

ORIGINAL ARTICLE

Biochemical Factors Affecting Thrombosis Development in Permanent Tunneled Hemodialysis Catheter

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SUMMARY

Background: It is critical to clarify the biochemical factors associated with thrombosis development following tunneled dialysis catheter (TDC) insertion.

Methods: The study involved retrospective analysis of charts of patients hospitalized for permanent TDC placement between 2013 and 2020 in a tertiary academic center. Patients undergoing a hemodialysis schedule with permanent TDC for more than three months were included in the study. To determine predictive factors associated with thrombosis development in permanent TDC, patients were assigned to one of two groups, according to the extent of thrombosis. The groups were compared in terms of demographic characteristics, blood test values, complication and length of follow-up period.

Results: A total of 350 patients (204 female, 146 male) were enrolled into the study. In patients with thrombosis the mean BMI was found significantly higher ($p = 0.001$) and presence of diabetes mellitus was significantly common ($p = 0.014$). Patients with thrombosis had significantly higher D-dimer (6.5 vs. 2.4 $\mu\text{g/mL}$, $p = 0.001$) and procalcitonin levels (4.1 vs. 1.4 ng/mL , $p = 0.001$). Additionally, patients with thrombosis had a significantly higher rate of infective complications ($p = 0.014$). Logistic regression analysis revealed that $\text{BMI} > 30 \text{ kg/m}^2$ and infective complications increased thrombosis risk 3.842 and 3.104 times ($p = 0.004$ and $p = 0.038$, respectively). Additionally, D-dimer level $> 3 \mu\text{g/mL}$ and procalcitonin level $> 2 \text{ ng/mL}$ were significantly associated with the development of thrombosis ($p = 0.001$ and $p = 0.007$).

Conclusions: The present study demonstrated that the presence of infection, higher $\text{BMI} > 30 \text{ kg/m}^2$, D-dimer level $> 3 \mu\text{g/mL}$ and procalcitonin level $> 2 \text{ ng/mL}$ were found to increase the incidence of thrombosis.

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KEY WORDS

hemodialysis, vascular access, thrombosis, tunneled hemodialysis catheter

INTRODUCTION

Chronic kidney disease (CKD) is very common, affecting almost 10% of the population worldwide [1]. Despite the advances in healthcare systems, millions of individuals with CKD lack access to adequate treatment, according to the World Health Organization. Liyagane et al. reported that almost 5 million lives were lost due to lack of access to chronic hemodialysis needed to treat

end-stage kidney disease [2]. Recently, arterio-venous fistulas, grafts, and permanent catheters have become access options for hemodialysis.

Tunneled dialysis catheter (TDC) was approved for use in hemodialysis; however, in the early 2000's, guidelines recommended avoiding the use of TDC without the provision for permanent access. In 2019, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative advised the use of TDC in the following cases: the absence of opportunity for arterio-venous access, multiple unsuccessful access creation without any option for hemodialysis access, and limited life expectancy [3]. Previous reports have demonstrated the effectiveness and reliability of TDC in patients undergoing permanent hemodialysis, while also highlighting serious possible complications of TDC placement. Arterial puncture, hematoma formation, nerve injury, pneumothorax, hemothorax, catheter dysfunction, and arrhythmia can be considered as early procedural complications. Late complications include catheter-associated infections, dislodgments, occlusions, sepsis, and thrombosis [4,5]. Arpacı et al. found a thrombosis rate of 25% after TDC placement, stating that 46% of these patients required TDC replacement [6]. In another study, Castro et al. found a 7.9% thrombosis following TDC insertion [3].

Although previous research investigated thrombosis rate following TDC placement in patients undergoing hemodialysis, no study has investigated the predictive factors for thrombosis development following hemodialysis access with TDC. In the present study, we aimed to clarify factors associated with thrombosis development following TDC insertion.

MATERIALS AND METHODS

Study population

The present study was conducted in accordance with the principles of the Declaration of Helsinki. After the Institutional Review Board approval (date/no.: 22.12.2020-3091), we reviewed charts of patients hospitalized for permanent TDC placement between 2013 and 2020 in a tertiary academic center. The informed consent for use of personal data in academic research was obtained from all patients and/or their relatives. Patients undergoing a hemodialysis schedule with permanent TDC for more than three months were included in the study. The indications of vascular access with permanent TDC were the inability to achieve vascular access with arterio-venous fistula, limited life expectation, and patients' choice. Also, permanent TDC was placed in patients awaiting transplantation and maturation of autogenous arterio-venous fistula. Patients were excluded if they were under 18 years old, had missing demographic data, or lost their lives in the follow-up period. Unsuccessful cases were also excluded.

An exhaustive medical history was obtained, and a detailed physical examination was conducted on all pa-

tients. Records were made of patients' demographic characteristics including age, gender, body mass index (BMI), comorbidities and thrombosis history, and also number of postoperative white blood cell (WBC) and blood platelet (PLT), fibrinogen concentration, procalcitonin, and D-dimer level.

Permanent TDC Placement Technique

All patients in the present study were evaluated by a nephrologist and referred by the cardiovascular surgery department. To determine any venous pathology, pre-procedural ultrasonography was performed for venous mapping and venous diameter assessment. All patients received standard instructions before permanent TDC placement. All procedures were performed by at least two experienced cardiovascular surgeons. After being given local anesthesia with prilocaine (Citanest® Astra Zeneca, Germany) and/or sedation with 2 to 3 mg midazolam, patients underwent venous puncture under ultrasonography guidance to the targeted vein, and catheter location was confirmed by fluoroscopy. Each limb of the permanent TDC was flushed with 10 mL of sterile saline solution and 5,000 U/mL concentrated heparin which was left in situ until the next dialysis session. Records were made of the site and location of permanent TDC placement.

All patients were assessed in terms of complication and survival in follow-ups. Complications were classified as thrombosis, infective complications or other complications. Additionally, follow-up duration was also recorded. To determine predictive factors associated with thrombosis development in permanent TDC, patients were assigned to one of two groups according to the presence of thrombosis. The groups were compared in terms of demographic characteristics, blood test values, complications, and length of follow-up period.

Statistical analysis

The Statistical Package for Social Sciences version 25 (SPSS IBM Corp., Armonk, NY, USA) program was used. Normality of distribution of the variables was determined by Shapiro-Wilk test and Q-Q plots. Independent Student's *t*-test was used for comparison of the normally distributed variable between the groups, and Mann-Whitney U test was used for non-normally distributed data. Quantitative data are showed as mean \pm standard derivation values. Categorical variables were grouped and compared using the χ^2 test or Fisher's exact test. Binary logistic regression analysis was used to evaluate parameters that were significant in univariate regression analysis. Kaplan-Meier curve was used to evaluate thrombosis development times. The data were analyzed at a 95% confidence level, and a p-value of less than 0.05 was considered statistically significant.

Table 1. Demographic data and procedure information of all patients included in the study.

n:350	
Age (years)	60.8 ± 14.6
Gender	
Female	204 (58.3%)
Male	146 (41.7%)
BMI (kg/m ²) *	26.5 ± 5.3
Comorbidity	
Hypertension	214 (61.1%)
Diabetes mellitus	177 (50.05%)
Coronary artery disease	182 (52.0%)
Chronic kidney disease	299 (85.4%)
ASA score *	2.1 ± 0.8
Thrombosis history	
Yes	17 (4.8%)
No	333 (95.2%)
Side	
Right	175 (50.0%)
Left	175 (50.0%)
Localization	
Internal jugular vein	324 (92.5%)
Femoral vein	7 (2.1%)
Subclavian vein	19 (5.4%)
WBC (L) *	6.1 ± 2.6
Platelet (x 10 ³ /μL)	211.7 ± 81.5
Fibrinogen (mg/dL)	1.4 ± 0.5
D-dimer (μ/L)	4.1 ± 2.2
Procalcitonin (ng/mL)	2.2 ± 1.8
Creatinine (mg/dL)	1.6 ± 1.5
ALT (IU/L) *	26.8 ± 21.2
AST (IU/L) *	29.7 ± 28.7
Infective complications	
Yes	26 (7.4%)
No	324 (92.6%)
Other complications	
Yes	33 (9.4%)
No	317 (90.6%)
Death	28 (8.0%)

* mean ± standard deviation, ALT - alanine transaminase, ASA - American Society of Anesthesiologists, AST - aspartate transaminase, BMI - body mass index, TPN - total parenteral nutrition, WBC - white blood cell.

RESULTS

For the final evaluation, 350 patients (204 female, 146 male) with a mean age of 60.8 ± 14.6, were enrolled into the study. The mean BMI of study population was 26.5 kg/m². Thrombosis history was detected in 17 patients (4.8%). Internal jugular vein was the most commonly used vessel (92.5%) for permanent TDC placement. The mean WBC level and platelet count were 6.1 L and 211.7 (x 10³/μL). Also, the mean fibrinogen, D-dimer and procalcitonin levels were 1.4 mg/dL, 4.1 μg/mL and 2.2 ng/mL, respectively. Infective complications were seen in 26 patients (7.4%) and death in 28 (8.0%). Infection complications were tunnel infection in 19 patients, presence of metastatic infection disease in two patients, and sepsis in five patients. Except for infectious complication, hematoma around puncture side was detected in 21 patients, arrhythmia was seen in five patients, leg pain was observed in six patients, and loss of sense around puncture area occurred in one patient (Table 1).

For the two groups of patients, i.e., with and without thrombosis, there were similarities between age, gender, ASA score, and thrombosis history (p = 0.408, p = 0.153, p = 0.786, and p = 0.955, respectively). In patients with thrombosis, the mean BMI was found significantly higher (30.1 vs. 25.7 kg/m², p = 0.001) and presence of diabetes mellitus was significantly common (65.0% vs. 47.6%, p = 0.014). In both groups, the side and location of permanent TDC placement were comparable (p = 0.395 and p = 0.935). The WBC level, platelet count, fibrinogen level, and creatinine level had no effect on thrombosis development (p = 0.792, p = 0.654, p = 0.754, and p = 0.865, respectively). However, patients with thrombosis had significantly higher D-dimer (6.5 vs. 2.4 μg/mL, p = 0.001) and procalcitonin levels (4.1 vs. 1.4 ng/mL, p = 0.001). Additionally, patients with thrombosis had a significantly higher rate of infective complications (15.0% vs. 5.9%, p = 0.014). The death rate was not significantly different between groups (p = 0.917) (Table 2).

Logistic regression analysis revealed that diabetes mellitus had no effect on thrombosis development in patients with permanent TDC (p = 0.125). In contrast, BMI > 30 kg/m² and infective complications increased thrombosis risk 3.842 and 3.104 times (p = 0.004 and p = 0.038, respectively). Additionally, D-dimer level > 3 μg/mL and procalcitonin level > 2 ng/mL were significantly associated with the development of thrombosis after permanent TDC placement (p = 0.001 and p = 0.007) (Table 3). Kaplan-Meier curve of thrombosis development time according to infectious complication status, D-dimer level, procalcitonin level, and BMI are presented in Figure 1, 2, 3, 4, respectively.

Table 2. Comparison of patient demographic data, hematological parameters, procedural information and results between groups.

	No thrombosis (n:290)	Thrombosis (n:60)	p-value
Age (years)	60.5 ± 13.4	62.2 ± 19.5	0.408
Gender			
Female	174 (60.0%)	30 (50.0%)	0.153
Male	116 (40.0%)	30 (50.0%)	
BMI (kg/m ²) *	25.7 ± 5.1	30.1 ± 4.9	<u>0.001</u>
Comorbidity			
Hypertension	172 (59.3%)	42 (70.0%)	0.122
Diabetes mellitus	138 (47.6%)	39 (65.0%)	<u>0.014</u>
Coronary artery disease	151 (52.1%)	31 (51.7%)	0.955
Chronic kidney disease	245 (84.5%)	54 (90.0%)	0.270
ASA score *	2.1 ± 0.8	2.0 ± 0.9	0.786
Thrombosis history			
Yes	14 (4.9%)	3 (5.0%)	0.955
No	276 (95.1%)	57 (95.0%)	
Side			
Right	142 (48.9%)	33 (55.0%)	0.395
Left	148 (51.1%)	27 (45.0%)	
Localization			
Internal jugular vein	270 (93.1%)	54 (90.0%)	0.935
Femoral vein	5 (1.7%)	2 (3.3%)	
Subclavian vein	15 (5.2%)	4 (6.7%)	
WBC (L) *	6.0 ± 2.5	6.1 ± 2.7	0.792
Platelet (x 10 ³ /μL)	210.3 ± 78.2	214.5 ± 88.9	0.654
Fibrinogen (mg/dL)	1.3 ± 0.4	1.5 ± 0.6	0.754
D-dimer (μ/L)	2.4 ± 1.8	6.5 ± 3.9	<u>0.001</u>
Procalcitonin (ng/mL)	1.4 ± 1.1	4.1 ± 4.3	<u>0.001</u>
Creatinine (mg/dL)	1.6 ± 1.4	1.5 ± 1.3	0.865
ALT (IU/L) *	25.2 ± 31.1	28.6 ± 27.2	0.657
AST (IU/L) *	28.8 ± 33.3	31.4 ± 28.4	0.589
Infective complications			
Yes	17 (5.9%)	9 (15.0%)	<u>0.014</u>
No	273 (94.1%)	51 (85.0%)	
Other complications			
Yes	26 (8.9%)	7 (11.7%)	0.515
No	264 (91.1%)	53 (88.3%)	
Death	23 (7.9%)	5 (8.3%)	0.917

* mean ± standard deviation, ALT - alanine transaminase, ASA - American Society of Anesthesiologists, AST - aspartate transaminase, BMI - body mass index, TPN - total parenteral nutrition, WBC - white blood cell.

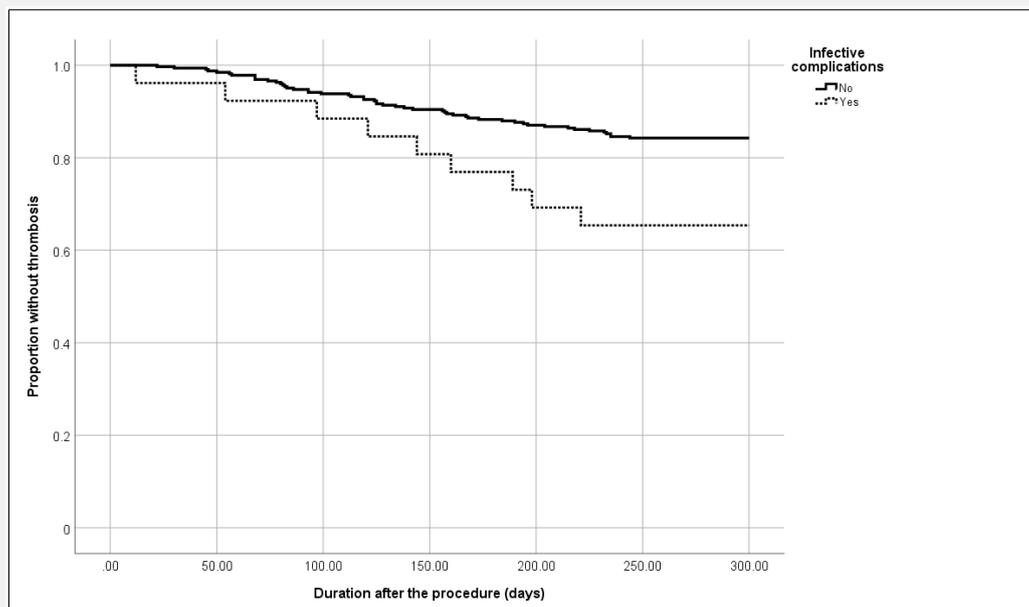
DISCUSSION

Thrombosis in permanent TDC is associated with catheter dysfunction, deterioration in life quality, increments

in hospital admission and health expenses, morbidity and mortality [7,8]. Numerous previous reports investigated thrombosis rates following permanent TDC placement; however, few focused on predictive factors for thrombosis. We believe that an understanding of predic-

Table 3. Logistic regression analysis in terms of risk of developing thrombosis.

	Odds ratio	% 95 CI	p-value
BMI ($\leq 30 \text{ kg/m}^2$ vs. $> 30 \text{ kg/m}^2$)	3.842	1.774 - 7.063	<u>0.004</u>
Presence of diabetes mellitus	1.692	0.766 - 3.738	0.193
D-dimer ($\leq 3 \mu\text{L}$ vs. $> 3 \mu\text{L}$)	4.680	2.244 - 9.674	<u>0.001</u>
Procalcitonin ($\leq 2 \text{ ng/mL}$ vs. $> 2 \text{ ng/mL}$)	3.415	1.295 - 6.282	<u>0.007</u>
Presence of infective complications	3.104	1.914 - 4.284	<u>0.038</u>

**Figure 1. Kaplan-Meier curve of thrombosis development time according to infectious complication status.**

tive factors for thrombosis development following permanent TDC may play a role in the prevention of the condition and related complications. In the present study, presence of infective complications, higher BMI, D-dimer and procalcitonin levels were determined as predictive factors for thrombosis development after permanent TDC placement.

Patients undergoing hemodialysis are faced with increased hemorrhage risk due to uremic status and systemic anticoagulation caused by heparinization. However, previous studies reported controversial results regarding the effect of obesity on thrombosis. Nadolski et al. found no effect of obesity on thrombosis following translumbar TDC placement, but this result may have been influenced by the definition of normal weight as BMI $< 25 \text{ kg/m}^2$ [9]. In contrast, Naffouje and col-

leagues stated that hemodialysis catheter thrombosis was significantly more common in obese patients [10]. In the present study, we found that BMI $> 30 \text{ kg/m}^2$ was associated with significantly increased thrombosis risk in patients with permanent TDC.

D-dimer is a product of fibrin degradation, which can be detected by fragments of protein in blood after clots are dissolved by fibrinolysis. Thus, D-dimer concentration is regarded as an important blood test for diagnosis in cases of suspected thrombosis disorders [11]. Zhu et al., investigating the risk factors of catheter associated thrombosis in right jugular vein, found high D-dimer level is a predictive factor for catheter related complications [12]. Similarly, Chen and colleagues determined D-dimer as a predictive factor for thrombosis in peripherally inserted central catheter [13]. The literature there-

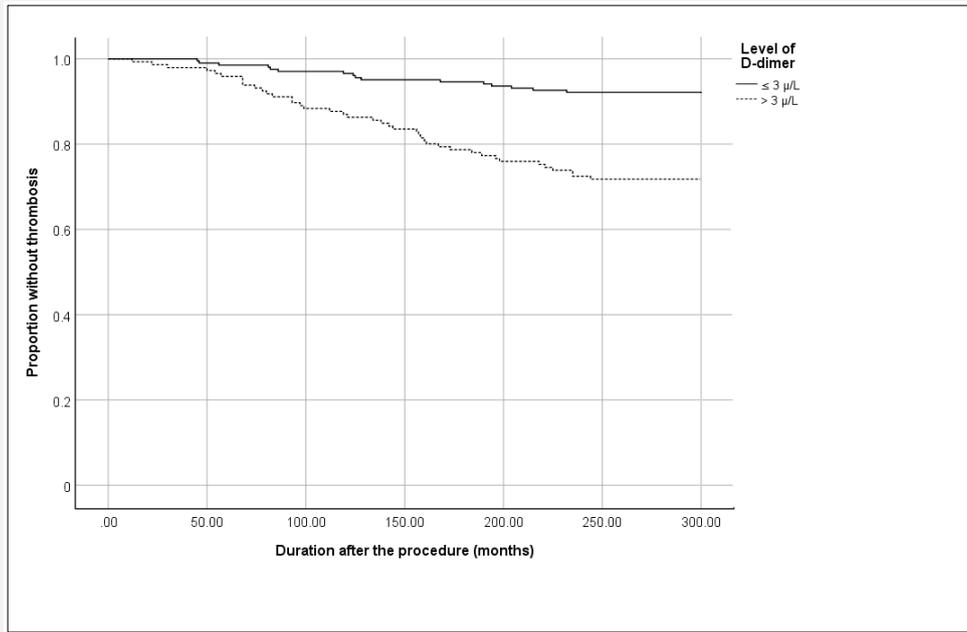


Figure 2. Kaplan-Meier curve of thrombosis development time according to level of D-dimer.

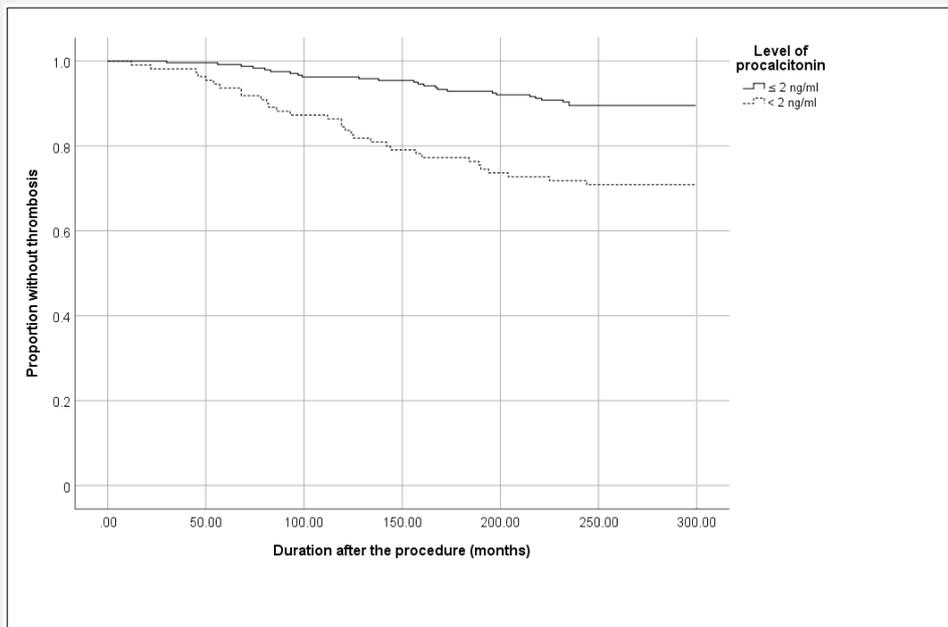


Figure 3. Kaplan-Meier curve of thrombosis development time according to level of procalcitonin.

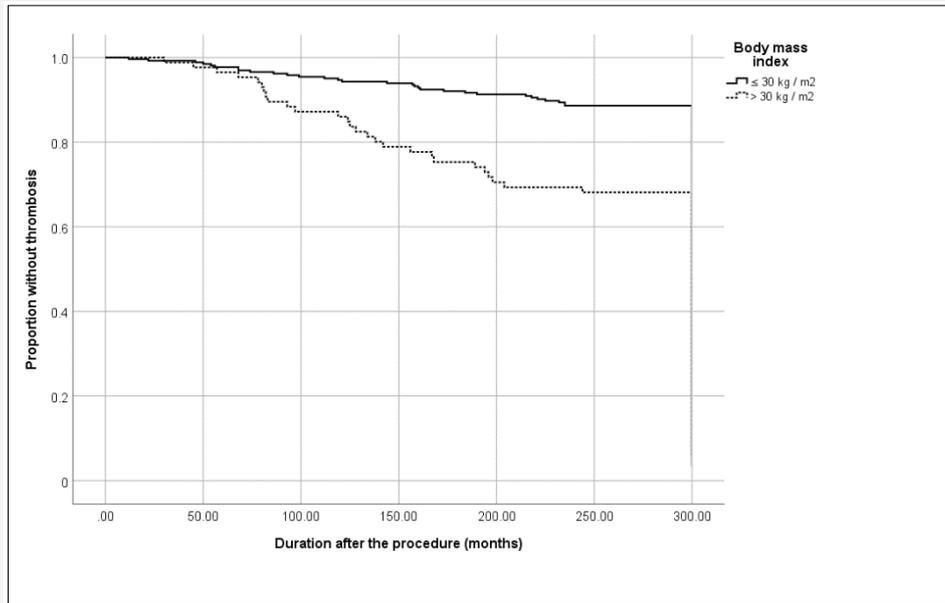


Figure 4. Kaplan-Meier curve of thrombosis development time according to body mass index.

fore identifies D-dimer as a predictive factor for thrombosis in patients with permanent TDC placement. Procalcitonin is a precursor of calcitonin hormone, and procalcitonin levels are elevated in a response to inflammatory events, especially in an infective status. Erickson et al. identified procalcitonin as a potential marker of infective complication associated with thrombotic events [14]. In another study, Rast and colleagues found a significant relationship between procalcitonin level and deep vein thrombosis in the setting of a hospital emergency department [15]. Our finding adds to this evidence that higher procalcitonin level and infective complication increases the risk of thrombosis in patients with permanent TDC.

A nomogram is defined as a graphic calculating device, which creates a two-dimensional diagram to calculate the likelihood of a clinical event. In many medical disciplines, nomograms are used to predict procedure success, possible complications, and follow-up results. Ozgor et al. pointed out the utility of nomograms in the areas of patient counselling, surgical and post-surgical planning, and objective evaluation of procedure outcomes [16]. Additionally, a nomogram allows for formal scientific reporting. Our findings on predictive factors for thrombosis development following permanent TDC placement were not used to develop a new nomogram, as this was outside the scope of this study. However, this finding is potentially valuable for future studies aiming to create such a nomogram.

Limitations

The present study has some limitations. The main limitation was the retrospective nature of the study. Secondly, procedures were performed by different cardio-vascular surgeons; however, it should be noted that all surgeons were from the same team, had completed their learning curve, and carried out procedures using the same algorithm. The scope of the study did not include the analysis of either the cost of procedures with and without thrombosis, or patients' quality of life, which are subjects for possible future work. Lastly, the present study is not focused on relationship between duration and catheter thrombosis.

CONCLUSION

This retrospective study demonstrated that the presence of infection and higher BMI > 30 kg/m² were risk factors for thrombosis development after permanent TDC placement. Additionally, D-dimer level > 3 µg/mL and procalcitonin level > 2 ng/mL were found to increase the incidence of thrombosis 4.680 and 3.415 times, respectively. However, we recognize that prospective-randomized studies with larger patient numbers are needed to confirm the results of the present study.

Prior Publication:

This article is an original work and it has not been published or submitted for publication elsewhere. All authors agree to the submission.

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Nothing to declare.

Ethical Approval:

Clinical and laboratory information was collected during clinical workout and the study was approved by the Ethical Committee of Brescia (certificate no.: 3091). The study was carried out in accordance with the Declaration of Helsinki and with the terms of the local legislation.

Statistical Analysis:

Statistical analysis was performed by Helin El Kilic, MD.

Declaration of Interest:

We declared that we have no commercial, financial, and other relationships in any way related to the subject of this article all that might create any potential conflict of interest.

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