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# The relationship of pregnancy losses with frequently-used hematologic parameters

## *Gebelik kayıplarının sık kullanılan hematolojik parametrelerle ilişkisi*

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## ABSTRACT

**Aim:** Recurrent pregnancy loss (RPL) is a common and undesirable condition in hematology and obstetrics practice. Pathogenesis for most cases remains undetermined. Thrombophilia may be a potential factor for these patients. Here, we aimed to investigate hematological parameters that have the potential to contribute to or predict RPL and to present our data as a single-center experience.

**Materials and Methods:** One hundred seventy female patients with at least one pregnancy loss between the years 2012 and 2024 were included retrospectively. The mean age of the patients was 34.48 ± 6.02. Patients with antiphospholipid antibodies and miscarriage due to an identifiable etiology (maternal anatomic and endocrine abnormalities, infectious causes, trauma, chromosomal abnormalities) were excluded from the study. Patients were divided into two groups, defined as patients with one or two miscarriages and more than two miscarriages, respectively. Thrombophilia screening tests (mutations and protein C/S/antithrombin levels), blood count and coagulation parameters were recorded and investigated whether there was a significant correlation in terms of miscarriage in the two groups.

**Results:** Nine patients (5.3%), 71 patients (41.8%), 60 patients (35.3%), 21 patients (12.4%), four patients (2.4%), and five patients (2.9%) had a history of one, two, three, four, five, and six miscarriages, respectively. No significant difference was found between the genetic mutations investigated in terms of thrombophilia, protein C, S, and antithrombin levels, and the number of pregnancy losses in both groups. There was no significant difference between hemogram parameters and coagulation parameters except aPTT for both groups. The aPTT value of group B was found to be significantly lower than that of group A (p=0.04).

**Conclusion:** Conflicting results in hematologic parameters in case of RPL are common and it is not easy to obtain homogeneous results. However, a low aPTT value, a parameter that can be easily and quickly measured, may be a parameter that can help predict RPL.

**Keywords:** coagulation; miscarriage; pregnancy; thrombophilia; thrombosis

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## ÖZ

***Amaç:*** *Tekrarlayan gebelik kaybı (TGK), hematoloji ve obstetrik alanında sık karşılaşılan ve endişe verici bir konudur; patogenezi belirsizdir. Bu çalışma, TGK ile potansiyel olarak ilişkili hematolojik faktörleri, özellikle trombofiliyi araştırmayı amaçlamaktadır.*

***Gereç ve Yöntem:*** *2012-2024 yılları arasında en az bir gebelik kaybı yaşamış 170 kadın hastayı retrospektif olarak analiz ettik; anrifosfolipit antikorları veya tanımlanabilir nedenleri olanlar dışlandı. Hastalar, bir veya iki düşük yapmış olanlar (grup A) ve ikiden fazla düşük yapmış olanlar (grup B) şeklinde iki gruba ayrıldı. Trombofili tarama testleri, hemogram ve koagülasyon parametrelerini değerlendirdik; analiz için SPSS 25.0 sürümü kullanıldı ve p <0,05 değeri anlamlı kabul edildi.*

***Bulgular:*** *Dokuz hastanın (%5,3) bir, 71 hastanın (%41,8) iki, 60 hastanın (%35,3) üç, 21 hastanın (%12,4) dört, dört hastanın (%2,4) beş ve beş hastanın (%2,4) altı düşük öyküsü mevcuttu. Trombofili, protein C, S ve antitrombin seviyeleri açısından araştırılan genetik mutasyonlar ile her iki gruptaki gebelik kaybı sayısı arasında anlamlı bir fark bulunamadı. Hemogram parametreleri ve koagülasyon parametreleri arasında, her iki grup için aPTT dışında anlamlı bir fark yoktu. Grup B'nin aPTT değeri, grup A'nınkinden anlamlı derecede düşük bulundu (p = 0,04).*

***Sonuç:*** *TGK durumunda hematolojik parametrelerde çelişkili sonuçlar yaygındır ve homojen sonuçlar elde etmek kolay değildir. Kolay ve hızlı bir şekilde ölçülebilen düşük bir aPTT değeri, TGK'nin öngörülmesine yardımcı olabilecek bir parametre olabilir.*



***Anahtar Sözcükler:*** *koagülasyon, düşük, gebelik, trombofili, tromboz*


## INTRODUCTION

Pregnancy loss is an undesired event occasionally resulting from various causes including thrombophilia. Pathogenesis for most cases remains undetermined (1). Causes related to thrombophilia may underlie these undetermined cases. Recurrent pregnancy loss (RPL) definition varies. While the Practice Committee of the American Society for Reproductive Medicine proposes two or more miscarriages, the European Society of Human Reproduction and Embryology proposes three or more miscarriages as the RPL definition (2-3). These patients are commonly evaluated by hematologists, by direct application to the outpatient clinic or consultation from the obstetrics. Besides factors responsible for thrombophilia such as inherited mutations (especially Factor V Leiden-FVLM and Prothrombin G20210A mutations-PGM), protein C/S/anti-thrombin deficiency and antiphospholipid antibodies, it is a matter of curiosity whether other hematological parameters such as blood count or coagulation parameters commonly used in hematology practice may be associated with the pathogenesis of RPL, at least related to thrombophilia, or have potential in predicting RPL.

Prothrombin time (PT) tests the extrinsic and common pathways of the coagulation cascade and represents the time, in seconds, for the patient's plasma to clot after the addition of calcium and extrinsic pathway activator (thromboplastin). Activated partial thromboplastin time (aPTT) is a coagulation test used as a measure of the integrity of the intrinsic and common pathways of the cascade and represents the time, in seconds, for patient plasma to clot after the addition of phospholipid and calcium, an intrinsic pathway activator. The normal or reference range for PT and APTT tests varies from laboratory to laboratory (4). There are studies showing that the normal duration of aPTT and PT shortens during normal pregnancy and returns to normal after pregnancy (5,6). The relationship of these changes to pregnancy loss is not illustrated. Here, we would like to reveal whether these factors have value in predicting pregnancy loss(es) and present the retrospective data of these patients as a single-center experience.

## MATERIALS AND METHODS

One hundred and seventy female patients who were evaluated due to at least one pregnancy loss in the hematology outpatient clinic of Aydın Adnan Menderes University between the years of 2012 and 2024 were included in the study. It was designed to be a single-center, retrospective, multidisciplinary, analytic, and cross-sectional study. Ethical committee approval has been obtained (Aydın Adnan Menderes University/Aydın, Türkiye. Date: 20.11.2023-Number: 453317). The research was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants prior to their involvement in the study.

Participants were provided with information about the purpose, methods, potential risks, and benefits of the research, and it was emphasized that their participation was voluntary. Furthermore, participants were informed of their right to withdraw from the study at any time.

The mean age of the patients was 34.48 ± 6.02. Treatment management was carried out by gynecologists and/or hematologists according to gynecology and/or hematology-thrombosis guidelines and, in some patients, at the clinician's discretion (7,8). Patients with anticardiolipin antibodies IgG or IgM and anti-beta2 glycoprotein I antibodies IgG and IgM by enzyme-linked immunosorbent assay (ELISA) (above 40 GPL) or lupus anticoagulant positivity (above the upper limit of normal laboratory value), as well as patients with a known etiology for pregnancy loss (maternal anatomic and endocrine abnormalities, infectious causes, trauma, chromosomal abnormalities), were excluded from the study. Patients were divided into two groups: Groups A and B defined the patients with one or two miscarriages and more than two miscarriages, respectively. The distinction between Groups A and B was based on the European Society of Human Reproduction and Embryology's definition of RPL as three or more miscarriages (3). The parameters included in genetic thrombophilia screening (i.e. FVLM, PGM, Methylenetetrahydrofolate reductase-MHFR, Plasminogen activator inhibitor-PAI, Beta fibrinogen, and Factor-XIII gene mutations), and protein C, S and antithrombin levels of the patients were recorded for both groups, and their relationship with recurrent pregnancy loss was investigated. Laboratory parameters were recorded one month after the first abortion and reference values of the hospital laboratory were used to decide high or low values. Blood count parameters (leukocyte, neutrophil, lymphocyte, monocyte, eosinophil, basophil ($10^3$/mkrL for each), hemoglobin (gr/dL), and platelet ($10^3$/mkrL) counts, mean corpuscular volume (fL), mean platelet volume (fL) and red cell distribution width (%)) were recorded for available patients. Regarding coagulation tests, aPTT, PT, international normalized ratio (INR), fibrinogen, d-dimer, and homocysteine were also recorded and the correlation between hemogram and coagulation parameters with pregnancy losses was investigated.

**Statistical Analysis**

SPSS version 25.0 for data analysis was used. The suitability of continuous variables to normal distribution was investigated using visual (histogram and probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). For the descriptive statistics of the research, mean and standard deviation were used. Chi-Square Test was used in the study to show whether there was a difference between categorical variables. The student-T Test was used to compare continuous variables with parametric properties in independent groups, and Mann Whitney U Test was used to compare continuous variables without parametric properties in independent groups. For statistical significance, a p-value of less than 0.05 was accepted.

**RESULTS**

The descriptive characteristics of the patients in groups A and B and the comparison of hematological parameters are shown in (Table 1). Nine patients (5.3%), 71 patients (41.8%), 60 patients (35.3%), 21 patients (12.4%), four patients (2.4%), and five patients (2.9%) had a history of one, two, three, four, five and six miscarriages, respectively. The number of patients that have homozygous FVLM and homozygous PGM were 2 and 0, respectively. Also, the number of patients with double heterozygosity for FVLM and PGM was 5. In 9 patients in group A and 17 in group B with FVL mutation; 7 and 16 of them, respectively, were accompanied by at least one other mutation (the mutations demonstrated in Table-1). In addition, of the 4 patients in group A and 5 patients in group B with PGM, at least one more mutation was detected in 2 and 5, respectively.

Fourty-one patients (24.1%), 11 patients (6.5%), and 21 patients (12.4%) have a history of using low-molecular-weight heparin (LMWH), aspirin, and LMWH +aspirin during the last pregnancy period and/or the postpartum period, respectively. Ninety-three patients (54.7%) have not used any antiaggregant /anticoagulant treatment. We could not obtain any records regarding drug history for four patients (2.4%). Three patients (1.8%) and two patients (1.2%) had also a history of venous and arterial thrombosis in their lifetime, respectively. All arterial thrombosis cases were in the form of ischemic stroke. In terms of venous thrombosis type, it was deep vein thrombosis in 2 cases and intra-abdominal vein thrombosis in 1

case. The rest of the patients have not experienced any kind of documented thrombosis previously.

No significant difference was found between the genetic mutations investigated in terms of thrombophilia, protein C, S, and antithrombin levels and the number of pregnancy losses in both groups. Based on laboratory reference values, the number of patients with protein C, S, and AT deficiency were 0, 15, and 2, respectively, for group A and 3, 23, and 2, respectively, for group B.

Blood count parameters were evaluated in terms of their effect on miscarriage. Cut-off values were accepted as the cut-off values of our hospital laboratory and were examined by grouping as low/normal/high or normal/high according to the parameter. No significant correlation with leukocyte (WBC) (<4,230/mm$^3$ vs 4,230-9,070/mm$^3$ vs 9,070/mm$^3$ <), neutrophil (<1,780/mm$^3$ vs 1,780-5,380/mm$^3$ vs 5,380/mm$^3$ < ), monocyte (<300/mm$^3$, 300-820 vs 820/mm$^3$ < ), hemoglobin (<13 gr/dL vs 13-16 gr/dL vs 16 gr/dL<), mean corpuscular volume (MCV) (<79 fL vs 79-92 fL vs 92 fL<), platelet count (<100,000/mcrL vs 100,000-450,000/mcrL vs 450,000 mcrL<), and mean platelet volume values (<9.4 fL vs 9.4-12.4 fL vs 12.4 fL< ) were detected between in group A and B. Also, there was no statistical significance regarding INR (0.8> vs 0.8-1.2 vs 1.2<), prothrombin time (PT, <8 sec, 8-13.5 sec and 13.5 sec<), fibrinogen (<284 mg/dL vs 284-580 mg/dL vs 580 mg/dL<), homocysteine (<15 Umol/L vs15 Umol/L<), d-dimer (<243 ng/ml DDU vs 243 ng/ml DDU <) values (p>0.05). However, the aPTT (<25.4 sec vs 25.4-38.4 sec vs 38 sec <) value of group B was found to be significantly lower than that of group A. (p=0.04). (Table-1).

**Table-1.** The descriptive characteristics of the patients in groups A and B and the comparison of hematologic and coagulation parameters.

| | **Group A (n:80)** | **Group B (n:90)** | **p** |
|---|---|---|---|
| **Number of Miscarriages (mean±SD)** | 1.89±0.31 | 3.49±0.82 | |
| **Age (mean±SD)** | 34.18±6.22 | 34.74±5.85 | p>0.05 |
| **History of previous thrombosis (n)** | Venous:2<br>Arterial:1 | Venous:1<br>Arterial:1 | |
| **Homozygous FVLM (n)** | - | 2 | |
| **Homozygous PGM (n)** | - | - | |
| **Double heterozygous for FVLM and PGM (n)** | 2 | 3 | |
| **MTHFR C677T** | Homozygous:8<br>Heterozygous:26<br>Negative:40 | Homozygous:16<br>Heterozygous:36<br>Negative:33 | p>0.05 |
| **MTHFR A1298C** | Homozygous:9<br>Heterozygous:25<br>Negative:40 | Homozygous:12<br>Heterozygous:31<br>Negative:42 | p>0.05 |
| **PAI gene mutation** | 4G4G: 3<br>4G5G: 3<br>5G5G: 2 | 4G4G: 3<br>4G5G: 3<br>5G5G: 3 | p>0.05 |
| **Beta fibrinogen mutation** | Homozygous:3<br>Heterozygous:15<br>Negative:8 | Homozygous:2<br>Heterozygous:19<br>Negative:5 | p>0.05 |
| **Factor-XIII gene mutation** | Homozygous:1<br>Heterozygous:25<br>Negative:39 | Homozygous:2<br>Heterozygous:19<br>Negative:57 | p>0.05 |

| | | | |
|---|---|---|---|
| **Protein-C (%)*** | 92.05±20.83 | 100.28±25.38 | p>0.05 |
| **Protein-S (%)*** | 69.51±22.90 | 67.11±20.93 | p>0.05 |
| **Antithrombin (%)*** | 98.90±11.46 | 97.99±8.91 | p>0.05 |
| **History of antiaggregant or anticoagulant use (n)** | LMWH:15<br>ASA:5<br>LMWH+ASA:7<br>Not used:50<br>Unknown:3 | LMWH:26<br>ASA:6<br>LMWH+ASA:14<br>Not used:43<br>Unknown:1 | p>0.05 |
| **Blood count parameters(mean±SD)** | | | |
| *WBC count (/mkrL)* | 9138.87±2667.01 | 9449.74±3073.12 | p>0.05 |
| *Neutrophil count (/mkrL)* | 6309.84±2678.57 | 6390.38±3157.79 | |
| *Lymphocyte count(/mkrL)* | 2115.97±653.54 | 2293.33±708.09 | |
| *Monocyte count(/mkrL)* | 536.61±197.26 | 542.18±180.06 | |
| *Eosinophil count(/mkrL)* | 147.90±143.23 | 172.82±183.07 | |
| *Basophil count(/mkrL)* | 32.26±16.63 | 30.00±14.68 | |
| *MCV (fL)* | 85.27±7.61 | 83.80±7.77 | |
| *MPV (fL)* | 10.18±1.18 | 10.45±1.19 | |
| *RDW (%)* | 13.87±1.35 | 14.12±1.94 | |
| *Platelet (/mkrL)* | 255,290.32±76,184.50 | 256,807.69±74,363.45 | |
| *Hemoglobin (gr/dL)* | 12.28±1.50 | 12.24±1.44 | |
| **Coagulation Tests (mean±SD)** | | | |
| aPTT (sec.) | **25.90±2.91** | **25.06±2.79** | **p<0.05** |
| PT (sec.) | 12.43±1.25 | 12.11±1.30 | p>0.05 |
| INR | 0.94±0.08 | 0.94±0.08 | p>0.05 |
| Fibrinojen (mg/dL) | 403.17±139.15 | 368.11±98.22 | p>0.05 |
| D-dimer (g/ml DDU) | 981.54±1456.78 | 734.31±1094.48 | p>0.05 |
| Homocysteine (Umol/L) | 12.91±7.62 | 11.69±6.39 | p>0.05 |

* Normal range for Protein C, Protein S and Antithrombin as follows: 70-140%, 60-130%,83-118%, respectively.
ASA: acetylsalicylic acid, aPTT: activated partial thromboplastin time, FVLM: Factor V Leiden Mutation
INR: international normalized ratio, LMWH: Low-molecular-weight heparin, MCV: Mean Corpuscular Volume
MPV: Mean Platelet Volume, MTHFR: methylenetetrahydrofolate reductase, n: number
PAI: plasminogen activator inhibitor, PGM: Prothrombin Gene Mutation, PT: prothrombin time
RDW: red cell distribution width, SD: Standard Deviation, Sec.: second, WBC: White Blood Cell

## DISCUSSION

RPL is an undesired event, and it is a condition that has psychological effects as well as physical health problems. The population prevalence of women who have had one miscarriage is 10.8% (10.3-11.4%), two miscarriages is 1.9% (1.8-2.1%), and three or more miscarriages is 0.7% (0.5-0.8%) (9). Several causes play a role in RPL including maternal age (9–75%), endocrine diseases (17–20%), uterine morphological pathologies (10–15%), chromosomal abnormalities (2–8%), thrombophilia, infectious agents (0.5–5%), and autoimmune disorders (20%). In approximately 50–75% of RPL cases, the exact cause is not clearly identified and, therefore, remains unexplained (10).

It is important to identify treatable causes of RPL which can be prevented by applying medical treatments such as referral to genetic counseling if there is a parental karyotype abnormality, surgery if there are correctable uterine anatomical abnormalities such as uterine septum, adhesions, submucosal myoma, aspirin, and heparin treatment if antiphospholipid antibody syndrome is present and medical treatment for these if there is thyroid dysfunction, hyperprolactinemia and/or diabetes mellitus (11). The combination of hereditary thrombophilia and pregnancy may mean a higher risk of RPL. However, due to the heterogeneity of samples in most studies, there is not much strong evidence for an association between inherited thrombophilia and RPL. Apart

from antiphospholipid antibody syndrome, whether the pregnant woman has thrombophilia or not; there is no evidence that aspirin or heparin treatment, which is frequently used in pregnant women, improves pregnancy outcomes (12,13). In most cases, the patient's expectation for the future after experiencing a pregnancy loss forces the physician to start medication, even though its effectiveness has not been proven. This approach, as with anticoagulant treatments, leaves the patient open to complications of the drug started, such as bleeding.

Various studies have examined the relationship between hematological parameters and pregnancy loss. In a case-control study by Erdem ZS et al, 50 patients between 18-40 years and a history of at least three consecutive recurrent pregnancy losses were included and it was suggested that high MPV, RDW, plateletcrit count, and low MCHC among blood count parameters could be an important indicator of recurrent miscarriages (14). In another prospective controlled study of 184 patients designed by Al-Husban et al., increased platelet and leukocyte counts in the first trimester are associated with an increased risk of miscarriage (15). We have not observed any correlation between RPL and blood count parameters in either group.

Regarding our study, we found that a decrease in aPTT was significantly correlated with the number of miscarriages. The effect of shortening aPTT value on pregnancy loss was supported by various studies. Ogasawara M, et al included 261 patients with a history of two consecutive first-trimester spontaneous abortions who had no antiphospholipid antibodies, and they were examined for aPTT, prothrombin time, and fibrinogen before the next pregnancy. Fifty-eight percent of 261 patients (22.2%) had a subsequent spontaneous abortion. Significantly elevated spontaneous abortion rates in patients with preconception-shortened aPTT were detected. The possible mechanism may be associated with thrombosis in syncytiotrophoblasts or the spiral artery induced by a hypercoagulable state. It was suggested that short aPTT values before pregnancy can indicate pregnancy loss (16). In the study conducted by Yao et al., 48 patients with recurrent abortion were divided into Group A (two miscarriages, n=21), Group B (three miscarriages, n=16), and Group C (≥ four miscarriages, n=11) according to the number of miscarriages, and recurrent pregnancy loss was found to be associated with decreased aPTT, prothrombin time and increased fibrinogen and D-Dimer levels (17). In another study by Ali A. et al, a significant relationship was found between recurrent miscarriages and increased factor VIII levels as well as decreased aPTT among 68 patients with RPL (18).

The assumption that thrombophilic status increases the risk of thrombosis at the low-flow maternal-placental interface, leading to placenta-mediated complications such as RPL, prevails among most clinicians. However, the role of hereditary deficiencies and mutations in the etiology of RPL has not been proven, and the risk is probably increased in high-risk thrombophilia (AT deficiency, FVL or Prothrombin G20210A variant homozygote mutations, concurrent heterozygosity for both FVL and Prothrombin G20210A variants, and rare combined thrombophilias such as AT deficiency plus FVL mutation) (19).

Although the effects of genetic mutations and protein C/S/AT deficiency on RPL have been investigated in various studies in different populations, conflicting results have been obtained regarding the presence of the correlation (20-27) In a cross-sectional multicenter study of 1384 patients conducted by Preston F. et al, it was emphasized that the probability of pregnancy loss (as both miscarriage and stillbirth) increased especially in those with protein C/S and antithrombin deficiency and that this situation increased even more clearly, especially in those with AT deficiency and in the patient group with multiple genetic thrombophilic defects (28). In a meta-analysis by Liu et al, 89 studies including 30,254 patients were compiled and found that FVL mutation, PGM and Protein S deficiency may increase the risk of RPL by 2.44-fold, 2.08-fold, and 3.45-fold, respectively. No significant correlation was found between antithrombin and protein C deficiency with RPL. The relationship with other genetic mutations (MTHFR, PAI, Beta fibrinogen, Factor XIII) was not investigated (29). Regarding FVL and PGM mutation; an association with these mutations and abortion has not been found in various studies (30-33). In our study, there were only two patients (all in group B) with FVL mutation (homozygous), while there were no patients with PGM homozygous mutation. There were two patients in group A and group B with double heterozygous mutations, respectively. In addition, there were no patients with protein

C/S/AT deficiency. Although it is not clear how much these mutations (FVL and PGM) seen in our patients affected the results, it would be reasonable to assume that this effect is limited since they are present in a small number of patients. Since there are not enough studies in the literature to investigate the contribution of other mutations (MTHFR, PAI, Beta fibrinogen, Factor-XIII gene mutations) in the etiology of RPL, it would not be appropriate to comment on their effect on our study and it is presented only as demographic data.

## CONCLUSION

RPL continues to aggrieve pregnant women as an undesirable condition due to the multiple causes that lead to RPL, their different pathogenetic mechanisms, the difficulty of homogenization of patient groups, and ultimately the inability of studies to determine a parameter(s) that will predict this condition. As a parameter that can be easily and quickly assayed, a low aPTT value may be a parameter that can help predict RPL (30-33).

### Limitations of the study

Although no risk factor is identified in 50-70% of couples with recurrent pregnancy loss; in our study, various parameters such as advanced maternal age, number of previous miscarriages, obesity (body mass index >30kg/m2), lifestyle factors (stress, smoking, and excessive alcohol consumption) may affect laboratory results as well as pregnancy outcomes, however, patients were not excluded from evaluation in this respect (34). Another limitation of the study is the patients who use antiaggregant and anticoagulant drugs due to previous thrombotic profiles that may affect further miscarriages as well as laboratory values. These circumstances may show that a relatively heterogeneous population has been evaluated. In addition, patients in group A may have continued pregnancy loss in their subsequent pregnancies, if any, and therefore may have the potential to move to group B. This is a limitation arising from the retrospective and cross-sectional design of our study.

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### Declarations

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**Conflicts of interest:** Authors declared no conflict of interest.

**Availability of data and material:** The authors approve that all necessary papers regarding this report can be offered on request.

**Ethics approval:** Ethical committee approval has been obtained (Aydın Adnan Menderes University Date: 20.11.2023-Number: 453317)

**Consent to participate:** Informed consent form approving participation was obtained from the patients.

**Consent for publication:** Informed consent form approving publication was obtained from the patients.

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