

Level of Evidence on Platelet-rich Plasma in Plastic Surgery

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Background: Despite the increased popularity of platelet-rich plasma (PRP) in plastic surgery, there is no detailed analysis on the level of evidence on PRP use in plastic surgery. As the number of applications of PRP in plastic surgery increases, it is important for plastic surgeons to understand the scientific and validated evidence behind its use. Therefore, we performed a literature review to identify current level of evidence on platelet-rich plasma in plastic surgery.

Methods: We performed a computerized search of platelet-rich plasma in plastic surgery using the MEDLINE, Cochran Library, and EMBASE databases. Data regarding the type of study, PRP application, and outcomes were collected. Then, the level of evidence was assigned using the American Society of Plastic Surgeons Level of Evidence Rating.

Results: Our search identified 105 articles, and about 78.1% of studies were lower-quality studies: 37 level-III articles (35.2%), 32 level-IV articles (30.5%), and 13 level-V articles (12.4%). There were only 6 level-I articles and 17 level-II studies. Level-I studies were on facial rejuvenation using a laser, carpal tunnel release, cleft lip repair, trauma wounds, breast reconstruction using latissimus dorsi, and hair regrowth.

Conclusions: Our review of the literature shows that the level of evidence on PRP use in plastic surgery is low (21.9%). Nevertheless, we believe level-III to level-V studies are still valuable, as performing high-level quality studies in plastic surgery is difficult due to variability in surgical techniques, experiences, and materials. (*Plast Reconstr Surg Glob Open* 2021;9:e3379; doi: [10.1097/GOX.0000000000003379](https://doi.org/10.1097/GOX.0000000000003379); Published online 15 April 2021.)

INTRODUCTION

According to the 2018 American Society for Plastic Surgeons database, the number of cosmetic procedures using platelet-rich plasma (PRP) as soft tissue fillers accounted for 0.8% of all cosmetic non-surgical procedures.¹ In contrast to 2017, PRP use has increased by 12%, which accounts for the fourth fastest growing cosmetic procedure. As PRP has been progressively becoming popular in plastic surgery, its uses in plastic surgery have expanded to aesthetic, craniofacial, hand, and reconstructive surgery.^{2,3}

Currently, platelet-rich plasma is used in various types of procedures and surgery, given its theorized benefits of

enhancing wound healing, collagen production, angiogenesis, and remodeling.⁴ It can be used as topical applications or injections, and it is widely popularized in aesthetic and craniofacial surgery. In aesthetic surgery, it can be used in facelifts to decrease ecchymosis and edema, lasers to assist with wound healing, fat grafting to increase fat retention, and hair transplantation to enhance hair regrowth.⁵⁻⁸ For craniofacial surgery, it is used in bone grafts, fistula repairs, dental implants, and maxillofacial reconstruction.⁹⁻¹¹

Despite the increased popularity of PRP in plastic surgery, there is no detailed analysis on the level of evidence on PRP in plastic surgery. As the number of applications of PRP in plastic surgery increases, it is important for plastic surgeons to understand the scientific and validated evidence behind its use. Therefore, we performed a literature review to identify current level of evidence on platelet-rich plasma in plastic surgery.

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METHODS

We performed a computerized search of the MEDLINE, Cochran Library, and EMBASE databases using the search term, platelet-rich plasma, and following search terms:

- Aesthetic surgery
- Breast surgery
- Craniofacial surgery
- Hand surgery
- Plastic surgery
- Reconstruction

The following limits were applied for each search:

- Subjects: humans
- Language: English
- Dates: no limits
- Age groups: no limits

Exclusion criteria were as follows: (1) review articles; (2) animal studies; and (3) articles not in English.

All studies were reviewed and evaluated by one of the authors (MJC). Data regarding the type of study, PRP application, objective measurement of the outcomes, PRP preparation method (baseline and final platelet count, force and length of centrifugation, use of anticoagulation), and journal type were collected. Then, each article was reviewed, and the level of evidence was assigned to each article using the American Society of Plastic Surgeons Level of Evidence Rating Scale (Table 1).^{12,13}

RESULTS

The computerized search was performed on April 11, 2020. A total of 854 articles were identified from the initial search: aesthetic surgery, $n = 101$; breast surgery, $n = 25$; craniofacial surgery, $n = 287$; hand surgery, $n = 44$; plastic surgery, $n = 99$; and reconstructive surgery, $n = 298$. After reviewing the abstracts of each article, 105 studies of potential relevance remained: aesthetic surgery, $n = 39$; breast surgery, $n = 4$; craniofacial surgery, $n = 23$; hand surgery, $n = 3$; plastic surgery, $n = 15$; and reconstructive surgery, $n = 21$ (Fig. 1).

All 105 articles were further evaluated, and the level of evidence for each article was determined using the American Society of Plastic Surgeons Evidence Rating Scale. The analysis of 106 studies revealed 6 level-I articles (5.7%), 17 level-II articles (16.2%), 37 level-III articles (35.2%), 32 level-IV articles (30.5%), and 13 level-V articles (12.4%) (Fig. 2, Table 2).

Aesthetic Surgery

Of the 101 articles from the initial search, 39 articles remained after the initial review: 1 level-I, 3 level-II, 17 level-III, 15 level-IV, and 3 level-V studies (Table 3). The majority of the studies were on fat grafting, followed by microneedling and injection of PRP for facial rejuvenation. Of the 4 high-quality evidence-based studies, level-I study was a prospective, blinded study on the patients who received a fractional carbon dioxide laser with PRP.¹⁴ Level-II studies were on the following: microneedling, acne scar, and lipofilling of face. Apart from these 4 studies, 89.7% of the studies had a lower level of evidence.

Breast Surgery

Four articles were identified on the use of PRP on breast surgery (1 level-I and 3 level-III articles). The level-I article studied the effect of PRP to minimize drain amount and to prevent seroma formation in latissimus dorsi breast reconstruction, whereas level-III articles were on breast fat grafting.¹⁵

Craniofacial Surgery

For the craniofacial surgery, the majority of the studies were on bone graft (74%), and the remaining 26% of the studies were on cleft lip repair, cleft palate repair, distraction osteogenesis, oronasal fistula repair, and osteonecrosis. There was one level-I study on the effect of PRP on the scar width of primary cleft lip repair.¹⁶ For the level-II study, a study on the effect of PRP in distraction osteogenesis was identified.¹⁷ Similar to the other fields, the majority of the studies were lower-quality studies such as level III (17.3%), level IV (39.1%), and level V (26%).

Hand Surgery

Three articles were identified for PRP use in hand surgery (1 level I and 2 level IV).¹⁸ The level-I study was on the effect of PRP on the carpal tunnel release. Level-IV studies were on the use of PRP in the setting of amputation and in patients with basal thumb arthritis.

Plastic Surgery and Reconstructive Surgery

Fifteen studies were identified using the search term, "plastic surgery." Of the 15 studies, there were 2 level-I studies: randomized placebo-controlled trial on the effect of PRP in hair regrowth and use of PRP in the management of acute trauma wounds.^{19,20} The level-II studies were on the use of PRP on blepharoplasty, chronic wounds, alopecia, and fractional CO₂ laser therapy.²¹⁻²⁴ Other studies were lower quality studies on fat grafting (3), keloid (1), osteonecrosis (1), wound healing (2), and meta-analysis (1).

For the reconstructive surgery, bone graft was the most commonly studied (28.6%), followed by wound healing and fat grafting to breast. The majority of the studies were lower-quality studies (66.7%), and level-III studies (38%) were the most common level of evidence.

PRP Preparation and Efficacy

Of the 105 studies we reviewed, the concentration of baseline and final platelets was reported only in 18.3% and 21.5%, respectively. The force and length of the centrifugation was documented in 74.2%, and the use of anticoagulation was reported in 9.7% of the studies. For the PRP efficacy, only 53.8% of the studies objectively measured the outcomes after the PRP application.

DISCUSSION

Recently, application of platelet rich plasma has become popular in the field of plastic surgery, given its theoretical ability to promote wound healing, stimulate collagen production, and improvement in overall

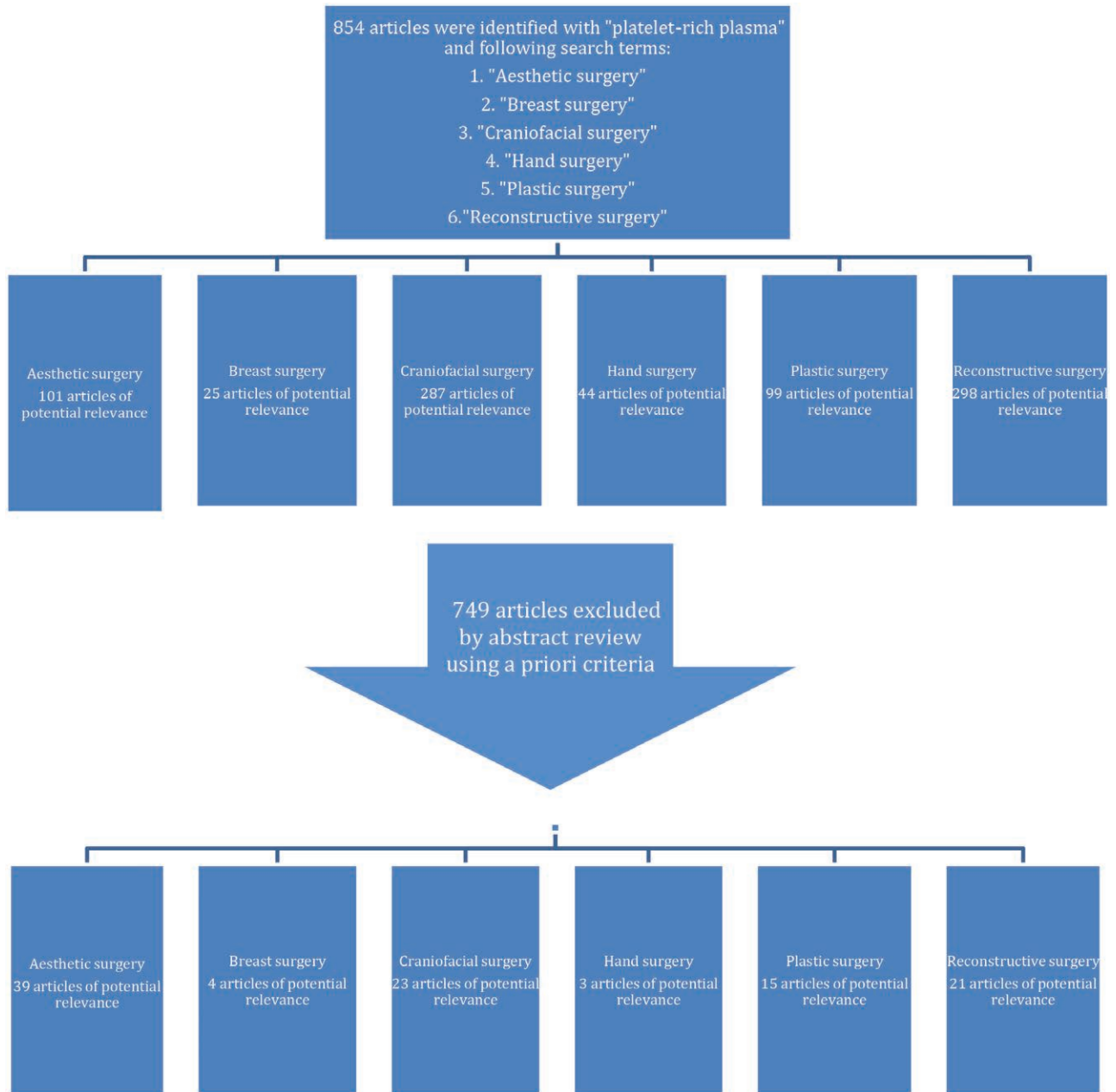


Fig. 1. Article selection process.

healing.^{2,25,26} Therefore, many surgical specialties such as dentistry, oral and maxillofacial surgery, orthopedics, ophthalmology, and gynecology have begun to use PRP in their practice.²⁷⁻³¹ Similarly, plastic surgeons have begun to use PRP in their practice, especially in aesthetic procedures such as fat grafting, alopecia, facial rejuvenation, and laser.

Despite the increased popularity of PRP in plastic surgery, there is no detailed analysis on the level of evidence of PRP applications in plastic surgery at this time. Therefore, we performed a computerized search to determine the level of evidence on PRP applications using aesthetic surgery, breast surgery, craniofacial surgery, hand surgery, plastic surgery, and reconstructive surgery as search terms.

Our search identified 105 articles, and 78.1% of studies were lower-quality studies: 37 level-III articles (35.2%), 32 level-IV articles (30.5%), and 13 level-V articles (12.4%). There were only 6 level-I articles and 17 level-II studies. Level-I studies were on facial rejuvenation using a laser, carpal tunnel release, cleft lip repair, trauma wounds, breast reconstruction using latissimus dorsi, and hair regrowth. Level-II studies were on distraction osteogenesis, bone graft, wound healing, burns, facelift, blepharoplasty, alopecia, laser, microneedling, lipofilling of face, and skin graft.

Our review of the literature revealed that the level of evidence on PRP use in plastic surgery is low (21.9%). This phenomenon is in agreement with the published finding

Distribution of level of evidence in studies

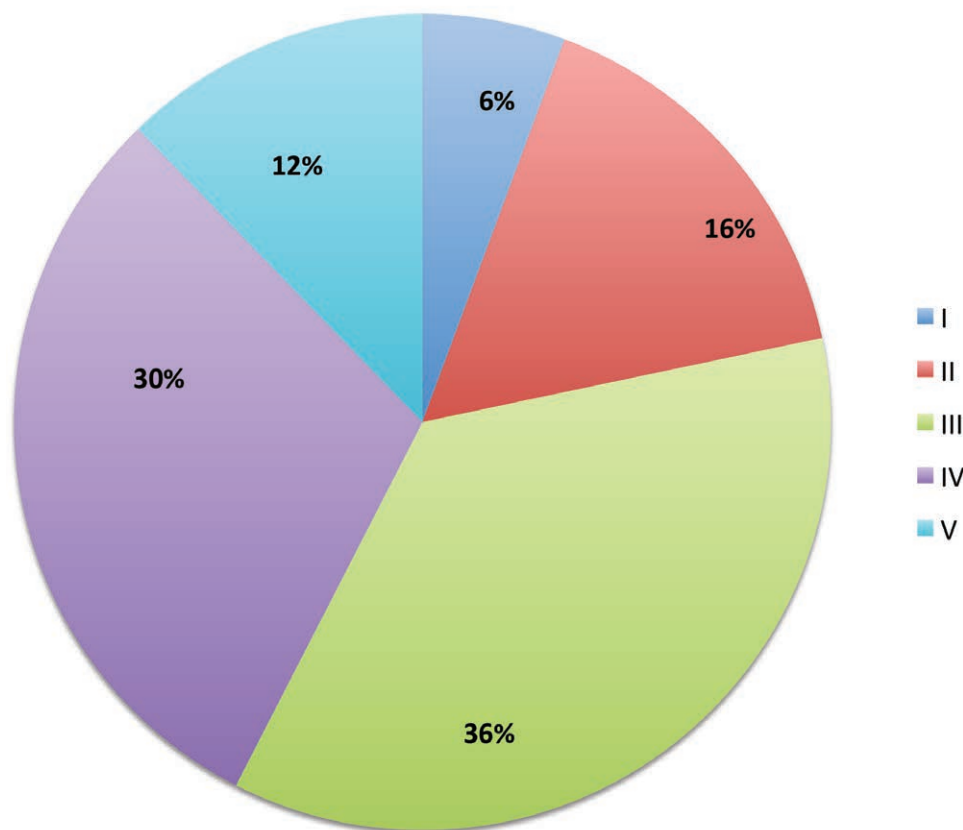


Fig. 2. Distribution of level of evidence in studies.

of low level of evidence in plastic surgery.³²⁻³⁴ Sinno et al found that the average level of evidence in plastic surgery is low (*PRS*, 3.05; *JPRAS*, 3.35; *Annals*, 3.31, and *Aesthetic*, 3.11), and only 2.2% of studies were level I³². The average level of evidence in our study was 3.3, and over 40% of the studies were level IV or V, which were case series or case reports. Of these, the majority of the studies were on bone graft, which was most likely due to theoretical advantages of enhancing bony healing with growth factors from the platelets.^{27,35} The popularity of PRP was also observed in

the field of dentistry and maxillofacial surgery.³⁶ Similarly, a large percentage of level-III studies were on fat grafting and facial rejuvenation.

In addition to the low level of evidence on PRP use in plastic surgery, the quality of PRP preparation and assessment of PRP efficacy was inadequate. The majority of the studies did not report baseline or final platelet concentration, which determines the dose and effectiveness of the factors in the PRP. Furthermore, the vast majority of the studies did not report previous use of anticoagulation by the patient (90.3%), which also impacts the efficacy of the platelets. Several systematic reviews on the clinical efficacy of PRP in aesthetic surgery have already shown that there is a lack of consistency and standardization in the preparation and application of the PRP.^{2,25} In addition, many studies did not assess the clinical efficacy of PRP objectively.²⁵ This phenomenon was also observed in our study, which identified 53.8% of studies reporting objective measurement of PRP efficacy.

Furthermore, we performed a detailed analysis of level-I studies using the Jadad scale. The Jadad scale evaluates the quality of randomized trials³⁷ by asking these 3 questions: (1) Was the study described as randomized? (2) Was the study described as double blind? (3) Was there a description of withdrawals and dropouts? For each question, score 1 was given if the answer was “yes.” Of the 6 level-I studies, 4 studies had a Jadad score of 1, and 2

Table 1. American Society of Plastic Surgeons Evidence Rating Scale for Therapeutic Studies

Level of Evidence	Qualifying Studies
I	High-quality, multi-centered or single-centered, randomized controlled trial with adequate power; or systematic review of these studies
II	Lesser quality, randomized controlled trial; prospective cohort or comparative study; or systematic review of these studies
III	Retrospective cohort or comparative study; case-control study; or systematic review of these studies
IV	Case series with pre/post test; or only post test
V	Expert opinion developed via consensus process; case report or clinical example; or evidence based on physiology, bench research or “first principles”

Table 2. Detailed Analysis of the Studies Based on the Level of Evidence

Level of Evidence	No. Articles
Aesthetic surgery	
I	1
II	3
III	17
IV	15
V	3
Breast surgery	
I	1
III	3
Craniofacial surgery	
I	1
II	3
III	4
IV	9
V	6
Hand surgery	
I	1
IV	2
Plastic surgery	
I	2
II	4
III	5
IV	3
V	1
Reconstructive surgery	
II	7
III	8
IV	3
V	3

studies had a Jadad score of 2. This finding reveals that randomized controlled trials, which are the highest level of evidence studies, were poorly performed.

Our study shows that the current level of evidence in platelet-rich plasma is low, and this phenomenon is most likely due to the inherent nature of our specialty. Historically, plastic surgery fell behind the other specialties in adopting evidence-based medicine due to the lack of objective assessment, steep learning curves, and difficulty with standardization in the field of plastic surgery.³⁸ However, there has been an increase in the average level of evidence in the past several decades, and we anticipate that there will be an increase in the number of higher quality studies on PRP use in the near future.^{34,38,39}

CONCLUSIONS

Since the introduction of evidence-based medicine in the 1980s, it has become commonplace for physicians to practice evidence-based healthcare.^{40,41} However, plastic surgeons have been slow to adopt evidence-based medicine compared with the other specialties.^{39,40,42} Our review of the literature reveals that there is a limited number of high-quality studies on PRP use in plastic surgery. In addition, the quality of PRP preparation and assessment PRP efficacy performed in these studies was low. However, we believe level-III to level-V studies are still valuable, as performing high-level quality studies in plastic surgery can be challenging. Furthermore, we anticipate that there will be an increase in the number of higher quality studies on PRP use, as its use continues to expand.

Table 3. Distribution of Articles per Sub-specialty

	No. Articles
Aesthetic surgery	
Alopecia	1
Acne scar	1
Fat grafting to breast	4
Fat grafting to face	7
Facelift	2
Hyaluronic acid	2
Hyperpigmentation	1
Keloid	1
Laser	3
Microneedle	5
PRP injection	5
Radiofrequency	1
Rhinoplasty	2
Striae	2
Wound healing	2
Breast surgery	
Drain	1
Fat grafting	3
Craniofacial surgery	
Bone graft	17
Cleft lip repair	1
Cleft palate repair	1
Distraction osteogenesis	1
Oronasal fistula repair	1
Osteonecrosis	2
Hand surgery	
Amputation	1
Arthritis	1
Carpal tunnel syndrome	1
Plastic surgery	
Alopecia	3
Blepharoplasty	1
Fat grafting to face	2
Fat grafting to breast	1
Keloid	1
Laser	1
Meta-analysis	1
Osteonecrosis	1
Wound healing	4
Reconstruction	
Acne scar	1
Alopecia	1
Blepharoplasty	1
Bone graft	6
Burn	1
Facelift	1
Fat grafting to breast	2
Hidradenitis	1
Skin graft	1
Soft tissue atrophy	1
Systemic review	1
Wound healing	4

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REFERENCES

1. Surgeons ASOP. 2018 Plastic Surgery Statistics Report. Available at <https://www.plasticsurgery.org/documents/News/Statistics/2018/plastic-surgery-statistics-full-report-2018.pdf>. Published 2018. Accessed July 1, 2019.
2. Frautshi RS, Hashem AM, Halasa B, et al. Current evidence for clinical efficacy of platelet rich plasma in aesthetic surgery: A systematic review. *Aesthet Surg J*. 2017;37:353–362.
3. Moraes VY, Lenza M, Tamaoki MJ, et al. Platelet-rich therapies for musculoskeletal soft tissue injuries. *Cochrane Database Syst Rev*. 2009;27:158–167.

4. Dohan Ehrenfest DM, Rasmusson L, Albrektsson T. Classification of platelet concentrates: From pure platelet-rich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (L-PRF). *Trends Biotechnol.* 2009;27:158–167.
5. Lee JW, Kim BJ, Kim MN, et al. The efficacy of autologous platelet rich plasma combined with ablative carbon dioxide fractional resurfacing for acne scars: A simultaneous split-face trial. *Dermatol Surg.* 2011;37:931–938.
6. Redaelli A, Romano D, Marciánó A. Face and neck revitalization with platelet-rich plasma (PRP): Clinical outcome in a series of 23 consecutively treated patients. *J Drugs Dermatol.* 2010;9:466–472.
7. Willemsen JC, van der Lei B, Vermeulen KM, et al. The effects of platelet-rich plasma on recovery time and aesthetic outcome in facial rejuvenation: Preliminary retrospective observations. *Aesthetic Plast Surg.* 2014;38:1057–1063.
8. Keyhan SO, Hemmat S, Badri AA, et al. Use of platelet-rich fibrin and platelet-rich plasma in combination with fat graft: Which is more effective during facial liposuction? *J Oral Maxillofac Surg.* 2013;71:610–621.
9. Whitman DH, Berry RL, Green DM. Platelet gel: An autologous alternative to fibrin glue with applications in oral and maxillofacial surgery. *J Oral Maxillofac Surg.* 1997;55:1294–1299.
10. Grageda E. Platelet-rich plasma and bone graft materials: A review and a standardized research protocol. *Implant Dent.* 2004;13:301–309.
11. Marx RE. Platelet-rich plasma: Evidence to support its use. *J Oral Maxillofac Surg.* 2004;62:489–496.
12. American Society of Plastic Surgeons. Scales for Rating Levels of Evidence. Available at: <http://www.plasticsurgery.org/Documents/medical-professionals/health-policy/evidence-practice/ASPS-Rating-Scale-March-2011.pdf>. Accessed August 1, 2016.
13. Sullivan D, Chung KC, Eaves FF III, et al. The level of evidence pyramid: Indicating levels of evidence in Plastic and Reconstructive Surgery articles. *Plast Reconstr Surg.* 2011;128:311–314.
14. Kim H, Gallo J. Evaluation of the effect of platelet-rich plasma on recovery after ablative fractional photothermolysis. *JAMA Facial Plast Surg.* 2015;17:97–102.
15. Harper JG, Elliott LF, Bergery P. The use of autologous platelet-leukocyte-enriched plasma to minimize drain burden and prevent seroma formation in latissimus dorsi breast reconstruction. *Ann Plast Surg.* 2012;68:429–431.
16. Refahee SM, Aboulhassan MA, Abdel Aziz O, et al. Is PRP effective in reducing the scar width of primary cleft lip repair? A randomized controlled clinical study. *Cleft Palate Craniofac J.* 2020;57:581–588.
17. Menezes DJ, Shibli JA, Gehrke SA, et al. Effect of platelet-rich plasma in alveolar distraction osteogenesis: A controlled clinical trial. *Br J Oral Maxillofac Surg.* 2016;54:83–87.
18. Trull-Ahuir C, Sala D, Chismol-Abad J, et al. Efficacy of platelet-rich plasma as an adjuvant to surgical carpal ligament release: A prospective, randomized controlled clinical trial. *Sci Rep.* 2020;10:2085.
19. Gentile P, Garcovich S, Bielli A, et al. The effect of platelet-rich plasma in hair regrowth: A randomized placebo-controlled trial. *Stem Cells Transl Med.* 2015;4:1317–1323.
20. Kazakos K, Lyras DN, Verettas D, et al. The use of autologous PRP gel as an aid in the management of acute trauma wounds. *Injury.* 2009;40:801–805.
21. Vick VL, Holds JB, Hartstein ME, et al. Use of autologous platelet concentrate in blepharoplasty surgery. *Ophthalmic Plast Reconstr Surg.* 2006;22:102–104.
22. Liao X, Liang JX, Li SH, et al. Allogeneic platelet-rich plasma therapy as an effective and safe adjuvant method for chronic wounds. *J Surg Res.* 2020;246:284–291.
23. Ince B, Yildirim MEC, Dadaci M, et al. Comparison of the efficacy of homologous and autologous platelet-rich plasma (PRP) for treating androgenic alopecia. *Aesthetic Plast Surg.* 2018;42:297–303.
24. Hui Q, Chang P, Guo B, et al. The clinical efficacy of autologous platelet-rich plasma combined with ultra-pulsed fractional CO₂ laser therapy for facial rejuvenation. *Rejuvenation Res.* 2017;20:25–31.
25. Motosko CC, Khouri KS, Poudrier G, et al. Evaluating platelet-rich therapy for facial aesthetics and alopecia: A critical review of the literature. *Plast Reconstr Surg.* 2018;141:1115–1123.
26. Leo MS, Kumar AS, Kirit R, et al. Systematic review of the use of platelet-rich plasma in aesthetic dermatology. *J Cosmet Dermatol.* 2015;14:315–323.
27. Kumar KA, Rao JB, Pavan Kumar B, et al. A prospective study involving the use of platelet rich plasma in enhancing the uptake of bone grafts in the oral and maxillofacial region. *J Maxillofac Oral Surg.* 2013;12:387–394.
28. Everts PA, Malanga GA, Paul RV, et al. Assessing clinical implications and perspectives of the pathophysiological effects of erythrocytes and plasma free hemoglobin in autologous biologics for use in musculoskeletal regenerative medicine therapies. A review. *Regen Ther.* 2019;11:56–64.
29. Fanning J, Murrain L, Flora R, et al. Phase I/II prospective trial of autologous platelet tissue graft in gynecologic surgery. *J Minim Invasive Gynecol.* 2007;14:633–637.
30. Alio JL, Abad M, Artola A, et al. Use of autologous platelet-rich plasma in the treatment of dormant corneal ulcers. *Ophthalmology.* 2007;114:1286–1293.e1.
31. Alio JL, Rodriguez AE, Martinez LM, et al. Autologous fibrin membrane combined with solid platelet-rich plasma in the management of perforated corneal ulcers: A pilot study. *JAMA Ophthalmol.* 2013;131:745–751.
32. Sinno H, Neel OF, Lutfy J, et al. Level of evidence in plastic surgery research. *Plast Reconstr Surg.* 2011;127:974–980.
33. Nguyen A, Mahabir RC. An update on the level of evidence for plastic surgery research published in plastic and reconstructive surgery. *Plast Reconstr Surg Glob Open.* 2016;4:e798.
34. McCarthy JE, Chatterjee A, McKelvey TG, et al. A detailed analysis of level I evidence (randomized controlled trials and meta-analyses) in five plastic surgery journals to date: 1978 to 2009. *Plast Reconstr Surg.* 2010;126:1774–1778.
35. Gerard D, Carlson ER, Gotcher JE, et al. Effects of platelet-rich plasma on the healing of autologous bone grafted mandibular defects in dogs. *J Oral Maxillofac Surg.* 2006;64:443–451.
36. Gentile P, Bottini DJ, Spallone D, et al. Application of platelet-rich plasma in maxillofacial surgery: Clinical evaluation. *J Craniofac Surg.* 2010;21:900–904.
37. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Control Clin Trials.* 1996;17:1–12.
38. Hassanein AH, Herrera FA, Hassanein O. Challenges of randomized controlled trial design in plastic surgery. *Can J Plast Surg.* 2011;19:e28–e29.
39. Rohrich RJ, Cho MJ. Evidence-based medicine in aesthetic surgery: The significance of level to aesthetic surgery. *Plastic Reconstruct Surg.* 2017;139:1195e–1202e.
40. Burns PB, Rohrich RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. *Plast Reconstr Surg.* 2011;128:305–310.
41. Sauerland S, Lefering R, Neugebauer EA. The pros and cons of evidence-based surgery. *Langenbecks Arch Surg.* 1999;384:423–431.
42. Sackett DL, Rosenberg WM, Gray JA, et al. Evidence based medicine: What it is and what it isn't. *BMJ.* 1996;312:71–72.