Advancements in the Study of Dilated Cardiomyopathy Biomarkers

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Abstract: Dilated cardiomyopathy (DCM) is the leading cause of sudden cardiac death (SCD) and heart failure (HF) in children and adults worldwide, and it is also the main indication of heart transplantation. DCM remains a significant cause of heart transplantation despite recent improvements in treatment, which is related to the enormous financial strain placed on the world's healthcare system. Therefore, determining the prognosis of individuals with DCM is crucial for providing them with a customized course of treatment. Genetic testing, microvolt T-wave alternation, and late gadolinium-enhanced cardiac magnetic resonance imaging have developed into potent methods for predicting the occurrence of sudden cardiac death and optimizing patient selection. Despite the availability of numerous novel diagnostic techniques, further tests are still required to enhance or partially substitute current methods of risk categorization. As a result, biomarkers are robust and straightforward tools that can identify people at risk for unfavorable cardiovascular events. Thus, this article aims to review the state of the research on biomarkers for DCM.
***Keywords*:** dilated cardiomyopathy, biomarkers, heart failure, risk stratification

1. Introduction

Dilated cardiomyopathy (DCM) is one leading cause of HF with reduced ejection fraction. It is characterized by left or double ventricular enlargement with systolic dysfunction, mainly manifested as cardiac enlargement, progressive HF, arrhythmia, thromboembolism, and sudden cardiac death (SCD) [1]. The most common types of DCM are idiopathic and familial disorders. Mutations in several genes, such as those encoding structural components of sarcomeres and desmosomes can lead to DCM. At the same time, various etiologies can cause non-genetic DCM, including myocardial inflammation caused by infection (primarily viral), drug, toxin, allergen exposure, and autoimmune or systemic endocrine diseases[2]. The heterogeneity of DCM's etiology and clinical manifestations makes accurate and timely diagnosis challenging[3]. DCM has a poor long-term prognosis and can result in death (cardiac pump failure or sudden cardiac death). To promote the life quality and survival rate of patients with DCM, early diagnosis, treatment, disease monitoring, and prognosis judgment are of great significance. Unfortunately, due to the complex and diverse clinical manifestations of DCM, existing monitoring methods frequently fail to meet the needs of clinicians in actual clinical work for the management of patients' conditions. Hence, as a straightforward tool, circulating blood-based biomarkers may offer crucial details on the diagnosis, prognosis, risk assessment, and the treatment of DCM.

2. Diagnostic biomarkers of DCM

2.1 C-reactive protein (CRP) and high-sensitivity C-reactive protein (hs-CRP)

C-reactive protein is an acute-phase reactant that significantly rises in response to physical trauma, severe bacterial infections, and other inflammatory disorders[4]. The inflammatory process is found in HF, as in other chronic diseases, for instance, systemic arterial hypertension, diabetes, cancer, and chronic kidney disease. Studies have shown that serum hs-CRP levels are higher in patients with chronic heart failure, regardless of the causes[5, 6]. In patients with DCM in NYHA grades III and IV, there is evidence of elevated hs-CRP, accompanied by left ventricular systolic dysfunction and increased dilation of right and left atrial diameters. In a retrospective cohort study of 622 DCM patients, hs-CRP was found to be an independent predictor of all-cause mortality in patients with DCM. This study discovered elevated hs-CRP in NYHA class III and IV DCM patients, along with left ventricular systolic dysfunction and enlarged right ventricle or left atrium diameters. Specifically, at an average follow-up of 2.6 years, all-cause mortality in Patients with hs-CRP > 3.90 pmol/L was higher than those with hs-CRP < 3.90 pmol/L[6]. In addition, Celina et al. studied the relationship between CRP and the severity of HF in patients with DCM, and they found an increase in hs-CRP levels according to the NYHA grades and LVEF[7]. As a result, CRP and hs-CRP can be used to predict the prognosis of DCM patients as biomarkers.

2.2 B-type natriuretic peptide (BNP) and N-terminal-pro Hormone BNP (NT-proBNP)

BNP is a hormone produced by cardiac ventricular myocytes in response to myocardial stretchings like stress or volume overload. It is released as the hormone proBNP when the myocardium is exposed to a stretched state. ProBNP is then enzymatically split into inactive NT-proBNP (76 amino acids) and the biologically active BNP (32 amino acids)[8]. BNP and NT-proBNP have traditionally been utilized for HF screening, diagnosis, and prognosis. HF is the terminal symptom of all heart illnesses, while DCM is classed as a non-ischemic heart disease with a dilated heart and an EF < 45%. Hence, BNP and NT-proBNP testing is recommended for DCM patients with heart failure symptoms[9]. Noori et al. conducted a study that compared plasma BNP levels in children with DCM. They discovered that the mean value of BNP was higher in children with DCM than in healthy children and positively correlated with the severity of DCM[10]. In addition, Tigen and his colleagues examined the prognostic value of the right ventricular systolic function in DCM patients as well as its correlation with plasma NT-BNP levels. They revealed that combining plasma NT-proBNP levels with tissue doppler-derived right ventricular systolic function parameters could help identify high-risk populations for non-ischemic dilated cardiomyopathy (NIDCM) [11]. In summary, BNP and NT-proBNP can be used as prognostic biomarkers for DCM. However, large-scale investigations are required to confirm that.

2.3 High-sensitivity cardiac troponin T (hs-cTnT)

Cardiac troponin I and cardiac troponin T have good sensitivity and specificity as makers of myocardial necrosis[12]. These two troponins can also forecast unfavorable outcomes in DCM patients. Unfortunately, the low sensitivity of conventional commercial detection technologies restricts their clinical application. Consequently, a sensitive commercial test for cardiac troponin T and hs-cTnT has become available since then, and various trials have investigated its predictive relevance in patients with NIDCM. Kawahara et al. were the first to demonstrate that hs-cTnT plays a predictive function in people with NIDCM. According to their investigations, high blood concentrations of hs-cTnT are a helpful predictor of prognosis in CHF patients with non-ischemic DCM, regardless of LVEF or BNP[13]. In another research, Weinmann et al. disclosed that the more decreased serum hs-cTnT levels, the improved left ventricular function in DCM patients during immunosorbent therapy. Finally, they propose that hs-cTnT can be used as a biomarker to monitor the recovery of left ventricular function after immunosorbent therapy in DCM patients[14]. In a word, hs-cTnT has the potential as a biomarker for monitoring DCM.

2.4 Matrix metalloproteinases (MMPs)

MMPs are a series of zinc-dependent endopeptidases that primarily degrade proteins in the extracellular matrix. Matrix metalloproteinases have been proposed as biomarkers for various pathological conditions and have been explored as potential therapeutic targets for cardiovascular, musculoskeletal, and cancer diseases[15]. Antonov et al. compared the levels of MMP-1, MMP-9, and relevant inhibitor TIMP-1 in autopsy samples and their expression in myocardial cell cultures from normal and DCM patients. They detected a 1.5-9-fold expression of these markers in autopsy samples and myocardial cultures from patients with DCM, implying that they are helpful in predicting DCM and assessing treatment efficacy[16]. Besides, researchers uncovered that MMP-2 and MMP-9 play a significant part in myocardial remodeling in patients with chronic Chagas disease, an inflammatory DCM[17]. Overall, MMPs are of great value in evaluating the prognosis of DCM patients.

2.5 Soluble suppression of tumorigenicity 2 (sST2)

Both sST2 and transmembrane ST2 (ST2L) are members of the interleukin-1 receptor family, produced by cardiomyocytes and myocardial fibroblasts. sST2 expression varies independently of age, weight, sex, renal function, and heart failure, and it also has a high degree of specificity. For this advantage, patients with HF, myocardial congestion, or acute coronary syndrome can use sSt2 to evaluate tissue fibrosis and cardiac remodeling[18]. About the prognostic value of sST2 in patients with DCM, Binas and his colleagues studied the effect of sST2 in patients with DCM. After observing 262 DCM patients for an average of 3.9 years, they concluded that sST2 could independently predict all-cause and cardiac mortality [19]. In addition, researchers have confirmed the association between levels of sST2 and prognosis in pediatric DCM. In this study, they measured sST2 and BNP levels in 94 pediatric patients with DCM and discovered that sST2 was superior in identifying children with DCM who were at high risk[20]. On the whole, sST2 is now considered as a significant biomarker for DCM prognosis and monitoring, and is included in the American Heart Association's 2017 updated heart failure guidelines[21].

2.6 MicroRNAs (miRNAs)

MiRNAs are a type of small endogenous RNA that ranges in length from 20 to 24 nucleotides and play a variety of crucial regulatory roles in cells. MicroRNAs (miRNAs) are expected to be used as biomarkers for cardiovascular disease[22]. Yang

et al. investigated the relationship between symptom severity and miRNA expression levels in patients with DCM. They found that plasma miR-3135b ($p<0.001$), miR-3908 ($p<0.001$), and miR-5571-5p ($p<0.001$) were obviously upregulated in patients with DCM, implying that circulating miRNAs (miR-3135b, miR-3908, and miR-5571-5p) have potential as diagnostic biomarkers for DCM[23]. Furthermore, researchers investigated the relationship between DCM progression and miR-185, dividing 50 patients with DCM into miR-185 (low) and miR-185 (high) groups. After one year of follow-up, patients in the miR-185 (high) group showed significant improvement in left ventricular ejection fraction and left ventricular end-diastolic diameter. Besides, cardiovascular mortality and overall heart failure rehospitalization rates decreased accordingly. As a result, they believe that circulating miR-185 has the potential to be a biomarker for predicting the prognosis of patients with DCM[24]. In short, with the advancement of biotechnology, the clinical application of microRNAs as circulating biomarkers in DCM patients is worth looking forward to.

2.7 Growth differentiation factor-15 (GDF-15)

GDF-15 belongs to a distal branch of the transforming growth factor-β superfamily[25]. GDF-15 is involved in a number of pathological conditions, including inflammation, cancer, cardiovascular, pulmonary, and renal disease. As a biomarker, it can be used in patients with cardiovascular disease in conjunction with conventional prognostic factors (NT-proBNP and hs-TnT)[26]. In addition, GDF-15 has excellent preanalytical characteristics and can be identified in plasma by immunoassay and serum [27]. May et al. conducted a prospective observational study involving 148 patients with non-ischemic DCM who underwent a comprehensive clinical and laboratory evaluation, including measurement of serum GDF-15. The study's endpoints were severe arrhythmic events (including appropriate implantable cardioverter defibrillator therapy and sudden cardiac death) and all-cause mortality[28]. Finally, they discovered that serum GDF-15 levels were independently linked with significant arrhythmic events and overall mortality, and that GDF-15 may be utilized to predict severe arrhythmic events in DCM patients. In another study, researchers evaluated GDF-15 levels in patients with DCM while they were on left ventricular assist device support and discovered that elevated GDF-15 circulating levels were related to the degree of myocardial fibrosis and decreased to near-normal levels after 1 month[29]. Furthermore, Stojkovic et al. investigated the prognostic value of GDF-15 and sST2 in terms of all-cause mortality and fatal arrhythmias in DCM patients, and discovered that GDF-15 had advantage to sST2 in predicting all-cause mortality and fatal arrhythmias in DCM patients, and risk assessment by GDF-15 can provide more information on the basis of LVEF and also be used to identify patients with fatal arrhythmias[30].

2.8 Circular RNAs (circRNAs)

CircRNAs are endogenous non-coding RNA molecules with a wide distribution and multiple cellular functions. Non-coding RNAs play a crucial role in adjusting the networks which control the physiology and pathology of cardiovascular disease[31]. With the development of RNA sequencing technology and bioinformatics, numerous Circular RNAs have been found and identified, and circRNAs are momentous in the pathological processes of numerous diseases. Recent studies have demonstrated that circRNAs play key role in the physiological and pathological development of the cardiovascular system[32]. Moreover, circRNAs have specific expression and long-term stability, and are readily available in body fluids[33]. In a recent multicenter case study on the etiology of DCM, researchers divided 130 subjects into five study groups (healthy control, idiopathic DCM, ischemic DCM, LMNA related DCM and BAG3 related DCM), and then analyzed differentially expressed circRNA in plasma samples from each group using quantitative RT-PCR, which was linked to relevant systolic and diastolic parameters. Compared to healthy controls, four circRNAs were overexpressed: hsa-circ-0003258, has-circ-0051238, has-circ-0051239 in patients with LMNA-related DCM, and has-circ-0089762 in patients with ischemic DCM. As a result, circRNAs are associated with some diastolic and systolic echocardiographic parameters, which have significant diagnostic potential in DCM patients, and circular RNAs as noninvasive biomarker may contribute to the etiological diagnosis of DCM[34]. Besides, Sun et al. investigated differential expression of circRNAs in pediatric DCM and discovered that has-circ-0067735 and has-circ-00699772 were significantly down-regulated while has-circ-0070186 was up-regulated when compared to healthy children, indicating that they could be candidate biomarkers for children with PDCM[35]. In a nutshell, while circRNAs as a DCM biomarker is looking forward to, we still need to study their role in DCM pathogenesis in depth in order to develop early diagnostic techniques and advance new therapeutic targets.

3. Conclusion

In conclusion, despite recent advances in the study of DCM, it remains an unacceptable disease with unacceptable morbidity and mortality. Therefore, a reliable biomarker to identify patients at high risk of pump failure and sudden cardiac death is urgently needed. Biomarkers are a promising tool for assessing risk stratification in patients with DCM, but their

widespread use in preclinical practice still requires extensive validation to provide critical information for the diagnosis, prognosis, risk stratification, and treatment of DCM patients.

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