JOURNAL LA LIFESCI
VOL. 07, ISSUE 02 (117-131), 2026
DOI: 10.37899/journallalifesci.v7i2.3136

Alterations in *VKORC1* Gene and Cardiac Enzymes in Acute and Chronic Congestive Heart Failure

Dhuha Abdullah Abbas[1]

[1]*Department of Pathological Analyses, College of Science, University of Al-Qadisiyah, Al-Qadisiyah, Iraq*

**Corresponding Author: Dhuha Abdullah Abbas*
Email: dhuha.abdallah@qu.edu.iq

Article Info

Article history:
Received 24 February 2026
Received in revised from 2 March 2026
Accepted 9 April 2026

Keywords:
Enzyme linked immunosorbent assay (ELISA)
Iraq
Polymerase chain reaction (PCR)
Single nucleotide polymorphism (SNP)
Vitamin K epoxide reductase complex subunit 1 (VKORC1)

Abstract

Congestive heart failure (CHF) is a structural and functional cardiac disorder that activates compensatory mechanisms, including neurohormonal responses and circulatory adjustments, which initially preserve perfusion but later contribute to systemic and pulmonary congestion. This study examined the effect of acute and chronic CHF on VKORC1 gene overexpression and measured serum cardiac enzymes, namely troponin I (cTn I), creatine kinase MB (CK MB), lactate dehydrogenase (L LDH), and myoglobin (MYO MB), at each disease phase. The study included 40 CHF patients, consisting of 20 with acute CHF (ACHF) characterized by severe sudden cardiac symptoms and 20 with chronic CHF (CCHF) showing gradual progression, along with 20 healthy participants as a negative control group. Venous blood samples were collected for molecular analysis using quantitative PCR and for serological assessment of cardiac enzymes using quantitative ELISA. Statistical significance was determined using GraphPad Prism at $p < 0.05$. The results showed that, across all groups, the GG genotype frequency was significantly higher than GA and AA. However, allele frequency analysis of VKORC1 (-1639G>A) rs9923231 revealed significantly increased GA and AA frequencies in both ACHF and CCHF patients. Serologically, cTn I, CK MB, L LDH, and MYO MB levels were significantly elevated in both patient groups compared with controls. Between ACHF and CCHF, only CK MB was significantly higher in CCHF, while cTn I, L LDH, and MYO MB showed no significant difference. This appears to be the first Iraqi study linking VKORC1 with CHF phases, suggesting its potential as an indicator of both acute and chronic CHF, although further investigation is needed.

Introduction

CHF is a complex clinical syndrome characterized by inability of heart to pump a sufficient quantity of blood to either meet the metabolic demands of the body or doing at an elevated filling pressures (Boorsma et al., 2020; Franjić, 2020). The etiology of CHF encompasses a diverse spectrum of structural and functional precipitants in addition to a number of factors; however, the pathophysiology involves maladaptive cardiac remodeling and neurohormonal activation where the reduced cardiac output stimulates the sympathetic nervous system and the renin-angiotensin-aldosterone system, resulting in fluid retention, vasoconstriction, and increased myocardial workload (Roger, 2021; Triposkiadis et al., 2022; Geavlete et al., 2025). These compensatory responses, mediated by the release of noradrenaline and angiotensin II, initially sustain cardiac output through increased heart rate and contractility but eventually promote myocardial fibrosis, cellular dysfunction, and progressive ventricular dilation (Grassi et al., 2021; Minatoguchi, 2022; Wang et al., 2023). Myocardial injury of various etiologies may lead to cardiac dysfunction as evident by reduced cardiac output and ejection fraction,

ISSN 2721-1304 (Print), ISSN 2721-1207 (online)
Copyright © 2026, Journal La Lifesci, Under the license CC BY-SA 4.0

which resulted in reduced blood flow characterizing heart failure that promotes activation of neurohormonal systems which leads to fluid retention, often exhibited as pulmonary congestion, peripheral edema, dyspnea, and fatigue (Tanai and Frantz, 2016; Khadse et al., 2020; Abassi et al., 2022). Despite the intensive research, the exact mechanisms underlying edema formation in heart failure are poorly characterized, though the unique relationship between the heart and kidneys plays a central role in this phenomenon (Alevroudis et al., 2023; Kiseleva et al., 2024).

However, myocardial injury and cellular necrosis associated with heart failure can to the release of cardiac biomarkers in blood, and being the gold-standard for diagnosis, prognosis and severity assessment (Castiglione et al., 2022). Additionally, recent advancements in bioinformatics and genomic analyses have provided novel insights into the complex molecular mechanisms underpinning hear failure progression, highlighting the potential of genetic variants as predictive tools (Bastos et al., 2025; Elsaka, 2025; Ferro et al., 2025). One such promising candidate is the VKORC1 gene that plays a crucial role in vitamin K metabolism and has been implicated in various cardiovascular conditions (Vesa et al., 2020; Al Zaidi et al., 2024). Beyond its direct role in coagulation, VKORC1 gene is primarily expressed in the liver, with similar quantities detectable in the pancreas and heart, underscoring its broader physiological impact in hepatic function (Lacombe and Ferron, 2018). Furthermore, SNPs within noncoding regions of the VKORC1 gene such as -1639>A and 1173>T have been associated with significant variations in warfarin dosage requirements, suggesting the wide functional impact beyond basic enzymatic activity (Jia et al., 2017; Barbosa et al., 2025). These genetic variations impact hepatic VKORC1 mRNA abundance and warfarin sensitivity, indicating a broader regulatory role that could extend to other physiological processes relevant to cardiac health (Lacombe and Ferron, 2018; Zhao et al., 2020). Moreover, the established link between VKORC1 polymorphisms and differential drug response highlights its utility in pharmacogenomics where genetic variations dictate therapeutic efficacy and adverse event susceptibility in cardiovascular disease management (Rai, 2024; Shorbaji et al., 2025). Thus, this study aims to indicate the effect of acute and chronic CHF on overexpression of VKORC1 gene, and estimate the levels of serum cardiac enzymes including cTn-I, CK-MB, L-LDH), and MYO-MB at each phase of disease.

Methods

Ethical approval

This study was licensed by the Scientific Committee in the Department of Pathological Analyses (College of Science, University of Al-Qadisiyah).

Samples

This study composed a totally 40 CHF patients of different demographic factors were attended to the private cardiovascular clinics in Al-Dewaniyah city (Al-Qadisiyah, Iraq) during August-December (2025). The study population was composed 20 individuals who exposed to severe acute onset of cardiac symptoms (ACHF) and 20 individuals who experienced a slow progressive chronic condition (CCHF). In addition, an overall 20 healthy participants were selected as a negative control (NC) group. The study population was subjected to obtaining 10ml of venous blood from each individual using a disposable syringe, which divided as 2ml into an EDTA anticoagulant tube (whole blood) to be utilized for molecular examination using the quantitative PCR assay, as well as 8ml into free-anticoagulant glass-gel tube that centrifuged. The obtained sera was kept in labeled Eppendorf tubes and subjected later for serology.

ISSN 2721-1304 (Print), ISSN 2721-1207 (online)
Copyright © 2026, Journal La Lifesci, Under the license CC BY-SA 4.0

Molecular examination

Following the manufacturer instructions of Blood Protocol in the gSYNC^{TM} DNA Extraction Kit (Geneaid, Taiwan), DNAs were extracted from the whole blood samples and tested by the Nanodrop system for evaluation of its purity and concentration. For identification of *VKORC1* (1639G>A) rs9923231 gene polymorphism, one set of specific primers as described by Al-Sahib et al. (2021) and the GoTaq^{TM} G2 Green Master Mix Kit (Promega, USA) were used to preparing the MasterMix tubes at 25µl to be subjected of PCR amplification in the Thermal Cycler system (Tables 1, 2). Finally, electrophoresis of Agarose-gel (1.5%) stained with Ethidium Bromide was done at 100V and 80Am for 90min, and the bands were photographed under the UV transilluminator.

Table 1. Primers utilized for *VKORC1* (1639G>A) rs9923231 gene polymorphism

Primer			Product size
Allele		Sequence (5′→3′)	
Mutant type (A)	F1	CACAGACGCCAGAGGAAGAGAG	119bp
	R1	CGTGAGCCACCGCACCT	
Wild type (G)	F2	GAAGACCTGAAAAACAACCATTGGCCG	208bp
	R2	CTCAGCCTCCCAAGTAGTTTGG	

Table 2. Conditions of the Thermal Cycler system for PCR amplification

Step	Temperature (°C)	Time (minute)	Cycle
Initial denaturation	95	10	1
Denaturation	95	1	30
Annealing	61	1	
Extension	72	1	
Final extension	72	5	1

Cardiac enzymes

Quantitative ELISAs' kits (SunLong Biotech, China) for cTn-I (Cat.No:SL0411Hu), CK-MB (Cat.No:SL0536Hu), L-LDH (Cat.No:SL1090Hu) and MYO-MB (Cat.No:SL1232Hu) were used in the current study. Following the manufacturer instructions, the contents of each kit in addition to serum samples were prepared at room temperature, processed, and the optical density (OD) was measured at an absorbance of 450nm. Then, the concentrations of each marker in serum samples were calculated through utilization of Standard Curve in the Microsoft Office Excel.

Statistical analysis

Two-Way ANOVA in the GraphPad Prism Software was applied to detect significant differences between study groups (healthy, treated, and non-treated) at $p<0.05$ (*), $p<0.01$ (**), $p<0.001$ (***), and $p<0.0001$ (****). Additionally, 95% confidence interval (95%CI), odds ratio (OR), relative risk (RR), and number needed to treat (NNT) were calculated by the MedCalc statistical software to indicate significance between alleles and genotypes frequency (Gharban et al., 2025).

ISSN 2721-1304 (Print), ISSN 2721-1207 (online)
Copyright © 2026, Journal La Lifesci, Under the license CC BY-SA 4.0

Results and Discussion

VKORC1 (1639G>A) rs9923231 gene polymorphism

Among the individuals of NC, the findings shown a significant elevation (p<0.0106; 95%CI: 46.52 to 113.2) in values of GG allele [70% (14/20)] when compared to GA [20% (4/20)] and AA [10% (2/20)] alleles. Also, frequency of GA allele was higher than AA allele (Figure 1).

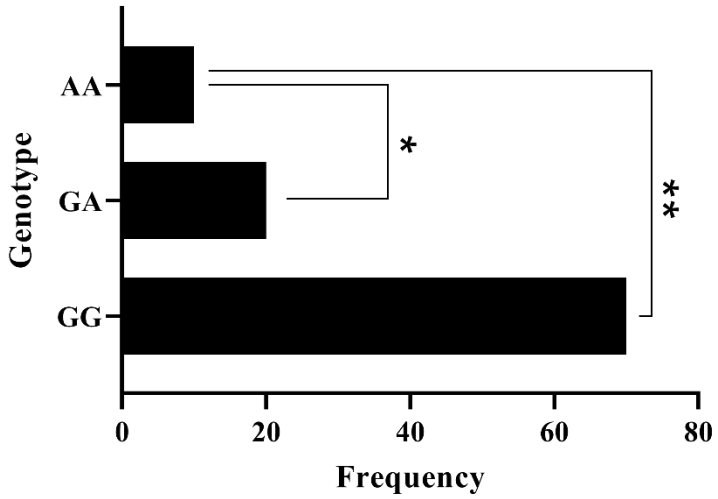

Figure 1. Genotyping frequency according to VKORC1 gene in NC population

In a population of ACHF, there was a significant elevation (p<0.0444; 95%CI: 2.075 to 64.59) in values of GG [45% (9/20)] in comparison with those of GA [35% (7/20)] and AA [20% (4/20)] alleles. In addition, frequency of GA allele was higher than AA allele (Figure 2).

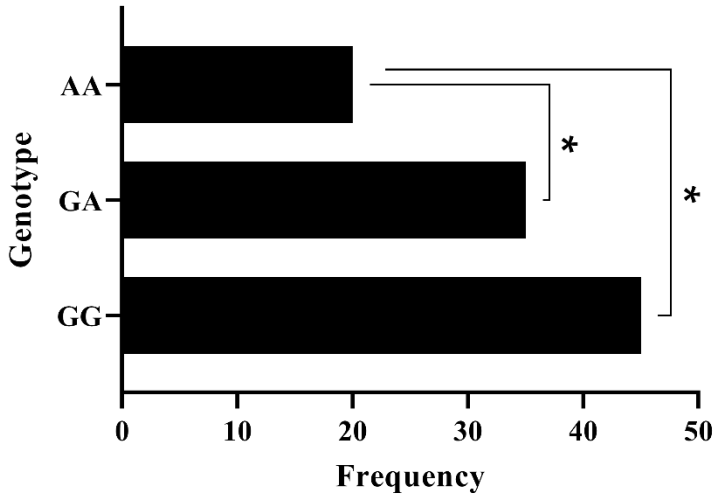

Figure 2. Genotyping frequency according to VKORC1 gene in ACHF population

Throughout individuals of CCHF, genotyping frequency of GG allele [55% (11/20)] was significantly (p<0.0204; 95%CI: 16.86 to 83.53) higher than detected in GA [30% (6/20)] and AA [15% (3/20)] alleles. Subsequently, frequency of GA allele was elevated significantly (p<) more than AA allele (Figure 3).

ISSN 2721-1304 (Print), ISSN 2721-1207 (online)
Copyright © 2026, Journal La Lifesci, Under the license CC BY-SA 4.0

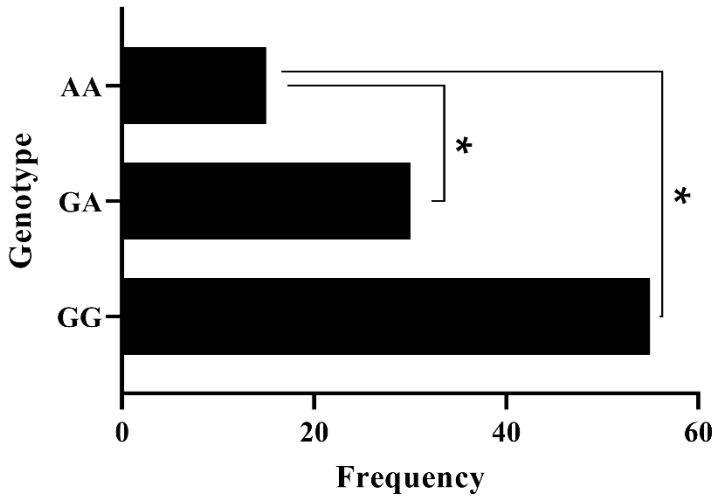

Figure 3. Genotyping frequency according to VKORC1 gene in CCHF population

In comparison with the values of NC [70% (14/20)], the frequency of GG allele was significantly ($p<0.0160$; 95%CI: 25.41 to 87.92) lowered in both ACHF [45% (9/20)] and CCHF [55% (11/20)] study groups. Additionally, the findings of ACHF were markedly lower than those of CCHF (Figure 4).

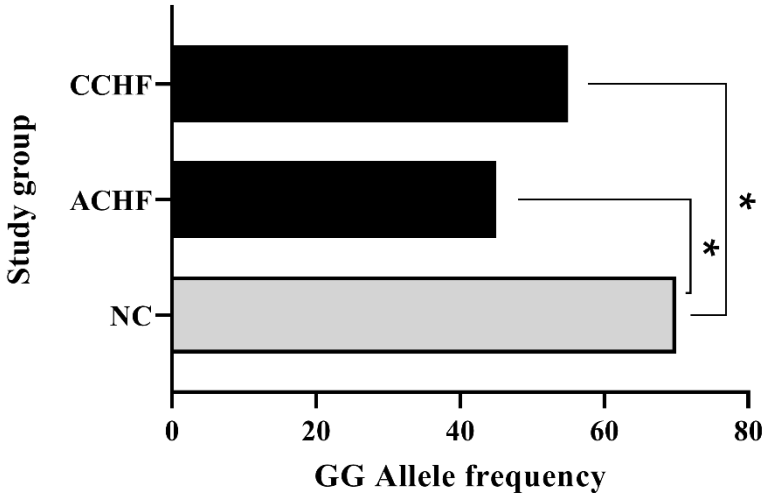

Figure 4. Frequency of GG allele according to VKORC1 gene among the groups of study population

Significantly ($p<0.0234$; 95%CI: 9.360 to 47.31), the frequency of GA allele was increased in ACHF [35% (7/20)] and CCHF [30% (6/20)] more than the values of NC [20% (4/20)]. However, no significant differences ($p<0.0622$) were identified between the values of ACHF and CCHF (Figure 5).

ISSN 2721-1304 (Print), ISSN 2721-1207 (online)
Copyright © 2026, Journal La Lifesci, Under the license CC BY-SA 4.0

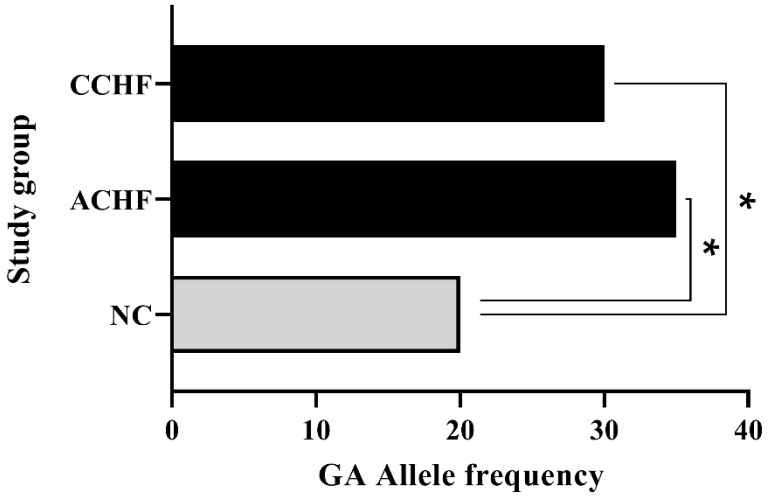

Figure 5. Frequency of GA allele according to VKORC1 gene among the groups of study population

For frequency of AA allele, significant higher values (p<0.0351; 95%CI: 2.579 to 27.42) were detected in patients of ACHF [20% (4/20)] but not in those of CCHF [15% (3/20)] when compared to those of NC group [10% (2/20)]. Also, no significant variation was seen between values of study patients, ACHF and CCHF (Figure 6).

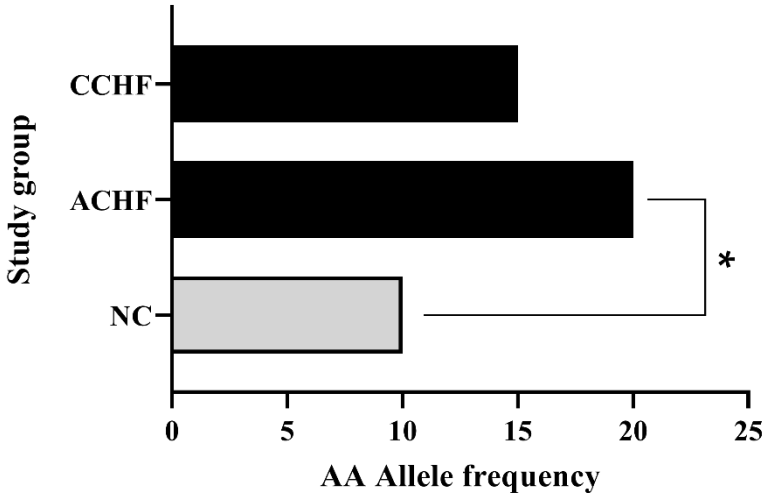

Figure 6. Frequency of AA allele according to VKORC1 gene among the groups of study population

However, all discovered SNP's genotype and allele frequencies were in agreement with the expected Hardy-Weinberg proportions and the risk (OR, RR) of *VKORC1* (-1639G>A) rs9923231 gene polymorphism in patients of ACHF (1.6154, 1.2963) was increased significantly (p<0.0001) more than those of CCHF (1.1299, 0.8901) and NC (0.5192, 0.6795) group (Table 4).

Table 4. Association between the risk of *VKORC1* (-1639G>A) rs9923231 gene polymorphism the groups of study population

Study population	No. of allele frequency			Risk			
	GG	GA	AA	OR	RR	NNT	95%CI

ISSN 2721-1304 (Print), ISSN 2721-1207 (online)
Copyright © 2026, Journal La Lifesci, Under the license CC BY-SA 4.0

NC	14	4	2	0.5192	0.6795	12.720 (Benefit)	8.290 (Harm) to ∞ to 3.599 (Benefit)
ACHF	9	7	4	1.6154	1.2963	16.875 (Harm)	3.953 (Harm) to ∞ to 7.438 (Benefit)
CCHF	11	6	3	1.1299	0.8901	35.100 (Benefit)	5.747 (Harm) to ∞ to 4.329 (Benefit)
p-value				0.0001	0.0001	-	-
95%CI				0.2763 to 2.453	0.1765 to 1.734	-	-

Cardiac enzymes

Concerning values of serum CTn-I, significant elevation ($p<0.0001$; 95%CI: 98.68 to 1189) was identified among the populations of both study patients, ACHF (693.75±36.77pg/ml) and CCHF (696.35±45.41pg/ml) when compared to healthy individuals of NC (246±16pg/ml). However, no significant differences ($p<0.2047$) were observed between the values of both study patients, ACHF and CCHF (Figure 7).

On the other hand, the findings of serum CK-MB were revealed a significant elevation ($p<0.0007$; 95%CI: 1.533 to 11.67) in values of both study patients, ACHF (6.55±0.36ng/ml) and CCHF (6.653±0.42ng/ml), when compared to those of NC group (2±0.07ng/ml). Among the groups of study patients, the findings of CCHF group were significantly ($p<0.0392$) higher than recorded in ACHF group (Figure 8).

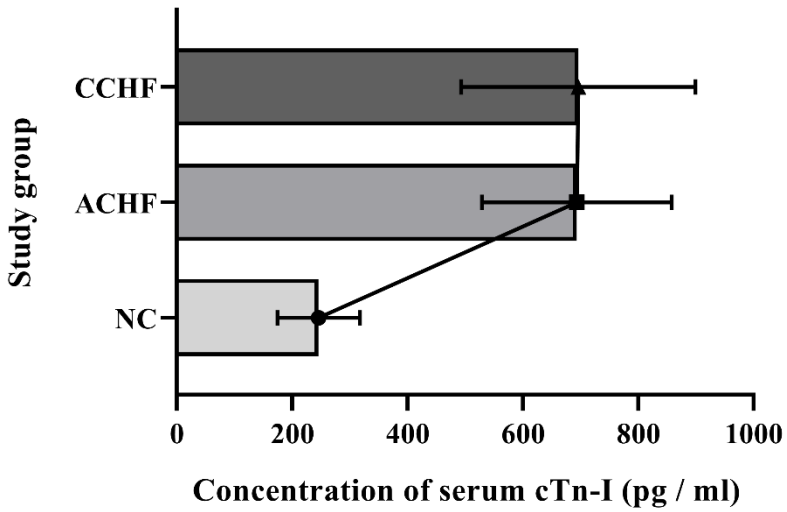

Figure 7. Quantitative measurement of serum cTn-I among study population

ISSN 2721-1304 (Print), ISSN 2721-1207 (online)
Copyright © 2026, Journal La Lifesci, Under the license CC BY-SA 4.0

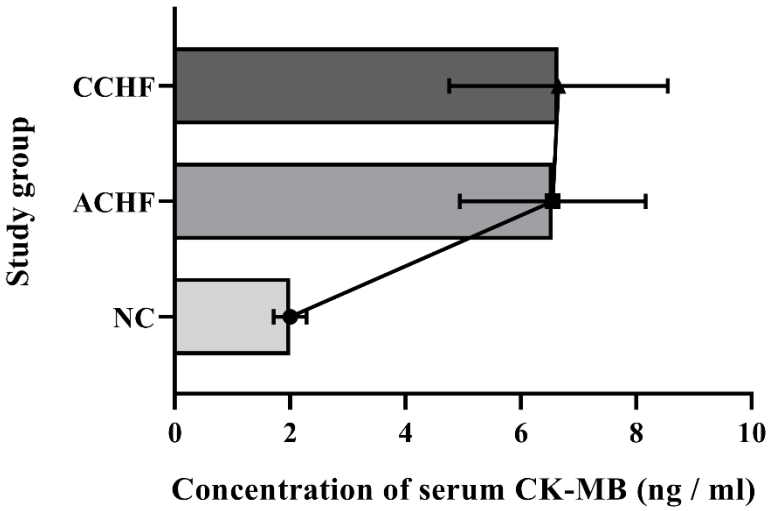

Figure 8. Quantitative measurement of serum CK-MB among study population

Relation to serum L-LDH, though the values of study patients, ACHF (941.1±50.74pg/ml) and CCHF (912.5±40.95pg/ml), were significantly ($p<0.0036$; 95%CI: 127.6 to 1425) higher than those of healthy individuals of NC group (475.2±52.04pg/ml), no significant differences ($p<0.0862$) were seen between the values of patient groups, ACHF and CCHF (Figure 9).

For serum MYO-MB, there were significant increases ($p<0.0289$; 95%CI: 321.9 to 753.1) in values of both the patients' groups, ACHF (578.15±53.22pg/ml) and CCHF (596.55±28.45pg/ml), when compared to those of healthy NC group (437.85±28.65pg/ml). However, significant variation was lacked ($p<0.1742$) between values of patient groups, ACHF and CCHF (Figure 10).

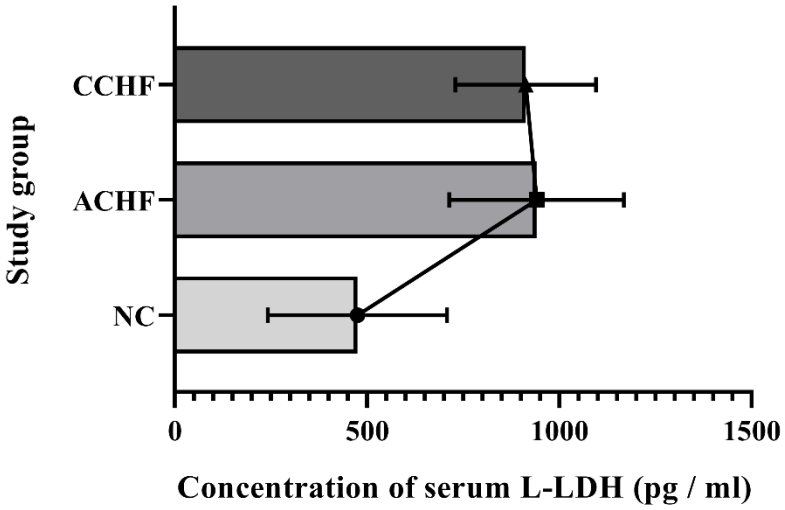

Figure 9. Quantitative measurement of serum L-LDH among study population

ISSN 2721-1304 (Print), ISSN 2721-1207 (online)
Copyright © 2026, Journal La Lifesci, Under the license CC BY-SA 4.0

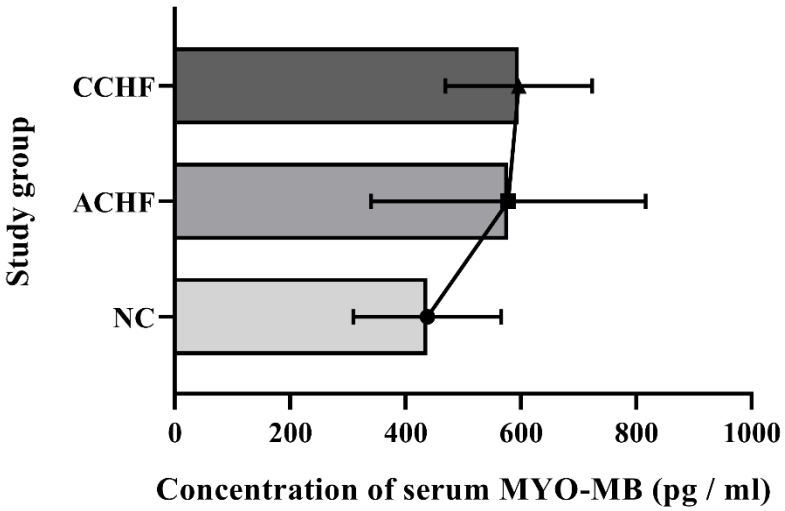

Figure 10. Quantitative measurement of serum MYO-MB among study population

Since the first study of *VKORC1* gene in 2004, several researchers have been investigated its genetic variants in various diseases (Owen et al., 2010; Fung et al., 2012; He et al., 2021). In Iraq, only two studies have performed to indicate the role of *VKORC1* genetic polymorphism in warfarin dose requirements (Sahib et al., 2021) and relationship to incidence of COVID-19 (Al-Fattli and Abd-Alraoof, 2022). This study revealed the overexpression of *VKORC1* gene in acutely and chronically CHF patients when compared to control healthy ones. This genetic variability can significantly influence on susceptibility of individuals to cardiac diseases and their responses to related pharmacotherapies particularly with presence of specific polymorphisms. Also, it may reduce the amount of functional *VKORC1* enzyme, thereby influencing the activation of clotting proteins and potentially impacting cardiovascular health (Shafique et al., 2022). Specifically, SNPs in *VKORC1* have been identified as the key determinants in the efficacy and appropriate dosage of anticoagulant medications like warfarin, a widely used drug in preventing and treating thromboembolic events in cardiac patients (Al Hamad, 2025). Among several identified SNPs in the *VKORC1* gene, -1639G>A is particularly notable because of its impact and causing changes in the enzymatic activities (Czogalla et al., 2015; Lacombe and Ferron, 2018; Ghafoor et al., 2022). Several studies mentioned that the -1639G>A polymorphism can significantly decrease *VKORC1* expression, and consequently, reducing warfarin metabolism and coagulation factors, a phenomenon with substantial implications for therapeutic dosing (Vesa et al., 2020; Mar et al., 2022; Putriana et al., 2025). Furthermore, genetic mutations within the promoter region of *VKORC1* including rs9923231, rs9934438, rs749671 and rs7294, can directly modulate the hepatic expression of *VKORC1* mRNA transcripts, thereby impacting an individual's sensitivity to warfarin therapy (Chen et al., 2025; Vesa et al., 2026). This reduced the expression of functional VKORC1 protein leads to a heightened response to lower doses of coumarin-based anticoagulants and increased risk of associated adverse events, particularly in carriers of the *VKORC1* polymorphism (Kraimi et al., 2021; Zhang et al., 2024). Other studies indicated that the 1173C>T polymorphism, found in the first intron, is closely linked to the -1639G>A variant and also influences *VKORC1* expression and sensitivity to anticoagulant especially warfarin, indicating a consistent effect across various ethnic population (Kayani et al., 2025; Lars et al., 2025).

In the presents study, the findings of cardiac enzymes were shown a significant elevation in values of cTn-I, CK-MB, L-LDH, and MYO-MB markers among both study populations of

ISSN 2721-1304 (Print), ISSN 2721-1207 (online)
Copyright © 2026, Journal La Lifesci, Under the license CC BY-SA 4.0

patients' groups (ACHF and CCHF) when compared to those of healthy NC group. Among the patients of both study groups, though no significant differences were detected in values of cTn-I, L-LDH, and MYO-MB, the findings of CK-MB was significantly higher in CCHF group than those of ACHF. Several studies identified that cTns particularly cTn-I have evolved from being considered sole indicators of myocardial infarction to broader markers of cardiomyocyte damage across a spectrum of clinical conditions. This expanded understanding includes their utility in assessing and prognosting outcomes in patients with both acute and chronic CHF, where even subtle elevations can signify ongoing myocardial injury or stress (Agusala et al., 2019; Canty, 2022; Chaulin, 2022; Crisci et al., 2023). The differential release and clearance mechanisms of cTn-I alongside its high sensitivity offer distinct insights into the pathophysiology of heart failure, differentiating it from Tn-T in certain clinical contexts (Lazar et al., 2022). Nevertheless, relationship between elevated cTn-I levels and increased mortality and hospitalization rates in heart failure patients with reduced ejection fraction is well-established (Zangana and AL-Tawil, 2017; Berezin and Berezin, 2023). However, Myhre et al. (2019, 2024) indicated that elevated concentrations of high-sensitivity cTn-I, unlike cTn-T, are specifically linked to future deterioration in left ventricular function, even though both predict dyspnea, incident heart failure, and mortality. While cTns (I and T) demonstrate a non-random diurnal variations and are highly sensitive indicators of myocardial injury, CK has been gain more attention since the 1960s as fundamental biomarker in diagnosing of myocardial infarction with offering more important complementary information (Qi et al., 2025). The discovery of CK-MB since the 1970s had significantly enhanced the accuracy of myocardial damage diagnosis as a critical biomarker for detecting myocardial necrosis and evaluating acute myocardial infarction (Wu et al., 2020; Liu et al., 2024). However, in contrast to our findings, Khalil (2022) mentioned that the distinct temporal profile of CK-MB is characterized by it elevation 4-6 hours post-injury and return to baseline within 48-72 hours, offers an advantage in identifying re-infection, as its earlier clearance compared to cTn that allows for the detection of recurrent myocardial injury within a shorter timeframe. On other hand, L-LDH has emerged as a non-specific indicator of cellular damage across various clinical conditions (Sen et al., 2022; Zhang et al., 2025); however, various researchers have documented extensively the presence of elevated levels of L-LDH in patients experiencing myocardial damage, thus highlighting its role as a diagnostic marker in various cardiac pathologies (Vasbinder et al., 2022; Zhao et al., 2024; Ade Vittal and Gajanan, 2025). Additionally, Draghici et al. (2021) reported that the dynamic changes in L-LDH levels in response to therapeutic interventions in both ACHF and CCHF can provide valuable insight into treatment efficacy and disease modulation. Consequently, damage to muscle tissue particularly in acute myocardial diseases or other critical illnesses can lead to rapid release of MYO-MB in blood stream making it a valuable early biomarker for diagnosing these diseases and distinguishing between various etiologies and physiological presentations of cardiac conditions (Chauin, 2021; Thupakula et al., 2022; Tilea et al., 2022).

Conclusion

This might represent the first study in Iraq investigate association between VCORC1 gene and phases of CHF; in which, genotyping frequency of GA and allele frequency of rs9923231 SNP was significantly higher in patients' groups (ACHF and CCHF). This demonstrates that VCORC1 gene is potential as an indicator for acute and chronic CHF but warrants further investigation due to its possible involvement in pathways that critical to cardiac function and pharmacogenomics relevance. In addition, the ongoing advancements in sequencing technologies are bringing personalized medicine closer to clinical application, allowing for a more tailored approach to cardiovascular therapeutics. For cardiac enzymes, our data

ISSN 2721-1304 (Print), ISSN 2721-1207 (online)
Copyright © 2026, Journal La Lifesci, Under the license CC BY-SA 4.0

demonstrate the high levels among the study patients indicating that this distinction underscores the importance of biomarker selection in assessing cardiac risk and guiding therapeutic strategies in heart failure.

Acknowledgments

Author thanks all cardiovascular clinicians and their related laboratories for supporting this work by providing the required information and blood samples.

Conflict of interests

No.

References

Abassi, Z., Khoury, E.E., Karram, T., and Aronson, D. (2022). Edema formation in congestive heart failure and the underlying mechanisms. Frontiers in cardiovascular medicine, 9, 933215.

Ade Vittal, D.S.B., and Gajanan, M. (2025). Diagnostic Evaluation of Troponin I, CPK-MB, and LDH in Patients with Acute Myocardial Infarction: A Clinical Study. Journal of Heart Valve Disease, 30, 65-68.

Agusala, V., Khera, R., Cheeran, D., Mody, P., Reddy, P.P., and Link, M.S. (2019). Diagnostic and prognostic utility of cardiac troponin in post-cardiac arrest care. Resuscitation, 141, 69-72.

Al Hamad, M. (2025). The Genetic Polymorphisms of CYP2C9 and VKORC1 in the Saudi Population and Their Impact on Anticoagulant Management. Medicina, 61(10), 1872.

Al Zaidi, M., Repges, E., Tiyerili, V., Oldenburg, J., Jansen, F., Nickenig, G., and Aksoy, A. (2024). Vitamin K2 and the Vitamin-K-Cycle-Enzyme VKORC1L1 improve endothelial regeneration by inhibiting endothelial-mesenchymal transition, inflammatory cell activation and ferroptosis. European Heart Journal, 45(Supplement_1), ehae666-3820.

Alevroudis, I., Kotoulas, S.C., Tzikas, S., and Vassilikos, V. (2023). Congestion in heart failure: from the secret of a mummy to today's novel diagnostic and therapeutic approaches: a comprehensive review. Journal of Clinical Medicine, 13(1), 12.

Al-Fattli, H.H.H., and Abd-Alraoof, T.S. (2022). Investigation of Relationship Between (rs9923231) SNP in (VKORC1) Gene with Incidence of COVID-19. Journal of Pharmaceutical Negative Results¦ Volume, 13(2), 23.

Barbosa, T., Morais, S.L., Carvalho, R., Magalhaes, J.M., Domingues, V.F., Delerue-Matos, C., and Barroso, M.F. (2025). Vitamin K Epoxide Reductase Complex (VKORC1) Electrochemical Genosensors: Towards the Identification of 1639 G> A Genetic Polymorphism. Chemosensors, 13(7), 248.

Bastos, J.M., Scala, N., Perpétuo, L., Mele, B.H., and Vitorino, R. (2025). Integrative bioinformatic analysis of prognostic biomarkers in heart failure: Insights from clinical trials. European Journal of Clinical Investigation, 55(4), e70010.

Berezin, A.E., and Berezin, A.A. (2023). Biomarkers in heart failure: from research to clinical practice. Annals of laboratory medicine, 43(3), 225-236.

ISSN 2721-1304 (Print), ISSN 2721-1207 (online)
Copyright © 2026, Journal La Lifesci, Under the license CC BY-SA 4.0

Boorsma, E.M., Ter Maaten, J.M., Damman, K., Dinh, W., Gustafsson, F., Goldsmith, S., and Voors, A.A. (2020). Congestion in heart failure: a contemporary look at physiology, diagnosis and treatment. Nature reviews cardiology, 17(10), 641-655.

Canty Jr, J.M. (2022). Myocardial injury, troponin release, and cardiomyocyte death in brief ischemia, failure, and ventricular remodeling. American Journal of Physiology-Heart and Circulatory Physiology, 323(1), H1-H15.

Castiglione, V., Aimo, A., Vergaro, G., Saccaro, L., Passino, C., and Emdin, M. (2022). Biomarkers for the diagnosis and management of heart failure. Heart failure reviews, 27(2), 625-643.

Chauin, A. (2021). The main causes and mechanisms of increase in cardiac troponin concentrations other than acute myocardial infarction (part 1): physical exertion, inflammatory heart disease, pulmonary embolism, renal failure, sepsis. Vascular Health and Risk Management, 601-617.

Chaulin, A.M. (2022). The importance of cardiac troponin metabolism in the laboratory diagnosis of myocardial infarction (comprehensive review). BioMed Research International, 2022(1), 6454467.

Chen, D.H., Vermeer, C., Cockcroft, J. R., Wheeler, D.C., O'Shaughnessy, K.M., and Yasmin. (2025). Vitamin K Epoxide Reductase Complex Subunit 1 (VKORC1) Gene Polymorphisms Predict Arterial Stiffness and Serum MGP Levels in Chronic Kidney Disease Patients. Genes, 16(12), 1396.

Crisci, G., Bobbio, E., Gentile, P., Bromage, D.I., Bollano, E., Ferone, E., and Salzano, A. (2023). Biomarkers in acute myocarditis and chronic inflammatory cardiomyopathy: an updated review of the literature. Journal of clinical medicine, 12(23), 7214.

Czogalla, K.J., Watzka, M., and Oldenburg, J. (2015). Structural modeling insights into human VKORC1 phenotypes. Nutrients, 7(8), 6837-6851.

Draghici, A., Buzea, C.A., Delcea, C., Vijan, A., and Gheorghe, A.D. (2021). Predictors associated with increased troponin in acute decompensated and chronic heart failure patients. Revista Română de Medicină de Laborator= Romanian Journal of Laboratory Medicine, 29(2), 153-164.

Elsaka, O. (2025). Unveiling the Genetic Foundations of Heart Failure: Exploring Genomic Perspectives. Iranian Journal of Cardiovascular Medicine, 14(2), 55-68.

Ferro, A., Segreti, A., Crispino, S.P., Cricco, R., Di Cristo, A., Ciancio, M., and Grigioni, F. (2025). Exploring the Role of Genetic and Genomic Factors in Therapeutic Response to Heart Failure: A Comprehensive Analytical Review. Genes, 16(7), 801.

Franjić, S. (2020). Heart failure in family medicine. International Journal of Global Health, 1(1), 18-24.

Fung, E., Patsopoulos, N.A., Belknap, S.M., O'Rourke, D.J., Robb, J.F., Anderson, J.L., and Moore, J.H. (2012, November). Effect of genetic variants, especially CYP2C9 and VKORC1, on the pharmacology of warfarin. In Seminars in thrombosis and hemostasis (Vol. 38, No. 08, pp. 893-904). Thieme Medical Publishers.

Geavlete, O., Collins, S.P., Mebazaa, A., Ye, L., Palazzuoli, A., Antohi, L., and Chioncel, O. (2025). Hypertensive acute heart failure: a critical perspective on definition, epidemiology, pathophysiology, and prognosis—a narrative review: a joint session

ISSN 2721-1304 (Print), ISSN 2721-1207 (online)
Copyright © 2026, Journal La Lifesci, Under the license CC BY-SA 4.0

with the Romanian Society of Cardiology (part II). Heart failure reviews, 30(6), 1323-1340.

Ghafoor, M.B., Yasmeen, F., Khalid, A.W., Mustafa, G., Khaliq, S., and Mohsin, S. (2022). VKORC1 gene polymorphism (-1639G> A) in warfarin therapy patients of Pakistani population. J Pak Med Assoc, 72, 418-423.

Gharban, H.A., Ajaj, E.A., and Mohammad, H.A. (2025). Molecular detection, seroprevalence, and phylogenetic analysis of Brucella suis in wild pigs (Sus scrofa) in Iraq: Implications for One Health surveillance. Veterinary World, 18(9), 2733-2745.

Grassi, G., Quarti-Trevano, F., and Esler, M.D. (2021). Sympathetic activation in congestive heart failure: an updated overview. Heart Failure Reviews, 26(1), 173-182.

Jia, L., Wang, Z., Men, J., Cai, H., and Wei, M. (2017). Polymorphisms of VKORC1 and CYP2C9 are associated with warfarin sensitivity in Chinese population. Therapeutics and Clinical Risk Management, 421-425.

Kayani, M., Sangeetha, G.K., Sarangi, S., Leela Sarmada, G., Sharma, S., Adedara, V.O., and Nazir, Z. (2025). Pharmacogenomics and its role in cardiovascular diseases: a narrative literature review. Current Cardiology Reviews.

Khadse, N.A., Wankhade, A.M., and Gaiki, A.G. (2020). Myocardial infraction: etiology, risk factors, pathophysiology, diagnosis and management. Am J PharmTech Res, 10, 1-18.

Khalil, H. (2022). Traditional and novel diagnostic biomarkers for acute myocardial infarction. The Egyptian Journal of Internal Medicine, 34(1), 87.

Kiseleva, D.G., Kirichenko, T.V., Markina, Y.V., Cherednichenko, V.R., Gugueva, E.A., and Markin, A.M. (2024). Mechanisms of myocardial edema development in CVD pathophysiology. Biomedicines, 12(2), 465.

Kraimi, A., Belboukhari, N., Sekkoum, K., and Aboul-Enein, H.Y. (2021). Chiral anticoagulants drugs based on coumarin. Aditum Journal of Clinical and Biomedical Research, 2(1), 1-13.

Lacombe, J., and Ferron, M. (2018). VKORC1L1, an enzyme mediating the effect of vitamin K in liver and extrahepatic tissues. Nutrients, 10(8), 970.

Lars, M., Geisler, T., Klaus, M., Meinrad, G., and Steeg, M. (2025). Problems in anticoagulation of a patient with antibiotic treatment for endocarditis: interaction of rifampicin and vitamin K antagonists. BMJ Case Reports, 2018, bcr-2016.

Lazar, D.R., Lazar, F.L., Homorodean, C., Cainap, C., Focsan, M., Cainap, S., and Olinic, D.M. (2022). High-sensitivity troponin: a review on characteristics, assessment, and clinical implications. Disease Markers, 2022(1), 9713326.

Liu, Y., Tang, X. L., Ni, Y., Duan, L.Z., and Jing, F.J. (2024). Diagnostic value of the creatine kinase-MB/creatine kinase and neutrophil/lymphocyte ratios in acute myocardial infarction. Journal of Cardiothoracic Surgery, 19(1), 227.

Mar, P.L., Gopinathannair, R., Gengler, B.E., Chung, M.K., Perez, A., Dukes, J., and from the American Heart Association Electrocardiography and Arrhythmias Committee of the Council of Clinical Cardiology. (2022). Drug interactions affecting oral anticoagulant use. Circulation: arrhythmia and electrophysiology, 15(6), e007956.

ISSN 2721-1304 (Print), ISSN 2721-1207 (online)
Copyright © 2026, Journal La Lifesci, Under the license CC BY-SA 4.0

Minatoguchi, S. (2022). Heart failure and its treatment from the perspective of sympathetic nerve activity. Journal of cardiology, 79(6), 691-697.

Myhre, P.L., Claggett, B., Ballantyne, C.M., Hoogeveen, R.C., Selvin, E., Matsushita, K., and Shah, A.M. (2024). NT-proBNP and cardiac troponin I, but not cardiac troponin T, are associated with 7-year changes in cardiac structure and function in older adults: the ARIC study. Circulation, 150(23), 1847-1857.

Myhre, P.L., Claggett, B., Ballantyne, C.M., Selvin, E., Røsjø, H., Omland, T., and Shah, A.M. (2019). Association between circulating troponin concentrations, left ventricular systolic and diastolic functions, and incident heart failure in older adults. JAMA cardiology, 4(10), 997-1006.

Owen, R.P., Gong, L., Sagreiya, H., Klein, T.E., and Altman, R.B. (2010). VKORC1 pharmacogenomics summary. Pharmacogenetics and genomics, 20(10), 642-644.

Putriana, N.A., Latarissa, I.R., Rusdiana, T., Rostinawati, T., and Akbar, M.R. (2025). Pharmacodynamic Modeling of Warfarin Dosing Algorithm for Cardiovascular Patients in Indonesia: A Tailored Method to Anticoagulation Therapy. Drug Design, Development and Therapy, 671-681.

Qi, Y., Cai, M., Kang, Y., and Liu, J. (2025). Progress in biomarkers and diagnostic approaches for myocardial infarction. Clinica Chimica Acta, 120629.

Rai, S. (2024). Pharmacogenomics: Personalized Medicine for Cancer Treatment and Drug Response Variability of Cardiovascular Drugs. Pharmacogenomics, 1(5), 85-91.

Roger, V.L. (2021). Epidemiology of heart failure: a contemporary perspective. Circulation research, 128(10), 1421-1434.

Sahib, A.S., Saleh, M.A., Kadhim, M.H., Abdulamir, A.S., and Altawil, R. (2021). The effect of CYP2C9 and VKORC1 genetic polymorphism on warfarin dose requirements in a sample of Iraqi patients. Journal of Kerman University of Medical Sciences, 28(2):139-149.

Sen, A., Nigam, A., and Vachher, M. (2022). Role of polypeptide inflammatory biomarkers in the diagnosis and monitoring of COVID-19. International Journal of Peptide Research and Therapeutics, 28(2), 59.

Shafique, H., Ashraf, N.M., Rashid, A., Majeed, A., Afsar, T., Daly, A.K., and Razak, S. (2022). Determination of pleiotropic effect of warfarin in VKORC1 and CYP2C9 genotypes in patients with heart valve replacement. Frontiers in Cardiovascular Medicine, 9, 895169.

Shorbaji, A., Pushparaj, P.N., Al-Ghafari, A.B., Mira, L.S., Basabrain, M.A., Naseer, M.I., and Bakhashab, S. (2025). A narrative review of research advancements in pharmacogenetics of cardiovascular disease and impact on clinical implications. NPJ Genomic Medicine, 10(1), 54.

Tanai, E., and Frantz, S. (2016). Pathophysiology of heart failure. Comprehensive physiology, 6(1), 187-214.

Thupakula, S., Nimmala, S.S.R., Ravula, H., Chekuri, S., and Padiya, R. (2022). Emerging biomarkers for the detection of cardiovascular diseases. The Egyptian Heart Journal, 74(1), 77.

ISSN 2721-1304 (Print), ISSN 2721-1207 (online)
Copyright © 2026, Journal La Lifesci, Under the license CC BY-SA 4.0

Tilea, I., Varga, A., and Serban, R.C. (2021). Past, present, and future of blood biomarkers for the diagnosis of acute myocardial infarction-promises and challenges. Diagnostics, 11(5), 881.

Triposkiadis, F., Xanthopoulos, A., Parissis, J., Butler, J., and Farmakis, D. (2022). Pathogenesis of chronic heart failure: cardiovascular aging, risk factors, comorbidities, and disease modifiers. Heart failure reviews, 27(1), 337-344.

Vasbinder, A., Chen, Y., Procureur, A., Gradone, A., Azam, T.U., Perry, D., and Hayek, S.S. (2022). Biomarker trends, incidence, and outcomes of immune checkpoint inhibitor–induced myocarditis. Cardio Oncology, 4(5), 689-700.

Vesa, Ș.C., Ichim, V.M., Iluț, S., Miglietta, S., Lupu, M., Coada, C.A., and Sabin, O. (2026). Association Between VKORC1 Gene Polymorphisms and Osteopenia and Osteoporosis: A Systematic Review and Meta-Analysis. Medicina, 62(1), 180.

Vesa, S.C., Vlaicu, S.I., Vacaras, V., Crisan, S., Sabin, O., Pasca, S., and Buzoianu, A.D. (2020). CYP4F2 and VKORC1 polymorphisms amplify the risk of carotid plaque formation. Genes, 11(7), 822.

Wang, Y., Zhang, J., Wang, Z., Wang, C., and Ma, D. (2023). Endothelial-cell-mediated mechanism of coronary microvascular dysfunction leading to heart failure with preserved ejection fraction. Heart failure reviews, 28(1), 169-178.

Wu, Y.W., Ho, S.K., Tseng, W.K., Yeh, H.I., Leu, H.B., Yin, W.H., and Chen, J.W. (2020). Potential impacts of high-sensitivity creatine kinase-MB on long-term clinical outcomes in patients with stable coronary heart disease. Scientific reports, 10(1), 5638.

Zangana, S.N., and AL-Tawil, N.G. (2017). Role of Cardiac Troponin I Level in Predicting in Hospital Outcomes in Patients with ST-segment Elevation Myocardial Infarction in Erbil-Iraq. Diyala Journal of Medicine, 13(1), 1-7.

Zhang, M., Guo, R., Xi, X., and Li, H. (2025). U-shaped association of serum lactate dehydrogenase with all-cause mortality in cancer patients: a retrospective cohort study. BMC cancer, 25(1), 1143.

Zhang, S., Zhao, M., Zhong, S., Niu, J., Zhou, L., Zhu, B., and Qin, S. (2024). Association between CYP2C9 and VKORC1 genetic polymorphisms and efficacy and safety of warfarin in Chinese patients. Pharmacogenetics and Genomics, 34(4), 105-116.

Zhao, L., Wang, J., Shi, S., Wu, Y., Liu, J., He, S., and Ye, H. (2020). Plasma miRNA profiles associated with stable warfarin dosage in Chinese patients. PeerJ, 8, e9995.

Zhao, Y., Da, M., Yang, X., Xu, Y., and Qi, J. (2024). A retrospective analysis of clinical characteristics and outcomes of pediatric fulminant myocarditis. BMC pediatrics, 24(1), 553.

ISSN 2721-1304 (Print), ISSN 2721-1207 (online)
Copyright © 2026, Journal La Lifesci, Under the license CC BY-SA 4.0