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Review Article:

Role of Cholinesterase Enzymes as Rising Biomarkers in Cardiovascular Disease Diagnosis and Prognosis

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Abstract

Background: Cardiovascular diseases remain the leading cause of mortality worldwide, necessitating the identification of reliable biomarkers to improve risk assessment and therapeutic strategies. Cholinesterases, particularly acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), have emerged as potential prognostic indicators due to their involvement in metabolic and inflammatory pathways linked to cardiovascular pathology. **Methods:** This review systematically examines recent studies evaluating the relationship between cholinesterase activity and cardiovascular diseases, including hypertension, ischemic heart disease, and heart failure. Literature sources were selected based on relevance to clinical and experimental research, focusing on the predictive value of cholinesterases for major adverse cardiovascular events (MACE). **Results:** Findings indicate a complex interaction, with some studies reporting an inverse correlation between cholinesterase activity and cardiovascular risks, while others associate elevated BChE levels with metabolic syndrome. Age and disease progression appear to influence this relationship, highlighting the need for further investigation. **Conclusion:** This review underscores the significance of cholinesterase enzymes as potential biomarkers and calls for additional research to establish their clinical utility in cardiovascular risk stratification.

1. Introduction

1.1. Cholinesterase: An overview

Cholinesterases are a category of enzymes that catalyze the hydrolysis of acetylcholine and other choline esters (**Figure 1a**). Cholinesterase appears in two primary forms with unique biochemical characteristics. Acetylcholinesterase—also known as true cholinesterase—is found in every excitable tissue, including the central and peripheral nervous systems, muscles, and red blood cells. It is distinguished by its rapid catalytic turnover, high affinity for acetylcholine, and a marked preference for this neurotransmitter over other esters that do not contain choline. Significantly, elevated levels of acetylcholine can suppress its function (1,2).

An alternative form of the enzyme—often referred to as nonspecific cholinesterase, pseudocholinesterase, serum cholinesterase, or butyrylcholinesterase—functions to break down choline and aliphatic esters. Butyrylcholinesterase (BChE) is an alpha-glycoprotein that is distributed in both the central and peripheral nervous systems, as well as in various other organs, including the liver. Elevated levels of acetylcholine do not suppress it owing to its reduced affinity. The half-life of BChE is approximately 12 days, with typical values ranging from 5,900 to 13,200 IU/L (3,4). AChE resembles BChE by over 50 % (**Figure 1b**), yet the two enzymes occupy distinct sites in the body and fulfill separate biological functions.

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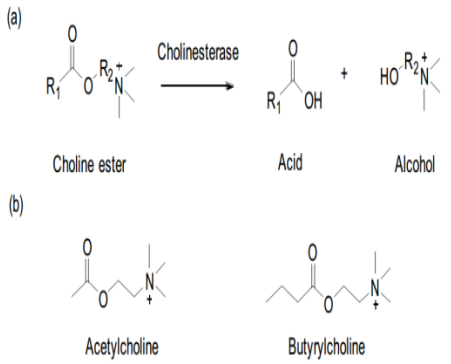

Figure 1 (**a**) Choline esters are broken down by cholinesterase, resulting in the formation of their corresponding acid and alcohol. (**b**) Chemical structure of acetylcholine, which is an important neurotransmitter in cholinergic neurons, and butyrylcholine, which is hydrolyzed by BChE (5)

BChE plays a well-known role in anesthetic practice by degrading neuromuscular blockers such as succinylcholine and mivacurium (6). Mutant variants of the enzyme display lower or ineffective activity, leading to persistent apnea under the administration of these muscle relaxants. BChE concentrations are diminished in systemic pathologies such as hepatic disorders, renal insufficiencies, malnutrition, neoplastic diseases, and thermal injuries (7). It plays a critical role in the initial phase of detoxification processes targeting both endogenous and exogenous toxins (8).

It has now become evident that the inflammatory process initiates and progresses atherosclerosis, a major cause of mortality in cardiovascular disease (CVD). The evaluation of traditional risk elements such as cholesterol levels and arterial blood pressure plays an important role in heart condition assessment. Nevertheless, additional parameters are necessary for increased accuracy (9). Dysfunction of the parasympathetic nervous system is correlated with systemic inflammation and an increased susceptibility to CVD (10–12). ACh is implicated in the modulation of immune responses and consequently is involved in the pathophysiology of CVD (13,14).

Vagus nerve and cytokine suppression: Beyond its hemodynamic effects, ACh is a key modulator of the immune system. The cholinergic anti-inflammatory pathway (CAP) is a neuroimmune reflex wherein vagal efferent fibers release ACh that binds receptors on immune cells to dampen inflammation. A pivotal component is the α7 nicotinic acetylcholine receptor (α7nAChR) on macrophages. When activated by ACh, α7nAChR initiates an intracellular cascade that inhibits nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) nuclear translocation and activity (15). In fact, ACh (via nicotinic and muscarinic receptors on immune cells) has been shown to inhibit the release of major inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1 beta (IL-1β), and interleukin-18 (IL-18). This results in a systemic anti-inflammatory effect. ACh also helps maintain immune homeostasis by influencing T-cell activity and other leukocyte functions, skewing responses away from excessive inflammation (16).

Impact of cholinesterase activity: The level of AChE/BChE activity can modulate the strength of the cholinergic anti-inflammatory pathway. High cholinesterase activity means ACh is hydrolyzed before it can sufficiently stimulate α7nAChRs on macrophages or muscarinic receptors on lymphocytes (17,18). Consequently, the braking effect on inflammation is lost, leading to elevated cytokine levels and unchecked inflammatory signaling. This scenario is detrimental in CVD: chronic low-grade inflammation is a known contributor to atherosclerotic plaque formation and progression (19). Increased circulating TNF-α, IL-6, and other cytokines promote endothelial activation, recruit inflammatory cells to vessel walls, and exacerbate cardiac remodeling. Notably, clinical studies have observed that cholinesterase activity correlates with inflammation markers in CVD patients (20). In other words, individuals with higher AChE/BChE activity often exhibit higher inflammatory profiles, linking overactive cholinesterases to an inflammatory milieu. On the other hand, preserving ACh (e.g. during vagus nerve stimulation or AChE inhibition) markedly dampens inflammation.

Having said this, heart diseases are linked to imbalanced sympathetic and parasympathetic activity, so it's important to find biomarkers of parasympathetic activity that are easy to measure to predict the likelihood of developing cardiovascular issues. In line with this concept, studies have shown a relationship between indirect measures of cardiac parasympathetic dysfunction, such as increased resting heart rate, slowed post-exercise heart rate recovery, reduced heart rate elevation during physical activity, adverse cardiovascular outcomes (21,22). Different types of studies have linked changes in these parameters to sudden cardiac death (10,21) and death from all causes (22–25), but there aren't yet any biomarkers that have been clinically proven to measure the parasympathetic system (10).

The most severe manifestation of atherosclerosis, acute coronary syndrome (ACS), is coupled with significant morbidity and mortality (26). An extensive understanding of variables associated with cardiovascular diseases facilitates personalized risk assessment among coronary artery disease (CAD) patients. Assessing long-term cardiovascular prognosis is an important strategy to prevent recurrent cardiovascular events in people who have had ACS and to lower the number of hospital readmissions and deaths overall (27). Previous studies (28,29) have indicated a potential causal association of BChE in the pathogenesis of CAD as well as a prognostic significance of BChE for cardiac mortality.

1.2. Aim of the study

This study seeks to compile the primary, historical, and contemporary information documented in the literature about the developing function of ChEs as a prognostic indicator in certain cardiovascular diseases and their consequences.

1.3. Parasympathetic dysfunction: Exploring surrogate markers

Dysregulation of autonomic nervous system (ANS) functioning is correlated with adverse cardiovascular outcomes (10). More precisely, diminished parasympathetic activity has been associated with metabolic dysfunction, systemic inflammatory responses, and an increased risk of subsequent major adverse cardiovascular events (MACE) (11,30,31). Nonetheless, there is currently a lack of clinically validated biomarkers for the evaluation of the parasympathetic system, and the principal neurotransmitter, acetylcholine (ACh), exhibits considerable instability and presents significant challenges

for quantification in the bloodstream. Consequently, utilizing its hydrolytic enzymes as an indirect assessment for parasympathetic dysfunction may provide a valuable surrogate marker in various clinical contexts (11).

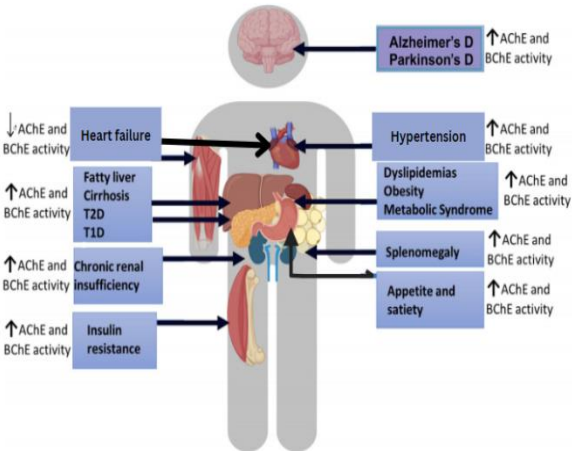

Figure 2. Illustrates the association between metabolic pathologies and neurodegenerative disorders with increased AChE and BChE activity in various organs. D: disease (32).

Given the involvement of parasympathetic dysfunction in systemic inflammation, it is important to examine how cholinesterase activity correlates with specific cardiovascular conditions (**Figure 2**).

2. Clinical associations

Total serum cholinesterase (ChE)" refers to Ellman-based activity measured in serum or plasma, which reflects BChE in > 95 % of cases. Where individual enzymes were assayed, we use the specific abbreviations AChE or BChE. Conclusions are labeled accordingly.

2.1. Cholinesterase and hypertension

Recent findings indicate that inflammatory mechanisms contribute to the pathophysiology of hypertension (33). These inflammatory processes have the potential to elicit alterations in cardiac function, augment peripheral vascular resistance, and disrupt renal regulatory processes governing plasma electrolytes and fluid volume (34). Moreover, the presence of renal and vascular inflammation may exacerbate oxidative stress and compromise endothelial function, thereby promoting the progression of atherosclerosis (35). The cholinergic anti-inflammatory pathway is mediated by the vagus nerve and ACh, which interacts with the alpha-7 subtype of nicotinic acetylcholine receptor on immune cells to suppress inflammation (36). BChE activity is associated with obesity, blood pressure, and other cardiovascular risk factors, indicating its potential as a biomarker for hypertension (37).

- Several independent studies converge on the same finding: elevated butyrylcholinesterase (BChE) activity accompanies arterial hypertension and mirrors the underlying low-grade inflammatory state.
- Alcantara et al., 2002 first showed a statistically significant positive association between serum BChE activity and arterial hypertension (29) .
- Mahmoud et al., 2013 corroborated this in a cross-sectional cohort of 50 hypertensive patients versus 20 normotensive controls, linking higher BChE activity not only to blood-pressure status but also to increased triglyceride and total-cholesterol levels—further evidence that BChE tracks systemic inflammation (38).
- Sidhu et al., 2020 extended the observation to isolated systolic hypertension (ISH), reporting significantly higher cholinesterase concentrations in 30 ISH patients compared with 30 matched controls and a clear step-wise rise in activity alongside increasing high-sensitivity C-reactive protein (hs-CRP) (39).

2.2. Cholinesterase and ischemic heart diseases

The quick and accurate evaluation of life-threatening conditions continue to pose considerable difficulty in clinical practice. Ongoing research seeks to identify diagnostic markers that can help assess the risk of fatal diseases, with the intention to lower both morbidity and mortality. ACS includes a spectrum of disorders resulting from a sudden reduced blood flow to the heart, embracing unstable angina and myocardial infarction (STEMI), known as a heart attack (40).

An early ischemic assessment before it advances into myocardial damage presents barriers to effective diagnosis and treatment. Assuming ischemia is identified before it progresses to tissue necrosis, there may be an opportunity to intervene sooner than current practices allow, potentially reducing or preventing myocardial damage. Diagnosing ACS accurately in the emergency department (ED) remains a challenge, driving scholars to consider unique biomarkers that change in serum concentrations preceding myocardial tissue damage. A key area of research focuses on the early recognition of coronary thrombosis at the time of the initial, reversible phase of ACS (41,42).

A prospective study by Goliasch et al. (2012) involving 720 patients with coronary artery disease (CAD) found that BChE activity was inversely associated with all-cause mortality and cardiovascular mortality in CAD patients, indicating a potential impact of butyrylcholinesterase activity (43). A pilot study by Arbel et al. (2014) found that parasympathetic dysfunction, as indicated by reduced serum cholinesterase activities, predicts the risk of major adverse cardiac events (MACE) in patients with cardiovascular disease. A total of 192 patients were recruited and followed for up to 40 months. Lowered ChE concentrations at the time of catheterization had a significantly elevated risk of MACE (44).

Age-related differences on the prognostic ability of BChE for heart-related death were studied by Sulzgruber et al. (2015) in a retrospective cohort study involving 624 patients with ACS. The age group (45-64 years) exhibited the strongest predictive ability of the BChE test for heart-related death, whereas the age group (65-84 years) demonstrated a less robust connection (45). Delving into ACS, Kocabaş et al. (2016) conducted a cross-sectional study where BChE was measured in 85 patients diagnosed with acute myocardial infarction (AMI). They found that serum BChE levels were significantly lower in AMI patients ($p < 0.001$). Moreover, a moderate negative correlation between BChE activity and the presence of AMI was observed ($r = –0.363$, $p < 0.001$). A ROC curve analysis showed that BChE could differentiate AMI patients from controls, with a sensitivity of 51.2% and a specificity of 84.4% (46).

Interestingly, a prospective study by Shenhar-Tsarfaty et al. (2020) involving 1002 consecutive patients undergoing

coronary angiography found that lower serum AChE activity was associated with higher mortality rates over 10 years. The study found that patients with lower AChE activity had significantly higher mortality rates, even after adjusting for other risk factors. AChE activity was also inversely correlated with inflammation markers. The study concluded that low AChE activity is a significant predictor of long-term mortality in coronary angiography patients (47). In 2022, a study by Reddy et al. about a prospective observational study involving 100 patients with acute ST-segment elevation myocardial infarction (STEMI) examined the correlation between serum ChE levels and MACEs. Results showed that ChE levels were significantly lower in patients experiencing MACEs compared to those who did not. The study also identified a cutoff value for ChE levels on day 5 that could predict an increased risk of MACEs (48).

In contrast to the previously mentioned studies, according to research by Mito et al. in 2021, a retrospective study involving 559 patients with stable CAD found that ChE levels significantly influenced myocardial ischemia. The study found that higher ChE levels were associated with higher BMI, dyslipidemia, and younger age. The specificity and sensitivity of myocardial ischemia at a ChE level of 286 IU/L were 0.599 and 0.658, respectively. Elevated serum ChE was identified as an independent risk factor for myocardial ischemia in patients with CAD (49). In summary, most studies indicate that decreased ChE activity is linked to a higher risk of IHD and adverse events such as MACE. However, some research suggests that elevated ChE levels may also be associated with IHD and ischemia. Further investigation is necessary to understand better the intricate relationship between ChE activity, age, and different IHD outcomes.

2.3. Cholinesterase and Heart Failure

The prognosis of patients with chronic heart failure (CHF) is affected by several variables, including heart function, physical endurance, lung performance, biochemical markers from blood and urine, and various clinical features (50,51). Cardiac cachexia reflects a severe condition in CHF. Reports have highlighted that nutritional indicators such as BMI, cholesterol levels, lymphocyte concentration, and albumin content serve as strong prognostic markers (47–49). In turn, in liver cirrhosis, serum cholinesterase levels are recognized as the most significant predictive factor, with malnutrition and severe liver dysfunction contributing to its reduction (52).

Sato et al. investigated in 2014 and, among 465 chronic heart failure patients, found that nutritional indicators such as lymphocyte, total protein, albumin, cholinesterase, and BMI significantly impact prognosis. Patients with lower serum cholinesterase levels experienced a higher incidence of cardiac events than those with normal levels, underscoring cholinesterase as a key independent predictor of outcomes in chronic heart failure (52). Seo et al. in 2020 carried out a research involving 274 patients with acute decompensated heart failure and found that low cholinesterase levels were independently associated with poor outcomes. Cholinesterase levels provided more prognostic information than other nutritional indices and had an incremental value over the MAGGIC risk score in these patients. Both studies emphasize the relationship between reduced cholinesterase levels and negative outcomes in heart failure patients, contributing to the expanding data associating cholinesterase with inflammation and cancer (53).

Shiba et al.'s study in 2021 investigated the relationship between serum cholinesterase levels at discharge and clinical outcomes in patients hospitalized for acute heart failure (AHF). The study found that low cholinesterase levels were associated with more severe AHF and a higher risk of death and hospitalization for heart failure (54). Doi et al. when they looked at 1954 heart failure patients. They found that patients with lower cholinesterase, estimated GFR, and Geriatric Nutritional Risk Index (GNRI) had more cardiac events (CEs) than patients who did not have any CEs. Reduced serum cholinesterase and GNRI serve as predictors of cardiac mortality risk in patients with systolic heart failure and impaired kidney function (55).

This trend was also observed in a subgroup of 1,204 older patients (≥65 years). The study also compared the predictive ability of ChE for all-cause death with existing nutritional parameters and scores. ChE was found to have a higher predictive ability for all-cause death compared to both the Controlling Nutritional Status (CONUT) and Geriatric Nutritional Risk Index (GNRI) scores. Additionally, ChE had an almost consistently high predictive ability compared to other blood biochemical tests. The authors concluded that ChE is a useful predictor of all-cause death and a good indicator of undernutrition in patients with HF (56). These studies suggest that serum cholinesterase is a valuable prognostic marker in heart failure. Low levels may indicate a higher risk of adverse outcomes, while higher levels suggest a better prognosis. Cholinesterase appears to be a particularly useful predictor of all-cause death and a good indicator of undernutrition in these patients.

2.4. Cholinesterase correlation with cardiovascular disease and lipid profile

The physiological substrate and exact biological activities of BChE remain unidentified; nevertheless, its activity has been demonstrated to elevate in individuals with hyperlipoproteinemia and diabetes (57) The combination of BChE/high-density lipoprotein (HDL) and total cholesterol/HDL ratios enhances the predictive accuracy for heart disease (58). Multiple investigations have demonstrated a direct relationship between BChE and total TC, VLDL, LDL, and triglycerides, with a slight inverse relationship between BChE and HDL (59). Lipoproteins possess a phosphorylcholine moiety that can bind to BChE (60). In a similar manner, CRP possesses a calcium-mediated phosphorylcholine binding region capable of binding to lipoproteins, including LDL and VLDL. The interactions of BChE and CRP with lipoproteins indicate their potential involvement in lipoprotein metabolism (61,62).

In 2006, Calderon-Margalit et al. conducted an observational study of a period spanning ten years involving 1800 participants. In this large community-based study, it was found that low circulating BChE activity as a possible contributor to elevated mortality among elderly participants (28). Another study by Stojanov et al. in 2011 investigated the association of serum BChE activity with risk factors for CAD in a cross-sectional population of 1512 healthy young individuals aged 18-25. Results showed higher BChE activity was associated with triglycerides, total cholesterol, and LDL-C in males (63). According to Vallianou et al. (2014), the relationship between BChE and lipid levels was assessed in a cross-sectional study involving 490 healthy adults as indicators of cardiovascular disease development. Results showed that LDL-cholesterol, total cholesterol, and triglycerides were positively associated with serum BChE activity, with abnormal BMI

or waist circumference being the most important predictors (64).
A study was conducted in Thailand by Tangvarasittichai et al. (2015) to investigate the association between abdominal obesity and elevated serum BChE activity and changes in the serum lipid profile. The study involved 642 women aged over 40, with 500 with abdominal obesity and 142 non-abdominally obese women as the control group. Results showed that women with abdominal obesity had significantly higher BMI, BP, glucose, LDL-C, triglycerides, BChE and significantly lower HDL-C (65). A study by Oda (2015) which was a retrospective observational study at the Tachikawa Medical Center in Japan that investigated the long-term relationship between ChE with cholesterol and triglycerides among 3866 participants. Results showed ChE was strongly correlated with hyper-LDL cholesterolemia and hypertriglyceridemia; however, in women, only hypertriglyceridemia remained associated with ChE following additional adjustments for baseline lipid levels (66).
A study by Pytel et al. in 2017 investigated the impact of intensive lipid-lowering therapies (using statins like rosuvastatin and atorvastatin, alone or in combination with ezetimibe) on the activity of two enzymes, AChE and BChE, in patients with CAD. The study found that CAD patients exhibit elevated levels of both AChE and BChE, alongside increased 'bad' cholesterol (LDL) and triglycerides and decreased 'good' cholesterol (HDL) (67).

2.5. Cholinesterase correlation with cardiovascular disease and metabolic syndrome

The metabolic syndrome (MetS) constitutes a complex clinical entity that occurs together, described by central adiposity, lipid disorder, elevated blood pressure, and reduced insulin sensitivity. MetS has drawn greater interest as a significant epidemiological indicator for anticipating heart diseases and type 2 diabetes. The presence of any three of these risk factors is often used to diagnose metabolic syndrome (68). On a global scale, the aggregate prevalence of MetS may differ based on population characteristics, demographics, geographic location, associated variables, and clinical guidelines (69). The prevalence of metabolic syndrome among Iraqi adults was found to be 39.4%, according to the 2015 STEPS survey conducted by the World Health Organization and the Iraqi Ministry of Health (70). Biochemical analysis related to inflammation is recognized to vary with obesity in certain mammalian species. Research indicates that the activity of BChE is elevated in human obesity (71). Even though its biological function remains inadequately defined, this marker appears to play a role in inflammation, lipid metabolism, elevated blood pressure, and both type 1 and type 2 diabetes mellitus, indicating a connection between BChE and MetS (29).
Epidemiological investigations within the general population have indicated a strong correlation between inflammation and MetS along with its constituent conditions (72,73), such as impaired insulin sensitivity and excessive body weight, which are tightly and mutually interconnected. Inflammation can elicit a diverse array of alterations in the plasma concentrations of lipids and lipoproteins (74). Research has shown that adipose tissue releases various biologically active compounds. These compounds contribute to the chronic inflammation often observed in people with MetS, further solidifying the relationship between obesity and this condition (75).
Randell et al.'s study (2005), investigated the link between serum BChE activity and metabolic syndrome in healthy adults. The study involved 1097 participants aged 19 to 61, with a majority being female. The researchers found that BChE activity was linked to insulin homeostasis, fasting insulin levels, and insulin resistance. It was higher in individuals with metabolic syndrome risk factors, particularly males. BChE activity was most strongly correlated with serum triglyceride levels and abdominal obesity indicators (71).
As part of their investigation into MetS, De Bona et al. (2013) investigated the relationship between MetS and alterations in enzymatic activities. It involved 87 volunteers, including 39 MetS participants and 48 healthy subjects. The observed increase in BChE activity among individuals with MetS, along with the significant correlations identified, suggests a potential role for BChE in the pathogenesis of metabolic syndrome. (76). Another study by Han et al. (2019), which conducted a cross-sectional study of 1236 Chinese adolescents, this study found that obesity was correlated to a greater proportion of individuals falling into the highest plasma BChE tier relative to underweight, normal weight, and overweight groups. Overweight boys exhibited a notably higher occurrence of elevated upper stratum BChE levels. Additionally, triglycerides, TC, LDL, and apolipoprotein B concentrations showed a positive correlation with upper stratum BChE levels. Metabolic syndrome—and each of its constituent risk factors—were observed more often among individuals with elevated upper stratum BChE levels (77).
Research by da Silva et al. in 2024 assessed the effects of three different exercise protocols in adolescents with MetS. The study lasted for 12 weeks. The participants were randomly divided into four distinct cohorts: a control group, an aerobic-training group, a strength-training group, and a combined concurrent-training group. All training groups showed improvements in most MetS indicators, with aerobic training being particularly effective in reducing BChE activity and improving lipid profile (62). Studies consistently show that people with MetS have higher BChE activity than those without. This suggests that BChE could be a useful marker for identifying individuals at risk for MetS.

3. Insights and limitations

3.1. Point of view

The relationship between cardiovascular disease, inflammation, and ChE is complex and involves multiple biological pathways. Inflammation is a key factor in the progression of CVD, and the cholinergic system, particularly through the nicotinic acetylcholine receptor, plays a significant role in modulating this inflammation. This interplay suggests potential diagnostic applications in managing CVD and related inflammatory conditions.

3.2. Limitation

A key limitation is the heterogeneity among the studies reviewed, which vary in design (e.g., small pilot studies vs. large cohort investigations), populations (adolescents vs. older adults), and measurement methods. This variability challenges the direct comparison of findings and may restrict the generalizability of conclusions. Although multiple studies reveal significant correlations, it is critical to emphasize that correlation does not imply causation. Future research should strive for standardized study

designs, consistent inclusion criteria, and uniform measurement protocols to enhance comparability and strengthen the validity of conclusions regarding ChE activity in cardiovascular disease.

4. Conclusion

Many studies suggested that ChE is a potential biomarker for parasympathetic dysfunction and inflammation-related diseases, with its predictive value differing among various health conditions. While some studies have shown a correlation between low ChE activity and an increased risk of IHD and adverse events, other studies suggest that higher ChE levels are linked to IHD and ischemia. More research are needed to fully understand the complex relationship between ChE activity and IHD outcomes. In the context of heart failure, low levels of ChE may indicate a higher risk of adverse outcomes, while higher levels suggest a better prognosis. Additionally, ChE appears to be a useful predictor of all-cause death and a good indicator of undernutrition in these patients. ChE activity shows a correlation with hypertension and related metabolic disorders; the exact nature of this association remains unclear. The findings indicate that ChE may serve more as a marker of metabolic disorders than as a direct cause of hypertension.

Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

5. References

1. Soreq H, Seidman S. Acetylcholinesterase — new roles for an old actor. *Nature Reviews Neuroscience* 2001;2(4):294-302.
2. Gerlits O, Blakeley M P, Keen D A, Radić Z, Kovalevsky A. Room-temperature crystallography of human acetylcholinesterase bound to a substrate analogue 4K-TMA: towards a neutron structure. *Current Research in Structural Biology* 2021;3:206-215.
3. Masson P, Lockridge O. Butyrylcholinesterase for protection from organophosphorus poisons: catalytic complexities and hysteretic behaviour. *Archives of Biochemistry and Biophysics* 2010;494:107-120.
4. Santarpia L, Grandone I, Contaldo F, Pasanisi F. Butyrylcholinesterase as a prognostic marker: a review of the literature. *Journal of Cachexia, Sarcopenia and Muscle* 2013;4:31-39.
5. Ha Z Y, Mathew S, Yeong K Y. Butyrylcholinesterase: a multifaceted pharmacological target and tool. *Current Protein & Peptide Science* 2019;21(1):99-109.
6. Delacour H, Dedome E, Courcelle S, Hary B, Ceppa F. Butyrylcholinesterase deficiency. *Annales de Biologie Clinique* 2016;74(3):279-285.
7. Andersson M L, Møller A M, Wildgaard K. Butyrylcholinesterase deficiency and its clinical importance in anaesthesia: a systematic review. *Anaesthesia* 2019;74(4):518-528.
8. Pohanka M. Butyrylcholinesterase as a biochemical marker. *Bratislava Medical Journal* 2013;114(12):726-734.
9. Kullo I J, Gau G T, Tajik A J. Novel risk factors for atherosclerosis. *Mayo Clinic Proceedings* 2000;75(4):369-380.
10. Lahiri M K, Kannankeril P J, Goldberger J J. Assessment of autonomic function in cardiovascular disease. *Journal of the American College of Cardiology* 2008;51(18):1725-1733.
11. Shenhar-Tsarfaty S, Berliner S, Bornstein N M, Soreq H. Cholinesterases as biomarkers for parasympathetic dysfunction and inflammation-related disease. *Journal of Molecular Neuroscience* 2014;53(3):298-305.
12. da Silva Gonçalves Bós D, Van Der Bruggen C E E, Kurakula K, et al. Contribution of impaired parasympathetic activity to right ventricular dysfunction and pulmonary vascular remodelling in pulmonary arterial hypertension. *Circulation* 2018;137(9):910-924.
13. Roy A, Guatimosim S, Prado V F, Gros R, Prado M A M. Cholinergic activity as a new target in diseases of the heart. *Molecular Medicine* 2014;20:527-537.
14. Ulleryd M A, Mjörnstedt F, Panagaki D, et al. Stimulation of α7 nicotinic acetylcholine receptor inhibits atherosclerosis via immunomodulatory effects on myeloid cells. *Atherosclerosis* 2019;287:122-133.
15. Keever K R, Cui K, Casteel J L, et al. Cholinergic signalling via the α7 nicotinic acetylcholine receptor regulates migration of monocyte-derived macrophages during acute inflammation. *Journal of Neuroinflammation* 2024;21(1):3.
16. Liu C M C, Wang X, Gentile C. Protective role of acetylcholine and the cholinergic system in the injured heart. *iScience* 2024;27(9):110726.
17. Liu E Y L, Xia Y, Kong X, et al. Interacting with α7 nAChR is a new mechanism for AChE to enhance the inflammatory response in macrophages. *Acta Pharmaceutica Sinica B* 2020;10(10):1926-1942.
18. Fujii T, Mashimo M, Moriwaki Y, et al. Expression and function of the cholinergic system in immune cells. *Frontiers in Immunology* 2017;8:Article 1094.
19. Mitteregger M, Steiner S, Willfort-Ehringer A, et al. Cholinesterase and inflammation: exploring its role and associations with inflammatory markers in patients with lower-extremity artery disease. *Biomedicines* 2025;13(4):Article 764.
20. Waiskopf N, Shenhar-Tsarfaty S, Soreq H. Serum cholinesterase activities as biomarkers of cardiac malfunctioning. In: *Biomarkers in Cardiovascular Disease*. Dordrecht: Springer; 2015:1-22. https://doi.org/10.1007/978-94-007-7678-4_10
21. Jouven X, Empana J P, Schwartz P J, et al. Heart-rate profile during exercise as a predictor of sudden death. *The New England Journal of Medicine* 2005;352(19):1951-1958.
22. Leeper N J, Dewey F E, Ashley E A, et al. Prognostic value of heart-rate increase at onset of exercise testing. *Circulation* 2007;115(4):468-474.
23. Cole C R, Blackstone E H, Pashkow F J, Snader C E, Lauer M S. Heart-rate recovery immediately after exercise as a predictor of mortality. *The New England Journal of Medicine* 1999;341(18):1351-1357.
24. Arena R, Guazzi M, Myers J, Peberdy M A. Prognostic value of heart-rate recovery in patients with heart failure. *The American Heart Journal* 2006;151(4):851.e7-851.e13.
25. Savonen K P, Kiviniemi V, Laukkanen J A, et al. Chronotropic incompetence and mortality in middle-aged men with coronary heart disease. *European Heart Journal* 2008;29(15):1896-1902.
26. Thygesen K, Alpert J S, White H D. Universal definition of myocardial infarction. *Circulation* 2007;116(22):2634-2653.

27. Graham I, Atar D, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice (executive summary). *European Heart Journal* 2007;28(19):2375-2414.
28. Calderon-Margalit R, Adler B, Abramson J H, et al. Butyrylcholinesterase activity, cardiovascular risk factors and mortality in Jerusalem. *Clinical Chemistry* 2006;52(5):845-852.
29. Alcântara V M, Chautard-Freire-Maia E A, Scartezini M, et al. Butyrylcholinesterase activity and risk factors for coronary artery disease. *Scandinavian Journal of Clinical and Laboratory Investigation* 2002;62(5):399-404.
30. Rao A A, Sridhar G R, Das U N. Elevated butyrylcholinesterase and acetylcholinesterase may predict type 2 diabetes mellitus and Alzheimer's disease. *Medical Hypotheses* 2007;69(6):1272-1276.
31. Hansen C S, Vistisen D, Jørgensen M E, et al. Adiponectin, biomarkers of inflammation and changes in cardiac autonomic function: the Whitehall II study. *Cardiovascular Diabetology* 2017;16:153.
32. Villeda-González J D, Gómez-Olivares J L, Baiza-Gutman L A. New paradigms in the study of the cholinergic system and metabolic diseases: acetyl- and butyrylcholinesterase. *Journal of Cellular Physiology* 2024;239(8):e00000.
33. Aboukhater D, Morad B, Nasrallah N, et al. Inflammation and hypertension: underlying mechanisms and emerging understandings. *Journal of Cellular Physiology* 2023;238(6):1148-1159.
34. Harrison D G, Bernstein K E, Guzik T J. Inflammation and immunity in hypertension. In: *Hypertension*. Amsterdam: Elsevier; 2024:93-100.
35. Montecucco F, Pende A, Quercioli A, Mach F. Inflammation in the pathophysiology of essential hypertension. *Journal of Nephrology* 2011;24(1):23-34.
36. Zouali M. Pharmacological and electroceutical targeting of the cholinergic anti-inflammatory pathway in autoimmune diseases. *Pharmaceuticals* 2023;16(8):1089.
37. Benyamin B, Middelberg R P, Lind P A, et al. GWAS of butyrylcholinesterase activity identifies four novel loci. *Human Molecular Genetics* 2011;20(22):4504-4514.
38. Mahmoud A A, Moghazy H M, Nor El-Din A K A. Serum leptin level and butyrylcholinesterase activity in essential hypertension. *Journal of Applied Sciences Research* 2013;9(1):294-297.
39. Sidhu W, Bhatia L, Vohra K. Serum cholinesterase level as a marker of systemic low-grade inflammation in isolated systolic hypertension. *European Journal of Medical and Health Sciences* 2020;2(6):e00000.
40. Alavi M M, Diercks D B. Pathophysiology and definition of the acute coronary syndromes. In: *Acute Coronary Syndromes—Pathophysiology and Clinical Management* 2022:61-68.
41. Dominguez-Rodriguez A, Abreu-González P. Current role of ischemia-modified albumin in routine clinical practice. *Biomarkers* 2010;15(8):655-662.
42. Erenler A K, Yardan T, Kati C, et al. Role of ischemia-modified albumin in clinical practice. *Laboratoriums Medizin* 2015;39(4):241-247.
43. Goliasch G, Haschemi A, Marculescu R, et al. Butyrylcholinesterase activity predicts long-term survival in patients with coronary artery disease. *Clinical Chemistry* 2012;58(6):1055-1058.
44. Arbel Y, Shenhar-Tsarfaty S, Waiskopf N, et al. Decline in serum cholinesterase activities predicts two-year major adverse cardiac events. *Molecular Medicine* 2014;20:38-45.
45. Sulzgruber P, Koller L, Reiberger T, et al. Butyrylcholinesterase predicts cardiac mortality in young patients with acute coronary syndrome. *PLOS ONE* 2015;10(5):e0120000.
46. Kocabaş R, Erenler A K, Yetim M, et al. Butyrylcholinesterase as an additional marker in the diagnostic network of acute myocardial infarction. *Laboratoriums Medizin* 2016;40(2):147-152.
47. Shenhar-Tsarfaty S, Brzezinski R Y, Waiskopf N, et al. Blood acetylcholinesterase activity is associated with increased 10-year all-cause mortality after coronary angiography. *Atherosclerosis* 2020;313:144-149.
48. Parvathareddy K K R, Balla R V, Nagula P, et al. Prognostic significance of serum cholinesterase in acute myocardial infarction. *Journal of Clinical and Preventive Cardiology* 2022;11(3):69-74.
49. Mito T, Takemoto M, Antoku Y, et al. Influence of serum cholinesterase levels on patients suspected of having stable coronary artery disease. *Internal Medicine* 2021;60(8):1145-1150.
50. Otaki Y, Watanabe T, Takahashi H, et al. Acidic urine is associated with poor prognosis in chronic heart failure. *Heart and Vessels* 2013;28(6):735-741.
51. Yang H Y, Chiu W C, Huang J H, et al. Sex differences in hospitalisation for heart failure: a ten-year nationwide analysis. *Heart and Vessels* 2013;28(6):721-727.
52. Sato T, Yamauchi H, Suzuki S, et al. Serum cholinesterase is an important prognostic factor in chronic heart failure. *Heart and Vessels* 2015;30(2):204-210.
53. Seo M, Yamada T, Tamaki S, et al. Prognostic significance of serum cholinesterase in acute decompensated heart failure with preserved ejection fraction: insights from the PURSUIT-HFpEF registry. *Journal of the American Heart Association* 2020;9(1):e014100.
54. Shiba M, Kato T, Morimoto T, et al. Serum cholinesterase as a prognostic biomarker for acute heart failure. *European Heart Journal — Acute Cardiovascular Care* 2021;10(3):335-342.
55. Doi T, Noto T, Mita T, et al. Prognostic value of nutritional parameters in systolic heart failure with renal dysfunction. *PLOS ONE* 2022;17(5):e0260000.
56. Yamashita M, Kamiya K, Hamazaki N, et al. Predictive value of cholinesterase in patients with heart failure: a new blood biochemical marker of under-nutrition. *Nutrition, Metabolism and Cardiovascular Diseases* 2023;33(10):1914-1922.
57. Rustemeijer C, Schouten J A, Voerman H J, et al. Is pseudocholinesterase activity related to markers of triacylglycerol synthesis in type II diabetes mellitus? *Clinical Science* 2001;101(1):29-35.
58. Turecký L, Kupčová V, Urfinová M, et al. Serum butyrylcholinesterase/HDL-cholesterol ratio and atherogenic index of plasma in patients with fatty-liver disease. *Vnitřní Lékařství* 2021;67(E-2):4-8.
59. Alcântara V M, Oliveira L C, Réa R R, et al. Butyrylcholinesterase activity and metabolic syndrome in obese patients. *Clinical Chemistry and Laboratory Medicine* 2005;43(3):e00000.
60. Zhou H H, Tang Y L, Xu T H, Cheng B. C-reactive protein: structure, function, regulation and role in clinical diseases. *Frontiers in Immunology* 2024;15:Article 123456.

61. Kirkgöz K. C-reactive protein in atherosclerosis — more than a biomarker, but not just a culprit. *Reviews in Cardiovascular Medicine* 2023;24(10):297-305.
62. da Silva G R, Terra G D S V, de Oliveira D M, et al. Effects of different physical-training protocols on metabolic-syndrome indicators and butyrylcholinesterase activity in adolescents: a randomised clinical trial. *Metabolites* 2024;14(8):422.
63. Stojanov M, Stefanović A, Džingalašević G, et al. Butyrylcholinesterase activity in young men and women: association with cardiovascular risk factors. *Clinical Biochemistry* 2011;44(8-9):623-626.
64. Vallianou N G, Evangelopoulos A A, Bountziouka V, et al. Association of butyrylcholinesterase with cardiometabolic risk factors among apparently healthy adults. *Journal of Cardiovascular Medicine* 2014;15(5):377-383.
65. Tangvarasittichai S, Pongthaisong S, Meemark S, Tangvarasittichai O. Abdominal obesity associated with elevated serum butyrylcholinesterase, insulin resistance and reduced HDL-cholesterol. *Indian Journal of Clinical Biochemistry* 2015;30(3):275-280.
66. Oda E. Associations between serum cholinesterase and incident dyslipidaemias as well as lipid changes in a health-screening population. *Atherosclerosis* 2015;241(1):1-5.
67. Pytel E, Bukowska B, Koter-Michalak M, et al. Effect of intensive lipid-lowering therapies on cholinesterase activity in patients with coronary artery disease. *Pharmacological Reports* 2017;69(1):150-157.
68. Phillips C, Lopez-Miranda J, Perez-Jimenez F, McManus R, Roche H M. Genetic and nutrient determinants of the metabolic syndrome. *Current Opinion in Cardiology* 2006;21(3):185-193.
69. Batsis J A, Nieto-Martinez R E, Lopez-Jimenez F. Metabolic syndrome: from global epidemiology to individualised medicine. *Clinical Pharmacology & Therapeutics* 2007;82(5):509-524.
70. Pengpid S, Peltzer K. Prevalence and associated factors of metabolic syndrome among Iraqi adults: results of the 2015 STEPS survey. *International Journal of Diabetes in Developing Countries* 2021;41(3):427-434.
71. Randell E W, Mathews M S, Zhang H, et al. Relationship between serum butyrylcholinesterase and the metabolic syndrome. *Clinical Biochemistry* 2005;38(9):799-805.
72. Festa A, D'Agostino R, Howard G, et al. Chronic subclinical inflammation as part of the insulin-resistance syndrome: the IRAS study. *Circulation* 2000;101(1):123-130.
73. Ridker P M, Buring J E, Cook N R, Rifai N. C-reactive protein, the metabolic syndrome and cardiovascular risk: an eight-year follow-up of 14 719 women. *Circulation* 2003;107(3):391-397.
74. Haas M J, Mooradian A D. Inflammation, high-density lipoprotein and cardiovascular dysfunction. *Current Opinion in Infectious Diseases* 2011;24(3):265-272.
75. Elks C M, Francis J. Central adiposity, systemic inflammation and the metabolic syndrome. *Current Hypertension Reports* 2010;12(2):99-104.
76. De Bona K S, Bonfanti G, Bitencourt P E R, et al. Cholinesterase and γ-glutamyltransferase activities and oxidative-stress markers are altered in metabolic syndrome but are not affected by body-mass index. *Inflammation* 2013;36(6):1539-1547.
77. Han Y, Ma Y, Liu Y, et al. Plasma cholinesterase is associated with adolescent overweight/obesity and metabolic-syndrome prediction in China. *Diabetes, Metabolic Syndrome and Obesity* 2019;12:685-702.

دور إنزيمات الكولينستراز كمؤشرات حيوية صاعدة في تشخيص أمراض القلب والأوعية الدموية والتنبؤ بمآلها

الخلاصة:

الخلفية: لا تزال أمراض القلب والأوعية الدموية السبب الرئيسي للوفاة في جميع أنحاء العالم، مما يستدعي تحديد مؤشرات حيوية موثوقة لتحسين تقييم المخاطر والاستراتيجيات العلاجية. وقد برزت إنزيمات الكولينستراز، وخاصة أستيل كولينستراز (AChE) وبوتيريل كولينستراز(BChE) ، كمؤشرات تنبؤية محتملة نظرًا لدورها في المسارات الأيضية والالتهابية المرتبطة بأمراض القلب والأوعية الدموية. **المنهجية:** تستعرض هذه الدراسة بشكل منهجي الدراسات الحديثة التي تقيّم العلاقة بين نشاط الكولينستراز وأمراض القلب والأوعية الدموية، بما في ذلك ارتفاع ضغط الدم، ومرض القلب الإقفاري، وفشل القلب. وقد تم اختيار مصادر الأدبيات بناءً على صلتها بالبحوث السريرية والتجريبية، مع التركيز على القيمة التنبؤية للكولينستراز للأحداث القلبية الوعائية الضارة الرئيسية (MACE). **النتائج:** تشير النتائج إلى وجود تفاعل معقد، حيث أفادت بعض الدراسات بوجود علاقة عكسية بين نشاط الكولينستراز ومخاطر الإصابة بأمراض القلب والأوعية الدموية، بينما ربطت دراسات أخرى ارتفاع مستويات BChE بمتلازمة التمثيل الغذائي. يبدو أن العمر وتطور المرض يؤثران على هذه العلاقة، مما يُبرز الحاجة إلى مزيد من البحث. **الخلاصة:** تُؤكد هذه المراجعة على أهمية إنزيمات الكولينستراز كمؤشرات حيوية محتملة، وتدعو إلى إجراء المزيد من البحوث لتحديد جدواها السريرية في تصنيف مخاطر أمراض القلب والأوعية الدموية.

الكلمات المفتاحية: أستيل كولينستراز؛ بوتيريل كولينستراز؛ قصور القلب؛ ارتفاع ضغط الدم؛ مرض القلب الإقفاري