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Tunneled hemodialysis catheter and hemodialysis outcomes: a retrospective case-control study

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INTRODUCTION

The number of patients with end-stage chronic kidney disease (ESRD) in need of renal replacement therapy increases progressively in Europe and worldwide.[1] This puts CKD among the significant factors of morbidity and mortality and represents a growing public health issue.

In patients on hemodialysis (HD) treatment, possible long-term vascular access (VA) types are: arteriovenous fistula (AVF), arteriovenous graft (AVG) and tunnelled hemodialysis central venous catheter (TDC). Since native AVF that Brescia and Cimino described in 1966 has the longest survival and the lowest frequency of complications among all other types of VA for HD, it should be the first choice for VA whenever possible.[1,2,3] However, there are vast differences in the use of certain VA types in different countries and the use of TDC is still noticeably high, in spite of current guidelines. The rate of patients who are dialyzed through TDC among all patients on HD varies from only 1.6% in Japan up to 52% in Canada.[4]

Central venous catheters (CVC) are used for the rapid establishment of adequate VA when there is an an urgent need for HD, as a bridge during AVF maturation process and in patients who have eventually exhausted all other VA types.[1,3,5] According to the K/DOQI guidelines temporary catheters should be used up to one week, while the usage of TDC is recommended in all other cases, where catheter is unavoidable.[6] TDC are usually placed according to the modified Seldinger method.[7] The insertion site of choice should be right internal jugular vein.[8] Alternatively, TDC can be inserted through the subclavian or femoral vein. Subclavian vein should be generally avoided because of the high incidence of stenosis and thrombosis, while the femoral vein should be considered only when all other insertion sites have been excluded.[1] The advantages of TDC include the ability to use it immediately after placement, no repeated venipuncture nor hemodynamic consequences, and no need for vascular surgeon during placement.[4] Nevertheless, TDCs are associated with significantly higher long-term risk of death, infections, cardiovascular events and hospitalization in comparison with other VA types.[9] However, some of the associated conditions and diseases affect the patient survival as well as the VA choice and survival. Therefore, although many studies consistently show that TDC are associated with poorer patient survival, it is not entirely clear whether the risk arises from TDC exclusively or from the associated conditions and diseases that are often present in patients who are dialyzed through TDC. [9,10]

The aim of this study was to determine HD outcomes with respect to VA; patient survival with respect to VA, VA survival and factors that influence VA choice and VA survival.

PATIENTS AND METHODS

Patients

This retrospective case-control study was approved by the Hospital Ethics Committee of the Merkur Hospital, Zagreb, Croatia. Patients gave their written informed consent for anonymised HD data collection for research purposes. We analysed the survival of patients dialysed through TDC in comparison with a group of patients who were dialysed through an AVF. We also analysed TDC survival. The study included a total of 253 patients who were treated with HD in 21 dialysis centre in Croatia; median 16 (IQR 10, 21) per centre. With respect to VA, the TDC:AVF ratio was approximately 2:1. The study subjects were selected to include all 156 patients who received a total of 190 TDC at Renal Division in University Hospital 'Merkur' from the beginning of 2010 to the end of 2012. Then 97 patients who were dialysed through AVF were selected from the same dialysis centres. Eligible patients dialysed through AVF had to start with HD treatment at about the same time as patients dialysed through TDC. The insertion site of choice for TDC was right jugular vein. Other sites were used in case of inability to insert in the right jugular vein or when laying over previously inserted TDC in another vein.

Methods

Data were collected from Renal Division's TDC placement programme database and by questionnaire sent to 21 HD centres whose patients underwent TDC placement procedure in our Division. In the questionnaire was asked for the following information: demographic data, the date of first HD, did the patient have a CVC before the observed TDC, did the patient have an attempt to create AVF or AVF which ceased to function, the cause of CKD, concomitant diseases, did the patient have catheter sepsis, did the patient have an infection of TDC's tunnel, were there problems with wound healing after TDC placement, were there any mechanical problems with TDC and what was TDC usually closed with upon the completion of HD treatment. If TDC was in function, it was asked for the blood pump speed, arterial and venous pressure during HD treatment. If TDC ceased to function, we recorded the date of cessation of TDC function, the reason for cessation of TDC function, current VA if the patient was still treated with HD, the date of transplantation if the patient underwent a kidney transplantation and the date of death if the patient died. A similar, modified questionnaire was used to collect data about patients who were dialyzed through AVF.

Statistical analysis

Numerical data are presented as mean±SD in case of continuous variables with normal distribution or as median with IQR in case of not normal distribution. The difference between two groups in continuous variables was tested with Student's t-test in normal distributed variables or with Mann-Whitney's U test in non-normally distributed variables. The difference between two groups in categorical variables was tested with Pearson's chi-squared test. Survival analysis which included patient survival, overall VA survival and death-censored VA survival was performed by using Kaplan-Meier's analysis. Univariate and multivariate Cox regression were performed to determine variables independently associated with patient and VA survival. All variables that were associated with respective outcome in bivariate

analysis (at $p \leq 0,1$) were included in the multivariate Cox regression. Results are presented as hazard ratio (HR) with the corresponding 95% confidence interval (CI). Statistical significance was considered at p value < 0.05. All statistical analyses were performed by using SPSS 17.0.

RESULTS

Characteristics of patients dialysed through TDC

Patient characteristics are shown in Table 1. There were 156 patients dialysed through TDC, 88 (56%) were men. They were a mean of 65±14 years old (range 26-92). The average time since the initiation of HD treatment was 658 (IQR 374-1114) days. The cause of ESRD was diabetic nephropathy in 42.3% of patients, hypertensive kidney disease in 23.1%, glomerulonephritis in 9.6%, polycystic kidney disease in 5.8% and other diseases in 19.2% of patients. 69.9% of patients had a temporary dialysis catheter prior to the observed TDC, 20.5% had previous TDC and 50.6% had an attempt to create AVF or AVF which ceased to function. Considering concomitant diseases, 44.2% of patients had diabetes, 20.5% had significant coronary heart disease (coronary revascularization or prior myocardial infarction) and 16.7% of patients had a stroke. 19.9% of patients had peripheral vascular disease (15.4% of patients had an amputation while 6.4% of patients had a revascularization of peripheral arteries by creating a bypass or by stent implantation).

Characteristics of patients dialysed through AVF

There were 97 patients dialysed through AVF, 64 (66%) were men. They were a mean of 67±13 years old (range 22-88). The average time passed since the initiation of HD treatment was 536 days (IQR 320, 1139). The cause of ESRD was diabetic nephropathy in 40.2% of patients, hypertensive kidney disease in 20.6%, glomerulonephritis in 11.3%, polycystic kidney disease in 10.3% and other diseases in 17.5% of patients. 23.7% of patients an attempt to create AVF or AVF which ceased to function prior to the observed AVF. Considering concomitant diseases, 40.2% of patients had diabetes, 20.6% had coronary heart disease (coronary revascularization or prior myocardial infarction) and the same proportion of patients had a peripheral vascular disease (12.4% of patients had an amputation while 6.2% had a revascularization of peripheral arteries by creating a bypass or by stent implantation). 4.1% of patients had a stroke. Patient characteristics are also shown in Table 1.

Patient survival

Patient survival is shown in Figure 1a. Cumulative one-year overall patient survival since the initiation of HD treatment was 93.2%. In univariate analysis of risk factors for the overall patient survival, there were eight negative risk factors: TDC as current VA (p=0.001), TDC as an exclusive VA (p=0.001), male gender (p=0.065), older age at the initiation of HD treatment (p=0.006), concomitant diabetes mellitus (p=0.021), stroke in patient's history (p= 0.028), concomitant coronary heart disease (p=0.017) and prior peripheral artery

revascularization (p=0.028). Factors positively associated with overall patient survival were less time spent on HD treatment prior to the observed VA (p=0.004) and an attempt to create

Table 1 Characteristics of patients

	all patients	TDC	AVF	P
The age of patients at the initiation of HD treatment (years)*	62,69±14,02	62,08±14,39	63,85±13,23	0,215
The age of patients at the VA creation (years)*	63,75±13,87	63,69±14,20	64,01±13,39	0,737
The age of patients at the end of follow-up (years)*	65,81±13,86	65,24±14,27	66,94±12,98	0,248
Sex (m/f)		88/68	64/33	0,081
HD vintage (days)**	607 (335, 1088)	658 (374, 1114)	536 (320, 1139)	0,836
HD vintage before the observed VA creation (days)**	50 (5, 348)	204 (33, 799)	7 (0, 66)	<0,001
Diabetes mellitus	42,7%	44,2%	40,2%	0,464
Coronary heart disease	20,6%	20,5%	20,6%	0,851
Stroke	11,9%	16,7%	4,1%	0,001
Peripheral vascular disease	20,2%	19,9%	20,6%	0,902
Peripheral artery revascularization	6,3%	6,4%	6,2%	0,228
Partial or total limb amputation	14,2%	15,4%	12,4%	0,599
* mean ± SD ** median with IQR				

AVF or AVF which ceased to function prior to the observed VA (p=0.037). With respect to ESRD, hypertensive renal disease (p=0.001) and glomerulonephritis (p=0.002) were positively associated with overall patient survival. The results of univariate analysis are shown in Table 2. In the multivariate Cox regression two factors turned out as an independent negative risk factors for the overall patient survival: male gender (p=0.012) and older age at the initiation of HD treatment (p=0.037). Less time spent on HD treatment prior to the observed VA (p<0.001), hypertensive renal disease (p=0.002) and glomerulonephritis (p=0.018) were independently positively associated with overall patient survival. TDC was independently negatively associated with patient survival in the multivariate analysis (HR 23,037, 95% CI 6.221-85.308).

Patient survival with respect to VA is shown in Figure 1b. Cumulative one-year survival of patients who were dialyzed exclusively through TDC was 91.2% and of those who were dialyzed exclusively through AVF 97.1% (p=0.001). With respect to VA conversion, one-

year survival of patients who were converted from AVF to TDC was 95% (p=0.102 in comparison with AVF as an exclusive VA; p = 0.002 in comparison with TDC as an exclusive VA).

In univariate analysis of risk factors for the survival of patients who were dialysed exclusively through TDC, there were four negative risk factors: male gender (p=0.010), concomitant diabetes mellitus (p=0.006), concomitant coronary artery disease (p=0.004) and prior peripheral artery revascularization (p=0.003). Factors positively associated with survival were less time spent on HD treatment prior to the observed VA (p<0.001), an attempt to create AVF or AVF which ceased to function prior to the observed VA (p=0,001), hypertensive renal disease (p=0.001) and glomerulonephritis (p=0.006). The results of univariate analysis are shown in table 2. In the multivariate Cox regression only male gender turned out as an independent negative risk factor (p=0,019), while less time spent on HD treatment prior to the observed VA (p<0,001), an attempt to create AVF or AVF which ceased to function prior to the observed VA (p=0,039) and hypertensive kidney disease as the cause of ESRD were independently positively associated with survival.

Vascular access survival

Among the total of 190 TDC's, 124 (65.3%) were placed *de novo*. 58% of TDC's were placed in the right jugular vein, 11.2% in the left jugular vein, 17.6% in the right subclavian vein, 8.5% in the left subclavian vein, 2.7% in the right femoral vein and 2.1 % in the left femoral vein. The most frequent long-term complications were TDC thrombosis and infection (table 4). 6.8% of infections lead to TDC-associated sepsis and 6.3% were tunnel infections. 35.3% of these infections were cured, without catheter removal. TDC was replaced in 47.1% of infection cases and permanently removed in 5.9% of cases. 11.8% of infections ended in lethal outcome. The wound healing problems after TDC placement occurred in 5,8% of patients. Mechanical problems (rupture or separation of catheter lines, puncture or rupture of the clamp or cap) were reported in 7% of cases. The mean blood pump speed for TDC's in use was 288±36 mL/min, mean pressure in the venous line of the dialysis machine was 158±35 mmHg while mean pressure in the arterial line was -184±39 mmHg. 20,3% of TDC's were closed with sodium citrate (Duraloc®) exclusively, 67,4% with heparin exclusively, the rest was closed occasionally with sodium citrate and occasionally with heparin. During a HD treatment it was necessary to switch TDC lines every time in 10.5% TDC's, occasionally in 62.1%, and never in 27.4%. During this monitoring process 50% of TDC's ceased to function. The causes of cessation are shown in Table 3.

Table 2. Patient survival- the results of univariate analysis

		1-year survival	2-year survival	p	HR (95% CI)	p
VA type	TDC	91,2%	77,7%	0,001*	3,826 (1,633-8,963)	0,002
	AVF	97,2%	95,7%			
Sex	m	91,1%	79,0%	0,065*	1,739 (0,957-3,157)	0,069
	f	96,5%	89,0%			
An attempt to create AVF or AVF which ceased to function prior to the observed VA	Yes	95,7%	87,4%	0,037*	1,794 (1,028-3,130)	0,040
	No	91,3%	78,6%			
Concomitant diabetes mellitus	Yes	91,2%	76,7%	0,021*	0,519 (0,294-0,915)	0,023
	No	94,8%	87,5%			
Stroke in patient's history	Yes	94,6%	72,9%	0,028*	0,486 (0,252-0,938)	0,031
	No	93,0%	84,9%			
Concomitant coronary heart disease	Yes	93,2%	68,9%	0,017*	0,507 (0,288-0,894)	0,019
	No	93,3%	88,2%			
Peripheral artery revascularization	Yes	100%	57,9%	0,028*	0,455 (0,220-0,938)	0,033
	No	92,7%	86,2%			
VA conversion	A	86,4%	64,8%	<0,001*	2,785 (1,547-5,015)	0,001
	B	97,1%	95,5%			
	C	95,0%	86,5%			
Hypertensive kidney disease		96,0%	96,0%	<0,001*	0,172 (0,061-0,479)	0,002
Glomerulonephritis		100,0%	100,0%	<0,001*	0,039 (0,005-0,311)	0,018
The age of patients at the initiation of HD treatment (years)					1,033 (1,009-1,057)	0,037
Time from the initiation of HD treatment to the observed VA creation (months)					0,836 (0,735-0,950)	0,006

* Log Rank (Mantel-Cox) test
A TDC as an exclusive VA
B AVF as an exclusive VA
C The conversion of VA from AVF to TDC

TDC death-censored survival is shown in Figure 2. One-year death-censored TDC survival was 76.7%. In univariate analysis, there were four risk factors negatively associated with TDC survival: an attempt to create AVF or AVF which ceased to function prior to the observed VA (p=0.010), TDC associated sepsis (p<0.001), tunnel infection (p<0.001) and mechanical problems with TDC (p<0.001). The results of univariate analysis are shown in table 5. In the multivariate Cox regression an attempt to create AVF or AVF which ceased to function prior to the observed VA (p=0.014), mechanical problems with TDC (p=0.002) and TDC lines' puncture or rupture (p=0,001) were independently negatively associated with TDC death-censored survival.

The mean blood pump speed for AVF in use was 318±36 mL/min, mean pressure in the venous line of the dialysis machine was 137±32 mmHg while mean pressure in the arterial

line was -154±37 mmHg. During this monitoring process 13,4% of AVF ceased to function. The causes of cessation are shown in Table 4.

AVF death-censored survival is shown in Figure 2. One-year death-censored AVF survival was 96%. In univariate analysis, male gender was negatively associated with AVF death-censored survival (p=0,004). The univariate analysis results are shown in table 7. No variable was independently associated with death-censored AVF survival in multivariate Cox regression,

VA death-censored survival (both TDC and AVF) is shown in Figure 2. In univariate analysis, there were three factors negatively associated with VA death-censored survival: TDC as VA type (p<0,001), an attempt to create AVF or AVF which ceased to function prior to the observed VA (p<0,001) and TDC as an exclusive VA (p<0,001). In multivariate Cox regression, AVF as an exclusive VA was independently positively associated with VA survival (p<0,001).

Table 3. The causes of TDC function cessation

Death of a patient	43,0%
TDC thrombosis	16,3%
TDC infection	10,5%
VA conversion from TDC to AVF	9,3%
Kidney transplantation	7,0%
Recovery of renal function	2,3%
Catheter fell out	1,2%

Table 4. The causes of AVF function cessation

Death of a patient	38,5%
AVF thrombosis	30,8%
Vein rupture	15,4%
Difficult AVF puncture or inadequate bloodflow	15,4%

DISCUSSION

This analysis defined factors associated with VA and patient survival in a real life situation, in a patient population treated in 21 dialysis centres across Croatia. The cause of ESRD in studied group of patients completely coincided with Croatian Registry of Renal Replacement Therapy data.[11] The frequency of concomitant diseases was alike in other developed countries. One year patient survival in this study was excellent, probably reflecting good hemodialysis care in Croatia. Female gender was independently positively associated with overall patient survival. This was previously shown in CHOICE study by Astor et al.[12] TDC as current VA, male gender and older age at initiation of HD treatment were independently negatively associated with overall patient survival.

In a recent cohort study of 3752 dialysis patients one-year survival of patients who were dialysed through TDC was 75% and factors independently negatively associated with survival were age at first treatment, late referral, coronary artery disease, peripheral vascular disease and cerebrovascular disease. One-year survival of patients dialysed through AVF was 90%.[13] There are several other studies that showed statistically significant difference in patient survival with respect to VA type.[12,14] Our study largely confirms previously observed statistically significant difference in survival between the two groups of HD patients and in the identified independent risk factors for the survival of patients who were dialyzed through TDC. However, our results showed that patients included in this study who were dialyzed through TDC and those who were dialyzed through AVF had better survival in comparison with previously published studies. Several studies showed that patient survival is associated with VA conversion and is better in patients who are converted from TDC to AVF during the first year of HD treatment.[10,15] Although our study did not include enough patients who underwent this kind of VA conversion analysis, we showed that survival was not significantly different in patients who were dialyzed exclusively through AVF and those who were converted from AVF to TDC. Therefore, it is likely that there are other factors, beside TDC, responsible for lower survival of patients dialysed exclusively through TDC. Multivariate Cox regression showed that VA type is an independent risk factor for patient survival. The association of VA type with patient survival is controversial. Multiple studies, including ours, suggested negative correlation between TDC and patient survival.[9,10,12,14,16] On the other hand, according to several retrospective studies, TDC *per se* may not be negatively associated with poor patient survival.[17,18] This issue could be clarified only by the implementation of adequate prospective studies, which are unlikely to be performed for ethical reasons.

Studying of the association of TDC with HD patient outcomes is important, because the number of patients who are dialyzed through TDC is steadily-increasing.[19,20] Possible reasons are late referral to a nephrologist, a lack of experience, education or surgeon availability for the AVF creation and elderly patients who are not eligible for AVF creation due to their poor blood vessels status.[21] In one British study of 812 TDC's one-year death-censored TDC survival of 61% was demonstrated.[22] Another study of 200 Tessio catheters reported an one-year death-censored catheter survival of 60%.[23] Our results show significantly better one-year TDC survival, in comparison with these previously published studies. According to guidelines, right jugular vein was the insertion site of choice at our

centre, but this study did not find a statistically significant difference between the insertion site and TDC survival (data not shown). This may be due to low power of this study for this analysis, as number of TDC inserted at other sites was low.

Though K/DOQI guidelines recommend that less than 10% of all patients treated with HD should be dialyzed through TDC, this goal remains unachieved.[20] The number of patients who initiate HD treatment through TDC is also much higher than recommended.[19]

In conclusion, TDC is an independent negative risk factor for patient survival and has shorter lifetime in comparison with AVF.

ABSTRACT

Objectives: Studies have reported that tunneled dialysis catheter (TDC) is associated with inferior hemodialysis (HD) patient survival, in comparison with arteriovenous fistula (AVF). Since many cofactors may also affect survival of HD patients, it is unclear whether the risk for the worse survival arises from TDC *per se,* or from associated conditions. Therefore, the aim of this study was to determine in a multivariate analysis the long-term outcome of HD patients, with respect to vascular access (VA).

Design: Retrospective case-control study

Participants: This retrospective case-control study included all 156 patients with TDC placed from 2010 to 2012 at Merkur University Hospital. Control group consisted of 97 patients dialysed through AVF. The groups were matched according to dialysis unit and time of VA placement. The site of choice for the placement of TDC was right jugular vein. Kaplan-Meier analysis with log-rank test was used to assess patient survival. A multivariate Cox regresion analysis was used to determine independent variables associated with the patient survival.

Primary outcome measures: Patient survival with respect to VA.

Results: Cumulative one-year survival of patients who were dialysed exclusively through TDC was 86.4 % and of those who were dialysed exclusively through AVF the survival was 97.1 % (p=0.002). In a multivariate Cox regression analysis, male sex and older age were independently negatively associated with the survival of HD patients, while shorter duration of HD before the creation of the observed VA, hypertensive renal disease and glomerulonephritis were positively associated with survival. TDC was an independent risk factor for survival of HD patients (HR 23,037, 95% CI 6.221-85.308).

Conclusion: TDC is an independent negative risk factor for the survival of patients on HD.

STRENGHTS AND LIMITATIONS OF THIS STUDY

This is a retrospective case-control study, in which well matched patients followed by multiple dialysis centres were included. Therefore, study results account for variations in routine patient care at different centres and are reflective of a real life practice. This is important, because a prospective randomized trial comparing patient survival with respect to vascular access type (AV fistula and tunneled dialysis catheter) is highly unlikely.

Main outcomes (patient and vascular access survival) were analyzed by a multivariate analysis.

The main limitation of this study is its retrospective and non-randomized design. However, the two patient groups were well matched in majority of the variables that may have affected the outcome.

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CONTRIBUTORSHIP STATEMENT

Dr Pašara participated in designing the study, collected and analysed data and wrote the manuscript.
Dr. Maksimović, Gunjača and Mihovilović participated in designing the study and collection of the data and critically reviewed the manuscript.
Dr. Lončar, Kudumija and Žabić participated in designing the study, data collection and critically reviwed the manuscript.
Dr. Knotek supervised design of the study, co-ordinated and supervised data collection and analysis and has participated in writing the manuscript.

COMPETING INTERESTS

None.

FUNDING

None.

DATA SHARING STATEMENT

The original data may be obtained by requesting permission from the first and the corresponding author.

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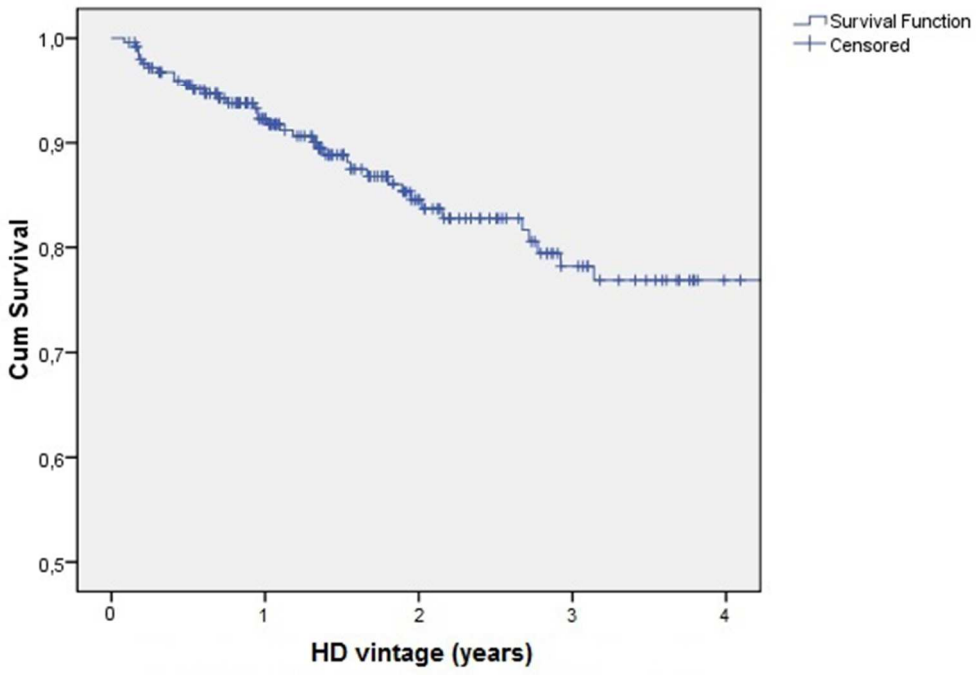

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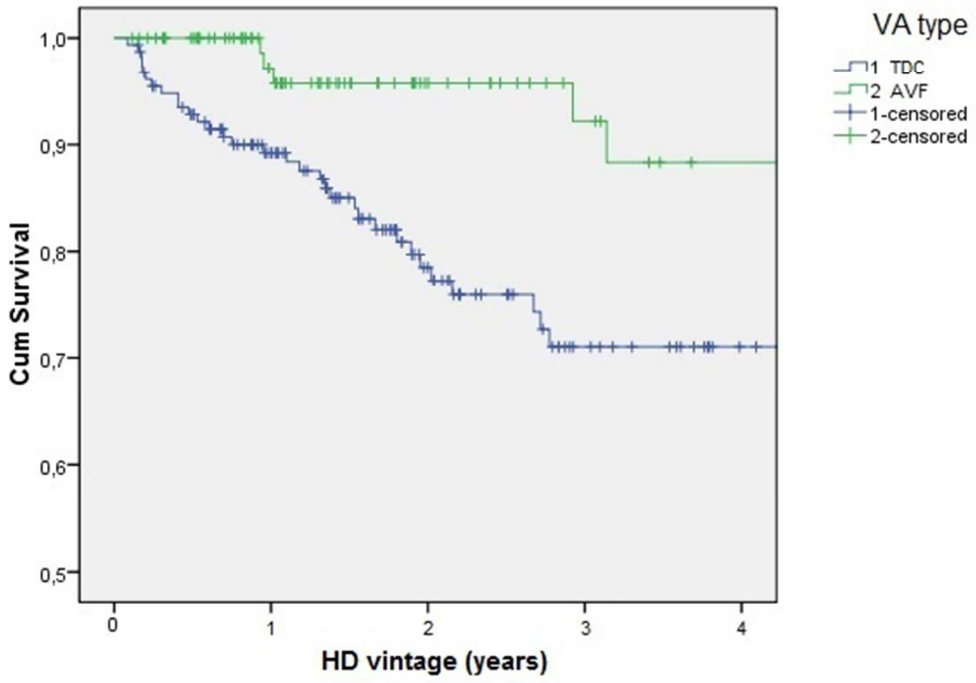

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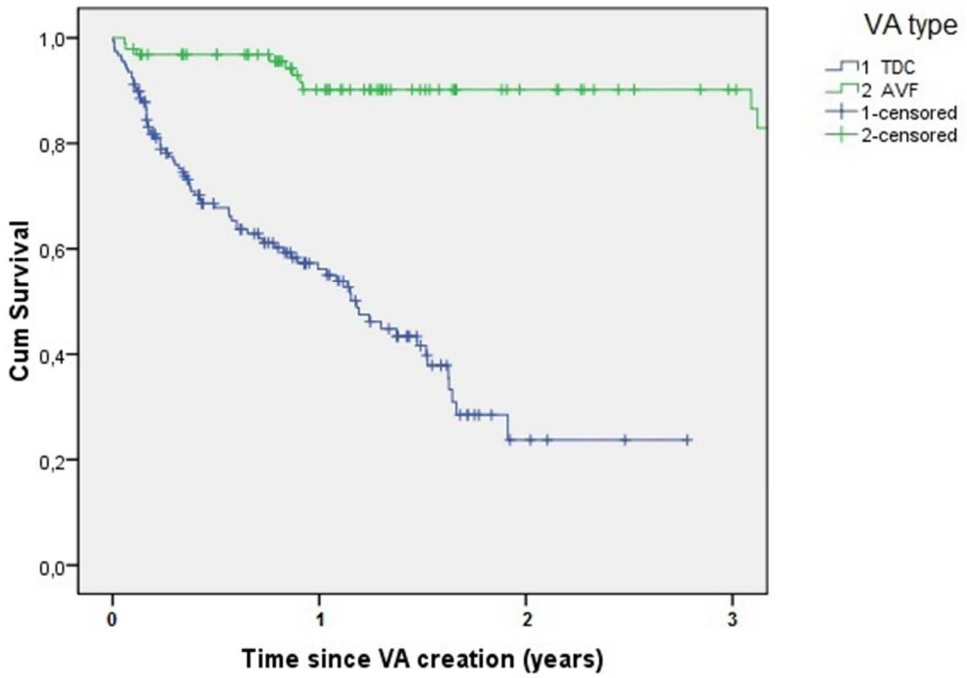

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Tunneled hemodialysis catheters and hemodialysis outcomes: a retrospective cohort study

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ABSTRACT

Objectives: Studies have reported that tunneled dialysis catheter (TDC) is associated with inferior hemodialysis (HD) patient survival, in comparison with arteriovenous fistula (AVF). Since many cofactors may also affect survival of HD patients, it is unclear whether the risk for the worse survival arises from TDC *per se,* or from associated conditions. Therefore, the aim of this study was to determine in a multivariate analysis the long-term outcome of HD patients, with respect to vascular access (VA).

Design: Retrospective cohort study

Participants: This retrospective cohort study included all 156 patients with TDC placed from 2010 to 2012 at University Hospital Merkur. Control group consisted of 97 patients dialysed via AVF. The groups were matched according to dialysis unit and time of VA placement. The site of choice for the placement of TDC was right jugular vein. Kaplan-Meier analysis with log-rank test was used to assess patient survival. A multivariate Cox regresion analysis was used to determine independent variables associated with the patient survival.

Primary outcome measures: Patient survival with respect to VA.

Results: Cumulative one-year survival of patients who were dialysed exclusively via TDC was 86.4 % and of those who were dialysed exclusively via AVF the survival was 97.1 % (p=0.002). In a multivariate Cox regression analysis, male sex and older age were independently negatively associated with the survival of HD patients, while shorter HD vintage before the creation of the observed VA, hypertensive renal disease and glomerulonephritis were positively associated with survival. TDC was an independent risk factor for survival of HD patients (HR 23.0, 95% CI 6.2-85.3).

Conclusion: TDC may be an independent negative risk factor for HD patient survival.

STRENGHTS AND LIMITATIONS OF THIS STUDY

- This is a retrospective cohort study, in which well matched patients followed by multiple dialysis centres were included. Therefore, study results account for variations in routine patient care at different centres and are reflective of a real life practice. This is important, because a prospective randomized trial comparing patient survival with respect to vascular access type (AV fistula and tunneled dialysis catheter) is highly unlikely.
- Main outcomes (patient and vascular access survival) were analyzed by a multivariate analysis.
- The main limitation of this study is its retrospective and non-randomized design. However, the two patient groups were well matched in majority of the variables that may have affected the outcome.

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A portion of this study has been accepted for poster presentation at the 2015 American Society of Nephrology Annual Meeting, San Diego, CA

CONTRIBUTORSHIP STATEMENT

Dr Pašara participated in designing the study, collected and analysed data and wrote the manuscript.

Dr. Maksimović, Gunjača and Mihovilović participated in designing the study and collection of the data and critically reviewed the manuscript.

Dr. Lončar, Kudumija and Žabić participated in designing the study, data collection and critically reviwed the manuscript.

Dr. Knotek supervised design of the study, co-ordinated and supervised data collection and analysis and has participated in writing the manuscript.

COMPETING INTERESTS

None.

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DATA SHARING STATEMENT

No additional data available.

INTRODUCTION

The number of patients with end-stage chronic kidney disease (ESRD) in need of renal replacement therapy increases progressively in Europe and worldwide.[1] This puts CKD among the significant factors of morbidity and mortality and represents a growing public health issue.

In patients on hemodialysis (HD) treatment, possible long-term vascular access (VA) types are: arteriovenous fistula (AVF), arteriovenous graft (AVG) and tunnelled hemodialysis central venous catheter (TDC). Since native AVF that Brescia and Cimino described in 1966 has the longest survival and the lowest frequency of complications among all other types of VA for HD, it should be the first choice for VA whenever possible.[1,2,3] However, there are vast differences in the use of certain VA types in different countries and the use of TDC is still noticeably high, in spite of current guidelines. The rate of patients who are dialyzed via TDC among all patients on HD varies from only 1.6% in Japan up to 52% in Canada.[4] In Croatia approximately 20% of patients are dialysed via TDC, while the rest is dialysed via AVF (Knotek M, personal communication). Arteriovenous graft is infrequently used in Croatia.

Central venous catheters (CVC) are used for the rapid establishment of adequate VA when there is an an urgent need for HD, as a bridge during AVF maturation process and in patients who have eventually exhausted all other VA types.[1,3,5] According to the K/DOQI guidelines temporary catheters should be used up to one week, while the usage of TDC is recommended in all other cases, where catheter is unavoidable.[6] TDC are usually placed according to the modified Seldinger method.[7] The insertion site of choice should be right internal jugular vein.[8] Alternatively, TDC can be inserted through the subclavian or femoral vein. Subclavian vein should be generally avoided because of the high incidence of stenosis and thrombosis, while the femoral vein should be considered only when all other insertion sites have been excluded.[1] The advantages of TDC include the ability to use it immediately after placement, no repeated venipuncture nor hemodynamic consequences, and no need for vascular surgeon during placement.[4] Nevertheless, TDCs are associated with significantly higher long-term risk of death, infections, cardiovascular events and hospitalization in comparison with other VA types.[9] However, some of the associated conditions and diseases affect at the same time the patient survival, as well as the VA choice and survival. Therefore, although many studies show that TDC are associated with poorer patient survival, it is not entirely clear whether the risk arises from TDC exclusively or from the associated conditions and diseases that are often present in patients who are dialyzed via TDC. [9,10]

The aim of this study was to determine HD patient and VA survival with respect to VA type.

PATIENTS AND METHODS

Patients

This retrospective cohort study was approved by the Hospital Ethics Committee of the University Hospital Merkur, Zagreb, Croatia. Patients gave their written informed consent for anonymised HD data collection for research purposes. We analysed the survival of patients dialysed via TDC in comparison with a group of patients who were dialysed via an AVF. We also analysed TDC survival. The study included a total of 253 patients who were treated with HD in 21 dialysis centre in Croatia; median 16 (IQR 10, 21) per centre. With respect to VA, the TDC:AVF ratio was approximately 2:1. The study subjects were selected to include all 156 patients who received a total of 190 TDC at Renal Division in University Hospital Merkur from the beginning of 2010 to the end of 2012. Then 97 patients who were dialysed via AVF were selected from the same dialysis centres. Eligible patients dialysed via AVF had to start with HD treatment at about the same time as patients dialysed via TDC. The insertion site of choice for TDC was right jugular vein. Other sites were used in case of inability to use right jugular vein or when exchanging over previously inserted TDC in another vein.

Methods

Data were collected from the Renal Division TDC placement programme database and by a questionnaire sent to 21 HD centres whose patients underwent TDC placement procedure in our Division. In the questionnaire we asked for the following information: demographic data, the date of first HD, history of a temporary CVC before the observed TDC, history of an attempt to create AVF or history of functional AVF which ceased to function, the cause of CKD, concomitant diseases, history of catheter sepsis, history of an infection of TDC tunnel, were there problems with wound healing after TDC placement, were there any mechanical problems with TDC and what solution was TDC usually locked with upon the completion of HD treatment. If the TDC was in function, it was asked for the blood pump speed, and for arterial and venous pressure during HD treatment. If TDC ceased to function, we recorded the date of cessation of TDC function, the reason for cessation of TDC function, current VA if the patient was still treated with HD, the date of transplantation if the patient underwent a kidney transplantation and the date of death if the patient died. A similar, modified questionnaire was used to collect data about patients who were dialyzed via AVF.

Statistical analysis

Numerical data are presented as mean±SD in case of continuous variables with normal distribution or as median with IQR in case of not normal distribution. The difference between two groups in continuous variables was tested with Student's t-test in normal distributed variables or with Mann-Whitney's U test in non-normally distributed variables. The difference between two groups in categorical variables was tested with Pearson's chi-squared test. Survival analysis which included patient survival, overall VA survival and death-censored VA survival was performed by using Kaplan-Meier's analysis. Univariate and multivariate Cox regression were performed to determine variables independently associated with patient and VA survival. All variables that were associated with respective outcome in bivariate

analysis (at $p \leq 0.1$) were included in the multivariate Cox regression. Results are presented as hazard ratio (HR) with the corresponding 95% confidence interval (CI). Statistical significance was considered at p value < 0.05. All statistical analyses were performed by using SPSS 17.0.

RESULTS

Characteristics of patients dialysed via TDC

Patient characteristics are shown in Table 1. There were 156 patients dialysed via TDC. The cause of ESRD was diabetic nephropathy in 42.3% of patients, hypertensive kidney disease in 23.1%, glomerulonephritis in 9.6%, polycystic kidney disease in 5.8% and other diseases in 19.2% of patients. 69.9% of patients had a temporary dialysis catheter prior to the observed TDC, 20.5% had previous TDC and 50.6% had an attempt to create AVF or AVF which ceased to function. During follow-up 152 (97,4%) patients were dialyzed via TDC exclusively, while 4 (2,6%) switched to AVF.

Table 1 Characteristics of patients

	all patients	TDC	AVF	P
The age of patients at the initiation of HD treatment (years)*	62.7±14.0	62.1±14.4	63.9±13.2	0.215
The age of patients at the VA creation (years)*	63.8±13.9	63.7±14.2	64.0±13.4	0.737
The age of patients at the end of follow-up (years)*	65.8±13.9	65.2±14.3	66.9±12.9	0.248
Sex (m/f)	152/101	88/68	64/33	0.081
HD vintage (days)**	607 (335, 1088)	658 (374, 1114)	536 (320, 1139)	0.836
HD vintage before the observed VA creation (days)**	50 (5, 348)	204 (33, 799)	7 (0, 66)	<0.001
Diabetes mellitus	42.7%	44.2%	40.2%	0.464
Coronary heart disease	20.6%	20.5%	20.6%	0.851
Stroke	11.9%	16.7%	4.1%	0.001
Peripheral vascular disease	20.2%	19.9%	20.6%	0.902
Peripheral artery revascularization	6.3%	6.4%	6.2%	0.228
Partial or total limb amputation	14.2%	15.4%	12.4%	0.599

* mean ± SD

** median with IQR

Characteristics of patients dialysed via AVF

There were 97 patients dialysed via AVF. The cause of ESRD was diabetic nephropathy in 40.2% of patients, hypertensive kidney disease in 20.6%, glomerulonephritis in 11.3%, polycystic kidney disease in 10.3% and other diseases in 17.5% of patients. 23.7% of patients an attempt to create AVF or AVF which ceased to function prior to the observed AVF. During follow-up 91 (93,8%) patients were dialyzed via AVF exclusively, while 6 (6,2%) switched to TDC. Patient characteristics are also shown in Table 1.

Patient survival

Patient survival is shown in Figure 1a. Cumulative one-year overall patient survival since the initiation of HD treatment was 93.2%. In univariate analysis of risk factors for the overall patient survival, there were eight negative risk factors: TDC as current VA (p=0.001), TDC as an exclusive VA (p=0.001), male gender (p=0.065), older age at the initiation of HD treatment (p=0.006), concomitant diabetes mellitus (p=0.021), stroke in patient's history (p= 0.028), concomitant coronary heart disease (p=0.017) and prior peripheral artery revascularization (p=0.028). Factors positively associated with overall patient survival were shorter HD vintage prior to the observed VA (p=0.004) and an attempt to create AVF or history of AVF which ceased to function prior to the current VA (p=0.037). With respect to ESRD, hypertensive renal disease (p=0.001) and glomerulonephritis (p=0.002) were positively associated with overall patient survival. The results of univariate analysis are shown in Table 2. In the multivariate Cox regression two factors turned out as an independent negative risk factors for the overall patient survival: male gender (p=0.012) and older age at the initiation of HD treatment (p=0.037). Shorter HD vintage prior to the observed VA (p<0.001), hypertensive renal disease (p=0.002) and glomerulonephritis (p=0.018) were independently positively associated with overall patient survival. TDC was independently negatively associated with patient survival in the multivariate analysis (HR 23.0, 95% CI 6.2-85.3).

Table 2. Patient survival- the results of univariate and multivariate analysis

		1-year survival	2-year survival	p	HR (95% CI)	p
VA type	TDC	91.2%	77.7%	0.001*	3.8 (1.6-8.9)	0.002
	AVF	97.2%	95.7%			
Sex	m	91.1%	79.0%	0.065*	1.7 (0.9-3.2)	0.069
	f	96.5%	89.0%			
An attempt to create AVF or AVF which ceased to function prior to the observed VA	Yes	95.7%	87.4%	0.037*	1.8 (1.1-3.1)	0.040
	No	91.3%	78.6%			
Concomitant diabetes mellitus	Yes	91.2%	76.7%	0.021*	0.5 (0.3-0.9)	0.023
	No	94.8%	87.5%			
Stroke in patient's history	Yes	94.6%	72.9%	0.028*	0.5 (0.3-0.9)	0.031
	No	93.0%	84.9%			
Concomitant coronary heart disease	Yes	93.2%	68.9%	0.017*	0.5 (0.3-0.9)	0.019
	No	93.3%	88.2%			

Peripheral artery revascularization	Yes	100%	57.9%	0.028*	0.5 (0.2-0.9)	0.033
	No	92.7%	86.2%			
VA conversion	A	86.4%	64.8%	<0.001*	2.8 (1.5-5.0)	0.001
	B	97.1%	95.5%			
	C	95.0%	86.5%			
Hypertensive kidney disease		96.0%	96.0%	<0.001*	0.2 (0.1-0.5)	0.002
Glomerulonephritis		100%	100%	<0.001*	0 (0-0.3)	0.018
The age of patients at the initiation of HD treatment (years)					1.0 (1 -1.1)	0.037
Time from the initiation of HD treatment to the observed VA creation (months)					0.8 (0.7-0.9)	0.006

* Log Rank (Mantel-Cox) test
A TDC as an exclusive VA
B AVF as an exclusive VA
C The conversion of VA from AVF to TDC

Patient survival with respect to VA is shown in Figure 1b. Cumulative one-year survival of patients who were dialyzed exclusively via TDC was 91.2% and of those who were dialyzed exclusively via AVF 97.1% (p=0.001). With respect to VA conversion, one-year survival of patients who were converted from AVF to TDC was 95% (p=0.102 in comparison with AVF as an exclusive VA; p=0.002 in comparison with TDC as an exclusive VA).

In univariate analysis of risk factors for the survival of patients who were dialysed exclusively via TDC, there were four negative risk factors: male gender (p=0.010), concomitant diabetes mellitus (p=0.006), concomitant coronary artery disease (p=0.004) and prior peripheral artery revascularization (p=0.003). Factors positively associated with survival were shorter HD vintage prior to the current VA (p<0.001), an attempt to create AVF or AVF which ceased to function prior to the current VA (p=0.001), hypertensive renal disease (p=0.001) and glomerulonephritis (p=0.006). The results of univariate analysis are shown in Table 2. In the multivariate Cox regression only male gender turned out as an independent negative risk factor (p=0.019), while shorter HD vintage prior to the current VA (p<0.001), an attempt to create AVF or AVF which ceased to function prior to the current VA (p=0.039) and hypertensive kidney disease as the cause of ESRD were independently positively associated with survival.

Vascular access survival

Among the total of 190 TDC's, 124 (65.3%) were placed *de novo*. 58% of TDC's were placed in the right jugular vein, 11.2% in the left jugular vein, 17.6% in the right subclavian vein, 8.5% in the left subclavian vein, 2.7% in the right femoral vein and 2.1 % in the left femoral vein. The most frequent long-term complications were TDC thrombosis and infection. 6.8% of infections lead to TDC-associated sepsis and 6.3% were tunnel infections. 35.3% of these infections were cured, without catheter removal. TDC was replaced in 47.1% of infection cases and permanently removed in 5.9% of cases. 11.8% of infections ended in lethal outcome. The wound healing problems after TDC placement occurred in 5.8% of patients. Mechanical problems (rupture or separation of catheter lines, puncture or rupture of the clamp

or cap) were reported in 7% of cases. The mean blood pump speed for TDC's in use was 288±36 mL/min, mean pressure in the venous line of the dialysis machine was 158±35 mm Hg while mean pressure in the arterial line was -184±39 mm Hg. 20.3% of TDC's were closed with sodium citrate (Duraloc®) exclusively, 67.4% with heparin exclusively, the rest was closed occasionally with sodium citrate and occasionally with heparin. During a HD treatment it was necessary to switch TDC lines every time in 10.5% TDC's, occasionally in 62.1%, and never in 27.4%. During this monitoring process 50% of TDC's ceased to function. The causes of cessation are shown in Table 3.

Table 3. The causes of TDC function cessation

Cause	N (%)
Death of a patient	37 (43.0)
TDC thrombosis	14 (16.3)
TDC infection	9 (10.5)
VA conversion from TDC to AVF	8 (9.3)
Kidney transplantation	6 (7.0)
Recovery of renal function	2 (2.3)
Catheter fell out	1 (1.2)

TDC death-censored survival is shown in Figure 2. One-year death-censored TDC survival was 76.7%. In univariate analysis, there were four risk factors negatively associated with TDC survival: an attempt to create AVF or AVF which ceased to function prior to the current VA (p=0.010), TDC associated sepsis (p<0.001), tunnel infection (p<0.001) and mechanical problems with TDC (p<0.001). In the multivariate Cox regression an attempt to create AVF or AVF which ceased to function prior to the current VA (p=0.014), mechanical problems with TDC (p=0.002) and TDC lines' puncture or rupture (p=0.001) were independently negatively associated with TDC death-censored survival.

The mean blood pump speed for AVF in use was 318±36 mL/min, mean pressure in the venous line of the dialysis machine was 137±32 mmHg while mean pressure in the arterial line was -154±37 mmHg. During this monitoring process 13.4% of AVF ceased to function. The causes of cessation are shown in Table 4.

Table 4. The causes of AVF function cessation

Cause	N (%)
Death of a patient	5 (38.5)
AVF thrombosis	4 (30.8)
Vein rupture	2 (15.4)
Difficult AVF puncture or inadequate bloodflow	2 (15.4)

AVF death-censored survival is shown in Figure 2. One-year death-censored AVF survival was 96%. In univariate analysis, male gender was negatively associated with AVF death-censored survival (p=0.004). No variable was independently associated with death-censored AVF survival in multivariate Cox regression.

VA death-censored survival (both TDC and AVF) is shown in Figure 2. In univariate analysis, there were three factors negatively associated with VA death-censored survival: TDC as VA type (p<0.001), an attempt to create AVF or AVF which ceased to function prior to the observed VA (p<0.001) and TDC as an exclusive VA (p<0.001). In multivariate Cox regression, AVF as an exclusive VA was independently positively associated with VA survival (p<0.001).

DISCUSSION

This analysis defined factors associated with VA and patient survival in a real life situation, in a patient population treated in 21 dialysis centres across Croatia. The cause of ESRD in studied group of patients completely coincided with Croatian Registry of Renal Replacement Therapy data.[11] The frequency of concomitant diseases was alike in other developed countries. One year patient survival in this study was excellent, probably reflecting good hemodialysis care in Croatia. Female gender was independently positively associated with overall patient survival. This was previously shown in CHOICE study by Astor et al.[12] TDC as current VA, male gender and older age at initiation of HD treatment were independently negatively associated with overall patient survival.

In a recent cohort study of 3752 dialysis patients one-year survival of patients who were dialysed via TDC was 75% and factors independently negatively associated with survival were age at first treatment, late referral, coronary artery disease, peripheral vascular disease and cerebrovascular disease. One-year survival of patients dialysed via AVF was 90%.[13] There are several other studies that showed statistically significant difference in patient survival with respect to VA type.[12,14] Our study largely confirms previously observed statistically significant difference in survival between the two groups of HD patients and in the identified independent risk factors for the survival of patients who were dialyzed via TDC. However, our results showed that patients included in this study who were dialyzed via TDC and those who were dialyzed via AVF had better survival in comparison with previously published studies. Several studies showed that patient survival is associated with VA conversion and is better in patients who are converted from TDC to AVF during the first year of HD treatment.[10,15] Although our study did not include enough patients who underwent this kind of VA conversion analysis, we showed that survival was not significantly different in patients who were dialyzed exclusively via AVF and those who were converted from AVF to TDC. Therefore, it is likely that there are other factors beside TDC, that are responsible for lower survival of patients dialysed exclusively via TDC. Multivariate Cox regression showed that VA type is an independent risk factor for patient survival. The association of VA type with patient survival is controversial. Multiple studies, including ours, suggested negative correlation between TDC and patient survival.[9,10,12,14,16] On the other hand, according to

several retrospective studies, TDC *per se* may not be negatively associated with poor patient survival.[17,18] This issue could be clarified only by prospective randomized control studies, which are unlikely to be performed for ethical reasons.

Studying of the association of TDC with HD patient outcomes is important, because the number of patients who are dialyzed via TDC is steadily-increasing.[19,20] Approximately 20% of dialysis patients in Croatia are dialysed via TDC (Knotek M, personal communication). Although K/DOQI guidelines recommend that less than 10% of all patients treated with HD should be dialyzed via TDC, this goal remains unachieved.[20] The number of patients who initiate HD treatment via TDC is also much higher than recommended.[19] Possible reasons are late referral to a nephrologist, a lack of surgeon availability for the AVF creation and increasing proportion of elderly patients who are not eligible for AVF creation due to their poor blood vessels status.[21]

In one British study of 812 TDC, one-year death-censored TDC survival of 61% was demonstrated.[22] Another study of 200 Tessio catheters reported an one-year death-censored catheter survival of 60%.[23] Our results show significantly better one-year TDC survival, in comparison with these previously published studies. According to guidelines, right jugular vein was the insertion site of choice at our centre, but this study did not find a statistically significant difference between the insertion site and TDC survival (data not shown). This may be due to low power of this study for this analysis, as number of TDC inserted at other sites was low.

In conclusion, we found in the present study that TDC may be an independent negative risk factor for HD patient survival and has shorter lifetime in comparison with AVF. However, our results stem from a retrospective study and adequately powered prospective randomized controlled trial would be necessary to prove causality of association of TDC with worse hemodialysis patient outcome.

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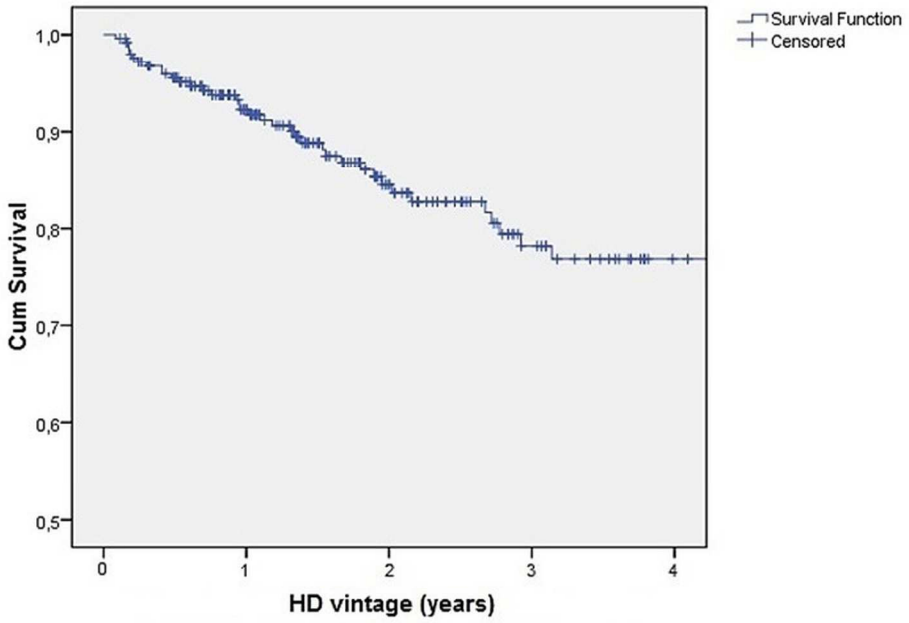
Figures:

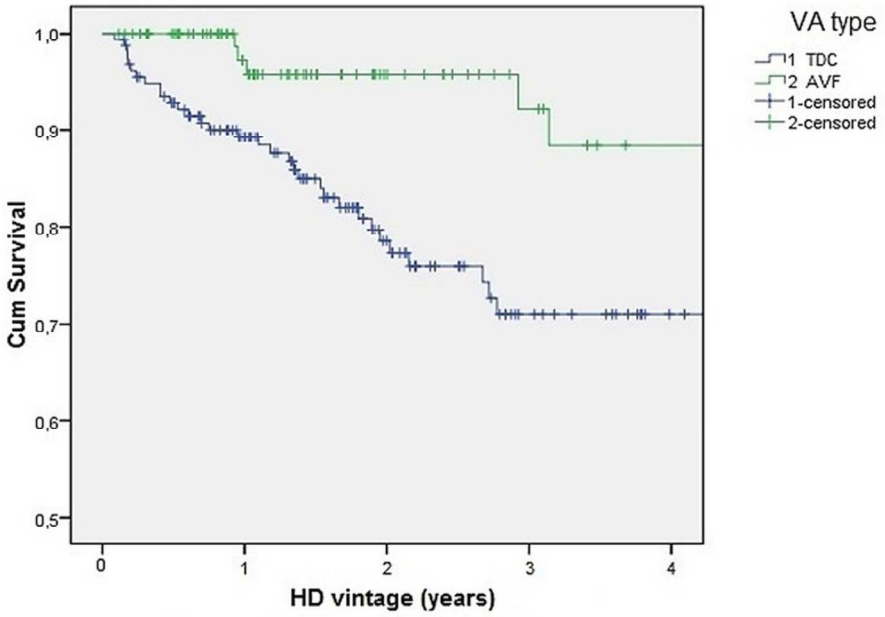
Figure 1a. Kaplan-Meier Curve for Overall HD Patients Survival

Figure 1b. Kaplan-Meier Curve for HD Patients Survival With Respect to Vascular Access

Figure2. Kaplan-Meier Curve for Vascular Access Death-censored Survival



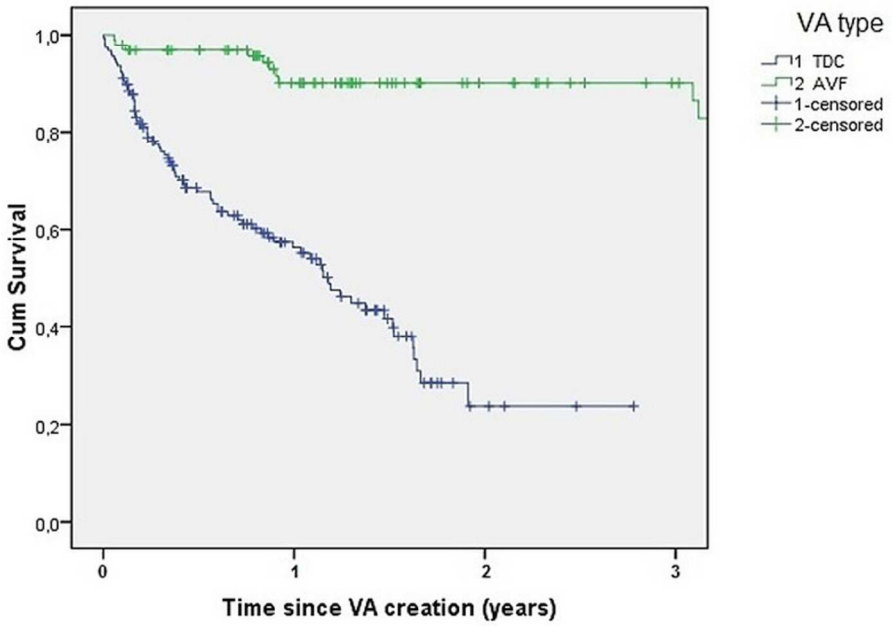
Overall patient survival
169x142mm (300 x 300 DPI)



No. at risk

TDC	156	140	129	124	124
AVF	97	95	94	93	92

Patient survival with respect to vascular access
177x155mm (300 x 300 DPI)



No. at risk

TDC	190	139	100	96
AVF	97	89	88	86

Vascular access death-censored survival
176x154mm (300 x 300 DPI)

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Tunneled hemodialysis catheter and hemodialysis outcomes: a retrospective cohort study in Zagreb, Croatia

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Tunneled hemodialysis catheter and hemodialysis outcomes: a retrospective cohort study in Zagreb, Croatia

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ABSTRACT

Objectives: Studies have reported that tunneled dialysis catheter (TDC) is associated with inferior hemodialysis (HD) patient survival, in comparison with arteriovenous fistula (AVF). Since many cofactors may also affect survival of HD patients, it is unclear whether the risk for the worse survival arises from TDC *per se,* or from associated conditions. Therefore, the aim of this study was to determine in a multivariate analysis the long-term outcome of HD patients, with respect to vascular access (VA).

Design: Retrospective cohort study

Participants: This retrospective cohort study included all 156 patients with TDC placed from 2010 to 2012 at University Hospital Merkur. Control group consisted of 97 patients dialysed via AVF. The groups were matched according to dialysis unit and time of VA placement. The site of choice for the placement of TDC was right jugular vein. Kaplan-Meier analysis with log-rank test was used to assess patient survival. A multivariate Cox regresion analysis was used to determine independent variables associated with the patient survival.

Primary outcome measures: Patient survival with respect to VA.

Results: Cumulative one-year survival of patients who were dialysed exclusively via TDC was 86.4 % and of those who were dialysed exclusively via AVF the survival was 97.1 % (p=0.002). In a multivariate Cox regression analysis, male sex and older age were independently negatively associated with the survival of HD patients, while shorter HD vintage before the creation of the observed VA, hypertensive renal disease and glomerulonephritis were positively associated with survival. TDC was an independent risk factor for survival of HD patients (HR 23.0, 95% CI 6.2-85.3).

Conclusion: TDC may be an independent negative risk factor for HD patient survival.

STRENGHTS AND LIMITATIONS OF THIS STUDY

- This is a retrospective cohort study, in which well matched patients followed by multiple dialysis centres were included. Therefore, study results account for variations in routine patient care at different centres and are reflective of a real life practice. This is important, because a prospective randomized trial comparing patient survival with respect to vascular access type (AV fistula and tunneled dialysis catheter) is highly unlikely.
- Main outcomes (patient and vascular access survival) were analyzed by a multivariate analysis.
- The main limitation of this study is its retrospective and non-randomized design. However, the two patient groups were well matched in majority of the variables that may have affected the outcome.

INTRODUCTION

The number of patients with end-stage chronic kidney disease (ESRD) in need of renal replacement therapy increases progressively in Europe and worldwide.[1] This puts CKD among the significant factors of morbidity and mortality and represents a growing public health issue.

In patients on hemodialysis (HD) treatment, possible long-term vascular access (VA) types are: arteriovenous fistula (AVF), arteriovenous graft (AVG) and tunnelled hemodialysis central venous catheter (TDC). Since native AVF that Brescia and Cimino described in 1966 has the longest survival and the lowest frequency of complications among all other types of VA for HD, it should be the first choice for VA whenever possible.[1,2,3] However, there are vast differences in the use of certain VA types in different countries and the use of TDC is still noticeably high, in spite of current guidelines. The rate of patients who are dialyzed via TDC among all patients on HD varies from only 1.6% in Japan up to 52% in Canada.[4] In Croatia approximately 20% of patients are dialysed via TDC, while the rest is dialysed via AVF (Knotek M, personal communication). Arteriovenous graft is infrequently used in Croatia.

Central venous catheters (CVC) are used for the rapid establishment of adequate VA when there is an an urgent need for HD, as a bridge during AVF maturation process and in patients who have eventually exhausted all other VA types.[1,3,5] According to the K/DOQI guidelines temporary catheters should be used up to one week, while the usage of TDC is recommended in all other cases, where catheter is unavoidable.[6] TDC are usually placed according to the modified Seldinger method.[7] The insertion site of choice should be right internal jugular vein.[8] Alternatively, TDC can be inserted through the subclavian or femoral vein. Subclavian vein should be generally avoided because of the high incidence of stenosis and thrombosis, while the femoral vein should be considered only when all other insertion sites have been excluded.[1] The advantages of TDC include the ability to use it immediately after placement, no repeated venipuncture nor hemodynamic consequences, and no need for vascular surgeon during placement.[4] Nevertheless, TDCs are associated with significantly higher long-term risk of death, infections, cardiovascular events and hospitalization in comparison with other VA types.[9] However, some of the associated conditions and diseases affect at the same time the patient survival, as well as the VA choice and survival. Therefore, although many studies show that TDC are associated with poorer patient survival, it is not entirely clear whether the risk arises from TDC exclusively or from the associated conditions and diseases that are often present in patients who are dialyzed via TDC. [9,10]

The aim of this study was to determine HD patient and VA survival with respect to VA type.

PATIENTS AND METHODS

Patients

This retrospective cohort study was approved by the Hospital Ethics Committee of the University Hospital Merkur, Zagreb, Croatia. Patients gave their written informed consent for anonymised HD data collection for research purposes. We analysed the survival of patients dialysed via TDC in comparison with a group of patients who were dialysed via an AVF. We also analysed TDC survival. The study included a total of 253 patients who were treated with HD in 21 dialysis centre in Croatia; median 16 (IQR 10, 21) per centre. With respect to VA, the TDC:AVF ratio was approximately 2:1. The study subjects were selected to include all 156 patients who received a total of 190 TDC at Renal Division in University Hospital Merkur from the beginning of 2010 to the end of 2012. Then 97 patients who were dialysed via AVF were selected from the same dialysis centres. Eligible patients dialysed via AVF had to start with HD treatment at about the same time as patients dialysed via TDC. The insertion site of choice for TDC was right jugular vein. Other sites were used in case of inability to use right jugular vein or when exchanging over previously inserted TDC in another vein. All TDC were manufactured by the Medcomp Inc. (Harleysville, PA). For internal jugular and subclavian approach either SST28SE or SST32SE catheters were used, while SST40SE catheters were used for femoral approach. All catheters were 14F.

Methods

Data were collected from the Renal Division TDC placement programme database and by a questionnaire sent to 21 HD centres whose patients underwent TDC placement procedure in our Division. In the questionnaire we asked for the following information: demographic data, the date of first HD, history of a temporary CVC before the observed TDC, history of an attempt to create AVF or history of functional AVF which ceased to function, the cause of CKD, concomitant diseases, history of catheter sepsis, history of an infection of TDC tunnel, were there problems with wound healing after TDC placement, were there any mechanical problems with TDC and what solution was TDC usually locked with upon the completion of HD treatment. If the TDC was in function, it was asked for the blood pump speed, and for arterial and venous pressure during HD treatment. If TDC ceased to function, we recorded the date of cessation of TDC function, the reason for cessation of TDC function, current VA if the patient was still treated with HD, the date of transplantation if the patient underwent a kidney transplantation and the date of death if the patient died. A similar, modified questionnaire was used to collect data about patients who were dialyzed via AVF.

Statistical analysis

Numerical data are presented as mean±SD in case of continuous variables with normal distribution or as median with IQR in case of not normal distribution. The difference between two groups in continuous variables was tested with Student's t-test in normal distributed variables or with Mann-Whitney's U test in non-normally distributed variables. The difference between two groups in categorical variables was tested with Pearson's chi-squared test. Survival analysis which included patient survival, overall VA survival and death-censored

VA survival was performed by using Kaplan-Meier's analysis. Univariate and multivariate Cox regression were performed to determine variables independently associated with patient and VA survival. All variables that were associated with respective outcome in bivariate analysis (at $p \leq 0.1$) were included in the multivariate Cox regression. Results are presented as hazard ratio (HR) with the corresponding 95% confidence interval (CI). Statistical significance was considered at p value < 0.05. All statistical analyses were performed by using SPSS 17.0.

RESULTS

Characteristics of patients dialysed via TDC

Patient characteristics are shown in Table 1. There were 156 patients dialysed via TDC. The cause of ESRD was diabetic nephropathy in 42.3% of patients, hypertensive kidney disease in 23.1%, glomerulonephritis in 9.6%, polycystic kidney disease in 5.8% and other diseases in 19.2% of patients. 69.9% of patients had a temporary dialysis catheter prior to the observed TDC, 20.5% had previous TDC and 50.6% had an attempt to create AVF or AVF which ceased to function. During follow-up 152 (97,4%) patients were dialyzed via TDC exclusively, while 4 (2,6%) switched to AVF.

Table 1 Characteristics of patients

	all patients	TDC	AVF	P
The age of patients at the initiation of HD treatment (years)*	62.7±14.0	62.1±14.4	63.9±13.2	0.215
The age of patients at the VA creation (years)*	63.8±13.9	63.7±14.2	64.0±13.4	0.737
The age of patients at the end of follow-up (years)*	65.8±13.9	65.2±14.3	66.9±12.9	0.248
Sex (m/f)	152/101	88/68	64/33	0.081
HD vintage (days)**	607 (335, 1088)	658 (374, 1114)	536 (320, 1139)	0.836
HD vintage before the observed VA creation (days)**	50 (5, 348)	204 (33, 799)	7 (0, 66)	<0.001
Diabetes mellitus	42.7%	44.2%	40.2%	0.464
Coronary heart disease	20.6%	20.5%	20.6%	0.851
Stroke	11.9%	16.7%	4.1%	0.001
Peripheral vascular disease	20.2%	19.9%	20.6%	0.902
Peripheral artery revascularization	6.3%	6.4%	6.2%	0.228
Partial or total limb amputation	14.2%	15.4%	12.4%	0.599

* mean ± SD

** median with IQR

Characteristics of patients dialysed via AVF

There were 97 patients dialysed via AVF. The cause of ESRD was diabetic nephropathy in 40.2% of patients, hypertensive kidney disease in 20.6%, glomerulonephritis in 11.3%, polycystic kidney disease in 10.3% and other diseases in 17.5% of patients. 23.7% of patients an attempt to create AVF or AVF which ceased to function prior to the observed AVF. During follow-up 91 (93,8%) patients were dialyzed via AVF exclusively, while 6 (6,2%) switched to TDC. Patient characteristics are also shown in Table 1.

Patient survival

Patient survival is shown in Figure 1a. Cumulative one-year overall patient survival since the initiation of HD treatment was 93.2%. In univariate analysis of risk factors for the overall patient survival, there were eight negative risk factors: TDC as current VA (p=0.001), TDC as an exclusive VA (p=0.001), male gender (p=0.065), older age at the initiation of HD treatment (p=0.006), concomitant diabetes mellitus (p=0.021), stroke in patient's history (p= 0.028), concomitant coronary heart disease (p=0.017) and prior peripheral artery revascularization (p=0.028). Factors positively associated with overall patient survival were shorter HD vintage prior to the observed VA (p=0.004) and an attempt to create AVF or history of AVF which ceased to function prior to the current VA (p=0.037). With respect to ESRD, hypertensive renal disease (p=0.001) and glomerulonephritis (p=0.002) were positively associated with overall patient survival. The results of univariate analysis are shown in Table 2. In the multivariate Cox regression two factors turned out as an independent negative risk factors for the overall patient survival: male gender (p=0.012) and older age at the initiation of HD treatment (p=0.037). Shorter HD vintage prior to the observed VA (p<0.001), hypertensive renal disease (p=0.002) and glomerulonephritis (p=0.018) were independently positively associated with overall patient survival. TDC was independently negatively associated with patient survival in the multivariate analysis (HR 23.0, 95% CI 6.2-85.3).

Table 2. Patient survival- the results of univariate and multivariate analysis

		1-year survival	2-year survival	p	HR (95% CI)	p
VA type	TDC	91.2%	77.7%	0.001*	3.8 (1.6-8.9)	0.002
	AVF	97.2%	95.7%			
Sex	m	91.1%	79.0%	0.065*	1.7 (0.9-3.2)	0.069
	f	96.5%	89.0%			
An attempt to create AVF or AVF which ceased to function prior to the observed VA	Yes	95.7%	87.4%	0.037*	1.8 (1.1-3.1)	0.040
	No	91.3%	78.6%			
Concomitant diabetes mellitus	Yes	91.2%	76.7%	0.021*	0.5 (0.3-0.9)	0.023
	No	94.8%	87.5%			
Stroke in patient's history	Yes	94.6%	72.9%	0.028*	0.5 (0.3-0.9)	0.031

	No	93.0%	84.9%			
Concomitant coronary heart disease	Yes	93.2%	68.9%	0.017*	0.5 (0.3-0.9)	0.019
	No	93.3%	88.2%			
Peripheral artery revascularization	Yes	100%	57.9%	0.028*	0.5 (0.2-0.9)	0.033
	No	92.7%	86.2%			
VA conversion	A	86.4%	64.8%	<0.001*	2.8 (1.5-5.0)	0.001
	B	97.1%	95.5%			
	C	95.0%	86.5%			
Hypertensive kidney disease		96.0%	96.0%	<0.001*	0.2 (0.1-0.5)	0.002
Glomerulonephritis		100%	100%	<0.001*	0 (0-0.3)	0.018
The age of patients at the initiation of HD treatment (years)					1.0 (1 -1.1)	0.037
Time from the initiation of HD treatment to the observed VA creation (months)					0.8 (0.7-0.9)	0.006

* Log Rank (Mantel-Cox) test
A TDC as an exclusive VA
B AVF as an exclusive VA
C The conversion of VA from AVF to TDC

Patient survival with respect to VA is shown in Figure 1b. Cumulative one-year survival of patients who were dialyzed exclusively via TDC was 91.2% and of those who were dialyzed exclusively via AVF 97.1% (p=0.001). With respect to VA conversion, one-year survival of patients who were converted from AVF to TDC was 95% (p=0.102 in comparison with AVF as an exclusive VA; p=0.002 in comparison with TDC as an exclusive VA).

In univariate analysis of risk factors for the survival of patients who were dialysed exclusively via TDC, there were four negative risk factors: male gender (p=0.010), concomitant diabetes mellitus (p=0.006), concomitant coronary artery disease (p=0.004) and prior peripheral artery revascularization (p=0.003). Factors positively associated with survival were shorter HD vintage prior to the current VA (p<0.001), an attempt to create AVF or AVF which ceased to function prior to the current VA (p=0.001), hypertensive renal disease (p=0.001) and glomerulonephritis (p=0.006). The results of univariate analysis are shown in Table 2. In the multivariate Cox regression only male gender turned out as an independent negative risk factor (p=0.019), while shorter HD vintage prior to the current VA (p<0.001), an attempt to create AVF or AVF which ceased to function prior to the current VA (p=0.039) and hypertensive kidney disease as the cause of ESRD were independently positively associated with survival.

Vascular access survival

Among the total of 190 TDC's, 124 (65.3%) were placed *de novo*. 58% of TDC's were placed in the right jugular vein, 11.2% in the left jugular vein, 17.6% in the right subclavian vein, 8.5% in the left subclavian vein, 2.7% in the right femoral vein and 2.1 % in the left femoral vein. The most frequent long-term complications were TDC thrombosis and infection. 6.8% of infections lead to TDC-associated sepsis and 6.3% were tunnel infections. 35.3% of these infections were cured, without catheter removal. TDC was replaced in 47.1% of infection

cases and permanently removed in 5.9% of cases. 11.8% of infections ended in lethal outcome. The wound healing problems after TDC placement occurred in 5.8% of patients. Mechanical problems (rupture or separation of catheter lines, puncture or rupture of the clamp or cap) were reported in 7% of cases. The mean blood pump speed for TDC's in use was 288±36 mL/min, mean pressure in the venous line of the dialysis machine was 158±35 mm Hg while mean pressure in the arterial line was -184±39 mm Hg. 20.3% of TDC's were closed with sodium citrate (Duraloc®) exclusively, 67.4% with heparin exclusively, the rest was closed occasionally with sodium citrate and occasionally with heparin. During a HD treatment it was necessary to switch TDC lines every time in 10.5% TDC's, occasionally in 62.1%, and never in 27.4%. During this monitoring process 50% of TDC's ceased to function. The causes of cessation are shown in Table 3.

Table 3. The causes of TDC function cessation

Cause	N (%)
Death of a patient	37 (43.0)
TDC thrombosis	14 (16.3)
TDC infection	9 (10.5)
VA conversion from TDC to AVF	8 (9.3)
Kidney transplantation	6 (7.0)
Recovery of renal function	2 (2.3)
Catheter fell out	1 (1.2)

TDC death-censored survival is shown in Figure 2. One-year death-censored TDC survival was 76.7%. In univariate analysis, there were four risk factors negatively associated with TDC survival: an attempt to create AVF or AVF which ceased to function prior to the current VA ($p=0.010$), TDC associated sepsis ($p<0.001$), tunnel infection ($p<0.001$) and mechanical problems with TDC ($p<0.001$). In the multivariate Cox regression an attempt to create AVF or AVF which ceased to function prior to the current VA ($p=0.014$), mechanical problems with TDC ($p=0.002$) and TDC lines' puncture or rupture ($p=0.001$) were independently negatively associated with TDC death-censored survival.

The mean blood pump speed for AVF in use was 318±36 mL/min, mean pressure in the venous line of the dialysis machine was 137±32 mmHg while mean pressure in the arterial line was -154±37 mmHg. During this monitoring process 13.4% of AVF ceased to function. The causes of cessation are shown in Table 4.

Table 4. The causes of AVF function cessation

Cause	N (%)
Death of a patient	5 (38.5)
AVF thrombosis	4 (30.8)

Vein rupture	2 (15.4)
Difficult AVF puncture or inadequate bloodflow	2 (15.4)

AVF death-censored survival is shown in Figure 2. One-year death-censored AVF survival was 96%. In univariate analysis, male gender was negatively associated with AVF death-censored survival (p=0.004). No variable was independently associated with death-censored AVF survival in multivariate Cox regression.

VA death-censored survival (both TDC and AVF) is shown in Figure 2. In univariate analysis, there were three factors negatively associated with VA death-censored survival: TDC as VA type (p<0.001), an attempt to create AVF or AVF which ceased to function prior to the observed VA (p<0.001) and TDC as an exclusive VA (p<0.001). In multivariate Cox regression, AVF as an exclusive VA was independently positively associated with VA survival (p<0.001).

DISCUSSION

This analysis defined factors associated with VA and patient survival in a real life situation, in a patient population treated in 21 dialysis centres across Croatia. The cause of ESRD in studied group of patients completely coincided with Croatian Registry of Renal Replacement Therapy data.[11] The frequency of concomitant diseases was alike in other developed countries. One year patient survival in this study was excellent, probably reflecting good hemodialysis care in Croatia. Female gender was independently positively associated with overall patient survival. This was previously shown in CHOICE study by Astor et al.[12] TDC as current VA, male gender and older age at initiation of HD treatment were independently negatively associated with overall patient survival.

In a recent cohort study of 3752 dialysis patients one-year survival of patients who were dialysed via TDC was 75% and factors independently negatively associated with survival were age at first treatment, late referral, coronary artery disease, peripheral vascular disease and cerebrovascular disease. One-year survival of patients dialysed via AVF was 90%.[13] There are several other studies that showed statistically significant difference in patient survival with respect to VA type.[12,14] Our study largely confirms previously observed statistically significant difference in survival between the two groups of HD patients and in the identified independent risk factors for the survival of patients who were dialyzed via TDC. However, our results showed that patients included in this study who were dialyzed via TDC and those who were dialyzed via AVF had better survival in comparison with previously published studies. Several studies showed that patient survival is associated with VA conversion and is better in patients who are converted from TDC to AVF during the first year of HD treatment.[10,15] Although our study did not include enough patients who underwent this

kind of VA conversion analysis, we showed that survival was not significantly different in patients who were dialyzed exclusively via AVF and those who were converted from AVF to TDC. Therefore, it is likely that there are other factors beside TDC, that are responsible for lower survival of patients dialysed exclusively via TDC. Multivariate Cox regression showed that VA type is an independent risk factor for patient survival. The association of VA type with patient survival is controversial. Multiple studies, including ours, suggested negative correlation between TDC and patient survival.[9,10,12,14,16] On the other hand, according to several retrospective studies, TDC *per se* may not be negatively associated with poor patient survival.[17,18] This issue could be clarified only by prospective randomized control studies, which are difficult to perform.

Studying of the association of TDC with HD patient outcomes is important, because the number of patients who are dialyzed via TDC is steadily-increasing.[19,20] Approximately 20% of dialysis patients in Croatia are dialysed via TDC (Knotek M, personal communication). Although K/DOQI guidelines recommend that less than 10% of all patients treated with HD should be dialyzed via TDC, this goal remains unachieved.[20] The number of patients who initiate HD treatment via TDC is also much higher than recommended.[19] Possible reasons are late referral to a nephrologist, a lack of surgeon availability for the AVF creation and increasing proportion of elderly patients who are not eligible for AVF creation due to their poor blood vessels status.[21]

In one British study of 812 TDC, one-year death-censored TDC survival of 61% was demonstrated.[22] Another study of 200 Tessio catheters reported an one-year death-censored catheter survival of 60%.[23] Our results show significantly better one-year TDC survival, in comparison with these previously published studies. According to guidelines, right jugular vein was the insertion site of choice at our centre, but this study did not find a statistically significant difference between the insertion site and TDC survival (data not shown). This may be due to low power of this study for this analysis, as number of TDC inserted at other sites was low.

In conclusion, we found in the present study that TDC may be an independent negative risk factor for HD patient survival and has shorter lifetime in comparison with AVF. However, our results stem from a retrospective study and adequately powered prospective randomized controlled trial would be necessary to prove causality of association of TDC with worse hemodialysis patient outcome.

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A portion of this study has been accepted for poster presentation at the 2015 American Society of Nephrology Annual Meeting, San Diego, CA

CONTRIBUTORSHIP STATEMENT

Dr Pašara participated in designing the study, collected and analysed data and wrote the manuscript.
Dr. Maksimović, Gunjača and Mihovilović participated in designing the study and collection of the data and critically reviewed the manuscript.
Dr. Lončar, Kudumija and Žabić participated in designing the study, data collection and critically reviwed the manuscript.
Dr. Knotek supervised design of the study, co-ordinated and supervised data collection and analysis and has participated in writing the manuscript.

COMPETING INTERESTS

None.

FUNDING

None.

DATA SHARING STATEMENT

No additional data available.

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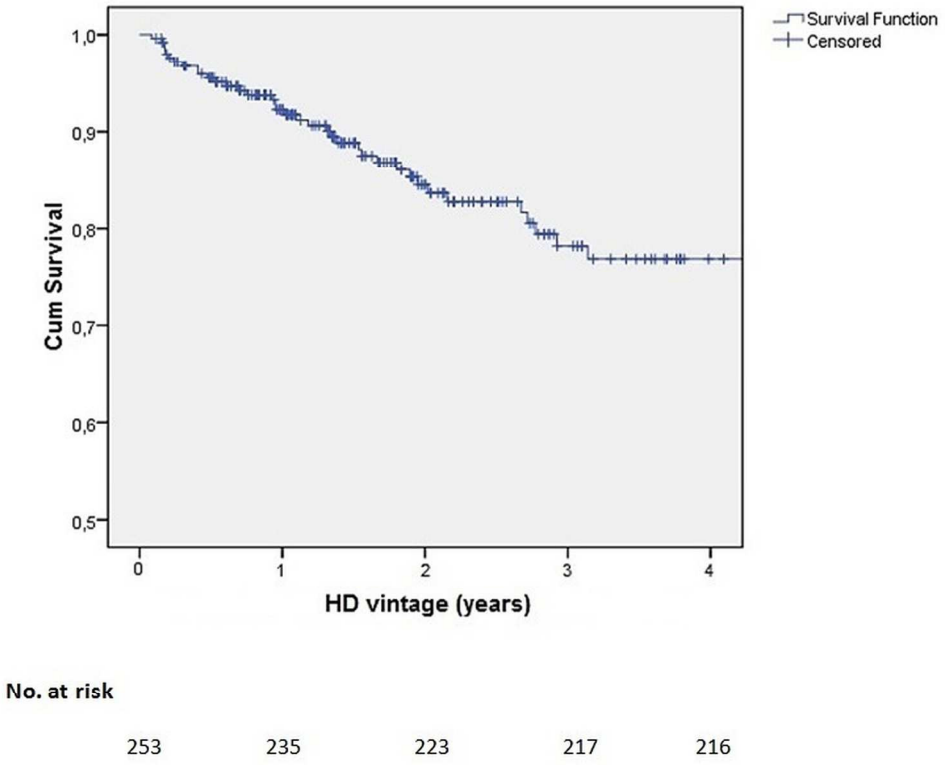
Figures:

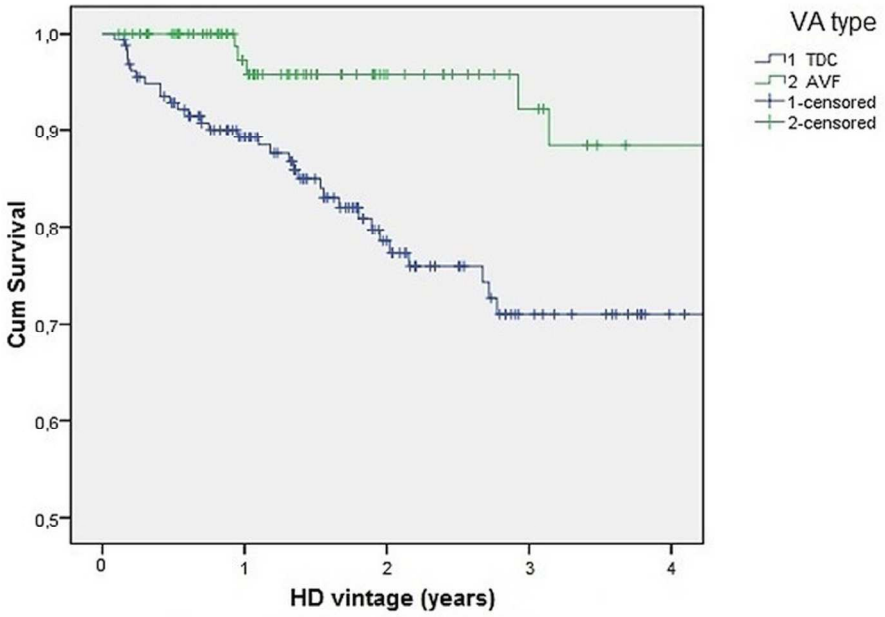
Figure 1a. Kaplan-Meier Curve for Overall HD Patients Survival

Figure 1b. Kaplan-Meier Curve for HD Patients Survival With Respect to Vascular Access

Figure2. Kaplan-Meier Curve for Vascular Access Death-censored Survival



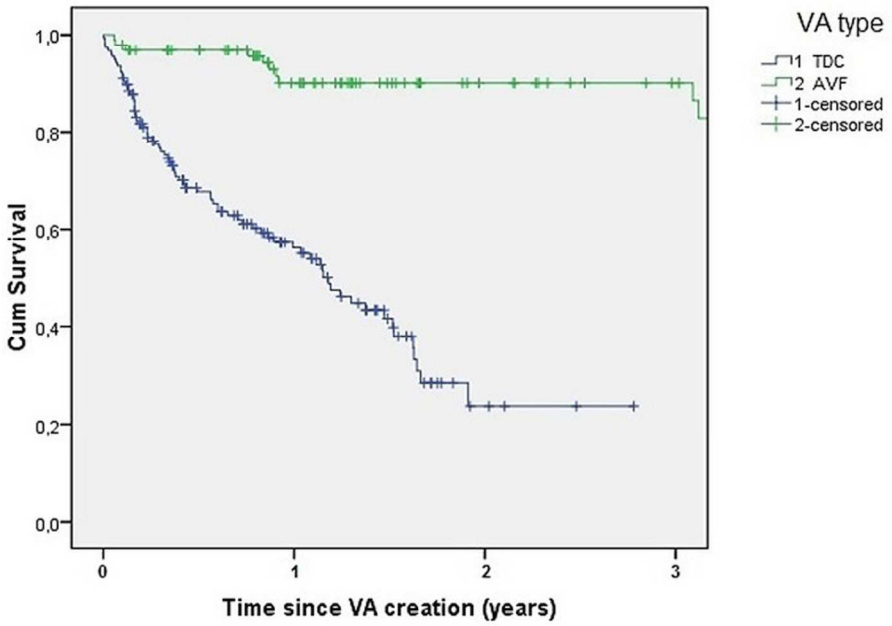
Overall patient survival
169x142mm (300 x 300 DPI)



No. at risk

TDC	156	140	129	124	124
AVF	97	95	94	93	92

Patient survival with respect to vascular access
177x155mm (300 x 300 DPI)



No. at risk

TDC	190	139	100	96
AVF	97	89	88	86

Vascular access death-censored survival
176x154mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **[Within the title page 1 and design section of the abstract page 2]**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **[See participants and results section of abstract page 2]**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **[Introduction page 3]**
Objectives	3	State specific objectives, including any prespecified hypotheses **[Within objectives section of the abstract page 2 and Introduction page 3]**
Methods		
Study design	4	Present key elements of study design early in the paper **[Patients and methods page 5]**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **[Page 5]**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **[Page 5]** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **[Page 5]**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **[Page 5]**
Bias	9	Describe any efforts to address potential sources of bias **[Page 5]**
Study size	10	Explain how the study size was arrived at **[Page 5]**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **[Page 5]**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **[Pages 5-6]**
		(*b*) Describe any methods used to examine subgroups and interactions **[Pages 5-6]**
		(*c*) Explain how missing data were addressed **[N/A]**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed **[N/A]** *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy

(*e*) Describe any sensitivity analyses **[N/A]**

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **[Pages 6-7, Table 1 and within results section of the abstract page 2]**
		(b) Give reasons for non-participation at each stage **[N/A]**
		(c) Consider use of a flow diagram **[N/A information in Table 1]**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **[Pages 6-7, Table 1]**
		(b) Indicate number of participants with missing data for each variable of interest **[N/A]**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **[Pages 6-7, Table 1-4]**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **[Pages 6-7, Table 1-4]**
		(*b*) Report category boundaries when continuous variables were categorized **[N/A]**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **[N/A]**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **[N/A]**
Discussion		
Key results	18	Summarise key results with reference to study objectives **[Pages 10-11]**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **[Pages 10-11 and within Strenghts and limitations section page 3]**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **[Pages 10-11]**
Generalisability	21	Discuss the generalisability (external validity) of the study results **[Pages 10-11]**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **[within funding section page 3]**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.