Review Article

Systematic review of platelet-rich fibrin (PRF) centrifugation protocols in oral and maxillofacial surgery and the introduction of AR^{2}T^3: an easy to remember acronym to correctly report vertical and horizontal PRF centrifugation

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Background: Platelet-rich fibrin (PRF) is a blood concentrate widely used in dentistry and in oral and maxillofacial surgery obtained through centrifugation. Recent studies have shown that the centrifugation protocols (CP) and the centrifuge machine affect the final characteristic of PRF. It is therefore essential to review the various CP outlined in the literature with the aim of increasing their reproducibility. The aim of this systematic review is to revise the existence of standardization of the latest CP.

Methods: A systematic approach was used to perform the electronic literature search. Included studies were those performed in humans. The research question was formulated as follow: "Is the reporting of PRF's centrifugation protocols standardized?". The last electronic search was conducted in October 2020 in biomedical search engines. The results were gathered in table format, analyzed and discussed.

Results: A total of 121 articles were found in the literature to be eligible for qualitative evaluation. The search gave as a result vertical and horizontal centrifugation protocols. Twenty-nine different CP and 16 different centrifuge machines were used to produce PRF. Fixed-angle rotors ranged from 33° to 45° and the radius-max from 85 to 130 mm. The protocols reported in RPM ranged from 700 to 3,500 rpm and the protocols reported in RCF (×g) ranged from 44 to 1,000 g. The treatment with the highest diversity of CPs [RPM/RCF (×g)/time] was the enhancement of soft tissue healing.

Conclusions: It was found an absence of standardization in the reporting of the centrifugation protocols of PRF. In this regard, the present review involves a general discussion of all the principles that influence the final content of PRF and introduces the AR^{2}T^3 acronym. The purpose of AR^{2}T^3 is to increase the reproducibility of future PRF studies. The use of the acronym will allow the elaboration of meta-analyses and guidelines that are not yet available due to the heterogeneity of the data.

Keywords: Platelet-rich fibrin (PRF); centrifugation protocols; horizontal centrifugation; fixed-angel centrifugation; platelet concentrate

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Introduction

Blood is a complex organ and it is constituted of three main cell components in variable proportions, namely, red blood cells (≈43%), white blood cells (≈1%) and platelets (≈1%) suspended in plasma (≈55%). By applying centrifugal force through acceleration, these cells can be separated from plasma. The effect of centrifugation on cells depends on their different mass, which is the product of their volume and density (density of erythrocytes: 1,090–1,100 kg/m^3, leukocytes; 1,050–1,085 kg/m^3, platelets 1,040–1,060 kg/m^3, plasma 1,025 kg/m^3) (1). Consequently, due to the higher mass of the erythrocytes, when blood is centrifuged, erythrocytes settle faster at the bottom of a recipient, while leukocytes and platelets deposit on top of the erythrocytes, followed by plasma over the cells (2).

The speed of acceleration exerted to blood through centrifugation is known as the relative centrifugation force (RCF) and it is expressed in multiples of earth's gravitational force (9.8.1 m/s^2) and abbreviated as "*g*". Thus, the higher the mass of cells and the RCF applied, the faster cells will settle at the bottom of a tube. The speed in which suspended cells move outside of the blood plasma and sediment at the bottom of the tubes is known as sedimentation (3). The speed of sedimentation is dependent on cells volume and the difference between the density of cells and the density of plasma when the gravitational force is applied. In other words, the sedimentation speed of cells will decrease as the density of plasma increases and will increase as the RCF increases. As blood is an organ highly influenced by age, gender, nutrition, liquid intake and systemic health, the quantity of cells in blood and its viscosity can vary within each individual patient, consequently, resulting in changes in the ratio of fractioning after centrifugation (4,5).

The aforementioned principles apply to all blood derivates used to improve wound healing, i.e., platelet concentrates (6). Platelet-rich fibrin (PRF) is a second-generation cell concentrate derived from human blood containing platelets, white blood cells, stem-like cells and growth factors (6,7). It is obtained through a one-step centrifugation and since its introduction in dentistry and maxillofacial surgery in 2001, has found many applications (7). A recent review involving 72 studies and 1,822 patients in total described the applications of PRF in the fields of endodontic, implantology, maxillofacial surgery, orthodontics and periodontology. 38 from these studies, involving 70% of the patients treated, were conducted with a high scientific rigor (randomized and controlled prospect studies) and showed that PRF is a beneficial tool that significantly improves bone and soft tissue regeneration (7).

According to the tubes used to collect blood, a solid/clot PRF or a liquid/injectable PRF can be obtained (8,9). The centrifugation process and the surface of the tubes initiates the coagulation cascade of blood and activates platelets, causing bioactive molecules (hemostatic factors, angiogenic factors, growth factors, proteases, serotonin) to be released from the alpha and dense granules (10). In the case of solid/clot PRF, a glass tube provides a well-established clot after centrifugation since the coagulation cascade is activated by the contact of blood with glass due to its negatively charged surface (11,12). On the contrary, for a liquid/injectable PRF a plastic tube is required. The plastic tubes cause the slow activation of prekallikrein (PK)—Factor XII complex, providing the clinicians a mean of 12.95 minutes after centrifugation for the liquid/injectable PRF to coagulate (11,13). The final product after centrifugation consists of a fibrin matrix, in which platelets are trapped. Previous studies have shown that the mean concentration of platelets in PRF is five times the amount of undivided blood (14). Thus, its use in the clinical setting, provides a quick source of a high concentration of bioactive molecules that promote wound healing (15).

White blood cells are also found within the PRF. White blood cells can be divided in 5 categories: neutrophils, monocytes, eosinophils, basophils and lymphocytes. Neutrophils as effector cells of the innate immune system, make up the majority of white blood cells (40–80%) and are densely packed with secretory granules (16,17). A recent study that intended to characterize PRF, showed the presence of B- and T-lymphocytes, monocytes, progenitor cells and neutrophilic granulocytes after centrifugation within solid/clots PRF and liquid/injectable PRF (18). The binding of platelets, neutrophils and monocytes increases through centrifugation. This raises degranulation of the inflammatory cytokines interleukin 1-Beta (IL-1β) and interleukin 8 (IL-8) (19), as well as the pro-wound healing cytokines interleukin 4 (IL-4) and vascular endothelial growth factor (VEGF) (20).

In the literature, diversities of centrifugation protocols (CP) to obtain PRF are described. Recent published studies have shown that the protocol of centrifugation and the centrifuge machine used affect the final characteristic of PRF (6,21). Furthermore, preclinical a clinical research in dentistry and maxillofacial surgery describes augmented healing properties (e.g., Increased bone regeneration and vascular formations) by adjusting the g-force to specific indications (7-9,18). It is therefore crucial to report without omission all parameters to produce PRF in order to obtain reproducible results. The aim of this review article is to revise the existence of standardization in the report of the latest protocols to produce PRF. I present the following article in accordance with the PRISMA reporting checklist (available at https://fomm.amegroups.

Table 1 Methodological approach

Steps	General activities	Specific activities
I	Formation of working group	Maxillofacial surgeon with experience in blood concentrates and writing systematic literature reviews
II	Formulation of the review question	"Is the reporting of PRF's centrifugation protocols standardized?"
III	Identification of relevant studies on PubMed, Cochrane and Key Journals	(I) Selection of Keywords
		(II) Use of Boolean operators (AND; OR; NOT)
		(III) Search (*Table 2* Search strategy)
		(IV) Inclusion criteria
		(V) Elimination of duplicates
		(VI) Manual search
IV	Analyses and presentation	All data is shown in tables and graphs

Adapted from Herrera-Vizcaino C, Albilia JB. Front Oral Maxillofac Med, 2021 (15). PRF, platelet-rich fibrin.

Table 2 Search strategy

Search strategy	Database
Systematic search	
Keywords: (((Platelet-rich fibrin) OR (PRF)) AND (dentistry))	PubMed
Hand search	
International Journal of Oral and Maxillofacial Surgery, Journal of Oral and Maxillofacial Surgery, Journal of Cranio-Maxillofacial Surgery, Oral and Maxillofacial Surgery Clinics of North America, Oral Surgery Oral Medicine Oral Pathology Oral Radiology and British Journal of Oral & Maxillofacial Surgery	–

com/article/view/10.21037/fomm-21-40/rc).

Methods

Search strategy

To reduce bias of selection, a systematic approach was used to perform the electronic literature search following the steps described by Egger *et al.* (22). The research question was formulated as follow: "Is the reporting of PRF's centrifugation protocols standardized?" conforming to the FINER framework (*Table 1*). The electronic search was conducted in the biomedical search engine "National Library of Medicine" (PubMed-MEDLINE) with a combination of Medical Subject Heading search terms (i.e., MeSH) together with Boolean operators to further refine the search (*Table 2*). Articles that fulfilled the inclusion criteria were those performed in humans in the fields of dentistry and oral and maxillofacial surgery, articles written in English and those including the word "platelet-rich fibrin" or "PRF" in the title. No limitations were set regarding the publication year. The first search was conducted on March 2020 and a second search was conducted on October 2020 for horizontal centrifugation protocols. The full texts of the selected articles were examined by the author and the data was extracted using extraction sheets designed for this review. Previous published reviews were not included in the study but were used to identify potentially relevant information. References of the selected articles were scrutinized to search for the description of the PRF's protocol and its clinical application. The following information was extracted: Name of first author, year of publication and the protocol to obtain solid/clot or liquid/injectable PRF as follows: revolutions per minute-rpm, time of centrifugation, RCF (×g), radius of the rotor measured from the axis of the rotor to the base of the tube (RCF-max), name of the centrifuge machine, angle of centrifugation and the characteristics of the tubes. Additionally, articles describing the use of PRF as the only

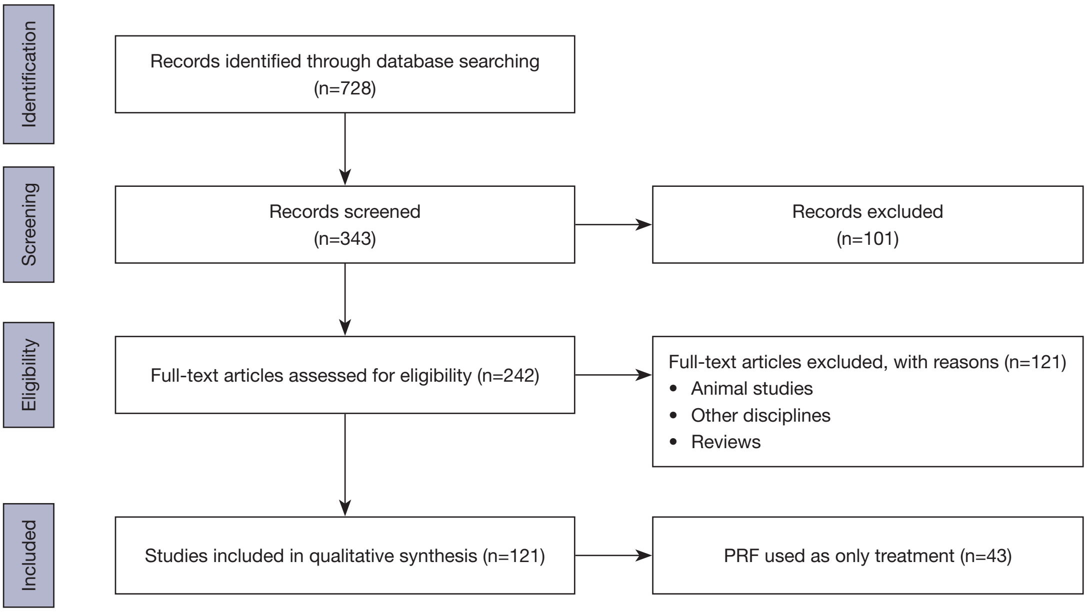

Figure 1 PRISMA flowchart of research methods. PRF, platelet-rich fibrin.

treatment in maxillofacial surgery were selected and the diagnostics of the involved subjects and the clinical results were recorded. A manual search was performed in the following relevant journals of oral and maxillofacial surgery: *International Journal of Oral and Maxillofacial Surgery*, *Journal of Oral and Maxillofacial Surgery*, *Journal of Cranio-Maxillofacial Surgery*, *Oral and Maxillofacial Surgery Clinics of North America*, *Oral Surgery Oral Medicine Oral Pathology Oral Radiology* and *British Journal of Oral & Maxillofacial Surgery*. The results were gathered in table format, analyzed and discussed. A flow chart describing the search methodology was depicted using the PRISMA template (*Figure 1*) (23).

Results

Many studies fulfilled the inclusion criteria but were excluded because they were performed in animals and/or other medical fields. A total of 121 articles were found in the literature to be eligible for qualitative evaluation (*Figure 1*). The search showed the increment of published articles beginning in 2016 and the highest pick in 2018 with 39 articles. The search gave a result of 29 different protocols of PRF involving solid/clot and liquid/injectable versions (*Tables 3*-7). Sixteen centrifuge machines were mentioned in the reviewed articles; however, the characteristics of the centrifuge machines were not always available in the literature found (*Table 8*). Additional information was gathered from the manufacturers. Our analysis of the different centrifuges revealed that the angulations of the tube within the fixed-angle centrifuge machines range from 33° to 45° and the radius maximum (r-max—distance from the center of rotation to the bottom of the tubes) from 85 to 132 mm.

Protocols of centrifugation reported with RPM

Protocols of centrifugation in a high range of RPM [3,500–2,900]

A total of 70 articles described a PRF protocol using an RPM within this range. For the solid/clot PRF, the protocol found in the literature with the highest RPM was "3,500 rpm ×12–15 min". Only one study was found using this protocol (*Table 3*). The name of the centrifuge machine was mentioned with no additional characteristics (24). Sixty [60] studies described the protocol "3,000 rpm for 10 minutes", which made it the most cited protocol in the high range of RPM. From these 60 studies, only 29 named the centrifuge machine used. In total, 12 different centrifuge machines were used to produce PRF (*Table 3*). The second most cited protocol in this range was "3,000 rpm ×12 min" (85-90). Five studies reported two different centrifuge machines and one study did not report which centrifuge was used (87). In this group, no further

Table 3 Protocols of fixed-angle centrifugation in a high range of RPM [3,500–2,900]. The protocols reported with RPM are reproducible if the centrifuge machine to be implemented is identical to the one reported by the authors

Published studies	Protocols/centrifuge
Moussa *et al.* [2016] (24)	Protocols: 3,500 rpm ×12–15 min Centrifuge: Centrifuge 800, China (24)
Dohan *et al.* [2006] (25), Aroca *et al.* [2009] (26), Sharma *et al.* [2011; 2011] (27,28), Simonpieri *et al.* [2011] (29), Tatullo *et al.* [2012] (30), Jankovic *et al.* [2012] (31), Singh *et al.* [2013] (32), Bajaj *et al.* [2013] (33), Bansal *et al.* [2013] (34), Suttapreyasri *et al.* [2013] (35), Geeta *et al.* [2013] (36), Soydan *et al.* [2014] (37), Joseph *et al.* [2014] (38), Yelamali *et al.* [2015] (39), Kumar *et al.* [2015] (40), Inchingolo *et al.* [2015] (41), Dhiman *et al.* [2015] (42), Hamzacebi *et al.* [2015] (43), Boora *et al.* [2015] (44), Shawky *et al.* [2016] (45), Ajwani *et al.* [2015] (46), Mathur *et al.* [2015] (47), Pradeep *et al.* [2015] (48), Sandhu *et al.* [2015] (49), Pradeep *et al.* [2016] (50), Doiphode *et al.* [2016] (51), Munoz *et al.* [2016] (52), Kanayama *et al.* [2016] (53), Kumar *et al.* [2016] (54), Subash *et al.* [2016] (55), Asaka *et al.* [2017] (56), Park *et al.* [2017] (57), Kanoriya *et al.* [2017] (58), Varghese *et al.* [2017] (59), Bilginaylar [2017] (60), Zhang *et al.* [2017] (61), Gülşen *et al.* [2017] (62), Goel *et al.* [2017] (63), Cömert Kılıç *et al.* [2017] (64), Pripatnanont *et al.* [2017] (65), Bajaj *et al.* [2017] (66), Patel *et al.* [2017] (67), Sharma *et al.* [2018] (68), Afat *et al.* [2018] (69), Eshghpour *et al.* [2018] (70), Asmael *et al.* [2018] (71), Bahammam *et al.* [2018] (72), Pichotano *et al.* [2018] (73), Pinto *et al.* [2018] (74), Zhou *et al.* [2018] (75), Unsal *et al.* [2018] (76), Santhakumar *et al.* [2018] (77), Nageh *et al.* [2018] (78), Mahajan *et al.* [2018] (79), Bilginaylar [2019] (80), Lv *et al.* [2018] (81), Mazzone *et al.* [2018] (82), Caymaz *et al.* [2019] (83), Diana *et al.* [2018] (84)	Protocols: 3,000 rpm ×10 min Centrifuges: (I) EBA 20 Andreas Hettich, Tuttlingen, Germany (26,35,61); (II) PC-02; Process, France (29,43); (III) REMI Laboratories, India (33,42,46-48,50,55,59,63,67); (IV) Almicro™ Instruments, India (38); (V) Centrifugette model 4206, ALC, France (41); (VI) Elektro-mag M415P, Turkey (60,80,83); (VII) NUVE NF 200, Turkey (62); (VIII) Labofuge centrifuge, Heraeus Kulze (65,70,74); (IX) Centrifuge Xiangtian, Jiangsu China (71); (X) Kasvi K140815, Curitiba, Brazil (73); (XI) Nüve Laboratory Equipments, NF200, Turkey (76); (XII) Not reported (25,27,28,30-32,34,36,37,39,40,44,45,49,51-54,56,58,64,66,68,69,72) and (75,77-79,81,82,84)
Chang *et al.* [2011] (85), Bains *et al.* [2012] (86), Dar *et al.* [2016] (87), Khan *et al.* [2018] (88), Thorat *et al.* [2017] (89), Ragab *et al.* [2019] (90)	Protocols: 3,000 rpm ×12 min Centrifuge: (I) PC-02, Process, France (85); (II) REMI Laboratories, India (86,88,89); (III) Centrifuge Model 801, China (90); (IV) Not reported (87)
Kizildağ *et al.* [2018] (91)	Protocols: 3,000 rpm ×10 min Centrifuge: EBA 20, Hettich Centrifuges, Germany (91)
Al-Ahmady *et al.* [2018] (92)	Protocols: 3,000 rpm ×20 min Centrifuge: Not reported (92)
Cortese *et al.* [2016] (93)	Protocols: 3,000 rpm ×13 min Centrifuge: Not reported (93)

characteristics of the centrifuge machines were mentioned. Four additional protocols using 3,000 rpm were found with a variation in the time of centrifugation (92-94). The search did not show protocols used to obtain liquid/injectable PRF within this range. All the studies reported the time of centrifugation, but none described the RCF-min/clot/max, the r-max or the angle of centrifugation. In this range of RPM, the study performed by Kizildağ *et al.* (91) was the only study reporting the protocol of centrifugation using RPM and RCF.

Protocols of centrifugation in a middle range of RPM (2,800–1,600)

A total of 33 articles described a PRF protocol using an RPM within this range (*Table 4*). For the solid/clot PRF, the protocol described with the highest rpm was "2,800 rpm ×12 min" obtained with 3 different centrifuge machines (94–98). Two studies reported the protocol of centrifugation but did not report the centrifuge machine used (94,95). No additional characteristics of the centrifuge machines were reported. The most cited protocol in this range was

Table 4 Protocols of fixed-angle centrifugation in a middle range of RPM [2,800–1,600]. The protocols reported with RPM are reproducible if the centrifuge machine to be implemented is identical to the one reported by the authors

Published studies	Protocols/centrifuge
Ustaoğlu *et al.* [2016] (94), Arabaci *et al.* [2017] (95), Tabrizi *et al.* [2018] (96), Pirebas *et al.* [2018] (97), Daugela *et al.* [2018] (98)	Protocols: 2,800 rpm ×12 min
	Centrifuge: (I) IntraSpin centrifuge Boca Raton, FL, USA (96); (II) Mikro 22 R Hettich Centrifugal Machine, Tuttlingen, Germany (97,98); (III) EBA 20, Andreas Hettich (98); (IV) Not reported (94,95)
Sammartino *et al.* [2011] (99)	Protocols: 2,700 rpm ×18 min
	Centrifuge: Centrifuge PRF DUO Process, France (99)
Ruga *et al.* [2011] (100), Marenzi *et al.* [2015] (101), Öncü *et al.* [2015] (102), Kotsakis *et al.* [2016] (103), Bakhtiar *et al.* [2017] (104), Kapustecki *et al.* [2016] (105), Anwandter *et al.* [2016] (106), Gönen *et al.* [2017] (107), Gurler *et al.* [2016] (108), Cortese *et al.* [2016] (93), Temmerman *et al.* [2016] (109), Öncü *et al.* [2017] (110), Sezgin *et al.* [2017] (111), Ozcan *et al.* [2017] (112), Patidar *et al.* [2017] (113), Pinto *et al.* [2017] (114), Uzun *et al.* [2018] (115), Shah *et al.* [2017] (116), Betancourt *et al.* [2017] (117), Culhaoglu *et al.* [2018] (118), Asutuay *et al.* [2017] (119), Temmerman *et al.* [2018] (120), S Medikeri *et al.* [2018] (121), Dixit *et al.* [2018] (122), Liang *et al.* [2018] (123)	Protocols: 2,700 rpm ×12 min
	Centrifuge: (I) Centrifuge PRF DUO Process, France (100,102,106); (II) PC-02, process, France (101,110,111,118); (III) Intra-Spin, Boca-Raton, FL, USA (101,104,108,109,114,120,124); (IV) Nüve Laboratory Equipments, NF200, Ankara, Turkey (115); (V) Hettich Centrifugal Machine, Tuttlingen, Germany (112); (VI) Labo-fuge® 300; Heraus GmbH, Hanau, Germany (117); (VII) REMI-8C, Laboratory (121); (VIII) Not reported (93,103,105,107,113,116,119, 122,123)
Cortellini *et al.* [2018] (124)	Protocols: 2,700 rpm/408 g ×12 min
	Centrifuge: Intra-Spin, Boca-Raton, FL, USA. r-max 5 cm (124)
Cortellini *et al.* [2018] (124)	Protocols: 2,700 rpm ×3 min
	Centrifuge: Intra-Spin, Boca-Raton, FL, USA. r-max 5 cm (124)
Choukroun *et al.* [2006] (125), Gamal *et al.* [2016] (126)	Protocols: 2,500 rpm (about 280 g) ×10 minutes
	Centrifuge: (I) Centrifuge PRF DUO Process, France (126); (II) Not reported (125)

"2,700 rpm ×12 min" with 24 studies. Seven different centrifuge machines were used to prepare PRF with this protocol. From the 29 studies, 9 did not report the centrifuge machine used (93,103,105,107,113,116,119,122,123). A second study reporting a protocol with 2700 rpm was found but with a centrifugation time of 18 minutes (99). Notably, only one study reported additionally the r-max and the RCF ("2,700 rpm/408 g ×12 min" and r-max 5 cm) (124). Three additional studies reported the protocol of centrifugation using RPM and RCF—"2,500 rpm (about 280 g) ×10 minutes" (125,126). Furthermore, one study was found reporting a liquid/injectable PRF protocol (2,700 rpm ×3 min) in this range of centrifugation with a considerable lower time (124). Similarly, to the aforementioned range, all of the studies reported the time of centrifugation, but only one described the RCF and the r-max of the rotor (124). None of the studies reported the angle of centrifugation.

Protocols of centrifugation in a low range of RPM [1,500–700]

A total of 6 articles described a PRF protocol using RPM within this range (83,127-131) (*Table 5*). For the solid/clot PRF, the most cited protocol found was "1,500 rpm × 14 min". Two studies were found using this protocol. The search showed an additional protocol using 1,500 rpm but with 8-min centrifugation. This study did not report the centrifuge machine used (128). Three additional studies reported a protocol using the same RPM, centrifuge machine but a different time of centrifugation ["1,300 rpm ×14 min" (129) and "1,300 rpm ×8 min" (130,131)]. Additionally, three studies reported two different protocols to obtain liquid/injectable PRF within this range. The protocol with the highest RPM was "1,300 rpm ×5 min" (143) followed by a protocol with a lower RPM and time of centrifugation—"700 rpm ×3 min" (130,131). One of the studies from the liquid/injectable PRF

Table 5 Protocols of fix-angle centrifugation in a low range of RPM (1,500–700). The protocols reported with RPM are reproducible if the centrifuge machine to be implemented is identical to the one reported by the authors

Published studies	Protocols/centrifuge
Lei *et al.* [2019] (127), Caymaz *et al.* [2019] (83)	Protocols: 1,500 rpm ×14 min
	Centrifuge: (I) Centrifuge PRF DUO Process, France (127); (II) Elektro-mag M415P, Istanbul, Turkey (83)
Demetoglu *et al.* [2018] (128)	Protocols: 1,500 rpm ×8 min
	Centrifuge: Not reported (128)
Nørholt *et al.* [2016] (129)	Protocols: 1,300 rpm ×14 min
	Centrifuge: Centrifuge PRF DUO Process, France (129)
Chenchev *et al.* [2017] (130), Fortunato *et al.* [2018] (131)	Protocols: 1,300 rpm ×8 min
	Centrifuge: Centrifuge PRF DUO Process, France (130,131)
Chenchev *et al.* [2017] (130), Fortunato *et al.* [2018] (131)	Protocols: 700 rpm ×3 min
	Centrifuge: Centrifuge PRF DUO Process, France (130,131)

Table 6 Protocols of fixed-angle centrifugation reported with g force in a high (1,000–878 g)/middle (500–208 g)/low (60 g) range. The protocols reported with g-force can be reproduced in any adjustable centrifuge machine

Published studies	Protocols/centrifuge
Lekovic *et al.* [2012] (132)	Protocols: 1,000 g ×10 min
	Centrifuge: Labofuge 300; Heraus GmbH, Hanau, Germany (132)
Olgun *et al.* [2018] (133)	Protocols: 878 g ×12 min
	Centrifuge: Mikro 22R Hettich Centrifugal Machine, Tuttlingen, Germany (133)
Choukroun and Ghanaati [2018] (134)	Protocols: 710 g ×8 min
	Centrifuge PRF DUO Process, France (134)
Meza *et al.* [2019] (135)	Protocols: 500 g ×12 min
	Centrifuge: Intra-Spin, Boca-Raton, FL, USA (135)
Thorat *et al.* [2011] (136), Peck *et al.* [2011] (137), Agarwal *et al.* [2014] (138), Bolukbasi *et al.* [2015] (139), Nizam *et al.* [2018] (140), de Almeida Barros Mourão *et al.* [2018] (141)	Protocols: 400 g ×12 min
	Centrifuge: (I) PLC-03, Hi-care International, Taiwan (137); (II) Centrifuge PRF DUO Process, France (139); (III) Nüve Laboratory Equipment, Turkey (140); (IV) Montserrat®, São Paulo, Brazil (141); (V) Not reported (136,138)
Lorenz *et al.* [2018] (142)	Protocols: 208 g ×8 min
	Centrifuge: Centrifuge PRF DUO Process, France (142)
Nacopoulos *et al.* [2019] (143)	Protocols: 208 g ×5 min
	Centrifuge: Centrifuge PRF DUO Process, France (143)
Choukroun and Ghanaati [2018] (134)	Protocols: 177 g ×8 min
	Centrifuge PRF DUO Process, France (134)
Lorenz *et al.* [2018] (142), Nacopoulos *et al.* [2019] (143)	Protocols: 60 g ×3 min
	Centrifuge: Centrifuge PRF DUO Process, France (142)
Choukroun and Ghanaati [2018] (134)	Protocols: 44 g ×8 min
	Centrifuge PRF DUO Process, France (134)

Table 7 Protocols of horizontal centrifugation reported with g force. The protocols reported with g-force can be reproduced in any adjustable centrifuge machine

Published studies	Protocols/centrifuge
Miron *et al.* [2020] (144)	Protocols: 400–700 g ×8 min
	Eppendorf 5702 horizontal centrifuge (Hamburg, Germany) (144)
Miron *et al.* [2020] (144)	Protocols: 200–400 g ×5 min
	Eppendorf 5702 horizontal centrifuge (Hamburg, Germany) (144)

Table 8 Characteristics of the centrifuge machines

Centrifuges	Radius (r-max)	Fixed-angle/horizontal
PC-02, Process, France	88 mm	Fixed-angle—33°
Intra-Spin Boca-Raton, FL, USA	85 mm	Fixed-angle—33°
Centrifuge PRF DUO Process, France	110 mm	Fixed-angle—41.3°
EBA 200 Centrifuge, Andreas Hettich, Tuttlingen, Germany	≈86 mm	Fixed-angle—33°
PLC-03, Hi-care International, Taiwan	NR	NR
Labofuge 300; Heraus GmbH, Hanau, Germany	NR	NR
REMI Laboratories, India	NR	NR
Almicro™ Instruments, India	NR	NR
Centrifuge 800, China	NR	NR
Elektro-mag M415P, Istanbul, Turkey	90 mm	Fixed angle—35°
Nüve Laboratory Equipments, NF200, Turkey	101 mm	NR
Mikro 22R Hettich Centrifugal Machine, Germany	≈86 mm	Fixed angle—35°
Kasvi K140815, Curitiba, Brazil	103 mm	Fixed-angle—36°
Montserrat®, São Paulo, Brazil (Modelo 80-2B)	130 mm	Fixed-angle—45°
Eppendorf 5702 horizontal centrifuge (Hamburg, Germany)	132 mm	Horizontal
Centrifuge Xiangtian, Jiangsu China	NR	NR

Data was extracted from the analyzed papers and from the manufacturer's information. NR, not reported.

reported the RCF (×g) and the r-max of the centrifuge (143). All the studies reported the time of centrifugation; one described the RCF (×g) and the r-max, but none of the studies reported the angle of centrifugation.

Protocols of centrifugation reported with g-force

Protocols of centrifugation in a high (1,000–700 g)/ middle (500–208 g)/ low (60–44 g) range of g-force

A total of 13 articles described a PRF protocol using g-force (*Tables 6*,*7*). Two from these did not report the centrifuge machine used (136,138). Two studies described two different protocols of centrifugation of solid/clot PRF in the high range using a fixed-angle centrifuge (132,133) or horizontal centrifugation (144). The protocol with the highest g-force was "1,000 g × 10 min" (132). The three studies reported the name of the centrifuge machine without further characteristics. In the middle range of centrifugation, 10 studies reported 4 different protocols of centrifugation. The highest protocol reported was 500 g × 12 min (135). Six studies reported using 400 g with 12 min of centrifugation and one with 8 min. Four different centrifuge machines were named in this range to produce PRF. Although two studies reported the use of 280 g for the CP, the centrifugation time differed (142,143). In high and middle range, none of the protocols were used to produce liquid/injectable PRF. In the low range, three studies were found reporting the protocols 60 g × 3 min and 44 g × 8 min. to produce liquid/injectable PRF (134,142,143). Both studies named the same centrifuge machine without further characteristics. All the studies reported the time of centrifugation and only one study reported the radius of the rotor of the centrifuge machine (143).

Time of centrifugation

The articles included in the review described the time (min) used for the centrifugation of PRF with a broad variability. The highest times reported were 20 and 18 min of centrifugation. These times of centrifugation were reported by only 2 articles (92,99). A similar exception was also observed with 15 min and 13 min of centrifugation with only 2 articles reporting its use (24,93). The most reported times of centrifugation to obtain solid PRF were 14 min in 2 protocols (2 articles), 12 min in 9 protocols (44 articles), 10 min in 4 protocols (64 articles) and 8 min in 6 protocols (3 articles) (*Tables 4-7*). The protocols with lower times of centrifugation were implemented to obtain liquid PRF. The lowest time used were 5 min in 1 article and 3 min in 4 articles.

Tube's size and material

In general, the solid/clot PRF are prepared with empty glass-coated tubes and silica-coated plastic tubes. The liquid/injectable PRF are prepared with empty plastic tubes without additive. Additionally, 4 studies were found describing the use of titanium tubes to prepare solid/clot PRF (94,97,115,133). The search also showed a variety of tube sizes used to produce PRF. The size most commonly used was 10mL, nonetheless, different sizes were found ranging from 5 to 15 mL tubes.

Clinical applications of PRF in oral and maxillofacial surgery

In total, 43 studies were found reporting to have used PRF as a sole treatment. From these, 29 were controlled studies compared to natural wound healing (https://cdn.amegroups.cn/static/public/fomm-21-40-1.pdf). The pathologies treated were socket preservation, implant stability and bone regeneration, reduction of pain and swelling, sinus lift, management of bisphosphonate-related osteonecrosis of the jaw, closure of oroantral communication, filling of bone defects with PRF after cyst debridement, enhancement of soft tissue healing and management of pain, haemostatic control of patients with anticoagulant oral therapy and bone augmentation procedures. Forty studies reported positive outcomes with statistical improvement in the groups treated with PRF. PRF was implemented the highest to enhance soft tissue healing (8 articles), and to increase implant stability by inducing bone regeneration (7 articles). Three studies investigating the reduction of pain and swelling implemented CPs in the high (3,000 rpm × 10 min) and middle range (2,700 rpm × 12 min) and did not observed statistically significant reduction of pain between the PRF and control groups (62,69,119). However, one additional study using a CP in the high range reported statistically significant reduction of pain and swelling the first post-operative day compared to control (40). 24 CPs reported in RPM and 2 in RFC (×g) were implemented within the high, middle and low range. The treatment with the highest diversity of CPs [RPM/RCF (×g)/time] was the enhancement of soft tissue healing, in which the use of solid/clot and liquid/injectable was reported. This was followed by implant stability and bone regeneration, where 4 different CPs were implemented.

Discussion

In recent years, the use of PRF in dentistry and maxillofacial surgery has broaden. The constant introduction of new protocols, i.e., most recently horizontal centrifugation, and without enough time for the new knowledge to settle in, omission to report the CPs correctly continue to be a burden for the scientific community. During the review, some difficulties were encountered in order to obtain all the information related to the protocols. A handmade search was necessary in order to complete the information needed to describe the protocols available. Additionally, when necessary, the corresponding authors were contacted to request additional information. Nevertheless, the limited number of data sources and the manually checked journals can be considered a limitation of the study. The results of this work showed a great heterogeneity in the reported protocols, patients characteristics and pathologies treated. Although there are *in vitro* and *in vivo* studies demonstrating the superiority of PRF CPs over others, concerning cellular proliferation, osteogenic differentiation and vascular

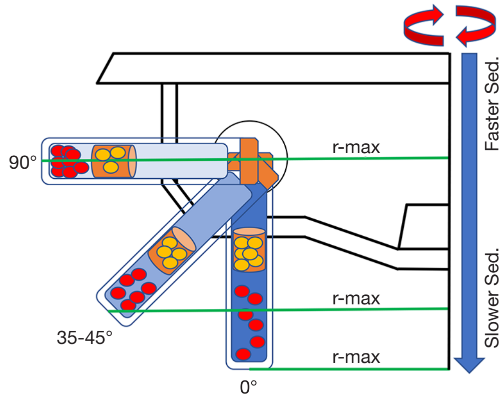

Figure 2 Angle/Radius-max. By changing the angle of centrifugation from 0° to 90° the distance from the rotor to the bottom of the tube increases (green line). This increases the g-force and its effect over blood components (red circles: erythrocytes and yellow circles: platelets) and the speed of sedimentation. The position and the content of the PRF clot in the tube can vary (orange). PRF, platelet-rich fibrin.

Table 9 Mathematical equations to calculate the relative centrifugation force

$$RCF = 1.12 \times r \times \left(\frac{RPM}{100}\right)^2$$

$$g - Force = \left(RPM\right)^2 \times 1.18 \times 10^5 \times r$$

$$RPM - rmax\text{:} \sqrt{\left[\frac{RCF}{r \times 1.18}\right]} \times 1 \times 10^5$$

RCF (×g) = relative centrifugation force, RPM = revolutions per minute. rmax = radius of rotor measured from the axis of the rotor to the base of the tube expressed in cm.

formation, this research did not find such a clinical study (145,146). Furthermore, studies with a high scientific evidence (i.e., clinical trials) comparing the superiority of one single CP to treat one specific pathology were not found, and therefore recommendations cannot be made in this regard. Further studies are needed to understand whether other components in this cell concentrate, not affected or slightly affected by the CP, are playing a pivotal role in its tissue regeneration capacity. For this reason, this work introduces the AR^2T^3 acronym. The acronym includes all principles that affect PRF through centrifugation and can serve as an instrument to increase the understanding of PRF and its reproducibility in future studies.

The AR^2T^3 principles to report the centrifugation of Platelet concentrates

Angle/Radius maximum (r-max)

The angulations in which the tube is centrifuged and the r-max significantly affects the g-force applied to the tube (*Figure 2*). For example, based on the mathematical formulas stated in *Table 9* (147), a slight increase in the r-max will significantly increase the g-force, ultimately affecting the final PRF generated in terms of cell content, size of clot, the distribution of the cells within the clot and indeed the entire morphology of the PRF clot. This was assessed by Miron *et al.* who recently described that horizontal centrifugation yielded PRF with more accumulations of leukocytes and platelets in comparison to the PRF produced via the fixed-angled technique (144).

As shown by the results of this review, the majority of the studies failed to report the angulation of the tubes and the radius of the rotor (*Tables 3-7*). It is therefore essential that future research in this field clearly states the tube angulation and the radius of the rotor of the centrifuge to ensure uniformity of reports and reproducibility of the protocols by other authors.

RCF (g)

For a PRF study to be reproducible, it needs to include the specifications of a precise centrifugation conditions in terms of RCF expressed in units of gravity (×g) (148) (*Figure 3*). A higher g-force exerted over the blood components, increases its sedimentation speed in the blood plasma according to each blood component's mass (e.g., white blood cells and red blood cells). The fragmentation of blood gives as a result a PRF clot. If the RCF changes, the fragmentation ratio of all blood components changes and consequently the content of PRF. A clinician can always control the RPM in the available centrifuges. But the table centrifuge machines have normally a fixed radius, as observed in many of the papers reviewed. The radius and the angle can vary in different brands of commercially available centrifuges (*Table 8*). If a clinician tries to reproduce one of the protocols collected in this review with a centrifuge machine where the radius and angle at which the tubes spin differ from the original article, the content of the PRF clot will differ.

It is also important to note that the g-force should always be calculated at the RCF-max as this can be easily standardized and reproduced as opposed to calculating it at RCF-clot which can alter depending on many factors as

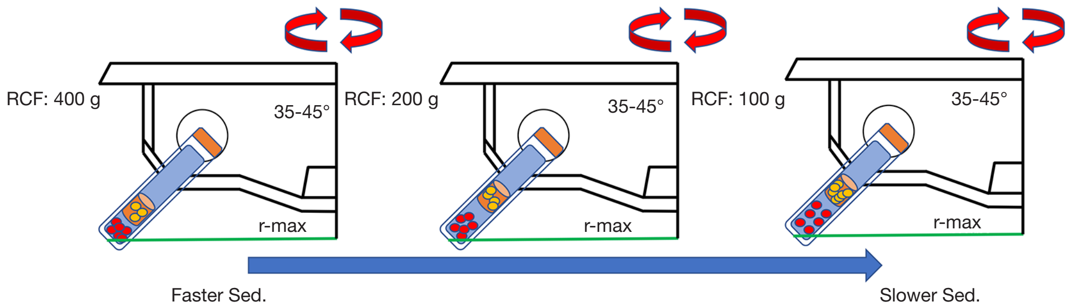

Figure 3 RCF. Increasing the RCF (×g) (e.g., from 100 to 400 g) accelerate the sedimentation of blood components (red circles: erythrocytes and yellow circles: platelets). The position and the content of the PRF clot in the tube can vary (orange). RCF, relative centrifugation force; PRF, platelet-rich fibrin.

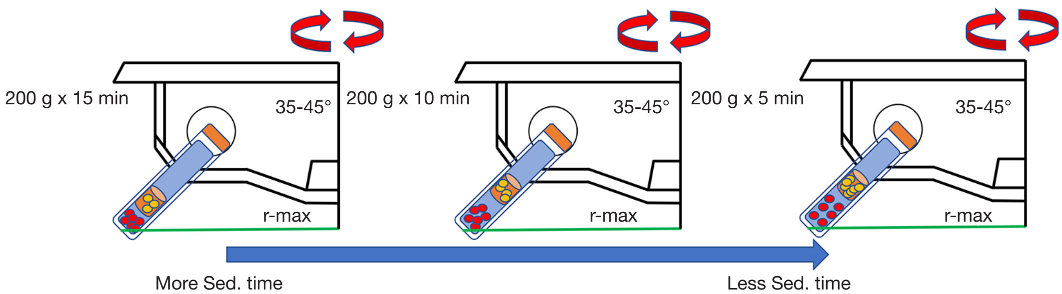

Figure 4 Time of centrifugation. Modifying the time of centrifugation modifies also the time the g-force influences blood components. A higher time means a higher number of blood components (red circles: erythrocytes and yellow circles: platelets) are going to deposit at the bottom of the tube. This will give as a result a clot with lower number of cells.

elucidated by Miron *et al.* (149) and Ghanaati *et al.* (150) in their recent reviews. They were able to point out that the RPM, time, angle of the tube and the rotor size affect the position of the clot and therefore a change in these variables will lead to changes in the g-force. Additionally, they opined that the differences in the packed cell volume (PCV) levels of individual subjects could also lead to varying positions of clot formation along the tube during PRF collection. Therefore, to avoid all these errors in wrongly reporting the RCF, it is safest to report the g-force at the RCF-max i.e. at the end of the tube, which is a constant measurement, differently to the RCF-clot. Putting all these factors into consideration will ensure future reproducibility of research methodologies.

Time of centrifugation (T)

The time of centrifugation determines the distance the cells travel within the tube. The development from advanced PRF (A-PRF) to advanced PRF-plus (A-PRF$^+$) is an example of the principle. The A-PRF and A-PRF$^+$ protocols have the same RPM and RCF using an 11 cm radius rotor with a fixed-angel, but the time was reduced, causing a greater concentration of white blood cells to remain higher in the PRF clot (*Figure 4*) (18). Increasing the centrifugation time and speed leads to the formation of a larger size PRF clot. Nevertheless, the clot formed in this instance has been shown to contain less cells and growth factors (40). By reducing the RCF, a higher content of cells was found in the solid and liquid versions of PRF. The description of this natural behavior was called the Low Speed centrifugation concept (LSCC). A lower RCF slows the sedimentation speed and might result in a smaller PRF clot and a reduced fraction of liquid/injectable PRF. On the other hand, a lower RCF produces clots with evenly distributed platelets and a higher concentration of growth factors. This has already been described by previous studies who postulated that reducing the RCF and thereby using the so-called LSCC, they were able to selectively increase the accumulation of leukocytes, platelets and growth factors within the injectable PRF (9,151). This approach, according to the studies cited

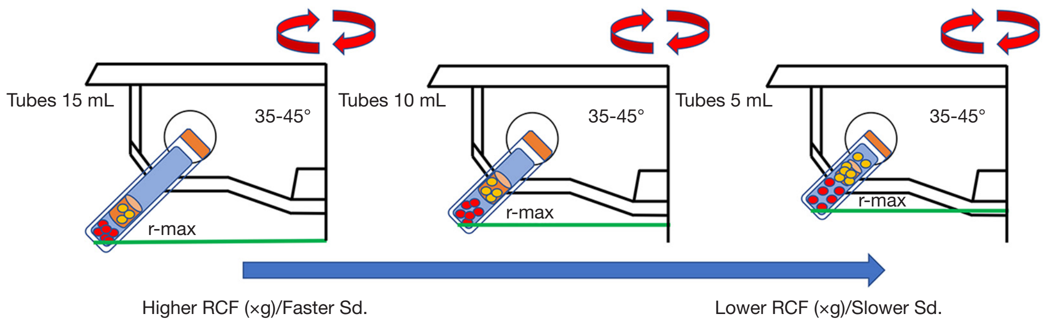

Figure 5 Size of the tube. A longer tube will translate in a larger distance between the bottom of the tube and the rotor of the centrifuge machine, giving as result a higher radius-max. RCF, relative centrifugation force.

above, may improve the regenerative potential of PRF.

Tubes size and characteristics

The search showed three different types of tubes to produce solid/clot PRF and one to produce liquid/injectable PRF (94,97,115,133) (*Figure 5*). A recent study showed that the characteristics of the tubes determine the quality of the solid/clot of PRF independently of the protocol used (43). References about the use of a titanium tube were found in the literature. It is hypothesize that the titanium tubes may be more effective in activating platelets and reducing the risk of silicosis caused by silica-coated tubes (152). In order to confirm this hypothesis further studies are necessary. In the case of the liquid/injectable PRF, the community seems to have reached a consensus on the use of plastic tubes. Furthermore, during the review it was observed that a variety of tube sizes ranging from 5 to 15 mL are being used. The tube's size determines the final r-max, which is measured by measuring the distance from the rotational axis of the centrifuge to the bottom of the tube. In this sense, a shorter tube results in a shorter r-max and lower RCF (×g) (*Figure 5*). Up to date, systematic studies characterizing PRF have been performed using mainly 9 or 10 mL tubes. However, in smaller tubes, cells require less time to sediment at the bottom of the tube and the cell content is altered.

Taken all into consideration, to systematically conduct research on platelets concentrate with reproducible results, the angle of the rotor, r-max, RPM (×g), time of centrifugation, size and characteristics of the tubes need to be specified (AR^2T^3). Modification of these 6 components could give innumerous combinations of platelet concentrates to researchers with the option to develop direct therapies toward specific pathologies. Furthermore, the use of the acronym will allow the elaboration of meta-analyses and guidelines that are not yet available due to the heterogeneity of the data. Moreover, it will help unmask whether or not there is any significance in further fine-tuning the platelet concentrates, or if there are variables that are not yet taken into consideration. Noteworthy, the protocols of centrifugation reported in RPM are only reproducible if the clinician is using exactly the same centrifuge machine reported by the author of the protocol. On the contrary, protocols reported on g-force can be adjusted to any type of centrifuge. This applies for vertical and horizontal centrifugation.

Three mathematical equations can be found in the literature that allow clinicians to calculate missing data from previous articles and achieve reproducible PRF results in any centrifuge machine available to them (see *Table 9*). Finally, we provide a template to report protocols of platelet concentrates according to the AR^2T^3 principles: "PRF was centrifuged using a table-top centrifuge (Name of the centrifuge machine; angle X°, X cm radius-max) following a standardized protocol described by X *et al.* (X rpm, X g, X min). Blood was withdrawn according to the best practices in phlebotomy into X-mL sterile (characteristic of the tube; plastic, glass or titanium) tubes (Name of the manufacture). This protocol was reported following the AR^2T^3 acronym" (see example in *Table 10*).

Conclusions

The centrifugation protocol (CP) is one of the most important steps in the generation of PRF as it affects the final characteristics. The present review analyzed CPs used in oral and maxillofacial surgery. The findings indicate that many authors and researchers gave incomplete details

Table 10 Reporting the production of PRF implementing the AR^2T^3 acronym

	Low RCF	Middle RCF	High RCF
AR^2T^3 (solid)			
A	41.3°	41.3°	41.3°
R	11 cm	11 cm	11 cm
R	44 g	177	710
T	8 min	8 min	8 min
T	10 mL	10 mL	10 mL
T	Glass	Glass	Glass
AR^2T^3 (liquid)			
A	41.3°	41.3°	41.3°
R	11 cm	11 cm	11 cm
R	44 g	177	710
T	8 min	8 min	8 min
T	10 mL	10 mL	10 mL
T	Plastic	Plastic	Plastic

Protocol: the "Low Speed Centrifugation Concept (LSCC)"; Centrifuge: PRF DUO Process. PRF, platelet-rich fibrin; RCF, relative centrifugation force.

regarding the centrifugation machines and the protocols used in obtaining their PRF samples. In fact, only a few of the reviewed articles gave enough information that could make their works reproducible by other researchers. This paucity of detailed reporting has led to various errors in methodologies with some variables like g-force being wrongly calculated and applied, thereby leading to misinformation as to the correct g-force applied during centrifugation. This review has therefore exposed three mathematical equations that can be used by PRF researchers and clinicians in the future to calculate all the missing variables in any previous incomplete research methodology thereby ensuring accurate reporting and duplication of the methods. Additionally, it is here proposed the AR^2T^3 acronym as a guide for all authors in the field of platelet concentrates to ensure uniformity in reporting of the protocols. Adherence to this recommended guideline will ensure uniformity of the CP and harmonization in the field.

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Footnote

Reporting Checklist: The author has completed the PRISMA reporting checklist. Available at https://fomm.amegroups.com/article/view/10.21037/fomm-21-40/rc

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at https://fomm.amegroups.com/article/view/10.21037/fomm-21-40/coif). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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