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Risk Assessment Tool Implementation in Congenital Heart Disease-Associated Pulmonary Arterial Hypertension

ABSTRACT

Background: Risk assessment is recommended for patients with congenital heart disease-associated pulmonary arterial hypertension. This study aims to compare an abbreviated version of the risk assessment strategy, noninvasive French model, and an abridged version of the Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management 2.0 risk score calculator, Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management Lite 2.

Methods: We enrolled a mixed prevalent and incident cohort of patients with congenital heart disease-associated pulmonary arterial hypertension (n = 126). Noninvasive French model comprising World Health Organization functional class, 6-minute walk distance, and N-terminal pro-hormone of brain natriuretic peptide or brain natriuretic peptide was used. Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management Lite 2 includes functional class, systolic blood pressure, heart rate, 6-minute walk distance, brain natriuretic peptide/N-terminal pro-hormone of brain natriuretic peptide, and estimated glomerular filtration rate.

Results: The mean age was 32.17 ± 16.3 years. The mean follow-up was 99.41 ± 58.2 months. Thirty-two patients died during follow-up period. Most patients were Eisenmenger syndrome (31%) and simple defects (29.4%). Most patients received monotherapy (76.2%). Most patients were World Health Organization functional class I-II (66.6%). Both models effectively identified risk in our cohort ($P = .0001$). Patients achieving 2 or 3 noninvasive low-risk criteria or low-risk category by Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management Lite 2 at follow-up had a significantly reduced risk of death. Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management Lite 2 approximates noninvasive French model at discriminating among patients based on c-index. Age, high risk by Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management Lite 2, and the presence of 2 or 3 low-risk criteria by noninvasive French model emerged as an independent predictors of mortality (multivariate hazard ratio: 1.031, 95% CI: 1.005-1.058, $P = .02$; hazard ratio: 4.258, CI: 1.143-15.860, $P = .031$; hazard ratio: 0.095, CI: 0.013-0.672, $P = .018$, respectively).

Conclusions: Both abbreviated risk assessment tools may provide a simplified and robust method of risk assessment for congenital heart disease-associated pulmonary arterial hypertension. Patients not achieving low risk at follow-up may benefit from aggressive use of available therapies.

Keywords: Congenital heart disease, Eisenmenger syndrome, pulmonary arterial hypertension, risk assessment

INTRODUCTION

Congenital heart disease-associated pulmonary arterial hypertension (CHD-PAH) represents a very heterogeneous patient population. Much of our knowledge about long-term outcomes in CHD-PAH is derived from multi-institutional patient registries. Although low-risk CHD-PAH may have a better prognosis compared to other subsets of group 1 pulmonary hypertension (PH), intermediate-/high-risk CHD-PAH may have a poor long-term outcome.[1] Predictors of worse outcomes in adult CHD-PAH are World Health Organization (WHO) functional class (FC) III-IV, exercise intolerance assessed by 6MWD, or peak VO_2, history of

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hospitalization for right HF, biomarkers [N-terminal prohormone of brain natriuretic peptide (NT-proBNP): 500 pg/mL, C-reactive protein: 10 mg/mL, high serum creatinine, and low albumin levels], iron deficiency, and echocardiographic indices of right ventricle (RV) dysfunction.[2] However, with timely and effective clinical intervention, clinical status and survival may improve. The 2020 ESC Guidelines for adult CHD recommend timely and regular risk assessment for all CHD-PAH patients.[3] However, real-world evidence indicates that risk assessment in the clinical setting is suboptimal.[4] There might be several reasons for under-implementation of risk assessment tools. Risk assessment tools using fewer variables may be preferable. Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) Lite 2 is a simplified risk calculator derived from REVEAL 2.0 risk score calculator.[5] It incorporates 6 evaluable elements considered important for the outcome [e.g. 6-minute walking distance (6MWD), renal function, and NT-proBNP].[6] The 2015 ESC/ERS PH risk table derived noninvasive French model uses WHO FC, 6MWD, and NT-proBNP.[7] Whether upfront combination therapies are necessary in CHD-PAH, especially in Eisenmenger syndrome (ES) is uncertain. A large multicenter study showed that mortality in adults with ES was predicted by the presence of pretricuspid shunt, advancing age, low rest oxygen saturation, absence of sinus rhythm, and presence of pericardial effusion.[8] The purpose of this report is to compare an abbreviated version of the risk assessment strategy, noninvasive French model, and an abridged version of the REVEAL 2.0 risk score calculator, REVEAL Lite 2 in patients with CHD-PAH.

METHODS

The study design was retrospective. We enrolled a mixed prevalent and incident group of patients with CHD-PAH with sufficient variables to permit model application from 6 PAH centers from January 2006 to December 2019. Congenital heart disease-associated pulmonary arterial hypertension was defined by transesophageal echocardiography, CT angiography, and right heart catheterization. Specific therapy had been given at the discretion of the treating physician. Noninvasive French model comprising FC, 6MWD, and NT-proBNP or BNP was used. Registry to Evaluate Early and Long-term PAH Disease Management Lite 2 includes FC, systolic blood pressure, heart rate, 6MWD, BNP/NT-proBNP, and estimated glomerular filtration rate (eGFR). Survival status was determined by the treating physician by either contacting the patient or checking an electronic database. Either BNP or NT-proBNP was included. Patients were grouped into 3 categories according to the number of noninvasive low-risk criteria (French model: 0 low-risk criterion, 1 low-risk criterion, and ≥2 low-risk criteria)[6] and REVEAL Lite 2 scores (low risk: ≤5, intermediate risk: 6-7, and high risk: ≥8).[4] According to French model, FC I-II, 6MWD > 440 m, and NT-proBNP < 300 ng/L/BNP < 50 ng/L were low-risk criteria. The presence of ≥2 low-risk criteria by French model was considered as good prognostic. Risk was calculated based on the last available assessment at 12 months' follow-up, starting from enrollment.

HIGHLIGHTS

- Abbreviated risk assessment tools may be useful for congenital heart disease-associated pulmonary arterial hypertension.
- Eisenmenger syndrome patients might not have a better prognosis as previously thought.
- High-risk patients may need aggressive use of available therapies.

Statistical Analysis

Data were collected, checked, and entered by the treating physician. All statistical analyses were performed using Statistical Package for the Social Sciences software version 25.0 [IBM SPSS Statistics 25 software (IBM Corp., Armonk, NY, USA)]. Continuous data are presented as mean ± SD and median (minimum–maximum values) and categorical data are presented as number and percent. The Kaplan–Meier (KM) method was used to estimate survival in patients in each risk group up to 60 months from 1 year after the diagnosis with all-cause mortality as the end point, and log-rank test was used to compare estimates. Univariate and multiple Cox proportional hazard model was used to test variables that were associated with survival. Mean ± SD, 95% CI, 5 year cumulative survival, and concordance statistics (c stat) values were used for interpretation of survival analysis. The level of statistical significance was set at $P < .05$. The number of low-risk criteria at diagnosis and follow-up were not included in the multiple logistic regression analyses. Functional class, 6MWD, and NT-proBNP were considered as a criterion rather than absolute numbers in the multiple logistic regression analyses.

RESULTS

A total of 126 patients were enrolled, who had survived at least 1 year after the diagnosis with sufficient data available for analyses. The mean age was 32 ± 16 years at diagnosis. Most patients were women (70.6%). The mean follow-up was 99.41 ± 58.2 months and the median follow-up was 98.38 months. Thirty-two patients had died. Most patients were ES (31%) or had simple defects (29.4%). Most patients had received monotherapy (76.2%). Approximately 66.6% of patients were WHO FC I-II, 29.3% III, and 3.9% IV (Table 1). Both models effectively discriminated risk in our cohort ($P = .0001$). Patients achieving 2 or more noninvasive low-risk criteria or low-risk category by REVEAL Lite 2 at follow-up had a significantly reduced risk of death. Figure 1 demonstrates KM survival curves for noninvasive French model (A) and REVEAL Lite 2 (B). About 51% of patients achieved 2 or more low-risk criteria at follow-up. About 56% of patients were in low risk at follow-up (REVEAL Lite 2). The estimated survival rate at 5 years of patients meeting 2 and more low-risk criteria at follow-up was 100% versus 86.8% for patients meeting 1 low-risk criterion and 59.6% for patients meeting 0 low-risk criterion. The corresponding survival rate was 65% for high-risk patient, 76.2% for intermediate-risk patient, and 100% for low-risk patient (REVEAL Lite 2; $P = .0001$ by log-rank test; Figure 1). Registry to Evaluate Early and Long-term

Table 1. Clinical and Laboratory Characteristics of the Patients

Characteristic	n	%
CHD-PAH subset		
Eisenmenger syndrome	39	31
Prevalent left to right shunt		
Simple defect	37	29.4
Multiple combined defects	12	9.5
Complex defects	12	9.5
Small defects	3	2.4
Repaired defects	23	18.2
Age, years [mean ± SD; median (minimum–maximum)]	32.17 ± 16.3	26.5 (7- 82)
Gender		
Female	89	70.6
Male	37	29.4
NYHA/WHO FC		
I	9	7.1
II	75	59.5
III	37	29.3
IV	5	3.9
6MWD, m [n = 100; mean ± SD; median (minimum–maximum)]	393.96 ± 115.99	417.5 (50-600)
NT-proBNP, pg/mL [n = 69; mean ± SD; median (minimum–maximum)]	841.96 ± 1167.64	292 (39-5746)
Down's syndrome	6	4.8
Arterial hypertension	8	6.3
Atrial fibrillation	10	7.9
Comorbidities		
Diabetes mellitus	7	5.6
BMI ≥ 30 kg/m^2	12	9.5
Chronic kidney disease	6	4.8
Hypothyroidism	8	6.3
Hyperlipidemia	8	6.3
Obstructive sleep apnea syndrome	2	1.6
Risk categories at follow-up		
The number of low-risk criteria (by noninvasive French model)		
0	30	23.8
1	32	25.4
≥2	64	50.8
REVEAL Lite 2		
Low	69	55.6
Intermediate	26	21
High	29	23.4
Treatment		
Monotherapy	96	76.2
Dual sequential therapy	22	17.5
Dual upfront therapy	8	6.3

6MWD, 6-minute walk distance; BMI, body mass index; CHD-PAH, congenital heart disease-associated pulmonary arterial hypertension; FC, functional class; NT-proBNP, N-terminal pro-hormone of brain natriuretic peptide; NYHA, New York Heart Association; REVEAL, Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management; WHO, World Health Organization.

PAH Disease Management Lite 2 approximates noninvasive French model at discriminating among patients at low, intermediate, or high risk based on c-index. In univariate logistic regression analysis, age, the presence of atrial fibrillation, chronic kidney disease, WHO FC at follow-up, BNP/NT-proBNP at follow-up, 6MWD at follow-up, the number of low-risk criteria at follow-up, and the REVEAL Lite 2 scores at follow-up were associated with survival. On multiple

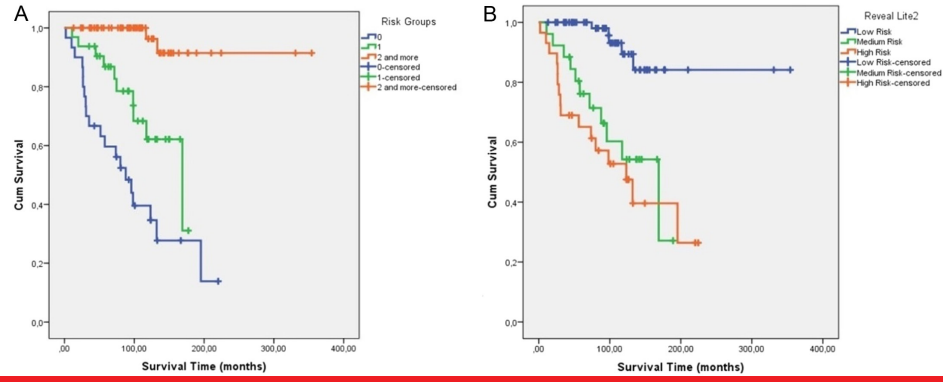

Figure 1. Survival plot demonstrates Kaplan–Meier survival curves for noninvasive French model (A) and REVEAL Lite 2 (B).

analysis after the adjustments, age, the high-risk status by REVEAL Lite score, and the presence of 2 or 3 low-risk criteria by noninvasive French model remained associated with survival (Table 2). There were no differences in terms of mortality between patients who received mono- and combination therapies. The effect of treatment strategy was not significant on univariate analysis (Table 2). Treatment strategy was not significant on log-rank test, either $P = .718$. In univariate logistic regression analysis, age was associated with survival. Sixteen patients were under age 18. Those patients were between 7 and 16 years of age. There were no differences in terms of mortality between patients with pediatric and adult age ranges on log-rank test ($P = .059$; data not shown). Approximately 37.7% of patients had 0 low-risk criterion at diagnosis, 35.2% of patients had 1 low-risk criterion at diagnosis, and 37.7% of patients had 2 or 3 low-risk criteria at diagnosis. Approximately 24.6% of patients had 0 low-risk criterion at follow-up, 24.5% of patients had 1 low-risk criterion at follow-up, and 50.9% of patients had 2 or 3 low-risk criteria at follow-up.

DISCUSSION

Our study evaluated the noninvasive French model and REVEAL Lite 2 in CHD-PAH. Congenital heart disease-associated pulmonary arterial hypertension comprises the most frequent etiology in this country.[9] We have demonstrated that both models are prognostic for mortality. Therefore, both models using fewer variables may be preferable to expedite risk assessment in the clinic and avoid potentially unnecessary invasive procedures.

The 2020 ESC Guidelines for the management of adult congenital heart disease recommend risk assessment for all patients with CHD-PAH. Noninvasive French model comprises WHO FC, 6MWD, and NT-proBNP or BNP. It was found to discriminate risk better than the average score model in the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) registry.[10] Registry to Evaluate Early and Long-term PAH Disease Management Lite 2 comprises 6 noninvasive variables—WHO FC, systolic BP, heart rate, 6MWD, BNP/NT-proBNP, and eGFR —and provides a simplified method of risk assessment. In this study, both models discriminated (identified?) risk at 5-year follow-up. Patients who achieved low-risk status according to either model did much better than other risk categories in the long term.

Data on targeted PAH therapy, outcomes, and risk assessment in adults with CHD-PAH are scarce compared with idiopathic PAH. Even if patients with CHD-PAH were included in the trials, data have not sufficiently been presented separately from data on other PH subsets. Therefore, there is a limited evidence about risk assessment and PAH therapies for CHD-PAH. There are only a few data to support upfront/early sequential oral combination therapy for ES.[11,12] Sequential combination therapy is frequently initiated only upon symptomatic clinical worsening. In this study, most patients were diagnosed with ES consistent with the previous nationwide The Turkish Congenital Heart Disease – Associated Pulmonary Arterial Hypertension Study (THALES) registry.[13] Initial treatment strategy had no effect on mortality. However, after therapy, less patients had 0 low-risk criterion (24.6% vs. 37%) and 1 low-risk criterion (24.5% vs. 35.2%); more patients had 2 or 3 low-risk criteria (50.9% vs. 37.7%). This finding suggests that treatment improves risk in those patients and more aggressive therapy may be useful in those who have not achieved low risk at follow-up.

Approximately 50.9% of patients achieved 2 or more low-risk criteria at follow-up. About 56% of patients were in low risk at follow-up (REVEAL Lite 2). The estimated survival rate at 5 years of patients meeting 2 and more low-risk criteria at follow-up was 100% versus 86.8% for patients meeting 1 low-risk criterion and 59.6% for patients meeting 0 low-risk criterion. The corresponding survival rate was 65% for high-risk patient, 76.2% for intermediate-risk patient, and 100% for low-risk patient (REVEAL Lite 2). This is in contrast to previous misbelief that patients with ES have much better survival in comparison with other PH subtypes. It also underscores the need for aggressive use of available therapies for higher risk patients. A recent study accounting for immortal time bias showed that untreated patients have a poor survival with 10-year mortality rates ranging between 30% and 40%.[14] Similarly, mortality rates for WHO FC II patients with ES were considerable.[15] The primary treatment goal for all patients with PAH is to achieve low-risk status. Most centers follow a sequential combination therapy starting with an oral endothelin receptor antagonist (ERA)/phosphodiesterase (PDE)-5 inhibitor and escalating therapy if symptoms persist.

Table 2. Univariate and Multiple Cox Proportional Hazard Regression Analysis of Parameters Associated with Survival

		Univariate				Multiple			
		P	HR	95% CI Lower	95% CI Upper	*P*	HR	95% CI Lower	95% CI Upper
Ref: Absent	The presence of comorbidity	.574	0.656	0.151	2.853	—	—	-	-
	Down syndrome	.408	0.046	0	67.764	—	—	-	-
	Atrial fibrillation	.0001*	6.203	2.463	15.622	.533	1.433	0.462	4.443
	Chronic kidney disease	.01*	4.058	1.407	11.705	.177	2.269	0.692	7.443
	Obesity	.415	1.549	0.541	4.433	—	—	-	-
	Hypothyroidism	.384	0.412	0.056	3.025	—	—	-	-
	Hypertension	.682	1.35	0.321	5.676	—	—	-	-
	Hyperlipidemia	.471	1.552	0.47	5.122	—	—	-	-
	Diabetes mellitus	.66	0.64	0.087	4.699	—	—	-	-
Continuous	6-minute walk distance at diagnosis	.033*	1.406	1.028	1.925	—	—	-	-
	NT-proBNP at diagnosis	.007*	1.548	1.128	2.126	—	—	-	-
	6-minute walk distance at follow-up	.001*	1.76	1.245	2.489	—	—	-	-
	NT-proBNP at follow-up	.009*	1.59	1.121	2.256	—	—	-	-
Continuous	Age at diagnosis	.0001*	1.048	1.028	1.068	.02*	1.031	1.005	1.058
Ref: Female	Male gender	.739	0.872	0.39	1.949	—	—	-	-
Ref: Mono	Dual sequential therapy	.418	1.417	0.61	3.294	—	—	-	-
	Dual upfront therapy	.928	1.097	0.146	8.242	—	—	-	-
	WHO functional class I at diagnosis	.918	0.922	0.199	4.276	—	—	-	-
	WHO functional class II at diagnosis	.16	2.879	0.66	12.57	—	—	-	-
	WHO functional class III at diagnosis	.185	3.181	0.574	17.638	—	—	-	-
Continuous	The number of low-risk criteria at diagnosis	.001*	0.447	0.274	0.731	—	—	-	-
Ref: 0	1 low-risk criterion at diagnosis	.084	0.503	0.231	1.096	.952	0.970	0.366	2.573
	2 or 3 low-risk criteria at diagnosis	.004*	0.165	0.048	0.566	.487	1.767	0.354	8.813
	WHO functional class I at follow-up	.459	1.633	0.446	5.983	—	—	-	-
	WHO functional class II at follow-up	.005*	5.983	1.693	21.135	—	—	-	-
	WHO functional class III at follow-up	.0001*	17.278	4.29	69.595	—	—	-	-
Continuous	The number of low-risk criteria at follow-up	.0001*	0.297	0.188	0.472	—	—	-	-
Ref: 0	1 low-risk criterion at follow-up	.02*	0.402	0.187	0.866	.552	0.736	0.268	2.021
	2 or 3 low-risk criteria at follow-up	.0001*	0.034	0.008	0.144	.018*	0.095	0.013	0.672
Ref: Low-risk group	Intermediate-risk group by REVEAL Lite 2 at follow-up	.001*	6.527	2.263	18.826	.077	3.258	0.881	12.052
	High-risk group by REVEAL Lite 2 at follow-up	.0001*	8.882	3.241	24.344	.031*	4.258	1.143	15.860

*$P < .05$ statistically significant.
HR, hazard ratio; NT-proBNP, N-terminal pro-hormone of brain natriuretic peptide; Ref, in reference to.

Therefore, patients worsening or not improving on monotherapy should be offered sequential combination therapy, whereas patients with severe form of ES should be tried on upfront combination therapy. This study demonstrates that the high-risk status by REVEAL Lite score and the presence of 2 or 3 low-risk criteria by noninvasive French model at follow-up are prognostic of mortality; therefore, future studies involving CHD-PAH might consider these parameters at follow-up as treatment target.

The COMPERA-CHD registry also reports that survival of patients with CHD-PAH is significantly better than that of idiopathic PAH-patients. The 5-year survival rate of treated patients in our cohort was 74.6% which is similar to the COMPERA registry.[16] Risk discrimination of patients in our cohort using the French noninvasive method seems more accurate than that obtained using REVEAL Lite 2. The c-index obtained using the French noninvasive method was 0.821 and using REVEAL Lite 2 was 0.766. In contrast, REVEAL 2.0, when compared with COMPERA and The French pulmonary hypertension registry (FPHR), showed greater risk discrimination than either of the 2 ESC/ERS-based risk assessment strategies.[6] This may be because patient populations are different. Our cohort comprises only CHD-PAH patients, most of which are ES and simple defects. Whereas the registries and major drug studies enrolled patients with repaired simple congenital systemic-to-pulmonary shunts, but not patients with ES. In the REVEAL registry, CHD-PAH accounted for about 10% of the whole cohort, whereas CHD-PAH was an exclusion criterion in French registry.[5,7] This study comprising exclusively CHD-PAH patients confirms the potential applicability of those 2 risk prediction models in CHD-PAH populations to determine patients with low-risk status. However, distinguishing high-risk patients who may require more intensive upfront therapies from the beginning is also an important issue. Recently, Sonnweber et al[17] underlined this issue and showed that 7 different risk assessment tools including noninvasive French model and REVEAL 2.0 lack accuracy to differentiate mortality between intermediate- and high-risk groups in a cohort consisted of idiopathic PAH, connective tissue-associated PAH, and chronic thromboembolic pulmonary hypertension.[17] Of note, according to our results, the prognostic separation between intermediate and high-risk groups remains challenging. It confirms a limitation of utilizing mainly noninvasive risk parameters to discriminate the prognostic risk between intermediate- and high-risk CHD-PAH patients. Despite valuable insights into discriminating low-risk patients by using noninvasive parameters in the clinical practice, discriminating intermediate- and high-risk patients warrants further research.

Study Limitations

Strengths include the relatively large sample size of CHD-PAH, the inclusion of various types of CHD-PAH including ES, and the "real-life" setting. Our results underline the relevance of both strategies to risk assessment at follow-up in CHD-PAH with a wide range of real-world demographic characteristics. It reiterates the relevance of regular risk monitoring in the clinics. The study has several limitations. This was a retrospective study. Only 6 PAH centers had contributed. Because patients in each CHD-PAH subset were small in number, we were not able to perform a reliable mortality analysis. We did not collect data with respect to the initiation of new or combined medication treatment or rehospitalization because of PAH worsening. Another important limitation is that we did not collect any echocardiographic data either. The risk status could not be assessed by REVEAL Lite score in 2 patients who were inadvertently included with missing data.

CONCLUSIONS

Our analysis confirms the still-unfavorable prognosis and reduced survival rates of patients with CHD-PAH. It supports the implementation of the noninvasive French model and REVEAL Lite 2 into clinical practice for the follow-up of patients with CHD-PAH. Only slightly more than one-third of the patients were low risk at diagnosis and that number just increased to half of the patients at follow-up. There were several novel elements to the study, including the enrollment of patients with ES and various types of CHD. Furthermore, it provides important insight into the conduct of future clinical studies of risk assessment in CHD patients such as the consideration of the number of low-risk criteria/the low-risk status as a treatment target.

Data Sharing Statement: Data supporting the findings of this study are available from the corresponding author on request.

Disclosure: The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. This study did not receive any funding. Y.T.Y. has received speaker fees from AstraZeneca, Bayer, Boehringer-Ingelheim, and Janssen; has served on a scientific advisory board for Exeltis, outside the submitted work.

Ethics Committee Approval: This study complied with the principles outlined in the Declaration of Helsinki. The study protocol was approved by the Medical Ethics Committee of Pamukkale University. Approval date: July 8, 2020. Reference number: 60116787-020/41119.

Informed Consent: Verbal informed consent was obtained from the patients who agreed to take part in the study.

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Author Contributions: Concept – Y.T.Y.; Design – Y.T.Y., İ.B., B.K.A., H.Ş.; Supervision – B.Y., M.M., Ü.Y.S., M.M., İ.B., B.K.A., H.Ş., S.N., M.S.K., Z.Ö.; Data collection &/or processing – Y.T.Y., İ.B., B.K.A., B.Y., M.M., Ü.Y.S., H.Ş., S.N., M.S.K., Z.Ö.; Analysis &/or interpretation – Y.T.Y., İ.B., H.Ş.; Literature search – Y.T.Y., İ.B., H.Ş.; Writing – Y.T.Y., İ.B., H.Ş.; Critical review – Y.T.Y., İ.B., B.K.A., B.Y., M.M., Ü.Y.S., H.Ş., S.N., M.S.K., Z.Ö.

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