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Research Article

Hierarchy of risk factors for stenosis of arteriovenous fistula in chronic hemodialysis patients using TOPSIS method

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Abstract. Objective: The consequence of stenosis of the arteriovenous fistulas (AVF) consists in thrombosis and vascular access failure in hemodialysis patients, with important effect on the morbidity and mortality. Detecting and ranking the risk and protective factors could identify the optimal treatment and predict the outcome of the AVF. The aim of our study was to assess and rank factors associated with stenosis of AVF. Material and method: The study included 97 chronic hemodialysis patients (61.28±12.90 years, 23.58% diabetics, 58% males, mean time in dialysis of 62.13±51.29 months) with functional AVFs. Clinical data were collected, the history of vascular access, ultrasonographic examination of morphological (vessel diameters, the presence of stenosis) and functional (blood flow of the brachial artery, Resistivity Index) parameters of the AFV was performed. Laboratory parameters regarding the mineral metabolism, anemia, lipid balance and inflammation were collected. The Technique for Order of Preference by Similarity to Ideal Solution (TOPSIS) method was used to rank the risk factors for stenosis of the AVF. Results: According to the TOPSIS method results, the first five risk factors associated with stenosis were the radial-cephalic localization of the anastomosis, phosphorus, male gender, the delayed maturation of the fistula and antecedents of fistulas with reduced primary permeability. As protective factors we identified: triglycerides, anastomosis diameter, fistula vintage, albumin, diabetes mellitus, high density lipoprotein (HDL), feeding artery diameter and the anastomosis with the brachial artery. Conclusions: TOPSIS could be a useful method to rank the risk factors for stenosis of the arteriovenous fistulas. According to our study, the most important risk factors for stenosis were the vessel anatomy, the history of vascular access, parameters of mineral metabolism and the male gender; as protective factors we identified high Body Mass Index and high HDL.

Key Words: multiple criteria decision making; TOPSIS method; arteriovenous fistula; Doppler ultrasonography; risk factors.

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Introduction

Multi-criteria methods were used frequently in medical fields in previous studies (Ferrari et al 2005; Mullen 2004; Elstein et al 2005; Istrate et al 2004; Colosi et al 2002) with different aims in the medical decision. There are many multiple criteria decision making methods, but only a few which can be applied in medical field: to rank treatments, health providers, health priorities etc. Several authors used The Technique for Order of Preference by Similarity to Ideal Solution (TOPSIS) in their research in the medical field (Ferrari et al 2005; Mullen 2004). For ranking the risk factors were used TOPSIS and VIKOR (Multicriteria Optimization and Compromise Solution) method to our knowledge: in asthma, diabetes occurred after transplant, diabetic nephropathy (Gherman et al 2004; Bondor et al 2006; Bondor et al 2013; Bondor et al 2012).

Vascular access dysfunction is a major factor of morbidity and mortality in hemodialysis patients (United States Renal Data System 2013 - USRDS). Costs derived from hospitalization and treatment of vascular access dysfunction, are a significant burden for health-care systems; in the United States according to USRDS (2013), 1 billion dollars are spent each year with the hospitalization and treatment of this patients. Native arteriovenous fistulas (AVF) are so far the best option as vascular access in hemodialysis patients, being associated with lesser complications and better outcome than catheters or grafts (Turmel-Rodrigues et al 2000), therefore preservation of functionality of AVF is of utmost importance. The most frequent cause of AVF dysfunction is stenosis (Turmel-Rodrigues 2012), which has been associated to numerous conditions related to the patient or to the surgical procedure (Lee et al 2009). These factors associated with stenosis and its severity need to be defined and ranked in order to identify patients at risk in due time for prophylactic measures. To our knowledge, such an attempt at ranking of risk for AVF stenosis has not been conducted yet. Early correction of these factors could avoid the evolution to thrombosis.

The aim of our study was to assess factors associated with stenosis of AVF in a prevalent hemodialysis population and establish a hierarchy among several identified risk factors for stenosis and its hemodynamic significance.

Material and Method

We conducted a transversal observational study including chronic hemodialysis patients (97 patients, 61.28±12.90 years, 23.58% diabetics, 58% males, mean time in dialysis of 62.13±51.29

months) treated in the dialysis center of Deva between 01.06.2014-20.02.2015. The inclusion criteria were the presence of a functional AVF used as dialysis access. Exclusion criteria were the presence of central venous catheters, acute illness (such as infection, cardiovascular disease) and already diagnosed malignancies. All patients gave their informed consent for the inclusion in our study. The study was approved by "Iuliu Hatieganu" University of Medicine and Pharmacy ethics committee.

Clinical and laboratory data were collected as follows: age, body mass index, dialysis vintage, the history of vascular access (number of failed AVFs in the past, the number of central venous catheters, the presence of delayed maturation) and the age of the currently used AVF, the period of time on dialysis (months), presence of atherosclerosis (defined as presence of coronary artery disease, antecedents of stroke, peripheral arterial disease), diabetes mellitus, smoking habit, concomitant medication (calcium-containing phosphorus binders, sevelamer, rennin-angiotensin system blockers, another hypotensive medications, vitamin D, Venofer, statins, fibrates, darbepoetin alfa, antiaggregants, anticoagulants). Laboratory analysis were: ferritin (electrochemiluminescence immunoassay), intact parathyroid hormone (iPTH) (electrochemiluminescence immunoassay), phosphorus (photometry), total calcium (photometry), haemoglobin (Impedance Analysis System, Flow Cytometry), hematocrit (Impedance Analysis System, Flow Cytometry), albumin (photometry), alkaline phosphatase (photometry), serum glucose (photometry), C-reactive protein (turbidimetry), total cholesterol (photometry), high-density lypoprotein (HDL)(photometry), triglycerides (TGL)(photometry). Parameters with impact on the efficacy of the dialysis session (dialysis blood flow, arterial and venous pressures in the blood lines, the time of dialysis/session, blood volume/session) were noted.

The diameter of the brachial artery, feeding artery, anastomosis, venous outflow, blood flow in the brachial artery at the elbow, Resistivity Index (RI) were measured and the presence of stenosis, thrombosis or other anatomical or blood flow abnormalities were noted. The stenosis was defined as the reduction of the diameter of the vessel of more than 50% (The National Kidney Foundation Kidney Disease Outcomes Quality Initiative Guidelines 2006 (NKF KDOQI guidelines 2006); Rajabi-Jaghargh et al 2015) and/or residual diameter under 3 mm; a hemodynamic significant stenosis was defined as the presence of previous anomalies and a blood flow<500 ml min-1 and/or a RI≥0.6 (NKF KDOQI guidelines 2006; Rajabi-Jaghargh et al 2015). Stenoses were classified as: arterial stenosis (feeding artery), juxtaanastomotic stenosis (anastomosis and the first 5 cm of the venous outflow), puncture site stenosis, proximal stenosis (stenosis downstream of the puncture sites but not central veins stenosis) and central vein stenosis (stenosis of the subclavian vein, brachiocephalic trunks, superior vena cava).

The ultrasound examination was performed on a General Electric P6 ultrasound machine with a 7.5 MHz frequency linear transducer; the examination was performed by a single operator with experience in vascular sonography.

We used TOPSIS method to compute the risk factor hierarchy (Bondor et al 2006). We define n criteria C_i, $i=\overline{1,n}$ and m alternatives V_j, $j=\overline{1,m}$ and we suppose that we have p number of patients. The cutoffs of the criteria were taken the normal maximum or minimum values. We ranked the alternatives base on the set of criteria using TOPSIS method by a new algorithm.

Results

In the following, we present the algorithm to obtain the matrix of consequences $A=[a_{ij}]$ $i=\overline{1,n}$, $j=\overline{1,m}$.

1. If V_j, $j=\overline{1,m}$ is a quantitative alternative than compute the median.
2. Transform V_j, $j=\overline{1,m}$ the alternative from a quantitative alternative in a qualitative alternative V_j^*, $j=\overline{1,m}$:
if $v_{ij}<median_j, k=\overline{1,p}$ than v_{ij}^* =0 else v_{ij}^* =1.
3. Compute frequency of 0 and 1 from V_j and v_{ij}^* for each C_i, $i=\overline{1,n}$, obtaining the matrix of consequences $A=[a_{ij}]$ $i=\overline{1,n}$, $j=\overline{1,m}$.

Decision criteria C_i, $i=\overline{1,6}$ were given in Table 1.

In table 2 we presented the matrix of consequences.

$A=[a_{ij}]$ $i=\overline{1,6}$, $j=\overline{1,6}$

In table 3 we presented the results of the TOPSIS method.

Discussion

There are a several factors which could influence the permeability of a native AVF. By prioritizing risk factors using the TOPSIS method we were able to pinpoint some of the most important risk and protection factors with regard to the occurrence and severity of AVF stenosis: Our study reveals as most frequently associated with stenosis, conditions associated with vessel anatomy and history of the AVF, parameters of mineral metabolism and the male gender, whereas high Body Mass Index (BMI) and high value of the HDL are associated with better function of AVF.

Obviously, outcome and function of AVF is influenced by anatomic substrate (Turmel-Rodrigues et al 2000; Rajabi-Jaghargh et al 2015; Ernandez et al 2005), fact confirmed in our study: radiocephalic AVF is a major risk factor to developing stenosis (and severe stenosis) while fistulas on the brachial artery (brachial-cephalic and brachial-basilic fistulas) were correlated with a low risk of stenosis.

Failure to mature of a fistula was previously recognized as an important cause of AVF dysfunction (NKF KDOQI guidelines 2006) and, as in case of thrombosis, stenosis is the underling factor (Rajabi-Jaghargh et al 2015). The association between stenosis and the failure to mature of fistulas was revealed by our data too; also fistulas with a prolonged time of maturation seem to develop more severe stenosis in time. History of previously failed AVF is an important prediction factor for stenosis as it reflects overall risk in a given patient.

In what regards parameters of mineral metabolism and calcifications as a risk factor for stenosis of AVF and their maturation, we identified phosphate and venous calcifications as the most important risk factors for occurrence of stenosis; severity of the latter was also predicted by phosphate and iPTH. This is in line with previous studies (Morena et al 2006; Roca-Tey et al 2009; Jaberi et al 2007).

Opposed to factors predicting risk for stenosis, our analysis reveals some conditions that are associated with lower risk for stenosis and/or lesser severity. As such, a higher BMI seems to offer protection with regard to stenosis; a likely explanation relies on the „reverse epidemiology" of the hemodialysis patient: presence of the malnutrition, inflammation and atherosclerosis

Table 1. The decision criteria $C_i, i=\overline{1,6}$

Criteria C_i	Name	Description	Type of criteria
C_1	Diameter <3 mm	42 (82.35%) patients with stenosis <3 mm	Maximum
C_2	Diameter ≥3 mm	9 (17.65%) patients with stenosis ≥3 mm	Minimum
C_3	Flow <500 ml/min	11 (16.18%) patients with flow <500 ml/min	Maximum
C_4	Flow ≥500 ml/min	57 (83.82%) patients with flow ≥500 ml/min	Minimum
C_5	RI <0.60	23 (76.67%) patients with IR<0.6	Maximum
C_6	RI ≥0.60	7 (23.33%) patients with IR ≥0.6	Minimum

Table 2a. The matrix of consequences $A=[a_j]\quad i=\overline{1,6},\quad j=\overline{1,6}$

Parameter	Diameter <3 mm	Diameter ≥3 mm	Flow <500 ml/min	Flow ≥500 ml/min	RI <0.6	RI ≥=0.6
Sex (male)	69	44.4	54.5	54.4	34.8	57.1
Arterial stenosis	7.1	0	18.2	2.9		
Juxtaanastomotic stenosis	64.3	44.4	45.5	61.8	66.7	57.1
Puncture area stenosis	26.2	0	18.2	20.6	33.3	14.3
Multiple stenosis	14.6	25	20	9.4	6.7	16.7
Radiocephalic fistula	57.1	11.1	81.8	49.1	52.2	57.1
Brachiocephalic fistula	21.4	44.4	18.2	35.1	21.7	28.6
Brachiobasilic fistula	21.4	44.4	0	15.8	26.1	14.3
Smoking habbit	14.3	0	18.2	10.5	17.4	14.3
Diabetes mellitus	26.2	44.4	9.1	24.6	21.7	0
Atherosclerosis	76.2	88.9	81.8	59.6	60.9	85.7
Hypertension	85.7	88.9	72.7	91.2	82.6	71.4
Calciphylaxy	9.5	0	9.1	3.5	8.7	0
Central venous catheters antecedents	83.3	71.4	87.5	78.6	86.4	71.4
Fistulas with reduced primary permeability antecedents	25	14.3	44.4	7.1	13	14.3
Delayed maturation	27.8	0	22.2	14.3	13	28.6
Venous calcifications	12.5	37.5	30	17.5	17.4	71.4
Arterial calcifications	30	25	50	21.1	30.4	28.6
Vitamin D treatment	51.4	33.3	44.4	55.4	36.4	28.6
Statins	27	11.1	22.2	16.1	22.7	0
Lipanthyl	10.8	22.2	22.2	14.3	18.2	28.6
Antihypertensives non-ACEI/ARA2	75.7	55.6	44.4	76.8	77.3	57.1
ACEI/ARA2	37.8	66.7	44.4	35.7	31.8	28.6
Parathyroidectomy	17.5	0	20	14	21.7	0
Iron therapy	40.5	44.4	22.2	35.7	27.3	28.6
Erythropoietin	83.8	88.9	88.9	71.4	77.3	71.4
Phosphate binders with calcium	83.8	77.8	77.8	78.6	81.8	85.7
Phosphate binders without calcium	10.8	11.1	0	12.5	13.6	14.3
Antiaggregants	48.6	44.4	11.1	46.4	31.8	42.9
Anticoagulants	5.4	0	11.1	1.8		
Age (≥64.00 years)	48.7	88.9	60	48.2	45.5	71.4
Brachial artery diameter (≥5.20 mm)	56.2	50	57.1	62.1	60	57.1
Feeding artery diameter (≥4.10 mm)	56	60	42.9	59.5	63.2	50
Anastomosis diameter (≥4.00 mm)	44	75	66.7	59	70.6	40
Systolic blood pressure (≥140.00 mmHg)	62.5	71.4	66.7	62.5	60.9	71.4

Table 2b. The matrix of consequences $A=[a_j]$ $i=\overline{1,6}$, $j=\overline{1,6}$

Parameter	Diameter <3 mm	Diameter ≥3 mm	Flow <500 ml/min	Flow ≥500 ml/min	RI <0.6	RI ≥=0.6
Diastolic blood pressure (≥70.00 mmHg)	59.4	57.1	44.4	71.4	69.6	85.7
Intima-media thickness (≥0.50 mm)	51.4	62.5	37.5	50	59.1	71.4
Ferritin (≥656.50 mcg l-1)	51.3	44.4	44.4	54.4	47.8	42.9
iPTH (≥250.30 ng l-1)	46.2	55.6	66.7	57.9	39.1	42.9
Phosphorus (≥5.29 mg dl-1)	50	44.4	66.7	40.4	34.8	57.1
Calcium (≥8.71 mg dl-1)	56.8	33.3	44.4	51.8	40.9	57.1
Hematocrit (≥34.8 %)	45.9	44.4	55.6	46.4	45.5	71.4
Hemoglobin (≥11.35 g dl-1)	47.4	44.4	55.6	47.4	47.8	71.4
Albumin (≥4.42 g dl-1)	45.9	55.6	44.4	61.8	54.5	42.9
Alkaline phosphatase (≥64.32 IU dl-1)	55.6	33.3	44.4	64.8	61.9	42.9
Glycaemia (≥103.94 mg dl-1)	52.8	55.6	33.3	44.4	42.9	42.9
C-reactive protein (≥0.50 mg dl-1)	50	44.4	55.6	45.6	56.5	42.9
HDL (≥37.52 mg dl-1)	44.4	88.9	44.4	51.9	57.1	71.4
Total cholesterol (≥168.00 mg dl-1)	52.8	66.7	33.3	59.3	57.1	71.4
TGL (≥133.07 mg dl-1)	50	44.4	22.2	63	61.9	42.9
Body mass index (≥25.39 kg m^{-2})	48.8	55.6	36.4	51.8	40.9	42.9
Fistula vintage (≥30.50 months)	46.9	57.1	33.3	67.9	60.9	57.1
Dialysis vintage (≥36.00 months)	53.7	55.6	70	68.4	56.5	42.9
Fistulas/patient (>1.00)	40.6	28.6	44.4	25	30.4	14.3
Proximal stenosis	2.4	55.6	18.2	11.8	0	28.6
Hepatitis viruses	9.5	0	18.2	7	8.7	0

Table 3a. Odds ratio and TOPSIS results

Parameter	OR diameter	OR blood flow	OR RI	TOPSIS parameter	Place in the hierarchy
Radiocephalic fistula	-	-	-	0.62	1
Phosphorus (≥5.29 mg dl-1)	1.25	3.13	2.5	0.59	2
Sex (male)	2.79	1.01	2.5	0.57	3
Delayed maturation	-	1.71	2.67	0.56	4
Fistulas with reduced primary permeability antecedents	2	10.4	1.11	0.56	5
Venous calcifications	0.24	2.01	1.9	0.55	6
Hematocrit (≥34.8 %)	1.06	1.44	3	0.55	7
Hemoglobin (≥11.35 g dl-1)	1.13	1.39	2.73	0.55	8
Calcium (≥8.71 mg dl-1)	2.63	0.74	1.93	0.55	9
Arterial calcifications	1.29	3.75	0.91	0.54	10
Atherosclerosis	0.4	3.04	3.86	0.54	11
Arterial stenosis	-	-	-	0.52	12
Fistulas/patient (>1.00)	-	-	-	0.52	13
Smoking habbit	-	1.89	0.79	0.52	14
Anticoagulants	-	6.88	1	0.51	15
Multiple stenosis	0.51	2.42	2.8	0.51	16
Lipantil	0.42	1.71	1.8	0.51	17
Calciphylaxy	-	2.75	-	0.51	18
Puncture area stenosis	-	-	-	0.51	19
Hepatitis viruses	-	2,94	-	0,51	20

Table 3b. Odds ratio and TOPSIS results

Parameter	OR diameter	OR blood flow	OR RI	TOPSIS parameter	Place in the hierarchy
Phosphate binders with calcium	1.48	0.95	1.33	0.5	21
Parathyroidectomy	-	1.53	-	0.5	22
Systolic blood pressure (≥140.00 mmHg)	0.67	1.2	1.61	0. 50	23
iPTH (≥250.30 ng l-1)	0.69	1.45	1.17	0. 50	24
Erythropoietin	0.65	3.2	0.74	0. 50	25
Statins	2.96	1.49	-	0. 50	26
Central venous catheters antecedents	2	1.91	0.39	0. 50	27
Vitamin D treatment	2.11	0.65	0.7	0.49	28
C-reactiv protein (≥0.50 mg dl-1)	1.25	1.49	0.58	0.49	29
Age (≥64.00 years)	0.12	1.61	3	0.49	30
Brachial artery diameter (≥5.20 mm)	-	-	-	0.49	31
Phosphate binders without calcium	0.97	-	1.06	0.49	32
Proximal stenosis	-	-	-	0.48	33
Juxtaanastomotic stenosis	-	-	-	0.48	34
Ferritin (≥656.50 mcg l-1)	1.32	0.67	0.82	0.48	35
Diastolic blood pressure (≥70.00 mmHg)	1.1	0.32	2.63	0.48	36
Iron therapy	0.85	0.51	1.07	0.48	37
Intima-media thickness (≥0.50 mm)	0.64	0.6	1.73	0.47	38
Glycaemia (≥103.94 mg dl-1)	0.89	0.63	1	0.47	39
Dialysis vintage (≥36.00 months)	0.93	1.08	0.58	0.47	40
Antiaggregants	1.18	0.14	1.61	0.47	41
Alkaline phosphatase (≥64.32 IU dl-1)	2.5	0.72	0.46	0.46	42
Body mass index (≥25.39 kg m^{-2})	0.76	0.53	1.08	0.46	43
ACEI/ARA2	0.3	1.44	0.86	0.46	44
Hypertension	0.75	0.26	0.53	0.46	45
Total cholesterol (≥168.00 mg dl-1)	0.56	0.34	1.88	0.45	46
Brachiocephalic fistula	-	-	-	0.45	47
Antihypertensive non-ACEI/ ARA2	2.49	0.24	0.39	0.44	48
Brachiobasilic fistula	-	-	-	0.43	49
Feeding artery diameter (≥4.10 mm)	0.85	0.51	0.58	0.43	50
HDL (≥37.52 mg dl-1)	0.1	0.74	1.88	0.43	51
Diabetes mellitus	0.44	0.31	0	0.43	52
Albumin (≥4.42 g dl-1)	0.68	0.49	0.63	0.42	53
Fistula vintage (≥30.50 months)	0.66	0.24	0.86	0.41	54
Anastomosis diameter (≥4.00 mm)	0.26	1.39	0.28	0.4	55
TGL (≥133.07 mg dl-1)	1.25	0.17	0.46	0.4	56

syndrome was identified as a major risk factor for cardiovascular disease. Thus higher BMI is associated to better cardiovascular outcomes and in our case to patency of AVF. The presence of diabetes among the „protective" factors was confirmed by other studies (Ernandez et al 2005) but it could be explained by the higher BMI in diabetic patients (data not shown).

Higher HDL was demonstrated as protective factor for AVF thrombosis by some authors, the mechanism being related to severity of atherosclerotic changes in the arteries (Kirkpantur et al 2008). In our study the protective effect was confirmed with regard to the probability of stenosis as well as its severity. Although other authors did not find a significant association between complicated AVF and TGL levels (Kirkpantur et al 2008), higher triglycerides seem to be associated to lesser stenosis in our study; this is to be interpreted in light of the association of higher triglycerides to obesity, as discussed above.

Antiplatelet therapy seems to have a role in the prevention of the AVF failure (Ghorbani et al 2009); our data suggest a protective role against the AVF stenosis.

In this new algorithm for matrix of consequences we take as a cut-off for quantitative alternatives the median. We want to resolve the null values from the consequences matrix that correspond to the frequencies of alternatives, frequencies gave by other type off cut-offs used before: cut-offs obtain with ROC (receiver operating characteristic) curve and normal medical values cut-offs (Gherman et al 2004; Bondor et al 2006; Bondor et al 2013; Bondor et al 2012). There still appear null frequencies in the consequences matrix, because the cut-offs use for criteria may be not adequate.

Conclusion

TOPSIS could be a useful method to rank the risk factors for stenosis of the arteriovenous fistulas. According to our study, the most important risk factors for stenosis were the vessel anatomy (i.e. the radiocephalic localization), the history of vascular access, parameters of mineral metabolism and the male gender; as protective factors we identified high BMI and high HDL cholesterol.

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