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Total de artigos publicados em 2022: 22

LINHA DE PESQUISA: HEMOGLOBINOPATIAS (8 artigos)

1- Endocrine, Metabolic & Immune Disorders Drug Targets, 22(9): 954-962, 2022.

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Growth Hormone/Insulin-Like Growth Factor 1 Axis Associated with Modifiers Factors in Children with Sickle Cell Anemia

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Background: Sickle cell anemia is a disease that develops episodes of acute pain and multiple organ dysfunction that can affect the growth hormone/insulin-like growth factor 1 (GH/IGF-1) axis. The severity of sickle cell anemia is influenced by modifying factors, such as levels of fetal hemoglobin (HbF), the co-inheritance of alpha-thalassemia, or treatment with hydroxyurea.

Methods: This cross-sectional study in children with sickle cell anemia evaluated bone age (BA), adult height prediction (AHP) using BA, a target height (TH) calculated as the mean SDS of the parents, and laboratory parameters. Children were grouped according to serum levels of HbF, co-inheritance of alpha-thalassemia, and hydroxyurea therapy.

Results: The mean age of the 39 children was 8.2±2.2 years old. The average height was -0.75±0.30 SDS, and 10.3% (4/39) had short stature. Adjusted levels of IGF-1 or IGFBP-3 were significantly higher in children with sickle cell anemia on hydroxyurea treatment, in children with HbF levels >10%, and in those without alpha-thalassemia. Using SDS, the growth potential of children with sickle cell anemia in relation to their parents, calculated by the difference between AHP and TH, as well as the difference between

children's height and their TH, were lower in children with co-inheritance of alpha-thalassemia Conclusion: The study showed an association between modifying factors and the GH/IGF-1 axis in children with sickle cell anemia. Additionally, the co-inheritance of alpha-thalassemia was associated with decreased height in these children when adjusted for their parents' height.

2- Arquivos Brasileiros de Cardiologia, 118(3): 565-575, 2022.

https://doi.org/10.36660/abc.20200437

Exercise Testing In Patients with Sickle Cell Disease: Safety, Feasibility and Potential Prognostic Implication

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Background: Patients with sickle cell disease (SCD) are at increased risk for cardiovascular complications. Exercise testing is used as a prognostic marker in a variety of cardiovascular diseases. However, there is a lack of evidence on exercise in SCD patients, particularly regarding its safety, feasibility, and possible prognostic role.

Objectives: We used the maximal treadmill test to determine safety and feasibility of the exercise testing in SCD patients. Additionally, the factors associated with exercise duration, as well as the impact of exercise-induced changes on clinical outcome, were also assessed.

Methods: One-hundred thirteen patients with SCD, who underwent exercise testing, were prospectively enrolled. A comprehensive cardiovascular evaluation, including echocardiography and B-type natriuretic peptide (BNP) levels, were obtained. The long-term outcome was a composite endpoint of death, severe acute painful episodes, acute chest syndrome, or hospitalization for other SCD-related complications. Cox regression analysis was performed to identify the variables associated with the outcome. A p-value<0.05 was considered to be statistically significant.

Results: The mean age was 36 ± 12 years (range, 18-65 years), and 62 patients were women (52%). Ischemic electrocardiogram and abnormal blood pressure (BP) response to exercise were detected in 17% and 9%, respectively. Two patients experienced pain crises within 48 hours that required hospitalization. Factors associated with exercise duration were age, sex, tricuspid regurgitation (TR) maximal velocity, and E/e' ratio, after adjustment for markers of disease severity. During the mean follow-up of 10.1 months (ranging from 1.2 to 26), the endpoint was reached in 27 patients (23%). Independent predictors of adverse events were hemoglobin concentration, late transmitral flow velocity (A wave), and BP response to exercise.

Conclusions: Exercise testing in SCD patients who were clinically stable is feasible. Exercise duration was associated with diastolic function and pulmonary artery pressure. Abnormal BP response was an independent predictor of adverse events.

3- The Journal of Clinical Investigation, 132(4): e156060, 2022.

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Clonal hematopoiesis in sickle cell disease

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BACKGROUND: Curative gene therapies for sickle cell disease (SCD) are currently undergoing clinical evaluation. The occurrence of myeloid malignancies in these trials has prompted safety concerns. Individuals with SCD are predisposed to myeloid malignancies, but the underlying causes remain undefined. Clonal hematopoiesis (CH) is a premalignant condition that also confers significant predisposition to myeloid cancers. While it has been speculated that CH may play a role in SCD-associated cancer predisposition, limited data addressing this issue have been reported. METHODS: Here, we leveraged 74,190 whole-genome sequences to robustly study CH in SCD. Somatic mutation calling methods were used to assess CH in all samples and comparisons between individuals with and without SCD were performed. RESULTS: While we had sufficient power to detect a greater than 2-fold increased rate of CH, we found no detectable variation in rate or clone properties between individuals affected by SCD and controls. The rate of CH in individuals with SCD was unaltered by hydroxyurea use. CONCLUSIONS: We did not observe an increased risk for acquiring detectable CH in SCD, at least as measured by whole-genome sequencing. These results should help guide ongoing efforts and further studies that seek to better define the risk factors underlying myeloid malignancy predisposition in SCD and help ensure that curative therapies can be more safely applied.

4- Transplantation and Cellular Therapy, 28(10): 708.e1-708.e8, 2022. Epub 2022 Jul 3.

https://doi.org/10.1016/j.jtct.2022.06.024

Is Severity Score Associated with Indication for Hematopoietic Stem Cell Transplantation in Individuals with Sickle Cell Anemia?

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Background: Manifestations of sickle cell disease (SCD) begin early in childhood and cause morbidity and decreased life expectancy. Hematopoietic stem cell transplantation (HSCT) is curative but associated with risk of mortality attributable to the transplant. This risk should be counterbalanced with SCD morbidity and mortality. A severity score using a Bayesian network model was previously validated to predict the risk of death in adult individuals with SCD.

Objective(s): The objective of this study is to calculate the severity scores of participants in a multi-center cohort of Brazilians with SCD, using a previously published Bayesian network-derived score, associated with risk of death and then compare the severity scores between participants with and without an indication for hematopoietic stem cell transplantation (HSCT) as defined by the Brazilian Ministry of Health (MoH) criteria.

Study design: This is an observational, retrospective study. We analyzed 2063 individuals with sickle cell anemia (SS, SBeta0) from the Recipient Epidemiology and Donor

Evaluation Study-III (REDS-III) Brazil SCD cohort and applied a Bayesian network-derived score to compare candidates and non- candidates for HSCT according to the Brazilian MoH transplant criteria. Classical statistical methods were used to analyze data and make comparisons.

Results: We compared severity scores between cohort members with (n=431) and without (n=1632) HSCT indications according to Brazilian MoH. Scores were not different in adult participants with ≥1 HSCT indication when compared to those with no indication (mean= 0.342 vs. 0.292; median=0.194 vs. 0.183, p=0.354) and ROC curves did not demonstrate an obvious threshold to differentiate participants with or without HSCT indications.

Conclusion(s): Severity score may predict risk of death but does not differentiate HSCT candidates. Current indications should be evaluated to ensure patients with more severe disease who might benefit from HSCT are appropriately identified.

5- Revista Médica de Minas Gerais, 32: e-32204, 2022.

https://doi.org/10.5935/2238-3182.2022e32204

Aspects of care in patients with Sickle Cell Disease in the context of the COVID-19 pandemic

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Introduction: The pandemic caused by the new coronavirus (Sars-CoV-2), a disease called COVID-19, has reached more than 219 countries with great damage and impact on global health. The viral infection triggers an explosive, hyperactive and uncontrolled immune response, with severe clinical manifestations in people with underlying diseases. Sickle Cell Disease (SCD), a genetic condition that determines immunosuppression, causes patients a greater risk of respiratory infections and pulmonary complications within the context of the pandemic. Objective: To analyze the impact of COVID-19 in patients with SCD and propose a guideline to care for this population. Methods: This is a systematic literature review where studies were

analyzed, originally published in English, between March and December 2020, using the MedLine, SciELO and LILACS databases as references. The search was carried out by consulting MeSH with the descriptors "sickle cell disease", "covid-19" and "guideline". 64 articles were identified from the search phrase. After applying the inclusion criteria, 7 articles were chosen for the study. Results and Conclusion: The infection with the new coronavirus could cause complications in patients with SCD, such as vaso-occlusive crises and acute chest syndrome. Considering these data, the authors formulated a guideline for guidance and care for individuals with SCD.

6- Journal of Human Genetics, 67(12): 701-709, 2022. Epub 2022 Sep 27.

https://doi.org/10.1038/s10038-022-01079-0

Fetal hemoglobin-boosting haplotypes of BCL11A gene and HBS1L-MYB intergenic region in the prediction of clinical and hematological outcomes in a cohort of children with sickle cell anemia

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Single nucleotide polymorphisms (SNPs) of BCL11A gene and HBS1L-MYB intergenic region (named HMIP-2) affect both fetal hemoglobin (HbF) concentration and clinical outcomes in patients with sickle cell anemia (SCA). However, no previous study has examined the interaction among these SNPs in the regulation of HbF. We examined whether HbF-boosting haplotypes combining alleles of functional SNPs of BCL11A and HMIP-2 were associated with clinical outcomes and hematological parameters, and whether they interact to regulate HbF in a cohort of Brazilian children with SCA. The minor haplotype of BCL11A ("TCA", an allele combination of rs1427407, rs766432, and rs4671393) was associated with higher HbF, hemoglobin and lower reticulocytes count compared to reference haplotype "GAG". The minor haplotype of HMIP-2 ("CGC", an allele combination of rs9399137, rs4895441, and rs9494145) was associated with higher

HbF and hemoglobin compared to reference haplotype "TAT". Subjects carrying minor haplotypes showed reduced rate of clinical complications compared to reference haplotypes. Non-carriers of both minor haplotypes for BCL11A and HMIP-2 showed the lowest HbF concentration. Subjects carrying only the minor haplotype of BCL11A showed significantly higher HbF concentration than non-carriers of any minor haplotype, which showed no significant difference compared to subjects carrying only the minor haplotype of HMIP-2. Interestingly, subjects carrying both minor haplotypes of BCL11A ("TCA") and HMIP-2 ("CGC") showed significantly higher HbF levels than subjects carrying only the minor haplotype of BCL11A. Our novel findings suggest that HbF-boosting haplotypes of BCL11A and HMIP-2 can predict clinical outcomes and may interact to regulate HbF in patients with SCA.

7- Blood Cells, Molecules & Diseases, 98: 102703, 2022. Epub 2022 Sep 13

https://doi.org/10.1016/j.bcmd.2022.102703

Plasma immune mediators as laboratorial biomarkers for Sickle Cell Disease patients according to the hydroxyurea therapy and disease severity

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In the present work, the impact of Sickle Cell Disease (SCD) degrees of severity, as well hydroxyurea treatment on the systemic immunological signatures of patients was evaluated. Based on a high-throughput chemokine, cytokine and growth factor multiplex analysis, it was possible to obtain the systemic immunological profile of patients with SCD (n = 40), treated or not with hydroxyurea, as compared to healthy controls (n = 40). Overall, SCD patients with severe disease displayed increased levels of

almost all biomarkers analyzed. Our data demonstrated that CXCL8, CCL3 and CXCL10 were pointed out as universal biomarkers of SCD. The results also indicated that HU-untreated patients with indication of HU-therapy display a more prominent increase on plasma immune mediators in a similar way as those with severe SCD disease. Together, these findings provided a comprehensive landscape of evidence that may have implications for further therapeutic strategies and SCD clinical management.

8- Hematology, Transfusion and Cell Therapy, S2531-1379(22)01308-6, 2022.

https://doi.org/10.1016/j.htct.2022.09.1184

Analysis of the costs of the basic care line for sickle cell disease in Brazilian children under 5 years of age

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Objective: To evaluate and estimate the cost of basic care in sickle cell disease (SCD) for patients under five years of age, within the scope of the Unified Health System (SUS) and to discuss the costs related to possible complications of the disease from the literature.

Methods: The main management and conduct recommendations in the SCD up to five years of age, with healthy and baseline health status, were extracted from the Basic Guidelines of the Care Line in the SCD of the Ministry of Health. Systematic data regarding costs of medicines were extracted from the Medicine Market Regulation Chamber. The SUS Table of Procedures, Medicines and Orthotics, Prosthetics and Auxiliary Means of Movement Management System was the guide for the values of complementary exams, as well as for medical consultations. The values applied to calculate the vaccination schedule were extracted from the Pan American Health Organization, adopting the perspective of the SUS-paying costs.

Results: The total cost obtained for basic care of SCD in children up to five years of age, including the use of antibiotic prophylaxis, immunizations and the performance of transcranial Doppler ultrasound in the prevention and early detection of cerebrovascular accidents was, on average, $1020.96.

Conclusion: The cost-effectiveness of prophylaxis in SCD, up to five years of age, exceeds the expenses resulting from hospitalizations due to complications of the disease. The

study of expenses associated with SCD could be used to establish public policies, improve prevention strategies and treat the symptoms and complications of the disease.

LINHA DE PESQUISA: DOAÇÃO DE SANGUE E COMPONENTES (6 artigos)

1- Emerging Infectious Disease, 28 (4): 734-742, 2022. Epub 2022 Feb 18.

https://doi.org/10.3201/eid2804.211961

SARS-CoV-2 IgG seroprevalence among blood donors as a monitor of the COVID-19 epidemic, Brazil

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During epidemics, data from different sources can provide information on varying aspects of the epidemic process. Serology-based epidemiologic surveys could be used to compose a consistent epidemic scenario. We assessed the seroprevalence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) IgG in serum samples collected from 7,837 blood donors in 7 cities of Brazil during March–December 2020. Based on our results, we propose a modification in a compartmental model that uses reported number of SARS-CoV-2 cases and serology results from blood donors as inputs and delivers estimates of hidden variables, such as daily values of SARS-CoV-2 transmission rates and cumulative incidence rate of reported and unreported SARS-CoV-2 cases. We concluded that the information about cumulative incidence of a disease in a city's population can be obtained by testing serum samples collected from blood donors. Our proposed method also can be extended to surveillance of other infectious diseases.

2- Transfusions and Apheresis Science, 61(5): 103439, 2022. Epub 2022 Apr 1.

https://doi.org/10.1016/j.transci.2022.103439

Impact of COVID-19 on the efficacy of meeting the transfusion demand by a Brazilian blood banks network

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One of the effects of the pandemic in the hemotherapy services was the reduction in the attendance of blood donors and production of blood components. It is relevant to investigate how the capacity to meet the demand for blood components was affected, especially in blood centers located in the regions most affected by the pandemic, such as Brazil. This study aimed to describe the impact of the pandemic on the capacity to meet the demand for different types of blood components by a Brazilian blood center in 2020, compared to the historical series of 2016-2019 and to discuss the measures adopted to mitigate the effects of the pandemic. Retrospective cross-sectional study was carried out with comparative analysis of the blood components requested and attended in the period from 2016 to 2020. Data analysis was performed by Graphpad Prism 5. The spread of COVID-19 cases since March 2020 had impact on the blood components production and transfusions. The reduction in the production of blood components was observed prior to the restriction measures, in March 2020. In comparison to 2016-2019, there was a reduction in the number of transfusions performed in all months of 2020. The results suggest that the measures adopted in a Brazilian blood center to face the COVID-19 pandemic resulted in reasonable regularity in the supply of blood components. The sharing of experiences between blood banks in different regions, social and epidemiological contexts can contribute to the improvement of strategies to reduce the impact of COVID-19 in transfusion medicine.

3- Cytokine, 154: 155874, 2022. Epub 2022 Apr 4.

https://doi.org/10.1016/j.cyto.2022.155874

Pro-inflammatory immune profile mediated by TNF and IFN-γ and regulated by IL-10 is associated to IgG anti-SARS-CoV-2 in asymptomatic blood donors

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The SARS-CoV-2 virus has infected and killed millions of people, but little is known about the risk factors that lead to the development of severe, mild or asymptomatic conditions after infection. The individual immune response and the balance of cytokines and chemokines have been shown to be important for the prognosis of patients. Additionally, it is essential to understand how the production of specific antibodies with viral neutralizing capacity is established. In this context, this study aimed to identify positive individuals for IgG anti-SARS-CoV-2 in a large population of blood donors (n = 7837) to establish their immune response profile and to evaluate its viral neutralization capacity. The prevalence found for IgG anti-SARS-CoV-2 was 5.6% (n = 441), with male blood donors (61.9%) being more prevalent among the positive ones. The results showed that positive individuals for IgG anti-SARS-CoV-2 have high serum concentrations of chemokines, TNF, IFN-γ and IL-10. The analyses showed that the positivity index for IgG anti-SARS-CoV-2 is associated with the neutralizing capacity of the antibodies, which, in turn, is significantly related to lower serum concentrations of CCL5 and CXCL10. The results allow us to hypothesize that the development and maintenance of IgG anti-SARS-CoV-2 antibodies in infected individuals occurs in a pro-inflammatory microenvironment well regulated by IL-10 with great capacity for recruiting cells from the innate and adaptive immune systems.

4- Revista da Sociedade Brasileira de Medicina Tropical, 55: e0239, 2022. eCollection 2022.

https://doi.org/10.1590/0037-8682-0239-2022

A potent inflammatory response is triggered in asymptomatic blood donors with recent SARS-CoV-2 infection

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Background: The inflammatory response plays a significant role in the outcome of coronavirus disease (COVID-19).

Methods: We investigated plasma cytokine and chemokine concentrations in non-infected (NI), asymptomatic severe acute respiratory.

syndrome-coronavirus-2 (SARS-CoV-2)-infected blood donors (AS), and patients with severe COVID-19 (SC).

Results: The SC group showed significantly higher levels of interleukin 6 (IL-6), IL-10, and CCL5 than the AS and NI groups. The SC and AS groups had considerably greater CXCL9 and CXCL10 concentrations than the NI group. Only NI and infected people showed separate clusters in the principal component analysis.

Conclusions: SC, as well as AS was characterized by an inflammatory profile.

5- Vaccines (Basel), 10(9): 1437, 2022.

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Predicting SARS-CoV-2 Variant Spread in a Completely Seropositive Population Using Semi-Quantitative Antibody Measurements in Blood Donors

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SARS-CoV-2 serologic surveys estimate the proportion of the population with antibodies against historical variants, which nears 100% in many settings. New approaches are required to fully exploit serosurvey data. Using a SARS-CoV-2 anti-Spike (S) protein chemiluminescent microparticle assay, we attained a semi-quantitative measurement of population IgG titers in serial cross-sectional monthly samples of blood donations across seven Brazilian state capitals (March 2021-November 2021). Using an ecological analysis, we assessed the contributions of prior attack rate and vaccination to antibody titer. We compared anti-S titer across the seven cities during the growth phase of the Delta variant and used this to predict the resulting age-standardized incidence of severe COVID-19 cases. We tested ~780 samples per month, per location. Seroprevalence rose to >95% across all seven capitals by November 2021. Driven by vaccination, mean antibody titer increased 16-fold over the study, with the greatest increases occurring in cities with the highest prior attack rates. Mean anti-S IgG was strongly correlated (adjusted R2 = 0.89) with the number of severe cases caused by Delta. Semi-quantitative anti-S antibody titers are informative about prior exposure and vaccination coverage and may also indicate the potential impact of future SARS-CoV-2 variants.

6- Elife, 11: e78233, 2022.

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SARS-CoV-2 antibody dynamics in blood donors and COVID-19 epidemiology in eight Brazilian state capitals: A serial cross-sectional study

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Background: The COVID-19 situation in Brazil is complex due to large differences in the shape and size of regional epidemics. Understanding these patterns is crucial to understand future outbreaks of SARS-CoV-2 or other respiratory pathogens in the country.

Methods: We tested 97,950 blood donation samples for IgG antibodies from March 2020 to March 2021 in 8 of Brazil's most populous cities. Residential postal codes were used to obtain representative samples. Weekly age- and sex-specific seroprevalence were estimated by correcting the crude seroprevalence by test sensitivity, specificity, and antibody waning.

Results: The inferred attack rate of SARS-CoV-2 in December 2020, before the Gamma variant of concern (VOC) was dominant, ranged from 19.3% (95% credible interval [CrI] 17.5-21.2%) in Curitiba to 75.0% (95% CrI 70.8-80.3%) in Manaus. Seroprevalence was consistently smaller in women and donors older than 55 years. The age-specific infection fatality rate (IFR) differed between cities and consistently increased with age. The infection hospitalisation rate increased significantly during the Gamma-dominated

second wave in Manaus, suggesting increased morbidity of the Gamma VOC compared to previous variants circulating in Manaus. The higher disease penetrance associated with the health system's collapse increased the overall IFR by a minimum factor of 2.91 (95% CrI 2.43-3.53).

Conclusions: These results highlight the utility of blood donor serosurveillance to track epidemic maturity and demonstrate demographic and spatial heterogeneity in SARS-CoV-2 spread.

LINHA DE PESQUISA: DOENÇAS TRANSMISSÍVEIS POR TRANSFUSÃO E TRANSPLANTE (5 artigos)

1- Frontiers in Medicine (Lausanne), 9: 844265, 2022. eCollection 2022.

https://doi.org/10.3389/fmed.2022.844265

Prevalence and Risk Factors for Human T-Cell Lymphotropic Virus (HTLV) in Blood Donors in Brazil-A 10-Year Study (2007-2016)

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It is unknown whether HTLV-1/2 prevalence has been stable or changing with time in Brazil. We present a 10-year (2007-2016) analysis of HTLV-1/2 infection in first-time blood donors from four blood banks in Brazil. The Brazilian blood centers participating

in this multicenter Recipient Epidemiology and Donor Evaluation Study (REDS) are located in Recife in the Northeast and in São Paulo, Rio de Janeiro and Belo Horizonte located in the Southeast of the country. A previous REDS study using the same database from 2007 to 2009 showed that the prevalence per 100,000 donors was 222 in Recife, 83 in Belo Horizonte and 101 in São Paulo. From 2007 to 2016, HTLV-1/2 prevalence was calculated by year, blood center and birth cohort. Covariates included age, gender, schooling, self-reported skin color and type of donation. From 1,092,174 first-blood donations, in the general analysis, HTLV-1/2 infection predominated in females, donors over 50 years of age, black skin color and less educated. The average prevalence was 228 per 100,000 donors in Recife, 222 in Rio de Janeiro, 104 in Belo Horizonte and 103 in São Paulo. In the 10-year analysis, HTLV-1/2 prevalence was stable, but a trend was observed toward an increase in HTLV-1/2 infection among younger people ($p < 0.001$), males ($p = 0.049$), those with white skin color ($p < 0.001$), and higher education ($p = 0.014$). Therefore, this 10-year surveillance of the infection showed stable HTLV-1/2 prevalence overall but a trend toward increased prevalence among the younger and more educated donors despite Brazilian policies to control sexually transmitted infections being in place for more than 10 years.

2- Frontiers in Immunology, 13: 795815, 2022. eCollection 2022.

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A New Flow Cytometry-Based Single Platform for Universal and Differential Serodiagnosis of HTLV-1/2 Infection

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In the present work, we developed and evaluated the performance of a new flow cytometry-based single platform, referred to as "FC-Duplex IgG1 (HTLV-1/2)", for

universal and differential serodiagnosis of HTLV-1/2 infection. The proposed technology employs a system for detection of IgG1 antibodies in a single competitive immunofluorescence platform by flow cytometry using fluorescently labeled MT-2/MoT cell line mix coupled to a highly sensitive development system (Biotin/Streptavidin/Phycoerythrin). The stability of fluorescent labeling and the antigenicity of MT-2 and MoT cell lines were confirmed upon storage at -20°C for 2, 6, and 12 months. The anti-HTLV-1/2 IgG1 reactivity, expressed as percentage of positive fluorescent cells (PPFC), was evaluated for each target antigen along the titration curve of test serum samples (1:32 to 1:4,096). Upon selection of target cell line and serum dilutions with higher segregation score between groups, the performance of "FIX" and "FIX & PERM" protocols was evaluated. The "FIX" protocol presented excellent performance indices (Se = 92%/Sp = 94%/AUC = 0.96; Se = 96%/Sp = 100%/AUC = 0.99) for the universal (HTLV-1/2 vs. NI) and differential (HTLV-1 vs. HTLV-2) diagnosis of HTLV-1 infection, respectively. Optimization of the "FIX" protocol using the principle of synchronous and asynchronous pairwise analysis further improved the performance of "FC-Duplex IgG1 (HTLV-1/2)", using the "FIX" protocol for differential diagnosis of HTLV-1 and HTLV-2 infections (Se = 100%/Sp = 100%/AUC = 1.00). In conclusion, the "FC-Duplex IgG1 (HTLV-1/2)" method represents an innovation in the biotechnology segment with the potential to compose a serological kit for differential diagnosis of HTLV-1/2 infection for reference laboratories and blood centers.

3- Frontiers in Public Health, 10: 884701, 2022. eCollection 2022.

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Multi-Epitope Protein as a Tool of Serological Diagnostic Development for HTLV-1 and HTLV-2 Infections

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A multi-epitope protein expressed in a prokaryotic system, including epitopes of Env, Gag, and Tax proteins of both HTLV-1 and HTLV-2 was characterized for HTLV-1/2 serological screening. This tool can contribute to support the implementation of public policies to reduce HTLV-1/2 transmission in Brazil, the country with the highest absolute numbers of HTLV-1/2 infected individuals. The chimeric protein was tested in EIA using serum/plasma of HTLV-infected individuals and non-infected ones from four Brazilian states, including the North and Northeast regions (that present high prevalence of HTLV-1/2) and Southeast region (that presents intermediate prevalence rates) depicting different epidemiological context of HTLV-1/2 infection in our country. We enrolled samples from Pará (n = 114), Maranhão (n = 153), Minas Gerais (n = 225) and São Paulo (n = 59) states; they are from blood donors' candidates (Pará and Minas Gerais), pregnant women (Maranhão) and HIV+/high risk for sexually transmitted infection (STI; São Paulo). Among the HTLV-1/2 positive sera, there were co-infections with viral (HTLV-1 + HTLV-2, HIV, HCV, and HBV), bacterial (*Treponema pallidum*) and parasitic (*Trypanosoma cruzi*, *Schistosma mansoni*, *Strongyloides stercoralis*, *Entamoeba coli*, *E. histolytica*, and *Endolimax nana*) pathogens related to HTLV-1/2 co-morbidities that can contribute to inconclusive diagnostic results. Sera positive for HIV were included among the HTLV-1/2 negative samples. Considering both HTLV-1 and HTLV-2-infected samples from all states and different groups (blood donor candidates, pregnant women, and individuals with high risk for STI), mono or co-infected and HTLV-/HIV+, the test specificity ranged from 90.09 to 95.19% and the sensitivity from 82.41 to 92.36% with high accuracy (ROC AUC = 0.9552). This multi-epitope protein showed great potential to be used in serological screening of HTLV-1 and HTLV-2 in different platforms, even taking into account the great regional variation and different profile of HTLV-1 and HTLV-2 mono or co-infected individuals.

4- Journal of Medical Virology, 94: 5535–5542, 2022. Epub 2022 Jul 29

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Decline in human T-cell lymphotropic virus seroprevalence in blood donors from Minas Gerais, Brazil over a 12-year period (2006-2017)

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To investigate a 12-year historical series (2006-2017) of human T-cell lymphotropic virus (HTLV)-positive blood donations from Fundação Hemominas, Minas Gerais, Brazil, an observational retrospective study was performed to evaluate data of blood donor candidates who were screened for HTLV-1/2 by enzyme-linked immunosorbent assay or chemiluminescence assays and confirmed by Western blot. We analyzed 3 309 716 blood donations covering 2006-2017 that were extracted from the institutional database. In a total of 3 308 738 donations that have complete algorithm tests, the global frequency of HTLV-positive donations was 0.012%. The seroprevalence in first-time blood donors was 28.82/100 000 donors; 0.95/100 000 donations were HTLV-positive in repeat blood donors. The frequency of HTLV-seropositive females was significantly higher than males (odds ratio = 1.85, $p < 0.001$) in first-time donors. The median age of HTLV-positive first-time and repeat donors was similar (36 and 32 years, respectively). First-time donors ≥41 years had higher odds to be infected. There was a clear tendency of decline in the HTLV-positive donations in the period analyzed, going from 19.26/100 000 donations to 8.50/100 000 donations. The increase in the proportion of repeat donors over the period analyzed (from 23% in 2006 to 67% in 2017) must be the principal factor that contributed to this drop. Our results showed a continuous decline in the frequency of HTLV-positive donations from Minas Gerais, Brazil throughout 12 years and emphasize the importance of having a high rate of repeat donors in blood centers to reduce the residual risk of transfusion-transmitted infections.

5- The Journal of Infectious Disease. 2022 Jun 11

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Surveillance for Zika, chikungunya and dengue virus incidence and RNAemia in blood donors at four Brazilian blood centers during 2016-2019

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Background: Except for public health case reports, the incidence of Zika virus (ZIKV), chikungunya virus (CHIKV) and dengue virus (DENV) infection are not available to assess the potential blood transfusion safety threat in Brazil.

Methods: Pools of 6 donation samples (MP6) left over from HIV, HBV, and HCV nucleic acid testing were combined to create MP18 pools (3 MP6 pools). Samples were tested using the Grifols triplex ZIKV, CHIKV and DENV real-time transcription mediated amplification assay to estimate prevalence of RNAemia, incidence, and to compare these results to case reports in São Paulo, Belo Horizonte, Recife and Rio de Janeiro, from April 2016 - June 2019.

Results: ZIKV, CHIKV and DENV RNAemia were found from donors who donated without overt symptoms of infection that would have led to deferral. The highest RNAemic donation prevalence was (1.2%, 95% CI 0.8-1.9) for DENV in Belo Horizonte in May 2019. Arbovirus infections varied by location, time of year, and were not always aligned with annual arbovirus outbreak seasons in different regions of the country.

Conclusions: Testing donations for arboviruses in Brazil can contribute to public health. Transfusion recipients were likely exposed to ZIKV, CHIKV, DENV viremic blood components during the study period.

LINHA DE PESQUISA: COAGULOPATIAS (2 artigos)

1- Journal of Thrombosis and Haemostasis, 20(11): 2526-2537, 2022. Epub 2022 Sep 26.

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Time between inhibitor detection and start of immune tolerance induction: Association with outcome in the BrazIT study

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Background: Immune tolerance induction (ITI) is the treatment of choice for eradication of anti-factor VIII (FVIII) neutralizing alloantibodies (inhibitors) in people with inherited hemophilia A and high-responding inhibitor (PwHA-HRi). The association between ITI outcome and time elapsed between inhibitor detection and start of ITI (Δtinhi-ITI) is debatable.

Objective: The aim of this study was to evaluate this association among a large cohort of severe PwHA-HRi.

Methods: Severe (factor VIII activity level <1%) PwHA-HRi on ITI (n = 142) were enrolled in 15 hemophilia treatment centers. PwHA-HRi were treated according to the Brazilian ITI Protocol. ITI outcomes were defined as success (i.e., recovered responsiveness to

exogenous FVIII) and failure (i.e., no responsiveness to exogenous FVIII and requirement of bypassing agents to control bleeding).

Results: Median ages at inhibitor detection and at ITI start were 3.2 years (interquartile range [IQR], 1.6-8.1) and 6.9 years [IQR, 2.6-20.1), respectively. PwHA-HRi were stratified according to Δtinhi-ITI quartiles: first (0.0-0.6 year), second (>0.6-1.7 year), third (>1.7-9.2 years), and fourth quartile (>9.2-24.5 years). The overall success rate was 65.5% (93/142), with no difference among first, second, third, and fourth quartiles (62.9%, 69.4%, 58.3%, and 71.4%, respectively) even after adjusting the analyses for potential confounders.

Conclusion: In conclusion, delayed ITI start is not associated with failure of ITI in PwHA-HRi. Therefore, ITI should be offered for these patients, regardless of the time elapsed between the detection of inhibitor and the ITI start.

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Phenotypic variation in severe hemophilia A is related to endogenous thrombin potential and plasma levels of factor VII

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Hemophilia A is a bleeding disorder caused by deficiency or low activity of circulating factor VIII characterized by prolonged blood coagulation time and often spontaneous bleeding. Patients with the severe form of the disease may present considerable heterogeneity in the occurrence of bleeding episodes and some of them have a mild hemophilia A phenotype. This study aimed to evaluate the association of biomarkers and coagulation parameters to the differential hemorrhagic profile of severe hemophilia A patients. Polymorphisms in the genes of proteins C and S, factors V and VII and prothrombin were evaluated in a group of severe hemophilia A patients with a broad spectrum of bleeding profile. Plasma levels of coagulation factors and thrombin generation were also analyzed. This study included 59 Brazilian hemophilia A patients who were allocated into low bleeding profile (LBP; n=33) and high bleeding profile (HBP; n=26) groups based on their joint and muscle bleeding episodes requiring treatment in the 5 years before inclusion in the study. Results evidenced that endogenous thrombin potential (ETP) and plasma factor VII levels were significantly higher in the LBP group.

Results indicate a prominent importance of FVII plasma activity and endogenous thrombin potential on the differential bleeding phenotype of hemophilia A patients.

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Clinical-epidemiology aspect of inpatients with moderate or severe COVID-19 in a Brazilian macroregion: disease and countermeasures

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COVID-19, also known as coronavirus disease 2019, is an infectious viral disease caused by SARS-CoV-2, a novel coronavirus. Since its emergence, its epidemiology has been explored; however, for some regions of the world, COVID-19's behavior, incidence, and impact remain unclear. In continental nations like Brazil, this lack of knowledge results in nonuniform control, prevention, and treatment measures, which can be controversial in some locations. This study aimed to describe the epidemiological profile of patients with COVID-19 in the macroregion of Triângulo Sul in the state of Minas Gerais (MG), Brazil. Between March 25 and October 21, 2020, data were collected and statistically analyzed from 395 hospitalized patients in the city of Uberaba, MG, suspected to have

moderate or severe forms of the disease. Of the 395 suspected cases, 82% were confirmed to be positive for COVID-19. The mean age of positive patients was 58.4 years, and 60.76% were male. Following these patients throughout their hospitalization, a mortality rate of 31.3% was observed. In the population positive for COVID-19, the risk of death increased by 4% for each year of the patient's age. Likewise, the older the patient, the longer their hospitalization and the higher the risk of developing acute respiratory failure. Among the treatments tested in patients, heparin was associated with protection against mortality, and the absence of anticoagulant use was linked to a more than six times greater risk of death. Finally, comorbidities in patients with COVID-19 were positively correlated with increased hospitalization time. In summary, this study revealed that age, presence of comorbidities, length of hospitalization, and drug treatment considerably altered COVID-19's lethality. To understand infection rates and the factors involved in COVID-19's lethality, knowledge of the local epidemiology is necessary.