# Echocardiographic phenotypes of patients with sickle cell disease. An unsupervised analysis based on etendard cohort

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**Backgroung:** Echocardiography is the cornerstone in the diagnosis of cardiopulmonary involvement in sickle cell disease (SCD). However, given the unique pathophysiology of SCD associating high cardiac output, and various degrees of peripheral vasculopathy, differentiate the pathological from the physiological using echocardiography can be particularly challenging.

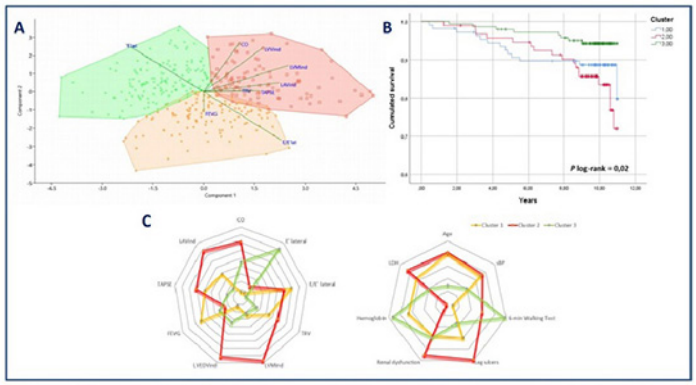
**Purpose:** This study sought to link cardiac phenotypes in homozygous SCD patients with clinical profiles and outcomes using cluster analysis.

**Methods:** We analyzed data of 379 patients with a sufficient echographic dataset included in the French Etendard Cohort, a prospective cohort initially designed to assess the prevalence of pulmonary hypertension. A cluster analysis was performed on echocardiographic variables, and the association between clusters and clinical profiles and outcomes was assessed.

**Results:** Three clusters were identified. Cluster 1 (N = 122) patients had the lowest cardiac output, only mild left cavities remodeling, diastolic dysfunction, and high tricuspid regurgitation velocity (TRV). They were predominantly female, as old as cluster 2, and displayed the most severe functional limitation. Cluster 2 (N = 103) patients had the highest cardiac output, left ventricular mass and a severely dilated left atrium. Diastolic function and TRV were similar to cluster 1. These patients had a higher blood pressure and a severe hemolytic anemia. Cluster 3 (N = 154) patients had mild left cavities remodeling, the best diastolic function and the lowest TRV. They were younger patients with the highest hemoglobin and lowest hemolytic markers. Right heart catheterization was performed in 94 patients. Cluster 1 gathered the majority of precapillary PH while cluster 2 gathered postcapillary PH and no PH was found in cluster 3. After a follow-up of 9.9 years (IQR: 9.3 to 10.5 years) death occurred in 38 patients (10%). Clusters 2 had the worst prognosis with 18% mortality rate vs. 12% in cluster 2 and 5% in cluster 1 (P log-rank = 0,02). Results are summarized in the central illustration.

**Conclusions:** Cluster analysis of echocardiographic variables identified 3 phenotypes among SCD patients, each associated with different clinical features and outcome. These findings underlines the necessity to rethink echocardiographic evaluation of SCD patients, with an integrative approach based on simultaneous evaluation of TRV along with left cavities remodeling and diastolic parameters.

Abstract Figure.




***A. K-means clustering*** *identified 3 clusters based on echocardiographic parameters. Biplot representation visualizes the relationships between variables* ***(lines)*** *used for building clusters while simultaneously displaying the patients* ***(dots, plus and squares)*** *based on their individual echocardiographic characteristics. Results are projected on to the 2 first dimensions yielded by principal component analysis. Colors for observations correspond to the 3-group solution from cluster analysis:* ***Orange dots*** *for cluster* ***1****,* ***Red squares*** *for cluster 2 and* ***Green plus*** *for cluster 3.* ***B. Kaplan-Meier analysis*** *displaying all-cause mortality across clusters .* ***C. Radar charts*** *showing the superposition of echocardiographic parameters based on cluster belonging (Left) and clinical profiles based on echocardiographic phenotypes (Right). Values are standardized and expressed as z-score from average values. Low values are in the center and high values are at the extremities.*
*LVEF indicates left ventricular ejection fraction; CO, cardiac output; LVMind, left ventricular mass indexed on body surface; LVVind, left ventricular end-diastolic volume indexed to body surface; LAVind, left atrial volume indexed on body surface; E, mitral inflow early filling velocity; E', lateral early diastolic myocardial velocity; TAPSE, tricuspid annular plane systolic excursion; TRV, tricuspid regurgitation velocity; sBP, systolic blood pressure.*