomyopathy (DCM) and stratifying cardiac function. Methods: A retrospective cohort of 482 participants (241 DCM patients and 241 healthy controls) was analyzed. DCM patients were further stratified by New York Heart Association (NYHA) class into better cardiac function (BCF; NYHA I-II) and poor cardiac function (PCF; NYHA III-IV) groups. Methylation-specific polymerase chain reaction (MSP) was used to assess SFRP2 methylation levels. Statistical analyses evaluated its diagnostic value, including receiver operating characteristic (ROC) curve analysis to determine sensitivity and specificity. Results: Plasma SFRP2 methylation levels were significantly higher in DCM patients than in controls ($P < 0.001$). ROC analysis revealed an area under the curve (AUC) of 0.942, indicating excellent diagnostic performance. Among DCM patients, the PCF group exhibited significantly higher SFRP2 methylation levels compared to the BCF group ($P < 0.001$). Additionally, SFRP2 methylation showed a strong positive correlation with worsening cardiac function ($r = 0.786$, $P < 0.001$). Conclusion: Elevated plasma SFRP2 methylation levels in DCM patients, particularly those with poor cardiac function, demonstrate its high diagnostic accuracy and potential to reflect disease severity, supporting its use as a non-invasive clinical biomarker for DCM diagnosis and risk stratification.

Keywords: Dilated cardiomyopathy, SFRP2 methylation, biomarker, cardiac function, diagnostic value, heart failure

Introduction

Dilated cardiomyopathy (DCM) is a critical subset of cardiomyopathies characterized by left ventricular enlargement and impaired systolic function, often leading to congestive heart failure and sudden cardiac death. Despite advances in understanding and treating heart failure, DCM remains a significant global health concern due to its high morbidity and mortality rates, underscoring the need for improved diagnostic and therapeutic strategies [1, 2]. Traditionally, the diagnosis and classification of DCM rely heavily on echocardiographic evaluations [3], such as measurements of left ventricular ejection fraction (LVEF), and clinical assessments based on the New York Heart Association (NYHA) functional classification system [4]. Although these methods are clinically useful, they exhibit limited specificity and often fail to identify subclinical disease or accurately predict disease progression.

Recent research has focused on the role of epigenetic modifications, particularly DNA methylation, in the pathogenesis of cardiovascular diseases. DNA methylation, predominantly occurring at CpG dinucleotides, acts as an epigenetic regulator that modulates gene expression without altering the DNA sequence. In the context of DCM, aberrant methylation patterns may provide insights into disease mechanisms

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and facilitate the development of novel biomarkers [5-7]. Secreted frizzled-related protein 2 (SFRP2), an inhibitor of the Wnt signaling pathway, has emerged as a pivotal molecule due to its roles in cellular proliferation, differentiation, and apoptosis, which are essential processes in cardiac development and repair [8].

The Wnt signaling pathway is known to be active in various cardiac pathologies, including heart failure, where it promotes maladaptive cardiac remodeling by stimulating fibroblast proliferation and enhancing extracellular matrix deposition [9, 10]. Dysregulation or hyperactivation of this pathway via epigenetic mechanisms plays a critical role in disease progression. For example, hypermethylation of SFRP2 may exacerbate pathological remodeling in DCM by reducing cardiomyocyte survival and increasing fibrosis, a hallmark of DCM progression [11]. Therefore, investigating the methylation status of SFRP2 in DCM patients is of significant interest.

This study focuses on assessing the methylation status of SFRP2 in the plasma of patients with DCM using methylation-specific polymerase chain reaction (MSP), a sensitive technique for detecting methylation patterns in cell-free circulating DNA.

Materials and methods

Study design

This study conducted a retrospective analysis of 482 participants who underwent MSP testing at JiuJiang No. 1 People's Hospital between January 2021 and December 2023. The study population included 241 individuals with a confirmed diagnosis of DCM and 241 matched healthy controls.

Inclusion criteria for DCM patients: (1) Diagnosed with dilated cardiomyopathy, defined as a left ventricular end-diastolic diameter (LVEDD) > 5.0 cm or left ventricular end-systolic diameter (LVESD) > 3.8 cm, with a left ventricular ejection fraction (LVEF) < 45%, and no definitive evidence of coronary artery disease, hypertensive heart disease, valvular heart disease, or other identifiable causes [12, 13]; (2) Age ≥ 18 years; (3) NYHA functional class I-IV; (4) Availability of complete medical records.

Exclusion criteria for DCM patients: (1) Presence of other cardiac diseases (e.g., ischemic heart disease, hypertrophic cardiomyopathy), malignancies, history of heart transplantation, ventricular aneurysm resection, or ventricular assist device implantation; (2) Current use of glucocorticoids, immunosuppressants, or drugs known to affect epigenetic regulation; (3) Pregnancy, breastfeeding, or planned pregnancy during the study period; (4) Receipt of radiotherapy, chemotherapy, or other treatments potentially altering DNA methylation within the past 12 months; (5) Severe psychiatric disorders (e.g., schizophrenia, major depressive disorder) or cognitive impairments affecting participation.

Inclusion criteria for non-DCM controls: (1) No structural heart disease, coronary artery disease, hypertension, or valvular disease; (2) Age ≥ 18 years; (3) No heart failure symptoms (NYHA class I); (4) Availability of complete medical records.

Exclusion criteria for non-DCM controls: (1) Any cardiovascular disease, uncontrolled hypertension, or diabetes with complications; (2) Use of cardiac medications or drugs affecting epigenetic regulation; (3) Malignancy, recent chemotherapy or radiotherapy, or major surgery; (4) Pregnancy, severe psychiatric disorders, or cognitive impairment.

This study was approved by the Ethics Review Committee and Institutional Review Board of JiuJiang No. 1 People's Hospital. Blood samples were obtained from the hospital's sample bank.

Participant selection criteria and data sources

DCM patients were grouped into a DCM cohort, while healthy subjects formed the non-DCM cohort. Within the DCM cohort, participants were further stratified based on cardiac function severity, as assessed by the NYHA functional classification system. This system categorizes patients into four classes reflecting limitations in physical activity, ranging from Class I (no limitation) to Class IV (symptoms at rest).

(1) Class I: No limitation of physical activity; ordinary activity does not cause undue fatigue, palpitations, or dyspnea. (2) Class II: Slight limitation of physical activity; comfortable at rest,

but ordinary activity results in fatigue, palpitations, or dyspnea. (3) Class III: Marked limitation of physical activity; comfortable at rest, but less-than-ordinary activity causes symptoms. (4) Class IV: Unable to carry out any physical activity without discomfort; symptoms of heart failure present even at rest.

Based on NYHA classification, the DCM group was subdivided into two subgroups: the better cardiac function (BCF) group (NYHA I-II, n = 151) and the poor cardiac function (PCF) group (NYHA III-IV, n = 90).

Gene methylation analysis

Venous blood samples (5 mL) were collected from fasting participants in the morning upon admission. Samples were centrifuged at 3,000 rpm for 10 minutes using a TLD 12A refrigerated high-speed centrifuge (Hunan Xiangxi Scientific Instrument Factory, China). Plasma was separated and stored at -80°C. Cell-free circulating DNA was extracted using the GeneJET Whole Blood Genomic DNA Purification Kit (K0712, Thermo Fisher Scientific Inc., USA) and underwent bisulfite conversion.

Two sets of primers were designed to specifically detect bisulfite-treated DNA templates: one for methylated sites (MSP-M/F: 5'-TGGGTTAAGAGATTATGAAGGAGGTGTTG-3'; MSP-M/R: 5'-CTCAACCCAACAAAAAATAAAAAAACAA-3') and another for unmethylated sites (MSP-U/F: 5'-TTGGGTTAAGAGATTATGAAGGAGGTGTTT-3'; MSP-U/R: 5'-CTCAACCCAACAAAAAATAAAAAAATAA-3'). PCR amplification was performed using these primers, with each system containing positive controls (known methylated or unmethylated DNA samples), negative controls (no-template controls), and experimental samples. Presence of methylated target genes was confirmed via agarose gel electrophoresis, and methylation levels were quantified using real-time quantitative PCR (qPCR) with a MA-1640Q instrument (Suzhou Yary Biotechnology Co., Ltd., China).

Patient demographic data, baseline disease characteristics, gene methylation levels, and clinical information were retrieved from electronic medical records. Baseline cardiac parameters were assessed via echocardiography (Consona AT system, Mindray Medical International Co., Ltd., China), including LVEF, LVEDD, left atrial diameter (LAD), and left atrial volume index (LAVI). Physiological monitoring was conducted using a multi-parameter monitor (IntelliVue MX40, Philips Healthcare, Netherlands) to record heart rate, systolic blood pressure, and diastolic blood pressure.

Statistical analysis

All analyses were performed using SPSS version 29.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were summarized as counts and percentages [n (%)], with chi-square tests used for comparisons. Continuous variables were tested for normality using the Shapiro-Wilk test. Normally distributed data were expressed as means ± standard deviations (M ± SD) and compared using independent samples t-tests. Statistical significance was set at $P < 0.05$. Diagnostic accuracy was assessed using receiver operating characteristic (ROC) curve analysis. Pearson's correlation was applied to normally distributed continuous variables, while Spearman's rank correlation was used for non-parametric or categorical data.

Results

Comparison of baseline characteristics between the non-DCM and DCM groups

Demographic comparisons revealed no significant differences in age, gender, BMI, prevalence of diabetes, smoking or alcohol history, education level, or marital status (all $P > 0.05$; **Table 1**). However, hypertension prevalence was significantly higher in the DCM group (39.83%) compared to the non-DCM group (19.92%) ($P < 0.001$), suggesting a potential association between hypertension and DCM. These findings underscore the need for further investigation into the role of hypertension in SFRP2 methylation among DCM patients. See **Table 1**.

Comparison of gene methylation levels between the non-DCM and DCM groups

The study assessed plasma methylation levels of several genes using the MSP method (**Figure 1**). Notably, SFRP2 methylation levels were significantly higher in the DCM group compared to the non-DCM group ($P < 0.001$). The GATA Binding Protein 4 (GATA4) gene also showed a

Table 1. Comparison of demographic characteristics between the non-DCM and DCM groups

Parameters	non-DCM group (n = 241)	DCM group (n = 241)	t/χ^2	P
Age (years)	55.06 ± 5.18	55.89 ± 4.64	1.871	0.062
Male/Female [n (%)]	147 (61%)/94 (39%)	159 (65.98%)/82 (34.02%)	1.289	0.256
BMI (kg/m^2)	23.37 ± 2.16	23.03 ± 2.27	1.660	0.098
Hypertension [n (%)]	48 (19.92%)	96 (39.83%)	22.817	< 0.001
Diabetes [n (%)]	14 (5.81%)	21 (8.71%)	1.510	0.219
Smoking history [n (%)]	57 (23.65%)	69 (28.63%)	1.547	0.214
Drinking history [n (%)]	33 (13.69%)	48 (19.92%)	3.339	0.068
Educational level (high school or below/junior college or above) [n (%)]	24 (9.96%)/217 (90.04%)	31 (12.86%)/210 (87.14%)	1.006	0.316
Marital Status (Married/Unmarried or Divorced) [n (%)]	209 (86.72%)/32 (13.28%)	202 (83.82%)/39 (16.18%)	0.809	0.368

DCM: Dilated Cardiomyopathy, BMI: Body Mass Index.

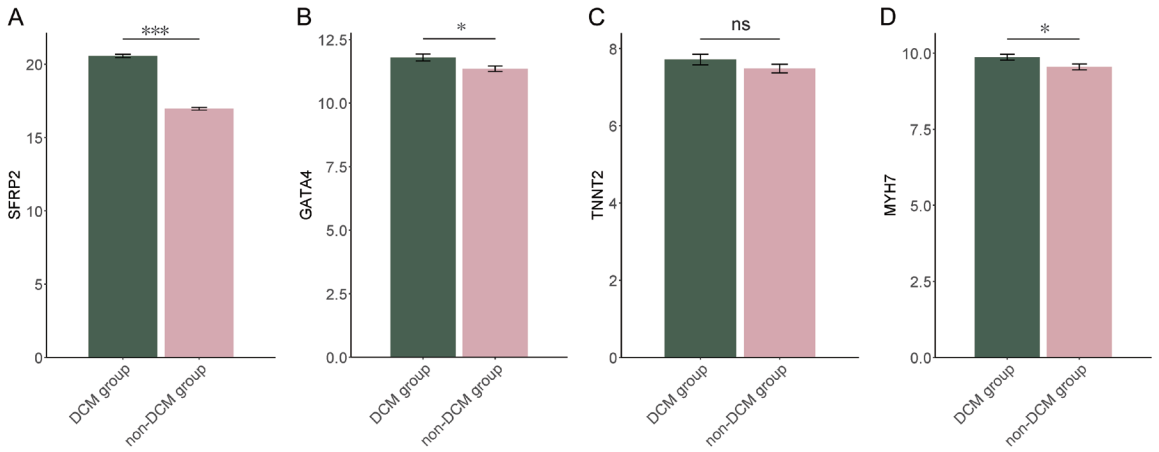

Figure 1. Comparison of gene methylation levels between the non-DCM and DCM groups. A: SFRP2; B: GATA4; C: TNNT2; D: MYH7. DCM: Dilated Cardiomyopathy, SFRP2: Secreted Frizzled-Related Protein 2, GATA4: GATA Binding Protein 4, TNNT2: Troponin T Type 2 (Cardiac), MYH7: Myosin, Heavy Chain 7. ns: No statistically significant difference; *: P < 0.05; ***: P < 0.001.

modest but statistically significant increase in methylation (P = 0.012). MYH7 methylation levels were significantly higher in the DCM group than in controls (P = 0.016). In contrast, TNNT2 methylation levels did not differ significantly between groups (P = 0.175). These results suggest that altered methylation patterns, particularly of SFRP2, may play a role in the pathophysiology and diagnostic assessment of DCM.

Diagnostic performance of gene methylation levels for DCM: ROC analysis

ROC analysis was conducted to evaluate the diagnostic utility of gene methylation levels for DCM (**Figure 2**). SFRP2 methylation exhibited the highest diagnostic value, with an area under the curve (AUC) of 0.942, indicating excellent discriminative ability. The optimal cutoff value for SFRP2 was 18.56, yielding a sensitivity of 0.867 and specificity of 0.909, resulting in a Youden index of 0.776 and an F1 score of 0.886.

In comparison, GATA4 and MYH7 methylation levels demonstrated lower diagnostic performance, with AUCs of 0.570 and 0.569, respectively. For GATA4, the optimal cutoff was 11.975, with sensitivity of 0.506, specificity of 0.664, a Youden index of 0.170, and an F1 score of 0.550. MYH7 had a cutoff value of 9.325, sensitivity of 0.656, specificity of 0.465, a Youden index of 0.121, and an F1 score of 0.598.

Comparison of baseline characteristics between BCF and PCF groups

Demographic characteristics were comparable between the BCF and PCF groups (**Table 2**).

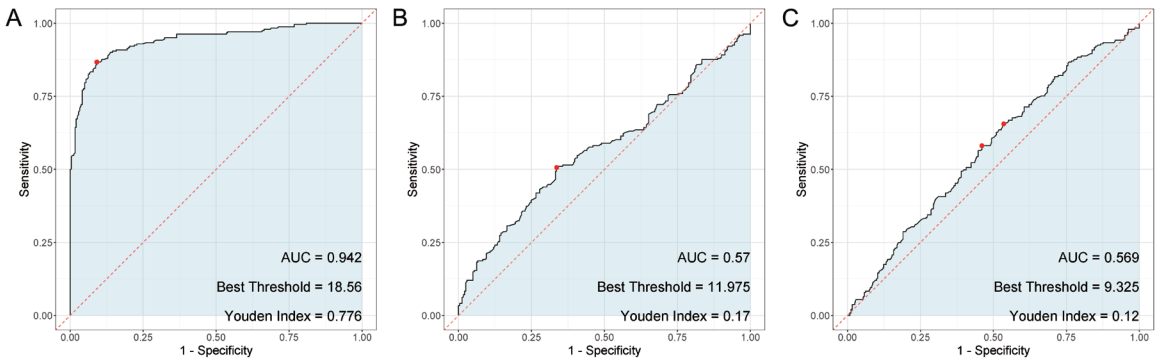

Figure 2. ROC analysis for gene methylation levels in DCM. A: ROC analysis of SFRP2; B: ROC analysis of GATA4; C: ROC analysis of MYH7. DCM: Dilated Cardiomyopathy, SFRP2: Secreted Frizzled-Related Protein 2, GATA4: GATA Binding Protein 4, MYH7: Myosin, Heavy Chain 7.

Table 2. Comparison of demographic characteristics between the BCF and PCF groups

Parameters	BCF group (n = 151)	PCF group (n = 90)	t/χ^2	P
Age (years)	55.74 ± 4.65	56.06 ± 4.17	0.546	0.586
Male/Female [n (%)]	96 (63.58%)/55 (36.42%)	62 (68.89%)/28 (31.11%)	0.705	0.401
BMI (kg/m^2)	22.87 ± 2.13	23.31 ± 2.32	1.492	0.137
Hypertension [n (%)]	55 (36.42%)	39 (43.33%)	1.132	0.287
Diabetes [n (%)]	12 (7.95%)	10 (11.11%)	0.681	0.409
Smoking history [n (%)]	42 (27.81%)	27 (30%)	0.132	0.717
Drinking history [n (%)]	31 (20.53%)	17 (18.89%)	0.095	0.758
Educational level (high school or below/junior college or above) [n (%)]	16 (10.6%)/135 (89.4%)	12 (13.33%)/78 (86.67%)	0.411	0.521
Marital Status (Married/Unmarried or Divorced) [n (%)]	125 (82.78%)/26 (17.22%)	76 (84.44%)/14 (15.56%)	0.113	0.737

BCF: better cardiac function, PCF: poor cardiac function, BMI: Body Mass Index.

There were no significant differences in age (P = 0.586), gender distribution (P = 0.401), BMI (P = 0.137), prevalence of hypertension (P = 0.287), diabetes (P = 0.409), smoking or alcohol history, education level, or marital status (all P > 0.05). This comparability allows for focused analysis of clinical and molecular differences between the groups.

Comparison of cardiac function parameters between BCF and PCF groups

The BCF group demonstrated significantly higher mean LVEF compared to the PCF group (P = 0.007), indicating better cardiac function (**Table 3**). Additionally, LAVI was significantly greater in the BCF group than in the PCF group (P = 0.014). Time since initial DCM diagnosis did not differ significantly (P = 0.261). There were no significant differences in LVEDD (P = 0.499) or LAD (P = 0.468). These findings indicate that LVEF and LAVI variations characterize cardiac function status in DCM patients.

Comparison of clinical characteristics between BCF and PCF groups

Heart rate was comparable between the groups (P = 0.752) (**Table 4**). Similarly, systolic blood pressure showed no significant difference (P = 0.170), and diastolic blood pressure was nearly identical (P = 0.942). These results suggest that heart rate and blood pressure were stable across both groups at baseline and post cardiac function evaluation.

Comparison of gene methylation levels between BCF and PCF groups

SFRP2 methylation levels were significantly higher in the PCF group compared to the BCF group (P < 0.001) (**Figure 3**). In contrast, methylation levels of GATA4, TNNT2, and MYH7 showed no significant differences between groups. These findings suggest that SFRP2 methylation may serve as a potential marker for distinguishing cardiac function status in DCM patients.

Table 3. Comparison of baseline disease characteristics between the BCF and PCF groups

Parameters	BCF group (n = 151)	PCF group (n = 90)	t	P
Time since initial DCM diagnosis (months)	61.26 ± 21.19	64.48 ± 21.77	1.127	0.261
LVEF (%)	26.95 ± 6.36	24.63 ± 6.45	2.721	0.007
LVEDD (mm)	75.77 ± 10.75	74.82 ± 10.47	0.676	0.499
LAD (mm)	51.34 ± 8.56	50.47 ± 9.65	0.727	0.468
LAVI (mL/m^2)	60.46 ± 7.21	58.36 ± 5.82	2.468	0.014

BCF: better cardiac function, PCF: poor cardiac function, DCM: dilated cardiomyopathy, LVEF: left ventricular ejection fraction, LVEDD: left ventricular end-diastolic dimension, LAD: left atrial diameter, LAVI: left atrial indexed volume.

Table 4. Comparison of clinical characteristics between the BCF and PCF groups

Parameters	BCF group (n = 151)	PCF group (n = 90)	t	P
Heart rate (bpm)	69.43 ± 2.65	69.31 ± 3.16	0.317	0.752
Systolic blood pressure (mmHg)	121.54 ± 5.52	120.54 ± 5.37	1.377	0.170
Diastolic blood pressure (mmHg)	75.22 ± 3.53	75.25 ± 3.26	0.073	0.942

BCF: better cardiac function, PCF: poor cardiac function.

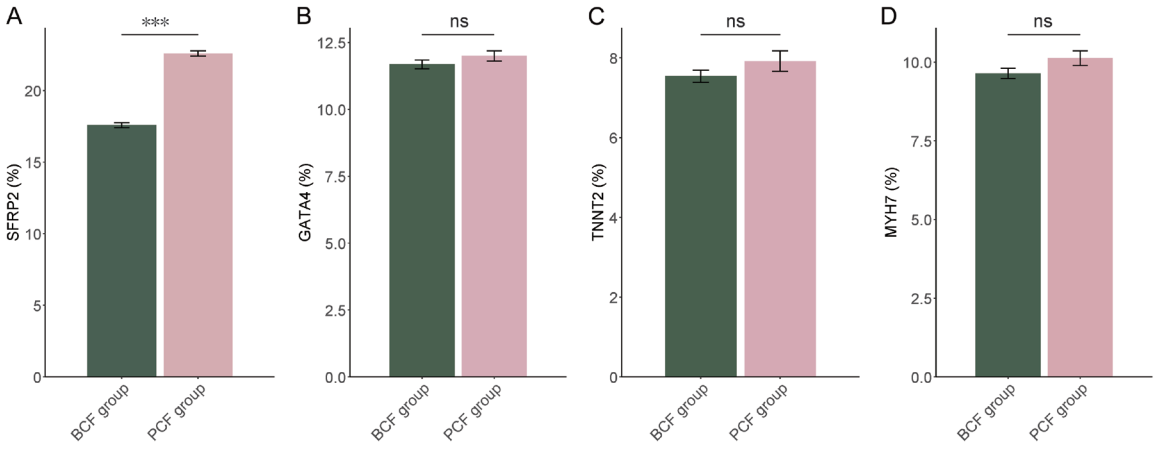

Figure 3. Comparison of gene methylation levels between the BCF and PCF groups. A: SFRP2; B: GATA4; C: TNNT2; D: MYH7. BCF: better cardiac function, PCF: poor cardiac function, SFRP2: Secreted Frizzled-Related Protein 2, GATA4: GATA Binding Protein 4, TNNT2: Troponin T Type 2 (Cardiac), MYH7: Myosin, Heavy Chain 7. ns: No statistically significant difference; ***: P < 0.001.

Correlation between gene methylation levels and cardiac function in DCM patients

Correlation analysis revealed that SFRP2 methylation levels were strongly positively correlated with cardiac function deterioration, with a correlation coefficient (r) of 0.786 (P < 0.001) (**Figure 4**). Additionally, LVEF showed a weak negative correlation with overall gene methylation levels (r = -0.150, P = 0.020), indicating that reduced LVEF may be associated with increased methylation. LAVI also demonstrated a weak negative correlation with methylation levels (r = -0.137, P = 0.034), suggesting a potential relationship between larger atrial size and elevated methylation levels.

Discussion

This study investigated plasma SFRP2 gene methylation levels in patients with DCM and assessed their clinical diagnostic value. Elevated SFRP2 methylation levels were observed in the DCM group, consistent with existing knowledge regarding epigenetic modifications in cardiovascular diseases. DNA

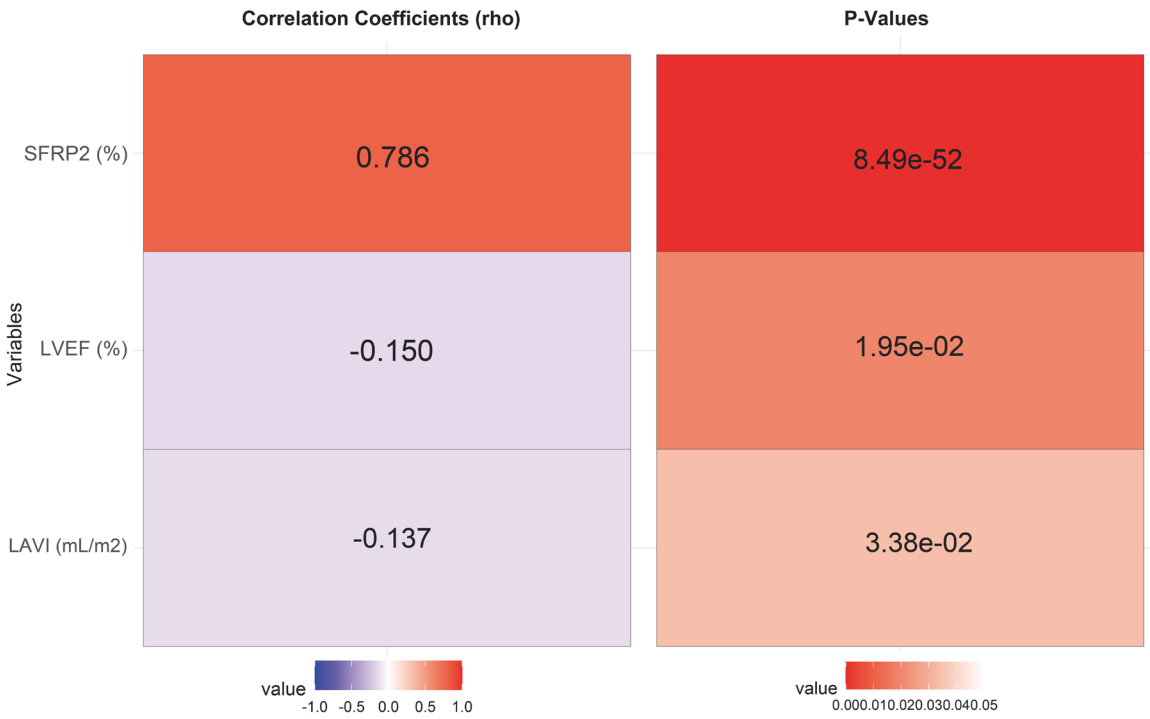

Figure 4. Correlation analysis of gene methylation levels and cardiac function in patients with DCM. SFRP2: Secreted Frizzled-Related Protein 2, LVEF: Left Ventricular Ejection Fraction, LAVI: Left Atrial Volume Index, DCM: Dilated Cardiomyopathy, SFRP2: Secreted Frizzled-Related Protein 2.

methylation typically represses gene expression by altering chromatin structure and interfering with transcription factor binding [14]. The SFRP2 gene encodes a member of the secreted frizzled-related protein family, functioning as an antagonist of the Wnt signaling pathway. Wnt signaling plays critical roles in cellular growth, differentiation, and apoptosis, all of which are essential for maintaining cardiac structure and function. Dysregulation of Wnt signaling through SFRP2 hypermethylation may contribute to DCM pathogenesis by promoting maladaptive cardiac remodeling, reducing cardiomyocyte survival, and enhancing fibrosis - hallmarks of heart failure [8, 15, 16].

The observed positive correlation between SFRP2 methylation levels and deteriorated cardiac function provides insight into molecular mechanisms underlying DCM progression. In heart failure, pathological cardiac remodeling progresses from compensatory adaptations to decompensated states characterized by extensive fibrosis, hypertrophy, and impaired contractility [17, 18]. Epigenetic modulation, particularly hypermethylation of genes inhibiting antifibrotic pathways, may drive or exacerbate these changes [19-22], as evidenced by the significant association between elevated SFRP2 methylation, reduced LVEF, and altered LAVI.

Furthermore, the strong positive correlation between SFRP2 methylation and parameters indicative of poor cardiac function supports the hypothesis that epigenetic modifications may reflect - or even mediate - the extent of cardiac dysfunction. This is further substantiated by considering SFRP2's role in tissue fibrosis. The Wnt signaling pathway antagonizes the Transforming Growth Factor-Beta/Smad (TGF-β/Smad) signaling pathway, which is implicated in fibrotic responses [23-25]. Therefore, hypermethylation and subsequent downregulation of SFRP2 could diminish its inhibitory effects on Wnt signaling [26], facilitating unchecked fibrosis that contributes to DCM pathology.

In addition to SFRP2, this study also identified modest increases in methylation levels of genes such as GATA4 and MYH7, although their diagnostic utility was less pronounced. GATA4 is a transcription factor involved in cardiac muscle growth and stress responses [27, 28], while MYH7 encodes beta-myosin heavy chain,

essential for cardiac contractility [29, 30]. The slight increases in their methylation levels may reflect secondary or compensatory epigenetic responses rather than direct contributors to disease pathogenesis, highlighting the predominant relevance of SFRP2 methylation.

The potential link between hypertension and increased SFRP2 methylation observed in this study is noteworthy. Given hypertension's established role in promoting cardiac remodeling and heart failure, it raises the question of whether methylation changes are more pronounced or diagnostically specific in hypertensive patients with cardiac complications. Hypertension-induced oxidative stress and inflammation could drive epigenetic modifications such as DNA methylation, potentially exacerbating SFRP2 hypermethylation [31-33].

Another significant implication of these findings is the potential utility of SFRP2 methylation as a minimally invasive diagnostic biomarker for DCM. Plasma DNA methylation assessment provides a feasible and less invasive alternative to traditional imaging techniques or myocardial biopsy, which are often resource-intensive [34]. The high discriminative ability of SFRP2 methylation, demonstrated by ROC analysis with robust sensitivity and specificity, supports its potential incorporation into clinical practice for improved diagnosis and stratification based on disease severity and progression.

Despite these promising results, several limitations must be acknowledged. The cross-sectional design precludes causal inferences between methylation patterns and disease progression; longitudinal studies are needed to elucidate temporal dynamics. Although this study links SFRP2 hypermethylation to Wnt pathway dysregulation, further experimental studies are required to establish causality. Additionally, while the sample size was robust, validation in larger and more diverse populations is necessary to generalize findings and account for potential population-specific confounding factors.

In conclusion, the significant elevation of plasma SFRP2 methylation levels in DCM patients, particularly those with severe cardiac dysfunction, highlights a potentially important epigenetic mechanism underlying DCM pathology. Identifying SFRP2 methylation as a potential biomarker holds promise for improving diagnostic accuracy and personalizing treatment strategies. Future research should focus on elucidating the precise molecular mechanisms by which SFRP2 methylation influences cardiac remodeling and exploring the therapeutic potential of modulating epigenetic modifications in DCM.

Disclosure of conflict of interest

None.

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