Large unstained cell count is a useful predictor of coronary artery disease co-existence in patients with severe aortic stenosis

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INTRODUCTION

The burden of aortic valve stenosis (SA) is growing due to demographic changes connected with population aging [1]. The appropriate diagnosis especially in patients with angina pectoris symptoms is of utmost importance due to its association with limited life expectancy. Coronary artery disease (CAD) and aortic valve degeneration share similar pathogenetic factors including lipid accumulation and calcium deposition [2]. There is a limited utility of angina pectoris symptoms in CAD diagnosis in patients with SA since chest pain is typical of both diseases. Previous reports demonstrated a 50% prevalence of angiographically significant coronary artery disease in patients presenting angina pectoris symptoms with already diagnosed SA [3].

Noninvasive stress tests are characterized by low specificity, and exercise tests usually performed in the assessment of coronary artery disease are contradicted in symptomatic SA patients. Several attempts to include non-invasive laboratory markers in diagnostics were undertaken [4, 5]. Some simple laboratory investigations might help in evaluation of cardiovascular patients. This study aimed to find a non-invasive easily accessible marker for detecting coronary artery disease in patients with aortic stenosis.

METHODS

We analyzed 200 consecutive patients with symptomatic SA with or without coronary artery disease admitted to the cardiac surgery department between November 2017 and September 2022. Subjects with active endocarditis or CAD with moderate SA and patients with a history of malignancy or rheumatic disorders were excluded from the study. The final study group comprised 190 patients with severe SA assigned to group 1 (n = 85, 44.7%) with absence or group 2 (n = 105, 55.3%) with the presence of CAD defined as coronary artery atherosclerotic changes covering at least 50% of the artery lumen. Demographic and clinical data were analyzed. Blood samples were collected on admission, and the results were related to echocardiographic findings.

All patients referred for a surgical procedure had preserved left ventricular ejection fraction. Echocardiographic intra- and inter-observer variability may be related to pre- and postoperative differences in the visualization; however, it remains low in the experienced centers. The echocardiographic methodology was presented in Supplementary material no. 2.

The study was approved by the local Institutional Ethics Committee (no. 198/2021).

Statistical analysis

Analysis was performed using MedCalc® Statistical Software version 20.027 (MedCalc/Software Ltd, Ostend, Belgium). Detailed information was presented in Supplementary material no. 3.

Table 1. Uni- and multivariable analysis for CAD prediction in SA patients

Parameters	Univariable analysis			Multivariable analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age (per 1 year)	1.062	1.021–1.104	0.003	1.056	1.012–1.101	0.012
Sex (male)	1.139	0.623–2.084	0.67	—	—	—
DM	2.792	1.460–5.338	0.002	2.765	1.413–5.410	0.003
HA	1.142	0.560–2.329	0.72	—	—	—
COPD	0.634	0.165–2.437	0.507	—	—	—
PAD	1.209	0.529–2.766	0.65	—	—	—
AF	2.222	0.879–1.205	0.05	—	—	—
LUC	1.890	1.122–3.182	0.02	1.737	1.040–2.901	0.035

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; CI, confidence interval; COPD, chronic pulmonary obstructive disease; DM, diabetes mellitus; HA, arterial hypertension; LUC, large unstained cells; OR, odds ratio; PAD, peripheral artery disease; SA, aortic stenosis

RESULTS AND DISCUSSION

Preoperative echocardiographic characteristics revealed a difference between groups in a median (interquartile range [IQR]) transvalvular aortic gradient: 58 (50–67) mm Hg vs. 54 (46–61) mm Hg ($P = 0.005$) and presented in detail in Supplementary material no. 1, *Table S1*. Patients in group 2 were older, and diabetes and atrial fibrillation occurred more often in this group. Detailed demographic and clinical data are presented in Supplementary material no. 1 and *Table S2*, and preoperative laboratory investigations in Supplementary material no. 1 and *Table S3*.

Large unstained cell (LUC) count was the only laboratory parameter from whole blood count excluding serum C-reactive protein, which varied in both subgroups ($P = 0.007$).

In the multivariable logistic regression model with a backward stepwise elimination method (Table 1), age ($P = 0.010$), diabetes mellitus ($P = 0.003$), and LUC count ($P = 0.035$) were revealed as predictors of the co-existence of CAD and severe SA even despite statin therapy. For LUCs, the estimated odds ratio [OR] was found to be 1.737 (95% confidence interval [CI], 1.040–2.901).

The multivariable analysis and ROC analysis established that the following indicators have the highest significance for CAD co-existence: LUC count above 0.19 K/µl (OR, 1.737; 95% CI, 1.040–2.901; $P = 0.035$; AUC = 0.602 with sensitivity of 68% and specificity of 51%), age (OR, 1.056; 95% CI, 1.012–2.101; $P = 0.010$; AUC = 0.612 with sensitivity of 82% and specificity of 36%), and diabetes mellitus (OR, 2.765; 95% CI, 1.413–5.410; $P = 0.003$; AUC = 0.608, giving sensitivity of 43% and specificity of 79%). Detailed information regarding uni- and multivariable analysis was presented in Table 1.

Our analysis presents a new approach to assessment of CAD co-existing with SA based on whole blood cell count analysis. To our best knowledge, this is the first study indicating that LUC count obtained from whole peripheral blood analysis is a simple and reliable predictor of CAD disease in SA patients.

There is over 50% co-existence of CAD in patients with severe SA [3]. The identification of accompanying diseases is crucial for therapy planning. Established CAD in SA was related to significantly higher risk of cardiac mortality [7]. The normal results of exercise tests were found in one-fifth of patients with asymptomatic SA and silent CAD [8]. Such observations indicate the necessity for conducting alternative non-invasive tests in this group of patients.

Both degenerative SA and CAD share similar risk factors including male sex, arterial hypertension, diabetes mellitus, smoking, and hypercholesterolemia. In our multivariable analysis, age and diabetes mellitus were found significant for CAD prediction.

Chest pain is the most typical presentation of obstructive CAD. In SA, anginal symptoms are related to an imbalance between hypertrophic myocardium oxygen demands acting in increased wall stress, secondary to left ventricular compensatory afterload and its blood flow supply [9]. Exercise tests may be inconclusive, especially in asymptomatic patients. Coronary flow reserve (CFR) in patients with SA is impaired due to reduced diastolic filling time and elevated left ventricular pressure combined with perivascular and myocardial fibrosis [10].

In our analysis, we focused on inflammatory characteristics in both diseases. The significance of inflammatory activation as an arterial hypertension trigger was postulated [11]. The results of our study point out the role of possible predictors for CAD co-existence in SA patients based on whole blood count analysis.

The link between altered monocytic phenotype and hypertension has been already shown [12]. The novelty of our finding is in presenting for the first time the importance of LUC in cardiovascular disorders. Knowledge about LUCs is scarce, and their role and significance are often overlooked. LUCs include activated lymphocytes and peroxidase-negative cells. Though LUCs are claimed to lack specificity, they represent a group of cells including blasts, atypical lymphocytes, plasma cells, and peroxidase-negative neutrophils [13]. Our previous report showed a prognostic value of LUC in assessing inflammatory activation and carotid artery stenosis characteristics [14].

Our results confirm previous reports of atherosclerosis development in patients with SA characterized by chronic inflammatory activation and show that this phenomenon may rely on a more advanced innate immune response

characterized by LUCs. The impossibility of evaluating the potential influence of the anti-inflammatory effect of statins and antidiabetic treatment may be a limitation of our study. In conclusion, a LUC count above 0.19 K/μl in whole blood analysis can be regarded as an indicator for possible co-exitance of coronary artery disease in patients with aortic stenosis.

Article information

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REFERENCES

1. Marzec K, Jaworska-Wilczyńska M, Kowalik I, et al. Comparison of long-term outcomes and risk factors of aortic stenosis treatment in patients undergoing transcatheter aortic valve implantation and surgical aortic valve replacement. Kardiol Pol. 2022; 80(7-8): 792–798, doi: 10.33963/KP.a2022.0122, indexed in Pubmed: 35521716.
2. de Oliveira Sá MP, Cavalcanti LR, Perazzo ÁM, et al. Calcific Aortic Valve Stenosis and Atherosclerotic Calcification. Curr Atheroscler Rep. 2020; 22(2): 2, doi: 10.1007/s11883-020-0821-7, indexed in Pubmed: 31912380.
3. Julius BK, Spillmann M, Vassalli G, et al. Angina pectoris in patients with aortic stenosis and normal coronary arteries. Mechanisms and pathophysiological concepts. Circulation. 1997; 95(4): 892–898, doi: 10.1161/01.cir.95.4.892, indexed in Pubmed: 9054747.
4. Olasińska-Wiśniewska A, Grodecki K, Urbanowicz T, et al. Pulmonary artery systolic pressure at 1-month predicts 1-year survival after transcatheter aortic valve implantation. Kardiol Pol. 2022; 80(7-8): 825–833, doi: 10.33963/KP.a2022.0128, indexed in Pubmed: 35575408.
5. Cionca C, Zlibut A, Orzan RI, et al. Left atrial geometric and functional remodeling parameters measured by cardiac magnetic resonance imaging and outcome prediction in patients with severe aortic stenosis. Kardiol Pol. 2023; 81(2): 150–159, doi: 10.33963/KP.a2022.0265, indexed in Pubmed: 36446068.
6. Urbanowicz T, Michalak M, Olasińska-Wiśniewska A, et al. Monocyte/Lymphocyte Ratio and MCHC as Predictors of Collateral Carotid Artery Disease-Preliminary Report. J Pers Med. 2021; 11(12), doi: 10.3390/jpm11121266, indexed in Pubmed: 34945738.
7. Lee W, Choi W, Kang SiH, et al. Long-term Prognosis of Mild to Moderate Aortic Stenosis and Coronary Artery Disease. J Korean Med Sci. 2021; 36(6): e47, doi: 10.3346/jkms.2021.36.e47, indexed in Pubmed: 33559407.
8. Banovic M, Iung B, Brkovic V, et al. Silent coronary artery disease in asymptomatic patients with severe aortic stenosis and normal exercise testing. Coron Artery Dis. 2020; 31(2): 166–173, doi: 10.1097/MCA.0000000000000801, indexed in Pubmed: 31577622.
9. Gould KL, Carabello BA. Why angina in aortic stenosis with normal coronary arteriograms? Circulation. 2003; 107(25): 3121–3123, doi: 10.1161/01.CIR.0000074243.02378.80, indexed in Pubmed: 12835405.
10. Carberry J, Ang D, Berry C. Coronary blood flow and severe aortic stenosis. Heart. 2022; 109(1): 6–7, doi: 10.1136/heartjnl-2022-321587, indexed in Pubmed: 36007936.
11. Szczepaniak P, Mikołajczyk TP, Cześnikiewicz-Guzik M, et al. Periodontitis as an inflammatory trigger in hypertension: From basic immunology to clinical implications. Kardiol Pol. 2021; 79(11): 1206–1214, doi: 10.33963/KP.a2021.0161, indexed in Pubmed: 34847238.
12. Imiela AM, Siedliński M, Dobrowolski P, et al. Altered monocytic phenotypes are linked to a hypertension form: A clinical observational study. Kardiol Pol. 2022; 80(3): 346–349, doi: 10.33963/KP.a2022.0036, indexed in Pubmed: 35129205.
13. Buttarello M, Plebani M. Automated blood cell counts: state of the art. Am J Clin Pathol. 2008; 130(1): 104–116, doi: 10.1309/EK3C7CTDKNVPXVTN, indexed in Pubmed: 18550479.
14. Urbanowicz TK, Rodzki M, Michalak M, et al. Large unstained cell (LUC) count as a predictor of carotid artery occlusion. Adv Clin Exp Med. 2023 [Epub ahead of print], doi: 10.17219/acem/159756, indexed in Pubmed: 36920263.