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Potential Protective Effect of COVID-19 Vaccination Against Coronary Stent Thrombosis: Insights from a Retrospective Study in Türkiye

Koroner Stent Trombozuna Karşı COVID-19 Aşılamasının Potansiyel Koruyucu Etkisi: Türkiye'de Yapılan Retrospektif Bir Çalışmadan Elde Edilen Bulgular

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ABSTRACT Objective: The aim of this study was to investigate the association between coronavirus disease-2019 (COVID-19) vaccination and stent thrombosis in patients with coronary stents. **Material and Methods:** This was a retrospective study conducted between January 2021 and December 2022. The study included patients with existing coronary stents who underwent coronary angiography for suspicion of stent thrombosis. A broad range of clinical data, including COVID-19 related data (disease history, number and brand of COVID-19 vaccinations), laboratory findings, follow-up time, and mortality data were obtained retrospectively. The endpoints of the study were coronary stent thrombosis and all-cause mortality. **Results:** A total of 969 patients were included in the study. Stent thrombosis was present in 538 patients (55.52%), who were significantly younger and had a higher proportion of males compared to those without stent thrombosis. Multivariable logistic regression revealed active smoking, hypertension, diabetes mellitus, and coronary artery bypass graft+stent history as being independently associated with higher risk for stent thrombosis. Whereas, anticoagulant use and receiving 4 or more vaccine doses were independently associated with lower likelihood of stent thrombosis. Diabetes mellitus, previous cerebrovascular disease, high urea, and stent thrombosis were independently associated with mortality; whereas hyperlipidemia and receiving the BioNTech vaccine were independently associated with lower risk for mortality. **Conclusion:** Receiving multiple COVID-19 vaccine doses (regardless of type) may reduce the likelihood of stent thrombosis, possibly by protecting against COVID-19. However, more research is needed to understand the potential pathophysiological links between COVID-19 vaccination and coronary stent thrombosis.

Keywords: Coronavirus disease-2019; vaccines; coronary artery disease; stent thrombosis

ÖZET Amaç: Bu çalışmanın amacı, koroner stentli hastalarda koronavirüs hastalığı-2019 [coronavirus disease-2019 (COVID-19)] aşılaması ile stent trombozu arasındaki ilişkiyi araştırmaktır. **Gereç ve Yöntemler:** Bu çalışma, Ocak 2021 ile Aralık 2022 tarihleri arasında yürütülen retrospektif bir çalışmadır. Çalışmaya, stent trombozu şüphesiyle koroner anjiyografi yapılan mevcut koroner stentli hastalar dâhil edildi. COVID-19 ile ilgili veriler (hastalık öyküsü, COVID-19 aşılarının sayısı ve markası), laboratuvar bulguları, takip süresi ve mortalite verileri dâhil olmak üzere geniş bir klinik veri retrospektif olarak elde edildi. Çalışmanın sonlanım noktaları, koroner stent trombozu ve tüm nedenlere bağlı mortalite idi. **Bulgular:** Çalışmaya toplam 969 hasta dâhil edildi. Stent trombozu 538 hastada (%55,52) mevcuttu ve bu hastalar stent trombozu olmayanlara kıyasla anlamlı derecede daha gençti ve erkek oranı daha yüksekti. Çok değişkenli lojistik regresyon aktif sigara kullanımı, hipertansiyon, diyabetes mellitus ve koroner arter bypass greft+stent öyküsünün stent trombozu için daha yüksek risk ile bağımsız olarak ilişkili olduğunu ortaya koymuştur. Antikoagülan kullanımı ve 4 veya daha fazla aşı dozu alınması ise stent trombozu olasılığının daha düşük olmasıyla bağımsız olarak ilişkilendirilmiştir. Diyabetes mellitus, geçirilmiş serebrovasküler hastalık, yüksek üre ve stent trombozu bağımsız olarak mortalite ile ilişkiliyken; hiperlipidemi ve BioNTech aşısı olmak bağımsız olarak daha düşük mortalite riski ile ilişkiliydi. **Sonuç:** Birden fazla COVID-19 aşısı dozu almak (tipine bakılmaksızın), muhtemelen COVID-19'a karşı koruma sağlayarak stent trombozu olasılığını azaltabilir. Bununla birlikte, COVID-19 aşılaması ile koroner stent trombozu arasındaki potansiyel patofizyolojik bağlantıları anlamak için daha fazla araştırmaya ihtiyaç vardır.

Anahtar Kelimeler: Koronavirüs hastalığı-2019; aşılar; koroner arter hastalığı; stent trombozu

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The global health crisis due to the coronavirus disease-2019 (COVID-19) pandemic spurred rapid and extensive efforts to develop effective vaccines, which were a critical step in combating the spread and lethality of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).[1,2]

Percutaneous coronary interventions (PCIs) are very common life-saving procedures, and have naturally continued throughout the pandemic. Complications following stent procedures are a crucial aspect of patient management.[2,3] Stent thrombosis, though rare, can cause mortalities in the early (<30 days), late (30 days to 1 year), or very late periods (>1 year).[3,4] Multiple underlying factors are recognized, including patient-, lesion-, device-, and procedure-related factors.[2,3] Studies exploring complications during the pandemic, despite being limited by small sample sizes, have reported an increase in stent thrombosis, with incidences between 8.1-21%.[1,5-7]

A total of 13,64 billion vaccine doses were administered until 2024.[8] Approximately 67% of the global population has been fully vaccinated, while an additional 32% have received at least one dose.[8] The general safety profiles of these vaccines have been extensively evaluated; however, research continues on potential side effects and complications. COVID-19 vaccines were not found to cause thrombosis or other adverse events aside from rare cases of anaphylaxis in their initial trials. However, as vaccination efforts expanded and follow-up data became more comprehensive, unexpected thrombotic events were associated with COVID-19 vaccination.[9,10] Interestingly, recent studies have suggested a reduced likelihood of thrombosis and cardiovascular complications among vaccine recipients.[11] Nevertheless, there is insufficient data regarding the possible link between COVID-19 vaccination and post-PCI stent thrombosis.

We hypothesized the existence of a relationship between stent thrombosis and vaccine type or the number of doses received. Therefore, we aimed to investigate the association between COVID-19 vaccination characteristics and stent thrombosis in patients with coronary stents by utilizing retrospective data analysis.

MATERIAL AND METHODS

ETHICS AND RECRUITMENT

The protocol for this study was approved by the Clinical Research Ethics Committee of Haseki Training and Research Hospital (date: April, 26 2023, decision no: 73-2023). The local ethics board confirmed that all steps of the study were appropriate with respect to the Declaration of Helsinki.

Patients with existing coronary stents who were hospitalized in the Cardiology Service or Coronary Intensive Care Unit of our clinic and underwent coronary angiography due to suspected stent thrombosis between January 2021 and December 2022, aged between 18 and 90 years, both male and female, with or without a history of COVID-19 infection, receiving regular antiplatelet therapy, and who had received a COVID-19 vaccination after stent placement, with a minimum interval of one month between the vaccination and the suspected stent thrombosis event, were included. The exclusion criteria were as follows: patients who could not be followed or treated due to refusal of treatment, a time interval of less than one month between stent placement and COVID-19 vaccination, and insufficient information available in hospital records or via the national e-health system regarding the variables included in the study.

DATA COLLECTION

Sociodemographic data, lifestyle risk factors (such as smoking), body mass index, comorbidities, history of coronary/peripheral artery or cerebrovascular disease, pulmonary embolism, and deep vein thrombosis, as well as antiplatelet and anticoagulant use status and type, COVID-19 disease history (none, once, twice), number and brand of COVID-19 vaccines received, laboratory findings, follow-up time, and mortality data were obtained retrospectively from hospital records and the national personal health system of the Turkish Ministry of Health (e-nabız). All-cause mortality information was included in the study. The follow-up period extended from stent placement to the date of data collection. Diabetes mellitus, hypertension, hyperlipidemia diagnoses were recorded based on the fact that the patients were receiving the relevant treatments in line with their previous diagnoses

at the time of application. Medication data was determined in light of patient declaration and/or e-nabız data.

Urea, creatinine, and absolute platelet counts, routinely obtained from venous blood samples prior to angiography, were analyzed in our certified biochemistry laboratories equipped with calibrated devices. Glomerular filtration rate (eGFR) in mL/min/1.73 m² was estimated based on Modification of Diet in Renal Disease.[12]

STUDY ENDPOINTS

Coronary stent thrombosis was the primary and all-cause mortality was the secondary endpoint.

ANGIOGRAPHIC EVALUATION AND DEFINITION OF STENT THROMBOSIS

Coronary angiography was performed in the presence of typical symptoms suggestive of ischemia and/or findings indicative of significant coronary artery stenosis. The routine approach to the assessment of coronary artery disease was based upon advanced imaging modalities, with the Philips Allura Xper FD20 system (Philips Healthcare, The Netherlands) being the preferred option at our center. Stent thrombosis was established based on the American Heart Association-Academic Research Consortium.[13] Identification of a complete or partial thrombotic occlusion within or bordering the stent in at least 2 angiographic projections was the basis for diagnosis. The occlusion was assessed with respect to the presence of a reduction in coronary artery flow or a decrease in the Thrombolysis In Myocardial Infarction (TIMI) flow grade.[14] All angiographic evaluations were independently reviewed by at least 2 experienced cardiologists. In cases of disagreement, a 3rd expert opinion was sought. Stent thrombosis is categorized based on the time elapsed after percutaneous coronary intervention and stent implantation: acute (within the first 48 hours), subacute (from 2 to 30 days), late (beyond 30 days), and very late (occurring after one year).[15]

DATA ANALYSIS

Data were collected into an IBM SPSS v25.0 (IBM Corp., Armonk, NY, USA) and were examined for a significance threshold of $p<0.05$ (2 tailed). Q-Q and histogram plots were examined to assess normality of distribution. Summarization of data were as follows for numerical variables: normal distribution: mean± standard deviation; non-normal: median (25^{th} percentile-75^{th} percentile). The former variables were compared with the Student's t-test, while the latter were subject to the Mann-Whitney U test. Categorical data were summarized for absolute&relative frequency and were analyzed via chi-square or Fisher's exact (or Freeman-Halton). Binary regression (condition-wise forward) was used to identify independent determinants of stent thrombosis or mortality. Univariate significances were added into the binary models.

RESULTS

A total of 969 patients (704 males; 72.65%) with a mean age of 61.42±10.19 were examined. Stent thrombosis was present in 538 patients (55.52%). Patients with stent thrombosis were significantly younger than those without ($p<0.001$) and had a higher male frequency ($p<0.001$). The stent thrombosis group had a higher frequency of active smokers and comorbidities, as well as significant differences in treatment, therapeutic approaches, creatinine levels, and mortality, which are detailed in Table 1. The frequency of unvaccinated individuals ($p<0.001$) and twice-vaccinated subjects ($p<0.001$) were significantly higher among patients with stent thrombosis. Furthermore, the stent thrombosis group had a significantly lower frequency of receiving the BioNTech (Pfizer, Mainz, Germany) + CoronaVac (Sinovac, Beijing, China) vaccine combination ($p<0.001$) (Table 2).

Stent thrombosis risk was independently increased by: active smoking (OR: 8.140), hypertension (OR: 1.755), diabetes mellitus (OR: 1.95) and coronary artery bypass graft (CABG)+Stent history (OR: 2.498). Stent thrombosis risk was independently decreased by: any anticoagulant use (OR: 0.313) and 4 or more COVID-19 vaccine doses (OR: 0.492) (Please see Table 3 for confidence intervals and p values). Other members of the model, age ($p=0.841$), sex ($p=0.744$), thyroid diseases ($p=0.605$), type of antiplatelet drug ($p=0.113$), type of COVID-19 vaccine ($p=0.978$) and creatinine ($p=0.056$) were found to be non-significant.

TABLE 1: Distribution of clinical and laboratory characteristics based on the detection of stent thrombosis.

		Stent thrombosis		
	Total (n=969)	**No (n=431)**	**Yes (n=538)**	**p value**
Age, years	61.42±10.19	62.77±9.82	60.34±10.36	**<0.001**†
Sex				
Female	265 (27.35%)	145 (33.64%)	120 (22.30%)	**<0.001**#
Male	704 (72.65%)	286 (66.36%)	418 (77.70%)	
Body mass index, kg/m^2	28.82±4.44	28.85±4.26	28.79±4.58	0.824†
Smoking status				
Non-smoker	231 (24.06%)	146 (33.95%)	85 (16.04%)*	
Ex-smoker	85 (8.85%)	50 (11.63%)	35 (6.60%)*	**<0.001**#
Passive smoker	311 (32.40%)	173 (40.23%)	138 (26.04%)*	
Active smoker	333 (34.69%)	61 (14.19%)	272 (51.32%)*	
Hypertension	599 (61.82%)	243 (56.38%)	356 (66.17%)	**0.002**#
Diabetes mellitus	411 (42.41%)	154 (35.73%)	257 (47.77%)	**<0.001**#
Hyperlipidemia	804 (82.97%)	358 (83.06%)	446 (82.90%)	0.947#
Chronic obstructive pulmonary disease	101 (10.42%)	47 (10.90%)	54 (10.04%)	0.660#
Renal diseases	152 (15.69%)	57 (13.23%)	95 (17.66%)	0.059#
Thyroid diseases	72 (7.43%)	40 (9.28%)	32 (5.95%)	**0.049**#
Malignancy	18 (1.86%)	10 (2.32%)	8 (1.49%)	0.474#
Previous coronary artery disease				
Only stent	2 (0.21%)	0 (0.00%)	2 (0.37%)	
PTCA+Stent	881 (90.92%)	404 (93.74%)	477 (88.66%)*	**0.010**¶
CABG+Stent	86 (8.88%)	27 (6.26%)	59 (10.97%)*	
Previous peripheral artery disease	62 (6.40%)	26 (6.03%)	36 (6.69%)	0.677#
Previous cerebrovascular disease	58 (5.99%)	19 (4.41%)	39 (7.25%)	0.086#
Previous deep vein thrombosis	3 (0.31%)	1 (0.23%)	2 (0.37%)	1.000§
Antiplatelet use	969 (100.00%)	431 (100.00%)	538 (100.00%)	N/A
Acetylsalicylic acid	471 (48.61%)	208 (48.26%)	263 (48.88%)	
Clopidogrel	110 (11.35%)	48 (11.14%)	62 (11.52%)	
Ticagrelor	1 (0.10%)	1 (0.23%)	0 (0.00%)	**0.048**¶
Acetylsalicylic acid+Clopidogrel	284 (29.31%)	140 (32.48%)	144 (26.77%)	
Acetylsalicylic acid+Ticagrelor	102 (10.53%)	34 (7.89%)	68 (12.64%)*	
Acetylsalicylic acid+Prasugrel	1 (0.10%)	0 (0.00%)	1 (0.19%)	
Anticoagulant use	36 (3.72%)	24 (5.57%)	12 (2.23%)	
Warfarin	4 (0.41%)	4 (0.93%)	0 (0.00%)	
Rivaroxaban	14 (1.44%)	6 (1.39%)	8 (1.49%)	**0.010**#
Apixaban	13 (1.34%)	10 (2.32%)	3 (0.56%)	
Edoxaban	5 (0.52%)	4 (0.93%)	1 (0.19%)	
Urea (mg/dL)	34 (27-41)	34 (28-41)	34 (27-42)	0.812‡
Creatinine (mg/dL)	0.90 (0.77-1.07)	0.89 (0.75-1.06)	0.92 (0.78-1.09)	**0.005**‡
Glomerular filtration rate (mL/min/1.73 m^2)	86 (69-98)	86 (69-97)	86 (68-99)	0.806‡
Platelet (x10^3)	240 (204-288)	242 (204-288)	239 (204-288)	0.910‡
Follow-up time, months	43 (12-65)	42 (12-64)	44.5 (11-65)	0.999‡
Time of thrombosis				
Acute	70 (7.22%)	-	70 (13.01%)	
Subacute	159 (16.41%)	-	159 (29.55%)	-
Late	274 (28.28%)	-	274 (50.93%)	
Very late	35 (3.61%)	-	35 (6.51%)	
Mortality	86 (8.88%)	20 (4.64%)	66 (12.27%)	**<0.001**#

Descriptive statistics were presented using $\bar{X}$±standard deviation for normally distributed continuous variables, median (25th percentile-75th percentile) for non-normally distributed continuous variables, and frequency (percentage) for categorical variables.

†Student's t test; #Chi-square test; ¶Fisher-Freeman Halton test; §Fisher's exact test; *Significantly different category for the variables with three or more categories; ‡Mann-Whitney U test. N/A: Non-applicable/abbreviations; CABG: Coronary artery bypass graft; PTCA: Percutaneous transluminal coronary angioplasty.

TABLE 2: COVID-19 history and vaccination data examined with regard to stent thrombosis.

		Stent thrombosis		
	Total (n=969)	No (n=431)	Yes (n=538)	p value
COVID-19 disease history				
None	458 (47.27%)	219 (50.81%)	239 (44.42%)	0.077#
One time	181 (18.68%)	81 (18.79%)	100 (18.59%)	
Two times	330 (34.06%)	131 (30.39%)	199 (36.99%)	
Number of vaccine doses				
None	82 (8.46%)	22 (5.10%)	60 (11.15%)*	**<0.001#**
One time	28 (2.89%)	9 (2.09%)	19 (3.53%)	
Two times	240 (24.77%)	93 (21.58%)	147 (27.32%)*	
Three times	320 (33.02%)	144 (33.41%)	176 (32.71%)	
Four times	186 (19.20%)	99 (22.97%)	87 (16.17%)*	
Five times	113 (11.66%)	64 (14.85%)	49 (9.11%)*	
Type of vaccine (brand)				
None	82 (8.46%)	22 (5.10%)	60 (11.15%)*	**<0.001¶**
Only BioNTech	374 (38.60%)	162 (37.59%)	212 (39.41%)	
Only Sinovac	192 (19.81%)	77 (17.87%)	115 (21.38%)	
Only Turkovac	1 (0.10%)	0 (0.00%)	1 (0.19%)	
BioNTech+Sinovac	288 (29.72%)	150 (34.80%)	138 (25.65%)*	
BioNTech+Turkovac	6 (0.62%)	5 (1.16%)	1 (0.19%)	
Sinovac+Turkovac	11 (1.14%)	5 (1.16%)	6 (1.12%)	
BioNTech+Sinovac+Turkovac	15 (1.55%)	10 (2.32%)	5 (0.93%)	

Descriptive statistics were presented using $\bar{X}$±standard deviation for normally distributed continuous variables, median (25th percentile-75th percentile) for non-normally distributed continuous variables, and frequency (percentage) for categorical variables.

#Chi-square test; *Significantly different category for the variables with three or more categories; ¶Fisher-Freeman Halton test.

TABLE 3: Significant factors independently associated with stent thrombosis, multivariable logistic regression.

	β coefficient	Standard error	p value	Exp(β)	95% CI for Exp(β)	
Smoking status, active smoker	2.097	0.175	**<0.001**	8.140	5.774	11.478
Hypertension, yes	0.563	0.157	**<0.001**	1.755	1.290	2.389
Diabetes mellitus, yes	0.671	0.154	**<0.001**	1.955	1.446	2.644
Previous coronary artery disease, CABG+Stent	0.915	0.271	**0.001**	2.498	1.468	4.251
Anticoagulant use, yes	-1.162	0.408	**0.004**	0.313	0.141	0.696
Number of vaccine doses, four or more	-0.709	0.162	**<0.001**	0.492	0.358	0.676
Constant	-0.878	0.152	**<0.001**	0.415		

Nagelkerke R^2=0.287; CI: Confidence interval; CABG: Coronary artery bypass graft.

Median follow-up was 43 months (minimum-maximum: 12-65) and 86 patients died during this period (8.88%). Deceased patients were older relative to survivors (p=0.005), but sex distribution was similar (p=0.378). In the mortality group, the frequencies of diabetes mellitus (p<0.001), renal diseases (p<0.001), previous cerebrovascular disease (p<0.001), anticoagulant users (p=0.011), unvaccinated subjects (p<0.001), only Sinovac recipients (p<0.001), and stent thrombosis (p<0.001) were significantly higher compared to the surviving group. These patients also had higher creatinine and urea (p<0.001 for both). The frequencies of hyperlipidemia (p=0.002), having received five doses (p<0.001), and only BioNTech recipients (p<0.001) were significantly lower in the deceased group, as well as eGFR (p<0.001) (Table 4 and Table 5).

For mortality, binary regression showed that diabetes mellitus (OR: 1.977), previous cerebrovascular disease (OR: 2.595), high urea (OR: 1.034) and

TABLE 4: Summary of variables with regard to mortality.

	Mortality		
	No (n=883)	**Yes (n=86)**	**p value**
Age, years	61.09±9.98	64.79±11.64	**0.005**†
Sex			
Female	238 (26.95%)	27 (31.40%)	0.378#
Male	645 (73.05%)	59 (68.60%)	
Body mass index, kg/m^2	28.78±4.46	29.16±4.15	0.453†
Smoking status			
Non-smoker	211 (23.92%)	20 (25.64%)	
Ex-smoker	78 (8.84%)	7 (8.97%)	0.898#
Passive smoker	284 (32.20%)	27 (34.62%)	
Active smoker	309 (35.03%)	24 (30.77%)	
Hypertension	541 (61.27%)	58 (67.44%)	0.261#
Diabetes mellitus	357 (40.43%)	54 (62.79%)	**<0.001#**
Hyperlipidemia	743 (84.14%)	61 (70.93%)	**0.002#**
Chronic obstructive pulmonary disease	89 (10.08%)	12 (13.95%)	0.348#
Renal diseases	123 (13.93%)	29 (33.72%)	**<0.001#**
Thyroid diseases	66 (7.47%)	6 (6.98%)	1.000#
Malignancy	15 (1.70%)	3 (3.49%)	0.210§
Previous coronary artery disease			
Only stent	2 (0.23%)	0 (0.00%)	0.361¶
PTCA+Stent	806 (91.28%)	75 (87.21%)	
CABG+Stent	75 (8.49%)	11 (12.79%)	
Previous peripheral artery disease	53 (6.00%)	9 (10.47%)	0.166#
Previous cerebrovascular disease	43 (4.87%)	15 (17.44%)	**<0.001#**
Previous deep vein thrombosis	3 (0.34%)	0 (0.00%)	1.000§
Antiplatelet use	883 (100.00%)	86 (100.00%)	N/A
Acetylsalicylic acid	429 (48.58%)	42 (48.84%)	
Clopidogrel	98 (11.10%)	12 (13.95%)	
Ticagrelor	1 (0.11%)	0 (0.00%)	0.493¶
Acetylsalicylic acid+clopidogrel	264 (29.90%)	20 (23.26%)	
Acetylsalicylic acid+ticagrelor	90 (10.19%)	12 (13.95%)	
Acetylsalicylic acid+prasugrel	1 (0.11%)	0 (0.00%)	
Anticoagulant use	28 (3.17%)	8 (9.30%)	
Warfarin	3 (0.34%)	1 (1.16%)	
Rivaroxaban	11 (1.25%)	3 (3.49%)	**0.011**§
Apixaban	10 (1.13%)	3 (3.49%)	
Edoxaban	4 (0.45%)	1 (1.16%)	
Urea (mg/dL)	33.7 (27-40.6)	39 (32-56)	**<0.001**‡
Creatinine (mg/dL)	0.90 (0.77-1.06)	1.00 (0.80-1.29)	**<0.001**‡
Glomerular filtration rate (mL/min/1.73 m^2)	86 (70-98)	69.5 (51-91)	**<0.001**‡
Platelet (x10^3)	241 (202-285)	238 (212-302)	0.215‡
Follow-up time, months	44 (12-65)	41.5 (13-62)	0.318‡
Stent thrombosis	472 (53.45%)	66 (76.74%)	
Acute	63 (7.13%)	7 (8.14%)	
Subacute	137 (15.52%)	22 (25.58%)	**<0.001#**
Late	239 (27.07%)	35 (40.70%)	
Very late	33 (3.74%)	2 (2.33%)	

Descriptive statistics were presented using $\bar{X}$±standard deviation for normally distributed continuous variables, median (25th percentile-75th percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables.

†Student's t test; #Chi-square test, §Fisher's exact test; ¶Fisher-Freeman Halton test; ‡Mann-Whitney U test. PTCA: Percutaneous transluminal coronary angioplasty; CABG: Coronary artery bypass graft; N/A: Non-applicable.

TABLE 5: Summary of COVID-19 related variables with regard to mortality.

	Mortality		
	No (n=883)	**Yes (n=86)**	**p value**
COVID-19 disease history			
None	424 (48.02%)	34 (39.53%)	0.283#
One time	161 (18.23%)	20 (23.26%)	
Two times	298 (33.75%)	32 (37.21%)	
Number of vaccine doses			
None	60 (6.80%)	22 (25.58%)*	
One time	23 (2.60%)	5 (5.81%)	
Two times	220 (24.92%)	20 (23.26%)	**<0.001#**
Three times	296 (33.52%)	24 (27.91%)	
Four times	175 (19.82%)	11 (12.79%)	
Five times	109 (12.34%)	4 (4.65%)*	
Type of vaccine (brand)			
None	60 (6.80%)	22 (25.58%)*	
Only BioNTech	356 (40.32%)	18 (20.93%)*	
Only Sinovac	166 (18.80%)	26 (30.23%)*	**<0.001¶**
Only Turkovac	1 (0.11%)	0 (0.00%)	
BioNTech+Sinovac	268 (30.35%)	20 (23.26%)	
BioNTech+Turkovac	6 (0.68%)	0 (0.00%)	
Sinovac+Turkovac	11 (1.25%)	0 (0.00%)	
BioNTech+Sinovac+Turkovac	15 (1.70%)	0 (0.00%)	

Descriptive statistics were presented using $\bar{X}$±standard deviation for normally distributed continuous variables, median (25th percentile-75th percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables.

#Chi-square test; *Significantly different category for the variables with three or more categories; ¶Fisher-Freeman Halton test.

TABLE 6: Significant factors independently associated with mortality, multivariable logistic regression.

	β coefficient	**Standard error**	**p value**	**Exp (β)**	**95% CI for Exp (β)**	
Diabetes mellitus, yes	0.681	0.253	**0.007**	1.977	1.203	3.247
Hyperlipidemia, yes	-0.795	0.282	**0.005**	0.452	0.260	0.785
Previous cerebrovascular disease, yes	0.953	0.363	**0.009**	2.595	1.274	5.285
Type of vaccine, BioNTech	-0.916	0.247	**<0.001**	0.400	0.247	0.650
Urea	0.034	0.007	**<0.001**	1.034	1.021	1.048
Stent thrombosis, yes	0.775	0.278	**0.005**	2.172	1.258	3.747
Constant	-3.481	0.443	<0.001	0.031		

Nagelkerke R^2=0.215; CI: Confidence interval.

stent thrombosis (OR: 2.172) were independently associated with increased risks. Whereas, hyperlipidemia (OR: 0.452) and BioNTech vaccination (OR: 0.400) were independently associated with decreased mortality risk (Please see Table 6 for confidence intervals and p values). Other members of the model were non-significant: age (p=0.178), renal disease (p=0.873), anticoagulant use (p=0.059), number of COVID-19 vaccine doses (p=0.146), creatinine (p=0.803) and GFR (p=0.669).

DISCUSSION

The current study supports prior research in showing that active smoking, comorbidities, and history of CABG and stent placement are independent factors that contribute to stent thrombosis. Notably, we also found that anticoagulant use and having received 4 or more vaccinations were independently associated with lower risk for coronary stent thrombosis, which is a crucial result showing separate benefits obtained

from COVID-19 vaccination. The secondary outcome, mortality likelihood, was found to be increased among patients with diabetes mellitus, a history of cerebrovascular disease, elevated urea levels, and stent thrombosis, whereas it was decreased among patients with hyperlipidemia and recipients of the BioNTech vaccine.

PCI is one of the most frequently performed life-saving medical procedures.[2,3] Although it is generally safe, stent thrombosis is a serious complication that can be life-threatening, as demonstrated by data showing 5-year mortality rates ranging from 5% to 45%.[3] The pandemic particularly affected patients with pre-existing cardiovascular diseases. An alarming phenomenon observed recently is that stent thrombosis risks appears to be 10 times more common in COVID-19 patients.[1,5-7] COVID-19 causes endothelial damage and can result in activation of the coagulation cascade and platelets, which can increase the risk of thrombotic complications. Furthermore, stents cause stasis and complete Virchow's triad.[16] We however found no relationship between COVID-19 history and coronary stent thrombosis. It must be noted that some studies have suggested an association between COVID-19 vaccines and increased thromboembolic events, even though vaccination has been shown to reduce overall thrombotic risks (especially relative to disease).[10,17-22] In this study, we found that receiving 4 or more vaccine doses was protective against coronary stent thrombosis, independent of other factors. Additionally, the BioNTech vaccine was identified as an independent factor reducing mortality.

The risks of thromboembolism associated with COVID-19 vaccines are lower compared to SARS-CoV-2 infection; however, these risks vary depending on the type of vaccine. Thromboembolic events and thrombocytopenia have been reported with some vaccines, leading to their suspension in certain countries.[11,17,19,21,22] The pathogenesis of potential hypercoagulability observed after COVID-19 vaccinations remains incompletely understood. Given this uncertainty, it is understandable that the possible relationship between these vaccines and stent thrombosis is also not yet fully elucidated. These mechanisms involve multifactorial aspects and include possible effects of vaccine components and host factors. Certain COVID-19 vaccines, particularly adenoviral vector vaccines, may lead to the formation of immune complexes, such as the platelet factor 4-polyanion complex, which has been directly associated with vaccine-induced immune thrombotic thrombocytopenia.[10] This condition could cause platelet activation, thrombocytopenia, and thrombosis, particularly increasing the risk of thrombosis in coronary arteries with stents. It is also possible that COVID-19 vaccines activate endothelial cells, which could enhance the inflammatory response and lead to a procoagulant state, particularly in the presence of a stent. The systemic inflammation induced by vaccines may lead to increased thrombotic activity in endothelial cells and platelets, potentially leading to stent thrombosis. Furthermore, the angiotensin converting enzyme 2 receptor might exhibit dysfunction upon interaction with the spike protein following vaccination, which could increase angiotensin II levels and a predisposition to thrombosis. Antibodies generated in response to the vaccine could lead to the formation of antigen-antibody complexes with the potential to create microvascular obstructions and thrombosis. Finally, anaphylactic or anaphylactoid reactions following vaccination could trigger allergic coronary artery spasm, known as Kounis syndrome, which may induce thrombotic effects.[5,23-26]

In our study we found that a history of COVID-19 and vaccine brand were unassociated with stent thrombosis; whereas, receiving four or more vaccine doses showed a significant protective effect. This interesting finding might be explained by several potential mechanisms: (I) Multiple doses of the vaccine might lead to a more robust and sustained immune response, reducing systemic inflammation and stabilizing atherosclerotic plaques, thereby lowering the risk of stent thrombosis. (II) Since severe COVID-19 is associated with a hypercoagulable state, multiple vaccine doses might prevent severe infections, thereby reducing the likelihood of thrombotic events, including stent thrombosis. (III) Vaccination might indirectly improve endothelial function by preventing COVID 19-induced endothelial damage, which is a critical factor in the pathogenesis of stent thrombosis. However, further studies and data are needed to

clarify this issue. Such studies could contribute to elucidating the pathophysiological mechanisms between vaccination and stent thrombosis in the context of COVID-19, and possibly, other vaccines developed with similar technologies.

The development of stent thrombosis is driven by multifactorial mechanisms, including patient-related factors; procedural factors like lesion complexity, bifurcation lesions, and inadequate stent placement; as well as post-procedural factors such as the type and duration of antiplatelet therapy.[3,27] These elements collectively contribute to the risk of stent thrombosis, making risk stratification at the individual patient level quite complex.[3,27] Although significant reductions in stent thrombosis rates have been achieved through advances in coronary stenting techniques, some strong risk factors remain effective, including antiplatelet therapy discontinuation, age, genetic predisposition, heart failure, numerous comorbidities, and smoking.[3,28] In the present study, active smoking, hypertension, and the presence of diabetes, along with a history of CABG and previous stenting, are demonstrated to increase stent thrombosis risks.

An intriguing finding in our study is that hyperlipidemia was identified as a factor associated with reduced mortality, which may be explained by several factors. (I) Patients with hyperlipidemia often use lipid-lowering medications, such as statins. Statins positively affect the lipid profile and may reduce inflammation. Consequently, such treatment might have contributed to reduced mortality. (II) These results may suggest that hyperlipidemia should be considered in conjunction with hypertension or diabetes, which could mitigate the adverse effects. (III) The characteristics of the study population and data analysis methods could also influence these findings. For example, hyperlipidemia might show more favorable outcomes in specific subgroups (e.g., those with high statin use). To validate these findings and better understand the effects and potential protective mechanisms of hyperlipidemia, further studies with detailed analyses are needed.

LIMITATIONS

Our study offers notable findings regarding the links between coronary stent thrombosis and COVID-19 vaccines. Despite drawing data from a large patient database, the single-center design of the study restricts the generalizability to some degree. The retrospective design prevents detailed analyses concerning parameters that were not recorded in patient databases; however, the e-nabız system provides comprehensive health-related data which contributed to data completeness and comprehensiveness. However, detailed laboratory findings (including coagulation parameters) and stent types could not be included in the analyses due to missing data. The study data were collected during the pandemic, which might have compromised the reliability of the reported stent thrombosis rates, as patients with stents may have avoided hospital visits due to fear of contracting COVID-19. Furthermore, the reduction in routine health checks and follow-ups during the pandemic may have led to undiagnosed cases of myocardial infarction, limiting the representation of the population. Also, mortality data was based on all-cause mortality rather than disease- or stent complication-attributable mortality. Lastly, some patients had very short follow-up periods, with 83 patients only followed for 1 month. This short duration could have introduced biases in the detected frequency of stent thrombosis and mortality, as well as in other variables.

CONCLUSION

This study identifies a protective effect of vaccines (regardless of brand) in terms of stent thrombosis following PCI. The administration of multiple COVID-19 vaccine doses provides significant protection not only against COVID-19 itself but also in preventing stent thrombosis.

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During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Özlem Özbek;* ***Design:*** *Özlem Özbek;* ***Control/Supervision:*** *Mehmet Mustafa Can;* ***Data Collection and/or Processing:*** *Özlem Özbek;* ***Analysis and/or Interpretation:*** *Özlem Özbek;* ***Literature Review:*** *Özlem Özbek;* ***Writing the Article:*** *Özlem Özbek;* ***Critical Review:*** *Mehmet Mustafa Can;* ***References and Fundings:*** *Özlem Özbek;* ***Materials:*** *Özlem Özbek.*

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