CLINICAL, BIOLOGICAL AND HISTOPATOLOGICAL ASPECTS OF DIALYSIS VASCULAR ACCESS FAILURE

PhD KALLER RÉKA
PhD Coordinator: Prod. Dr. Suciu Bogdan Andrei

Background: Autologous native arteriovenous fistula (AVF) created in the non-dominant arm is the gold standard vascular access for dialysis in end-stage renal disease, but the post-surgical vascular access dysfunction causes a reduction in the patient's quality of life. Dysfunction of vascular access has remained one of the leading causes of aggravation of the disease and increase in mortality in hemodialysis patients, in this context a functional arteriovenous fistula remains the dialysis patient's lifeline. In planning vascular access, it is necessary to check the diameters of the venous and arterial components for satisfactory long-term results. Furthermore some studies describe the role of intimal hyperplasia in AVF disfunction.

Objective: This study aims to verify the predictive role of inflammatory biomarkers (the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), systemic inflammatory index (SII), and C-reactive protein (PCR)), Ca-P product, the prognostic nutritional index (PNI), and the diameters of the vessels in the failure of AVF maturation. On the other side this study aims to discuss the predictive role of some systemic inflammatory biomarkers (NLR, PLR, SII, IL-6), intimal hyperplasia, and neoangiogenesis (CD31-positive relative surface) and inflammatory cells infiltration (CD-68 positivity) in AVF maturation failure. These hypothesises were demonstrated by two prospective studies.

Method: The present study was designed as an observational, analytical, and prospective cohort study, and included 125 patients with a diagnosis of Chronic Kidney Disease in stage IV and V with an indication of arterio-venous fistula. The exclusion criteria were as follows: ESRD patients who had already had an AVF, an active tumoral status, sepsis, hematological diseases, a personal history of a major surgery in the previous six months, and autoimmune diseases. Furthermore, patients with no palpable thrill at the level of anastomosis immediately after AVF construction and patients with no sign of permeability at the level of AVF at 4 and 8 weeks of follow-up were also excluded.

Physical and Doppler ultrasound exams as well as blood tests were conducted before surgery. During the surgical creation of AVF a circumferential venous segments were collected. The microscopic examination followed the most important vascular remodeling changes: focal or diffuse intimal hyperplasia, media hypertrophy, intima/media neovascularization, mononuclear inflammatory infiltrate around the vessels in the adventitia, foci of microcalcification, and the presence of intraluminal thrombi. The endothelial layers of neoformed vessels at the intima and media thickness and the chronic inflammatory cell population were visualized via immunohistochemistry using anti-CD31 respectiv anti-CD68 mouse monoclonal antibody

The patients included were divided into two groups based on their AVF maturation status at 8 weeks: "Maturation" (Group 1) and "Failed Maturation" (Group 2).

Results: Of the patients, 76 were male (60.80%) and the mean age was 61.64 ± 13.81 (21–84). As for the performed surgical procedures, an RC-AVF was chosen in 64 cases (51.2%) and a BC-AVF was chosen in 61 cases (48.8%). In the first 6 weeks, 22 AVFs suffered early thrombosis and 10 patients died. The 22 thrombosed AVFs were surgically revised as follows: a successful thrombectomy was performed on 16, while the other 6 patients required an additional enlargement angioplasty using bovine pericardium at the anastomosis level to achieve a palpable thrill. Of these patients, 13 reached maturation in the end, while 9 required the performance of a novel AVF.

Regarding the laboratory findings, patients in the Failed-Maturation group had higher neutrophil ($p < 0.0001$), serum phosphorous ($p < 0.0001$), Ca-P product ($p < 0.0001$), CRP ($p < 0.0001$), NLR ($p < 0.0001$), PLR ($p < 0.0001$), and SII ($p < 0.0001$) values as well as lower lymphocyte ($p < 0.0001$), serum albumin ($p < 0.0001$), serum calcium ($p < 0.0001$), and PNI ($p < 0.0001$) values. Regarding vessel diameter, in the Failed-Maturation group lower vessel diameters were found for both for RC-AVFs and BC-AVFs. Moreover, there were higher incidences of early thrombosis ($p = 0.0001$) and mortality ($p = 0.008$). However, the overall maturation rate was higher in the BC-AVF group . The multivariate analysis showed that a baseline value of NLR > 4.90 predicts AVF maturation failure (OR: 22.65; 95% CI: 8.32–61.67; $p < 0.001$) and early thrombosis (OR: 9.57; 95% CI: 3.21–28.45; $p < 0.001$), whereas an NLR > 5.83 predicts short-term mortality (OR: 19.0; 95% CI: 3.75–96.27; $p < 0.001$). Furthermore, a PLR > 172.29 value is a predictor of maturation failure (OR: 6.68; 95% CI: 2.85–15.63; $p < 0.001$), a PLR > 181.72 is a predictor of early thrombosis (OR: 6.80; 95% CI: 2.42–19.09; $p < 0.001$), and a PLR > 212.89 is an independent predictor of short-term mortality (OR: 16.9; 95% CI: 3.35–85.24; $p < 0.001$). A preoperative value of SII > 954.54 is also a predictor of maturation failure (OR: 9.66; 95% CI: 3.88–24.07; $p < 0.001$), an SII > 859.22 is a predictor of early thrombosis (OR: 7.08; 95% CI: 2.23–22.46; $p < 0.001$), and an SII > 949.71 is an independent predictor of short-term mortality (OR: 14.0; 95% CI: 1.71–114.28; $p = 0.01$). Additionally, high values of CRP and Ca-P product are negative prognostic factors for all of the recorded outcomes ($p < 0.001$, $p < 0.001$, and $p = 0.003$/$p = 0.01$). High PNI levels, on the other hand, are protective factors against adverse events ($p < 0.0001$).

Regarding the histpathological examination we found that higher value of inflammatory markers was correlated with a higher presence of CD31-positive microvessel density in the neointimal surface

Conclusions: Our findings concluded that higher preoperative NLR, PLR, SII, CRP, IL-6 and Ca-P product values determined before operations strongly predict AVF maturation failure, early thrombosis, and short-time mortality. Secondly, the small preoperative diameters of the vessels strongly predicted AVF maturation failure, early thrombosis, and short-time mortality. Moreover, a higher PNI value was a protective factor for any negative event. Furthermore we can declare that the systemic inflammatory markers (NLR, PLR, SII, IL-6), intimal hyperplasia, and CD31- positive relative surfaces and CD-68 positivity are predictors of arteriovenous fistula maturation failure.