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AUTHOR GUIDELINES

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Rockville. 1998. http://www.healthwise.org. Accessed 21 Sept 1998.

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Every conflict of interest-financially or non-financial-should be stated explicitly. Please state "None" if no conflict exists.

Sources of funding

All sources of support for the research should be listed under this heading.

Original Article

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Non–traditional Lipid Profile and Obstructive Coronary Artery Disease Based on CAD–RADS Score

Fatihatul Firdaus Munita,[1] Nuraini Yasmin Kusumawardhani,[1] Chaerul Achmad,[1] Astri Astuti,[1] Azizah Muthiah.[1]

Abstract

Background: The association between dyslipidemia and coronary artery disease (CAD) is undisputable. Current evidence suggests that, in comparison to conventional lipid parameters, a comprehensive non-traditional lipid profile serves as a more robust predictor of CAD. The evidence regarding the correlation between non-traditional lipid profile and severity of coronary lesions, as measured by the coronary artery disease-reporting and data system (CAD-RADS) score by Coronary Computed Tomography Angiography (CCTA), is still scarce. This study aimed to elaborate on the association between those parameters. Understanding these associations may improve risk stratification and management in CAD patients.

Methods: A cross-sectional single-center study was conducted in a large population of patients with suspected CAD. Data were obtained from medical records between January 2020 and February 2024. The CAD-RADS score was stratified into three groups: CAD-RADS 0 (no CAD), CAD-RADS 1-2 (stenosis <50%, classified as non-obstructive CAD), and CAD-RADS ≥3 (stenosis ≥50% in ≥1 coronary segment, classified as obstructive CAD). Logistic regression analysis analyzes the association between patients' lipid profiles and CAD-RADS scores. P-value <0.05 was considered statistically significant.

Results: A total of 543 (274 female) patients were included in this study. In the univariate analysis, the LDL/HDL ratio was significantly associated with the severity of CAD based on CAD-RADS scores. The multivariate analysis revealed that the LDL/HDL ratio was the most significant lipid parameter [Adj OR = 10.506, 95% CI (2.139-51.601), P 0,004] after adjustments for age, sex, smoker, and history of hypertension, diabetes mellitus, and chronic kidney disease. The LDL/HDL ratio cut-off value was 1.78 with a sensitivity of 68.90% and a specificity of 72.93%.

Conclusions: The LDL/HDL ratio was significantly associated with obstructive CAD, as assessed by the CAD-RADS score, with a cut-off value of 1.78 can be a predictor of obstructive CAD.

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Keywords: *lipid profile, coronary artery disease, CAD-RADS Score*.

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Introduction

Coronary artery disease (CAD) remains one of the leading causes of morbidity and mortality worldwide.[1,2] Understanding the underlying factors that contribute to the severity of CAD is crucial for improving diagnostic and therapeutic strategies. Traditionally, the assessment of lipid profiles has been fundamental in predicting cardiovascular risk; however, emerging evidence suggests that beyond the standard lipid parameters, additional lipid-related biomarkers may provide a more comprehensive risk assessment.[3]

This is currently an active research area where lipid profiles, both traditional and non-traditional, have been identified as independent predictors for cardiovascular disease across various patient populations. Several studies have demonstrated that low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), and the TC/HDL-C ratio are strong predictors of cardiovascular disease.[2-4] Compared to individual lipid parameters, comprehensive non-traditional lipid indices such as non-HDL-C (total cholesterol minus HDL-C), TC/HDL-C (Castelli Risk Index-I), LDL-C/HDL-C (Castelli Risk Index-II), non-HDL-C/HDL-C (Atherogenic Index, AI), log TG/HDL-C (Atherogenic Index of Plasma, AIP), and TC × TG × LDL/HDL-C (Lipoprotein Combined Index, LCI) are regarded as superior predictors of CAD.[5-8]

Research has proven the effectiveness of Coronary Computed Tomography Angiography (CCTA) in evaluating patients with CAD.[9] The CAD-RADS score is a standardized method for classifying the severity of coronary artery disease using CCTA. This system offers a detailed evaluation of coronary artery stenosis, which is essential for clinical decision-making and risk stratification.[10] Although the relationship between traditional lipid profiles and CAD has been well-documented, there is a growing need to explore the association between more comprehensive lipid profiles and the extent of obstructive CAD as assessed by CAD-RADS.

This study aims to investigate the relationship between an expanded lipid profile and the severity of obstructive CAD based on the CAD-RADS score. By analyzing a broader range of lipid parameters, this research seeks to provide deeper insights into how these factors correlate with the anatomical and functional severity of CAD. The findings could enhance the current understanding of lipid-related mechanisms in CAD progression and support the development of more targeted therapeutic approaches

Materials and Methods

Design of the Study and Subject Recruitment

The minimum sample size was calculated using the unpaired analytical study sample size formula. Between January 2020 and February 2024, 747 consecutive adult patients who underwent CCTA at Hasan Sadikin General Hospital - Faculty of Medicine, Universitas Padjadjaran, were enrolled in this study.

Adults aged 18 years and older with suspected CAD who underwent CCTA were included in this study. Eligible participants must have complete traditional and non-traditional lipid profile data available, which includes total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), non-HDL, TC/HDL ratio, LDL/HDL ratio, Atherogenic Index (AI), Lipoprotein Combine Index (LCI), and Atherogenic Index of Plasma (AIP). Additionally, participants must provide written informed consent to participate in the study.

Patients who have undergone percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery are excluded from the study. PCI and CABG procedures can affect CTA results due to the presence of stents and surgical grafts, which may introduce artifacts, reduce image clarity, or obscure native coronary anatomy. By excluding these patients, researchers might obtain clearer CTA images for analyzing native coronary artery atherosclerosis. Patients who have experienced acute coronary syndrome (ACS) within the past three months, have incomplete lipid profile data, or have unsatisfactory CCTA data are also excluded from the study. Furthermore, individuals with severe comorbid conditions such as active cancer, severe liver disease, or chronic inflammatory diseases, as well as pregnant women and those with known allergies to contrast agents used in CCTA, are excluded from the study. These criteria ensure a homogeneous study population and enhance the validity and reliability of the study findings regarding the association between lipid profiles and obstructive CAD based on CAD-RADS scores.

Table 1. Baseline characteristic.

Variable	Non CAD (n=111)	Non Obstructive CAD (n=133)	Obstructive CAD(n=299)	P value
Age, mean±SD	49±10 (13.5)	55±10 (13)	60±9 (12)	<0.001
Sex				
Male, n (%)	27 (5%)	58 (11%)	184 (34%)	<0.001
Female, n (%)	84 (15%)	75 (14%)	115 (21%)	
Family History, n (%)	11 (2%)	8 (1%)	22 (4%)	0.509
Diabetes Mellitus, n (%)	3 (1%)	9 (2%)	51 (9%)	<0.001
Hypertension, n (%)	39 (7%)	58 (11%)	166 (31%)	<0.001
Dyslipidemia, n (%)	28 (5%)	41 (8%)	159 (29%)	<0.001
Active smoker, n (%)	16 (3%)	20 (14%)	105 (19%)	<0.001
Chronic Kidney Disease, n (%)	26 (5%)	41 (8%)	175 (32%)	<0.001
Total Cholesterol, n (%)				0.002
<200 (normal)	70 (13%)	87 (16%)	191 (35%)	
200-239 (borderline)	34 (6%)	33 (6%)	53 (10%)	
≥240 (high)	7 (1%)	13 (2%)	55 (10%)	
LDL, n (%)				<0.001
<130 (normal)	73 (13%)	90 (17%)	176 (32%)	
130-159 (borderline)	23 (4%)	28 (5%)	42 (8%)	
≥160 (high)	15 (3%)	15 (3%)	81 (15%)	
HDL, n (%)				0.055
≥40 (normal)	87 (16%)	102 (19%)	204 (38%)	
<40 (low)	24 (4%)	31 (6%)	95 (17%)	
Triglyceride, n (%)				0.018
<150 (normal)	76 (14%)	89 (16%)	176 (32%)	
150-199 (borderline)	26 (5%)	21 (4%)	58 (11%)	
≥200 (high)	9 (2%)	23 (4%)	65 (12%)	
Total Cholesterol, mean±SD, mg/dl	184±36	186±37	190±52	0.735
LDL, mean±SD, mg/dl	116±33	120±34	126±43	0.063
HDL, mean±SD, mg/dl	49±14	48±13	46±12	0.014
Triglyceride, mean±SD, mg/dl	133±62	153±115	163±118	0.215
Non HDL, mean±SD, mg/dl	136±36	136±37	145±51	0.379
CRI I, mean±SD	3.9±1.1	4±1.3	4.4±1.7	0.061
CRI II, mean±SD	2.57±0.9	2.58±0.95	3±1.4	0.005
AI, mean±SD	2.9±1.1	3±1.3	3.4±1.8	0.033
LCI, mean±SD	71137±55760	82391±111059	114264±169313	0.041
AIP, mean±SD	0.4±0.2	0.45±0.3	0.49±0.3	0.025

CAD: Coronary Artery Disease, SD: Standard Deviation, LDL: Low-Density Lipoprotein, HDL: High-Density Lipoprotein, TC: Total Cholesterol, TG: Triglycerides, Non-HDL: Non-High-Density Lipoprotein Cholesterol; CRI: Castelli Risk Index (CRI-I: Total Cholesterol/HDL, CRI-II: LDL/HDL); AI: Atherogenic Index (Non HDL/HDL); LCI: Lipid Coefficient Index (TC.TG.LDL/HDL); AIP: Atherogenic Index of Plasma (log10[Trig/HDL]).

Table 2. Univariate and Multivariate Logistic Regression Model for Prediction of Obstructive CAD.

Variables		OR	(95% CI)	P value	Adj OR	(95% CI)	P value
Traditional lipid profile	TC	0.970	(0.917-1.027)	0.299	0.975	(0.908-1.048)	0.495
	TG	1.001	(0.993-1.009)	0.815	1.007	(0.997-1.016)	0.162
	HDL	1.007	(0.939-1.079)	0.847	1.015	(0.934-1.103)	0.726
	LDL	0.978	(0.948-1.008)	0.152	0.961	(0.928-0.996)	0.028
	Non HDL	1.051	(0.989-1.117)	0.109	1.06	(0.983-1.143)	0.133
Non-traditional lipid profile	TC/HDL	0.591	(0.157-2.222)	0.437	0.393	(0.068-2.276)	0.297
	LDL/HDL	4.393	(1.075-17.958)	0.039	10.506	(2.139-51.601)	0.004
	AI	0.432	(0.081-2.291)	0.324	0.459	(0.057-3.682)	0.464
	LCI	1.000	(1.000-1.000)	0.094	1.00	(1.000-1.000)	0.563
	AIP	0.361	(0.028-4.594)	0.432	0.076	(0.004-1.433)	0.086

Adj OR: Adjusted Odds Ratio, 95% CI: 95% Confidence Interval, TC: Total Cholesterol, TG: Triglycerides, HDL: High-Density Lipoprotein, LDL: Low-Density Lipoprotein, AI: Atherogenic Index, LCI: Lipid Coefficient Index, AIP: Atherogenic Index of Plasma.

Traditional Cardiovascular Risk Factors

Dyslipidemia was defined based on patient history and was not limited to those already on statin therapy. Essential hypertension (EH), diabetes mellitus (DM), and chronic kidney disease (CKD) were defined according to features described in a previous report. EH was defined as systolic pressure ≥140 mm Hg and/or diastolic pressure ≥90 mm Hg and/or a self-reported history of hypertension and/or use of anti-hypertensive drugs. DM was defined as fasting glucose levels ≥126 gr/dl, and/or a self-reported history of diabetes mellitus, and/or use of anti-diabetic drugs. CKD is defined as kidney damage or decreased kidney function for three months or more, irrespective of the cause, excluding patients on dialysis. Smoking was defined as daily cigarette smoking until the day of the interview.

Non-traditional lipid profile

Non-traditional lipid variables were calculated to provide a comprehensive assessment of lipid profiles in the study population. Non-HDL cholesterol was determined by subtracting HDL cholesterol from total cholesterol. Castelli's risk index-1 (CRI 1) was determined by the total cholesterol to HDL ratio (TC/HDL) and Castelli's risk index-2 (CRI 2) was determined by LDL to HDL ratio (LDL/HDL). The Atherogenic Index (AI), defined as the ratio of Non-HDL to HDL cholesterol, and the Atherogenic Index of Plasma (AIP), calculated as the logarithm of the ratio of plasma triglycerides to HDL cholesterol, were also included. Additionally, the Lipoprotein Combined Index (LCI) obtained from multiplying total cholesterol by triglycerides and LDL, then divided by HDL.

CCTA

CCTA is a non-invasive imaging modality to visualize coronary arteries. The protocol for CCTA in this study included the administration of a contrast agent to enhance the visualization of the coronary artery lumen and to identify the presence and extent of CAD. Patients underwent CCTA following standard preparation, including heart rate control with beta-blockers if necessary, to obtain high-quality images with minimal motion artifacts. The CAD-RADS is a standardized reporting system for CCTA findings, categorizing the severity of coronary stenosis from 0 (no stenosis) to 5 (total occlusion in at least one coronary segment). Obstructive CAD is defined as stenosis of ≥50% in at least one coronary segment on CCTA, corresponding to a CAD-RADS score of ≥3.

Statistical Analysis

The baseline characteristics of the study population will be summarized using descriptive statistics. The mean and standard deviation for continuous variables were compared using a k-independent samples t-test. The frequencies and percentages were compared using a Chi-square test for categorical variables. Univariate linear regression analysis will be performed to identify significant associations between each lipid parameter

Table 3. Multicollinearity of age, sex, hypertension, DM, smoking, CKD and LDL/HDL for Obstructive CAD.

Categorical variables	Coefficients beta	Coefficients std. error	t Value	P Value	R2	Adj R2
Constant	3.956339	0.389579	10.155	<0.001	0.09905	0.08418
Age	–0.024159	0.006498	-3.718	<0.001		
Sex	0.35918	0.145916	2.462	0.014		
Hypertension	-0.298539	0.12808	-2.331	0.02		
DM	0.121864	0.178713	0.682	0.495		
Smokers	-0.09115	0.157524	-0.579	0.563		
CKD	0.565755	0.133503	4.238	<0.001		

DM: Diabetes Mellitus, CKD: Chronic Kidney Disease

and obstructive CAD. Subsequently, multivariate logistic regression models will be constructed to adjust for potential confounding variables such as age, sex, hypertension, diabetes mellitus, chronic kidney disease, and smoking status. Include the identified confounding variables as covariates in the logistic regression model. The adjusted odds ratios (Adj OR) and 95% confidence intervals (CIs) will be calculated to determine the strength of the associations. Model performance will be evaluated using sensitivity, specificity, and accuracy metrics. Assumption made during analysis could be achieved by Linearity of Logits in which the relationship between the independent variables and the log odds of the dependent variable is assumed to be linear. This can be assessed through various diagnostic plots. The threshold for statistical significance will be established at $P < 0.05$. RStudio 4.3.2 will be employed to conduct all analyses.

Ethical Aspect and Research Approval

The data collection was categorized as low-risk as it was conducted using medical record data. After receiving approval and recommendations from the Ethics Committee Review Board of Hasan Sadikin General Hospital – Faculty of Medicine, Padjadjaran University, all procedures were performed in accordance with applicable guidelines and regulations. The registry number for this research was part of the CCTA registry, with the reference number LB.02.01/X.6.5.130/2023.

Results

Baseline characteristics

A total of 543 CAD patients were included in this study, out of a total of 747 CAD patients who underwent CCTA from 01 January 2020 to 28 February 2024. The remaining 139 patients were excluded due to incomplete fundamental clinical information, while nine patients were excluded due to missing or unsatisfactory CCTA data for analysis. Additionally, 56 additional patients were precluded as a result of history of PCI or CABG (Figure 1).

The baseline characteristics of the study population are shown in Table 1, which compares patients with obstructive CAD, non-obstructive CAD, and non-coronary artery disease (non-CAD). The mean age was significantly higher in the obstructive CAD group (60 years) compared to the non-CAD (49 years) and non-obstructive CAD (55 years) groups ($p < 0.001$). There was a higher proportion of males in the obstructive CAD group (34%) compared to the non-CAD (5%) and non-obstructive CAD (11%) groups ($p < 0.001$). The prevalence of diabetes mellitus, hypertension, dyslipidemia, active smoking, and chronic kidney disease was also significantly higher in the obstructive CAD group ($p < 0.001$ for each). Total cholesterol levels were higher in the obstructive CAD group, with more patients having cholesterol ≥240 mg/dl (10%) compared to the non-CAD (1%) and non-obstructive CAD (2%) groups ($p = 0.002$). LDL levels were also significantly higher in the obstructive CAD group, with more patients having LDL ≥160 mg/dl (15%) compared

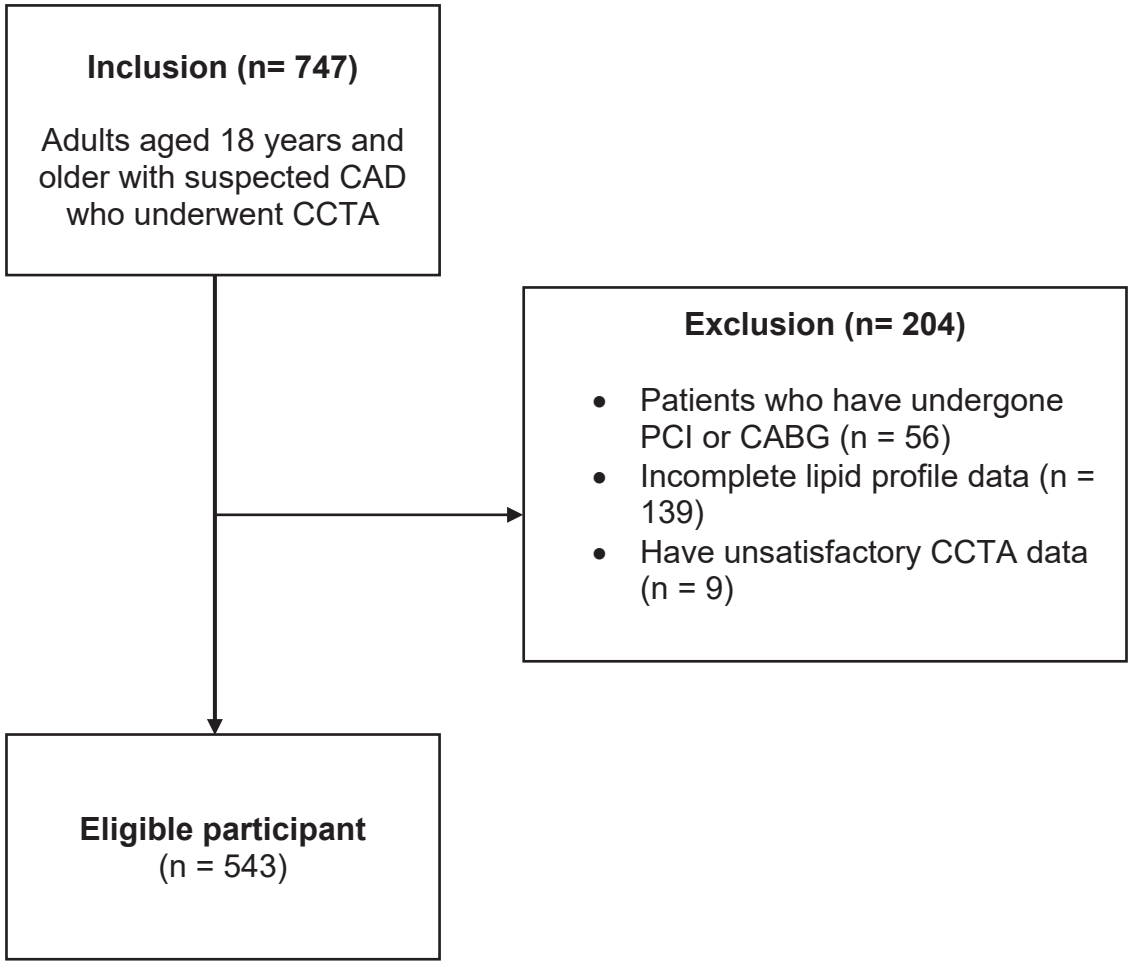

Figure 1. Patient Enrollment.

to the other groups (p < 0.001). Triglyceride levels were also higher in the obstructive CAD group, with more patients having triglyceride ≥200 mg/dl (12%) compared to the other groups (p 0.018). HDL levels were lower in the obstructive CAD group, with more patients having HDL <40 (17%) compared to the other groups (p 0.055). The mean of several non-traditional lipid measures, such as TC/HDL, AI, LCI, and AIP was higher in the obstructive CAD group and showed significant differences across the groups, indicating a worse lipid profile in the obstructive CAD group (p < 0.05 for each).

Univariate and Multivariate analysis

The univariate and multivariate logistic regression analysis table assesses the relationship between traditional and non-traditional lipid variables and obstructive CAD. There was no significant association between obstructive CAD and traditional lipid variables. (Table 2)

In contrast, among non-traditional lipid variables, only the LDL/HDL ratio was significantly associated with obstructive CAD [unadjusted OR 4.393, 95% CI (1.075-17.958), P 0.039), while non-HDL, TC/HDL, the AI, LCI, and AIP were not. After adjusting for potential confounding factors, which are established CAD risk factors, including age, sex, smoker, and history of hypertension, diabetes mellitus, and chronic kidney disease, we found that LDL/HDL ratio was significantly

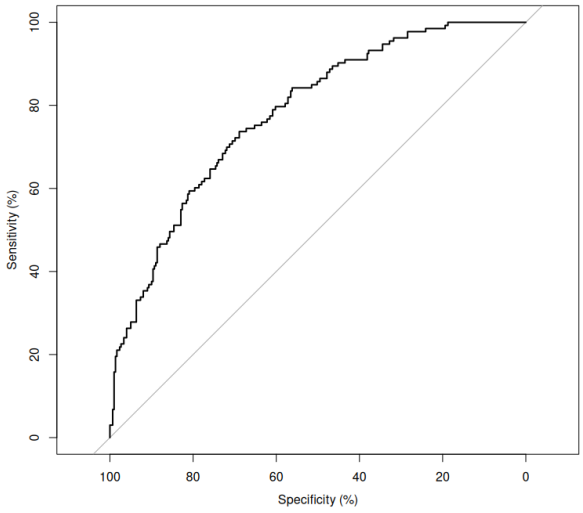

Figure 2. ROC curve of LDL/HDL Ratio.

associated with obstructive CAD [OR = 10.506, 95% CI (2.139-51.601), P 0,004] (Table 2). The variance inflation factor (VIF) is 1,1 in the multicollinearity regression model, which shows no collinearity between age, sex, hypertension, DM, smokers, CKD, and LDL/HDL ratio. (Table 3).

According to the ROC curve analysis, this study's cut-off value of LDL/HDL ratio was 1.78, with a sensitivity of 68.90% and specificity of 72.93. Area Under Curve (AUC) 77.99% (95% CI, accuracy 70.14%) shows fair performance in predicting obstructive CAD. (Figure 2).

Discussion

This study demonstrates a significant association between the LDL/HDL ratio and obstructive CAD as measured by the CAD-RADS score. The LDL/HDL ratio was a reliable marker across all models, even though other lipid measures did not show a significant correlation. This suggests that it might be useful for predicting obstructive CAD. Univariate analysis revealed that traditional lipid variables were not significantly associated with obstructive CAD, but the LDL/HDL ratio was a notable exception among non-traditional lipid variables. Multivariate analysis showed that the LDL/HDL ratio was consistently linked to obstructive CAD across all models, even after multiple covariates were taken into account. Other lipid measures did not show any significant associations.

Previous studies have demonstrated that dyslipidemia significantly influences coronary atherosclerosis, with reductions in HDL-C and increases in LDL-C being pivotal in the progression of atherosclerosis and the onset of CAD.[11-13] Elevated LDL-C levels are strong predictors of atherosclerotic cardiovascular diseases and lowering these levels can reduce the risks of events like AMI and ischemic stroke, while higher HDL-C levels are associated with a decreased risk. Research demonstrates that the LDL/HDL ratio serves as a robust predictor of CAD and long-term major adverse cardiac events (MACE), offering a more accurate risk assessment compared to solely measuring LDL or HDL.[14-17] Despite mixed results regarding the significance of lipid indices like AIP, AI, and LCI, their predictive values may vary with different scoring systems.[18-23] Additionally, adjusting for risk factors such as age, gender, hypertension, diabetes, chronic kidney disease and smoking status enhances the validity of CAD research findings, highlighting the complexity and multifactorial nature of CAD risk assessment.[1,24-27]

This study showed that the LDL/HDL ratio is associated with obstructive CAD based on the CAD-RADS score. Zhang et al. (2020) showed that the LDL-C/HDL-C ratio is a strong, independent indicator of MACE that will happen in people with CAD over the long term. The study highlighted the utility of the LDL-C/HDL-C ratio in evaluating CAD risk, especially for patients undergoing different types of treatments.[15] High levels of LDL can lead to plaque buildup in the artery walls, increasing the risk of atherosclerosis and eventually CAD. However, measuring LDL alone does not provide information about the beneficial cholesterol that can counteract LDL's harmful effects.[15,16] HDL helps transport cholesterol from the arteries back to the liver for disposal. High levels of HDL are associated with a lower risk of CAD. Measuring HDL alone is insufficient as it fails to indicate the extent to which HDL manages LDL.[15] The LDL/HDL ratio provides a better indication of CAD risk. A high ratio indicates that the amount of LDL is significantly higher than the HDL, suggesting a high risk for plaque formation in the arteries. Conversely, a low ratio indicates a better balance between LDL and HDL, meaning a lower risk of CAD.16 Several studies have shown that the LDL/HDL ratio is a better predictor of CAD compared to measuring LDL or non-HDL alone, as it reflects

the complex interaction between different types of cholesterol in the body.[17,18]

Moreover, the LDL/HDL ratio in this study had threshold value of 0.69 and cut-off value 1.78, which could be a predictor for obstructive CAD with a sensitivity of 68.90% and specificity of 72.93% and Area Under Curve (AUC) 77.99% (95% CI, accuracy 70.14%). The LDL/HDL ratio demonstrates moderate effectiveness as an indicator of obstructive coronary artery disease (CAD). It holds significant clinical relevance for preventing the progression of CAD and directing the treatment of coronary atherosclerosis. By applying this cut-off, we can implement effective strategies to lower the LDL/HDL ratio, consequently mitigating the advancement and severity of CAD. We have separately calculated LDL/HDL and CAD risk factors using the multicollinearity regression model. The findings revealed that the VIF is 1.1, indicating no multicollinearity between LDL/HDL and the variables of age, sex, hypertension, diabetes mellitus, chronic kidney disease, and smoking status. This finding is consistent with previous studies, which show that a higher LDL/HDL ratio was seen in patients with CAD than controls ($P < 0.05$). Their cut-off value of LDL/HDL ratio was 2.517, with a sensitivity of 64.5% and specificity of 61.3%, respectively, which may become a better predictor of CAD severity compared to LDL or HDL.[16]

A lower LDL/HDL ratio is beneficial in reducing the progression of atherosclerosis by minimizing LDL infiltration, enhancing cholesterol removal through HDL, decreasing inflammation, and stabilizing plaques. Conversely, a high LDL/HDL ratio promotes plaque growth and instability, increasing the risk of cardiovascular events. A high LDL/HDL ratio is associated with increased endothelial dysfunction and inflammation, both of which are central to atherosclerosis progression. Oxidized LDL particles trigger inflammatory responses by activating macrophages, which transform into foam cells and become part of the plaque structure. This ongoing inflammation contributes to plaque instability and the potential for rupture, leading to acute cardiovascular events. Conversely, a lower LDL/HDL ratio reduces this inflammatory cascade, thereby slowing the advancement of atherosclerosis. Changes in the LDL/HDL ratio can influence plaque composition. Higher LDL levels contribute to the formation of lipid-rich, unstable plaques that are more prone to rupture. HDL, on the other hand, has antioxidant and anti-inflammatory properties that help stabilize plaques by removing oxidized lipids and inhibiting further inflammatory cell infiltration. Studies show that lowering the LDL/HDL ratio is associated with an increase in fibrous cap thickness and a reduction in necrotic core size within plaques, making them less likely to rupture.[5-8,14-17,28]

This study found that there was a lack of significant association for AI, LCI, and AIP in multivariate models. To the best of the researchers' knowledge, no other studies have demonstrated that AI, LCI, or AIP are insignificant in predicting CAD. Numerous studies have emphasized the importance of the AIP and other lipid indices as predictors of CAD severity. A study involving 2,491 patients demonstrated a significant association between AIP and CAD severity as measured by the SYNTAX score, establishing AIP as an independent predictor.18 In the Chinese Han population, another study corroborated AIP's role as a strong predictor for CAD, emphasizing its clinical utility.[19] Further research involving 150 patients undergoing CABG revealed that both LCI and AI are significantly associated with CAD severity, with higher values observed in the CAD group compared to non-CAD controls.[20] The National Diabetes Survey of Pakistan identified a strong association between AIP and CAD risk factors, suggesting that higher AIP levels may serve as a marker for increased CAD severity.[21]

Lastly, a study of 896 patients with suspected CAD found a positive association between baseline AIP and the angiographic progression of CAD, underscoring AIP's potential in early risk stratification and monitoring of CAD progression.[22] Differences in research outcomes regarding the role of non-traditional lipids in CAD can be attributed to the use of different scoring systems. Various scoring systems used to assess the severity of CAD, such as CAD-RADS or other scoring methods, have different criteria and parameters for evaluating coronary artery narrowing and obstruction levels. This variation can lead to differences in classification and interpretation of results.

Metrics like AIP and AI may not demonstrate universal predictability across different populations. The predictive power of AIP and AI can vary due to factors like genetic background, lifestyle, and comorbidities, leading

to less consistent statistical significance compared to the more universally applicable LDL/HDL ratio. Some non-traditional lipid metrics may overlap with traditional measures like LDL and HDL, creating redundancy rather than additive predictive power. If LDL/HDL ratio already captures most of the atherogenic risk, additional indices may not significantly improve prediction due to shared variance. Non-traditional metrics like AIP and AI can be sensitive to other variables in the model or to smaller sample sizes, potentially limiting their statistical power. For instance, AIP's dependency on triglyceride levels may cause variability in significance depending on triglyceride distributions across the study population, especially in samples with lower overall cardiovascular risk.[21,23]

Limitations

A notable limitation of this study is that it was conducted in a single medical center, which may restrict the generalizability of the findings to other settings or populations with different characteristics. Additionally, the cross-sectional design of the study can establish associations but does not allow for the determination of causality. Furthermore, the study did not differentiate the duration of statin therapy among participants, which could significantly influence lipid levels and cardiovascular outcomes that leads to potential selection bias. Patients with longer exposure to statins may have more stabilized lipid profiles and potentially different clinical outcomes compared to those with shorter statin use. Although sample numbers achieved 543, larger samples are needed to adequately represent the broader population, which can affect the generalizability of the findings. Results derived from a small, specific group may not apply to different demographics or clinical settings. Future researchs for validation in larger, more diverse populations should consider stratifying patients based on their duration of statin therapy to better understand its effects on the study outcomes as well as longitudinal studies to assess the prognostic value of the LDL/HDL ratio in CAD progression.

Conclusions

The LDL/HDL ratio was significantly associated with obstructive CAD, as assessed by the CAD-RADS score, with a cut-off value of 1.78 can be a predictor of obstructive CAD. Adding LDL/HDL to traditional risk factors can further improve the comprehensive lipid-lowering treatment, guiding prevention strategies for obstructive CAD.

List of Abbreviations

CAD	Coronary Artery Disease
CAD-RADS	Coronary Artery Disease Reporting and Data System
CCTA	Coronary Computed Tomography Angiography
TC	Total cholesterol
TG	Triglycerides
HDL	High-Density Lipoprotein
LDL	Low-Density Lipoprotein
CRI	Castelli's Risk Index
AI	Atherogenic Index
LCI	Lipoprotein Combine Index
AIP	Atherogenic Index of Plasma
PCI	Percutaneous Coronary Intervention
CABG	Coronary Artery Bypass Grafting
ACS	Acute Coronary Syndrome
EH	Essential Hypertension
DM	Diabetes Mellitus
CKD	Chronic Kidney Disease
MACE	Major Adverse Cardiac Events

Declaration

Ethics Approval and Informed Consent to Participate

All methods were carried out by relevant guidelines and regulations after obtaining approval and recommendations from the Ethics Committee Review Board of Hasan Sadikin General Hospital – Faculty of Medicine, Universitas Padjadjaran, with reference number LB.02.01/X.6.5.130/2023. Since this study used secondary data, written informed consent was not applicable.

Consent for publication

Ethics Committee Review Board of Hasan Sadikin General Hospital – Faculty of Medicine, Padjadjaran Universitywaived the need for informed consent with reference number LB.02.01/X.6.5.130/2023

Availability of data and materials section

The authors declare that the patients' personal data in this study will not be shared based on patients' confidentiality.

Competing Interest

The authors have declared that no competing interest exist.

Funding

No funding.

Authors' contributions

FFM did the conception and design of the study, acquisition of data, analysis and interpretation of the data, drafting the manuscript and revising the manuscript critically for important intellectual content.

AM did the acquisition of data, analysis and interpretation of the data, and drafted the manuscript and revising the manuscript critically for important intellectual content.

NYK, CA, and AA did the supervision critically for important intellectual content.

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Original Article

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Clinical, Echocardiographic and Laboratory Cardiac Monitoring in Breast Cancer Patients Undergoing Chemotherapy with Anthracycline Agents: A Pilot Study on Cardioprotective Algorithms at Mohammad Hoesin General Hospital, Palembang

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Abstract

Background: Improved cancer therapy and early disease detection increase the survival rate, but also increase the risk of The risk of Cancer-Therapy Related Cardiac Dysfunction (CTRCD), which ranges between 2 and 48% for patients with breast cancer treated by anthracyclines. There was limited data about the prevalence of CTRCD in South Sumatra. Studying demographic factors and potential laboratory cardiac markers in a specific population will give others additional important information.

Methods: In 2024, from March until November, 30 breast cancer patients, aged 51.50 (41-69) years, were included in this analysis. All patients were receiving anthracycline chemotherapy at Mohammad Hoesin General Hospital. Demographic, laboratory, and echocardiographic data were collected at baseline and after 3 cycles of treatment.

Results: From 30 patients, cardiovascular risk factors were detected: hypertension 30%, diabetes 10%, dyslipidemia 13.3%, body mass index 23.32 (13.30- 31.18), and almost all patients were not smokers (96.7%). Baseline to serial echocardiography showed that anthracycline did not affect the decrease of left ventricular ejection fraction (LVEF) ($p=0.212$), but correlated with the decrease of left ventricle global longitudinal strain (GLS) ($p<0.05$). There were 16 patients with >15% global longitudinal strain (GLS) reduction, without significant clinical heart failure signs and symptoms, known as mild asymptomatic CTRCD. Laboratory examination showed anthracycline agent was not correlated with Troponin T ($p=0.093$), N-terminal pro B-type Natriuretic Peptide BNP ($p=0.150$), Serum Iron ($p=0.775$), Total Iron Binding Capacity (TIBC) ($p=0.692$), and Transferrin Saturation ($p=0.748$). Ferritin level was affected by anthracycline agents ($p = 0.026$).

Conclusion: Higher prevalence of CTRCD in the South Sumatra population was found. There was a low incidence of cardiovascular risk factors in this population, indicating a stronger isolated effect of the chemotherapy agent for cardiac dysfunction progression. GLS by echocardiography measurement remains a good marker for cardiotoxicity related to anthracycline agents. Ferritin level is a potential parameter in guiding the stages and strategies in cancer treatment.

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Keywords: *anthracycline, cardiac dysfunction, global longitudinal strain, ferritin.*

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Introduction

Breast cancer has the highest prevalence among women. The improvement of cancer therapy has increased the survival rate. Anthracycline is a common chemotherapy agent for patients with breast cancer. Increased survival has allowed to observe cardiotoxic effects of anthracycline. Early detection of myocardial dysfunction in patients treated by anthracyclines may improve cardiologic prognosis through chemotherapy dose adjust and ensure cardioprotective agents during chemotherapy.[1,2] Patients with cardiovascular risk factors increased the risk for cancer progression and cardiotoxicity since there were similar risk factors for both cardiovascular disease and cancer. Overweight and obesity are known to be risk factors for cardiotoxicity.[3] Detection of cardiotoxicity by echocardiography and biomarkers was important in early diagnosis of cancer-therapy related cardiac dysfunction (CTRCD).[4]

Echocardiography measurement includes cardiac mechanics by myocardial strain and ejection fraction. Speckle tracking echocardiography, also known as strain imaging, analyzes deformation by motion changes in a myocardial wall without relying on the endocardial border. This novel echocardiographic technique allows early detection of myocardial dysfunction, before global reduction of cardiac function.[5] The left ventricular ejection fraction (LVEF) is classically used to measure cardiac contractility and guide cardioprotective strategy during chemotherapy.[6,7] Unfortunately, LVEF was not sensitive enough in detecting minimal impairment of myocardium, until the cardiac dysfunction becomes moderate to severe.[8] Some echocardiography techniques are also potentially used to increase the accuracy of cardiotoxicity detection, such as stress echocardiography,[4] D, and contrast echocardiography.[9] Laboratory biomarkers, such as troponin measurement at completion of chemotherapy, are useful in predicting subsequent cardiotoxicity.[10,11] The earlier recognition of cardiotoxicity will help guide treatment to avoid cardiac disease progression. Future biomarkers and imaging techniques for CTRCD detection could enable pre-identify the risk of cardiotoxicity, so that a multidimensional approach can reduce cardiac disease progression while achieving the cancer treatment goal.

Methods

Study Design

This study is observational and correlational analytic with cross-sectional design. The measurement was applied to 30 breast cancer patients treated by anthracycline chemotherapy. Demographic data was collected, such as age, gender, cardiovascular risk factors, hypertension, dyslipidemia, diabetes, body mass index, and smoking status. Echocardiography and laboratory measurements were performed twice, at baseline data before chemotherapy and after the third cycle of chemotherapy.

Echocardiography

Standard trans-thoracal echocardiography for left ventricular ejection fraction value was performed, besides the main parameter, speckle tracking echocardiography or strain imaging. This study used an echocardiography machine, GE Vivid-E95. All patients were examined with conventional 2-dimensional, M-Mode, color Doppler ultrasonography and speckle tracking echocardiography. Left ventricular ejection fraction (LVEF) was performed using a method by Simpson. Echocardiography measurement was conducted by a cardiologist.

Cancer-Therapy Related Cardiac Dysfunction (CTRCD)

CTRCD based on clinical presentation and symptoms was included very severe to mild symptomatic CTRCD and severe to mild asymptomatic CTRCD. Asymptomatic mild CTRCD was defined if there was LVEF > 50% and a new relative decline of left ventricular global longitudinal score (GLS) by >15% from baseline measurement (before chemotherapy), and/or a new rise in cardiac biomarker.

Laboratory measurements

Recent studies have suggested that measurement of cardiac serum biomarkers, Troponin I or T, and N-terminal pro B-type natriuretic peptide (NT pro BNP) helps in stratifying the risk of cardiotoxicity of patients scheduled for chemotherapy. Other potential cardiac markers were important to measure since the rule

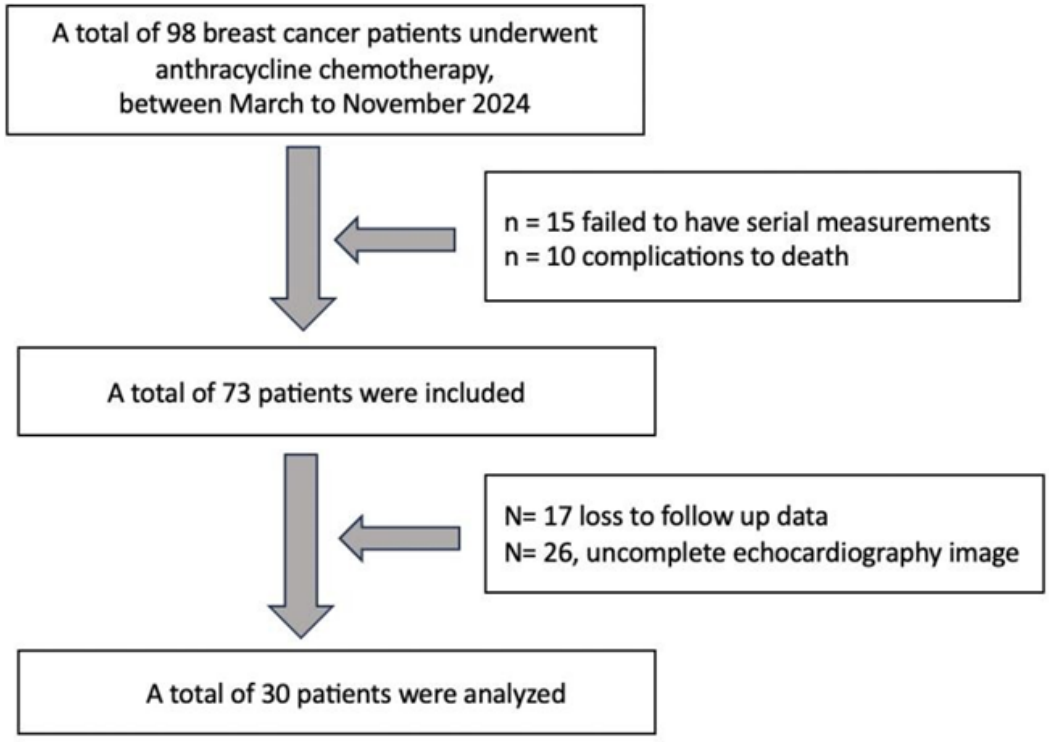

Figure 1. Study Population.

of heart failure consists of neurohormonal-metabolism pathways, such as serum iron, Total Iron-Binding Capacity (TIBC), ferritin, and transferrin saturation (TSAT).

Statistical Analysis

Statistical analysis was performed using SPSS software (SPSS, Chicago, IL). Data were expressed as mean ± SD for normal data and median (range) for abnormal data, with the Kolmogorov-Smirnov test. Bivariate analysis was used to obtain the correlation of the data in different variables.

Results

Study Population

A total of 30 patients were analyzed, from 98 patients included at the beginning of the study, who discontinued the study due to fatal incidence because of cancer and chemotherapy treatment, worsening general fitness, and failed to obtain optimal serial measurements.

Table 1 explains the baseline characteristics, echocardiographic, and laboratory parameters of the patient. The data was obtained before chemotherapy. Cardiotoxicity risk stratification was scored based on criteria from the Cardio-Oncology Study Group of the Heart Failure Association (HFA) of the ESC in collaboration with the International Cardio-oncology Society (HFA-ICOS). All patients were in low cardiotoxicity risk stratification.

Patients in this study was analyzed before and during anthracycline chemotherapy. The data before and during chemotherapy are expressed in Table 2.

The changes of laboratory parameters during chemotherapy in this study were significant in ferritin level with p value < 0.05 (p= 0.026), giving the probability that anthracycline chemotherapy correlated with ferritin level.

In this study, the LVEF of all patients were > 50%, and 16 patients (53.3%) with >15% decline of GLS, indicated asymptomatic mild CTRCD. Echocardiography parameters in 30 patients, before and during chemotherapy, showed LVEF baseline 61.33 ±

Table 1. Baseline characteristics.

	N = 30 Mean/Median ± SD
Age, years	52.70 ± 7.8
Body Mass Index,	23.52 ± 4.85
LVEF, %	61.33 ± 4.908
GLS, %	-15.94 ± 3.705
Troponin T, ng/L	24 ± 6.281
NT pro BNP, pg/ml	184,46 ± 207,095
Serum Iron, g/dL	55.2 ± 25.389
TIBC, g/dL	346.83 ± 30.748
Ferritin, ng/ml	347.15 ± 260.507
Transferrin saturation (%)	15.70 ± 4.949

4.908 reduced to 59.70 ± 6.727, with p value 0.212 (p>0.05) explained the weak correlation of LVEF and anthracycline chemotherapy. Mean baseline GLS was -15.940 ± 3.705 %. Mean decline of GLS was 22.559 ± 19.722 %, with p = 0.00, explained the correlation of GLS score with anthracycline chemotherapy (p<0.05). The patients with CTRCD have a mean age of 51.06 ± 8.136 years old and a body mass index 23.40 ± 5.69, with an incidence of hypertension 31.2%, type 2 diabetes mellitus 12.3%, dyslipidemia 12.3%, and 3.3% were smokers. Laboratory data of 16 patients with CTRCD were expressed in Table 3.

Ferritin level was significantly increased (p<0.05) from baseline to serial measurement, both in all 30 patients and 16 patients with CTRCD.

More echocardiography parameters were analyzed in 27 patients of this study, since 3 patients were identified to have incomplete data for analysis. Echocardiography parameters were expressed in Table 4.

Echocardiography data in Table 5 showed no significant correlation of those parameters before and during anthracycline chemotherapy in this study (p>0.05). In 27 patients, CTRCD was identified in the same patients of the total 30 samples. Mean decline of GLS was 22.559 ± 19.722 %, with p = 0.00.

Discussion

In this study, we found a high incidence of asymptomatic mild CTRCD (53,3%) and a higher incidence of cardiovascular risk factors in patients with CTRCD compared with a general population of patients with breast cancer treated with anthracycline chemotherapy. Age and preexisting left ventricular dysfunction have been identified most consistently as being associated with the development of clinical heart failure or a worsening of left ventricular function with chemotherapy. The cumulative dose of anthracycline or its formulation and additional chemotherapeutic agents such as anti-HER2, besides existing cardiovascular risk factors, have been known to be associated with the risk of cardiotoxicity.[13]

Laboratory findings

Ferritin level in this study was consistent to be significant associated with anthracycline chemotherapy. International guidelines on heart failure define iron deficiency as serum ferritin

<100 ng/mL or, when ferritin is 100-299 ng/mL, a transferrin saturation (TSAT) <20%. 14,15,16 However, a definition based basically on ferritin has several limitations. Most ferritin resides in cells where it binds to iron to prevent free radical production. Any cell damage, including activation of inflammatory pathways, may cause ferritin to be released; an increase in serum ferritin may occur even in the presence of iron deficiency.[17] Bone marrow biopsy as a gold-standard diagnosis demonstrates iron deficiency even when ferritin is higher.[18] Observational studies suggest that serum iron concentration and TSAT were strongly associated

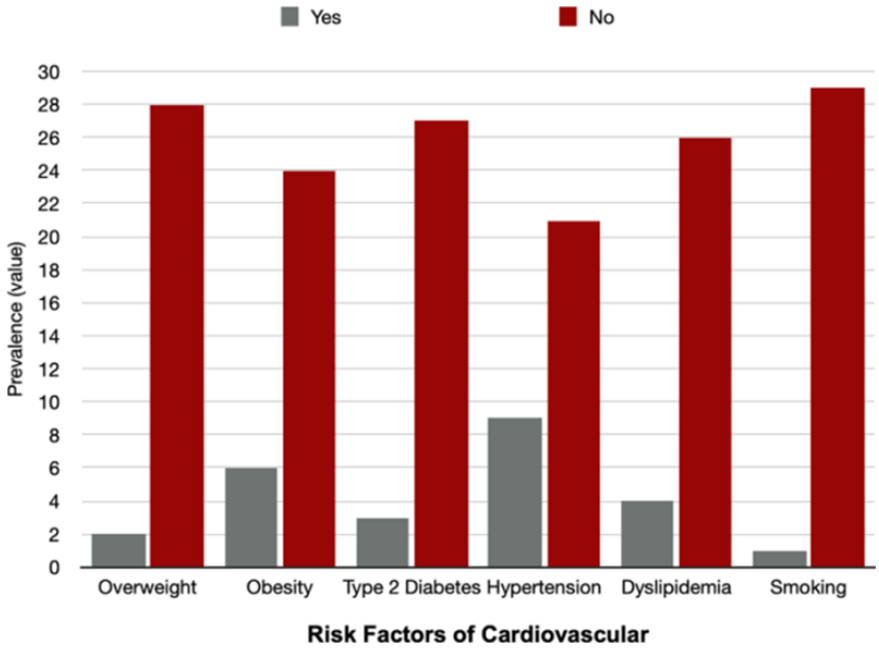

Figure 2. Incidence of cardiovascular/ cancer risk factors Patients in this study was analyzed before and during anthracycline chemotherapy.

with prognosis than serum ferritin; therefore might be a better guide to which patients benefit from parenteral iron supplementation.[18,19,20,21,22] Inflammation was an important process in the pathogenesis of cancer. The serum ferritin is elevated in inflammatory conditions and cancers. This is related to increased synthesis in macrophages, hepcidin promotes the entry of iron into the macrophages. Ferritin and ferritin/ Hb are helpful in the differential diagnosis of the stages of breast cancer. [23] Other biochemical parameters favorable for helping diagnose and stage breast cancer were hepcidin, hs-CRP, besides ferritin/Hb ratio. Increasing ferritin in breast cancer patients help identified the progressive stages of the cancer, including breast cancer patients with early cardiac dysfunction, identified as CTRCD.

Echocardiography parameters

Early cardiac dysfunction in this study was identified through speckle tracking echocardiography, producing a left ventricular global longitudinal strain (GLS) score. The 15% decline or more of GLS has strongly related to anthracycline chemotherapy in patients with breast cancer. Other parameters, including ejection fraction, RV distance, RV strain, TAPSE, RA area, and LAVI were not significantly associated with anthracycline chemotherapy. As those parameters already recommended by the international guideline of cardio-oncology, the routine measurement was still important to identified cardiac toxicity expressed with structural or functional changes in response to different chemotherapy agents.[12]

Implementation of cardiac monitoring, a guideline disparity

In Indonesia, generally cardiac monitoring related to chemotherapy was found as part of routine cardiac service in a cardiovascular clinic. The oncologist referred the patients to a cardiologist to be assessed and examined with echocardiography to stratify the cardiotoxicity risk, establish the cardiotoxicity diagnosis, and gave recommendations considering the result of the analysis. ESC ACC guideline of cardio-oncology listed the complete data of structural heart condition, chemotherapy agents, prior chemotherapy history, cardiovascular risk factors, and comorbid to establish cardiotoxicity risk stratification. In routine cardiology service, the data of chemotherapy agents was difficult to obtained, because of inadequate information in digital

Table 2. Echocardiographic parameters ratio between two groups.

	Mean/median ± SD (N=30)		p value
	Baseline	After 3 cycles	
Troponin T (ng/L)	24.00 ± 6.281	26.6 ± 6.055	0.093
NT pro-BNP (pg/ml)	184.46 ± 207.095	100.18 ± 111.259	0.150
Serum Iron (µg/dL)	55.20 ± 25.389	53.19 ± 11.228	0.775
TIBC (µg/dL)	346.83 ± 30.748	341.90 ± 18.613	0.692
Ferritin (ng/ml)	347.15 ± 260.507	462.06 ± 272.845	0.026
Transferrin saturation (%)	15.70 ± 4.949	15.53 ± 2.688	0.748

Table 3. Laboratory data of patients with CTRCD.

	Mean/median ± SD (N=16)		p value
	Baseline	After 3 cycles	
Troponin T (ng/L)	23.75 ± 6.213	26.94 ± 5.531	0.066
NT pro-BNP (pg/ml)	102.27 ± 158.919	110.69 ± 139.953	0.600
Serum Iron (µg/dL)	51.87 ± 9.378	52.93 ± 11.781	0.764
TIBC (µg/dL)	342.69 ± 22.057	338.94 ± 23.124	0.638
Ferritin (ng/ml)	260.27 ± 174.883	419.09 ± 298.142	0.021
Transferrin saturation (%)	15.13 ± 2.306	15.50 ± 2.805	0.684

Table 4. Echocardiography parameters.

	Mean/median ± SD (N=27)		p value
	Baseline	After 3 cycles	
RV distance (mm)	28.444 ± 4.585	28.593 ± 3.619	0.179
RA area (mm^2)	11.204 ± 2.985	11.137 ± 2.970	0.619
RV strain (%)	-17.57 ± 4.002	-18.71 ± 5.114	0.648
TAPSE (mm)	22.481 ± 3.167	23.481 ± 2.208	0.177
LAVI (ml/m^2)	26.76 ± 10.321	23.53 ± 7.617	0.158
LVEF (%)	61.11 ± 5.026	60.00 ± 6.397	0.389

RV, right ventricle; RA, right atrium; TAPSE, tricuspid annular plane systolic excursion; LAVI, left atrial volume index; LVEF, left ventricle ejection fraction

form sent by oncologists (medical record problem), and the flow of patients to the echocardiography unit was earlier than decision making for chemotherapy agents (patient's flow problem). The other condition was the dynamic response of chemotherapy, more over cancer progression, resulting in adjusted dose of chemotherapy agents and addition number of chemotherapy agents. On the other hand, the period of cardiac monitoring in the ESC ACC guideline was limited to only some chemotherapy agents. Furthermore complete digital system and well-organized patients' flow will support the better implementation of the ESC ACC guideline of cardio-oncology that rooted in cardiologist-oncologist collaboration.

Study Limitations

The patients' flow in several departments made the data was not well documented and became a limitation for the complete analysis. A structured collaborative working group in cancer treatment would minimize the data loss. This study also needs more samples to accurately analyze the incidence and factors contributing to cardiotoxicity in the South Sumatra population. A prospective long-period study will give useful data to reduce the incidence and progression of cardiac toxicity in a high-survival era of cancer treatment.

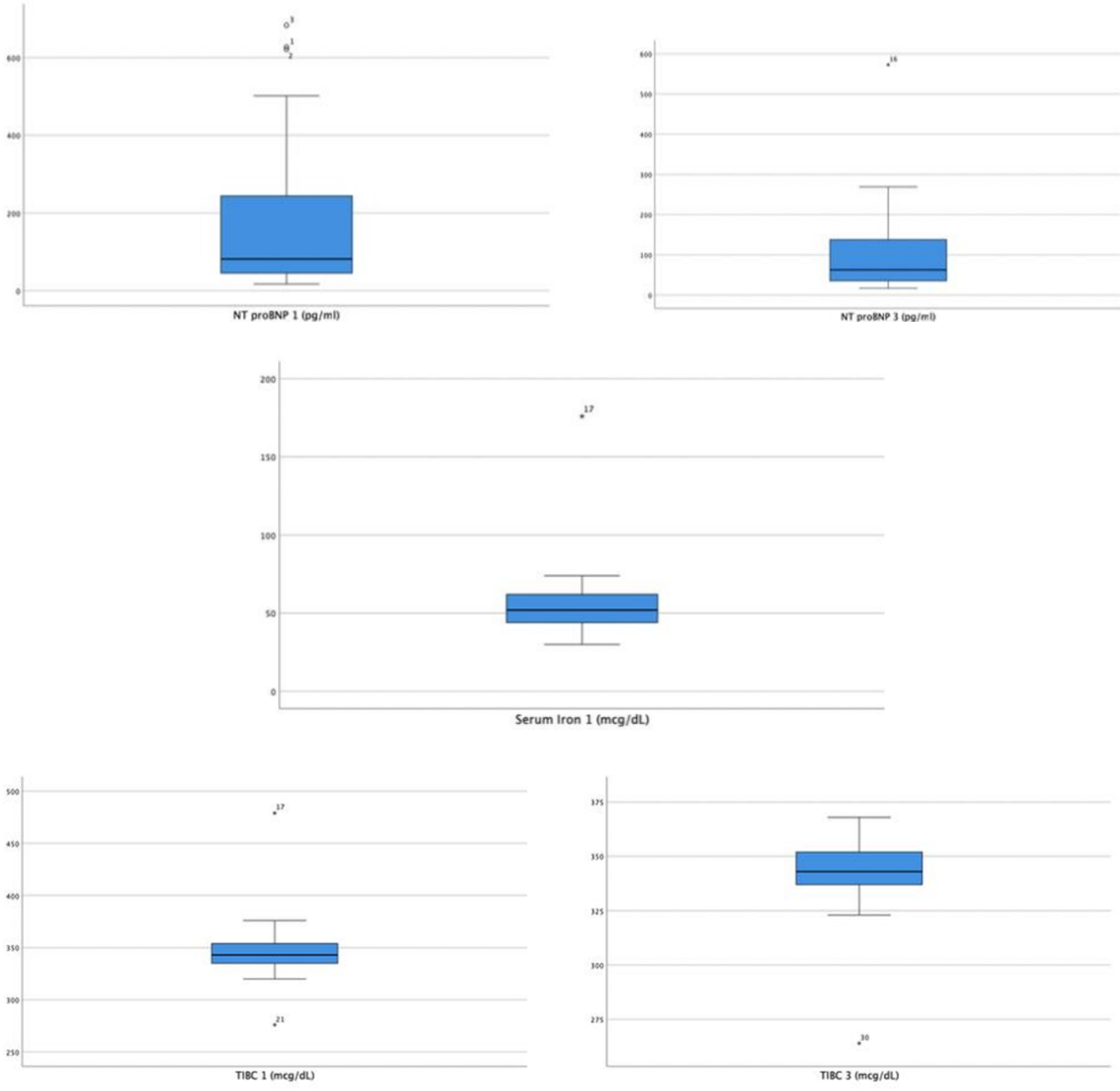

Figure 3. Outliers in laboratory data.

Conclusion

Speckle tracking echocardiography with left ventricular GLS score remains the main measurement to identify early cardiac dysfunction in patients with breast cancer who have undergone anthracycline chemotherapy, include in the South Sumatra population. A high incidence of cardiac toxicity was found, with a documented low incidence of cardiovascular risk factors. Laboratory parameters also play an important role in guiding stages and strategies in the treatment of cancer, together with optimal utilities of imaging modalities, including echocardiography. A future study was needed to identify specific potential factors that contribute to the incidence and progressivity of cardiotoxicity.

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List of Abbreviations

CRTCD	Cancer-therapy related cardiac dysfunction
HFA	Heart failure association
GLS	Global longitudinal strain
ICOS	International cardio-oncology society
LAVI	Left atrial volume index
LVEF	Left ventricular ejection fraction
NT pro-BNP	N-terminal pro B-type natriuretic peptide
RA	Right Atrial
RV	Right ventricle
TAPSE	Tricuspid annular pane systolic excursion
TIBC	Total iron-binding capacity
TSAT	Transferrin saturation

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Systematic Review

Predominant Pathogens in Sternal Wound Infections Following Cardiac Surgery

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Abstract

Sternal wound infection (SWI) is a surgical incision infection that typically occurs within a month after cardiac surgery, with various pathogens responsible for its development. Risk factors such as obesity, COPD, prolonged ventilation use, poor nutrition, diabetes, re-exploration for bleeding, age, surgery duration, hospital stay, surgical type, and postoperative blood transfusion contribute to the formation of SWI. The mortality rates for SWI following heart surgery can range from 10% to 47%, indicating the severity of this complication. This review aims to identify the microbes involved in SWI and assess their role in patient management to reduce post-surgical mortality and morbidity. A systematic review was performed following PRISMA guidelines, searching databases like PubMed, Science Direct, and Google Scholar until September 6th, 2024. The inclusion criteria focused on retrospective case-control studies or randomized controlled trials involving adults diagnosed with SWI post-open heart surgery. Eight relevant studies were selected from an initial 10,596 references. The most commonly identified microbes in SWI cases were coagulase-negative Staphylococcus (CoNS) and Staphylococcus epidermidis, which are part of normal human skin flora. Risk factors such as obesity, diabetes, and critical preoperative status were found to increase the likelihood of developing SWI, indicating a complex interaction between patient characteristics and microbial factors.

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Keywords: *sternal wound infection, cardiac surgery, microbe.*

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Introduction

There is a significant risk of infection from sternal wound for patients having sternotomy during cardiac surgery procedures. A surgical incision infection known as sternal wound infection (SWI) usually occurs within a month after cardiac surgery. The disease can be classified based on the depth of the infection. The incidence of superficial sternal wound infections involving the cutaneous tissue, subcutaneous tissue, and pectoralis fascia is 0.5% to 8% with morbidity rates ranging from 0.5% to 9%. Infections in superficial sternal wounds can usually be fully resolved with the use of intravenous antibiotics and local wound treatment. Deep SWIs, on the other hand, can involve muscle tissue, sternum, subchondral space and mediastinum. Although preventive efforts have advanced, the number of deep sternal wound infections is still high, ranging from 0.5% to 6.8%, with hospital mortality rates ranging from 7% to 47%. Fever, leukocytosis, and levels of C-reactive protein (CRP) are frequently unreliable indicators of infection. Major surgical reconstruction and repeated debridement may be necessary for certain patients.[1,2]

Additional risk factors that contribute to the formation of these infections include obesity, chronic obstructive pulmonary disease (COPD), and the long-term use of ventilation devices, poor nutrition, diabetes mellitus, re-exploration of bleeding event, age, duration of the surgery, duration of hospital stay, type of surgery, and postoperative blood transfusion. Risk factors include inadequate pre-operative procedures, blood transfusion, extended duration of surgery and perfusion time, sternal reattachment, postoperative hemorrhage, frequent electrocautery use, antimicrobial therapy, and intra-aortic balloon pump use. The elderly are the main population undergoing sternotomy, and age has a strong association with the likelihood of wound infection. This happens due to the elderly's limited tissue regeneration ability and systemic illnesses, which result in inadequate wound healing and increased susceptibility to infection. Obese patients have also been reported to develop SWI more frequently due to increased tension in the skin, greater body surface area, and thicker subcutaneous fat, insufficient blood supply of the subcutaneous tissue, and poor lymphatic function, which all have a negative impact on surgical wound healing. In addition, the absolute and relative insulin deficiency in diabetic patients will result in long-term hyperglycemia, which then forms a high-glucose local environment that will eventually lead to defense dysfunction, increasing the likelihood of infection and delaying wound healing.[1,2]

Coagulase-negative staphylococcus (CoNS) and Staphylococcus aureus are the most frequent organisms that cause SWI, followed by other gram positive bacteria and gram negative rod bacteria. The most prevalent microbe in SWI is Staphylococcus aureus, and increasingly linked to nasal colonization in patients.[3] Staphylococcus epidermidis is another significant pathogen in SWI, since approximately 75% of it strains are resistant to methicillin. The gram-positive, anaerobic bacteria Cutibacterium acnes, formerly known as Propionibacterium acnes, has low pathogenicity and slow growth. It is frequently observed on surgical wounds and in chest's sebaceous glands. Despite being regarded as a non-pathogenic component of the normal skin flora, C. acnes is currently known to be a significant pathogen in several kinds of surgical events. C. acnes has the ability to build biofilms, which improve its pathogenicity and could provide conditions conducive to other species. It also seems to be resistant to pre-operative skin disinfection using chlorhexidine in ethanol. Although these bacteria are often found in SWI cases, they can be missed as they require special culture conditions. During cardiac surgery, intravenous antibiotic prophylaxis is frequently administered to reduce the incidence of SWI.[4,5]

The mortality rates of sternal wound infections following heart surgery can vary from 10% to 47%, which presents a serious and potentially fatal consequence. Patients with SWI face disadvantages in both the short and long term, including higher re-hospitalization rates and longer hospital stays. Management of SWI involves a multidisciplinary approach including flap closure, vacuum-assisted closure therapy, surgical debridement, and sternal plate implantation. However, despite these interventions, the mortality rate remains high. Therefore, in order to effectively manage SWI patients and decrease the morbidity and mortality related to SWI following cardiac surgery, it is critical to recognize and address the risk factors as well as the microbes that cause infection. [6,7]

Table 1. Included Study Designs, Surgical Procedures, Risk Factors, and Microbes Involved.

No	Author	Title	Type of Research	Procedure	Risk factors	Microbes Involved
1	Khalid E et al, 2023	Sternal wound infection post open heart surgery: incidence, risk factors, pathogen and mortality	Retrospective study	Cardiac surgery	- Diabetes mellitus - Need for blood transfusion - Female gender - Length of stay in hospital	SSWI: - Coagulase-negative Staphylococcus (29.6%) - Klebsiella pneumoniae (20.4%) DSWI: - Coagulase-negative Staphylococcus (26.9%) - Staphylococcus aureus (19.2%) - Pseudomonas aeruginosa (19.2%)
2	Pan L et al, 2017	Deep sternal wound infection after cardiac surgery in the Chinese population: a single-centre 15-year retrospective study	Retrospective study	Cardiac surgery	- Body mass index - Reoperation	Gram-negative bacteria (34%) - Pseudomonas aeruginosa (8%) - Acinetobacter baumannii (21%) - Enterobacter cloacae (5%) Gram-positive bacteria (37%) - Staphylococcus aureus (24%) - Methicillin resistant staphylococcus aureus (MRSA) (5%) - Enterococcus faecalis (8%) - Mixed Infection (29%)
3	Lemaignen et al, 2015	Sternal wound infection post open heart surgery: incidence, risk factors, pathogen and mortality	Retrospective study	Cardiac surgery	- Obesity - Diabetes mellitus - Preoperative status - Old age (>70 years old), - Use of coronary artery graft (CABG), - Serum creatinine	- Staphylococcus aureus (19.9%) - Coagulase-Negative Staphylococci (CoNS) (7.9%) - Pseudomonas aeruginosa (4.5%) - Enterobacteriaceae (5.1%) - Enterococcus spp. (1.7%) - Polymicrobial Infections (9.6%).
4	Locke T et al, 2022	A bundle of infection control measures reduces postoperative sternal wound infection due to Staphylococcus aureus but not Gram-negative bacteria: a retrospective analysis of 6903 patient episodes	Retrospective cohort study	Cardiac surgery	- CABG (Coronary Artery Bypass Grafting) - Urgency of Operation - Season. - Gender Male - Duration of Hospitalization Before Surgery	Gram-positive bacteria - Staphylococcus aureus: 25.8% Gram-negative bacteria : 34.3% - Klebsiella spp. (28 kasus) - Escherichia coli (19 kasus) - Enterobacter spp. (18 kasus) - Pseudomonas spp. (18 kasus) - Proteus spp. (14 kasus)

5	Kotnis Gaska et al, 2018	Sternal wound infections following cardiac surgery and their management: a single-centre study from the years 2016–2017	Retrospective study	Cardiac surgery	- Obesity - Length of hospital stay - Diabetes Mellitus (DM) - Smoking, Alcoholism, and Age	- Staphylococcus epidermidis (26.6%) - Enterococcus faecium (12.2%) - Staphylococcus aureus (11.4%). - Klebsiella pneumoniae (8.4%) - Pseudomonas aeruginosa (6.8%)
6	Lea A et al, 2023	Incidence and predictors of sternal surgical wound infection in cardiac surgery: A prospective study	Prospective study	Cardiac surgery	- Diabetes Mellitus. - Infection causes before surgery - Length of stay in ICU	- Staphylococcus epidermidis (23%) - Pseudomonas aeruginosa (14%) - Staphylococcus aureus (13%) - Enterococcus fecalis (10%) - Escherichia coli (6.5%)
7	Fahad M et al, 2020	Incidence, types and outcomes of sternal wound infections after cardiac surgery in Saudi Arabia	Retrospective study	Cardiac surgery	- Diabetes Mellitus - Obesity - Smoking - Duration of Operation - Gender - Drug Usage - Lipid Lowering	- Staphylococcus aureus (45%) - Klebsiella spp. (12,5%) - Pseudomonas aeruginosa (12,5%) - Enterobacter spp. (10%). - Escherichia coli (2,5%) - Enterococcus spp. (2,5%) - Serratia spp. (2,5%)
8	Marie Dubert et al, 2015	Sternal Wound Infection after Cardiac Surgery: Management and Outcome	Retrospective study	Cardiac surgery	- EuroScore - Gender - Body mass index (BMI) - Length of stay in ICU - Clinical conditions such as severe sepsis or shock	- Coagulase-negative staphylococci (48%) - Enterobacteriaceae (43%) - Staphylococcus aureus (MRSA) (23%)

Methods

Here is the PRISMA flowchart. We conducted searches using predefined keywords in several search engines. In the initial search phase, we found 210 articles in PubMed, 4,594 in Science Direct, and 19,300 in Google Scholar. In the next phase, we applied criteria to the identified articles. This process resulted in a total of 10,596 articles. After removing non-PICO-compliant files and duplicates, we identified 12 articles. After title and abstract screening focusing on the research objectives, methods, and results relevant to our secondary research questions, 8 articles remained.

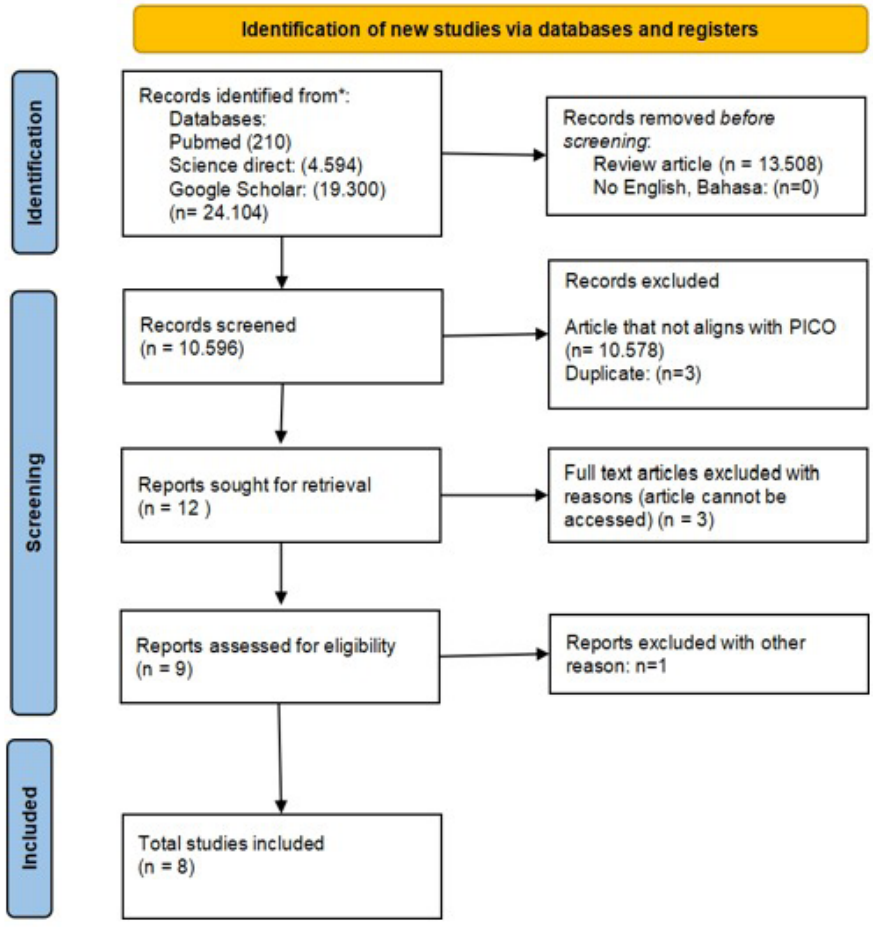

Figure 1. Flow chart showing the follow-up and inclusion process of the articles in the review.

Types of Microbes

Microbes are a collection of microorganisms that thrive in an ecosystem. Numerous types of microorganisms have the ability to contaminate and colonize exposed subcutaneous tissue. If the tissue has lost its vitality (hypoxic, ischemic, or necrotic), and the body's immune system is weakened, the environment is ideal for microorganism growth.[8] The microbial composition of post-heart surgery SWI has been widely studied with various methods and provides varied results. Knowledge of microbes in post-cardiac surgery SWIs has mostly been investigated by microbial culture methods. Samples for culture are taken through several methods, including deep swabbing, tissue harvesting, and pus aspiration. This is done to ensure that the microorganisms present can be detected accurately.[9,10]

Postoperative SWI was dominated by coagulase-negative Staphylococcus (CoNS) bacteria, accounting for 28% of cases. The next most common bacteria was *Staphylococcus epidermidis*, found in 24.8% of cases, followed by Enterobacteriaceae spp in 24% of cases. In addition, *Staphylococcus aureus* was also reported in seven of the eight journals reviewed, with 22.6% of SWI cases due to this bacteria. In addition, there was also involvement of other bacterial strains in SWI such as *Acinetobacter baumanni* (21%), *Klebsiella pneumoniae* (14.4%), *Enterococcus faecium* (12.2%), *MRSA* (11%), *Enterococcus faecalis* (9%), *Escherichia coli* (6.5%), *Enterobacter cloacae* (5%), and Mixed Infection of 19.25%.[1,9-15]

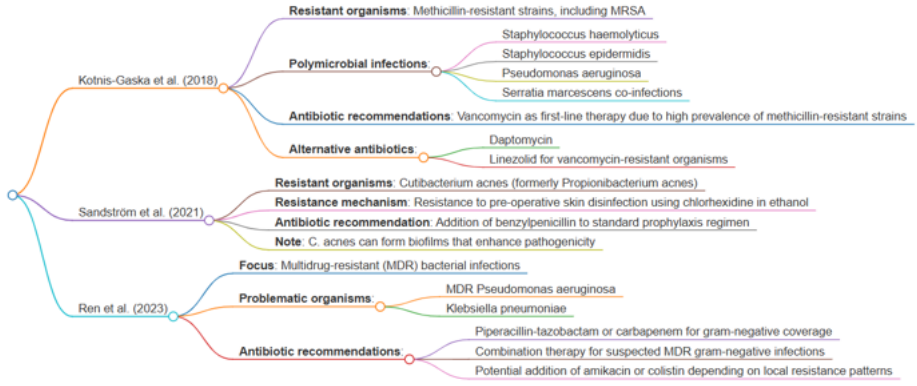

Figure 2. Microbial resistance mind map and list of antibiotics.

The landscape of microbial resistance in SWIs varies significantly across studies, highlighting the need for tailored antibiotic strategies. Kotnis-Gaska et al. reported a high prevalence of methicillin-resistant strains, including MRSA, in their cohort, leading to a recommendation of vancomycin as the first-line therapy, with daptomycin or linezolid reserved for vancomycin-resistant organisms.[1] In contrast, Sandström et al. (2021) focused on *Cutibacterium acnes* and its resistance to chlorhexidine-ethanol skin disinfection, advocating for the addition of benzylpenicillin to standard prophylaxis due to this organism's biofilm-forming capabilities.5 Locke et al. demonstrated the effectiveness of infection control bundles against *Staphylococcus aureus* but observed their limitations against Gram-negative bacteria, though specific antibiotic resistance patterns were not detailed. Ren et al. addressed the challenge of multidrug-resistant (MDR) bacterial infections, specifically highlighting MDR *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, and suggested the use of piperacillin-tazobactam or carbapenems for Gram-negative coverage, potentially combined with amikacin or colistin based on local resistance patterns.[13,17] While Lemaignen et al. (2015), Pan et al. (2017), Al-Ebrahim et al. (2023), and Dubert et al. (2015) provided valuable insights into risk factors and patient demographics associated with SWIs, they did not explicitly detail specific microbial resistance patterns in their excerpts. These varying findings underscore the importance of local surveillance data and consideration of prevalent resistant organisms when formulating antibiotic regimens and prophylactic strategies. The mind map of microbial resistance and the list of antibiotics that have just been visualized in Figure 2.

Risk Factors

The results of data extraction from eight articles that met the inclusion criteria showed that various factors can affect the growth of microorganisms that cause sternal wound infection post-cardiac surgery. Both procedure-related and patient-related risk factors are included. Certain risk factors not only increase the probability of SWI but also cause wounds that are difficult to heal.[2,10] Of all the articles found, not all of them described the risk factors and exhibited the same results.

Risk factors for SWI have been studied extensively, but no consensus has been found. Frequently recognized risk factors include diabetes mellitus, obesity, reoperation, prolonged operation time and blood transfusion.[10,11] Specific studies highlight that diabetes significantly increases the risk of SWI, with odds ratios showing a strong association.[9,10] High blood sugar levels in DM can inhibit leukocytes from phagocytosis, thus making the wound susceptible to microbial infection, in addition to prolonging the process of wound healing. Supporting this finding further, the condition of DM followed by extended hospitalization days increases the likelihood of polymicrobial wound infection. Polymicrobial infections identified included *Staphylococcus haemolyticus*, *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, and *Serratia marcescens*.[1]

Obesity is also a significant patient-related risk factor for microbial infection of the sternal wound. Obese patients are at risk of experiencing sternal instability. Therefore, in older patients undergoing median sternotomy for cardiac surgery, sternal instability could lead to the development of DSWI.[1,11,12,15] However, in contrast to the study conducted by jahad et al obesity was found to have an insignificant contribution to the development of SWI.[9]

In addition, urgent surgical procedures and the need for reoperation have been associated with higher infection rates.[13,14] Other factors such as gender, and age are also described in some articles.[9,10] Based on gender, women may have a higher risk for infections caused by gram negative bacteria. This is attributed to anatomical factors such as breast tension on skin wounds.[13,15] Age may not be a reliable indicator of SWI risk, since Locke et al. study found no noticeable age difference between patients who had SWI and those who did not. Conversely, the Lemaignen et al. study revealed that patients older than 70 were linked to a higher risk of SWI.[12,13]

Risk factors associated with certain procedures such as coronary artery bypass grafting (CABG) procedures, especially those classified as urgent, have a higher chance of developing SWI. The prevalence of SWI after CABG was reported at 5.0%, compared to 2.0% for non-CABG cardiac surgery. In addition, this study highlights that urgent cases often require prolonged hospitalization before surgery, potentially increasing exposure to nosocomial infections.[9,13] The need for reoperation and complications such as prolonged ICU stay are also associated with increased length of stay, which affects the patient's recovery process.[14]

Other risk factor for SWI is the dressing technique used in closing the wounds. However, among the eight articles we reviewed, none provided specific information about the wound dressing types used for closing sternal wounds after cardiac surgery. The articles primarily focused on the microbiological aspects of sternal wound infections, risk factors, and general management approaches, rather than detailing specific dressing techniques. Management of SWI involves a multidisciplinary approach, including flap closure, vacuum-assisted closure therapy, surgical debridement, and sternal plate implantation.[6,7.]

Discussions

After cardiac surgery, especially a median sternotomy, sternal wound infection (SWI) can be a dangerous and potentially fatal complication. This condition can substantially impact patient morbidity and mortality. SWI can be classified into two different groups according to the depth of infection: deep sternal wound infection (DSWI) can impact muscular tissue, sternum, substernum, and mediastinum, whereas superficial sternal wound infection (SSWI) only colonizes the cutaneous tissue, subcutaneous tissue, and profunda fascia. Once colonization occurs, pathogens can invade deeper tissues, including the sternum and mediastinum. DSWI develops as a result of this invasion, which prevents wound healing.[7,14]

Several risk factors can predict the occurrence of SWI. Obesity with body mass index (BMI) ≥30 kg/m², diabetes, age, history of undergoing a coronary artery bypass grafting procedure, are the most common risk factors for SWI.[7,14,16] Patients with DM followed by extended hospital days, increase the possibility of polymicrobial wound infections. Identified polymicrobial infections include *Staphylococcus haemolyticus, Staphylococcus epidermidis, Pseudomonas aeruginosa*, and *Serratia marcescens*.[1] In addition, surgical and perioperative factors also contribute to the development of SWI. Factors such as prolonged operating time, postoperative bleeding and reoperation are additional risk factors for SWI that can lead to increased morbidity and mortality in patients. In addition, preoperative skin preparation and postoperative wound care are also very important in preventing SWI.[3]

The presence of bacteria in sternal wounds is often exacerbated by patient comorbidities such as obesity, diabetes and COPD. These conditions weaken the immune system, allowing infection to develop more easily. The skin acts as the primary barrier against bacterial colonization. However, in conditions that weaken the immune system and damage the skin barrier, the skin barrier is disrupted, allowing bacteria to penetrate and colonize the skin. The breakdown of the skin barrier leads to changes in filaggrin and invlucrin regulation, lipid deficiency (cholesterol, free fatty acids, ceramide), increased water loss through the skin, and increased colonization activity. *Staphylococcus aureus* and *Streptococcus epidermidis* are normal flora on human skin, if there are comorbidity that impair the immune system and compromise skin barrier function, the risk of infection will increase significantly. Therefore,

understanding these dynamics is critical to developing effective strategies to prevent and treat SWI.[5,14]

The knowledge of microbes in post-cardiac surgery SWI has been mostly studied by microbial culture methods. Samples for culture are taken through several methods, including deep swabbing, tissue harvesting and pus aspiration. This is done to ensure that the microorganisms present can be detected accurately.[9,10] There are various microbiological profiles obtained from various studies related to SWI after cardiac surgery. The predominant bacteria in these SWI events are CoNS, followed by *Staphylococcus epidermidis* and Enterobacteriaceae spp. However, most studies report finding *Staphylococcus aureus* in their studies with significant frequency. There were also other bacterial strains found in smaller numbers such as *Acinetobacter baumanni, Klebsiella pneumoniae, MRS, Enterococcus faecium, Enterococcus faecalis, Enterobacter cloacae*, and *Escherichia coli*, as well as polymicrobial infections.[1,9-15]

The management of these infections is significantly influenced by the type of pathogen involved in SWI following cardiac surgery. *Staphylococcus aureus* and *Staphylococcus epidermidis*, which are commonly identified pathogens in SWI, often exhibit antibiotic resistance, particularly to methicillin and vancomycin. This resistance results in the need to use broader-spectrum antibiotics, which may increase the risk of other complications such as Clostridium difficile colitis, where long-term antibiotic use leads to an increased incidence of this condition. Vancomycin would be appropriate first-line therapy due to the high prevalence of methicillin-resistant strains. Alternatives could include daptomycin or linezolid, particularly in cases of vancomycin-resistant organisms.[1] Gram-negative bacteria, such as *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, also pose a challenge due to their multidrug-resistant (MDR) nature, which complicates treatment and increases the risk of multiple bacterial co-infections. Piperacillin-tazobactam or a carbapenem would provide appropriate coverage against most gram-negative pathogens. For suspected MDR gram-negative infections, combination therapy might be necessary, potentially adding amikacin or colistin depending on local resistance patterns. The presence of these MDR bacteria further calls attention to the need for early diagnosis and targeted antibiotic therapy, as well as strict adherence to aseptic technique during surgery to reduce the probability of infection. In addition, understanding patient-related risk factors, such as obesity and diabetes, is essential to select appropriate empirical antibiotic therapy and prevent polymicrobial wound infections.[1,17]

The role of prophylactic antibiotics in preventing SWI following cardiac surgery is multifaceted. Standard intravenous antibiotic prophylaxis is a cornerstone of care, with findings suggesting that augmenting this with agents like benzylpenicillin can further reduce deep SWI.[4,5] For high-risk patients, such as those with diabetes or obesity, a more targeted approach is essential, potentially involving broader coverage to address the increased likelihood of polymicrobial infections.[1,10,11] Furthermore, pre-operative strategies, including screening and decolonization of S. aureus nasal colonization, are valuable, though the resistance of C. acnes to standard skin disinfection necessitates reevaluation of current protocols. A critical consideration is the duration of prophylaxis; while extended coverage may benefit high-risk individuals, the rise of resistant organisms underscores the need for careful antibiotic stewardship to mitigate the selective pressure that prolonged use can exert. This creates a challenging clinical balance, requiring tailored approaches that optimize patient outcomes while minimizing the development of antibiotic resistance.[1,17] Therefore, by knowing the microbiological profile of SWI, clinicians can take a comprehensive therapeutic approach, including prophylactic antibiotic use, early diagnosis, and customized treatment strategies to effectively overcome antibiotic-resistant pathogens.

Based on the 8 articles we identified, we'll develop an empirical antibiotic regimen for SWI following cardiac surgery, along with periprocedural antibiotic prophylaxis recommendations.

First-line therapy:

- Vancomycin (15-20 mg/kg IV q12h, adjusted based on renal function and trough levels)
  - o Target trough levels: 15-20 µg/mL for serious infections
  - o Duration: Until culture results are available, then de-escalate as appropriate

PLUS

- Piperacillin-tazobactam (4.5g IV q6h, adjusted for renal function) OR
- Meropenem (1g IV q8 h) if high local prevalence of ESBL-producing organisms

Targeted Therapy Based on Culture Results :

Gram-positive organisms:

1. Methicillin-resistant Staphylococcus (MRSA, MR-

CoNS):
   - Continue vancomycin OR
   - Switch to daptomycin (6-8 mg/kg IV q24h) OR
   - Linezolid (600mg IV/PO q12h) if vancomycin MIC >1.5 µg/mL
2. Methicillin-sensitive Staphylococcus (MSSA, MS-CoNS):
   - De-escalate to cefazolin (2g IV q8h) OR
   - Nafcillin/oxacillin (2g IV q4h)
3. *Enterococcus faecalis*:
   - Ampicillin (2g IV q4-6h) if susceptible
   - Vancomycin if ampicillin-resistant
4. *Enterococcus faecium*:
   - Continue vancomycin if susceptible
   - Linezolid or daptomycin if vancomycin-resistant

Gram-negative organisms:
1. Enterobacteriaceae (E. coli, Klebsiella, Enterobacter):
   - De-escalate based on susceptibilities to the narrowest effective agent
2. *Pseudomonas aeruginosa*:
   - Cefepime (2g IV q8h) OR
   - Ceftazidime (2g IV q8h) +/- aminoglycoside
3. *Acinetobacter baumannii*:
   - Carbapenem if susceptible
   - For MDR strains: combination therapy with colistin (loading dose 5mg/kg, then 2.5mg/kg q12h) plus another agent based on susceptibilities

Polymicrobial infections:
- Continue broad-spectrum coverage tailored to susceptibilities
- Consider surgical consultation for debridement if not improving

Duration of Therapy:
- Superficial SWI: 7-10 days
- Deep SWI without osteomyelitis: 2-4 weeks
- Deep SWI with osteomyelitis: 6 weeks minimum
- Mediastinitis: 6-8 weeks

Standard Periprocedural Antibiotic Prophylaxis:
- First-line: Cefazolin 2g IV within 60 minutes before incision (3g if patient >120kg)
   - Additional dose if procedure >4 hours
   - Post-procedure doses for 24-48 hours

For β-lactam allergic patients:
- Vancomycin 15 mg/kg IV (start infusion 60-120 minutes before incision) PLUS
- Gentamicin 5 mg/kg IV (single dose)

For high-risk patients (obesity, diabetes, prolonged preoperative stay):
- Consider adding benzylpenicillin to standard prophylaxis as per the Sandström et al. study
- Screen for and decolonize S. aureus nasal carriers (mupirocin nasal ointment + chlorhexidine body wash for 5 days preoperatively)

Considerations for specific patient populations:
- MRSA colonization: Add vancomycin to standard prophylaxis
- High BMI (≥30): Consider higher dosing and longer duration (48h)
- Diabetic patients: Strict glycemic control (target 140-180 mg/dL) plus standard prophylaxis.

Conclusions

The most common microbes found in cases of sternal wound infection after cardiac surgery were coagulase-negative Staphylococcus (CoNS) followed by *Staphylococcus epidermidis*, which is the normal flora of human skin. In addition, the presence of obesity, diabetes, and critical preoperative status was related to a higher risk of SWI, explaining that there is a complex interaction between patient factors and microbial involvement.

Study Limitations

One limitation of this study is the small sample size. This study only looked at 8 studies, it possibly missing other relevant research. The lack of standardized microbiological techniques across studies could also affect the consistency of microbial identification. While some information on antibiotic resistance was presented, comprehensive data across all identified pathogens was lacking.

List of Abbreviations

BMI	Body mass index
CABG	Coronary artery bypass grafting
CoNS	Coagulase-negative staphylococcus
COPD	Chronic obstructive pulmonary disease

CRP	C-reactive protein
DM	Diabetes mellitus
DSWI	Deep sternal wound infection
MDR	Multidrug resistant
SWI	Sternal wound infection

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Case Series

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Pharmacological Management of Supraventricular Tachyarrhythmia in Right Atrial Enlargement Due to Pulmonary Hypertension

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Abstract

Background: Right atrial (RA) enlargement is a common finding in patients with pulmonary hypertension (PH). Supraventricular arrhythmia (SVA) is common in PH patients with RA enlargement. Treatment of SVA should be aggressive since it can cause hemodynamic worsening consequences, because RA function plays an important role in right heart function.

Case Illustration: Three cases of SVA in underlying right atrial enlargement with preserved ventricular function that successfully managed by pharmacological cardioversion according to the guidelines. The first case describes atrial flutter with right bundle branch block (RBBB) morphology with vital sign: heart rate (HR) 170 beats per minute with regular pulse, blood pressure (BP) 110/70 mmHg, respiratory rate (RR) 28 per minute, and peripheral oxygen saturation was 89 % which successfully converted to sinus rhythm by amiodarone (class III antiarrhythmic drug) administration, meanwhile the second and third cases demonstrate paroxysmal SVA with admission vital sign: HR 155 beats per minute, regular pulse, BP 152/115 mmHg, RR 27 per minute, peripheral oxygen saturation was 80 % in the second case and in the third case on admission vital sign: oxygen saturation was 70 %, BP 110/71 mmHg, RR 40 per minute, and the HR were 160 bpm, regular that converted to sinus rhythm by diltiazem (class IV antiarrhythmic drug) administration.

Conclusion: Supraventricular arrhythmia is a frequent arrhythmia that occurs in pulmonary hypertensive and right atrial dilation patients. The tachyarrhythmia in this patient population was tolerated poorly and led to hemodynamic perturbation. Pharmacological cardioversion is one of the effective approaches to alleviate patient symptoms with significant clinical improvement.

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Keywords: *supraventricular arrhythmia, pulmonary hypertension, right atrial enlargement, pharmacological cardioversion.*

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Introduction

Right atrial (RA) enlargement is a common finding in patients with pulmonary hypertension (PH). Long-standing atrial wall stretch is mediated by chamber dilation that will cause atrial electrical remodeling and arrhythmogenic substrate.[1,2] Supraventricular arrhythmia (SVA) is common in PH patients with RA enlargement. Treatment of SVA should be aggressive since it can cause hemodynamic worsening consequences, because RA function plays an important role in right heart function.[3] We reported a case series of three patients with SVA in pre-existed right atrial (RA) enlargement that resulted in hemodynamic insult leading to emergency ward visits. There was immediate clinical improvement after rhythm control by pharmacological cardioversion.

Case 1

A 57-year-old man presented to the emergency ward at our local community hospital with palpitations and shortness of breath for 3 hours. The patient also had abdominal pain for 4 days. Patient denied any prior chest pain, fever, cough, or other constitutional symptoms. Past medical history was unremarkable for significant prior illness. On admission, vital signs were: Patient was alert with heart rate 170 beats per minute, regular pulse, blood pressure (BP) 110/70 mmHg, respiratory rate 28 per minute, peripheral oxygen saturation was 89 %, and body surface area (BSA) of 1.41 m^2.

Electrocardiography showed wide-complex tachycardia with QRS rate 170x/minute with right bundle branch block morphology (RBBB) (Figure 1A). Chest x-ray revealed increased cardiothoracic ratio with upward apex and increased pulmonary vascular marking in the hilus area (Figure 2A). Initial laboratory examination results showed an increased D-dimer assay of 1330 ng/mL. The routine hematology, renal function, troponin I level, and serum electrolytes were normal.

The patient was diagnosed with unstable wide-complex tachycardia with differential diagnosis of monomorphic ventricular tachycardia, aberrant supraventricular tachycardia or supraventricular arrhythmia in underlying RBBB. Brugada algorithm analysis of patient ECG concluded that the rhythm was atrial flutter 2:1 conduction with RBBB. The absence of AV dissociation, fusion, and captured beat accompanied by the presence of RS complex in V3-V6 ECG leads to the conclusion to atrial flutter with RBBB.

The patient was planned for chemical cardioversion in the emergency ward with antiarrhythmic agent class III, amiodarone 150 mg intravenously administered. Immediately after i.v. amiodarone administration, the rhythm conversion to sinus takes place. Repeat 12-lead ECG showed sinus rhythm with QRS rate 75x per minute with complete RBBB morphology (Figure 1B). The patient's dyspnea and palpitation were instantaneously relieved after rhythm control management, then the patient was transferred to the intensive care unit (ICU) for further monitoring and management.

In the ICU ward, transthoracic echocardiography (TTE) was performed and revealed right atrial (RA) and right ventricular (RV) dilation (RV basal diameter 56 mm, RA area index 20.7 cm^2/m^2) (Figure 2C) with severe tricuspid regurgitation (TR), TR Vmax 3.79 m/s and high probability of PH with pulmonary artery systolic pressure (PASP) 70 mmHg (Figure 2D). Other valves were normal. Left ventricular (LV) appeared D-shaped at the systolic phase (Figure 2B). LV and RV systolic functions were preserved (EF 56 %, TAPSE 1.8 cm, RV S' 9 cm/s).

The patient was diagnosed with pulmonary hypertension (PH) with the suspicion of pulmonary vascular disease etiology (group 4) due to an increase in D-dimer value. The differential diagnosis is group 1 PH due to pulmonary arterial hypertension. The group 2 dan 3 PH were excluded from the differential diagnosis because of normal left heart function and relatively normal chest X-ray appearance. The lack of right heart catheterization (RHC) examination and contrast CT pulmonary angiography was the limitation of this case diagnostic work-up due to limited facilities at our local community hospital.

On admission, medical management was i.v furosemide 40 mg b.i.d, enoxaparin 0.6 cc subcutaneously twice daily for three days followed by warfarin 2 mg o.d, bisoprolol 2.5 mg o.d, and ramipril 5 mg o.d. There was no arrhythmia episode observed during 24-hour monitoring and the patient was discharged on third admission uneventfully with bisoprolol 2.5 mg o.d, ramipril 5 mg o.d, furosemide 40 mg o.d, and warfarin 2 mg o.d. The subsequent monthly outpatient visit was regularly attended by the patient. After 3 months

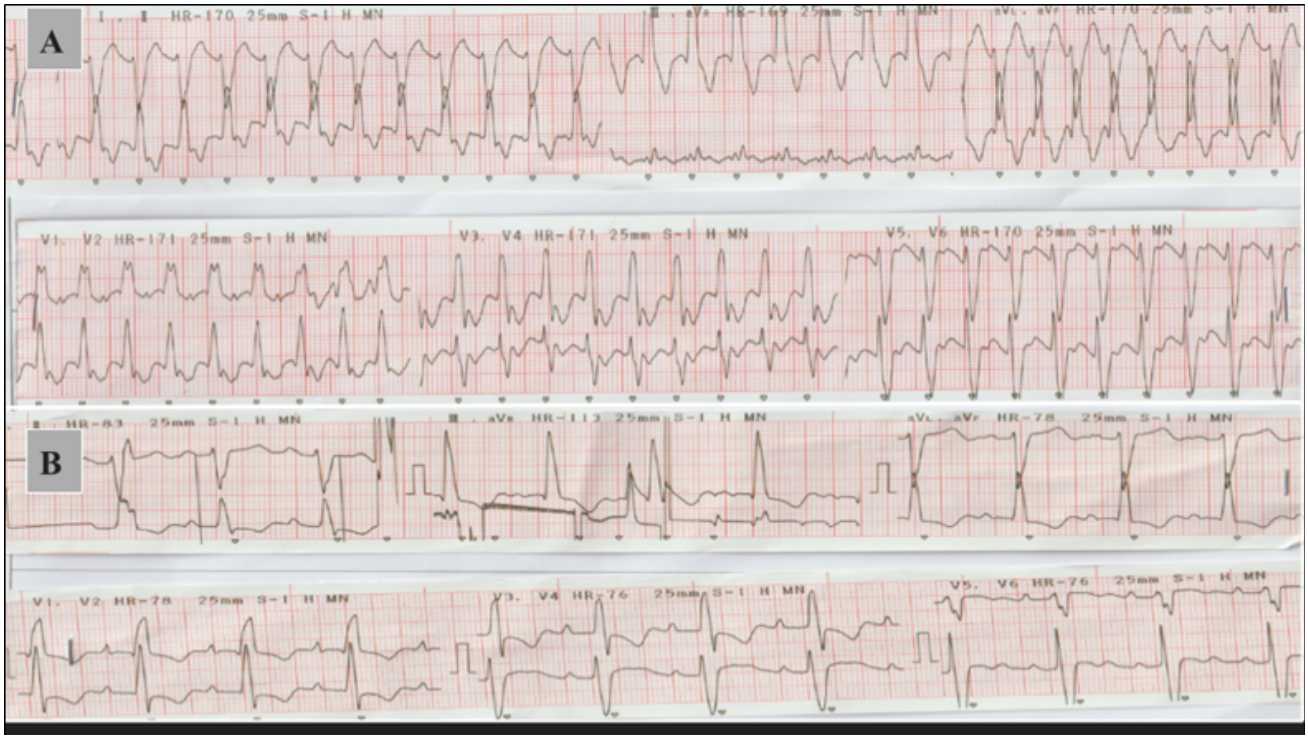

Figure 1. Electrocardiography in case 1. A: Initial ECG presentation at emergency ward showed wide-complex tachycardia with QRS rate 170x/minute with RBBB morphology; B: Post pharmacological cardioversion ECG showed sinus rhythm with QRS rate 75x per minute with complete RBBB morphology. ECG: electrocardiography; RBBB: right bundle branch block.

of follow-up, we added sildenafil up to a titrated dose of 50 mg t.i.d along with warfarin and bisoprolol. The patient was well without a hospitalization episode for the subsequent 8 months.

Case 2

A 44-year-old woman came to the emergency department at our local community hospital with restlessness and palpitation, chest discomfort, and shortness of breath for 1 hour prior to hospital admission. The symptom leads to difficulty of sleep that is caused by chest palpitations. There was no history of cough and fever, chest pain, and chest trauma prior to symptom development. Past medical history was history non-specific 'heart enlargement' without routine follow-up from other hospitals. The medical record files were unavailable. On admission, vital signs were: Patient was alert with heart rate 155 beats per minute, regular pulse, BP 152/115 mmHg, respiratory rate 27 per minute, peripheral oxygen saturation was 80 % and BSA of 1.74 m^2.

Electrocardiography showed narrow-complex tachycardia with QRS rate 155 x/minute with RBBB morphology with absence of P wave (Figure 3A). Thorax x-ray showed increased cardiothoracic ratio with upward apex, prominence of the pulmonary arteries segment and pruning pulmonary vascular marking in the hilus area (Figure 4A). Laboratory examination results were unremarkable. Bedside emergency transthoracic echocardiography showed preserved systolic function.

The patient was diagnosed as unstable narrow-complex tachycardia with the differential diagnosis of typical atrioventricular-node reentrant tachycardia (AVNRT) or atrioventricular reentrant tachycardia (AVRT) or atrial tachycardia (AT) in a pulmonary hypertension patient based on the patient's ECG and chest x-ray. The patient was planned for pharmacological cardioversion with antiarrhythmic agent class IV. Diltiazem 20 mg intravenously was administered. Rhythm conversion to sinus occurred immediately

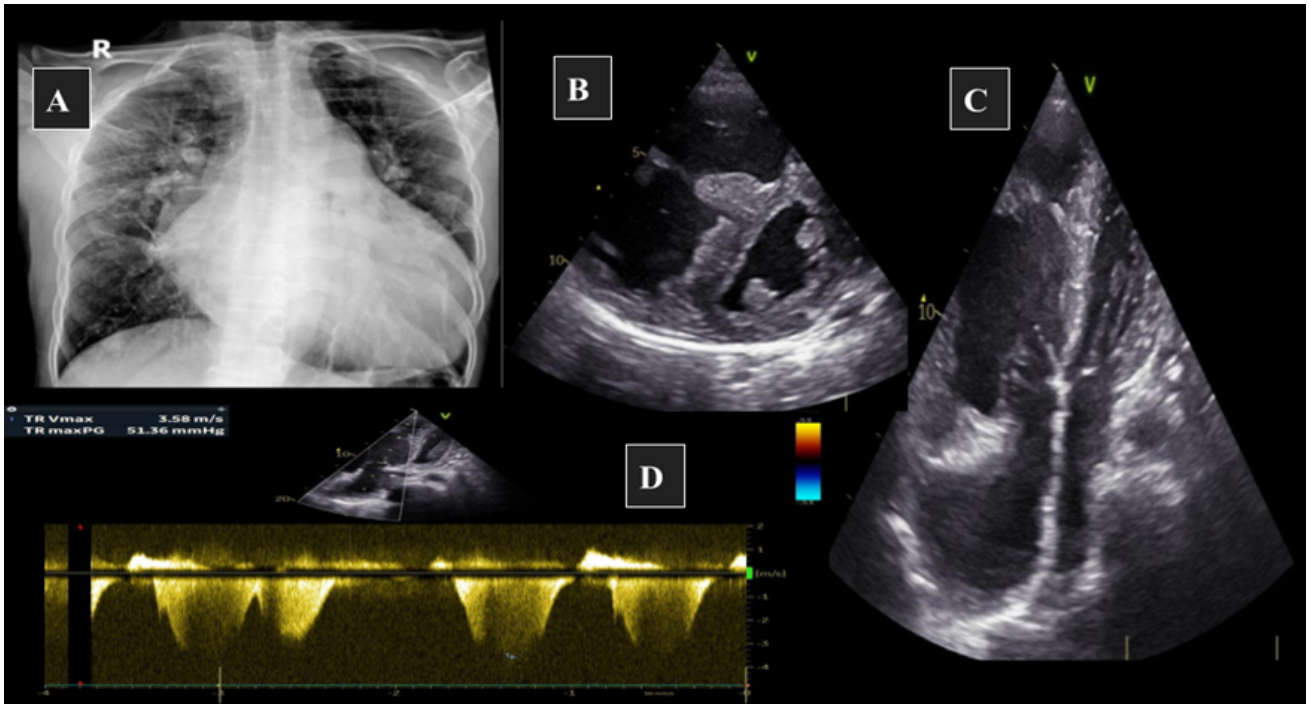

Figure 2. Case 1 X-ray and 2D echocardiography. A: Patient chest x-ray revealed increased cardiothoracic ratio with upward apex and increased pulmonary vascular marking in the hilus area; B: Parasternal short axis view 2D echocardiography showed D-shaped LV at systolic phase; C: apical 4-chamber view 2D echocardiography showed RA) and RV dilation (RV basal diameter 56 mm, RA area index 20.7 cm2/m2); D: severe TR with TR Vmax 3.79 m/s and high probability of PH with PASP 70 mmHg. LV: left ventricular; RA: right atrial; RV: right ventricular; TR: tricuspid regurgitation; PH: pulmonary hypertension; PASP: pulmonary artery systolic pressure.

after i.v diltiazem administration, which was followed by instantaneous symptom improvement. Repeat 12-lead ECG showed sinus rhythm with QRS rate 68x per minute with right axis deviation, right ventricular (RV) hypertrophy and strain and diffuse T wave inversion in precordial leads (Figure 3B). The patient was then transferred to the medical ward for further monitoring and management.

The TTE showed dilation of RA (RA area index 12.8 cm^2/m^2) and RV (Figure 4C) with severe TR, TR Vmax 4.5 m/s with high probability of PH with PASP of 93 mmHg (Figure 4D) and presence of PV notch of pulsed wave doppler (Figure 4B). Other valves were normal. Left ventricular (LV) appeared D-shaped at the systolic phase with normal LV and RV systolic functions (EF 60 %, TAPSE 2.3 cm, RV S' 14 cm/s). The interatrial septum is intact.

The patient was diagnosed with a high likelihood of pulmonary arterial hypertension (PAH). The group 2 and 3 PH were excluded for the same reason as case 1. The absence of RHC assessment and contrast CT pulmonary angiography for diagnostic workup also becomes a limitation of this case.

On admission, medical management was i.v furosemide 40 mg b.i.d, digoxin 0.25 mg o.d, bisoprolol 2.5 mg o.d, and sildenafil 20 mg t.i.d for pulmonary artery dilator purposes. On the second admission day, patient symptom improvement was observed with stable hemodynamics without other antiarrhythmic episodes during 24-hour monitoring. Patient was discharged on third admission uneventfully with bisoprolol 2.5 mg o.d and sildenafil 20 mg t.i.d. After 1 week post-discharge, the patient was followed up in an outpatient clinic without a tachyarrhythmia episode.

Case 3

A 36-year-old woman came to the emergency ward for respiratory distress. On admission: oxygen

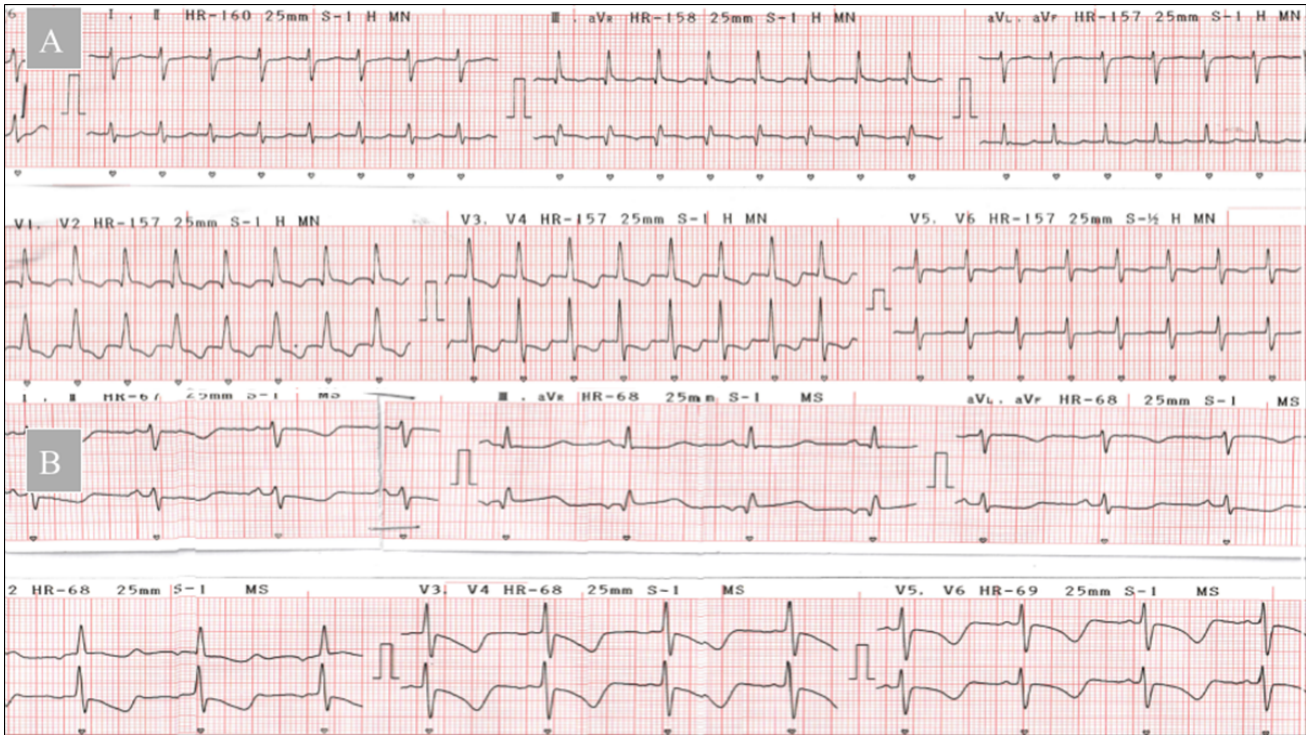

Figure 3. Electrocardiography in case 2. A: Initial ECG presentation at emergency ward showed narrow-complex tachycardia with QRS rate 155 x/minute with RBBB morphology with absence of P wave; B: Post pharmacological cardioversion ECG showed sinus rhythm with QRS rate 68x per minute with right axis deviation, RV hypertrophy and strain and diffuse T wave inversion in precordial leads. ECG: electrocardiography; RBBB: right bundle branch block; RV: right ventricular.

saturation was 70 %, blood pressure 110/71 mmHg, respiratory rate 40 per minute, and the heart rate was 160 bpm, regular. The electrocardiography (ECG) finding was wide complex tachycardia and right bundle branch block (RBBB) morphology. (Figure 5A) Serum lactate level was 2.40 mmol/l and PaO2 41 mmHg, TSH and FT4 were normal. Bedside echocardiography examination showed preserved ejection fraction (EF) with RA-RV dilation (Figure 6A and 6C). Pulmonary stenosis valvar type with peak pulmonary valve gradient 52 mmHg was also noted (Figure 6B and 6D). The patient was diagnosed with SVT with RBBB, type I acute respiratory failure with severe pulmonary stenosis.

The patient was administered intravenous diltiazem 20 mg and oxygen supplementation. ECG evaluation showed conversion to sinus rhythm with RBBB. (Figure 5B) The patient's symptom was relieved immediately after rhythm conversion and rate control with 98% oxygen saturation. Patient discharged on the 3rd day of admission.

Discussion

These case series highlight the importance of SVA as a precipitating factor for pulmonary hypertension exacerbation in RA enlargement.[3] Atrial tachyarrhythmia could precipitate RV failure in the setting of preexisting pulmonary hypertension, and the prevalence of SVA in PAH varied among studies from 9.9 % to 46.4 %. The most common SVA type in PAH is atrial fibrillation, followed by atrial flutter and AVNRT.[1] In paroxysmal SVA, female sex is predominant with 67.5% patients.[4] SVA causes profound hemodynamic insult in pre-existing RA dilation and pulmonary hypertension patients. Olsson et al reported that worsened right heart failure manifested in 30 % at the time of SVA detection in PH patients.[5]

These case series describe three cases with acute hemodynamic perturbation in pre-existing RA enlargement and PH, which were precipitated by supraventricular tachyarrhythmia. All cases were successfully managed with pharmacological management

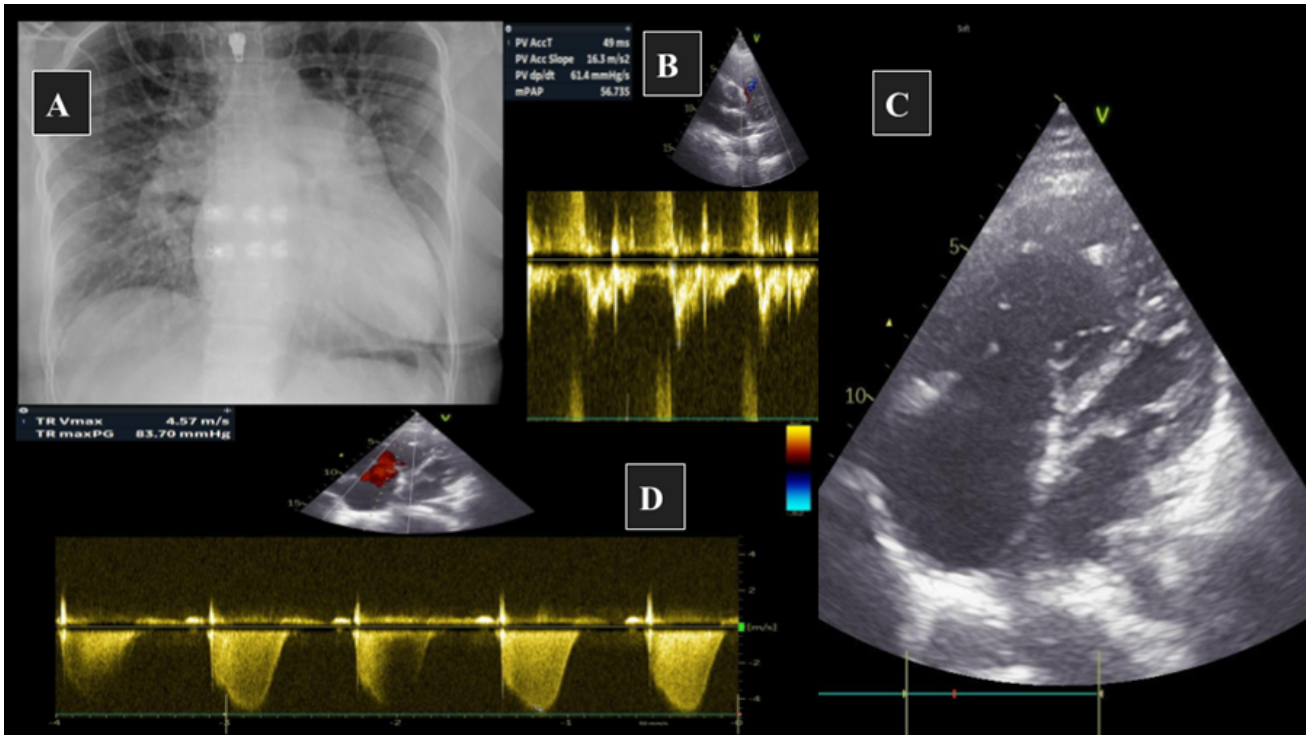

Figure 4. Case 2 X-ray and 2D echocardiography A: Patient chest x-ray revealed showed increased cardiothoracic ratio with upward apex, prominence of pulmonary arteries segment and pruning pulmonary vascular marking in the hilus area ; B: pulmonary artery notch by pulsed wave doppler; C: apical 4-chamber view 2D echocardiography showed dilation of RA (RA area index 12.8 cm2/m2) and RV; D: severe TR with TR Vmax 4.5 m/s with high probability of PH with PASP of 93 mmHg .RA: right atrial; RV: right ventricular; TR :tricuspid regurgitation; PH: pulmonary hypertension; PASP : pulmonary artery systolic pressure.

approaches, but with different antiarrhythmic (AAD) agent classes. The administration of AAD classes depends on the underlying arrhythmogenesis mechanism of each case according to the guidelines.[6,7]

In case 1, atrial flutter with 2:1 AV conduction and RBBB morphology is the type of SVA. The arrhythmogenesis origin of this SVA type arises from re-entry of an electrical circuit that is proposed to be caused by RA dilation via the cavotricuspid isthmus (CTI). Hence, amiodarone is chosen as an AAD in this circumstance because class III AAD will have prolonged action potential duration especially in phase III repolarization. This pharmacological mechanism will break the reentry circuit that formed and will terminate arrhythmia. Amiodarone is favorable and safe compared to other AAD in patients with structural heart disease.[5,8]

In the second and third cases, the patients develop AVNRT with unstable hemodynamics in case 2 but with respiratory distress in case 3. Unfortunately, given that both patients were still conscious in case 2 and 3, they were refused to electrically cardioverted due to personal reason; therefore pharmacological approach to manage the case undertaken. The class IV AAD, nondihydropyridine calcium channel blocker (CCB) is the drug of choice. Considering the arrhythmogenesis origin of AVNRT is a reentry process in the AV node via slow and fast pathway.[4,6] The conductive cells in AV nodes pose an action potential property of pacemaker cells. Hence, the influx of calcium is the crucial process of cell depolarization (phase 0). Administration intravenous nondihydropyridine CCB will terminate the micro-reentry electrical circuit in the AV node due to phase 0 rapid calcium influx suppression. A meta-analysis showed that conversion rate of non-dihydropyridine CCB does not differ significantly with adenosine administration in AVNRT patients. The limitation of nondihydropyridine CCB is its usage in patients with reduced EF is contraindicated.[4]

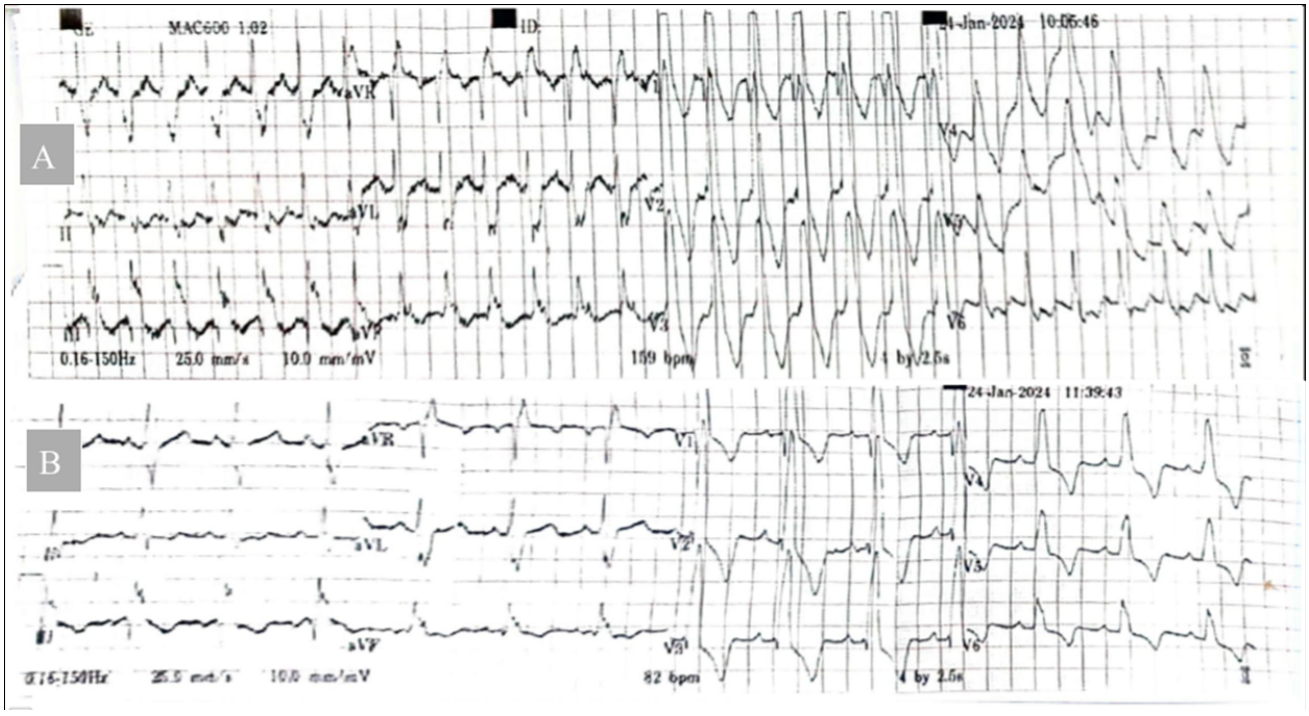

Figure 5. Electrocardiography in case 3. A: Initial ECG presentation at emergency ward showed wide complex tachycardia and RBBB morphology B: Post pharmacological cardioversion ECG showed sinus rhythm with RBBB. ECG: electrocardiography; RBBB: right bundle branch block.

All cases demonstrate successful rhythm conversion after AAD administration, which is followed by immediate symptom improvement. Supraventricular tachyarrhythmia in pre-existing RA enlargement poses a significant hemodynamic burden. Many reports which describe that SVA could precipitate acute RV dysfunction in PH, this situation prompted an early recognition and management to improve patient survival.[3,8,9,10]

There is a bidirectional relationship between PH and SVA, whereas RA dilation predisposes and triggers patients to develop SVA.[1,5,11] Waligóra et al found that in patients with PAH, the RA enlargement is associated with increased occurrence of SVA. In multivariate analysis, RA area index (RAai) is the only significant predictor of clinically significant SVA in PH (HR 1.23, $p < 0.001$). RAai value > 21.7 cm^2/m^2 becomes a discriminator for predicting significant SVA.1 On contrary our patiens RAai value were less than 21.7 cm^2/m^2. This finding highlighting that even in lower than referenced RAai value that mentioned, SVA is occurred in this patient population. Rajpold et al also reported that there is a significant association between RA dilation and SVA occurrence.[11] On the other hand, SVA becomes the precipitant factor for hemodynamic decompensation in previously enlarged RA or PH. These populations warrant for special attention, because correcting the precipitant cause of SVA will improve patient survival. The restoration and long-term sinus rhythm maintenance are of paramount importance in this special population, considering the lower survival in patients who developed atrial flutter or fibrillation compared to those who remained in sinus rhythm.[5,8,11.]

Conclusion

Supraventricular arrhythmia is a frequent arrhythmia that occurs in pulmonary hypertensive and RA dilation patients. The tachyarrhythmia in this patient population tolerated poorly and led to hemodynamic perturbation. Pharmacological cardioversion is one of the effective approaches to alleviate patient symptoms with significant clinical improvement.

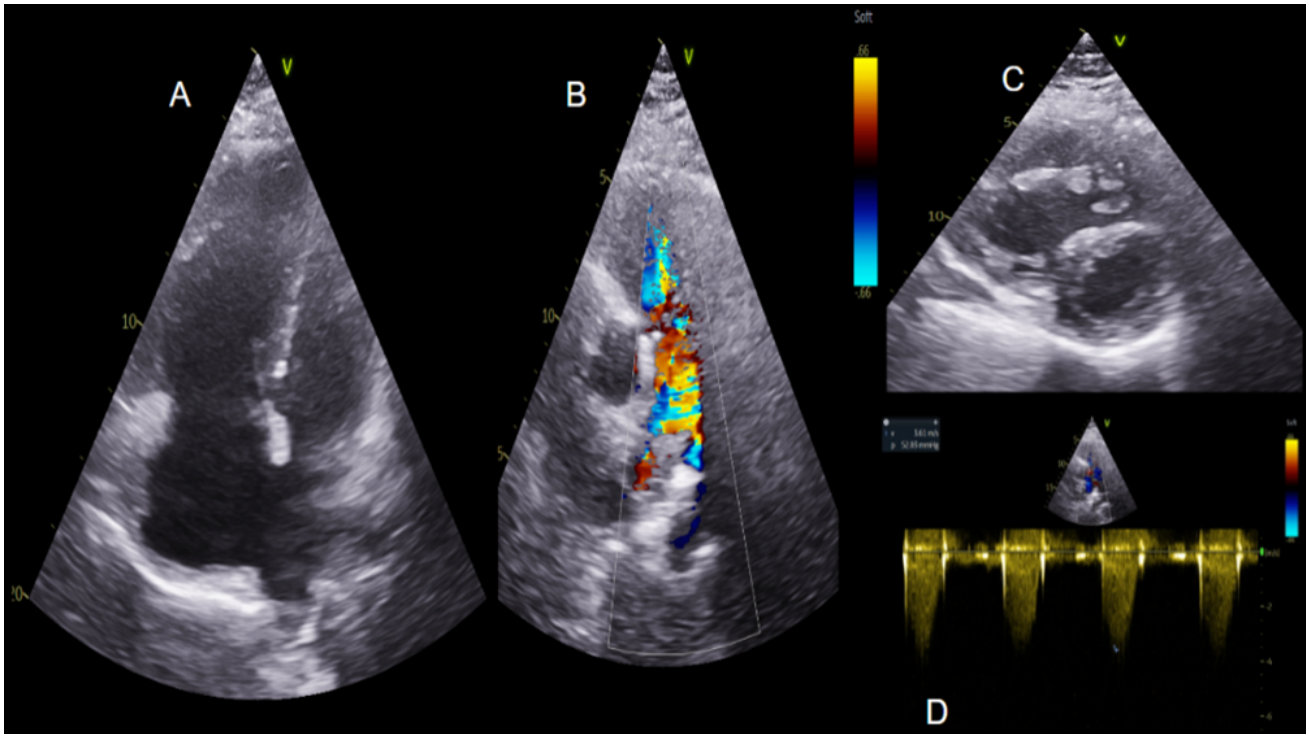

Figure 6. Case 3 2D echocardiography A and C: RA-RV dilation; B and D: Short axis view 2D echocardiography at great arteries level showed pulmonary stenosis valvar type with peak pulmonary valve gradient 52 mmHg. RA: right atrial; RV: right ventricular.

List of Abbreviations

AAD	Antiarrhythmic drugs
AVNRT	Atrioventricular-node reentrant tachycardia
AVRT	Atrioventricular reentrant tachycardia
AT	Atrial tachycardia
CCB	Calcium channel blocker
ECG	Electrocardiography
EF	Ejection fraction
LV	Left ventricular
ICU	Intensive care unit
PASP	Pulmonary artery systolic pressure
PAH	Pulmonary arterial hypertension
PH	Pulmonary hypertension
RA	Right atrial
RAai	RA area index
RBBB	Right bundle branch block
RHC	Right heart catheterization
RV	Right ventricular
SVA	Supraventricular arrhythmia
TR	Tricuspid regurgitation
TTE	Transthoracic echocardiography

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Case Report

Transient ST Elevation following Anaphylactic Shock: A Case Report of The Potential Kounis Syndrome.

I Putu Hendri Aryadi,[1] I Made Eryana,[1] I Dewa Gde Dwi Sumajaya.[2]

Abstract

Background: Anaphylactic shock rarely can induce allergic-induced acute coronary syndrome known as Kounis Syndrome. It involves the release of inflammatory cytokines through mast cell activation, which leads to coronary artery vasospasm and ST elevation presentation on electrocardiography (ECG).

Case Illustration: A 45-year-old woman with no known past medical history presented with weakness all over her body, dizziness, pain in her left hand, and a history of fainting immediately after being stung by small wasps. She was in hypotension with wheezing and weak peripheral pulses. Her laboratory examination showed leukocytosis, thrombocytosis, and high levels of blood sugar and triglycerides. Initial twelve-lead ECG demonstrated ST-segment elevation on the inferior leads (II, III, and aVF) and reciprocal ST-depression on the lateral lead. Diagnosis of anaphylactic shock caused by an insect bite was made, with a potential of becoming Kounis Syndrome. Treatment for anaphylactic shock was initiated with fluid resuscitation, intramuscular epinephrine, intravenous methylprednisolone, and ranitidine. A repeat ECG one hour post-intervention showed resolution of ST-segment elevations. The patient was discharged in stable condition two days later.

Discussion: Kounis Syndrome consists of three main types, including Type I Kounis Syndrome. Its treatment is mostly in the form of aborting the anaphylactic reaction until the symptoms resolved. Based on this case, the patient was a young non-smoker Asian woman with a low risk (<1% of 10-year risk) of fatal cardiovascular disease (CVD) in populations with high CVD risk. Clinically, the patient did not show any vascular thrombotic symptoms. In addition, administration of adrenaline, corticosteroid, and antihistamine relieved the patient's symptoms, thus, this case can be hypothesized as a potential Type I Kounis Syndrome. Emergency coronary angiography or echocardiography has to be done to clarify the diagnosis of this allergic-induced acute coronary syndrome.

Conclusion: Transient ST elevation could happen in some rare cases following an anaphylactic shock. The swift recognition, accurate diagnosis, and prompt treatment are important for optimal outcomes in the probability of Kounis Syndrome.

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Keywords: *anaphylactic shock, Kounis syndrome, ST elevation*.

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Introduction

Acute coronary syndrome following mast cell activation due to hypersensitivity, allergic, or anaphylactoid reactions was first described by Kounis and Zavras in 1991 and has been named "Kounis Syndrome" (KS) after its discoverer. The release of inflammatory cytokines through mast cell activation, which leads to coronary artery vasospasm and/or atheromatous plaque rupture, was the mechanism of KS.[1] Various presentations of this allergic angina have been documented following a variety of external exposures.[2] In this case report, we present transient allergic-induced ST-elevation in the patient without underlying coronary artery disease.

Case Presentation

A 45-year-old woman with no known past medical history presented with weakness all over her body, dizziness, pain in her left hand, and a history of fainting immediately after being stung by four small wasps 30 minutes prior to hospital admission. She also felt minimal discomfort on her chest a day before. Her initial vital signs were: blood pressure of 80/50 mmHg, pulse of 130 beats per minute, respiration rate of 28 breaths per minute, temperature of 36.7^{O}C, and oxygen saturation of 95% on room air. The examination revealed wheezing and weak peripheral pulses. Her laboratory examination showed leukocytosis (15.6µ10^{3}/µL), thrombocytosis (416µ10^{3}/µL), a slightly high level of random blood sugar (204 mg/dL), increased level of serum transaminase, and mild hypokalemia (3.3 mmol/L). The initial twelve-lead ECG demonstrated ST-segment elevation in the inferior leads (II, III, and aVF) and reciprocal ST-depression in the lateral leads (Figure 1). A diagnosis of anaphylactic shock caused by an insect bite was made. However, the ST elevation could not be concluded as acute ST elevation myocardial infarction because typical chest pain was absent, and initial myocardial enzyme levels (Troponin I) remained within the normal range. Treatment for anaphylactic shock was initiated with fluid resuscitation (1000 mL normal saline), 0.5 cc intramuscular epinephrine, 1 cc intravenous methylprednisolone (125 mg/mL), and 2 cc intravenous ranitidine (25 mg/mL), resulting in an improvement in the patient's symptoms. The patient's blood pressure also improved to 110/70 mmHg. A repeat ECG showed resolution of ST segment elevations an hour later (Figure 2). The patient was then transferred to the general ward. Vital sign was good and serial ECG did not show any abnormal changes during treatment. She experienced mild weakness and reduced pain in his left hand on the first day of her hospital stay. The redness and swelling at the site of the sting also subsided. The patient discharged in stable condition two days later. Unfortunately, no post-discharge follow-up data available for this patient.

Discussion

Kounis Syndrome is a rare type of acute coronary syndrome because of coronary artery spasm with or without the erosion or rupture of atherosclerotic plaque due to inflammatory factors released during an allergic reaction.[1,3] The exact mechanism is still unclear, however, the release of inflammatory mediators including histamine, platelet-activating factor, leukotrienes, neutral protease, cytokines, and prostaglandins, after the direct activation of mast cells, is believed to be the main inducer of this allergic-related coronary vasospasm.[4] Certain foods, drugs (commonly non-steroidal anti-inflammatory drugs and antibiotics), contrast media, and environmental exposure may provoke Kounis Syndrome.[5] More than half of the affected patients are 40-70 years old, although this syndrome can happen at any age. The patient in our case was 45 years old, belonging to the most commonly affected age group.

Both allergic reaction symptoms (including erythematous rash, hives, wheezing, and even angioedema) and acute myocardial ischemia symptoms (including chest pain, dyspnea, and palpitations) occurring concurrently are the main clinical characteristics of Kounis Syndrome. The diagnosis of this disease is primarily based on clinical manifestations. Laboratory tests (eosinophils, immunoglobulin E, and cardiac enzymes), ECG, echocardiography, and coronary angiography can be performed to clarify the diagnosis. An essential part of the diagnosis is still a careful review of the patient's clinical history, including allergy and medication history. The presence of elevated Immunoglobulin E level in the diagnosis of Kounis Syndrome remains unclear, and a normal level of it cannot exclude the possibility of the diagnosis.[6] The

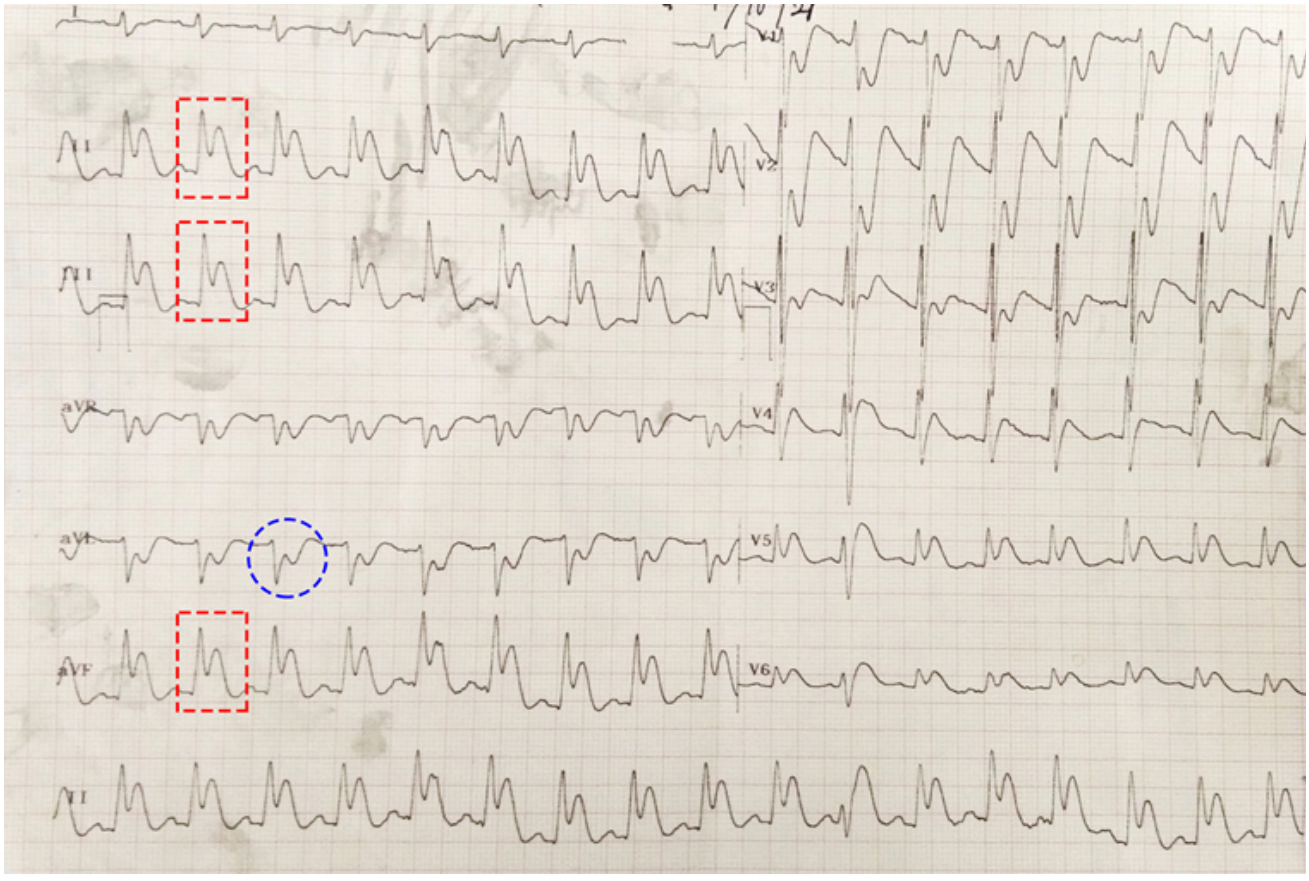

Figure 1. Initial electrocardiogram demonstrated ST-elevation in the inferior leads (red-dotted) and reciprocal ST-depression on the lateral leads (blue-dotted).

rise of cardiac enzymes in the disease implies that the allergic reaction decreases myocardial perfusion and eventually causes myocardial injury. The ECG features are commonly indistinguishable from those presented among patients with acute myocardial infarction or coronary heart disease.[7] Those ECG may vary from ST-T segment elevation or depression as the most common findings, to conduction defects, and even arrhythmias.[3] Therefore, ECG result alone could not be used to establish the diagnosis of KS. Echocardiography may indicate abnormal heart wall motion in the area supplied by the affected coronary artery. Further diagnostic tools such as coronary angiography or cardiac MRI are needed to definitively diagnose Kounis Syndrome and rule out other potential causes of ST-segment elevation. Both examinations may show the occurrence of coronary vasospasm or stenosis legibly.[8]

Kounis Syndrome consists of three main types according to clinical manifestation and coronary angiography result.[3] The most common type — Type I Kounis Syndrome — manifests as coronary artery vasospasm with or without cardiac biomarker elevation among patients without predisposing factors of coronary artery disease. This type differs from the second and third type, which present plaque erosion or thrombosis leading to myocardial infarction on patients with a history of cardiovascular disease.[3,8]

The treatment of Kounis Syndrome is still challenging and lacks consensus. The main goals are the treatment of anaphylaxis and myocardial revascularization. Removal of the allergens is the first thing to do, followed by antihistamines and corticosteroids administration to abort the allergic reaction.[9] Patients with anaphylactic shock also need appropriate fluid resuscitation. Vasodilators, including calcium channel blockers and nitrates, can help resolve the allergic vasospasm.

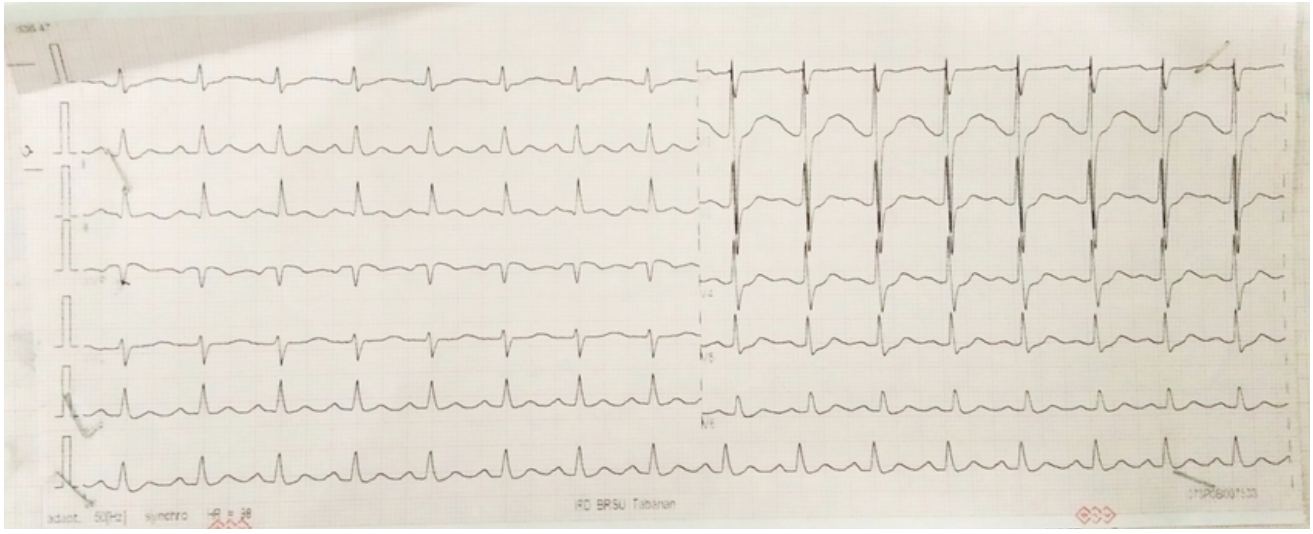

Figure 2. Repeated electrocardiogram showed resolution of inferior leads' ST-elevation.

However, the treatment of KS requires careful use of several common drugs. Epinephrine, which is used routinely in treating anaphylaxis, should be used with careful monitoring, as it may potentially worsen coronary vasospasm in KS.[10] The use of morphine, one important drug for treating acute chest pain, can be disadvantageous due to its histamine-releasing feature, which can exacerbate symptoms. Beta-blockers used in an acute exacerbation of KS may also induce coronary vasospasm due to unopposed alpha-adrenergic action.[10,11]

The patient in this case was a young Asian woman who was a non-smoker and had no history of dyslipidemia, hypertension, or type 2 diabetes mellitus. This was similar with the characteristics of patient from two Chinese reports.[8,12] Therefore, based on the Systematic Coronary Risk Estimation (SCORE) Chart, she was categorized as low risk (<1% of 10-year risk) for fatal cardiovascular disease (CVD) in populations with high CVD risk. Clinically, the patient did not show any vascular thrombotic symptoms. Some anaphylactic-related symptoms were the dominant finding, including generalized pruritic, rash, and breathlessness with/without chest discomfort.[12–14] In addition, the administration of adrenaline, corticosteroid and antihistamine relieved the patient's symptoms and normalized the ST elevation on the ECG. Some studies have shown that coronary vasospasm and allergic symptoms presented in the first type of Kounis Syndrome can be easily reversed through the administration of coronary vasodilators, steroids, and anti-histamine drugs, leading to a good prognosis with appropriate treatment.[12,15] However, due to this syndrome vagueness, some clinicians also treat it with the ACS (acute coronary syndrome) treatment algorithm, although no difference was found on the patient's outcome.[7,8,14] The patient and her family rejected any further diagnostic examinations, like echocardiography or coronary angiography, due to financial reasons. Thus, this case can be hypothesized as a potential Type I Kounis Syndrome. The comparison between previous Kounis Syndrome reports can be seen in Table 2.

Our patient also experienced hypokalemia, which is known can present various ECG abnormalities. Although this hypokalemia-related ECG changes mostly in the form of ST-segment depression, T-wave amplitude decrement, prominent U waves, and a ratio of U-wave to T wave >1.[16,17] Hypokalemia raises resting potential and subsequently accelerates depolarization, which raises the automaticity and excitability.[17] However, those phenomena mostly occur in severely low potassium state—i.e. 1.6 (3.5 - 5.1 mmol/L) in a case reported by Sethuraman et al.[17] and 1.8 mmol/L in a case reported by Petrov et al.16 It also gets trickier, because the improvement in ECG can be seen post potassium correction even before the serum potassium achieves normal level. The patient in one report had a complete resolution of ECG at a very low potassium level of 2.3 mmol/L (3.5 - 5.1 mmol/L).[16]

Table 1. Summary of the patient's clinical course.

	Hospital admission	1st Day	2nd Day (Discharged)
Specific symptom(s)	Weakness all over her body, dizziness, pain on her left hand	Slight weakness, pain on left hand was decreased	All symptoms were completely resolved
Related physical examination result(s)	Wheezing, weak peripheral pulses, redness, and swelling on the left hand	Redness and swelling on the sting site were slightly disappeared	No abnormalities found
Vital sign	Hypotension (BP: 80/50 mmHg) was found along with increased respiratory rate (28 breaths/minute)	The patient was fully awake, all vital signs were within normal limit	Vital signs were within normal limit
Laboratory examination result(s)	Laboratory examination result(s) Complete blood count RBC: 4.94 x 106/µL (4.60-6.20) HB: 14.1 g/dL (13.5-18.0) HCT: 44.0% (40-54) WBC: 15.64 x 103/µL (4.50-11.0) PLT: 416 x 103/µL (150-440) Blood chemistry test RBS: 204 g/dL (70-140) ALT: 32 U/L (11.0-34.0) AST: 42 U/L (5-34) BUN: 7.2 mg/dL (8.00-23.00) SC: 0.8 mg/dL (0.57-1.11) Na+: 139 mmol/L (136-145) K+: 3.3 mmol/L (3.50-5.10) Cl-: 105 mmol/L (94-110) Cardiac enzyme Troponin I: <0.10	Blood chemistry test RBS: 111 g/dL (70-140) Total cholesterol: 200 mg/dL (0-200) HDL: 40 mg/dL (40-60) LDL: 121 mg/dL (<100) TG: 194 mg/dL (<150)	N/A

BP = blood pressure; RBC = red blood cell; HB = hemoglobin; HCT = hematocrit; WBC = white blood cell; PLT = platelet; RBS = random blood sugar; ALT = alanine transaminase; AST = aspartate transaminase; BUN = blood urea nitrogen; SC = serum creatinine; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TG = triglyceride; N/A = not available

Conclusion

Transient ST elevation can occur in some rare cases following an anaphylactic shock, which can result in Kounis Syndrome. Therefore, it is important to have a serial ECG examination in patients with both systemic anaphylaxis and angina-equivalent symptoms at the same time. It is also essential to have a specific consensus regarding a personalized approach to treatment, since medications for allergy could potentially exacerbate myocardial ischemia, and vice versa.

List of Abbreviations

ACS	Acute coronary syndrome
CVD	Cardiovascular disease
ECG	Electrocardiography
KS	Kounier syndrome
SCORE	Systematic coronary risk estimation

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Table 2. Comparison between previous Kounis Syndrome case reports and this study.

	This study	Basnet et al. 2023[13]	Ebrahimi et al. 2024[14]	Liao et al. 2024[12]	Pradhan et al. 2018[7]	Wu et al. 2020[8]
Patient's characteristic	Female, 45-year-old, Indonesian	Male, 48-year-old, Nepali	Male, 51-year-old, Iranian	Female, 47-year-old, Chinese	Male, 22-year-old, German	Female, 48-year-old, Chinese
History	Got stung by four small wasps.	Got stung by around 40–50 wasps.	Got diclofenac intramuscular injection 30 minutes before. History of penicillin allergy.	Got bitten by bug (Cryptopteran) two days before. No history of medical issues.	Administered with a single dosage of amoxicillin.	Intramuscularly injected with 10 mg anisodamine.
Main symptoms	Weakness all over her body, dizziness, pain in her left hand, and a history of fainting.	Pain all over his body, light-headedness,	Generalized pruritic, rash, breathing difficulty, central heaviness in chest.	Itchy and pain on skin, pressuring sensation in the chest, and a slight shortness of breath.	Acute retrosternal pain and chest tightness.	Chest pain with sweating 10 minutes after injection of anisodamine.
Significant physical examination result	Wheezing and weak peripheral pulses.	GCS 3 of 15, pulse was very feeble, blood pressure could not be recorded, and SpO2 was unrecordable.	BP of 160/95 mmHg, HR of 130 beats per minute, RR of 25 breaths per min, and SpO2 94% on room air.	BP of 144/88 mmHg. Patchy brown-red rashes on the neck.	Tender throat and white patches over the tonsils.	Low BP (82/50 mmHg), erythematous pruritic rash on the chest, abdomen and limbs.
Significant additional examination result	ST-segment elevation in the inferior leads and reciprocal ST-depression in the lateral leads. Increased level of serum transaminase (ALT 32 U/L, AST 42 U/L), a mild hypokalemia (3.3 mmol/L), and Troponin I <0.10	ST-elevation in the inferior leads, while ST depressions in leads I, aVL, V1, V2, and V3. AST level of 452 U/L and ALT level of 595 U/L	ST depression in leads I, II, III, AVL, AVF, and V5-V6. ST-segment elevation in the AVR lead. LVEF was 65% and no abnormality heart's motion. Troponin I was negative.	ST-segment elevation in lead V1–V4. Hs-troponin 2.54 ng/ml, Hs-CRP 46.7 mg/L, and procalcitonin of 0.11 ng/ml. LVEF 67%. Emergency coronary angiography showed no stenosis, LCX and RCA patency, without any plaque grade stenosis.	ST elevations in II, III, aVF, V5, and V6. Positive troponin (300 pg/dL), elevated creatinine kinase (315 IU/L). Normal functioning heart with preserved LVEF during echocardiography.	ST-segment elevation in the inferior leads with ST-segment depression in the lateral leads. Coronary angiography showed no significant abnormalities. Immunoglobulin E level was 365 IU/mL, while the peak troponin I level was 0.247 ng/mL.

Treatment	Fluid resuscitation of (1000 mL) normal saline), 0.5 cc intramuscular epinephrine, 1 cc intravenous methylprednisolone (125 mg/mL), and 2 cc of intravenous ranitidine (25 mg/mL).	Initial: CPR with adrenaline, hydrocortisone (200 mg IV), pheniramine maleate (45.5 mg IV), enoxaparin (60 mg SC), clopidogrel and aspirin loading-dose orally. Later: ventilator support, sodium bicarbonate, inotropes.	Aspirin (325 mg orally), clopidogrel (300 mg orally), atorvastatin (80 mg orally), nitroglycerin (10 mcg per minute IV), an unfractionated heparin (UFH) infusion (60 U/kg/h), and metoprolol (50 mg orally)	Intravenous drip of calcium gluconate injection, topical halometasone ointment, and oral loratadine.	Heparin bolus, single antiplatelet therapy of acetylsalicylic acid (100 mg).	Initial: Saline solution, promethazine (25 mg) and dexamethasone (10 mg). Later: 300 mg aspirin and 180 mg ticagrelor for emergent coronary angiography.
Resolution	A repeat ECG showed resolution of ST segment elevations an hour later. Vital sign was good and serial ECG did not show any abnormal changes during treatment. The patient discharged in stable condition two days later.	His condition gradually deteriorated and died on the same day	The patient's ECG gradually returned to normal 12 hours later. Serial troponin levels were normal. Symptoms were completely resolved the day after. Good clinical outcome was confirmed at a follow-up visit 6 months later.	The patient's symptoms improved, ECG and troponin re-examination were normal. No symptoms during the one-week-after-discharge follow-up.	The patient was discharged in a stable condition after 5 days. A telephonic follow-up after a week revealed good recovery of the patient.	ST-segment elevation had disappeared 49 minutes after the first ECG. The patient was discharged without complications. During the 9-month follow-up, the patient avoided anisodamine injection and remained free of chest pain.

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