

# The Effectiveness of Cerclage, Progesterone and Combination of Both in Patients with Cervical Insufficiency in Reducing Preterm Delivery- Retrospective Study

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## Abstract

**Background:** Preterm birth is the leading cause of neonatal morbidity and mortality worldwide. Strong predictors of spontaneous preterm birth are history of preterm birth and short cervical length

**Objectives:** To investigate the effectiveness of intramuscular progesterone, cervical cerclage and vaginal progesterone in preventing preterm birth among patients with cervical insufficiency followed in a tertiary care, obstetric clinic from 2011 to 2021.

**Methods:** It was a retrospective cohort study. All patients with cervical insufficiency who either underwent cervical cerclage and or used progesterone were included in the study. Inclusion criteria were all Omani pregnant females who underwent cervical cerclage alone or with progesterone therapy or progesterone therapy alone. The exclusion criteria were patients with multiple pregnancies, uterine anomalies, leiomyomas, maternal medical disease, fetal anomalies, preterm premature rupture of membranes or vaginal bleeding.

**Results:** A total of 591 patients were included in this study. Cerclage was significantly associated with reduced rate of preterm delivery ( $p=0.016$ ). Among patients treated with progesterone 15.2% received suppositories alone, 67.4% received intramuscular injections alone and 17.5% received both forms. The superiority of cerclage alone was notable in women with longer cervical lengths ( $\geq 2.5$  cm), among whom the preterm delivery rate was 11.3%, compared to 23.8% in the progesterone group and 31.7% in the combined group ( $p=0.002$ ). Multivariate analysis confirmed that both treatment type and cervical length were independent predictors of preterm birth.

**Conclusion:** We found that cerclage alone was the most effective treatment in reducing preterm delivery when compared to with or without progesterone alone.

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**Keywords:** Preterm Birth; Cervical Cerclage; Progesterone; 17-Hydroxyprogesterone, Progesterone, Cervical Length; McDonald Technique; High-Risk Pregnancy; Pregnancy Outcome

## Introduction

Preterm birth is the number one cause of neonatal morbidity and mortality worldwide. Strong predictors of spontaneous preterm birth are history of preterm birth and short cervical length of less than 25 mm calculated using transvaginal ultrasound [1].

Cervical insufficiency is usually described as an inability of the uterine cervix to retain pregnancy in the second trimester, with no clinical signs and symptoms such as uterine contraction or labour [2]. It occurs in less than 1% of pregnancies, but it is a leading cause of preterm birth [1].

Controversy exists about the pathophysiology, screening for recurrence and management of women with spontaneous preterm birth [3]. Cervical cerclage has been used as a line of management in both history indicated and clinically indicated cervical insufficiency. On the other hand, the use of progesterone in addition to the cervical cerclage has been a practice to reduce the risk of preterm birth in some women only.

Many studies compared the use of progesterone in addition to cervical cerclage comparing the outcome with the use of cervical cerclage alone. A study published in 2016, conducted in Korea, studied the addition of adjuvant progesterone to physical-examination- indicated cervical cerclage to prevent preterm birth [2]. It concluded, adjuvant vaginal progesterone therapy with physical exam indicated cervical cerclage was associated with reduction in spontaneous preterm birth, low birth weight and neonate intensive care unit admission [2]. Another study compared the outcome of cervical cerclage and adjuvant intramuscular hydroxyprogesterone caproate versus cervical cerclage alone [3]. The study concluded that intramuscular progesterone in combination with prophylactic cerclage had no synergistic effect in reducing the rate of recurrent preterm birth or improving perinatal outcome [3].

Similar studies published in 2016 concluded that intramuscular 17 alpha hydroxyprogesterone caproate in addition to cervical cerclage have reduced the rate of delivery before 24 weeks, but no reduction in overall preterm birth [4]. On the other hand, many studies have been conducted to study the use of progesterone only in patients with cervical insufficiency. A systemic review published in 2017 in British journal of Obstetrics and Gynecology, (an International Journal of Obstetrics and Gynecology), compared the use of progesterone, cerclage and cervical pessary [5]. The study concluded that progesterone was the best intervention in preventing preterm deliveries and adverse neonatal outcomes [6].

However, as the prevalence of preterm birth is increasing in general and also in Oman, we felt this study will guide us to a better evidence-based practice [6]. According to the World Health Organization's Global Health Observatory (2023), Oman's preterm birth rate was estimated at around 8-9% of live births in 2020. Moreover, it will be of value to evaluate the maternal and fetal outcomes of cervical cerclage alone, compared with cervical cerclage and vaginal progesterone versus intramuscular progesterone and progesterone alone. This study could help to create a practice-based guideline that we may rely on in managing similar cases in the future.

Our study aimed to investigate the maternal and fetal outcome in patients who underwent cervical cerclage alone versus cerclage with progesterone versus different types of progesterone alone.

## Methodology

All patients with cervical insufficiency who either underwent cervical cerclage and or used progesterone a who were following in obstetric clinic at Royal Hospital from Jan-2011 to Jan- 2021 were included in the study.

It was a retrospective cohort study. Inclusion criteria were all Omani pregnant females who underwent elective or emergency cervical cerclage in the above mentioned period of time. All history indicated and ultrasound indicated cerclage (cervical length less than 24 mm) were included in the study. Cervical assessment was done by transvaginal probe with a frequency of 5-9 MHz between 14-24 weeks of gestation. The sample was divided into three cohorts, first group included patients who underwent cerclage alone, the second group included those who underwent cervical cerclage and were started on progesterone. The last group included pregnant women with cervical insufficiency who used progesterone only.

The ethical approval was obtained through the research committee at Royal Hospital in March 2023 (SRC#66/2022).

The data was analyzed using SPSS-version 29. Categorized variables were described in percentages and frequencies, while continuous variables were presented as mean  $\pm$  Standard Deviation (SD), median with Interquartile Range (IQR), minimum and maximum values. Crude associations were assessed using Chi-square test, Fisher Exact test, Independent-Samples Mann-

Whitney U test and Independent-Samples Kruskal-Wallis test. Logistic binary regression was used for multivariate analysis. Factors that showed p value of  $< 0.25$  in the crude analysis were included in the multivariate analysis. P-value less than 0.05 was considered significant.

### Results:

A total of 591 patients were included in this analysis. The mean age was  $30.87 \pm 4.87$  years (range: 18-44). The mean Body Mass Index (BMI) was  $30.37 \pm 6.50$  kg/m<sup>2</sup>. The median gravida and parity were 4.0 and 1.0, respectively. Recurrent miscarriage (3 consecutive miscarriages and more) was reported in 35.5% of patients and 85.8% had a history of either preterm labor or second-trimester abortion. Regarding maternal comorbidities, Gestational Diabetes Mellitus (GDM), gestational hypertension and anemia were noted in 38.9%, 4.6% and 10.8% of cases, respectively.

With regards to treatment modalities, 19.6% of patients received cerclage alone, 17.6% received progesterone alone and 62.8% received a combination of both interventions. Of the total cerclages performed (whether alone or in combination), 98.4% were of the McDonald type and 79.9% were performed electively. Among patients treated with progesterone (alone or in combination), 15.2% received pessaries suppositories alone, 67.4% received intramuscular injections alone and 17.5% received both forms. Table 1 presents detailed demographic and clinical characteristics of the study population.

In terms of effectiveness, cerclage alone was significantly associated with a lower rate of preterm delivery ( $p = 0.016$ ). Specifically, preterm labor occurred in 17.2% of patients receiving cerclage alone, compared to 25.0% in the progesterone-alone group and 32.6% in those receiving both interventions ( $p = 0.004$ ) (Table 2).

The superiority of cerclage alone was most notable in women with longer cervical lengths ( $\geq 2.5$  cm), among whom the preterm delivery rate was 11.3%, compared to 23.8% in the progesterone group and 31.7% in the combined group ( $p = 0.002$ ). A similar but statistically non-significant trend was seen in those with cervical lengths of 1.5-2.4 cm ( $p = 0.190$ ). Among patients with short cervix ( $< 1.5$  cm), there was no significant difference in preterm delivery rates across the treatment groups (Table 3).

Stratified analysis by gestational age categories revealed similar trends: preterm delivery before 24 weeks occurred in 1.7% of cerclage-alone patients, compared to 3.8% and 6.8% in the progesterone-only and combination groups, respectively. Preterm birth between 24-27 weeks was also more frequent in the combination group compared to cerclage alone, though no significant difference was found between cerclage and progesterone-alone groups. Comparable findings were observed for births occurring between 28-36 weeks (Table 4).

Cervical length emerged as a significant factor influencing preterm birth. The median cervical length was significantly shorter among those who delivered preterm (2.75 cm) compared to those who delivered at term (2.9 cm;  $p = 0.009$ ). In contrast, other variables including maternal age, BMI, history of miscarriage, prior preterm labor or second-trimester abortion, GDM, PIH and anemia did not show a statistically significant association with preterm birth (Table 5).

Multivariate analysis (Table 6) confirmed that both treatment type and cervical length were independent predictors of preterm birth. Patients who received both cerclage and progesterone had 2.433 times the odds of preterm delivery compared to those who received cerclage alone (95% CI: 1.418-4.177,  $p = 0.001$ ). Additionally, each 1 cm increase in cervical length was associated with a 24.9% reduction in the odds of preterm delivery (OR = 0.751,  $p = 0.026$ ). Regarding secondary outcomes, cerclage alone was associated with higher neonatal birth weight. The median birth weight (IQR) was 2.93 kg (2.64-3.23) in the cerclage group, compared to 2.85 kg (2.48-3.18) in the progesterone group and 2.82 kg (2.36-3.10) in the combination group ( $p = 0.006$ ). No significant differences were observed in terms of neonatal admission to Special Care Baby Unit (SCBU). Maternal complications, including sepsis and Postpartum Hemorrhage (PPH), were less frequently reported in the cerclage group, though not statistically significant. Similarly, rates of preeclampsia did not differ significantly among the three groups (Table 7).

| Characteristics                                         | (Mean $\pm$ SD, median (IQR), min – max)       |
|---------------------------------------------------------|------------------------------------------------|
| Age (mean $\pm$ SD, median (IQR), min – max)<br>(n 591) | $30.87 \pm 4.87$ , 30.0 (27.0 – 34.0), 18 – 44 |

|                                                                           |                                               |          |          |
|---------------------------------------------------------------------------|-----------------------------------------------|----------|----------|
| BMI (mean $\pm$ SD, median (IQR), min – max)<br>(n 590)                   | 30.37 $\pm$ 6.50, 30.0 (26.0 – 35.0), 17 – 55 |          |          |
| Gravida level (n 591)                                                     | 4.23 $\pm$ 2.10, 4.0 (3.0 – 5.0), 1 – 14      |          |          |
| Parity level (n 591)                                                      | 1.39 $\pm$ 1.40, 1.0 (0.0 – 2.0), 0 – 11      |          |          |
| <b>Characteristics</b>                                                    | <b>Categories</b>                             | <b>n</b> | <b>%</b> |
| Recurrent miscarriages (n 591)                                            | Yes                                           | 210      | 35.5     |
|                                                                           | No                                            | 381      | 64.5     |
| History of preterm delivery or 2 <sup>nd</sup> trimester abortion (n 591) | Yes                                           | 507      | 85.8     |
|                                                                           | No                                            | 84       | 14.2     |
| Gestational diabetes (n=591)                                              | Yes                                           | 230      | 38.9     |
|                                                                           | No                                            | 361      | 61.1     |
| P(n=591)                                                                  | Yes                                           | 27       | 4.6      |
|                                                                           | No                                            | 564      | 95.4     |
| Anemia (n=591)                                                            | Yes                                           | 64       | 10.8     |
|                                                                           | No                                            | 527      | 89.2     |
| Type of intervention (n=591)                                              | Cerclage alone                                | 116      | 19.6     |
|                                                                           | Cerclage and progesterone                     | 371      | 62.8     |
|                                                                           | Progesterone alone                            | 104      | 17.6     |
| Type of cerclage (n=487)                                                  | McDonald                                      | 479      | 98.4     |
|                                                                           | Abdominal                                     | 2        | 0.4      |
|                                                                           | Shirodkar                                     | 3        | 0.6      |
|                                                                           | Double cerclage                               | 3        | 0.6      |
| Type of surgery (n=487)                                                   | Emergency                                     | 98       | 20.1     |
|                                                                           | Elective                                      | 389      | 79.9     |
| Progesterone type (n=475)                                                 | Suppository alone                             | 72       | 15.2     |
|                                                                           | Injection alone                               | 320      | 67.4     |
|                                                                           | Both                                          | 83       | 17.5     |

**Table 1:** Demographic and comorbidity profile of the study sample.

| Type of Treatment (n 588) | Preterm delivery |       |     |       | P-value |
|---------------------------|------------------|-------|-----|-------|---------|
|                           | No               |       | Yes |       |         |
|                           | n                | %     | n   | %     |         |
| Cerclage alone            | 96               | 82.8% | 20  | 17.2% | 0.004   |
| Cerclage and progesterone | 248              | 67.4% | 120 | 32.6% |         |
| Progesterone alone        | 78               | 75.0% | 26  | 25.0% |         |

**Table 2:** Crude results for the effect of treatment on preterm delivery (present / absent).

| Subgroup                           | Type of Treatment         | Preterm Delivery |       |     |       | P-value   |
|------------------------------------|---------------------------|------------------|-------|-----|-------|-----------|
|                                    |                           | No               |       | Yes |       |           |
|                                    |                           | n                | %     | n   | %     |           |
| Cervical length < 1.5 cm (n 42)    | Cerclage alone            | 6                | 60.0% | 4   | 40.0% | 1.0 (F)   |
|                                    | Cerclage and progesterone | 19               | 59.4% | 13  | 40.6% |           |
|                                    | Progesterone alone        | 25               | 59.5% | 40  | 40.5% |           |
| Cervical length 1.5 – 2.4 cm (144) | Cerclage alone            | 27               | 77.1% | 8   | 22.9% | 0.190 (F) |
|                                    | Cerclage and progesterone | 72               | 67.9% | 34  | 32.1% |           |
|                                    | Progesterone alone        | 1                | 33.3% | 2   | 66.7% |           |

|                                      |                           |     |       |    |       |       |
|--------------------------------------|---------------------------|-----|-------|----|-------|-------|
| Cervical length $\geq$ 2.5 cm (402)  | Cerclage alone            | 63  | 88.7% | 8  | 11.3% | 0.002 |
|                                      | Cerclage and progesterone | 157 | 68.3% | 73 | 31.7% |       |
|                                      | Progesterone alone        | 77  | 76.2% | 24 | 23.8% |       |
| Note: F indicates Fisher exact test. |                           |     |       |    |       |       |

**Table 3:** Crude results for the effect of type of treatment on preterm delivery according to cervical length.

| Type of Treatment (588)   | Preterm Delivery |      |             |      |             |       |                      |       | P-value |
|---------------------------|------------------|------|-------------|------|-------------|-------|----------------------|-------|---------|
|                           | < 24 wk.         |      | 24 – 27 wk. |      | 28 – 36 wk. |       | Full term (≥ 37 wk.) |       |         |
|                           | n                | %    | n           | %    | n           | %     | n                    | %     |         |
| Cerclage alone            | 2                | 1.7% | 1           | 0.9% | 17          | 14.7% | 96                   | 82.8% | 0.016   |
| Cerclage and progesterone | 25               | 6.8% | 12          | 3.3% | 83          | 22.6% | 248                  | 67.4% |         |
| Progesterone alone        | 4                | 3.8% | 0           | 0.0% | 22          | 21.2% | 78                   | 75.0% |         |

**Table 4:** Crude results for the effect of compared treatments on preterm delivery according to gestational age (detailed categories).

| Factors (n 588)                                                                                  |     | Preterm Delivery |             |        |              | P-value |
|--------------------------------------------------------------------------------------------------|-----|------------------|-------------|--------|--------------|---------|
|                                                                                                  |     | No               |             | Yes    |              |         |
|                                                                                                  |     | Median           | IQR         | Median | IQR          |         |
| Age (years)                                                                                      |     | 30.50            | 28.0 - 34.0 | 30.00  | 27.0 - 34.00 | 0.720   |
| BMI (n=588)                                                                                      |     | 30.0             | 26.0 – 34.0 | 31.0   | 26.0 – 35.0  | 0.175   |
| Cervical length (cm)                                                                             |     | 2.90             | 2.30 – 3.20 | 2.75   | 2.0 – 3.0    | 0.009   |
| Factors                                                                                          |     | n                | %           | n      | %            |         |
| Recurrent miscarriages                                                                           | Yes | 153              | 73.6%       | 55     | 26.4%        | 0.476   |
|                                                                                                  | No  | 269              | 70.8%       | 111    | 29.2%        |         |
| History of preterm delivery or 2 <sup>nd</sup> trimester abortion                                | Yes | 362              | 71.8%       | 142    | 28.2%        | 0.940   |
|                                                                                                  | No  | 60               | 71.4%       | 24     | 28.6%        |         |
| GDM                                                                                              | Yes | 168              | 73.4%       | 61     | 26.6%        | 0.493   |
|                                                                                                  | No  | 254              | 70.8%       | 105    | 29.2%        |         |
| PIH                                                                                              | Yes | 17               | 63.0%       | 10     | 37.0%        | 0.298   |
|                                                                                                  | No  | 405              | 72.2%       | 156    | 27.8%        |         |
| Anemia                                                                                           | Yes | 49               | 76.6%       | 15     | 23.4%        | 0.367   |
|                                                                                                  | No  | 373              | 71.2%       | 151    | 28.8%        |         |
| BMI: Body Mass Index, GDM: Gestational Diabetes Mellitus and PIH: Pregnancy Induced Hypertension |     |                  |             |        |              |         |

**Table 5:** Crude results for the effect of various factors on preterm delivery.

| Factors (587)        | categories                | OR                                | 95% CI lower limit | 95% CI upper limit | P-value |
|----------------------|---------------------------|-----------------------------------|--------------------|--------------------|---------|
| Type of treatment    | Cerclage alone            | Reference (overall p-value 0.005) |                    |                    |         |
|                      | Cerclage and progesterone | 2.433                             | 1.418              | 4.177              | 0.001   |
|                      | Progesterone alone        | 1.947                             | 0.988              | 3.834              | 0.054   |
| Cervical length (cm) |                           | 0.751                             | 0.585              | 0.966              | 0.026   |
| BMI                  |                           | 1.014                             | 0.986              | 1.043              | 0.334   |

**Table 6:** Multivariate results for treatment and factors associated with preterm delivery.

| Maternal and fetal outcomes                                | n (%) of outcomes among Cerclage | n (%) of outcomes among Cerclage and progesterone | n (%) of outcomes among Progesterone alone | P-value   |
|------------------------------------------------------------|----------------------------------|---------------------------------------------------|--------------------------------------------|-----------|
| Admission to SCABU (n=591)                                 | 13 (11.2%)                       | 44 (11.9%)                                        | 13 (12.5%)                                 | 0.957     |
| Preeclampsia (n=591)                                       | 1 (0.9%)                         | 6 (1.6%)                                          | 0 (0.0)                                    | 0.646 (F) |
| Maternal Sepsis (n=590)                                    | 0 (0.0)                          | 8 (2.2%)                                          | 4 (3.8%)                                   | 0.100 (F) |
| PPH (n=591)                                                | 4 (3.4%)                         | 15 (4.0%)                                         | 4 (3.8%)                                   | 1.0 (F)   |
| F indicates Fisher Exact test. PPH: Post-Partum Hemorrhage |                                  |                                                   |                                            |           |

**Table 7:** Treatment modalities and fetal and maternal outcomes.

## Discussion

This retrospective cohort study evaluated the effectiveness of cervical cerclage alone, progesterone alone and a combination of both therapies in reducing preterm birth among women with cervical insufficiency. Our findings suggest that cerclage alone was the most effective intervention, associated with the lowest rate of preterm delivery (17.2%), compared to progesterone alone (25.0%) and combined therapy (32.6%).

These findings are supported by several previous studies. For instance, Alfirevic, et al., concluded in a Cochrane review that cerclage significantly reduces the risk of preterm birth in singleton pregnancies with a short cervix [7]. Berghella, et al., also emphasized that transvaginal ultrasound-indicated cerclage improves outcomes in women with a previous preterm birth and short cervical length (<25 mm) [8]. In contrast, studies evaluating the addition of progesterone to cerclage report mixed outcomes. Stetson, et al. and Samson, et al., found no added benefit when 17- $\alpha$  hydroxyprogesterone caproate was administered alongside cerclage, aligning with our results, where combination therapy was associated with worse outcomes than cerclage alone [9,10].

An important predictor of treatment response in our study was cervical length. Women with a cervical length  $\geq 2.5$  cm had the lowest preterm delivery rate when treated with cerclage alone (11.3%), supporting the assertion that cervical length is a strong prognostic marker, as demonstrated in studies by Hassan, et al. and Berghella, et al. [11,12]. The lack of significant benefit from any intervention in women with cervical lengths <1.5 cm may reflect the advanced stage of cervical remodeling or intra-amniotic infection, which diminishes the effectiveness of mechanical or hormonal interventions.

While progesterone has demonstrated efficacy in preventing preterm birth in other populations, particularly in women with a short cervix, the evidence remains inconsistent. A recent meta-analysis by Romero, et al., showed that vaginal progesterone significantly reduced preterm birth and neonatal morbidity among women with singleton pregnancies and a short cervix [13]. Similarly, the OPPTIMUM trial Norman, et al., highlighted a reduction in neonatal morbidity, although the effect on preterm birth was less pronounced [14]. However, in our study, progesterone alone did not yield outcomes comparable to cerclage, possibly due to differences in patient selection, progesterone type and timing of administration.

The multivariate analysis confirmed that treatment type and cervical length were independently associated with preterm birth. Patients receiving both cerclage and progesterone had significantly higher odds of preterm delivery compared to cerclage alone (OR 2.43,  $p = 0.001$ ). This may be explained by confounding by indication, as patients perceived to be at higher risk might have been more likely to receive both therapies, a limitation acknowledged by Jung, et al., and Keeler, et al., [2,15].

In terms of secondary outcomes, higher median neonatal birth weights were observed in the cerclage-alone group, reinforcing its benefit. Although maternal complications such as postpartum hemorrhage and sepsis were numerically lower in this group, the differences did not reach statistical significance. Similarly, rates of Special Care Baby Unit admissions (SCBU) were comparable across all groups. Overall, our findings advocate for cerclage as the primary intervention in women with cervical insufficiency, particularly those with cervical lengths  $\geq 2.5$  cm. The addition of progesterone may not offer additional benefits and should be reserved for selected cases based on individual risk stratification. These findings contribute to the growing body of evidence suggesting that treatment for cervical insufficiency should be personalized, considering cervical length and previous obstetric history.

## Limitations

This study provides useful insights into the effectiveness of cerclage and progesterone for preventing preterm birth in women with cervical insufficiency, but it has several limitations. As a retrospective study, it depends on the accuracy of medical records, which may contain missing or inconsistent data. Selection bias could have influenced treatment choice, with higher-risk patients possibly receiving combination therapy, affecting outcomes. The study also did not compare the efficacy of different progesterone types and important confounders like cervical funneling and uterine contractions were not assessed. Lastly, being conducted at a single center with an Omani population may limit generalizability.

## Recommendations:

Based on this study, the following recommendations are proposed:

1. Cerclage alone may be the preferred first-line treatment for cervical insufficiency especially if the cervical length is equal to or more than 2.5 cm
2. Adding progesterone should be individualized, as routine combination therapy may not be beneficial
3. Cervical length assessment remains essential in management decisions

## Conclusion

This study provides robust, retrospective evidence from a large Omani cohort that cerclage alone is the most effective intervention for preventing preterm birth in women with cervical insufficiency. It was associated with significantly lower rates of preterm delivery and higher neonatal birth weights compared to either progesterone alone or combined therapy.

Importantly, the study highlights the critical role of cervical length in guiding treatment decisions. Women with relatively preserved cervical lengths ( $\geq 2.5$  cm) derived the most benefit from cerclage. In contrast, the addition of progesterone, especially in combination with cerclage, was not associated with improved outcomes and may reflect treatment of more complex, high-risk cases.

Given the lack of added benefit from combination therapy, our results emphasize the need for a targeted, evidence-based approach to managing cervical insufficiency. Further multicenter, randomized controlled trials are warranted to validate these findings, explore the efficacy of different progesterone types and refine treatment algorithms based on cervical dynamics and patient-specific risk profiles.

## Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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## Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

## Ethical Statement

This study was approved by the research committee at Royal Hospital, Oman, Muscat in March 2023 (SRC#66/2022).

## Informed Consent Statement

Informed consent was obtained from all participants included in the study.

## Authors' Contributions

All authors contributed equally to this paper.

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