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Multi-Centric Clinical Study of EZPRF and EZGEL in Correction of the Nasolabial Folds

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Abstract

Objective: This study aims to evaluate the safety and efficacy of EZPRF (plasma rich in fibrin) and EZGEL (albumin gel and platelet rich fibrin) in reducing moderate to severe nasolabial folds over a six-month follow-up period.

Materials and methods: A multicentric study was conducted involving 25 patients aged 35 to 80 years, divided into two groups: Group 1 received a single treatment, while Group 2 received an additional treatment after one month. Injections were assessed using the Wrinkle Severity Rating Scale (WSRS) and the Global Aesthetic Improvement Scale (GAIS).

Results: Group 1 (mean age 53 years and mean WSRS at 2.5) showed a 50% reduction in nasolabial fold depth after one month, with sustained improvements of 40% at three months and 30% at six months. Group 2 (mean age 60 years and mean WSRS at 3.07) reported a 32% reduction at one month, 48% at three months, and 38% at six months. Both groups exhibited high satisfaction levels, with minimal side effects, primarily consisting of bruising and slight swelling.

Conclusions: The results indicate that EZPRF and EZGEL are ideal biomaterials for facial repair and regeneration, providing natural and lasting results. It is recommended to repeat the treatment after one month, particularly for elderly patients with high WSRS scores. These treatments are safe, well-tolerated, and contribute to a significant improvement in the appearance of nasolabial folds.

Keywords:

PRP EZPRF: Platelet Rich Plasma/Fibrinogen; Alb-PRF or EZGEL: Albumin gel and Platelet Rich Fibrin; NFL: Nasolabial Folds; WSRS: Wrinkle Severity Rating Scale; GAIS: Global Aesthetic Improvement Scale.

List of Abbreviations

NFL: Nasolabial Folds; WSRS: Wrinkle Severity Rating Scale; GAIS: Global Aesthetic Improvement Scale; PRP: Platelet-Rich Plasma; PRF or EZPRF: Platelet Rich Fibrin/fibrinogen; Alb-PRF or EZGEL: Albumin gel and Platelet Rich Fibrin; i-PRF: Injectable Platelet Rich Fibrin; C-PRF: Concentrated Platelet-Rich Fibrin; GF: Growth Factors; PDGF-AA: Platelet-Derived Growth Factor-AA; PDGF -AB: Platelet-Derived Growth Factor-AB; PDGF-BB: Platelet-Derived Growth Factor-BB; TGF-Beta1: Transforming Growth Factor-Beta 1; VEGF: Vascular Endothelial Growth Factor; EGF: Epidermal Growth Factor; MSCs: Mesenchymal Stem Cells; PPP: Platelet-Poor Plasma; IGF-1: Insulin-like Growth Factor-1; HGF: Hepatocyte Growth Factor

Introduction

Facial folds with an accumulation of altered elastic fibers and degradation and degeneration of collagen in the dermis are the results of aging process. Nasolabial folds is the first sign of facial aging and results from intrinsic processes affected by genetic background and extrinsic process influenced by environmental factors such as sun exposure, air pollution, smoking, alcohol consumption, and dietary habits. Noninvasive aesthetic facial rejuvenation treatments are highly in demand over the years driven by an aging population, and a growing emphasis on physical appearance. Non-autologous fillers with several side effects such as embolic complications, infection and both early and late inflammatory reactions (edema, irregularities, nodules) leading to facial disharmony following repeated procedures have been reported [1]. Consequently, there is a need for filler products that are well-tolerated by the body, devoid of short- or long-term complications, and that exhibit regenerative properties, long-term stability, and natural results.

Over the past decade we have seen the development of aesthetic and regenerative procedures based on autologous methods, beginning with the first generation of platelet-rich plasma (PRP) and progressing to injectable platelet-rich fibrin (iPRF and C-PRF) [2, 3]. More recently, Alb-PRF (albumin gel and platelet-rich fibrin, or EZGEL) has emerged as a promising injectable regenerative composite. The initial study on Alb-PRF was published in 2016 [4].

Current research indicates that the regenerative characteristics of Alb-PRF are attributed to the gradual release of growth factors contained in liquid PRF through the degradation of albumin gel [5]. Thus, the regenerative process of this autologous filler primarily involves the platelets and leukocytes present in the liquid PRF component. Denatured plasma contains proteins, predominantly albumin, but lacks viable cells and growth factors [6]. More than 80% of this autologous filler consists of albumin and fibrin, which

provide a natural scaffold for leukocytes, platelets, and newly formed tissue cells [5]. Albumin, the most abundant protein in plasma, plays critical metabolic roles, including the regulation of oncotic pressure, binding and transporting various molecules, scavenging free radicals, modulating immune responses, and facilitating blood clotting [7]. It is known as an anti-attachment protein, its application on implantable surfaces improves stem cell adhesion and proliferation [1]. The anticoagulant, antimicrobial, and anti-inflammatory properties of albumin further refine the biological response to tissue-engineered constructs. Additionally, it serves as a scaffold for cell therapy [8]. In this report, we present the results of a multicentric study that evaluated the efficacy and safety of EZPRF and EZGEL for facial rejuvenation.

Materials and Methods

Study design

This retrospective study aimed to assess the safety and effectiveness of EZPRF and EZGEL in reducing the appearance of moderate to severe nasolabial folds over a 6-month follow-up period. The cohort included 25 patients aged 35 to 80 years from four centers across Switzerland, Belgium, and Germany. Patients were evaluated for moderate to severe nasolabial folds using the WSRS. Injections were administered to each side of the periocular areas, cheekbones, temples, nasolabial folds, and upper lip. On average, 4 ml of EZPRF and 8 ml of EZGEL were injected per patient.

Each patient underwent an initial injection session with photographic documentation. After one month, the physician and patient determined the need for a second injection based on the results and patient satisfaction. Follow-up visits occurred in 3 and 6 months, during which questionnaires were completed. At the end of the study, at 6 months, new photographs were taken. The study compared two patient groups, Group 1 received a single treatment during the first visit, while Group 2 received a second treatment after one month.

Endpoints

Primary efficacy endpoints included the reduction in WSRS grade (Figure 1) as assessed by both the principal investigator and the subjects. The level of patient and practitioner satisfaction was evaluated using the GAIS score (Table 1). Secondary efficacy endpoints included photographic improvement in the appearance of nasolabial folds after 6 months.

Technique of preparation of EZPRF and EZGel:

Blood collection: Venipuncture was performed to collect the patient's blood into blue and orange 13 ml tubes (4 blue tubes and 2 orange tubes). The blue tubes were placed in the EZCOOL cup to prevent clotting.

Preparation of the self-assembled albumin: The orange tube was centrifuged at 2600 rpm for 7 minutes (G force=315). Following centrifugation, the albumin-rich plasma was collected using an 18G hypodermic needle and an orange EZ 5 ml heat-resistant syringe, yielding 2.5 to 3 cc of plasma.

Preparation of the EZPRF: To prepare EZPRF, the denatured heated plasma was mixed with the injectable fibrin-rich plasma, processed concurrently with the gel. The blue tube was centrifuged at 1100 rpm for 5 minutes (G force=61). The EZPRF was then collected using an 18G hypodermic needle and a blue 5 ml EZ syringe, yielding 1.5 to 2 cc of PRF.

Hematological control: Hematological controls were carried out using the SYSMEX XP-300 hematological instrument. For this, a part of blood taken before centrifugation and a part of PRF taken after centrifugation was placed in an EDTA microtube which allows stability of the product to be evaluated over 24 hours [9,10]. The platelet and leukocyte levels in the blood were evaluated before and after centrifugation (In fibrin-rich plasma). We studied the hematological quality of EZPRF which was mixed with denatured plasma and injected into the periocular area. The plasma which was taken to prepare the denatured albumin was not studied. Cells or growth factors present in the heat treated PRF cannot withstand the denaturation process [6].

Preparation of the EZGEL: EZGEL was prepared according to the manufacturer's instructions. After the heating cycle, the orange 5 mL EZ Heat Resistant Syringe was cooled to body temperature and connected to the blue EZ Syringe for mixing (Figure 2).

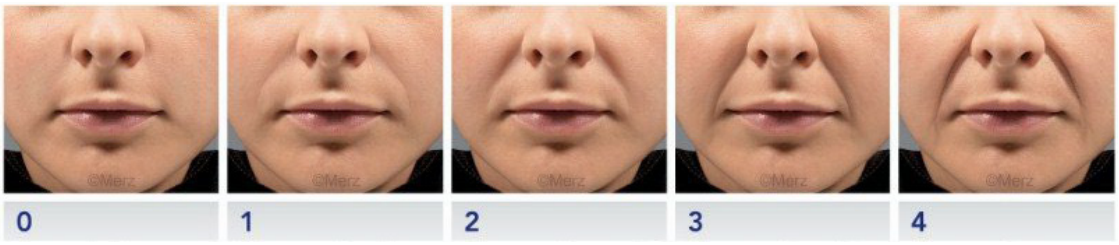


Figure 1: MWSRS grade.

Note: 0: Absence of nasolabial folds; 1: Discrete nasolabial folds; 2: Moderate nasolabial folds; 3: Severe nasolabial folds and 4: Very severe nasolabial folds.

Table 1: GAIS scoring (Global Aesthetic Improvement Scale).

1	Important improvement
2	Good improvement
3	Improvement noticed
4	No improvement
5	Worsening

Injection technique: An average of 2 ml of EZPRF was injected into each side of the periocular areas, with subsequent injections of 1 ml EZGEL at the cheekbones or temples, 2 ml through the nasolabial folds and upper lip, and 1 ml at the level of the bitterness folds. In total, an average of 4 ml of EZPRF and 8 ml of EZGEL was injected for the entire face (Figure 3).

Statistical analysis:

Statistical analysis was performed using SPSS® version 19.0.0.1 (IBM, Armonk, NY). Descriptive statistics for quantitative continuous variables were summarized as mean±standard deviation (SD). Student's t test (one-sample, paired) was used to compare continuous variables within the same participant before and after the treatment.

Results

In our cohort of 25 patients, 12 patients were in Group 1 (single treatment) and 13 patients in Group 2 (second treatment after 1 month). The average age of Group 1 was 53 years, while Group 2 had an average age of 60 years. The WSRS score for Group 1 was 2.5, compared to 3.07 for Group 2 (Table 2, 3 and 4).

One-month post-treatment, Group 1 exhibited an average improvement of 1.25 points (50%) in WSRS, with a satisfaction score of 2.5, leading to the decision not to repeat treatment. In contrast, Group 2, with a higher initial WSRS score, reported a 1-point (32%) reduction in nasolabial folds and a satisfaction score of 3.69, prompting a second treatment.

At the 3-month follow-up, Group 1 noted a 1-point (40%) improvement, with a final improvement of 0.75 points (30%) at 6 months, resulting in a satisfaction score of 3. Group 2 reported a 1.4-point (48%) improvement at 3 months and a final improvement of 1.17 points (38%) at 6 months, with satisfaction scores of 2.5 and 3, respectively. There were no significant differences in evaluations between the doctor and patient groups (Figure 4). Example of photos before and after 6 Months for the Group 1 and Group 2 are shown in Table 5.

EZPRF hematological measures: Platelet and white blood cell levels were measured for 20 out of 25 patients before and after centrifugation. An average of 1.8 ml of light red EZPRF was obtained, with an average platelet concentration factor of 2.2 and a leukocyte concentration factor of 0.88.

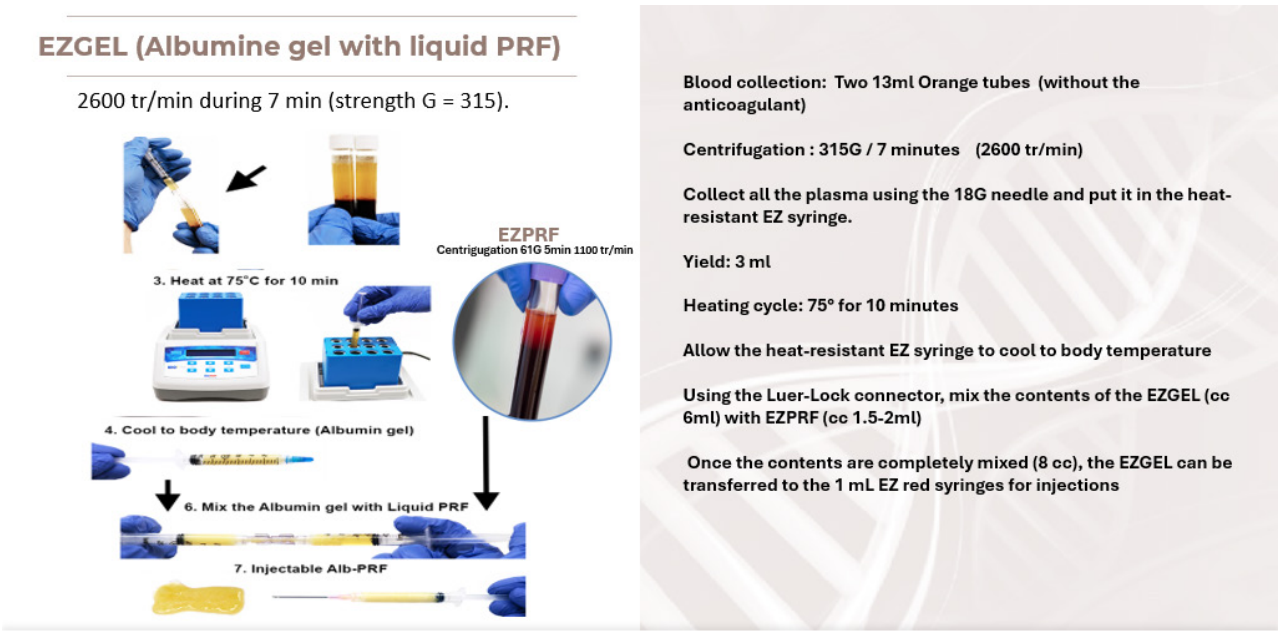


Figure 2: EZGEL preparation.

Figure 3: Injection technique

Table 2: Results all group (week 4).

Numbers	25
Age min-max	35-82
Average age	57
WSRS J0 Dr.	2.8
WSRS J0 Subject	2.8
WSRS W4 Dr.	1.68
WSRS W4 Subject	1.68
GAIS score Dr. W4	2.8
GAIS score Subject W4	3.28
Decrease J0-W4	40%

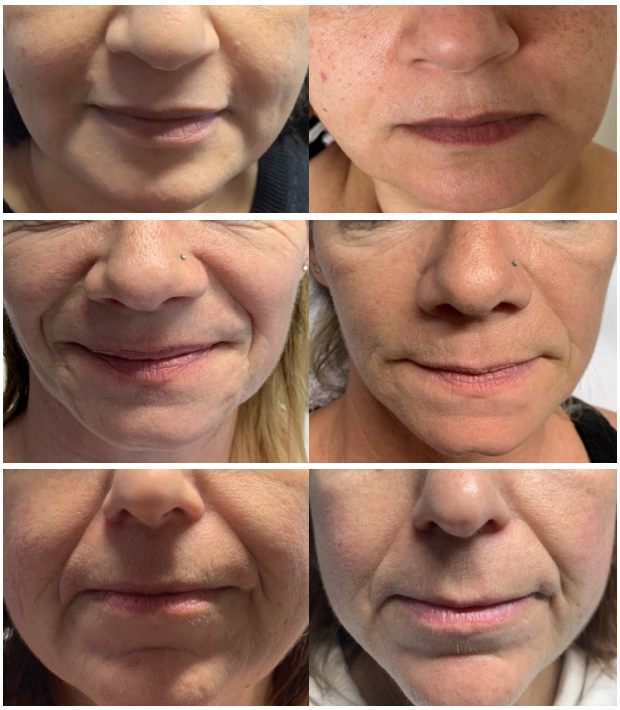
Table 3: Reduction of WSRS grade: Practitioner *vs.* patient.

	Group 1	**Group 2**
Numbers	12	13
Age min-max	35-68	46-82
Average age	53,41	60,61
WSRS J0	2,5	3,07
WSRS W4	1,25	2,07
WSRS W 12	1,5	1,61
WSRS W 24	1,75	1,9
Decrease J0-W4	50%	32%
Decrease J0-W12	40%	48%
Decrease J0-W24	30%	38%

Table 4: Doctor/patient satisfaction results-the GAIS scale.

	Group 1	**Group 2**
Numbers	12	13
GAIS score Dr. W4	2,58	3
GAIS score Subj W4	2,6	3
GAIS score Dr. W12	2,91	2,6
GAIS score Subj W12	2,9	2,76
GAIS score Dr. W24	3,1	2,76
GAIS score Subj W24	3,06	3,07

GROUP 1



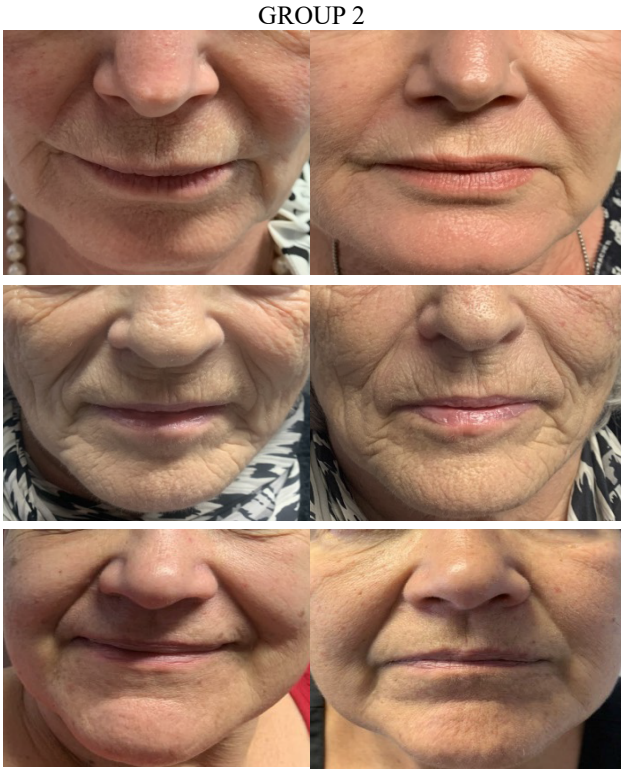


Figure 4: Example of photos before and after 6 months for the Group 1 and Group 2.

Table 5: Hematological measures of platelets and leukocytes.

Case N°	Platelets before centrifugation	Platelets after centrifugation	Leukocyte before centrifugation	Leukocyte after centrifugation	mean platelet concentration factor	mean leukocyte concentration factor
1	215	514	5,8	6,1	2,39	1,05
2	168	420	8,5	5,4	2,5	0,63
3	280	560	7,5	8,3	2	1,1
4	175	400	8,5	6,5	2,28	0,76
5	213	520	10,4	8,8	2,44	0,84
6	245	480	6,4	7,2	1,95	1,125
7	178	420	7,6	5,4	2,35	0,71
8	220	505	8,4	6,7	2,29	0,79
9	141	380	7,2	7,5	2,69	1,04
10	258	540	8,2	6,3	2,09	0,76
11	180	420	5,8	4,2	2,33	0,72
12	265	560	6,7	7,1	2,11	1,06
13	190	420	5,4	4,3	2,21	0,79
14	305	620	9,5	10,1	2,03	1,06
15	178	408	7,3	6,8	2,29	0,93
16	198	450	8,5	7,2	2,27	0,84
17	264	580	11,2	10,8	2,2	0,96
18	240	510	8,4	7,5	2,125	0,89
19	215	450	7,5	5,6	2,09	0,74
20	275	530	8,8	7,2	1,92	0,81
Average	220,15	484,35	7,88	6,95	2,22	0,88

Discussion

Albumin-rich platelet fibrin (Alb-PRF) has emerged as a novel bio-filler, with initial studies published in 2016. Research by Fujioka-Kobayashi from the University of Bern and others [5, 11-13] has explored the biological properties of Alb-PRF in vitro, particularly its effects on gingival fibroblast cells. They reported excellent viability at 24 hours, enhanced fibroblastic migration, and collagen synthesis (types I and II). In particular, they demonstrated a sustained release of growth factors, including PDGF-AA, PDGF-AB, PDGF-BB, TGF-Beta1, VEGF, EGF, and IGF-1, for up to 10 days.

In our cohort of 25 patients, 12 patients in group 1 received a single treatment, while 13 patients in group 2 underwent a second treatment after a one-month follow-up. The 12 patients in group 1 had a mean age of 53 years and an average WSRS score of 2.5. Following a series of EZPRF and EZGEL injections, patients achieved an average 50% reduction in nasolabial fold depth after one month, 40% after three months, and 30% after six months. The satisfaction rating (GAIS scale) was 3 at the end of treatment, with all patients reporting improvement in their nasolabial folds.

Group 2 comprised 13 patients with a mean age of 60 years and a mean pre-treatment WSRS score of 3.07. The treatment was repeated after one month, resulting in an average 32% reduction in nasolabial fold depth at one month, 48% at three months, and 38% at six months. The satisfaction score was 2.5 after three months and 3 after six months, with all patients noting visible improvements in their nasolabial folds. This aligns with findings from Dr. Namratha [14], who confirmed that Alb-PRF maintains growth factor release over time, with resorption exceeding four months. Furthermore, other studies [11,15] have indicated that Alb-PRF membranes exhibit superior stability compared to solid PRF.

Majewska [16] conducted an *in vivo* study with a younger cohort (average age 46.5 years) compared to our groups (53 and 60 years). They reported a 22.2% reduction in nasolabial fold depth after three months, which is lower than the 40% reduction observed in our Group 1. Their methodology involved high-frequency ultrasound analysis, providing a robust assessment of skin density and thickness.

The pilot study by Nathalie Gomez [4] divided PRF gel into low and high viscosity groups, demonstrating overall improvement in dermal thickness and patient satisfaction after 16 weeks. In contrast, our study's follow-up at 6 months revealed sustained improvements, with Group 2 achieving a 38.2% reduction in nasolabial folds.

Doctor Doghaim [17] analyzed plasma gel efficacy in a cohort of 52 women over three months, reporting a decrease in WSRS from 3.18 to 1.65. However, their preparation differed from ours, as their gel was activated with calcium gluconate and not combined with injectable PRF. Their findings reinforce the safety profile of plasma gel, as they noted minimal adverse effects.

In 2022, the Menoufia team [18] examined plasma gel injected alone, noting no adverse effects, suggesting that such injections carry a low risk of complications. However, our study emphasizes the enhanced regenerative potential of combining EZPRF with EZGEL, as supported by Dr. Namratha who highlighted the necessity of injectable PRF to preserve regenerative properties.

This study is unique in demonstrating the effectiveness of treatment six months post-injection, a timeframe not commonly reported in other studies. This extended efficacy could be attributed to the hematological quality of EZPRF, which showed a 2.2-fold increase in platelet concentration and a 0.88-fold increase in leukocyte concentration post-centrifugation. These results are consistent with findings from other studies [2,3,19-21], which emphasize the importance of optimizing centrifugation protocols to maximize the concentration of regenerative cells and growth factors. Although our study utilized a fixed-angle centrifugation method, future studies might explore the potential benefits of horizontal centrifugation, as suggested by Fujioka-Kobayashi et al. [10], to further enhance these properties.

Overall, our findings indicate that EZPRF and EZGEL are effective in treating nasolabial folds, with significant improvements in both objective and subjective assessments. The injections provide a volumetric filling effect, stability over time, and a natural scaffold for leukocytes and platelets, as well as newly formed tissue cells. The leukocytes and platelets present in the plasma gel act through the degranulation of their alpha granules, which contain pre-synthesized growth factors essential for skin regeneration [22-26]. These growth factors stimulate fibroblasts and mesenchymal stem cells, leading to neovascularization and neocollagenesis. Additionally, due to their biological functions and the properties of albumin, they mitigate the risk of bacterial contamination, infection development, and chronic inflammation.

Moreover, EZGEL injections are a cost-effective, safe, and well-tolerated technique for improving deep wrinkles such as nasolabial folds. Reported side effects were minimal and temporary, primarily consisting of bruising, swelling, and mild pain at the injection site, subsiding within 24-48 hours[27-30].

Conclusion

EZPRF and EZGEL are ideal biomaterials for facial repair and regeneration. They are injectable, easily prepared, and 100% natural, with no serious side effects reported to date. It is advisable to repeat the treatment after one month, particularly in elderly patients over 60 years with a WSRS score greater than 4. Improvements have been shown to be maintained after six months, with results appearing natural and not altering facial aesthetics. Future research could focus on optimizing the preparation and application protocols to enhance the regenerative outcomes and explore the potential of combining EZPRF and EZGEL with other regenerative therapies for synergistic effects.

Ethical approval

Written informed consent was obtained from all patients prior to participation, and they were informed about the study protocol and potential risks. All procedures adhered to the principles of the Declaration of Helsinki and complied with regional laws and good clinical practices.

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