Hematologia e Hemoterapia de Pernambuco. A genotipagem do polimorfismo rs11225395 do gene da MMP8 foi feita por PCR em tempo real. Por fim, foi feita a análise estatística pelo software SPSS Statistics 21.0 e GraphPad Prism 8.0, e todos os valores de P foram ajustados para os dois lados com nível de significância estatística de 0,05. Este estudo é um subprojeto de uma pesquisa aprovada pelo Comitê de Ética em Pesquisa (CAAE: 46931121.3.0000.5208). **Resultados:** Dentre os 264 pacientes com AF elegidos, 132 (50%) eram do sexo feminino e 132 (50%) do sexo masculino, com a mediana de idade de 15 anos (variação: 7 - 21). Foi calculado a frequência genotípica, na qual 127 (48,1%) pacientes possuíam o genótipo homozigoto selvagem GG, 114 (43,2%) eram heterozigotos AG e 23 (8,7%) eram homozigotos selvagem AA, apresentando-se dentro do equilíbrio de Hardy-Weinberg (p=0,71). Para análises de associação, adotou-se os modelos de herança dominante, sobredominante, recessivo e codominante. De acordo com o modelo recessivo, observou-se associação do SNP com a menor frequência de CVOs ao ano (p=0,018) e menores percentuais de reticulócitos (p=0,029) no grupo homozigoto selvagem AA. E, apesar da não associação estatística, esse genótipo apresentou níveis mais elevados de HbF em relação aos outros genótipos. **Discussão e conclusão:** Por fim, conclui-se que o indivíduos com genótipo homozigoto selvagem AA são menos suscetíveis a ocorrência de CVOs ao ano em comparação às outras populações estudadas. Esse resultado é respaldado por estudos que sugerem que a substituição do alelo A pelo G regula positivamente a expressão do mRNA, desequilibrando o processo de reparação e degradação do colágeno, aumentando a ocorrência de complicações vasculares. De modo complementar, os níveis mais elevados de HbF no genótipo AA sugerem o possível caráter protetivo neste grupo.

https://doi.org/10.1016/j.htct.2025.104157

ID – 1981

LABORATORY AND GENETIC CHARACTERISTIC ASSOCIATED WITH GALLBLADDER-RELATED OUTCOMES IN SICKLE CELL DISEASE IN BRAZIL: RESULTS FROM THE REDS-III MULTICENTER COHORT STUDY

AR Belisário [a], MC Ozahata [b], ICG Moura [c], C Miranda [a], EC Sabino [b], B Custer [d], S Kelly [e], CL Dinardo [f]

[a] *Fundação Hemominas, Belo Horizonte, MG, Brazil*
[b] *Universidade de São Paulo (USP), São Paulo, SP, Brazil*
[c] *Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil*
[d] *Vitalant Research Institute, United States*
[e] *UCSF Benioff Children's Hospital, United States*
[f] *Pró-Sangue, São Paulo, SP, Brazil*

Introduction: Sickle cell disease (SCD) is a monogenic disorder resulting from mutations in the β-globin gene, leading to chronic hemolytic anemia, and vaso-occlusion. These mechanisms contribute to a wide range of complications, including hepatobiliary diseases. Despite being a common morbidity, gallbladder disease remains underexplored. **Objectives:** To estimate the prevalence and cumulative risk of cholelithiasis, cholecystitis, and cholecystectomy, and to identify laboratory, and genetic factors associated with these outcomes in a large multicenter Brazilian cohort of individuals with SCD. **Material and methods:** This study analyzed data from 2,778 participants with confirmed SCD enrolled at six referral centers in Brazil as part of the REDS- III SCD cohort. Gallbladder-related outcomes were identified through comprehensive review of medical records and imaging reports. Laboratory data were collected from medical records. Whole-genome sequencing was performed as part of the NHLBI TOPMed program. Genome-wide association studies were conducted using logistic mixed models adjusted for sex, age, genotype, and population structure. **Results:** The prevalence of cholelithiasis, cholecystitis, and cholecystectomy was 35.9%, 25.1%, and 10.6%, respectively. Among participants with severe genotypes (HbSS, HbSβ^0, and HbSβ^+-severe), the cumulative risk of cholelithiasis reached 97.3% by age 70; for cholecystitis, 55.0% by age 62; and for cholecystectomy, 81.2% by age 62. In the HbSC group, risks were also elevated: 86.7% for cholelithiasis by age 73, 36.4% for cholecystitis by age 61, and 63.4% for cholecystectomy by age 63. Elevated indirect bilirubin ($\geq$ 75th percentile) was strongly associated with all outcomes (OR = 1.75 to 3.85, $p < 0.001$). Inflammatory markers, such as WBC and platelet counts, were also significantly associated with gallbladder-related outcomes. In HbSC participants, elevated platelet counts ($\geq$75th percentile) were significantly associated with cholecystitis (OR: 3.77; $p = 0.024$). GWAS confirmed the link between UGT1A1 variants and indirect bilirubin, and for the first time, showed genome-wide associations with cholecystectomy. Additionally, novel genome-wide significant associations were identified in FER1L6, LRFN5, and SDK2. **Discussion and conclusion:** Despite advances in disease-modifying therapies, the gallstone burden in this cohort mirrors those reported in the 1980s. These data highlight the need for better preventive strategies and surveillance protocols. Our findings also underscore the multifactorial etiology of gallbladder disease in SCD, implicating both hemolytic burden and inflammatory mechanisms. Genetic data reinforce the role of UGT1A1 and highlight novel candidate genes potentially involved in gallstone pathophysiology. FER1L6 is involved in vesicular transport and cytoskeletal organization and may influence gallbladder epithelial function. LRFN5 and SDK2 are cell adhesion molecules potentially linked to endothelial function and bilirubin metabolism. This study, the largest of its kind to date, demonstrates a persistently high burden of gallbladder-related disease in individuals with SCD in Brazil. Both hemolytic and inflammatory mechanisms are implicated. The identification of novel genetic loci and confirmation of known pathways offer new opportunities for risk stratification and future therapeutic targets. Interventions aimed at preventing gallstone formation are urgently needed to reduce morbidity in this population.

https://doi.org/10.1016/j.htct.2025.104158