Veterinary Integrative Sciences 2026; 24(2): e2026029-1-24. DOI: 10.12982/VIS.2026.029

Veterinary Integrative Sciences
ISSN; 2629-9968 (online)

Review article

Potential of cardiac myosin binding protein-C as an alternative biomarker in feline hypertrophic cardiomyopathy

Nutcha Tanakwang[1,2] and Wanpitak Pongkan[1,2] *

[1] Faculty of Veterinary Medicine, Chiang Mai University, Chiang Mai 50100, Thailand
[2] Cardiopulmonary Clinic, Small Animal Teaching Hospital, Faculty of Veterinary Medicine, Chiang Mai University, Chiang Mai 50100, Thailand

Abstract

Cardiac myosin binding protein-C (cMyBP-C) is a sarcomeric thick filament protein in cardiomyocytes. Its functions extend beyond cross-bridge regulation via dynamic phosphorylation to include sarcomere organization. Diminished cMyBP-C phosphorylation is associated with impaired cardiac function and the development of heart failure. Throughout the past decade, cMyBP-C has emerged as a new early cardiac biomarker for acute myocardial infarction (MI) due to its rapid release and clearance compared to cardiac troponin. In veterinary medicine, cMyBP-C remains a less understood biomarker. Recent studies suggest that genetic variations in cMyBP-C are related to hypertrophic cardiomyopathy (HCM) in cats, a common cardiac disorder defined by increased left ventricular (LV) thickness and diastolic dysfunction. Nevertheless, the role of circulating plasma cMyBP-C levels in feline HCM remains unestablished, representing a critical gap in veterinary cardiology research. Given the progressive nature of feline HCM and the lack of highly specific early biomarkers, plasma cMyBP-C could serve as a valuable tool for early detection and disease monitoring. This review presents a comprehensive analysis of the physiological and pathological roles of cMyBP-C in cardiac function, its association with cardiovascular diseases, the dynamics of its circulating levels, and the factors regulating its release. These insights highlight the potential of cMyBP-C as a promising early biomarker for diagnosing and monitoring feline hypertrophic cardiomyopathy.

Keywords: Cardiac biomarker, Cardiac myosin binding protein-C, Feline hypertrophic cardiomyopathy, Heart failure, Myocardial infarction

***Corresponding author**: Wanpitak Pongkan, Faculty of Veterinary Medicine, Chiang Mai University, Chiang Mai 50100, Thailand. E-mail: P.wanpitak@gmail.com.

Funding; *This work was supported by the CMU Presidential Scholarship, Chiang Mai University, Chiang Mai, Thailand.*
Nutcha Tanakwang is currently enrolled in the Master's Degree Program in Veterinary Science at the Faculty of Veterinary Medicine, Chiang Mai University, under the CMU Presidential Scholarship.

Article history; *received manuscript: 10 March 2025,*
revised manuscript: 17 April 2025,
accepted manuscript: 26 June 2025,
published online: 29 July 2025,
Academic editor; *Korakot Nganvongpanit*

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common myocardial disease in felines, affecting approximately 10-15% of the pet cat population. It is recognized by either diffuse or localized thickening of the left ventricular (LV) wall, accompanied by a non-dilated LV chamber (Riesen et al., 2007; Payne et al., 2015; Luis Fuentes et al., 2020). HCM is a silent but life-threatening disease (Ferasin and DeFrancesco, 2015; Pace, 2020) that poses significant challenges for early detection in cats (Luis Fuentes et al., 2020; Pace, 2020). Consequently, therapy for cats with preclinical feline HCM is often delayed, resulting in a missed opportunity to mitigate disease progression and prolong survival. This delay increases the risk of sudden, unexpected deaths, leaving owners devastated by the loss of their pets (Pierce et al., 2017; Tantisuwat et al., 2018). Therefore, identifying novel early diagnostic tools is crucial to improving treatment strategies, prognosis, and disease prevention for subclinical feline HCM.

cMyBP-C was initially recognized as a candidate biomarker for myocardial injury through proteomic analysis of proteins discharged into the coronary effluent during myocardial infarction, a discovery made in the early 2000s (Jacquet et al., 2009). This study demonstrated that the cardiac-specific isoform of myosin-binding protein C undergoes substantial alterations following ischemic injury and can be detected in the plasma of animal models with acute MI (Jacquet et al., 2009). Many published studies in human medicine have demonstrated that circulating cMyBP-C can be used as a diagnostic test for cardiovascular diseases, including myocardial injury/infarction, heart failure, and cardiomyopathy (Heather et al., 2011; Govindan et al., 2012; El Amrousy et al., 2017). These investigations demonstrate a notable elevation in circulating cMyBP-C levels in individuals with heart illness relative to healthy controls (Heather et al., 2011; Govindan et al., 2012; El Amrousy et al., 2017). Therefore, cMyBP-C may also have potential as a diagnostic and prognostic biomarker for feline HCM. However, to date, plasma or serum cMyBP-C levels in felines with HCM have not been well investigated in veterinary medicine. Further research is needed to determine the clinical utility of plasma cMyBP-C as a biomarker for early diagnosis, disease monitoring, and prognostic assessment in feline HCM. Establishing cMyBP-C as a reliable biomarker could provide a non-invasive and accessible diagnostic tool, facilitating timely intervention and potentially improving clinical outcomes for affected cats.

WHAT IS THE CARDIAC MYOSIN BINDING PROTEIN-C?

Myosin binding protein-C (MyBP-C) is a sarcomeric thick filament protein that is part of the intracellular immunoglobulin and fibronectin superfamily, located in the cardiac and skeletal muscles of vertebrates (Lin et al., 2018), which was first discovered 30 years ago as a contaminant during myosin preparation (Offer et al., 1973). It includes three isoforms: slow skeletal (ssMyBP-C), fast skeletal (fsMyBP-C), and cardiac (cMyBP-C), which are encoded by the *MYBPC1, MYBPC2*, and *MYBPC3* genes, respectively. (Lin et al., 2018). The ssMyBP-C and fsMyBP-C are expressed mainly in adult skeletal muscle tissue, whereas cMyBP-C exists only in cardiac tissue (Jacquet et al., 2009; Lin et al., 2018). cMyBP-C is a single polypeptide of molecular weight 135±15 kDa and distinguished from the skeletal isoforms by the presence of an additional immunoglobulin domain at the N-terminus (C0), phosphorylation motifs in the M domain (between C1 and C2), and an inserted loop of 28 residues within the C5 domain (Gautel et al., 1995) (Figure 1A).

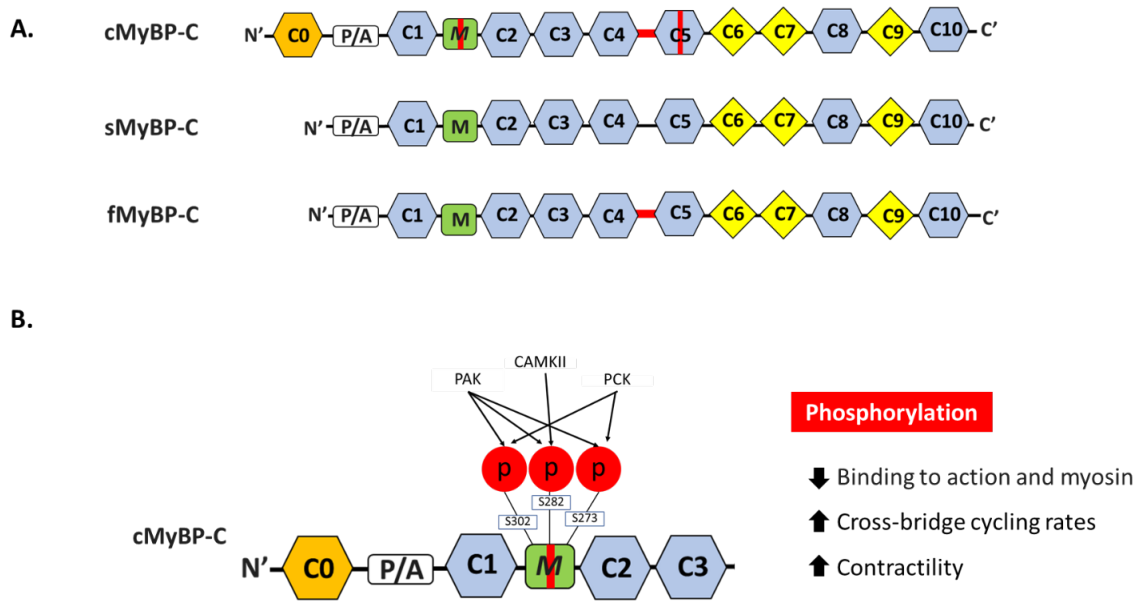

Figure 1 Three isoforms of myosin-binding protein C (MyBP-C) and their structural variations (A). Each MyBP-C isoform contains a proline–alanine (P/A)-rich region near the N-terminus, three fibronectin type III domains (depicted as rhombuses), and seven immunoglobulin domains (represented as hexagons). The cMyBP-C differs from the skeletal isoforms by the presence of an additional C0 domain (orange hexagon), a phosphorylation motif located at the M domain (red vertical band), and a 28-residue cardiac-specific insert within the C5 domain (red vertical band). Additionally, both the cardiac and fast skeletal isoforms share a conserved 'linker' region that connects the C4 and C5 domains (red horizontal bar). Cardiac myosin binding protein-C (cMyBP-C) has three key phosphorylation sites in the M-domain (S273, S282, and S302; mouse sequence), which can be targeted by various kinases (B). Protein kinase A (PKA) can phosphorylate all three sites on cMyBP-C. Protein kinase C (PKC) targets both S273 and S302, while Ca^{2+}/calmodulin-dependent kinase II (CaMKII) targets S282. The overall effect of cMyBP-C phosphorylation is the reduction of its binding to both actin and myosin, thereby promoting increased rates of cross-bridge formation and enhancing cardiac contractility. Adapted from (Main et al., 2020). cMyBP-C; cardiac myosin-binding protein C, ssMyBP-C; slow skeletal myosin-binding protein C, fsMyBP-C; fast skeletal myosin-binding protein C.

PHYSIOLOGICAL ROLES OF THE CARDIAC ISOFORM OF MYOSIN BINDING PROTEIN-C IN THE HEART

In the sarcomere, cMyBP-C is situated within the C-zone of the A-band, where it is arranged into two groups, divided by the bare H-zone (Figure 2A) (Barefield and Sadayappan, 2010). Structurally, cMyBP-C interacts with various components of the sarcomere: it attaches to the S2 area of myosin and actin at the C1-M-C2 domains, to the light meromyosin of myosin at the C10 domain, and to titin at the C8–C10 domains (Figure 2B) (Sadayappan and de Tombe, 2012). cMyBP-C plays a crucial role in the regulation of cross-bridge formation through dynamic phosphorylation. This process is mediated by several kinases, including protein kinase A (PKA), protein kinase C (PKC), and Ca^{2+}-calmodulin-dependent kinase II (CaMKII) (Figure 1B) (Barefield and Sadayappan, 2010; Main et al., 2020). The principal regulatory region of cMyBP-C is the M domain, which plays a crucial role in modulating muscle contraction. This domain contains multiple

phosphorylation sites, a defining characteristic of cMyBP-C in cardiomyocytes (Bezold et al., 2013).

Early studies in mouse, rabbit and chicken heart identified three key phosphorylation sites in the M domain (Ser-273, Ser-282, and Ser-302, mouse sequence), along with an additional site at Ser-307, which are phosphorylated by PKA (Gautel et al., 1995; Mohamed et al., 1998; Barefield and Sadayappan, 2010). After phosphorylation of cMyBP-C with PKA, the majority of thick filaments in rats exhibited a relaxed state (Levine et al., 2001) that inhibits attachment to myosin, altering the maximum Ca^{2+}-activated force (Barefield and Sadayappan, 2010). Furthermore, electron microscopy examination has demonstrated that the phosphorylation of cMyBP-C induces the displacement of cross-bridges from the thick filament backbone in rats (Weisberg and Winegrad, 1996), suggesting that phosphorylation alters filament orientation and contractile mechanics (Barefield and Sadayappan, 2010). However, in rats, the effects of PKA phosphorylation on actomyosin ATPase activity are influenced by the specific isoforms of myosin heavy chain present (Weisberg and Winegrad, 1998).

In rodent and chicken studies, unlike PKA, PKC phosphorylates only Ser-273 and Ser-302 (Mohamed et al., 1998; Pyle et al., 2003; Xiao et al., 2007). In bovine and rat studies suggested that PKC-mediated phosphorylation influences the frequency of relaxation, cross-bridge cycling kinetics, and actomyosin Mg^{2+}-ATPase activity (Lim et al., 1985; McClellan et al., 1994; Barefield and Sadayappan, 2010). In addition, CaMKII directly phosphorylates cMyBP-C at multiple sites in the chicken heart (Schlender and Bean, 1991). In vitro studies have proposed a hierarchical phosphorylation pattern, where CaMKII-mediated phosphorylation at Ser-282 is necessary for the following phosphorylation of PKC-targeted sites (Ser-273 and Ser-302) (Schlender and Bean, 1991; Gautel et al., 1995; McClellan et al., 2001) . Since Ca^{2+} signaling modulates myocardial contractility, CaMKII activation may selectively phosphorylate Ser-282 (Hartzell and Glass, 1984; Gautel et al., 1995), altering thick filament structure and cardiac contractility in the rat heart (McClellan et al., 2001). However, the precise physiological implications of CaMKII phosphorylation on cMyBP-C function in vivo have not been fully elucidated (Barefield and Sadayappan, 2010).

The phosphorylation state of the M domain directly influences the binding between cMyBP-C, myosin, and actin. In humans, rabbits, and bovine studies, upon phosphorylation of cMyBP-C, its C1-M-C2 domains dissociate from the myosin S2 region and actin, allowing interaction with thin filament proteins, including actin and α-tropomyosin (Gruen et al., 1999; Shaffer et al., 2009). Conversely, a rat study showed that when cMyBP-C is dephosphorylated, the C1-M-C2 domains strongly associate with the myosin S2 region, restricting its interaction with actin and subsequently modulating contractile force generation (Figure 2B and 2C) (Kulikovskaya et al., 2003). This dynamic phosphorylation mechanism indicates that cMyBP-C functions as a crucial regulatory component in the modulation of myocardial contractility (Barefield and Sadayappan, 2010). Furthermore, phosphorylation enhances actin and myosin interactions by either reducing structural constraints on myosin or decreasing cMyBP-C binding to the myosin S2 region, thereby facilitating closer actin-myosin proximity and increasing cross-bridge cycling rates in mice studies (Flashman et al., 2004; Stelzer et al., 2006; Stelzer et al., 2007; Tong et al., 2008).

Beyond its regulatory role in contractility, cMyBP-C is crucial for sarcomere organization and normal cardiac function. A study in early embryonic chicken heart rudiments showed that it contributes to myofibrillogenesis, ensuring proper myofibril assembly and muscle cell regeneration (Ehler et al., 1999). These findings highlight the significance of cMyBP-C in both structural integrity and dynamic regulation of the myocardium, further underscoring its potential role as a biomarker for cardiac disease progression.

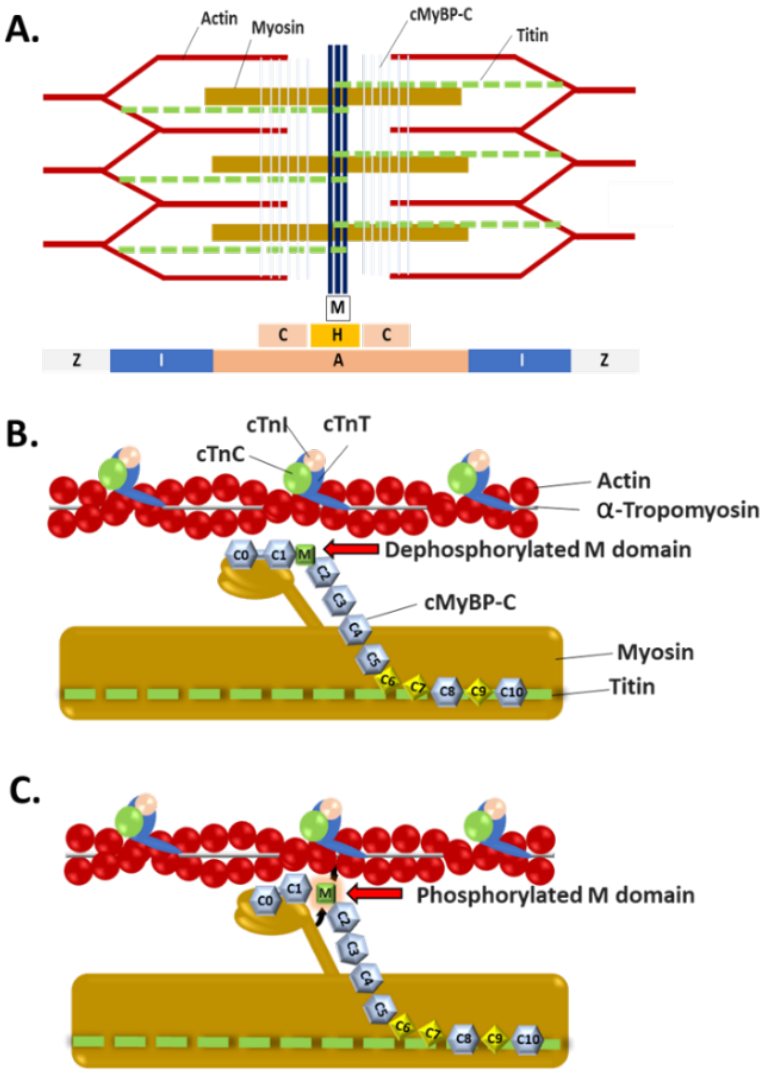

Figure 2 A schematic diagram of the cardiac sarcomere and the arrangement of cMyBP-C is presented. The cardiac sarcomere represents the fundamental contractile unit of striated cardiac muscle, bounded by two adjacent Z-lines. Within the sarcomere, key structural regions include the I-band, A-band, H-zone, and M-line. The thick filament is primarily composed of myosin, cMyBP-C, and titin, with cMyBP-C localized to the inner two-thirds of the A-band, specifically within the C-zone. Notably, cMyBP-C is oriented perpendicularly to the long axis of the myosin filaments, forming a distinct doublet pattern in the A-band, with two sets of 7–9 cMyBP-C bands symmetrically positioned on either side of the H-zone. The thin filament consists of actin monomers, troponins, and α-tropomyosin (A). cMyBP-C interacts with both the thick and thin filaments: its C-terminus binds to the light meromyosin (C10 domain) of myosin and the C8–C10 domains of titin, while its N-terminus interacts with the myosin S2 region and actin. The M domain, which is highly phosphorylatable, plays a critical role in regulating cross-bridge formation. When dephosphorylated, the C1-M-C2 domains bind tightly to the myosin S2 region, restricting its interaction with actin (B). In contrast, upon phosphorylation, the C1-M-C2 domains and the M domain dissociate from their interactions with myosin S2 and actin, resulting in structural alterations in the thick filament (C). However, the C1 domain remains associated with actin, regardless of the phosphorylation status of the M domain. Adapted from (Barefield & Sadayappan, 2010).

TEMPORAL DYNAMICS OF cMyBP-C IN BLOOD CIRCULATION: RELEASE, CLEARANCE, AND CIRCADIAN VARIATION

cMyBP-C has been acknowledged as a quickly releasable sarcomeric protein, as demonstrated in an in vitro study using rat left ventricular tissue (Govindan et al., 2012). Both intact cMyBP-C and its fragments were detectable in the PBS solution within one second of incubation, with the release gradually increasing over a 12-hour period (Govindan et al., 2012). Interestingly, full-length cMyBP-C was present at all time points, but its levels decreased at 12 hours, which coincided with the appearance of 40 kDa fragments (Govindan et al., 2012).

The kinetics of cMyBP-C release into circulation have been extensively investigated in various models of acute cardiac injury, including MI, alcohol ablation for hypertrophic cardiomyopathy, and coronary artery bypass grafting (Govindan et al., 2013; Kuster et al., 2014; Baker et al., 2015; Kaier et al., 2017; Alaour et al., 2021). These studies consistently indicate that cMyBP-C is released in higher quantities, at earlier time points, and is cleared more rapidly than cardiac troponins (Baker et al., 2015; Kaier et al., 2017). For instance, in a pig MI model, plasma cMyBP-C levels began to rise from baseline at 3 hours, peaked at 6 hours post-coronary ligation, and reached baseline levels again by 12 hours (Kuster et al., 2014). In contrast, elevations in plasma levels of cardiac troponin (cTn) and myosin light chain-3 were not observed until 6 hours after ligation (Kuster et al., 2014). The more rapid decline of serum/plasma cMyBP-C levels compared to cTn may be attributed to a combination of early release following myocardial injury, proteolytic cleavage into smaller, more soluble fragments, and enhanced clearance (Decker et al., 2012; Govindan et al., 2012; Kuster et al., 2014). However, the precise mechanisms underlying cMyBP-C clearance have yet to be fully elucidated.

Similarly, in human MI patients, plasma cMyBP-C levels exhibited a rapid decline within 12 hours following percutaneous transcoronary angioplasty (Govindan et al., 2013). In addition, recent studies have identified a physiological circadian rhythm in cMyBP-C levels, characterized by a gradual increase from the early afternoon to the early morning, peaking at approximately 3:03 AM (acrophase). In contrast, high-sensitivity cardiac troponin T (hs-cTnT) levels displayed a delayed increase, peaking later at around 8:01 AM (Alaour et al., 2021). However, the mechanisms underlying this rhythmic variation remain unclear.

Overall, cMyBP-C exhibits a faster rise-and-fall pattern in serum compared to cTn, encompassing its release, accumulation, and clearance (Baker et al., 2015). For example, cardiac troponin I follows a slower release profile, with detectable elevations occurring 6–12 hours after MI onset and a prolonged clearance phase, persisting in circulation for over two weeks. In contrast, the more dynamic kinetics of cMyBP-C suggest its potential utility as a timely and reliable biomarker for acute cardiac injury (Govindan et al., 2013; Baker et al., 2015).

THE ROLE OF cMyBP-C IN CARDICA PATHOLOGY: PHOSPHORYLATION, DEGRADATION, AND FUNCTIONAL IMPLICATIONS

A recent review highlighted the pivotal role of phosphorylation in regulating the activity of cMyBP-C in both physiological and pathological conditions, drawing insights from both mouse models and human studies. Dephosphorylation of cMyBP-C has been implicated in its accelerated degradation and is associated with the onset of heart failure (HF) (Barefield and Sadayappan, 2010). On the contrary,

phosphorylation of cMyBP-C has been identified as a potential therapeutic target, demonstrating protective effects against ischemia-reperfusion injury in a rat model (Barefield and Sadayappan, 2010).

Over the past decade, increasing evidence has associated alterations in the phosphorylation of heart contraction proteins with the pathogenesis of HF (Walker et al., 2013). A previous study revealed that the phosphorylation activity of cMyBP-C was significantly lower in the ischemic regions compared to non-ischemic areas and sham controls, as demonstrated in a rodent model of MI induced by coronary artery ligation (Govindan et al., 2012). Consistent with human research, it has been established that cMyBP-C undergoes significant deterioration during MI and in HF, with the release of its fragments as a direct consequence of cMyBP-C dephosphorylation (Govindan et al., 2012).

Moreover, a previous study in humans and canines with HF demonstrated that the ratio of Ser-282-cMyBP-C to total cMyBP-C in heart tissue was reduced by more than 50% in humans with HF and by more than 40% in dogs with HF (El-Armouche et al., 2007). In addition, findings from a mouse model of HF revealed a significant decrease in cMyBP-C phosphorylation during disease progression, suggesting that dephosphorylation plays a pivotal role in contractile dysfunction and HF pathogenesis (Sadayappan et al., 2005). Consistent with these findings, A previous study in human hypertrophic cardiomyopathy has reported diminished cMyBP-C phosphorylation in the end stages of HF (Jacques et al., 2008). Moreover, research on low-flow cardiac ischemia and reperfusion injury in dogs demonstrated that cMyBP-C dephosphorylation may trigger myofibrillar thick filament disassembly, leading to impaired actomyosin cross-bridge formation and, ultimately, contractile dysfunction (Figure 3) (Decker et al., 2005). A summary of the cMyBP-C activity in pathological heart conditions has been shown in Table 1.

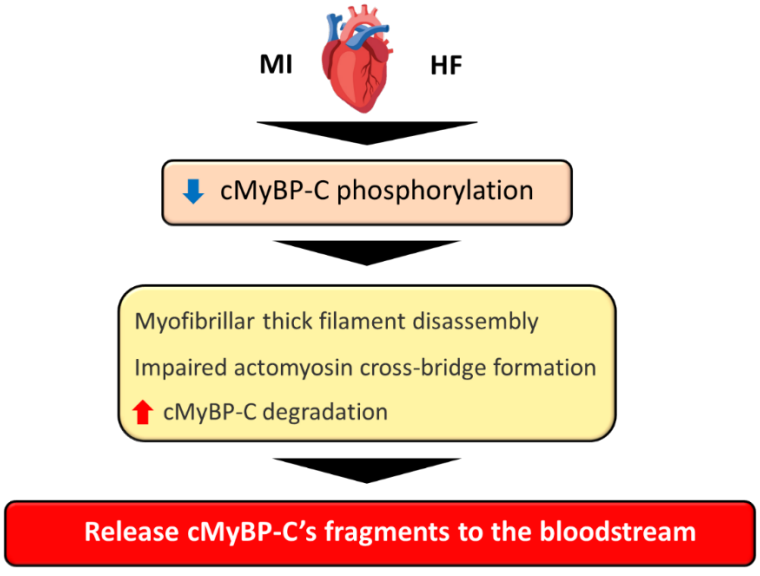

Figure 3 Schematic representation of the proposed pathway from cMyBP-C release to detection as a biomarker in myocardial infarction (MI) and heart failure (HF). In MI and heart failure HF, decreased phosphorylation of cMyBP-C promotes myofibrillar thick filament disassembly and impairs actomyosin cross-bridge formation, contributing to contractile dysfunction. The dephosphorylated state also facilitates cMyBP-C degradation, leading to the release of its fragments into the bloodstream, where they may serve as potential biomarkers of cardiac injury and disease progression.

Table 1 Summary of the studies reporting the activity of cMyBP-C in the pathological heart

Animal Species	Model	Number of samples	Major Findings	Ref.
In vitro; 3-day-old NRVMs	Post-hypoxia event	n = 4	- The phosphorylation status of cMyBP-C (Ser-273, Ser-282, and Ser-302) was markedly reduced - The decline in cMyBP-C phosphorylation, associated with a reduction in intact cMyBP-C and an increase in its fragments	(Govindan et al., 2012)
In vivo; rats heart	MI	n = 3	- cMyBP-C phosphorylation was lower in ischemic areas compared to normal areas of the MI heart - The cMyBP-C fragments were only present in ischemic LV tissue	
In vivo; human heart	ICM HF	Donor = 11 Patients =15	- cMyBP-C phosphorylation was decreased compared to the donor - In HF and MI, cMyBP-C was degraded, and the release of 40 kDa fragments was linked to cMyBP-C dephosphorylation	
Human and canine LV tissue	HF	Donor = 6 Patients = 12 Dog = 10 Dog with HF =10	- Phosphorylation levels of cMyBP-C are markedly diminished in both humans and dogs with HF	(El-Armouche et al., 2007)
Mouse	TAC induced hypertrophy HF IR	NTG = 6 MyBP-C$^{t/t}$ = 7 MyBP-C^{WT} = 7 MyBP-C^{AllP-} = 8	- cMyBP-C phosphorylation significantly decreases during HF, IR injury, or pathologic hypertrophy development - Increased dephosphorylation of cMyBP-C was linked to impaired contractility and HF	(Sadayappan et al., 2005)
Human myocardium (IVS)	HCM HF	HCM = 9 HF = 9 donor = 9	- Pathological muscle had lower levels of cMyBP-C phosphorylation than donor muscle - The reduction of cMyBP-C phosphorylation is not associated with cMyBP-C mutations	(Jacques et al., 2008)
Canine	Low-flow ischemia	n = 23	- After IR injury, total phosphorylation of cMyBP-C was diminished - The percentage of dephosphorylated cMyBP-C was negatively correlated with cross-bridge frequency and segment shortening	(Decker et al., 2005)

NRVMs; neonatal rat ventricular myocytes, MI; myocardial infarction, ICM; ischemic cardiomyopathy, HF; heart failure, TAC; transverse aortic constriction, IR; ischemia-reperfusion, NTG; non-transgenic mice, MyBP-C$^{t/t}$; transgenic mice expressing <10% of normal cMyBP-C levels, MyBP-C^{WT}; transgenic mice with that expressed normal cMyBP-C, MyBP-C^{AllP-}; transgenic mice with cMyBP-C phosphorylation sites mutated to non-phosphorylatable alanines, IVS; interventricular septum, HCM; hypertrophic cardiomyopathy.

THE RELATIONSHIP BETWEEN CIRCULATING cMyBP-C LEVELS AND HEART DISEASE

Feline hypertrophic cardiomyopathy (HCM) is the predominant heart condition characterized by generalized or localized thickening of the LV wall with a non-dilated LV chamber in cats (Luis Fuentes et al., 2020). The complex pathophysiology of HCM remains incompletely understood. However, existing reports indicate that the disease is associated with the disorganization of cardiomyocytes, interstitial fibrosis, leukocyte infiltration, and vascular abnormality (Kitz et al., 2019). In addition, myocardial infarction in feline HCM is thought to occur due to coronary thromboembolic disease (Kittleson and Cote, 2021).

Despite preserved systolic function, cats with HCM exhibit increased myocardial stiffness, leading to delayed relaxation and impaired diastolic filling, which ultimately results in heart failure (Betocchi et al., 1993; Kittleson and Cote, 2021). Based on current evidence, circulating cMyBP-C has the potential to be a candidate biomarker for feline HCM, as it is capable of accurately identifying myocardial injury, infarction, hypertrophy, and heart failure in human studies. However, it needs to be verified in the feline species.

Myocardial injury/infarction and circulating cMyBP-C levels

A previous in vitro study demonstrated that cMyBP-C exhibits high solubility, susceptibility to proteolysis, and a tendency for facile release from the sarcomere (Govindan et al., 2012). In addition, previous studies demonstrated that rats and patients with myocardial infarction show significantly increased plasma cMyBP-C compared to sham rats or healthy human controls (Govindan et al., 2012; Govindan et al., 2013; Baker et al., 2015; Kaier et al., 2017; Kaier et al., 2019). Moreover, humans and rats with post-MI showed a higher plasma cMyBP-C and its fragments than plasma cardiac troponin I (cTnI) (Govindan et al., 2012). A previous in vitro and in vivo study using rat models has demonstrated that cMyBP-C is released from the myocardium at a rate comparable to that of cardiac troponin and can be identified in peripheral blood (Baker et al., 2015). Moreover, a comparative analysis of cMyBP-C levels with six established cardiac biomarkers of myocardial infarction (MI)—including myoglobin, carbonic anhydrase, creatine kinase-MB, cTnI, glycogen phosphorylase, and heart-type fatty acid-binding protein—revealed a substantial elevation in plasma cMyBP-C concentrations in myocardial infarction patients (Govindan et al., 2013). MI patients with elevated cMyBP-C levels also exhibited significantly higher concentrations of myoglobin, carbonic anhydrase, and creatine kinase-MB (Govindan et al., 2013). Conversely, plasma concentrations of cTnI, glycogen phosphorylase, and heart-type fatty acid-binding protein exhibited no significant alterations in MI patients. Notably, a plasma cMyBP-C concentration of 68.1 ng/mL demonstrated 66.2% sensitivity and 100% specificity for diagnosing MI (Govindan et al., 2013).

Moreover, cMyBP-C levels were markedly reduced in patients at 12 hours post-percutaneous trans-coronary angioplasty (Govindan et al., 2013). When compared to cTn for the early diagnosis of acute MI, a previous study has demonstrated that cMyBP-C exhibits greater discriminatory ability than hs-cTnT (Kaier et al., 2019). For patients presenting with chest pain (onset within 3 hours), cMyBP-C exhibits higher sensitivity compared to hs-cTnT, as well as greater specificity than both hs-cTn (T and I) at the 10 ng/L rule-out threshold (Kaier et al., 2017). Similarly, in late presenters of chest pain, cMyBP-C exhibited higher specificity than hs-cTn (T and I) at the rule-out threshold while preserving similar sensitivity (Kaier et al., 2017). Furthermore, cMyBP-C demonstrated superior accuracy in predicting acute MI, mortality, and the composite endpoint (Kaier et al., 2017). A summary of studies investigating circulating cMyBP-C in association with myocardial injury and infarction is presented in Table 2.

Heart failure and circulating cMyBP-C levels

Previous clinical studies have highlighted the potential of plasma cMyBP-C as a biomarker for patients with HF (El Amrousy et al., 2017; El-Moghazy et al., 2020; Khatab et al., 2021; Kozhuharov et al., 2021). In children with acute HF, elevated plasma cMyBP-C levels were associated with disease severity (El Amrousy et al., 2017). A cutoff value of 45 ng/mL demonstrated 100% sensitivity and 96% specificity for HF diagnosis (El Amrousy et al., 2017). High plasma cMyBP-C levels (152 ng/mL) were predictive of adverse outcomes in HF patients, with 90% sensitivity and 93% specificity (El Amrousy et al., 2017).

In pediatric HF patients, plasma cMyBP-C has been shown to aid in both diagnosis and prognosis, although with varying cutoff values and diagnostic performance. For instance, in hospitalized children with HF, a cutoff value of 70 ng/mL showed a sensitivity of 69% and a specificity of 83% for diagnosis (Khatab et al., 2021). However, no notable alteration in cMyBP-C levels was observed before and after treatment in patients who did not survive, whereas those who recovered exhibited a significant post-treatment decrease (Khatab et al., 2021). Furthermore, a study from Zagazig University identified a cutoff value of 63.3 ng/mL

for prognostic prediction of acute HF in pediatric patients, with a sensitivity of 81.8% and a specificity of 75% (El-Moghazy et al., 2020).

Table 2 Summary of the studies reporting circulating cMyBP-C and myocardial infarction

Animal Species	Model	Number of samples	Conclusion	Ref.
Rat and Human	MI	18 rats; 11MI, 7 sham 26 people; 15 patients, 11 controls	- cMyBP-C concentration in the plasma of MI rats and patients was significantly higher than in the sham and control groups - In post-MI rats and humans, plasma cMyBP-C levels were higher than plasma cTnI levels - cMyBP-C is released from rodent myocardium at least as quickly as cTn and can be detected in the peripheral blood	(Govindan et al., 2012)
Mice	MI	8 mice; 6 LAD, 1 NoRe, 1 Sh, 1 HOM	- cMyBP-C is released from rodent myocardium as quickly as cTn	(Baker et al., 2015)
Human	MI	65 patients with MI 40 patients with PTCA 54 healthy controls	- Patients with MI had considerably higher plasma levels of cMyBP-C than healthy controls, and were significantly decreased after performing PTCA for 12 hours - Plasma cMyBP-C at a cutoff of 68.1 ng/mL provided a sensitivity = 66.2%, specificity = 100%, and AUC = 0.89	(Govindan et al., 2013)
Human	AMI	603 patients without AMI 173 patients with AMI	- cMyBP-C concentration in patients with AMI was markedly elevated with other diagnoses. - cMyBP-C had more discrimination power for AMI than hs-cTnT	(Kaier et al., 2019)
Human	AMI	1614 patients without AMI 340 patients with AMI	- cMyBP-C at threshold 10 ng/L: sensitivity 99.6%, negative predictive value 99.8% - cMyBP-C threshold 120 ng/L: specificity 94.7%, positive predictive value 71%. cMyBP-C has a higher ability to diagnose and prognosis AMI compared to cTn	(Kaier et al., 2017)

MI; myocardial infarction, cTnI; cardiac troponin I, LAD; left anterior descending coronary artery ligation, cTn; cardiac troponin, NoRe; no perfusion, Sh; sham-operated controls, HOM; murine heart homogenate, STEMI; ST-elevation myocardial infarction, TASH; trans-coronary therapeutic ablation of septal hypertrophy, CABG; coronary artery bypass surgery. PTCA; percutaneous trans-coronary angioplasty, AMI; Acute myocardial infarction, hs-cTnT; high-sensitivity cardiac troponin T.

A previous clinical study in adults with acute dyspnea reported that plasma cMyBP-C concentrations were higher in cases with acute HF compared to those with other diagnoses, achieving an area under the curve (AUC) of 0.81 for HF diagnosis (Kozhuharov et al., 2021), and the AUC was higher than that of high-sensitivity cardiac troponin (hs-cTn; AUC = 0.79) but lower than NT-proBNP (AUC = 0.91) (Kozhuharov et al., 2021). Notably, combining cMyBP-C with NT-proBNP did not enhance the AUC of NT-proBNP alone. Additionally, the AUCs of cMyBP-C combined with hs-cTnT or NT-proBNP showed no significant differences at 90, 180, and 360 days (Kozhuharov et al., 2021). A summary of circulating cMyBP-C and heart failure is presented in Table 3.

Cardiomyopathy and circulating cMyBP-C levels

Previous research on circulating cMyBP-C levels in cardiomyopathy remains limited, with only two studies addressing this topic. Previous study in humans with aortic stenosis demonstrated that serum cMyBP-C concentrations were correlated with indexed left ventricular mass measured via cardiac magnetic resonance imaging, fibrosis volume, and the severity of aortic stenosis as assessed by aortic valve maximum blood velocity measurement (Anand et al., 2018). Another study in DCM patients revealed that the concentration of serum cMyBP-C was elevated in DCM compared to the control groups (Sun et al., 2019). A summary of circulating cMyBP-C and cardiomyopathy is presented in Table 4.

Table 3 Summary of the studies reporting circulating cMyBP-C and heart failure

Animal Species	Model	Number of samples	Conclusion	Ref.
Human	HF	50 patients 25 controls	- cMyBP-C plasma levels were higher in HF patients compared to post-treatment and controls - For diagnosing HF, at a cutoff of 45 ng/mL, AUC = 0.999 - For predicting adverse outcomes; at a cutoff 152 ng/mL, AUC = 0.915	(El Amrousy et al., 2017)
Human	HF	35 patients 30 healthy	- The HF patients had increased cMyBP-C levels compared to healthy children (at a cutoff > 70 ng/ml, AUC =0.792) - In recovered patients, there was a notable decrease in cMyBP-C level after treatment	(Khatab et al., 2021)
Human	HF	26 patients with HF before and after treatment	- Inverse relation between plasma level of cMyBP-C and EF% and FS% - Increasing cMyBP-C is related to the severity of HF (Ross classification) - Increasing plasma levels of cMyBP-C were associated with a worse prognosis - As a prognostic predictor, cMyBP-C at a cutoff 63.3 ng/mL, sensitivity 81.8%, specificity 75%	(El-Moghazy et al., 2020)
Human	Acute HF	548 with cardiogenic dyspnea 535 with non-cardiogenic dyspnea	- Patients with AHF had higher cMyBP-C levels compared to those with other diagnoses - The AUC of cMyBP-C (0.81) was higher than hs-cTnT (0.79) but lower than NT-proBNP (0.91) - No substantial differences between the AUC of cMyBP-C, hs-cTnT, and NT-proBNP	(Kozhuharov et al., 2021)

HF; heart failure, hs-cTnT; high-sensitivity cardiac troponin T, NT-proBNP; N-terminal pro B-type natriuretic peptide.

While human studies have provided initial insights, research on cMyBP-C as a biomarker for cardiomyopathy in veterinary medicine remains sparse. To date, no comprehensive studies have evaluated circulating cMyBP-C levels in naturally occurring cardiomyopathies in animals. Given the prevalence of hypertrophic cardiomyopathy (HCM) in cats and dilated cardiomyopathy (DCM) in dogs, further investigation is warranted to determine the diagnostic and prognostic utility of cMyBP-C in veterinary patients. Expanding this research may enhance early detection and management strategies for cardiomyopathic conditions in companion animals (Freeman et al., 2017). Further insights into cardiomyopathy are provided by numerous reports on *MYBPC3* gene mutations, which are discussed in the next section.

Table 4 Summary of the studies reporting circulating cMyBP-C and cardiomyopathy

Animal Species	Model	Number of samples	Conclusion	Ref.
Human	AS	AS =161 healthy = 46	- In patients with AS, cMyBP-C concentration correlated with left ventricular mass, fibrosis volume, and extracellular volume, but not in controls - cMyBP-C exhibited no correlation with coronary calcium scores	(Anand et al., 2018)
Human	DCM	DCM =57 Normal = 34	- The concentration of cMyBP-c in the DCM group was markedly elevated compared to the normal group	(Sun et al., 2019)

AS; aortic stenosis, DCM; dilated cardiomyopathy.

THE MUTATION OF THE MYBPC3 GENE AND HEART DISEASE IN HUMANS VERSUS FELINES

Mutations in the *MYBPC3* gene have been strongly linked to an increased risk of developing certain cardiovascular diseases, particularly hypertrophic cardiomyopathy (HCM) (Nabeel et al., 2017). Data from the Human Gene Mutation Database in 2014 indicated that *MYBPC3* mutations were responsible for approximately 40% of patients diagnosed with HCM (Stenson et al., 2014). Furthermore, a subsequent study identified more than 350 distinct *MYBPC3* mutations associated with HCM, accounting for 40–50% of all HCM-related genetic mutations (Carrier et al., 2015).

MYBPC3 Mutations are typically linked to a postponed onset, reduced penetrance, less severe hypertrophy, and improved survival rate compared to β-myosin heavy chain (*MYH7*) mutations (Charron et al., 1998; Schlossarek et al., 2011). The most common mutation type in cMyBP-C is a missense mutation; however, other types, including insertions, deletions, premature termination codons, frameshifts, and intronic mutations, have also been reported (Nabeel et al., 2017). These mutations can occur in different domains of the cMyBP-C protein, leading to distinct structural abnormalities or functional impairments (Nabeel et al., 2017).

A previous study on HCM patients identified approximately 147 mutations in *MYBPC3*, which encodes cardiac myosin-binding protein C. Collectively, these mutations account for nearly 15% of all HCM cases (Tanjore et al., 2008). Moreover, a study conducted in German patients demonstrated that mutations in *MYBPC3* or *MYH7* contribute to both HCM (41%) and dilated cardiomyopathy (DCM, 11%) (Waldmuller et al., 2011). However, splice-site and frameshift mutations in *MYBPC3* were observed more frequently in hypertrophic than in dilated cardiomyopathy, suggesting that cardiac *MYBPC3* haploinsufficiency may contribute to HCM rather than DCM (Marín-García, 2014).

In veterinary medicine, mutations in the *MYBPC3* gene, which encodes the cMyBP-C protein, have been linked to feline HCM, particularly in Maine Coon and Ragdoll cats. The causal mutations have been identified as the A31P mutation, where alanine (A) at position 31 is replaced by proline (P) in Maine Coon cats, and the R820W mutation, where arginine (R) at position 820 is replaced by tryptophan (W) in Ragdoll cats (Cesta et al., 2005; Godiksen et al., 2011; Luis Fuentes et al., 2020). The prevalence of *MYBPC3* mutations among cats with HCM is estimated to be approximately 34–41.5% (Sukumolanan and Petchdee, 2020). In addition, A31P homozygous cats are a valuable hereditary model for HCM, showing early and severe disease progression, making them suitable for studies on therapeutic interventions (Stern et al., 2023). Given the genetic predisposition, the American College of Veterinary Internal Medicine (Luis Fuentes et al., 2020) consensus statement recommends genetic testing for *MYBPC3* mutations in Maine Coons and Ragdolls intended for reproduction, with the goal of reducing the occurrence of these mutations and the development of HCM within these breeds (Carlos Sampedrano et al., 2009; Longeri et al., 2013). However, genetic testing has certain limitations (Ho, 2012). In Maine Coon cats, the homozygosity of the *MYBPC3*-A31P mutation only explained 43% of feline HCM cases in the Maine Coon cats group study (Godiksen et al., 2011). Furthermore, some Maine Coon and Ragdoll cats diagnosed with HCM have tested negative for *MYBPC3* mutations (Carlos Sampedrano et al., 2009; Longeri et al., 2013). In addition, genetic testing for these specific mutations in other feline breeds is not recommended, as the *MYBPC3* mutations appear to be largely restricted to Maine Coon (A31P) and Ragdoll cats (R820W) (Luis Fuentes et al., 2020; Sukumolanan and Petchdee, 2020).

FACTOR THAT INTERFERES WITH CIRCULATING cMyBP-C LEVELS

The mutation of the *MYBPC3* gene

The study of HCM patients with *MYBPC3* mutations exhibits lower cMyBP-C protein levels and reduced *MYBPC3* mRNA expression in cardiac tissue compared to HCM patients without these mutations (Parbhudayal et al., 2018). In agreement with prior studies, a homogeneous group of familial HCM patients with frameshift *MYBPC3* mutations demonstrated that Western blotting revealed significantly reduced levels of full-length cMyBP-C in *MYBPC3*-mutated myocardium compared to control myocardium (van Dijk et al., 2009). These findings suggest that *MYBPC3* mutations contribute to cMyBP-C deficiency at both the transcriptional and protein levels, potentially playing a pivotal role in the pathophysiology of HCM. Further research is warranted to explore the downstream effects of this deficiency on myocardial function and its implications for targeted therapeutic strategies.

Signalment

The study of the biological variation of cMyBP-C in healthy humans showed that women had significantly lower median cMyBP-C concentration than men (Alaour et al., 2022). Nevertheless, when measured serially, cMyBP-C exhibits an acceptable reference change value and a low index of individuality II, suggesting it is suitable for disease monitoring, risk assessment, and prognosis (Alaour et al., 2022). These findings emphasize the potential of cMyBP-C as a reliable biomarker in clinical practice despite inherent biological variation. Further research is warranted to determine whether sex-specific reference intervals or adjusted diagnostic thresholds may improve the accuracy of cMyBP-C in disease detection and risk assessment.

Other Illnesses

The study in patients with renal impairment revealed a reduced diagnostic accuracy for cMyBP-C, NT-proBNP, and hs-cTnT (Kozhuharov et al., 2021). However, cMyBP-C exhibited superior prognostic performance for short-term outcomes compared to NT-proBNP in these patients (Kozhuharov et al., 2021). Moreover, in pediatric heart failure, cMyBP-C levels were directly proportional to the severity of heart failure (Modified ROSS score) and the severity of pulmonary hypertension (Alaour et al., 2022). Consistent with a study investigating novel biomarkers of hypertension in men revealed significantly higher cMyBP-C levels in hypertensive patients across various conditions compared to controls (Charkiewicz et al., 2022). These findings suggest that cMyBP-C may serve as a valuable prognostic biomarker across diverse cardiovascular and systemic conditions. While its diagnostic utility may be influenced by comorbidities such as renal dysfunction, its prognostic significance in heart failure, pulmonary hypertension, and hypertension highlights its potential role in risk stratification and patient management.

Comparison of cMyBP-C with Established and Emerging Cardiac Biomarkers in Cats

cMyBP-C has emerged as a novel biomarker with potential utility in the diagnosis and monitoring of feline cardiomyopathies. To contextualize its clinical value, it is important to compare cMyBP-C with both widely used and recently proposed biomarkers in feline cardiac diagnostics. cTn and NT-proBNP are among the most extensively validated and widely applied biomarkers in feline cardiology

(Luis Fuentes et al., 2020). These biomarkers are particularly useful for distinguishing cardiac from non-cardiac causes of respiratory distress and have demonstrated prognostic value in assessing the risk of cardiovascular mortality (Borgeat et al., 2014; Luis Fuentes et al., 2020). NT-proBNP, a biomarker of myocardial stretch and volume overload, has proven utility in differentiating cardiac from non-cardiac causes of dyspnea and in assessing the severity of heart failure (Ward et al., 2018; Luis Fuentes et al., 2020). Importantly, NT-proBNP is available in the form of a point-of-care SNAP test, which enables rapid, in-clinic assessment and facilitates timely clinical decision-making (Mainville et al., 2015). Nevertheless, NT-proBNP levels can be influenced by renal function and age, and do not directly reflect structural changes in the myocardium disease (Lalor et al., 2009; Singh et al., 2010; Hanas et al., 2020). cTnI and cTnT are highly specific indicators of myocardial cell injury (Langhorn et al., 2014). Elevated troponin concentrations are associated with active myocardial damage (Connolly et al., 2003; Langhorn et al., 2013; Hori et al., 2018; Katrukha and Katrukha, 2021). However, these elevations may also occur in systemic diseases such as sepsis, renal insufficiency, or hyperthyroidism, potentially limiting their specificity in distinguishing primary cardiomyopathy from secondary cardiac (Connolly et al., 2003; Eggers et al., 2019).

Recent studies have identified several emerging biomarkers that may offer additional insight into the pathophysiological mechanisms underlying feline cardiomyopathies. Galectin-3 (Gal-3), a β-galactoside-binding lectin, plays a role in inflammation and fibrogenesis (Gawor et al., 2017; Stack et al., 2023); its upregulation in cardiac fibrosis has demonstrated prognostic value in both human and veterinary medicine (Hara et al., 2020; Stack et al., 2023). Interleukin-18 (IL-18), a proinflammatory cytokine, is associated with myocardial inflammation and adverse remodeling (Chien et al., 2016; Kitz et al., 2019; Chong et al., 2024). Insulin-like growth factor binding protein 2 (IGFBP-2) serves as a metabolic marker within the IGF signaling pathway, which is known to be dysregulated in cardiac hypertrophy and failure (Chong et al., 2024). Brain-type glycogen phosphorylase (PYGB), an enzyme involved in glycogen metabolism, has been linked to myocardial stress and energy imbalance (Yang et al., 2024). Collectively, these emerging biomarkers hold considerable promise for enhancing the diagnosis, monitoring, and pathophysiological understanding of feline cardiac disease. Nevertheless, their clinical application in veterinary cardiology remains constrained by several factors, including limited clinical validation in cats with cardiomyopathy, the lack of standardized assays for routine veterinary use, and the potential for elevated levels in non-cardiac conditions (Lopez et al., 2015; Niwa, Noguchi, et al., 2020; Fonfara et al., 2021; Hara, Kozhuharov et al., 2021). Previous studies suggest that the mutation of cMyBP-C was associated with the development of HCM, and that circulating levels of cMyBP-C may increase during the earlier stages of the disease compared to established biomarkers such as NT-proBNP or cTn, thereby providing a potential window for earlier diagnosis (Singh et al., 2010; Baker et al., 2015; Kaier et al., 2017; Hanas et al., 2020; Olalekan et al., 2025). The rapid decline of serum cMyBP-C may limit its usefulness in detecting chronic myocardial remodeling, such as in established HCM. However, it may serve as a potential biomarker for acute MI or stress in at-risk cats (Govindan et al., 2013; Baker et al., 2015). Despite this potential, no studies have examined serum cMyBP-C levels in cats with cardiomyopathy, leaving its behavior in feline cardiac disease unclear. This gap highlights the need for further research to determine its diagnostic potential and its role in elucidating the molecular mechanisms of cardiomyopathy. A summary of the advantages and disadvantages of cardiac biomarkers in cardiomyopathic cats is presented in Table 5.

Table 5 Summary of the advantages and disadvantages of cardiac biomarkers in cardiomyopathic cats

Biomarker	Advantages	Disadvantages
NT-proBNP	- A marker of volume overload (Booth et al., 2010) - Facilitates the differentiation between cardiac and non-cardiac causes of respiratory distress (Connolly et al., 2009; Fox et al., 2009; Hassdenteufel et al., 2013). - Available as SNAP tests, giving rapid results (Mainville et al., 2015) - Strong evidence bases in veterinary cardiology with many peer-reviewed studies (Luis Fuentes et al., 2020; Lu et al., 2021)	- In chronic renal disease, levels are increased, complicating interpretation (Lalor et al., 2009). - Decreased sensitivity for mild severity of cardiac disease (Singh et al., 2010; Hanas et al., 2020)
cTnI	- High specificity for myocardial injury (Connolly et al., 2003; Park et al., 2017; Katrukha and Katrukha, 2021) - Correlates with disease severity, including the presence of left atrial enlargement or HF (Hori et al., 2018) - Help distinguish between HCM and non-HCM groups (Connolly et al., 2003; Langhorn et al., 2013; Hori et al., 2018) - Can be utilized to distinguish cats with cardiac causes of dyspnea from those with noncardiac conditions (Herndon et al., 2008; Wells et al., 2014)	- cTnI is elevated in any cause of myocardial injury—including myocarditis, trauma, sepsis, or toxins—so not HCM-specific (Connolly et al., 2003; Eggers et al., 2019) - Some healthy cats may have detectable or mildly elevated cTnI; reference ranges are narrow (Hori et al., 2018) - Can rise with acute stress or transient ischemia, such as during hospitalization or sedation (Hanas et al., 2022; Konishi et al., 2022) - Although trends can be informative, there are no universally accepted thresholds for staging feline HCM based on cTnI alone (Hori et al., 2018)
cTnT	- High specificity for myocardial injury like cTnI (Langhorn et al., 2014) - Longer half-life than cTnI: more stable and useful for chronic disease monitoring (Potter et al., 2022)	- cTnT is elevated in any myocardial injury, including myocarditis, trauma, hypoxia, or systemic disease (Tanindi and Cemri, 2011; Lindner et al., 2014; Eggers et al., 2019) - Not as widely available or standardized in veterinary diagnostics compared to cTnI or NT-proBNP
Gal-3	- An indicator of myocardial fibrosis, a key feature in the progression of HCM (Gawor et al., 2017; Stack et al., 2023) - Increased Gal-3 levels have been positively correlated with left atrial size in HCM cats, suggesting its role in cardiac remodeling (Stack et al., 2023) - Potential for early detection and prognostic value in various heart diseases in humans (Hara et al., 2020)	- Currently, there are no standardized assays or established reference ranges for Gal-3 in cats, limiting its clinical applicability - Gal-3 levels may be elevated in other conditions, such as systemic inflammation or kidney disease, which could confound its specificity for HCM (Lopez et al., 2015; Hara et al., 2020) - One study found no significant difference in Gal-3 levels between cats with ACVIM stage B and stage C HCM, questioning its utility in distinguishing disease severity (Stack et al., 2023)
IL-18	- Reflects inflammatory and fibrotic processes, key components in HCM pathogenesis (Chien et al., 2016; Kitz et al., 2019) - Serum IL-18 levels are elevated in HCM cats with CHF, indicating potential as a marker for disease severity (Chong et al., 2024)	- Lack of standardized assays: Currently, there are no standardized assays or established reference ranges for IL-18 in cats, limiting its clinical applicability - May be elevated in other conditions, such as systemic inflammation or kidney disease, which could confound its specificity for HCM (Fonfara et al., 2021)

Biomarker	Advantages	Disadvantages
IGFBP-2	- Serum IGFBP-2 RNA is highest in subclinical HCM cats, suggesting potential as an early-stage marker (Chong et al., 2024)	- IGFBP-2 levels may be elevated in other conditions, such as metabolic disorders, which could confound its specificity for HCM (Heald et al., 2006; Migita et al., 2010; Yang et al., 2020) - Limited clinical validation: While studies have shown differential expression of IGFBP-2 in cats with HCM, further research is needed to confirm its reliability and utility as a biomarker - Lack of standardized assays: Currently, there are no standardized assays or established reference ranges for IGFBP-2 in cats, limiting its clinical applicability
PYGB	- Reflects myocardial glycogen metabolism, which is crucial for energy production, especially under stress conditions (Yang et al., 2024) - A study suggests that PYGB levels can rise early after myocardial injury, potentially aiding in the early detection of cardiac issues (Yang et al., 2024)	- PYGB is also present in the brain and other tissues, which may lead to elevated levels in conditions unrelated to HCM, reducing its specificity (Jiang et al., 2022; Ren et al., 2024; Yang et al., 2024) - Limited clinical validation in cats: There is currently insufficient evidence to support PYGB as a reliable biomarker for HCM in cats, with studies showing no significant differences in PYGB levels between healthy cats and those with HCM (Chong et al., 2024)
cMyBP-C	- Insight into disease mechanism: Unlike NT-proBNP (which indicates stretch), cMyBP-C alterations may indicate myocyte damage or turnover (Helms et al., 2020) - Early biomarker for acute MI and HF in humans (El Amrousy et al., 2017; Kaier et al., 2017; Kozhuharov et al., 2021) - The mutation of this protein has an important role in the development of HCM (Doh et al., 2019)	- Other illnesses, sex, and gene mutations may interfere with circulating cMyBP-C levels (Parbhudayal et al., 2018; Kozhuharov et al., 2021; Alaour et al., 2022) - The rapid elevation and subsequent clearance of serum cMyBP-C may restrict its applicability in chronic conditions, such as HCM - No published studies have investigated serum cMyBP-C levels in cats with cardiomyopathy

NT-proBNP; N-terminal pro B-type natriuretic peptide, cTnI; cardiac troponin I, cTnT; cardiac troponin T, Gal-3; galactin3, IL-18; interleukin 18, IGFBP-2; insulin-like growth factor binding protein 2, PYG; brain-type glycogen phosphorylase B, MI; myocardial infarction, HCM; hypertrophic cardiomyopathy.

CONCLUSIONS

Cardiac myosin-binding protein C (cMyBP-C) is a sarcomeric protein expressed in cardiomyocytes and has been implicated in cardiac injury, ischemia, and the pathophysiology of cardiovascular diseases. Due to its rapid release, accumulation, and clearance kinetics, cMyBP-C has emerged as a promising biomarker for the early diagnosis and prognosis of feline HCM. Its implementation in clinical practice may facilitate early disease detection, inform timely intervention strategies, and enhance risk stratification for heart failure-related mortality. However, significant knowledge gaps remain regarding circulating cMyBP-C levels in cats, limiting its current clinical applicability. To effectively translate cMyBP-C research from bench to bedside, several steps are needed: (1) establishing species-specific reference intervals; (2) validating diagnostic and prognostic accuracy in well-characterized feline cohorts; (3) standardizing assays suitable for veterinary use; and (4) understanding the influence of genetic mutations, patient-specific factors, and comorbidities on biomarker levels. Furthermore, future research efforts should prioritize the inclusion of proteomic studies and longitudinal cohort studies within feline populations. These studies will be essential for elucidating the mechanisms of disease and for tracking biomarker dynamics over time. Such investigations will not only enhance the diagnostic utility of cMyBP-C as a potential biomarker but will also serve as valuable tools in uncovering the molecular mechanisms that drive the development and progression of cardiomyopathy.

AUTHOR CONTRIBUTIONS

Wanpitak Pongkan: Conceptualization (lead); writing – original draft (equal); data curation (equal); visualization (equal); writing – review and editing (equal).
Nutcha Tanakwang: Conceptualization (supporting); data curation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal); funding acquisition (lead).

CONFLICT OF INTEREST

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

Alaour, B., Kaier, T., Demir, Z., Van Doorn, W., Kimenai, D., Zar, A., Van Der Linden, N., Marber, M., Meex, S.J.E.H.J., 2021. Physiological circadian rhythm of cardiac myosin-binding protein C (cMyC) and cardiac troponin. Eur. Heart. J. 42, ehab724.1395.

Alaour, B., Omland, T., Torsvik, J., Kaier, T.E., Sylte, M.S., Strand, H., Quraishi, J., McGrath, S., Williams, L., Meex, S., Redwood, S., Marber, M., Aakre, K.M., 2022. Biological variation of cardiac myosin-binding protein C in healthy individuals. Clin. Chem. Lab. Med. 60(4), 576-583.

Anand, A., Chin, C., Shah, A.S.V., Kwiecinski, J., Vesey, A., Cowell, J., Weber, E., Kaier, T., Newby, D.E., Dweck, M., Marber, M.S., Mills, N.L., 2018. Cardiac myosin-binding protein C is a novel marker of myocardial injury and fibrosis in aortic stenosis. Heart. 104(13), 1101-1108.

Baker, J.O., Tyther, R., Liebetrau, C., Clark, J., Howarth, R., Patterson, T., Mollmann, H., Nef, H., Sicard, P., Kailey, B., Devaraj, R., Redwood, S.R., Kunst, G., Weber, E., Marber, M.S., 2015. Cardiac myosin-binding protein C: a potential early biomarker of myocardial injury. Basic Res. Cardiol. 110(3), 23.

Barefield, D., Sadayappan, S., 2010. Phosphorylation and function of cardiac myosin binding protein-C in health and disease. J. Mol. Cell. Cardiol. 48(5), 866-875.

Betocchi, S., Hess, O.M., Losi, M.A., Nonogi, H., Krayenbuehl, H.P., 1993. Regional left ventricular mechanics in hypertrophic cardiomyopathy. Circulation. 88, 2206-2214.

Bezold, K.L., Shaffer, J.F., Khosa, J.K., Hoye, E.R., Harris, S.P., 2013. A gain-of-function mutation in the M-domain of cardiac myosin-binding protein-C increases binding to actin. J. Biol. Chem. 288(30), 21496-21505.

Booth, J., Pinney, J., Davenport, A., 2010. N-terminal proBNP--marker of cardiac dysfunction, fluid overload, or malnutrition in hemodialysis patients? Clin. J. Am. Soc. Nephrol. 5(6), 1036-1040.

Borgeat, K., Sherwood, K., Payne, J.R., Luis Fuentes, V., Connolly, D.J., 2014. Plasma cardiac troponin I concentration and cardiac death in cats with hypertrophic cardiomyopathy. J. Vet. Intern. Med. 28(6), 1731-1737.

Carlos Sampedrano, C., Chetboul, V., Mary, J., Tissier, R., Abitbol, M., Serres, F., Gouni, V., Thomas, A., Pouchelon, J.L., 2009. Prospective echocardiographic and tissue Doppler imaging screening of a population of Maine Coon cats tested for the A31P mutation in the myosin-binding protein C gene: a specific analysis of the heterozygous status. J. Vet. Intern. Med. 23(1), 91-99.

Carrier, L., Mearini, G., Stathopoulou, K., Cuello, F., 2015. Cardiac myosin-binding protein C (MYBPC3) in cardiac pathophysiology. Gene. 573(2), 188-197.

Cesta, M.F., Baty, C.J., Keene, B.W., Smoak, I.W., Malarkey, D.E., 2005. Pathology of end-stage remodeling in a family of cats with hypertrophic cardiomyopathy. Vet. Pathol. 42(4), 458-467.

Charkiewicz, A.E., Garley, M., Ratajczak-Wrona, W., Jablonska, E., Miltyk, W., Motyka, J., Omeljaniuk, W.J., 2022. The diagnostic potential of novel biomarkers of hypertension in men. Arch. Med. Sci. 18(6), 1666-1671.

Charron, P., Dubourg, O., Desnos, M., Bennaceur, M., Carrier, L., Camproux, A.C., Isnard, R., Hagege, A., Langlard, J.M., Bonne, G., Richard, P., Hainque, B., Bouhour, J.B., Schwartz, K., Komajda, M., 1998. Clinical features and prognostic implications of familial hypertrophic cardiomyopathy related to the cardiac myosin-binding protein C gene. Circulation. 97(22), 2230-2236.

Chien, Y., Chien, C.S., Chiang, H.C., Huang, W.L., Chou, S.J., Chang, W.C., Chang, Y.L., Leu, H.B., Chen, K.H., Wang, K.L., Lai, Y.H., Liu, Y.Y., Lu, K.H., Li, H.Y., Sung, Y.J., Jong, Y.J., Chen, Y.J., Chen, C.H., Yu, W.C., 2016. Interleukin-18 deteriorates Fabry cardiomyopathy and contributes to the development of left ventricular hypertrophy in Fabry patients with GLA IVS4+919 G>A mutation. Oncotarget. 7(52), 87161-87179.

Chong, A., Joshua, J., Raheb, S., Pires, A., Colpitts, M., Caswell, J.L., Fonfara, S., 2024. Evaluation of potential novel biomarkers for feline hypertrophic cardiomyopathy. Res. Vet. Sci. 180, 105430.

Connolly, D.J., Cannata, J., Boswood, A., Archer, J., Groves, E.A., Neiger, R., 2003. Cardiac troponin I in cats with hypertrophic cardiomyopathy. J. Feline Med. Surg. 5(4), 209-216.

Connolly, D.J., Soares Magalhaes, R.J., Fuentes, V.L., Boswood, A., Cole, G., Boag, A., Syme, H.M., 2009. Assessment of the diagnostic accuracy of circulating natriuretic peptide concentrations to distinguish between cats with cardiac and non-cardiac causes of respiratory distress. J. Vet. Cardiol. 11, S41-50.

Decker, R.S., Decker, M.L., Kulikovskaya, I., Nakamura, S., Lee, D.C., Harris, K., Klocke, F.J., Winegrad, S., 2005. Myosin-binding protein C phosphorylation, myofibril structure, and contractile function during low-flow ischemia. Circulation. 111(7), 906-912.

Decker, R.S., Nakamura, S., Decker, M.L., Sausamuta, M., Sinno, S., Harris, K., Klocke, F.J., Kulikovskaya, I., Winegrad, S., 2012. The dynamic role of cardiac myosin binding protein-C during ischemia. J. Mol. Cell. Cardiol. 52(5), 1145-1154.

Doh, C.Y., Li, J., Mamidi, R., Stelzer, J.E., 2019. The HCM-causing Y235S cMyBPC mutation accelerates contractile function by altering C1 domain structure. Biochim. Biophys. Acta. Mol. Basis. Dis. 1865(3), 661-677.

Eggers, K.M., Jernberg, T., Lindahl, B., 2019. Cardiac Troponin elevation in patients without a specific diagnosis. J. Am. Coll. Cardiol. 73(1), 1-9.

Ehler, E., Rothen, B.M., Hammerle, S.P., Komiyama, M., Perriard, J.C., 1999. Myofibrillogenesis in the developing chicken heart: assembly of Z-disk, M-line and the thick filaments. J. Cell Sci. 112, 1529-1539.

El-Armouche, A., Pohlmann, L., Schlossarek, S., Starbatty, J., Yeh, Y.H., Nattel, S., Dobrev, D., Eschenhagen, T., Carrier, L., 2007. Decreased phosphorylation levels of cardiac myosin-binding protein-C in human and experimental heart failure. J. Mol. Cell. Cardiol. 43(2), 223-229.

El-Moghazy, E.M., Morsy, S.M., Abdallah, S.H., Ali, M.A., 2020. Cardiac myosin binding protein C plasma level as a diagnostic and prognostic biomarker in heart failure in children. 80(3), 1097-1102.

El Amrousy, D., Hodeib, H., Suliman, G., Hablas, N., Salama, E.R., Esam, A., 2017. Diagnostic and prognostic value of plasma levels of cardiac myosin binding protein-c as a novel biomarker in heart failure. Pediatr. Cardiol. 38(2), 418-424.

Ferasin, L., DeFrancesco, T., 2015. Management of acute heart failure in cats. J. Vet. Cardiol. 17 Suppl 1, S173-189.

Flashman, E., Redwood, C., Moolman-Smook, J., Watkins, H., 2004. Cardiac myosin binding protein C: its role in physiology and disease. Circ. Res. 94(10), 1279-1289.

Fonfara, S., Kitz, S., Monteith, G., Hahn, S., Kipar, A., 2021. Myocardial transcription of inflammatory and remodeling markers in cats with hypertrophic cardiomyopathy and systemic diseases associated with an inflammatory phenotype. Res. Vet. Sci. 136, 484-494.

Fox, P.R., Oyama, M.A., Reynolds, C., Rush, J.E., DeFrancesco, T.C., Keene, B.W., Atkins, C.E., Macdonald, K.A., Schober, K.E., Bonagura, J.D., Stepien, R.L., Kellihan, H.B., Nguyenba, T.P., Lehmkuhl, L.B., Lefbom, B.K., Moise, N.S., Hogan, D.F., 2009. Utility of plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) to distinguish between congestive heart failure and non-cardiac causes of acute dyspnea in cats. J. Vet. Cardiol. 11, S51-61.

Freeman, L.M., Rush, J.E., Stern, J.A., Huggins, G.S., Maron, M.S., 2017. Feline hypertrophic cardiomyopathy: a spontaneous large animal model of human HCM. Cardiol. Res. 8(4), 139-142.

Gautel, M., Zuffardi, O., Freiburg, A., Labeit, S., 1995. Phosphorylation switches specific for the cardiac isoform of myosin binding protein-C: a modulator of cardiac contraction? EMBO J. 14(9), 1952-1960.

Gawor, M., Spiewak, M., Janas, J., Kozuch, K., Wrobel, A., Mazurkiewicz, L., Baranowski, R., Marczak, M., Grzybowski, J., 2017. The usefulness of sST2 and galectin-3 as novel biomarkers for better risk stratification in hypertrophic cardiomyopathy. Kardiol. Pol. 75(10), 997-1004.

Godiksen, M.T., Granstrom, S., Koch, J., Christiansen, M., 2011. Hypertrophic cardiomyopathy in young Maine Coon cats caused by the p.A31P cMyBP-C mutation--the clinical significance of having the mutation. Acta Vet. Scand. 53, 7.

Govindan, S., Kuster, D.W., Lin, B., Kahn, D.J., Jeske, W.P., Walenga, J.M., Leya, F., Hoppensteadt, D., Fareed, J., Sadayappan, S., 2013. Increase in cardiac myosin binding protein-C plasma levels is a sensitive and cardiac-specific biomarker of myocardial infarction. Am. J. Cardiovasc. Dis. 3(2), 60-70.

Govindan, S., McElligott, A., Muthusamy, S., Nair, N., Barefield, D., Martin, J.L., Gongora, E., Greis, K.D., Luther, P.K., Winegrad, S., Henderson, K.K., Sadayappan, S., 2012. Cardiac myosin binding protein-C is a potential diagnostic biomarker for myocardial infarction. J. Mol. Cell. Cardiol. 52(1), 154-164.

Gruen, M., Prinz, H., Gautel, M., 1999. cAPK-phosphorylation controls the interaction of the regulatory domain of cardiac myosin binding protein C with myosin-S2 in an on-off fashion. FEBS Lett. 453(3), 254-259.

Hanas, S., Holst, B.S., Hoglund, K., Haggstrom, J., Tidholm, A., Ljungvall, I., 2020. Effect of feline characteristics on plasma N-terminal-prohormone B-type natriuretic peptide concentration and comparison of a point-of-care test and an ELISA test. J. Vet. Intern. Med. 34(3), 1187-1197.

Hanas, S., Larsson, A., Ryden, J., Lilliehook, I., Haggstrom, J., Tidholm, A., Hoglund, K., Ljungvall, I., Holst, B.S., 2022. Cardiac troponin I in healthy Norwegian Forest Cat, Birman and domestic shorthair cats, and in cats with hypertrophic cardiomyopathy. J. Feline Med. Surg. 24(10), e370-e379.

Hara, A., Niwa, M., Kanayama, T., Noguchi, K., Niwa, A., Matsuo, M., Kuroda, T., Hatano, Y., Okada, H., Tomita, H., 2020. Galectin-3: a potential prognostic and diagnostic marker for heart disease and detection of early stage pathology. Biomolecules. 10(9), 1277.

Hara, A., Niwa, M., Noguchi, K., Kanayama, T., Niwa, A., Matsuo, M., Hatano, Y., Tomita, H., 2020. Galectin-3 as a next-generation biomarker for detecting early stage of various diseases. Biomolecules. 10(3), 389.

Hartzell, H.C., Glass, D.B., 1984. Phosphorylation of purified cardiac muscle C-protein by purified cAMP-dependent and endogenous Ca2+-calmodulin-dependent protein kinases. J. Biol. Chem. 259(24), 15587-15596.

Hassdenteufel, E., Henrich, E., Hildebrandt, N., Stosic, A., Schneider, M., 2013. Assessment of circulating N-terminal pro B-type natriuretic peptide concentration to differentiate between cardiac from noncardiac causes of pleural effusion in cats. J. Vet. Emerg. Crit. Care (San Antonio). 23(4), 416-422.

Heald, A.H., Kaushal, K., Siddals, K.W., Rudenski, A.S., Anderson, S.G., Gibson, J.M., 2006. Insulin-like growth factor binding protein-2 (IGFBP-2) is a marker for the metabolic syndrome. Exp. Clin. Endocrinol. Diabetes. 114(7), 371-376.

Heather, L.C., Howell, N.J., Emmanuel, Y., Cole, M.A., Frenneaux, M.P., Pagano, D., Clarke, K., 2011. Changes in cardiac substrate transporters and metabolic proteins mirror the metabolic shift in patients with aortic stenosis. PLoS One. 6(10), e26326.

Helms, A.S., Thompson, A.D., Glazier, A.A., Hafeez, N., Kabani, S., Rodriguez, J., Yob, J.M., Woolcock, H., Mazzarotto, F., Lakdawala, N.K., Wittekind, S.G., Pereira, A.C., Jacoby, D.L., Colan, S.D., Ashley, E.A., Saberi, S., Ware, J.S., Ingles, J., Semsarian, C., Michels, M., Olivotto, I., Ho, C.Y., Day, S.M., 2020. Spatial and functional distribution of MYBPC3 pathogenic variants and clinical outcomes in patients with hypertrophic cardiomyopathy. Circ. Genom. Precis. Med. 13(5), 396-405.

Herndon, W.E., Rishniw, M., Schrope, D., Sammarco, C.D., Boddy, K.N., Sleeper, M.M., 2008. Assessment of plasma cardiac troponin I concentration as a means to differentiate cardiac and noncardiac causes of dyspnea in cats. J. Am. Vet. Med. Assoc. 233(8), 1261-1264.

Ho, C.Y., 2012. Genetic considerations in hypertrophic cardiomyopathy. Prog. Cardiovasc. Dis. 54(6), 456-460.

Hori, Y., Iguchi, M., Heishima, Y., Yamashita, Y., Nakamura, K., Hirakawa, A., Kitade, A., Ibaragi, T., Katagi, M., Sawada, T., Yuki, M., Kanno, N., Inaba, H., Isayama, N., Onodera, H., Iwasa, N., Kino, M., Narukawa, M., Uchida, S., 2018. Diagnostic utility of cardiac troponin I in cats with hypertrophic cardiomyopathy. J. Vet. Intern. Med. 32(3), 922-929.

Jacques, A.M., Copeland, O., Messer, A.E., Gallon, C.E., King, K., McKenna, W.J., Tsang, V.T., Marston, S.B., 2008. Myosin binding protein C phosphorylation in normal, hypertrophic and failing human heart muscle. J. Mol. Cell. Cardiol. 45(2), 209-216.

Jacquet, S., Yin, X., Sicard, P., Clark, J., Kanaganayagam, G.S., Mayr, M., Marber, M.S., 2009. Identification of cardiac myosin-binding protein C as a candidate biomarker of myocardial infarction by proteomics analysis. Mol. Cell. Proteomics. 8(12), 2687-2699.

Jiang, L., Liu, S., Deng, T., Yang, Y., Zhang, Y., 2022. Analysis of the expression, function and signaling of glycogen phosphorylase isoforms in hepatocellular carcinoma. Oncol. Lett. 24(2), 244.

Kaier, T.E., Stengaard, C., Marjot, J., Sorensen, J.T., Alaour, B., Stavropoulou-Tatla, S., Terkelsen, C.J., Williams, L., Thygesen, K., Weber, E., Marber, M., Botker, H.E., 2019. Cardiac myosin-binding protein C to diagnose acute myocardial infarction in the pre-hospital setting. J. Am. Heart. Assoc. 8(15), e013152.

Kaier, T.E., Twerenbold, R., Puelacher, C., Marjot, J., Imambaccus, N., Boeddinghaus, J., Nestelberger, T., Badertscher, P., Sabti, Z., Gimenez, M.R., Wildi, K., Hillinger, P., Grimm, K., Loeffel, S., Shrestha, S., Widmer, D.F., Cupa, J., Kozhuharov, N., Miro, O., Martin-Sanchez, F.J., Morawiec, B., Rentsch, K., Lohrmann, J., Kloos, W., Osswald, S., Reichlin, T., Weber, E., Marber, M., Mueller, C., 2017. Direct comparison of cardiac myosin-binding protein C with cardiac troponins for the early diagnosis of acute myocardial infarction. Circulation. 136(16), 1495-1508.

Katrukha, I.A., Katrukha, A.G., 2021. Myocardial injury and the release of troponins I and T in the blood of patients. Clin. Chem. 67(1), 124-130.

Khatab, A.A., El-Gazzar, B.A., Rizk, M.S., Ghani, M.G.F.A., 2021. Value of plasma levels of cardiac myosin-binding protein C as a diagnostic and prognostic biomarker in heart failure. Menoufia Med. J. 34(1), 221.

Kittleson, M.D., Cote, E., 2021. The feline cardiomyopathies: 2. hypertrophic cardiomyopathy. J. Feline. Med. Surg. 23(11), 1028-1051.

Kitz, S., Fonfara, S., Hahn, S., Hetzel, U., Kipar, A., 2019. Feline hypertrophic cardiomyopathy: the consequence of cardiomyocyte-initiated and macrophage-driven remodeling processes? Vet. Pathol. 56(4), 565-575.

Konishi, K., Sakamoto, M., Satake, C., Isaka, M., Okazaki, S., Kono, S., Nakamura, T., Tashiro, H., Ushigusa, T., 2022. Perioperative changes in cardiac biomarkers in juvenile cats during neutering. Front. Vet. Sci. 9, 1008765.

Kozhuharov, N., Wussler, D., Kaier, T., Strebel, I., Shrestha, S., Flores, D., Nowak, A., Sabti, Z., Nestelberger, T., Zimmermann, T., Walter, J., Belkin, M., Michou, E., Lopez Ayala, P., Gualandro, D.M., Keller, D.I., Goudev, A., Breidthardt, T., Mueller, C., Marber, M., Investigators, B.V., 2021. Cardiac myosin-binding protein C in the diagnosis and risk stratification of acute heart failure. Eur. J. Heart Fail. 23(5), 716-725.

Kulikovskaya, I., McClellan, G., Flavigny, J., Carrier, L., Winegrad, S., 2003. Effect of MyBP-C binding to actin on contractility in heart muscle. J. Gen. Physiol. 122(6), 761-774.

Kuster, D.W., Cardenas-Ospina, A., Miller, L., Liebetrau, C., Troidl, C., Nef, H.M., Mollmann, H., Hamm, C.W., Pieper, K.S., Mahaffey, K.W., Kleiman, N.S., Stuyvers, B.D., Marian, A.J., Sadayappan, S., 2014. Release kinetics of circulating cardiac myosin binding protein-C following cardiac injury. Am. J. Physiol. Heart Circ. Physiol. 306(4), H547-556.

Lalor, S.M., Connolly, D.J., Elliott, J., Syme, H.M., 2009. Plasma concentrations of natriuretic peptides in normal cats and normotensive and hypertensive cats with chronic kidney disease. J. Vet. Cardiol. 11 Suppl 1, S71-79.

Langhorn, R., Tarnow, I., Willesen, J.L., Kjelgaard-Hansen, M., Skovgaard, I.M., Koch, J., 2014. Cardiac troponin I and T as prognostic markers in cats with hypertrophic cardiomyopathy. J. Vet. Intern. Med. 28(5), 1485-1491.

Langhorn, R., Willesen, J.L., Tarnow, I., Kjelgaard-Hansen, M., 2013. Evaluation of a high-sensitivity assay for measurement of canine and feline serum cardiac troponin I. Vet. Clin. Pathol. 42(4), 490-498.

Levine, R., Weisberg, A., Kulikovskaya, I., McClellan, G., Winegrad, S., 2001. Multiple structures of thick filaments in resting cardiac muscle and their influence on cross-bridge interactions. Biophys. J. 81(2), 1070-1082.

Lim, M.S., Sutherland, C., Walsh, M.P., 1985. Phosphorylation of bovine cardiac C-protein by protein kinase C. Biochem. Biophys. Res. Commun. 132(3), 1187-1195.

Lin, B.L., Li, A., Mun, J.Y., Previs, M.J., Previs, S.B., Campbell, S.G., Dos Remedios, C.G., Tombe, P.P., Craig, R., Warshaw, D.M., Sadayappan, S., 2018. Skeletal myosin binding protein-C isoforms regulate thin filament activity in a Ca(2+)-dependent manner. Sci. Rep. 8(1), 2604.

Lindner, G., Pfortmueller, C.A., Braun, C.T., Exadaktylos, A.K., 2014. Non-acute myocardial infarction-related causes of elevated high-sensitive troponin T in the emergency room: a cross-sectional analysis. Intern. Emerg. Med. 9(3), 335-339.

Longeri, M., Ferrari, P., Knafelz, P., Mezzelani, A., Marabotti, A., Milanesi, L., Pertica, G., Polli, M., Brambilla, P.G., Kittleson, M., Lyons, L.A., Porciello, F., 2013. Myosin-binding protein C DNA variants in domestic cats (A31P, A74T, R820W) and their association with hypertrophic cardiomyopathy. J. Vet. Intern. Med. 27(2), 275-285.

Lopez, B., Gonzalez, A., Querejeta, R., Zubillaga, E., Larman, M., Diez, J., 2015. Galectin-3 and histological, molecular and biochemical aspects of myocardial fibrosis in heart failure of hypertensive origin. Eur. J. Heart Fail. 17(4), 385-392.

Lu, T.L., Cote, E., Kuo, Y.W., Wu, H.H., Wang, W.Y., Hung, Y.W., 2021. Point-of-care N-terminal pro B-type natriuretic peptide assay to screen apparently healthy cats for cardiac disease in general practice. J. Vet. Intern. Med. 35(4), 1663-1672.

Luis Fuentes, V., Abbott, J., Chetboul, V., Cote, E., Fox, P.R., Haggstrom, J., Kittleson, M.D., Schober, K., Stern, J.A., 2020. ACVIM consensus statement guidelines for the classification, diagnosis, and management of cardiomyopathies in cats. J. Vet. Intern. Med. 34(3), 1062-1077.

Main, A., Fuller, W., Baillie, G.S., 2020. Post-translational regulation of cardiac myosin binding protein-C: a graphical review. Cell. Signal. 76, 109788.

Mainville, C.A., Clark, G.H., Esty, K.J., Foster, W.M., Hanscom, J.L., Hebert, K.J., Lyons, H.R., 2015. Analytical validation of an immunoassay for the quantification of N-terminal pro-B-type natriuretic peptide in feline blood. J. Vet. Diagn. Invest. 27(4), 414-421.

Marín-García, J.J.E.A., 2014. Cardiomyopathies: a comparative analysis of phenotypes and genotypes. pp. 363-426.

McClellan, G., Kulikovskaya, I., Winegrad, S., 2001. Changes in cardiac contractility related to calcium-mediated changes in phosphorylation of myosin-binding protein C. Biophys. J. 81(2), 1083-1092.

McClellan, G., Weisberg, A., Winegrad, S., 1994. cAMP can raise or lower cardiac actomyosin ATPase activity depending on alpha-adrenergic activity. Am. J. Physiol. 267, H431-442.

Migita, T., Narita, T., Asaka, R., Miyagi, E., Nagano, H., Nomura, K., Matsuura, M., Satoh, Y., Okumura, S., Nakagawa, K., Seimiya, H., Ishikawa, Y., 2010. Role of insulin-like growth factor binding protein 2 in lung adenocarcinoma: IGF-independent antiapoptotic effect via caspase-3. Am. J. Pathol. 176(4), 1756-1766.

Mohamed, A.S., Dignam, J.D., Schlender, K.K., 1998. Cardiac myosin-binding protein C (MyBP-C): identification of protein kinase A and protein kinase C phosphorylation sites. Arch. Biochem. Biophys. 358(2), 313-319.

Nabeel, D., Zhang, J., Lu, X., 2017. MyBP-C in cardiac conditions and its potential use as novel biomarker: a review. Eur. Acad. Res. 5, 1352-1368.

Offer, G., Moos, C., Starr, R., 1973. A new protein of the thick filaments of vertebrate skeletal myofibrils. Extractions, purification and characterization. J. Mol. Biol. 74(4), 653-676.

Olalekan, S.O., Bakare, O.O., Okwute, P.G., Osonuga, I.O., Adeyanju, M.M., Edema, V.B., 2025. Hypertrophic cardiomyopathy: insights into pathophysiology and novel therapeutic strategies from clinical studies. Egypt Heart J. 77, 5.

Pace, C., 2020. A practical guide to the new feline cardiomyopathy consensus statement. Vet. Nurs. 11(8), 375-378.

Parbhudayal, R.Y., Garra, A.R., Gotte, M.J.W., Michels, M., Pei, J., Harakalova, M., Asselbergs, F.W., van Rossum, A.C., van der Velden, J., Kuster, D.W.D., 2018. Variable cardiac myosin binding protein-C expression in the myofilaments due to MYBPC3 mutations in hypertrophic cardiomyopathy. J. Mol. Cell. Cardiol. 123, 59-63.

Park, K.C., Gaze, D.C., Collinson, P.O., Marber, M.S., 2017. Cardiac troponins: from myocardial infarction to chronic disease. Cardiovasc. Res. 113(14), 1708-1718.

Payne, J.R., Brodbelt, D.C., Luis Fuentes, V., 2015. Cardiomyopathy prevalence in 780 apparently healthy cats in rehoming centres (the CatScan study). J. Vet. Cardiol. 17, S244-257.

Pierce, K.V., Rush, J.E., Freeman, L.M., Cunningham, S.M., Yang, V.K., 2017. Association between survival time and changes in NT-proBNP in cats treated for congestive heart failure. J. Vet. Intern. Med. 31(3), 678-684.

Potter, J.M., Hickman, P.E., Cullen, L., 2022. Troponins in myocardial infarction and injury. Aust. Prescr. 45(2), 53-57.

Pyle, W.G., Chen, Y., Hofmann, P.A., 2003. Cardioprotection through a PKC-dependent decrease in myofilament ATPase. Am. J. Physiol. Heart Circ. Physiol. 285(3), H1220-1228.
Ren, L.K., Lu, R.S., Fei, X.B., Chen, S.J., Liu, P., Zhu, C.H., Wang, X., Pan, Y.Z., 2024. Unveiling the role of PYGB in pancreatic cancer: a novel diagnostic biomarker and gene therapy target. J. Cancer Res. Clin. Oncol. 150(3), 127.
Riesen, S.C., Kovacevic, A., Lombard, C.W., Amberger, C., 2007. Prevalence of heart disease in symptomatic cats: an overview from 1998 to 2005. Schweiz. Arch. Tierheilkd. 149(2), 65-71.
Sadayappan, S., de Tombe, P.P., 2012. Cardiac myosin binding protein-C: redefining its structure and function. Biophys. Rev. 4(2), 93-106.
Sadayappan, S., Gulick, J., Osinska, H., Martin, L.A., Hahn, H.S., Dorn, G.W., Klevitsky, R., Seidman, C.E., Seidman, J.G., Robbins, J., 2005. Cardiac myosin-binding protein-C phosphorylation and cardiac function. Circ. Res. 97(11), 1156-1163.
Schlender, K.K., Bean, L.J., 1991. Phosphorylation of chicken cardiac C-protein by calcium/calmodulin-dependent protein kinase II. J. Biol. Chem. 266(5), 2811-2817.
Schlossarek, S., Mearini, G., Carrier, L., 2011. Cardiac myosin-binding protein C in hypertrophic cardiomyopathy: mechanisms and therapeutic opportunities. J. Mol. Cell. Cardiol. 50(4), 613-620.
Shaffer, J.F., Kensler, R.W., Harris, S.P., 2009. The myosin-binding protein C motif binds to F-actin in a phosphorylation-sensitive manner. J. Biol. Chem. 284(18), 12318-12327.
Singh, M.K., Cocchiaro, M.F., Kittleson, M.D., 2010. NT-proBNP measurement fails to reliably identify subclinical hypertrophic cardiomyopathy in Maine Coon cats. J. Feline Med. Surg. 12(12), 942-947.
Stack, J.P., Fries, R.C., Kruckman, L., Kadotani, S., Wallace, G., 2023. Galectin-3 as a novel biomarker in cats with hypertrophic cardiomyopathy. J. Vet. Cardiol. 48, 54-62.
Stelzer, J.E., Patel, J.R., Moss, R.L., 2006. Protein kinase A-mediated acceleration of the stretch activation response in murine skinned myocardium is eliminated by ablation of cMyBP-C. Circ. Res. 99(8), 884-890.
Stelzer, J.E., Patel, J.R., Walker, J.W., Moss, R.L., 2007. Differential roles of cardiac myosin-binding protein C and cardiac troponin I in the myofibrillar force responses to protein kinase A phosphorylation. Circ. Res. 101(5), 503-511.
Stenson, P.D., Mort, M., Ball, E.V., Shaw, K., Phillips, A., Cooper, D.N., 2014. The human gene mutation database: building a comprehensive mutation repository for clinical and molecular genetics, diagnostic testing and personalized genomic medicine. Hum. Genet. 133(1), 1-9.
Stern, J.A., Rivas, V.N., Kaplan, J.L., Ueda, Y., Oldach, M.S., Ontiveros, E.S., Kooiker, K.B., van Dijk, S.J., Harris, S.P., 2023. Hypertrophic cardiomyopathy in purpose-bred cats with the A31P mutation in cardiac myosin binding protein-C. Sci. Rep. 13(1), 10319.
Sukumolanan, P., Petchdee, S., 2020. Feline hypertrophic cardiomyopathy: genetics, current diagnosis and management. Vet. Integr. Sci. 18(2), 61-73.
Sun, Y.L., Dookhun, M.N., Lu, X.Z., 2019. Correlation between myocardial myosin-binding protein C, hypertension with left ventricular enlargement, and dilated cardiomyopathy. Cardiol. Plus. 4(4), 111-115.
Tanindi, A., Cemri, M., 2011. Troponin elevation in conditions other than acute coronary syndromes. Vasc. Health. Risk. Manag. 7, 597-603.
Tanjore, R.R., Rangaraju, A., Kerkar, P.G., Calambur, N., Nallari, P., 2008. MYBPC3 gene variations in hypertrophic cardiomyopathy patients in India. Can. J. Cardiol. 24(2), 127-130.
Tantisuwat, L., Puangampai, P., Panpakdee, P., Tangarsasilp, T., Surachetpong, S.D., 2018. Survival time and prognosis factors in hypertrophic

cardiomyopathy cats with congestive heart failure. Thai J. Vet. Med. 48(4), 655-662.

Tong, C.W., Stelzer, J.E., Greaser, M.L., Powers, P.A., Moss, R.L., 2008. Acceleration of crossbridge kinetics by protein kinase A phosphorylation of cardiac myosin binding protein C modulates cardiac function. Circ. Res. 103(9), 974-982.

van Dijk, S.J., Dooijes, D., dos Remedios, C., Michels, M., Lamers, J.M., Winegrad, S., Schlossarek, S., Carrier, L., ten Cate, F.J., Stienen, G.J., van der Velden, J., 2009. Cardiac myosin-binding protein C mutations and hypertrophic cardiomyopathy: haploinsufficiency, deranged phosphorylation, and cardiomyocyte dysfunction. Circulation. 119(11), 1473-1483.

Waldmuller, S., Erdmann, J., Binner, P., Gelbrich, G., Pankuweit, S., Geier, C., Timmermann, B., Haremza, J., Perrot, A., Scheer, S., Wachter, R., Schulze-Waltrup, N., Dermintzoglou, A., Schonberger, J., Zeh, W., Jurmann, B., Brodherr, T., Borgel, J., Farr, M., Milting, H., Blankenfeldt, W., Reinhardt, R., Ozcelik, C., Osterziel, K.J., Loeffler, M., Maisch, B., Regitz-Zagrosek, V., Schunkert, H., Scheffold, T., German Competence Network Heart Failure, 2011. Novel correlations between the genotype and the phenotype of hypertrophic and dilated cardiomyopathy: results from the German Competence Network Heart Failure. Eur. J. Heart Fail. 13(11), 1185-1192.

Walker, L.A., Fullerton, D.A., Buttrick, P.M., 2013. Contractile protein phosphorylation predicts human heart disease phenotypes. Am. J. Physiol. Heart Circ. Physiol. 304(12), H1644-1650.

Ward, J.L., Lisciandro, G.R., Ware, W.A., Viall, A.K., Aona, B.D., Kurtz, K.A., Reina-Doreste, Y., DeFrancesco, T.C., 2018. Evaluation of point-of-care thoracic ultrasound and NT-proBNP for the diagnosis of congestive heart failure in cats with respiratory distress. J. Vet. Intern. Med. 32(5), 1530-1540.

Weisberg, A., Winegrad, S., 1996. Alteration of myosin cross bridges by phosphorylation of myosin-binding protein C in cardiac muscle. Proc. Natl. Acad. Sci. U. S. A. 93(17), 8999-9003.

Weisberg, A., Winegrad, S., 1998. Relation between crossbridge structure and actomyosin ATPase activity in rat heart. Circ. Res. 83(1), 60-72.

Wells, S.M., Shofer, F.S., Walters, P.C., Stamoulis, M.E., Cole, S.G., Sleeper, M.M., 2014. Evaluation of blood cardiac troponin I concentrations obtained with a cage-side analyzer to differentiate cats with cardiac and noncardiac causes of dyspnea. J. Am. Vet. Med. Assoc. 244(4), 425-430.

Xiao, L., Zhao, Q., Du, Y., Yuan, C., Solaro, R.J., Buttrick, P.M., 2007. PKCepsilon increases phosphorylation of the cardiac myosin binding protein C at serine 302 both in vitro and in vivo. Biochemistry. 46(23), 7054-7061.

Yang, C., Wang, H., Shao, M., Chu, F., He, Y., Chen, X., Fan, J., Chen, J., Cai, Q., Wu, C., 2024. Brain-Type Glycogen Phosphorylase (PYGB) in the pathologies of diseases: a systematic review. Cells. 13(3), 289.

Yang, J., Griffiths, M., Nies, M.K., Brandal, S., Damico, R., Vaidya, D., Tao, X., Simpson, C.E., Kolb, T.M., Mathai, S.C., Pauciulo, M.W., Nichols, W.C., Ivy, D.D., Austin, E.D., Hassoun, P.M., Everett, A.D., 2020. Insulin-like growth factor binding protein-2: a new circulating indicator of pulmonary arterial hypertension severity and survival. BMC Med. 18(1), 268.

How to cite this article;
Nutcha Tanakwang, Wanpitak Pongkan. Potential of cardiac myosin binding protein-C as an alternative biomarker in feline hypertrophic cardiomyopathy. Veterinary Integrative Sciences. 2026; 24(2): e2026029-1-24.