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Total de artigos publicados em 2021: 16

LINHA DE PESQUISA: HEMOGLOBINOPATIAS (5 artigos)

1- Annals of Hematology, 100(2): 375-382, 2021. Epub 2021 Jan 6.

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ADAMTS-13-VWF axis in sickle cell disease patients

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Sickle cell disease (SCD) comprises a group of genetic disorders characterized by the presence of the hemoglobin (Hb) S in homozygosis or in heterozygosis with some other Hb variant or in interaction with thalassemia. SCD is characterized by a very complex pathophysiology, which determines a wide variability of clinical manifestations, including a chronic state of hypercoagulability responsible for the increased risk of thromboembolic events. ADAMTS13 and von Willebrand factor (VWF) play an important role in arterial and venous thrombosis. Thus, the aim of this study was to understand how the ADAMTS13-VWF axis behaves in sickle cell disease, as well as whether there is an association of these markers with the use of hydroxyurea (HU). This is a cross-sectional study conducted with 40 patients diagnosed with SCD and 40 healthy individuals. The analysis of the ADAMTS13-VWF axis was comparatively performed between groups of patients and controls and, afterwards, between patients with SCD who were users and non-users of HU. ADAMTS13 activity, ADAMTS13 activity/VWF:Ag, and ADAMTS13:Ag/VWF:Ag ratios were significantly lower and VWF:Ag levels significantly higher in SCD patients when compared to the controls. There was no statistically significant difference in ADAMTS13:Ag and VWF collagen binding (VWF:CB) levels between the groups evaluated. Among the categories of HU use, there was no

statistically significant difference in any of the evaluated markers. As a conclusion, we could observe that the ADAMTS13-VWF axis is altered in SCD when compared to healthy individuals and that there is no association between these markers and the use of HU.

2- Hematology, Transfusion and Cell Therapy, 44(4):478-484, 2022. Epub 2021 Jun 18.

https://doi.org/10.1016/j.htct.2021.05.001

Follow-up of children with sickle cell anemia screened with transcranial Doppler and enrolled in a primary prevention program of ischemic stroke

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Background: Stroke is a serious complication of sickle cell anemia (SCA). The transcranial Doppler (TCD) is the risk-screening tool for ischemic strokes. The objective of the study was to describe the clinical progression of children with SCA who presented with high risk for stroke by TCD or relevant changes by magnetic resonance angiography (MRA) and underwent the regular transfusion program (RTP) and/or hydroxyurea (HU) treatment between 2007 and 2018.

Method: This was a neonatal retrospective/prospective cohort study with children born between 1999 and 2014 with the homozygotic form (HbSS) or $S\beta^0$-thalassemia who underwent TCD at least once.

Results: Of the 718 children screened during this period, 675 had HbSS and 43 $S\beta^0$-thalassemia. In 54 children (7.5%), all with HbSS, a high-risk TCD (n = 45) or, when the TCD was inconclusive, an MRA with cerebral vasculopathy (n = 9) was used for detection. Of these, 51 started the RTP and the families of three refused treatment. Of the 43 children with a high-risk TCD who initiated the RTP, 29 (67.4%) reverted to low risk. In 18 of them (62%), HU was started at the maximum tolerated dose (MTD) before transfusion discontinuation. None of these 29 patients had a stroke. Eight children (18.6%) maintained a high-risk TCD, even using the RTP/HU and two had a stroke.

Conclusions: The TCD was confirmed as a viable tool for tracking patients with a risk for stroke. The RTP was effective in preventing the primary event. New strategies are necessary to prevent stroke using HU and new drugs, in addition to bone marrow transplantation.

3- Biomarkers in Medicine, 15(12): 999-1009, 2021. Epub 2021 Jul 22.

https://10.2217/bmm-2020-0769

Novel kidney injury biomarkers in a large cohort of children with sickle cell anemia

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Aim: The aim of this study was to compare novel kidney injury biomarkers in sickle cell anemia (SCA) children with and without albuminuria or glomerular hyperfiltration. Materials & methods: A total of 358 Brazilian children with SCA were studied. Fifteen kidney injury biomarkers in urine were measured. Albuminuria was defined as urine albumin/creatinine ratio >100 mg/g. Glomerular hyperfiltration was defined as estimated glomerular filtration rate ≥140 ml/min/1.73 m2. Results: After adjustment for age, sex and modifying therapies in use, EGF and collagen IV urinary levels were associated with albuminuria. Renin and clusterin levels were associated with hyperfiltration. Conclusion: Levels of novel kidney injury biomarkers were associated with albuminuria and hyperfiltration in Brazilian children with SCA, suggesting concomitant structural and functional abnormalities.

4- Annals of Hematolology, 101(2): 273-280, 2022. Epub 2021 Oct 19.

https://doi.org/10.1007/s00277-021-04695-6

Endothelial dysfunction biomarkers in sickle cell disease: is there a role for ADMA and PAI-1?

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Within the spectrum of sickle cell disease (SCD) are sickle cell anemia (SCA), presence of hemoglobin SS (HbSS), hemoglobin SC disease (HbSC), and sickle cell β-thalassemia (Sβ-thal). Asymmetric dimethylarginine (ADMA) competitively inhibits the binding of arginine to NOS, reducing NO production. In patients with HbSS, increased levels of ADMA have been reported, as well as changes in many hemostatic biomarkers, including the plasminogen activator inhibitor type 1 (PAI-1). We hypothesized that high levels of ADMA and PAI-1 may be associated with more severe SCD. Thus, ADMA and PAI-1 levels were determined in 78 individuals including 38 adult patients with SCD and 40 control subjects. Higher levels of ADMA were shown in HbSS and Sβ-thal patients compared to controls. Concerning PAI-1, all patients showed high levels of PAI-1 compared to controls. As a role of NO in the pathogenesis of SCD has already been established, we concluded that high levels of ADMA should compromise, at least in part, NO synthesis, resulting in endothelial dysfunction. Elevated plasma levels of PAI-1 in all patients may indicate not only endothelial dysfunction but also a hypofibrinolytic state favoring thrombotic complications. Finally, high levels of ADMA and PAI-1 may be associated with more severe SCD.

5- Hematology, Transfusion and Cell Therapy, 44(2): 169-176, 2022. Epub 2021 Dec 5

https://doi.org/10.1016/j.htct.2020.09.152

Association between inflammatory molecules, nitric oxide metabolites and leg ulcers in individuals with sickle cell anemia

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Introduction: Leg ulcers (LUs) are relatively common in patients with sickle cell anemia (SCA). The role of inflammation and nitric oxide (NO) pathways in the pathophysiology of the LU is not understood.

Objective: The aim of this study was to verify the association between inflammatory molecules and nitric oxide metabolites (NOx) and the occurrence of the LU in patients with SCA.

Method: It was a cross-sectional study on adult participants with SCA followed at Fundação Hemominas, a public blood center in Brazil. Eligible participants were recruited and included in one of two groups: Group 1, comprised of cases with SCA (Hb SS) and at least one LU at the time of inclusion in the study and Group 2, comprised of controls with SCA without a history of LU, matched by sex and age to cases. Participants were interviewed to obtain sociodemographic data and blood samples were collected. Clinical and laboratory data were abstracted from medical records. Nitric oxide metabolites (NOx) and inflammatory molecules were quantified using an immunoassay and Multiplex xMAP® technology, respectively. Eighty-seven individuals were included, ranging in age from 17 to 61 years (mean 40 ± 10.7 years); 30 had LU and 57 were controls without LU.

Results: Participants with LU had significantly higher levels of interleukin 8 (IL-8), IL-10, IL-15, NOx and platelet and white blood cell (WBC) counts, when compared to those without LU. Participants with LU had a significantly higher risk of having a history of osteomyelitis and a higher use of antiseptic soap in bathing, when compared to those without LU.

Conclusion: In conclusion, our results showed that NOx, inflammatory molecules and hematological features were associated with LU in Brazilian adults with SCA.

LINHA DE PESQUISA: COAGULOPATIAS (4 artigos)

1- Thrombosis and Haemostasis, 121(7): 891-899, 2021. Epub 2021 Jan 10.

https://doi.org/10.1055/s-0040-1722353

Effect of the First Factor VIII Infusions on Immunological Biomarkers in Previously Untreated Patients with Hemophilia A from the HEMFIL Study

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Hemophilia A (HA) is an inherited bleeding disorder which requires continuous replacement with factor (F) VIII concentrate. The main complication of HA is the development of neutralizing alloantibodies which inhibit FVIII activity (inhibitors). The objective of this study was to investigate the effect of the first FVIII infusions on immunological biomarkers in previously untreated patients with HA. Plasma samples were collected at enrollment before any FVIII infusion (T0) and at inhibitor development (INB +/T1) or up to 35 exposure days without inhibitors (INB -/T1). Anti-FVIII antibodies (immunoglobulin M, immunoglobulin G [IgG] 1, IgG3, and IgG4), chemokines (CCL2, CCL5, CXCL8, CXCL9, and CXCL10), and cytokines (interleukin [IL]-2, IL-4, IL-6, IL-10, interferon-γ, tumor necrosis factor, and IL-17) were assessed. A total of 71 children with severe HA were included, of whom 28 (39.4%) developed inhibitors. Plasma levels of anti-FVIII IgG4, IL-6, and CXCL8 were higher at INB +/T1 when compared with INB -/T1. This group presented a mixed cytokine profile and higher plasma levels of CXCL9 and CXL10 when compared with INB +/T1. We conclude that exposure to FVIII triggers a proinflammatory response mediated by IL-6 and CXCL8 in patients with HA who developed inhibitors. Regardless of inhibitor status, the immune system of all HA patients is stimulated after infusions of FVIII.

2- Journal of Patient Safety, 17(4): e262-e263, 2021.
https://doi.org/10.1097/pts.0000000000000823

Training program for home therapy of people with Factor XIII deficiency

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No abstract available

3- Blood Coagulation & Fibrinolysis, 32(7): 443-450, 2021.

https://doi.org/10.1097/MBC.0000000000001057

Risk factors for antibody formation in children with hemophilia: methodological aspects and clinical characteristics of the HEMFIL cohort study

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Up to 35% of patients with hemophilia A and 5% with hemophilia B develop neutralizing antibodies which can inhibit the therapeutic activity of factor replacement (inhibitors). Despite the clinical relevance of antifactor VIII and IX neutralizing antibodies, there is still a major gap on the knowledge of risk factors for their development. Furthermore, most of the studies on risk factors for inhibitor development come from Caucasian and Afro-American populations. The HEMFIL is a Brazilian prospective cohort study of previously untreated children with hemophilia, which primary aim is to identify new risk factors related to inhibitor development. This manuscript aims at describing the study design and its methodology. After the diagnosis, children are followed up to 75 exposure days or to inhibitor development. Standardized forms and blood samples are collected to describe clinical characteristics and to perform the measurement of immunological and genetic biomarkers at three time points; Inclusion time (T0), at inhibitor development or at 75 exposure days without inhibitors (T1) and after immune tolerance induction for patients in whom it is indicated and performed (T2). Currently, 120 children have been included, of whom, 95 have completed the follow-up. For severe/moderately severe hemophilia A, the cumulative incidence of inhibitors at 75 exposure days was 35% (95% confidence interval, 26-46%). The inclusion of additional patients and a longer follow-up will allow the analysis of risk factors for inhibitor development.

4- PLoS One, 16(8): e0256265, 2021.

https://doi.org/10.1371/journal.pone.0256265

Predictors of the outcome of immune tolerance induction in patients with haemophilia A and inhibitors: The Brazilian Immune Tolerance (BrazIT) Study protocol

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The development of inhibitors is the main complication of haemophilia A (HA) treatment. Immune tolerance induction (ITI) is the treatment of choice for inhibitor eradication. We describe the methodology of the Brazilian Immune Tolerance Induction (BrazIT) Study, aimed to identify clinical, genetic, and immune biomarkers associated with response to ITI and inhibitor recurrence. This cohort study includes people with HA (PwHA) and inhibitors (a) who require bypassing agents to treat and/or prevent bleeding, and (b) who are at any stage of ITI treatment. Patients are included in each haemophilia treatment centre (HTC). Factor VIII (FVIII) and inhibitor assessments are performed at local laboratories of each HTC. The ITI regimen followed the national protocol of the Brazilian Ministry of Health. All PwHA starts with low-dose ITI (50 IU/kg three times weekly); high-dose regimen (100 IU/kg daily) is used if there is lack of response to the low-dose ITI. Outcomes are classified as total or partial success, and failure. Standardized case report forms with clinical, laboratory, and treatment data are collected from medical files and interviews. Blood samples are collected for genetic and immune biomarkers at the time of inclusion in the study and at the end of ITI. The study is ongoing and, currently, 202/250 (80.8%) PwHA from 15 HTCs have been included. BrazIT Study is the largest cohort of PwHA and inhibitor under treatment with the same ITI regimen reported to date. This study is likely to contribute with novel predictors of ITI response.

LINHA DE PESQUISA: DOAÇÃO DE SANGUE E COMPONENTES (3 artigos)

1- Hematology, Transfusion and Cell Therapy, 44(3): 336-340, 2022. Epub 2021 Jan 27.

https://doi.org/10.1016/j.htct.2020.11.009

Hemoglobin S identification in blood donors: A cross section of prevalence

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Introduction: In Brazil, the sickle cell trait (SCT) has an average prevalence of 4% in the general population and 6-10% among Afro-descendants. Although SCT is highly prevalent, a large segment of the population ignores their status. The Therapeutic Guidelines prohibit the transfusion of SCT red blood cells into patients with hemoglobin disorders or severe acidosis and newborns.

Methods: This was a cross-sectional study with data from 37,310 blood donation candidates. The study included only eligible first-time donors qualified to be tested for the presence of hemoglobin S (HbS) at the Fundação Hemominas Juiz de Fora, Brazil. The variables studied were gender, skin color, age, type of donation, place of birth, blood type, result of the solubility test for hemoglobin S (HbST) and hemoglobin electrophoresis (HbEF). Statistical analysis was performed using the Q square test and the Kappa index of agreement for comparing biochemical methods. This project was approved by the National Research Ethics Committee.

Results: The analysis of first-time donor data showed that 7166 were considered eligible. A total of 127 of the 7166 donors were carriers of SCT (1.77%). Among the blood donors, 73.23% were from the local area. The HbST and HbEF were found to be 100% in concordance. Sensitivity was not tested in the present study.

Conclusions: The HbST is highly specific for identifying the HbS, but sensitivity was not tested in this study. The screening of blood donors for abnormal hemoglobins is useful, helping to detect and counsel heterozygous people. The study seeks to identify the prevalence of SCT in a region of Brazil.

2- Transfusion, 61(7):2137-2145, 2021. Epub 2021 Jun 10.

https://doi.org/10.1111/trf.16406

Analysis of current SARS-CoV-2 infection in a large population of blood donors evidenced that RNAemia is rare in plasma

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Background: Transmission of SARS-CoV-2 by asymptomatic individuals and by blood transfusion are important issues to understand in order to control the viral spread. In this work, we estimated the current SARS-CoV-2 infection rate in blood donors from Belo Horizonte, Brazil.

Study design and methods: Saliva and blood samples were collected from 4103 blood donors from June 15 to September 30, 2020. Saliva samples were tested by real-time RT-PCR for SARS-CoV-2 in mini-pools of four samples. Individual samples were tested for positive or inconclusive pools, and positive donors had their plasma tested.

Results: Twenty-seven (0.66%) blood donors were positive for SARS-CoV-2 in their saliva, but their plasma was negative, except for one, who presented a high viral load in saliva and nasopharyngeal samples and RNAemia in the plasma close to the limit of detection. Fourteen (56%) positive blood donors reported mild symptoms related to COVID-19 after donation, but the viral load levels were not statistically different between symptomatic and asymptomatic individuals.

Discussion: Despite the measures taken by Blood Centers to avoid blood donors with SARS-CoV-2 infection, asymptomatic or presymptomatic carriers are able to donate. The risk of the virus transmission by transfusion seems to be negligible since plasma RNAemia was seen at a very low level in only one (3.7%) of the positive donors, but other studies must be performed to confirm this finding.

3- Hematology, Transfusion and Cell Therapy, 44(4):526-534, 2022. Epub 2021 Dec 28.

https://doi.org/10.1016/j.htct.2021.09.021

Blood donor candidates and blood donations performed between 2005 and 2019 in Minas Gerais, Brazil: A time series analysis

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Introduction: Time series studies related to blood donor candidates and blood donations are rare in Brazil. Population aging suggests a better understanding of the context related to blood donor candidates and blood donations performed. Objective: The monthly series of candidates eligible to donate blood and actual donations between 2005 and 2019 at the Hemominas Foundation, Minas Gerais, Brazil, were described and analyzed. Methods: Ten time series were constructed of blood donor candidates and blood donations. Each series covered the period from January 2015 to December 2019. The stationarity of the series was verified by the unit root test; the data distribution, by the Shapiro-Wilk test; the trend, by the Cox-Stuart test, and; the seasonality, by the Fisher's test (significance levels of 10% for the first test and 5% for the last three). Results: All series were identified as non-stationary and presented trend and seasonality components. The rate of blood donor candidates and the rate of blood donations performed evidenced a positive upward trend until the last two-year analysis, when a drop occurred, from 1.75% and 1.42% in 2017 to 1.64% and 1.35% in 2019, respectively. The rate of blood donations trended downward, from 0.054% in 2005 to 0.046% in 2019. The proportion of unsuitable or unretained candidates reduced. Conclusion: The study emphasized the need to stimulate blood donation by specific groups and increase ways to reduce the demand for blood components through the implementation of programs that expand alternatives to blood transfusions.

LINHA DE PESQUISA: DOENÇAS TRANSMISSÍVEIS POR TRANSFUSÃO E TRANSPLANTE (3 artigos)

1- Transfusion Medicine, 31: 104-112, 2021. Epub 2021 Mar 4.

https://doi.org/10.1111/tme.12766

HIV primary drug resistance and associated HIV risk factors among HIV positive blood donors in Brazil from 2007 to 2017

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Background: Acquisition of HIV primary drug resistant (PDR) infection can lead to poor virologic and clinical outcomes in individuals and hampers public health efforts in epidemic control. Monitoring PDR in HIV-positive blood donors can be used to inform nationwide trends in the spread of drug-resistant HIV strains.

Methods: We conducted a cross-sectional study using genetic sequence analysis to assess HIV pol sequences, PDR, and risk factors for infection using audio computer-assisted structured interviews in four large blood centers in Brazil from 2007 to 2017.

Results: Of 716 HIV-positive blood donors, 504 (70.4%) were successfully sequenced. HIV clade B (73.2%) was the most prevalent subtype, followed by a mix of non-B (21.2%) sub-types. A twofold increase (from 4% to 8%) in recombinants prevalence was observed during the study period. Sixty-four (12.7%) presented PDR. Overall, HIV PDR prevalence remained stable during the study period. Drug resistance mutations for non-nucleoside reverse transcriptase inhibitors were found in 39 (7.7%) donors, while for nucleoside reverse transcriptase inhibitors were found in 26 (5.1%), and for protease inhibitors in 24 (4.8%) of HIV-infected donors. We did not find statistically significant differences in demographics, behavioural risk factors, or HIV genotypes when comparing volunteers with and without PDR.

Conclusion: The HIV PDR rate among donors remained stable during the study period. HIV-positive blood donors can be an informative population to monitor primary HIV resistance and ultimately may help to increase the knowledge and awareness of HIV risk factors and PDR.

2- Brazilian Journal of Infectious Disease, 25(5):101631, 2021. Epub 2021 Oct 14.

https://doi.org/10.1016/j.bjid.2021.101631

Prevalence of infection by human T Cell lymphotropic viruses (HTLV-1/2) in adult population in Vitória-ES

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Introduction: Brazil has a high number of HTLV-1/2 infections which are unequally distributed in the country. Most prevalence studies have focused on specific populations, such as blood donors and pregnant women. Some areas, for example the state of Bahia, have robust information about HTLV-1/2 infection, however there is no information available about this infection in the general population of Vitória, Espírito Santo, Brazil.

Objective: To determine the prevalence of HTLV-1/2 infection in adults from the municipality of Vitoria, ES.

Methods: A cross sectional study was performed from September 2010 to December 2011, in individuals of both sexes, aged 18 or older living in Vitória-ES. Venous blood samples were collected and tested for anti-HTLV-1/2 antibodies by chemiluminescent immunoassay (CMIA). Individuals with CMIA reactive results were submitted to a new blood collection for retesting by CMIA, followed by PCR to confirm infection and discriminate the viral type.

Results: From 1502 tested samples, eight were reactive in CMIA and all were confirmed by PCR. Therefore, the prevalence of HTLV-1/2 was 0.53% (8/1502, 95% CI: 0.2-1.0%). The infection rate was 0.7% in men (5/711, 95% CI: 0.17-1.51%), and 0.38% in women (3/791, 95% CI: 0-0.81%).

Conclusions: The prevalence of HTLV-1/2 infection was 0.53% (8/1502; 95% CI: 0.2-0.9%). Confirmatory test using real-time PCR (qPCR) identified seven individuals positive for HTLV-1 and one for HTLV-2. Considering the risk of infected individuals to develop high morbidity and mortality diseases, it would be important to implement public health policies aimed at stopping transmission of these viruses in this municipality.

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HCV infection in hemophilia A patients is associated with altered cytokines and chemokines profile and might modulate the levels of FVIII inhibitor

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Prevalence of hepatitis C virus (HCV) is high in hemophilia A patients and development of FVIII inhibitor is another challenge in the management of these individuals. The influence of HCV infection in the occurrence of inhibitors was investigated to the comparison of clinical and laboratorial data from non-infected (NI, n=96) and chronically HCV-infected (HCV, n=58) hemophilia A patients. Concentrations of plasmatic cytokines (IL-2, IL-4, IL-6, IL-10, TNF, IFN-γ, IL-17A) and chemokines (CCL2, CCL5, CXCL8, CXCL9, CXCL10) were quantified from patients' samples. The results showed that older age, use of cryoprecipitate and fresh frozen plasma and severe hemophilia were associated with HCV infection, whereas exclusive use of virus inactivated clotting factors was a protector factor to acquiring HCV infection. HCV infection was strongly associated with low levels of inhibitor (OR=20.53, p<0.001). Patients with history of inhibitor (INB+) presented a mixed immune profile characterized by higher levels of pro- and anti-inflammatory cytokines than those without history of inhibitor (INB-). Highest levels of CCL2 and CXCL8 were seen in HCV^{INB-}, whereas CXCL9 and CXCL10 in HCV^{INB+}. Heatmap analysis of the set of cytokines and chemokines concentration distributed HCV patients in two distinct clusters, HCV^{INB+} and HCV^{INB-}, both characterized by low concentrations of IL-4, while non-infected patients were grouped in a single block regardless inhibitor development history ($NI^{INB-/INB+}$). This finding suggests that the strong association between HCV infection and low levels of factor VIII inhibitors might be due to the modulation of the cytokine and chemokine network established by the antiviral response.

LINHA DE PESQUISA: TRANSPLANTES, ENXERTOS E TERAPIA CELULAR (1 artigo)

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Influence of laboratory procedures on post thawing cell viability and hematopoietic engraftment after autologous peripheral blood stem cell transplantation

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Background: The kinetics of hematopoietic recovery after autologous stem cell transplantation (ASCT) may be affected by laboratory procedures. The aim of this study was to evaluate the influence of characteristics of the cryopreserved units of peripheral blood stem cells (PBSC) on postthawing cell viability and engraftment outcomes after ASCT.

Study design and methods: This was a retrospective cohort study including individuals referred for ASCT. Cryopreservation was conducted at a single processing facility between 2014 and 2019, and patients received clinical care at six transplant centers. Covariates and outcome data were retrieved from participants' records.

Results: The study population comprised 619 patients (345 [55.7%] male). Median age was 53 years. Multiple myeloma was the most common diagnosis (62.7%). Higher preapheresis CD34+ cell count, lower nucleated cell (NC) concentration per cryobag, and composition of the cryoprotectant solution (5% dimethyl sulfoxide [DMSO] and 6% hydroxyethyl starch) were statistically significantly associated with higher postthawing cell viability. The linear regression model for time to neutrophil and platelet engraftment included the infused CD34+ cell dose and the composition of the cryoprotectant solution. Patients who had PBSC cryopreserved using 10% DMSO solution presented six times higher odds (odds ratio [OR] = 6.9; 95% confidence interval [CI]: 2.2-21.1; p = .001) of delayed neutrophil engraftment (>14 days) and two times higher odds (OR = 2.3, 95%CI: 1.4-3.7; p = .001) of prolonged hospitalization (>18 days).

Discussion: The study showed that mobilization efficacy, NC concentration, and the composition of the cryoprotectant solution significantly affected postthawing cell viability. In addition, the composition of the cryoprotectant solution significantly impacted engraftment outcomes and time of hospitalization after ASCT.