Original Article

Levels of Enzymes Involved in Polyamine Synthesis in Patients with Pulmonary Hypertension

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ABSTRACT

Background

Pulmonary hypertension (PH) is a multifactorial disease characterized by elevated pulmonary artery pressure and progressive vascular remodeling. Polyamines are implicated in cell proliferation and vascular pathology. While elevated polyamine levels have been observed in PH, the expression of key enzymes involved in their biosynthesis ornithine decarboxylase (ODC), arginine decarboxylase (ADC), and agmatinase (AGMAT) has not been thoroughly examined across PH subtypes.

Methods

This cross-sectional study included 78 individuals: 21 controls and 57 PH patients categorized into Group 1 (PAH), Group 2 (PH due to left heart disease), and Group 3 (PH due to lung diseases or hypoxia). PH diagnosis was based on current ESC/ERS guidelines. Serum levels of ODC, ADC, and AGMAT were measured using ELISA. Echocardiographic and laboratory parameters were also recorded.

Results

While intergroup comparisons among PH subtypes did not reveal significant differences in enzyme levels, patients in all PH groups exhibited numerically higher ODC and ADC levels compared to controls. Mean ODC concentrations were 12.8 ± 8.6 ng/mL in controls and ranged from 17.0 ± 11.8 to 18.4 ± 12.4 ng/mL in PH groups. Similarly, ADC levels were elevated in PH groups (83.4 ± 53.8 to 87.6 ± 55.8 ng/mL) compared to controls (70.8 ± 26.9 ng/mL). AGMAT levels showed no significant differences. Group 1 PH patients received targeted therapies per current guidelines. Echocardiographic assessments confirmed expected hemodynamic distinctions across groups.

Conclusion

Our findings suggest a potential upregulation of polyamine biosynthesis in PH, particularly via ODC and ADC pathways. Although not statistically significant, these trends support a metabolic contribution to PH pathophysiology. Further research with larger cohorts' studies is needed to validate these enzymes as biomarkers or therapeutic targets.

Keywords

Pulmonary Hypertension; Polyamine; Arginine Decarboxylase; Ornithine Decarboxylase; Agmatinase

INTRODUCTION

Pulmonary hypertension (PH) is a progressive and multifactorial disease characterized by elevated pulmonary arterial pressure, leading to increased pulmonary vascular resistance, right ventricular overload, and ultimately right heart failure [1]. Despite the heterogeneity among PH subtypes, common pathological features include endothelial dysfunction, vasoconstriction, and vascular remodelling [2]. A central aspect of PH pathogenesis involves reduced nitric oxide (NO) bioavailability and abnormal proliferation of pulmonary arterial smooth muscle cells, contributing to vascular remodeling and increased pulmonary vascular resistance [3,4]. Although the risk factors for the disease vary by gender, they are generally diabetes, dyslipidemia and smoking [5-7].

Polyamines -putrescine, spermidine, and spermine- are small organic cations essential for cellular proliferation, differentiation, and

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survival [8]. Their biosynthesis is tightly regulated through two primary pathways: the ornithine decarboxylase (ODC) pathway, converting ornithine to putrescine, and the arginine decarboxylase (ADC) followed by agmatinase (AGMAT) pathway, converting arginine to agmatine and subsequently to putrescine [9]. Agmatine, an intermediate in this pathway, is also known to modulate nitric oxide synthase (NOS) enzymes, linking polyamine metabolism to NO production [10, 11].

Recent experimental studies have highlighted the role of polyamine metabolism in PH [12]. For instance, alterations in polyamine regulatory pathways have been implicated in pulmonary vascular disease, suggesting that polyamine synthesis inhibitors and transport blockers could be considered for clinical trials in human pulmonary arterial hypertension [13]. Additionally, dysregulation of the polyamine pathway in endothelial cells has been shown to impair vascular homeostasis, leading to endothelial dysfunction and increased susceptibility to pulmonary arterial hypertension [14].

Furthermore, metabolomic analyses have reported increased levels of polyamines, such as putrescine and spermidine, in lung tissues from patients with PH, indicating a link between polyamine metabolism and pulmonary vascular remodelling [15, 16]. These findings suggest that polyamine metabolism not only contributes to the pathogenesis of PH but also offers potential targets for therapeutic intervention.

Despite these insights, the expression and activity levels of key polyamine-synthesizing enzymes in patients with PH remain largely unexplored. Moreover, it is unclear whether these enzyme levels vary among different PH subtypes. Therefore, this study aims to investigate the serum levels of ODC, ADC, and AGMAT in patients with and without PH, to explore their potential as biomarkers and their contribution to PH pathophysiology.

MATERIALS AND METHODS

2.1. Patients and control group

This study included patients diagnosed with pulmonary hypertension at the Cardiology Outpatient Clinic of Sivas Cumhuriyet University Faculty of Medicine. The diagnosis of pulmonary hypertension was established in accordance with current guideline recommendations, based on clinical findings, transthoracic echocardiography, and, when indicated, right heart catheterization [1]. All patients met the contemporary diagnostic criteria for pulmonary hypertension and were not receiving heparin at the time of blood sampling. The control group consisted of individuals with stable cardiovascular disease but without a diagnosis of pulmonary hypertension, as confirmed by echocardiographic evaluation and clinical assessment. Written informed consent forms were obtained from patients and healthy individuals for participation in the study.

2.2. Collecting blood samples

Peripheral venous blood samples were collected from all participants under fasting conditions. In the PH group, blood samples were collected prior to the administration of any medical treatment on the day of sampling. Samples were allowed to clot and were subsequently centrifuged at 1610 g for 10 minutes to obtain serum. The resulting serum samples were aliquoted and stored at −80°C until analysis.

2.3. Determination of polyamine synthesis pathway enzyme levels

ADC, ODC and AGMAT protein levels in the serum of all groups were measured using a commercial ELISA kit according to the manufacturer's instructions. In addition, other routine blood parameters were examined in the patient and control groups [17].

2.4. Statistical analysis

Data were analyzed using SPSS version 23. Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range) where appropriate. Group comparisons were made using analysis of variance (ANOVA) followed by Tukey's post hoc test for normally distributed variables. For non-normally distributed data, the Kruskal-Wallis test followed by Mann-Whitney U test was applied. A two-sided p value of <0.05 was considered statistically significant.

RESULTS

A total of 78 individuals were evaluated, including 21 controls and 57 patients with pulmonary hypertension (PH) across Group 1, Group 2, and Group 3. The mean age of participants was similar among the four groups (52.6 ± 13.2 years in controls vs 63.3 ± 13.1 in Group 2 PH, $p = 0.470$). However, the sex distribution differed significantly: Group 1 PH had a markedly higher proportion of female patients (88.2%) compared to controls (38.1%) and other PH subgroups (24.0%

in Group 2, 53.3% in Group 3; $p < 0.001$). Rates of most coexisting conditions – including hypertension, diabetes mellitus, atrial fibrillation, smoking history, and cerebrovascular disease – did not differ significantly between groups. In contrast, chronic obstructive pulmonary disease (COPD) was significantly more frequent in Group 3 PH patients (80.0%) versus the other groups (0% in Group 1; 40.0% in Group 2; 23.8% in controls; $p < 0.001$). Medication usage showed notable inter-group differences as well. Use of β-blockers was significantly higher in Group 2 PH (68.0%) compared to Group 1 PH (11.8%; $p < 0.001$). Group 2 PH patients also more frequently received renin–angiotensin system inhibitors (44.0%) and mineralocorticoid receptor antagonists (40.0%) than those in other groups ($p = 0.045$ and $p = 0.023$, respectively). Loop diuretics were commonly used in both Group 2 (68.0%) and Group 3 PH (73.3%), significantly more than in controls (9.5%; $p < 0.001$). By contrast, the use of aspirin, oral anticoagulants, and SGLT2 inhibitors was similar across all groups (Table 1).

Among patients with Group 1 pulmonary hypertension, specific targeted therapies were recorded (Table 2). Endothelin receptor antagonists such as bosentan and macitentan were used in 70.6% and 29.4% of patients, respectively. Phosphodiesterase-5 inhibitors, including tadalafil and sildenafil, were administered to 35.3% and 11.8% of patients, respectively, while the prostacyclin receptor agonist selexipag was used in 17.6%. These targeted therapies were not used in the other PH groups or in the control group.

Laboratory evaluation revealed significant differences in select biomarkers, while most routine parameters were similar between groups. Serum creatinine was higher in PH patients, especially in Group 2 (1.3 ± 0.6 mg/dL), compared to controls (1.1 ± 0.5 mg/dL; $p = 0.007$). Cardiac biomarkers were also elevated in the PH cohorts: median troponin levels were 18 (IQR 6–31) in Group 2 PH and 14 (5–34) in Group 3 PH, versus 5 (2–19) in controls ($p = 0.013$). Similarly, NT-proBNP levels were significantly higher in the PH groups (median 790 [198–4172] in Group 2) than in controls (111 [67–513]; $p = 0.004$). In contrast, there were no significant group differences in liver enzymes (ALT, AST), electrolytes (sodium, potassium), blood counts (hemoglobin, white blood cell count, platelets), lipid profile (triglycerides, LDL cholesterol), or C-reactive protein (Table 3).

Echocardiographic parameters demonstrated clear distinctions between controls and PH patients. Left ventricular ejection fraction (LVEF) was significantly reduced in Group 2 PH (46 ± 14%) compared to controls (59 ± 4%) and the other PH subgroups (which had means ~57%; $p = 0.003$). Left atrial diameter was markedly larger in the PH groups (for example, 46 ± 6 mm in Group 2) than in controls (35 ± 4 mm; $p < 0.001$). Systolic pulmonary artery pressure (sPAP) was substantially elevated in all PH subtypes (mean values ~39–47 mmHg) relative to the control group (16 ± 3 mmHg; $p < 0.001$) (Table 3).

Serum levels of enzymes in the polyamine synthesis pathway—ODC, ADC, and AGMAT—did not differ significantly among the different PH subgroups ($p = 0.477$, 0.938, and 0.775, respectively). However, compared to the control group, mean enzyme levels were numerically higher in all PH groups. Specifically, mean ODC was 12.8 ± 8.6 in controls versus 18.4 ± 12.4 in Group 1 PH, 17.0 ± 11.8 in Group 2 PH, and 18.0 ± 13.1 in Group 3 PH. Similarly, mean ADC levels were elevated in the PH subgroups (ranging from 83.4 ± 53.8 to 87.6 ± 55.8) compared to controls (70.8 ± 26.9). Mean AGMAT levels also showed a modest increase in the PH groups (84.8 ± 46.0 to 93.2 ± 46.6) compared to controls (90.6 ± 24.1) (Table 3).

Table 1. Basic demographic characteristics according to pulmonary hypertension groups

	Control (n=21)	Group 1 PH (n=17)	Group 2 PH (n=25)	Group 3 PH (n=15)	Total (n=78)	P value
Woman, n (%)	8 (38.1)	15 (88.2)	6 (24.0)	8 (53.3)	37 (47.4)	<0.001
Hypertension, n (%)	9 (42.9)	6 (35.3)	10 (40.0)	5 (33.3)	30 (38.5)	0.933
Diabetes Mellitus, n (%)	9 (42.9)	4 (23.5)	11 (44.0)	5 (33.3)	29 (37.2)	0.524
Atrial Fibrillation, n (%)	6 (28.6)	4 (23.5)	6 (24.0)	5 (33.3)	21 (26.9)	0.908

	Control (n=21)	Group 1 PH (n=17)	Group 2 PH (n=25)	Group 3 PH (n=15)	Total (n=78)	P value
Chronic Obstructive Pulmonary Disease, n (%)	5 (23.8)	0 (0.0)	10 (40.0)	12 (80.0)	27 (34.6)	<0.001
Smoking, n (%)	6 (28.6)	1 (5.9)	3 (12.0)	5 (33.3)	15 (19.2)	0.117
Previous Myocardial Infarction, n (%)	5 (23.8)	0 (0.0)	13 (52.0)	2 (13.3)	20 (25.6)	<0.001
Cerebrovascular Disease, n (%)	2 (9.5)	2 (11.8)	4 (16.0)	2 (13.3)	10 (12.8)	0.930
NYHA Functional Class III-IV	6 (28.6)	5 (29.4)	9 (36.0)	6 (40.0)	26 (33.3)	0.044
Acetylsalicylic acid, n (%)	8 (38.1)	8 (47.1)	17 (68.0)	6 (40.0)	39 (50.0)	0.165
Oral anticoagulant, n (%)	2 (9.5)	2 (11.8)	5 (20.0)	4 (26.7)	13 (16.7)	0.504
Beta blockers, n (%)	8 (38.1)	2 (11.8)	17 (68.0)	3 (20.0)	30 (38.5)	<0.001
Renin Angiotensin System Inhibitors, n (%)	7 (33.3)	1 (5.9)	11 (44.0)	3 (20.0)	22 (28.2)	0.045
Mineralocorticoid Receptor Antagonists, n (%)	1 (4.8)	1 (5.9)	10 (40.0)	1 (6.7)	13 (16.7)	0.023
Sodium Glucose Transporter-2 Inhibitors, n (%)	4 (19.0)	2 (11.8)	7 (28.0)	3 (20.0)	16 (20.5)	0.640
Loop diuretic, n (%)	2 (9.5)	4 (23.5)	17 (68.0)	11 (73.3)	34 (43.6)	<0.001

Table 2. Specific treatments used by Group 1 Pulmonary Hypertension patients

Treatment	N (%)
Bosentan	12 (70.6)
Masitentan	5 (29.4)
Tadalafil	6 (35.3)
Sildenafil	2 (11.8)
Selexipag	3 (17.6)

Table 3. Comparison of laboratory and echocardiographic data according to pulmonary hypertension groups

	Control (n=21)	Group 1 PH (n=17)	Group 2 PH (n=25)	Group 3 PH (n=15)	Total (n=78)	P value
Age (years)	52.6 ± 13.2	53.0 ± 13.9	63.3 ± 13.1	56.0 ± 14.6	56.8 ± 14.1	0.470
BMI	27.0 ±3.8	25.4 ± 3.1	26.8 ± 3.4	27.8 ± 4.5	26.7 ± 3.7	0.618
Creatine	1.1 ± 0.5	0.9 ± 0.3	1.3 ± 0.6	1.2 ± 0.4	1.2 ± 0.5	0.007
ALT	20 (14-32)	20 (16-26)	24 (13-41)	21 (16-30)	21 (15-30)	0.756
AST	18 (15-28)	19 (17-22)	25 (17-42)	22 (116-29)	22 (16-30)	0.234
Sodium	138 ± 5	138 ± 5	135 ± 5	138 ± 6	137 ± 5	0.079
Potassium	4.4 ± 0.6	4.6 ± 0.5	4.5 ± 0.6	4.6 ± 0.5	4.5 ± 0.5	0.567

	Control (n=21)	Group 1 PH (n=17)	Group 2 PH (n=25)	Group 3 PH (n=15)	Total (n=78)	P value
Hemoglobin	14.2 ± 2.6	14.0 ± 1.9	12.9 ± 2.7	13.3 ± (1.5)	13.6 ± 2.3	0.120
WBC	7230 (5155-8810)	6320 (4580-7150)	7920 (6000-8725)	7190 (5820-9900)	7140 (5295-8635)	0.105
Platelet	227 (177-301)	230 (195-315)	210 (176-260)	273 (179-318)	228 (183-300)	0.449
Triglyceride	159 ± 76	148 ± 43	161 ± 83	204 ± 109	166 ± 81	0.448
LDL	127 ± 28	108 ± 26	118 ± 47	131 ± 35	121 ± 37	0.187
CRP	3.3 (2.0-13)	4.0 (2.0-6.0)	7.0 (5.0-19.0)	5 (2.5-13.5)	5.0 (2.3-16)	0.129
Troponin	5 (2-19)	4 (2-11)	18 (6-31)	14 (5-34)	10 (3-23)	0.013
NT-proBNP	111 (67-513)	168 (128-503)	790 (198-4172)	452 (79-5629)	332 (115-1228)	0.004
EF (%)	59 ± 4	57 ± 3	46 ± 14	57 ± 5	54 ± 10	0.003
Left atrium (mm)	35 ± 4	38 ± 7	46 ± 6	42 ± 6	41 ± 7	<0.001
sPAB (mmHg)	16 ± 3	47 ± 16	39 ± 12	42 ± 16	35 ± 17	<0.001
ODC	12.8 ± 8.6	18.4 ± 12.4	17.0 ± 11.8	18.0 ± 13.1	16.4 ± 11.4	0.477
ADC	70.8 ± 26.9	87.6 ± 55.8	83.4 ± 53.8	86.7 ± 67.9	81.6 ± 51.2	0.938
AGMAT	90.6 ± 24.1	92.8 ± 48.2	93.2 ± 46.6	84.8 ± 46.0	90.8 ± 41.3	0.775

DISCUSSION

In this study, we evaluated serum levels of key enzymes in the polyamine synthesis pathway -ODC, ADC, and AGMAT - in patients with PH and control group. Our findings demonstrated numerically higher levels of ODC and ADC in all PH subgroups compared to the control group, although these differences did not reach statistical significance. Specifically, ODC levels were approximately 50% and ADC levels about 20% higher in PH patients. These results suggest a potential upregulation of polyamine biosynthesis in PH and implicate the polyamine pathway in disease pathogenesis.

Polyamines -including putrescine, spermidine, and spermine- are small, positively charged molecules found in nearly all eukaryotic cells [18]. They are involved in essential cellular processes such as chromatin remodeling, DNA replication, gene transcription and translation, ion channel regulation, and receptor signaling [19]. Because of their role in promoting cell proliferation, migration, and survival, dysregulated polyamine metabolism has been implicated in various proliferative and vascular diseases, including cancer and cardiovascular pathology [20, 21]. Intracellular polyamine concentrations are tightly controlled through synthesis, degradation, and membrane transport mechanisms to prevent toxicity [22].

Pulmonary hypertension is a heterogeneous condition with multiple clinical subtypes, but common pathophysiological features include endothelial dysfunction, vasoconstriction, pulmonary vascular remodeling, inflammation, and thrombosis in situ [1]. In addition, anxiety states in individuals and the resulting increase in stress-related hormones also form the basis for the development of hypertension [23,24]. However, it has been reported as a result of the study that even though low income status determines the emergence of the disease, it has no relation with nutrition [25]. Among these, reduced NO bioavailability, increased endothelin-1 signaling, and metabolic reprogramming are especially prominent. Given the role of polyamines in cellular growth and vascular biology, activation of the polyamine pathway may represent a unifying mechanism across PH groups.

In our cohort, baseline demographic characteristics, including age and sex distribution, varied significantly across PH subgroups. For instance, patients in Group 1

PH were predominantly female and younger compared to those in Groups 2 and 3 PH. These differences reflect well-established epidemiological patterns reported in large registries and are consistent with real-world distributions of PH subtypes, where PAH (Group 1) more commonly affects younger women, while PH due to left heart disease (Group 2) and lung disease (Group 3) is typically observed in older individuals with a higher burden of comorbidities [1, 26]. Although demographic heterogeneity may introduce variability in enzyme levels, it also mirrors clinical reality and enhances the translational relevance of our findings. Additionally, the control group in this study was carefully selected to match the PH groups in terms of general cardiovascular risk profile, including prevalent conditions such as hypertension, diabetes mellitus, and coronary artery disease, but without a clinical or echocardiographic diagnosis of PH. This allowed for a more focused comparison of enzyme levels, minimizing the confounding effects of non-PH cardiovascular pathology. Nevertheless, it is important to consider that polyamine metabolism can be influenced by age, sex, and comorbid conditions. Experimental and clinical studies have shown that aging is associated with increased polyamine turnover and altered expression of biosynthetic enzymes such as ODC, potentially contributing to vascular remodeling and endothelial dysfunction [27]. Similarly, metabolic conditions such as diabetes mellitus and hypertension have been linked to dysregulation of polyamine homeostasis, possibly via oxidative stress, mitochondrial dysfunction, or inflammation [28, 29]. Therefore, although enzyme elevations observed in our study were most prominent in PH patients, these potential modifiers should be considered in future analyses and multivariable modeling efforts.

In Group 1 PH, the pathophysiology is characterized by hyperproliferative remodeling of the pulmonary arteries [1]. In experimental models, silencing of spermine synthase or pharmacologic inhibition this proliferative response and attenuated disease progression [30]. Similarly, Rhodes et al. identified increased plasma concentrations of polyamine derivatives, including 4-acetamidobutanoate and N-acetylputrescine, in PAH patients [31]. However, these studies did not examine upstream enzymatic regulation. Our observation of elevated ODC and ADC levels in Group 1 PH may reflect activation of the polyamine axis as a contributing factor in vascular remodeling.

In our study, patients in Group 1 PH received guideline-directed, disease-specific therapies in accordance with the 2022 ESC/ERS guidelines for pulmonary arterial hypertension [1]. These included endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and prostacyclin analogs or receptor agonists, all of which are known to target key pathophysiological mechanisms such as endothelial dysfunction and impaired nitric oxide (NO) signaling. Although the direct effects of these therapies on the polyamine synthesis pathway have not been fully elucidated, the NO pathway represents a potential mechanistic intersection. Several experimental studies suggest that polyamines and NO synthase may influence each other's activity, particularly in vascular smooth muscle tone and remodeling [8, 10]. Importantly, enhancement of the NO pathway through agents like phosphodiesterase-5 inhibitors has been associated with improved hemodynamics, exercise capacity, and survival in PAH [32]. Therefore, while the link between PAH-targeted therapies and polyamine metabolism remains to be clarified, the observed clinical benefits of NO-based treatments in Group 1 PH may also indirectly modulate the cellular environment where polyamine dysregulation occurs.

In Group 2 PH (associated with left heart disease), pulmonary hypertension develops from chronically elevated left-sided filling pressures. In our study, Group 2 patients had significantly lower ejection fractions and higher NT-proBNP and troponin levels compared to other groups. Interestingly, ODC and ADC levels were also elevated in this group, suggesting that left ventricular dysfunction and resulting hemodynamic stress may induce compensatory metabolic changes, including polyamine biosynthesis. Prior research indicates that cardiac injury and oxidative stress can modulate polyamine metabolism and NOS function [10].

In Group 3 PH (due to lung diseases or hypoxia), chronic hypoxia and inflammation contribute to pulmonary vascular remodeling. In our cohort, this group showed the highest prevalence of COPD and elevated systolic pulmonary artery pressure. Although a direct link between hypoxia-induced HIF-1α activation and ODC expression in pulmonary tissue is not well established, hypoxia is known to influence metabolic pathways, including polyamine metabolism [22]. The observed elevation in ODC and ADC levels may reflect a metabolic adaptation to chronic hypoxic stress.

Collectively, these findings suggest that polyamine

metabolism is dysregulated across distinct PH subtypes -potentially via different initiating stimuli such as endothelial injury in PAH, ventricular dysfunction in Group 2 PH, and hypoxia in Group 3 PH. While AGMAT did not differ significantly between groups, the consistent increase in ODC and ADC highlights their possible role as surrogate biomarkers or therapeutic targets.

Importantly, understanding enzymatic activity within the polyamine pathway and how it varies across PH phenotypes could facilitate the development of subgroup-specific therapeutic approaches. Tailored targeting of metabolic pathways involved in vascular remodeling may improve outcomes, particularly in patient groups with distinct molecular profiles. Thus, characterizing these differences is not only biologically informative but also clinically valuable.

This study also has several limitations. First, the sample size was modest. Second, enzyme levels were measured in serum, which may not fully reflect local pulmonary vascular activity. Third, we did not quantify polyamine end-products (e.g., spermine) or assess catabolic or transport pathways, limiting insight into the full metabolic context. Lastly, enzyme measurements were performed using commercial ELISA kits without confirmation via orthogonal techniques such as Western blot or qRT-PCR, which may have introduced variability.

CONCLUSIONS

In conclusion, our findings suggest that ODC and ADC levels are elevated in patients with pulmonary hypertension, regardless of clinical subtype. These enzymes may serve as potential biomarkers or therapeutic targets. Future studies with larger cohorts, mechanistic investigations, and tissue-level analysis are warranted to validate and expand on these observations.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors's contribution

Data gathering and idea owner of this study: B-K and S-K, Study design: B-K, A-Ş and R-A Data gathering: S-K and A-Ş Writing and submitting manuscript: B-K and R-A, Editing and approval of final draft: B-K and S-K

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Ethics approval and consent to participate

Before starting the research study, an ethical permission document dated 02.05.2023 and numbered 2023-05/07 was obtained from Sivas Cumhuriyet University Clinical Research Ethics Committee.

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