

# Systematic Review of Platelet-Rich Plasma for Rotator Cuff Repair

## Are We Adhering to the Minimum Information for Studies Evaluating Biologics in Orthopaedics?

Madeleine G. DeClercq,\* BSc, Alyson M. Fiorentino,\* BA, Haylie A. Lengel,<sup>†</sup> BSc, Joseph J. Ruzbarsky,<sup>†</sup> MD, Sara K. Robinson,\* MS, Verena T. Oberlohr,\* BSc, Kaitlyn E. Whitney,\* BSc, Peter J. Millett,<sup>†</sup> MD, MS, and Johnny Huard,\*<sup>‡</sup> PhD

*Investigation performed at the Steadman Philippon Research Institute, Vail, Colorado, USA*

**Background:** The therapeutic efficacy of orthobiologic therapies for rotator cuff repair is difficult to evaluate owing to reporting inconsistencies. In response, the Minimum Information for Studies Evaluating Biologics in Orthopaedics (MIBO) guidelines were developed to ensure standard reporting on orthobiologic therapies.

**Purpose:** To systematically review clinical studies evaluating platelet-rich plasma (PRP) for full-thickness rotator cuff repair and adherence to MIBO guidelines.

**Study Design:** Scoping review; Level of evidence, 4.

**Methods:** A search was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines using PubMed, EMBASE, and the Cochrane Library databases. Inclusion criteria were clinical studies reporting on rotator cuff tears ( $\geq 1$  cm) surgically repaired with PRP. Patient demographics, biologic intervention, and adherence to the MIBO guidelines were systematically reviewed.

**Results:** A total of 19 studies (1005 patients) were included in this review. Across all studies, 58.5% of the MIBO checklist items for PRP were reported. Out of 47 checklist items, 19 were reported in over 85% of studies, whereas 22 were reported in less than half of studies. Details of whole-blood processing and characteristics, as well as PRP processing and characteristics, were reported inconsistently, and no study provided adequate information to enable the precise replication of preparation protocols for PRP.

**Conclusion:** This systematic review highlights the current reporting deficiencies within the scientific literature of important variables for evaluating PRP for full-thickness rotator cuff repair. There was widespread variability among published studies that evaluate PRP for this application and, more specifically, studies were limited by inconsistent universal reporting of whole-blood and PRP processing and postprocessing characteristics. To improve our understanding of biologic efficacy and to promote repeatability, stricter adherence to the MIBO guidelines is necessary. We propose that the checklist limitations be addressed and that modification of the MIBO guidelines be considered to improve the reporting of individual components within certain categories.

**Keywords:** Minimum Information for Studies Evaluating Biologics in Orthopaedics (MIBO); platelet-rich plasma (PRP); rotator cuff repair

Wear and tear of the rotator cuff is a common cause of shoulder pain in orthopaedic medical practice, affecting 9.7% of patients aged 20 years and younger and at least 30% to 50% of people older than 50 years.<sup>1,48,49</sup> Despite numerous improvements in technology and progressive arthroscopic techniques, retear rates and repair failures still occur.<sup>39</sup> In an attempt to decrease failure rates, platelet-rich plasma (PRP) is often augmented in

arthroscopic and open rotator cuff repair.<sup>5,36</sup> In fact, rotator cuff repair has become the third leading application of PRP use, just behind meniscal repair and other shoulder pathologies.<sup>5</sup>

PRP is a plasma-based product that is enriched with platelets and elevated or reduced white blood cell concentrations. It is thought that a high concentration of platelets degranulates essential growth factors that promote healing at the site of injury, particularly in areas with less blood flow.<sup>53</sup> To this end, a study found that long-term retear rates were decreased significantly in patients with rotator cuff-related abnormalities who received PRP.<sup>7</sup> In addition,

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the normal tendon-bone insertion site has been shown to be mechanically inferior to the native rotator cuff due to the development of scar tissue rich in type III collagen.<sup>21,27</sup> The inability to regenerate calcified cartilage formed during embryogenesis may reflect the failure of appropriate molecular signaling and cell differentiation at the site of injury.<sup>27</sup> Treatment strategies that encourage tissue regeneration and tendon-bone healing (as opposed to scarring) is an appealing approach to optimizing surgical rotator cuff repair and improving of patient outcomes.<sup>21</sup> However, there is a paucity of clinical data to support this treatment modality for clinical use. Two recent meta-analyses, which included a total of 1586 patients across 23 studies published between 2011 and 2018, concluded that PRP use significantly reduced the retear rate in small, medium, and large rotator cuff tears.<sup>4,54</sup> Despite the probable efficacy of PRP for rotator cuff repair, there are several variables associated with the treatment, often confounding specific clinical recommendations.<sup>33,45</sup>

In contemporary literature, the preparation of PRP adjuvants is extremely varied, and this can have a significant impact on treatment results and build on existing clinical challenges in establishing recommendations and guiding clinical decisions. For example, Mazzocca et al<sup>33</sup> observed significant variation in platelet concentration across 3 time points (0, 14, and 30 days) in the same 8 patients. Variation between individuals can affect the concentration of platelets received for the preparation of the PRP product. A patient with a low normal baseline count may receive a lower concentration of platelets in the PRP product compared with a patient with a high normal baseline count, despite the clinical recommendation of 1 million platelets in a PRP preparation.<sup>11</sup> These observations suggest that, even when preparation protocols are properly documented and reported, individual patients do not have consistent platelet counts in PRP.<sup>45,46,56</sup>

It is also important to highlight that there is very little known about the concentration of platelets and growth factors that are necessary for therapeutic use. In fact, LaPrade et al<sup>28</sup> found that a concentration of approximately 1 million platelets (4-fold difference from baseline count) negatively affected ligament repair, suggesting that there is a dose response to platelets during tissue regeneration and repair. Taking this information into account, there are several factors that cause PRP product variation in blood cell concentrations (ie, platelets, white blood cells), as well as growth factor concentrations,<sup>15</sup> regardless of the protocol used. Nonetheless, reporting on components of the preparation, delivery, and outcomes of PRP for full-thickness

rotator cuff repair is necessary, but of minimal value if not reported adequately.

In response to clear evidence of defective reporting methodologies, the American Academy of Orthopaedic Surgeons created the Minimum Information for Studies Evaluating Biologics in Orthopaedics (MIBO) guidelines for the use of PRP in orthopaedic treatment.<sup>37,38</sup> The MIBO guidelines are a checklist of critical reporting items that are suggested to be included in every manuscript submitted to a journal for publication. Consisting of 12 categories and 23 statements, this checklist ensures adequate assessment of orthobiologics as well as efficacy and reproducibility of the protocols used to produce autologous biologic therapies. Adherence to MIBO guidelines would promote increased transparency, reproducibility, and clinical evaluation capabilities.<sup>37,38</sup> A standardized reporting protocol will facilitate adequate comparison between orthobiologic products in full-thickness rotator cuff repair to improve understanding of their safety and efficacy and guide future use.

Based on this information, the purpose of this systematic review was to determine the overall adherence to MIBO guidelines of articles published on full-thickness rotator cuff repair augmented with autologous PRP. This information will provide knowledge that will help to assess discrepancies in evaluating and reporting on the use of orthobiologics. We hypothesized that adherence to MIBO guidelines would be varied and deficient.

## METHODS

### Search Strategy

This systematic review was performed in accordance with the PRISMA (Preferred Reporting Items for Systemic Reviews and Meta-Analyses) guidelines. A literature search was conducted using PubMed, EMBASE, and the Cochrane Library databases on February 20, 2020. Search terms included: (platelet-rich plasma OR PRP OR Platelet) AND (Rotator cuff OR Rotator cuff repair OR Rotator cuff tear). The following Medical Subject Headings (MeSH) terms were also searched in all 3 databases: ("Platelet-Rich Plasma"[MeSH] OR "Blood platelets"[MeSH] OR "Blood platelets"[MeSH]) AND ("Rotator Cuff"[MeSH] OR "Rotator Cuff Tear Arthroscopy"[MeSH] OR "Rotator Cuff Injuries"[MeSH]).

After the removal of duplicates, the titles and abstracts were screened by 2 reviewers independently (M.G.D. and H.A.L), and potentially eligible studies received a full-text review. Any discrepancies between authors were resolved

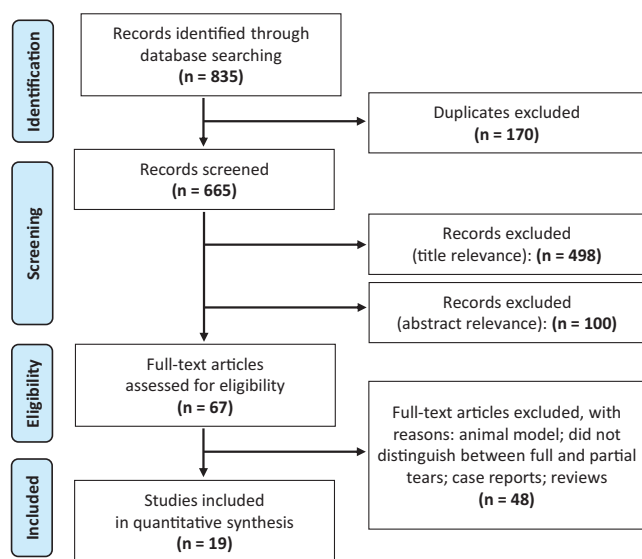
†Address correspondence to Johnny Huard, PhD, Steadman Philippon Research Institute, 181 West Meadow Drive, Vail, CO 81657, USA (email: jhuard@sprivaiv.org).

\*Center for Regenerative Sports Medicine, Steadman Philippon Research Institute, Vail, Colorado, USA.

†The Steadman Clinic, Vail, Colorado, USA.

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**Figure 1.** PRISMA (Preferred Reporting Items for Systemic Reviews and Meta-Analyses) guidelines for article inclusion. This diagram demonstrates the systematic review process performed in this study.

by a third reviewer (K.E.W.). All references were cross-referenced to avoid omitting relevant studies.

### Eligibility Criteria

Studies were included if they reported on rotator cuff tears  $\geq 1$  cm that were surgically repaired with the addition of PRP. Articles were excluded if they reported on any of the following: (1) full-thickness rotator cuff tears that were not surgically repaired, (2) rotator cuff repairs without the use of PRP, (3) treatment with platelet-poor plasma, (4) manufactured or allogeneic biologics, (5) cadaveric studies, (6) animal studies, (7) technical notes, (8) reviews, and (9) abstract-only articles.

A total of 835 studies were identified by the initial literature search. After removal of duplicates, 665 remained. After the titles and abstracts were screened, the full-text review was conducted on 67 publications. The most common reasons for exclusion at this level were nonsurgical interventions, partial-thickness tears, tear size, wrong biologic intervention, and no distinction between full-thickness and partial-thickness tears in the results. In total, 19 studies were included in this systematic review (Figure 1).<sup>§</sup>

### Data Extraction and Analysis

Relevant information regarding the study characteristics, including the study design, the level of evidence, mean follow-up time, and type of intervention was collected by 4 independent reviewers using a predetermined data sheet (M.G.D., H.A.L., A.M.F., V.T.O.). Four studies did not report level of evidence,<sup>30,32,44,52</sup> so it was determined based

on the Oxford Centre for Evidenced-Based Medicine guidelines.<sup>16</sup> Adherence to the MIBO guidelines was recorded for each study. We separated the original 23 checklist items into 47 checklist items of different point values (Table 1). Each article was scored from 0 to 1, awarding 1 point if the study reported information that pertained to the checklist item or 0 if nothing was reported. Partial points (0.5) were assigned for checklist items 5.2a, 5.2b, 7.4a, 7.4b, 12.3a, and 12.3b. Of note, if a study reported that there were no complications, the article received a zero for checklist item 12.3a. Although not a MIBO guideline, body mass index (BMI) reporting was collected for each study, but 0 points were given for recording BMI. The maximum score an article could receive on the modified MIBO was 40 points.

When calculating averages across groups, a weighted mean formula was used  $\left( = \frac{mean_1 * n_1 + mean_2 * n_2 + \dots}{n_1 + n_2 + \dots} \right)$  to account for the varying number of patients in each group.

### Quality Assessment

The modified Coleman Methodology Score was used to assess the quality of each study by 2 independent reviewers (V.T.O., J.J.R.).<sup>9,40</sup> Each study was given a score between 0 and 100 based on 11 criteria. Studies were considered to be of excellent quality if they scored 85 to 100, good quality if they scored 70 to 84, fair quality if they scored 55 to 69, and poor quality if they scored less than 55.<sup>9</sup>

## RESULTS

### Study Characteristics and Patient Demographics

The characteristics of the 19 included studies are reported in Table 2. There were a total of 1005 patients (481 male; 44.9%). All included studies were conducted between 2008 and 2019, with levels of evidence ranging from 1 to 4. The average modified Coleman Methodology Score was  $79.73 \pm 8.11$ , indicating good quality.

### MIBO Reporting Adherence

Studies reported information on 58.5% of the MIBO variables that should be reported by clinical studies evaluating PRP for the treatment of musculoskeletal conditions. The MIBO checklist items with adequate reporting are demonstrated in Figure 2. Compliance with the MIBO guidelines per category is shown in Figure 3.

**Study Design.** Of the 19 included studies, 11 (57.9%) were conducted in accordance with the CONSORT (Consolidated Standards of Reporting Trials) and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines<sup>||</sup>; 16 studies (84.2%) documented whether institutional or ethical approval had been granted to complete the study.<sup>¶</sup>

<sup>§</sup>References 2, 6, 10, 14, 17, 18, 23-25, 27, 30, 32, 33, 43-45, 52, 54, 57.

<sup>||</sup>References 2, 10, 14, 23, 24, 29, 31, 42, 43, 50, 55.

<sup>¶</sup>References 6, 10, 14, 17, 18, 23, 24, 29-32, 42-44, 50, 55.

TABLE 1  
Modified MIBO Checklist Items<sup>a</sup>

Item and Description (Points Awarded)	Item and Description (Points Awarded)
1 Study design	7 PRP processing
1.1 Conducted in accordance with CONSORT, STROBE, or PRISMA guidelines (1)	7.1 Commercial kit details (1) <sup>b</sup>
1.2 Relevant institutional and ethical approval (1)	7.2 Spin protocol (1) <sup>b</sup>
2 Patient demographics	7.3 Platelet recovery rate of protocol (1)
2.1 Age (1) <sup>b</sup>	7.4 PRP storage environment
2.2 Sex (1) <sup>b</sup>	7.4a Temperature (0.5) <sup>b</sup>
2.3 BMI (0) <sup>c</sup>	7.4b Light exposure (0.5) <sup>b</sup>
2.4 Use of current anti-inflammatory or antiplatelet medications (1)	7.5 Time between blood drawing and PRP processing (1) <sup>b</sup>
2.5 Comorbidities	7.6 Time between processing and delivery (1) <sup>b</sup>
2.5a Specifically, diabetes, blood dyscrasia or inflammatory conditions (1) <sup>b</sup>	8 PRP characteristics
2.5b Pre-existing joint pathology (1) <sup>b</sup>	8.1 PRP format (ie, liquid, gel, membrane) (1)
2.5c Smoking status (1) <sup>b</sup>	8.2 PRP platelet count of all samples (1) <sup>b</sup>
3 Injury details	8.3 PRP differential leukocyte and red cell analysis of all samples (1) <sup>b</sup>
3.1 Diagnosis	9 Activation
3.1a Relevant grade or measure of severity (1) <sup>b</sup>	9.1 Volume of activating agent (1) <sup>b</sup>
3.1b Chronicity specified (1) <sup>b</sup>	9.2 Concentration of activating agent (1) <sup>b</sup>
3.2 Results of any preoperative imaging (1)	10 Delivery
3.3 Previous surgical or biological treatments for current injury (1)	10.1 Point of delivery (1)
4 Surgical intervention	10.2 Volume delivered (1) <sup>b</sup>
4.1 Surgical intervention described in sufficient detail to enable replication (1)	10.3 Concomitant use of stem cells or cytokines (1) <sup>b</sup>
4.2 Relevant operative findings (1)	10.4 Details of carrier or scaffold (1) <sup>b</sup>
5 Whole-blood processing	11 Postoperative care
5.1 Processing details	11.1 Immobilization or mobilization protocol specified (1) <sup>b</sup>
5.1a Concentration of anticoagulant (1) <sup>b</sup>	11.2 Physical therapy specified (1) <sup>b</sup>
5.1b Volume of anticoagulant (1) <sup>b</sup>	12 Outcomes
5.2 Whole-blood storage environment	12.1 Timing of outcome assessments (1) <sup>b</sup>
5.2a Temperature (0.5) <sup>b</sup>	12.2 Functional outcomes (1) <sup>b</sup>
5.2b Light exposure (0.5) <sup>b</sup>	12.3 Complications
6 Whole-blood characteristics	12.3a Specifically, infection (0.5) <sup>b</sup>
6.1 Whole-blood platelet count of all samples (1) <sup>b</sup>	12.3b Specifically, further surgery (0.5) <sup>b</sup>
6.2 Red and white blood cell count in whole blood (1) <sup>b</sup>	12.4 Radiographic outcomes (1) <sup>b</sup>
	12.5 Physical examination findings (if assessed) (0) <sup>b</sup>
	12.6 Return to activities (if assessed) (0) <sup>b</sup>
	12.7 Satisfaction (if assessed) (0) <sup>b</sup>

<sup>a</sup>Adapted from the American Association of Orthopaedic Surgeons.<sup>37</sup> Total 40 points possible. BMI, body mass index; MIBO, Minimum Information for Studies Evaluating Biologics in Orthopaedics. PRP, platelet-rich plasma.

<sup>b</sup>Checklist items that were originally grouped together in the original MIBO guidelines but have been separated in this modification. For example, checklist items 2.1 Age and 2.2 Sex were published in the original version as "Recipient demographics (including age and gender)."

<sup>c</sup>Suggested addition to the MIBO guidelines.

**Recipient Demographics.** All studies (100%) reported on both age and sex.<sup>#</sup> The weighted mean age of included patients was 59 years (range, 28-81 years; 44.5% male) with a weighted mean follow-up of 21.1 months (range, 4-42 months). Comorbidities such as diabetes (10.5%; n = 2),<sup>2,17</sup> blood dyscrasia (36.84%; n = 7),<sup>6,10,18,23,24,30,44</sup> and smoking status (31.6%; n = 6),<sup>2,17,29,42,43,55</sup> were not reported consistently. Inflammatory conditions and pre-existing joint pathology were reported in 94.7% of studies (n = 18).<sup>\*\*</sup> However,

these were accounted for mostly by exclusion criteria. These studies excluded a range of inflammatory morbidities, including osteoarthritis, rheumatoid arthritis, and autoimmune conditions. Current anti-inflammatory and/or antiplatelet medications were reported in 26.3% (n = 5) of studies.<sup>10,18,23,24,30</sup> BMI was accounted for in only 1 study (5.3%).<sup>43</sup>

**Injury Details.** The grade/severity of the rotator cuff tear was reported in 89.5% (n = 17) of studies.<sup>††</sup> Chronicity of such tears was reported in only 5 studies (26.3%),<sup>22-24,30,55</sup>

<sup>#</sup>References 2, 6, 10, 14, 17, 18, 22-24, 29-32, 42-44, 50, 52, 55.

<sup>\*\*</sup>References 2, 10, 14, 17, 18, 22-24, 29-32, 42-44, 50, 52, 55.

<sup>††</sup>References 2, 6, 10, 14, 17, 18, 22-24, 30, 32, 42-44, 50, 52, 55.



TABLE 2  
Study Characteristics and Overall Quality<sup>a</sup>

Study	Year	LOE	Journal	Modified Coleman	MIBO Items Reported, %
Aurégan et al <sup>2</sup>	2019	3	<i>Orthopaedics &amp; Traumatology: Surgery &amp; Research</i>	76	55
Charousset et al <sup>6</sup>	2014	3	<i>Arthroscopy</i>	82	60
D'Ambrosi et al <sup>10</sup>	2016	1	<i>Musculoskeletal Surgery</i>	75	62.5
Ebert et al <sup>14</sup>	2017	1	<i>American Journal of Sports Medicine</i>	92	66.25
Flury et al <sup>17</sup>	2016	1	<i>American Journal of Sports Medicine</i>	90	57.5
Gwinner et al <sup>18</sup>	2016	3	<i>Archives of Orthopaedic and Trauma Surgery</i>	68	55
Jo et al <sup>22</sup>	2011	2	<i>American Journal of Sports Medicine</i>	87	76.3
Jo et al <sup>23</sup>	2013	1	<i>American Journal of Sports Medicine</i>	70	67.5
Jo et al <sup>24</sup>	2015	1	<i>American Journal of Sports Medicine</i>	75	76.3
Malavolta et al <sup>30</sup>	2012	4	<i>Revista Brasileira de Ortopedia</i>	78	70
Malavolta et al <sup>29</sup>	2014	1	<i>American Journal of Sports Medicine</i>	87	70
Malavolta et al <sup>31</sup>	2018	2	<i>American Journal of Sports Medicine</i>	90	73.8
Martinelli et al <sup>32</sup>	2019	3	<i>Indian Journal of Orthopaedics</i>	76	62.5
Pandey et al <sup>42</sup>	2016	1	<i>Journal of Shoulder and Elbow Surgery</i>	90	78.8
Randelli et al <sup>43</sup>	2011	1	<i>Journal of Shoulder and Elbow Surgery</i>	66	57.5
Randelli et al <sup>44</sup>	2008	4	<i>Disability and Rehabilitation</i>	76	68.8
Wang et al <sup>50</sup>	2015	1	<i>American Journal of Sports Medicine</i>	87	63.8
Werthel et al <sup>52</sup>	2014	3	<i>International Journal of Shoulder Surgery</i>	75	51.3
Zhang and Wang <sup>55</sup>	2010	1	<i>American Journal of Sports Medicine</i>	75	60

<sup>a</sup>Modified Coleman score expressed as weighted mean. LOE, level of evidence; MIBO, Minimum Information for Studies Evaluating Biologics in Orthopaedics.

with a weighted mean duration of symptoms of 19.7 months. Results of preoperative imaging were given in 84.2% (n = 16) of studies<sup>‡‡</sup>; 18 studies (94.7%)<sup>§§</sup> accounted for any previous surgical or biological treatments for the current injury, mostly by excluding patients with any previous treatment.

**Surgical Intervention.** All 19 studies offered information regarding the surgical procedure that was sufficient to enable replication, and 52.6% (n = 10) reported operative findings.<sup>||||</sup>

**Whole-Blood Processing.** One study (5.3%)<sup>43</sup> reported temperature of whole-blood storage environment, and no study provided information regarding light exposure during storage of the whole blood; 15 studies (78.9%)<sup>¶¶</sup> reported the use of an anticoagulant, but specific details varied. Of these 15 studies, only 3 (15.8%) provided information about the concentration of anticoagulant,<sup>29,31,32</sup> and 10 of the 15 studies (75%) reported the volume of anticoagulant used.<sup>###</sup> The most frequently used anticoagulant was acid citrate dextrose solution (ACD-A) in 12 (80%) of the 15 studies that used an anticoagulant.<sup>a</sup> Only 1 study reported the concentration of ACD-A used<sup>32</sup>; 3 studies used sodium citrate (20%) as the anticoagulating agent.<sup>29-31</sup>

**Whole-Blood Characteristics.** A total of 11 studies (57.9%) reported the whole-blood platelet count,<sup>6,10,22-24,29-31,42-44</sup> and it was reported most frequently as an exclusion criterion (eg, excluded if platelet counts were lower than 150,000/mm<sup>3</sup>). Of those 11 studies, only 3 reported information regarding whole-

blood red blood cell and white blood cell count.<sup>22-24</sup> All 3 of those articles were written by the same authors.

**PRP Processing.** All studies gave some sort information about the method of PRP processing. All 19 studies reported the commercial kit used. Only 3 of these, all written by the same authors, did not give the spin protocol used.<sup>22-24</sup> The most common commercial kit used was GPS II Plasmix-Platelet Concentration System (Biomet Biologics) (n = 10; 52.6%).<sup>6,10,29-32,42-44,55</sup>

Regarding PRP storage, all studies reported the storage environment of the PRP after processing, with PRP most commonly stored in a sterile syringe; 4 studies (21%) gave information about storage temperature,<sup>23-25,43</sup> but no study gave information about PRP light exposure. Time between blood drawing and PRP processing, and time between processing and delivery, were described adequately in 17 studies (89.5%).<sup>b</sup>

**PRP Characteristics.** In all studies, the format in which PRP was delivered was described. The most frequently observed PRP format was liquid (n = 16),<sup>c</sup> followed by gel (n = 3).<sup>22-24</sup> Only 21% (n = 4) of studies measured platelets, erythrocytes, and leukocytes in the PRP obtained.<sup>22-24,42</sup>

**Activation.** The most common activating reagent was calcium chloride (n = 5; 26.31%).<sup>14,32,42,50,55</sup> Other types of activators included thrombin (n = 4),<sup>6,10,43,44</sup> calcium gluconate (n = 3),<sup>22-24</sup> or a combination of thrombin and calcium chloride (n = 3)<sup>29-31</sup>; 2 studies stated that no activator was required,<sup>17,52</sup> and 2 studies gave no information regarding PRP activation.<sup>2,18</sup> Of the 15 studies that used an activator for PRP, 14 gave the volume of the PRP activator

<sup>‡‡</sup>References 6, 10, 14, 17, 18, 23, 24, 29, 30, 31, 32, 42-44, 50, 55.

<sup>§§</sup>References 2, 6, 10, 14, 17, 18, 22-24, 29-32, 43, 44, 50, 52, 55.

<sup>||||</sup>References 6, 14, 22, 29, 30, 42-44, 50, 52.

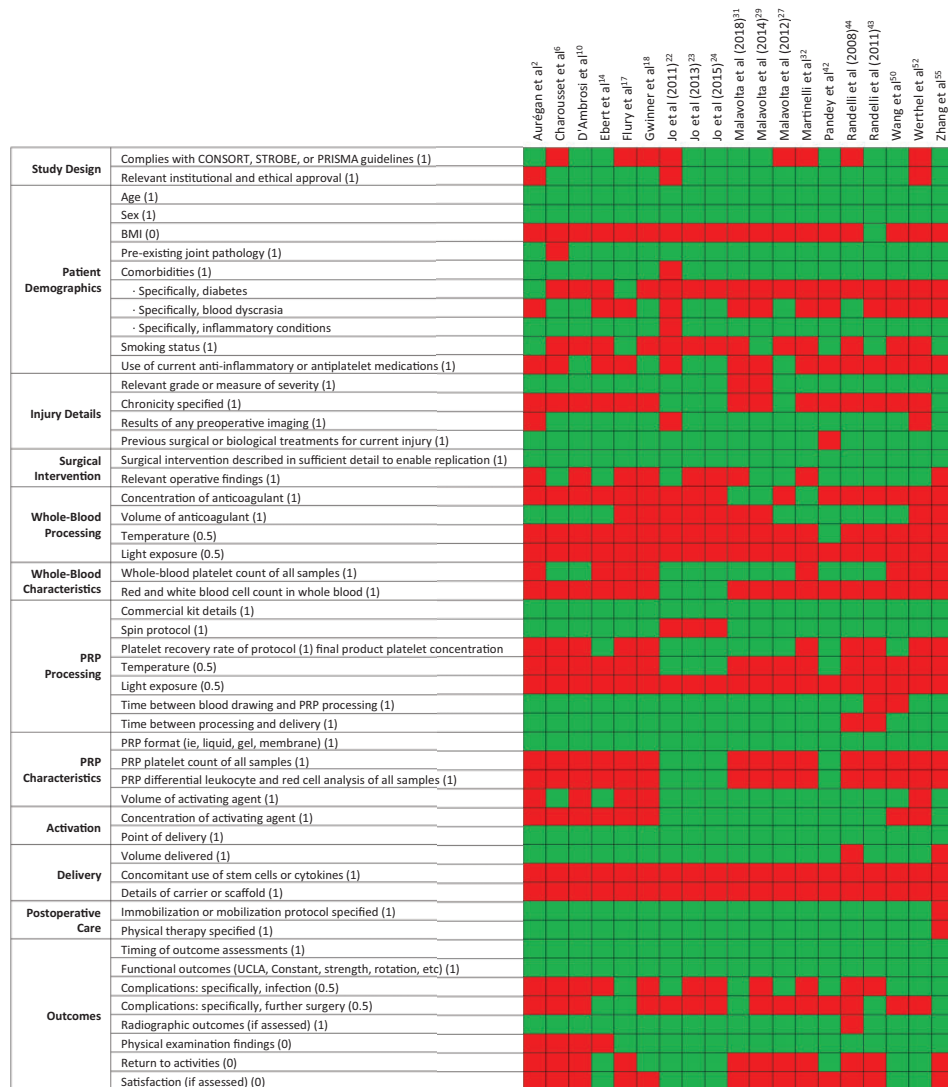
<sup>¶¶</sup>References 2, 6, 10, 14, 22, 23, 29-32, 42-44, 50, 55.

<sup>###</sup>References 2, 6, 10, 14, 30, 32, 42-44, 50.

<sup>a</sup>References 2, 6, 10, 14, 22, 23, 32, 42-44, 50, 55.

<sup>b</sup>References 2, 6, 10, 14, 17, 18, 22-24, 29-32, 42, 50, 52, 55.

<sup>c</sup>References 2, 6, 10, 14, 17, 18, 29-32, 42-44, 50, 52, 55.



**Figure 2.** Adherence heat map of the 47 MIBO checklist items for the 19 included studies. Adequate reporting is indicated by green shading and unreported variables are indicated by red shading. BMI, body mass index; CONSORT, Consolidated Standards of Reporting Trials; MIBO, Minimum Information for Studies Evaluating Biologics in Orthopaedics; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PRP, platelet-rich plasma; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; UCLA, University of California Los Angeles.

(73.68%),<sup>d</sup> and 11 (57.9%) also gave the concentration of the activator.<sup>e,22-24,29-32,42-44,55</sup>

**Delivery.** All studies reported the point of PRP delivery, most commonly given intraoperatively (n = 16; 84.2%).<sup>e</sup> One study administered PRP once at 7 to 14 days after surgery,<sup>50</sup> and 2 injected PRP in a serial fashion<sup>14,18</sup>; 17 studies (89.47%) reported the volume of PRP delivered.<sup>f</sup> No study reported the concomitant use of

stem cells, cytokines/growth factors, or any details of carrier or scaffold adjuncts.

**Postoperative Care.** The reporting variables relating to postoperative care (ie, immobilization and physical therapy interventions) were reported in 94% of studies (n = 18).<sup>g</sup>

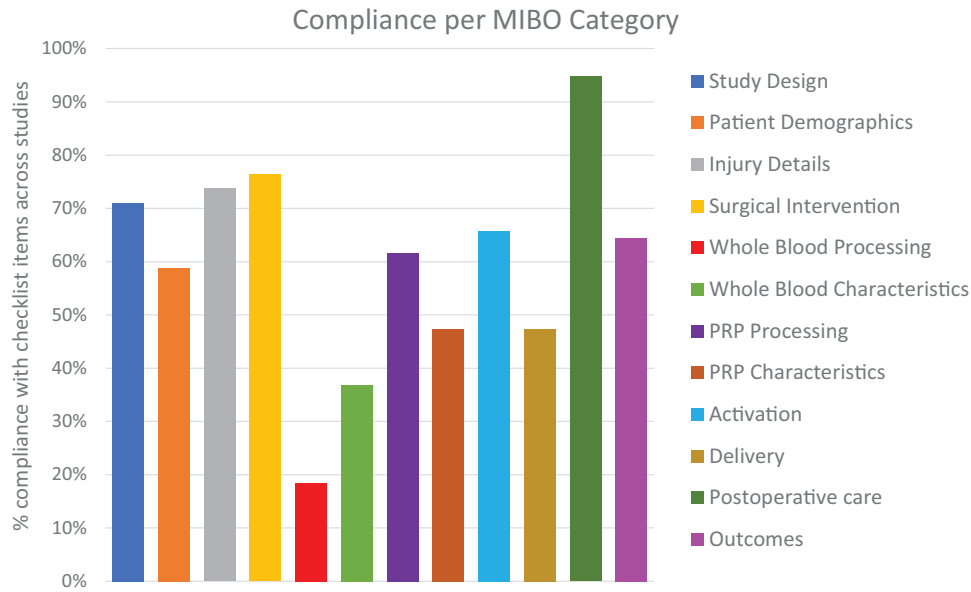
**Outcomes.** Only 64.5% of relevant outcome data was reported (Figure 3). Timing of outcome assessments and the utilization of a functional outcome score was reported in every study. Radiographic outcomes were recorded in

<sup>d</sup>References 6, 14, 22-24, 29-32, 42-44, 50, 55.

<sup>e</sup>References 2, 6, 10, 17, 22-24, 29-32, 42-44, 52, 55.

<sup>f</sup>References 2, 6, 10, 14, 17, 18, 22-24, 29-32, 42, 43, 50, 52.

<sup>g</sup>References 2, 6, 10, 14, 17, 18, 22-24, 29-32, 42-44, 50, 52.



**Figure 3.** Percentage of studies that reported information in each of the 12 MIBO categories. MIBO, Minimum Information for Studies Evaluating Biologics in Orthopaedics; PRP, platelet-rich plasma.

18 studies (94.7%).<sup>h</sup> Need for further surgery (n = 5; 26.3%),<sup>14,17,31,43,55</sup> and infection (n = 8; 42.1%),<sup>17,22,30,31,42,50,52,55</sup> were the least reported outcomes.

## DISCUSSION

PRP is a concentrated source of blood cells, growth factors, cytokines, and chemokines; however, there are several factors that are not yet known to produce the optimal PRP product for full-thickness rotator cuff repair. Biologically active factors in PRP are thought to direct tissue formation during tendon healing and accelerate the natural healing cascade.<sup>3,26,34,55</sup> The regenerative potential of PRP has increased scientific interest and an upsurge in clinical biologic treatments,<sup>35</sup> with the global market for PRP predicted to reach US\$590 million by 2025.<sup>20</sup> In consideration of the growing market for PRP and the minimal federal oversight, medical device companies have continued developing point-of-care devices to produce “custom-made” PRP products under proprietary rights.<sup>25,41</sup> As a result, different PRP point-of-care devices and preparation protocols exist, with differing compositions of platelet concentration, leukocyte count, activation methods, and centrifugation parameters.<sup>37</sup>

The heterogeneity in classification, preparation, and reporting of experimental data makes it difficult to assess quality and reproducibility to ultimately evaluate the therapeutic efficacy of PRP products. Unlike most biologics manufactured in the United States that undergo a standard progression from bench to bedside, orthobiologics, which fall under the human cell and tissue-based therapy provisions, have little oversight, with widespread clinical

adoption before safety or therapeutic efficacy has been proven. Several attempts have been made to establish a classification system that adequately assesses essential components and outcomes after PRP treatment,<sup>11,12</sup> and these systems served as an early framework to develop an all-encompassing checklist that has since been adopted by orthopaedic and sports medicine groups and organizations. Therefore, to enrich the current evidence on these therapies, strict adherence to the MIBO guidelines for orthobiologics is necessary to allow reproducibility and to adequately assess clinical efficacy.

For studies reporting the results of orthobiologic treatments, it is recommended that MIBO guidelines be required by publishing journals, similar to the PRISMA guidelines for systematic reviews and meta-analyses. However, it is notable that if these guidelines had been strictly adhered to, none of the studies included in the current review would have been published.

Regarding MIBO adherence for the use of PRP for full-thickness rotator cuff repair, we found that, on average, 58.5% of the critical reporting variables were reported across all studies. The percentage of critical reporting variables we observed was higher than that determined by Murray et al,<sup>39</sup> who found 42% of the critical variables reported in studies evaluating mesenchymal stem cells to treat musculoskeletal pathologies. It is important to note that the MIBO guidelines were not published until May 2017 and, therefore, many studies may be lacking these reporting standards due to absence of precedent. Interestingly, studies included in this review that were conducted after 2017 reported a similar average number of MIBO checklist items (n = 3 studies; 25.5 points; 63.8%) compared with those conducted before or during 2017 (n = 16 studies; 25.96 points; 64.9%).

<sup>h</sup>References 2, 6, 10, 14, 17, 18, 22-24, 29-32, 42,43, 50, 52, 55.

Of the 47 different checklist items among the 19 included studies on full-thickness rotator cuff repair, there was substantial variability in adherence to the MIBO guidelines. Only 7 MIBO checklist items were reported consistently across all 19 studies. Only 1 study, conducted by Pandey et al,<sup>42</sup> complied with more than 75% of the MIBO guidelines. Comorbidities such as pre-existing joint pathology, diabetes, blood dyscrasia, inflammatory conditions, current anti-inflammatory or antiplatelet medications, and smoking status were reported inconsistently. It is important to note that smoking has been found to increase clotting activity in PRP and to delay tendon-to-bone healing after rotator cuff repair surgery.<sup>13,40</sup> Diabetes has also been shown to affect healing rates following arthroscopic rotator cuff repair,<sup>8</sup> and antiplatelet/anti-inflammatory medications should be addressed because such medications inhibit platelet aggregation.<sup>11</sup> The influence of comorbidity factors on platelet function and PRP characteristics emphasizes the importance of recording comorbidities to evaluate the effectiveness of PRP as an adjunct in full-thickness rotator cuff tear repair. Furthermore, there was inconsistent reporting of details concerning whole-blood processing and characteristics, as well as PRP processing and characteristics; this subsequently limits study reproducibility for PRP preparation and makes comparison among studies challenging. Thus, stricter adherence to the MIBO guidelines is necessary to thoroughly evaluate the efficacy of PRP as an orthobiologic treatment for full-thickness rotator cuff repair.

We recognize that the MIBO checklist items are evolving guidelines with the intent to standardize scientific literature regarding the use of PRP in orthopaedics. The first iteration of these guidelines, however, is not without disadvantages. First, some checklist items, such as concomitant use of stem cells or cytokines, and/or details of carrier or scaffold when delivering PRP, do not apply to all products. While some checklist items preface the statement with "if performed," this checklist item does not. Yet, no study found in this review included information about the carrier or scaffold. Furthermore, there are 2 checklist items regarding the storage of PRP and whole blood. However, if PRP is administered at the point of care, the inclusion of information regarding storage preparation is unnecessary. Therefore, this checklist item should also be prefaced with the phrase "if performed." Third, BMI is not a MIBO guideline. BMI is important to report because higher BMI has been associated with higher levels of growth factors and worse clinical and functional outcomes following rotator cuff repair.<sup>28,51</sup>

In addition, the MIBO guidelines consist of 12 categories with 23 checklist items, but certain checklist items are condensed and do not encompass all reproducible options for the preparation and delivery of PRP. As an example, regarding MIBO item 21 in the "Delivery" category ("PRP delivery described sufficiently to enable reproducibility, including volume delivered, concomitant use of stem cells or cytokines, and details of carrier or scaffold"),<sup>37</sup> we found it difficult to grade certain criteria that had more than 1 individual component; therefore, the guidelines were subdivided into individual components (see Table 1 and Figure

2). Although the MIBO guidelines do an excellent job of creating reporting standards for studies evaluating PRP and mesenchymal stem cells, they do not apply to all orthopaedic and sports medicine-based biologic therapies. For example, 2 MIBO checklist items ask about anticoagulants (Table 1, checklist items 5.1a and 5.1b), but not all platelet concentrate products use an anticoagulant. If the checklist items that do not apply to all orthobiologics became "if/then" statements, it would potentially allow for greater versatility with other orthobiologics, such as bone marrow aspirate (BMAC) or adipose-derived products. These disadvantages of the MIBO guidelines may complicate consistent reporting and prevent widespread adoption. We highlighted these checklist limitations with the intention that these limitations be acknowledged and used to modify the current MIBO guidelines to improve reporting and reproducibility standards. Of note, our initial literature review included BMAC. However, it was discovered that there were too few BMAC ( $n = 1$ ) articles that fit our inclusion criteria to be considered in a systematic review.

Considering the number of variables associated with the preparation, delivery, and outcomes of PRP, some form of consistent reporting is required to compare published data and identify true clinical effectiveness. Although there are limitations to the current MIBO guidelines, the checklist items were developed by expert consensus with the intention to provide the orthopaedic research community with a framework to enhance study design, standardize treatment protocols, and improve reporting and reproducibility. Adherence to current and future iterations of the MIBO guidelines is important for our knowledge of PRP use in rotator cuff repair, but standardization will also help facilitate personalized treatment options. In fact, there are novel strategies under development to minimize PRP heterogeneity to enhance the therapeutic efficacy for intraoperative augmentation and postoperative treatment.

## Limitations

We acknowledge that there were limitations in the present study. First, this review was limited both by the number of studies available based on inclusion/exclusion criteria and the quality of these studies, as indicated by the modified Coleman score. Second, many MIBO guidelines encompass multiple items, such as item 12: "Outcome assessments that include functional outcomes and recording of complications (including infection and need for further surgery). If performed, physical examination findings, return to activities, and satisfaction [should be noted]." This caused evaluators to disagree on point values assigned per category. In response, it is suggested that the original 23-point checklist be increased to a 47-item checklist. In addition, some studies found in the initial search included both partial- and full-thickness tears but did not distinguish between groups when reporting results. This resulted in exclusion of several studies from the final analysis. Last, we chose not to include the efficacy of PRP augmentation (ie, patient-reported outcomes, physical examination, retear rates) to the MIBO reporting score due to significant heterogeneity



and variability among outcome endpoints in the studies evaluated.

A 2019 meta-analysis examining variability in intervention and outcomes in rotator cuff repair with and without PRP or fibrin matrix repair<sup>19</sup> found that patient-reported outcome scores (Constant, University of California Los Angeles [UCLA], and Simple Shoulder Test [SST]) improved and radiographic outcomes (retear rates) reduced with PRP treatment compared with control groups. Although this recent evidence suggests that PRP treatment in rotator cuff repair is clinically effective, variability in outcome assessment endpoints and reporting continues to be a major limitation evaluating the therapeutic or biological effectiveness of PRP augmentation in rotator cuff repair.<sup>47</sup> Thus, there is an urgent need to establish specific outcome assessments and endpoints for PRP treatment in rotator cuff repair to uniformly evaluate therapeutic and biological efficacy. We propose that subcategories be added to the outcomes section of the MIBO guidelines to encourage more consistent reporting and to highlight valuable endpoint data—specifically, patient-reported outcome measurements including visual analog scale, UCLA, Constant, SST, and postprocedure imaging (eg, magnetic resonance imaging), to document structural changes.

## CONCLUSION

This systematic review highlights the current reporting deficiencies within the scientific literature of important variables for evaluating PRP for full-thickness rotator cuff repair. There was widespread variability among published studies that evaluate PRP for this application and, more specifically, studies were limited by inconsistent universal reporting of whole-blood and PRP processing and postprocessing characteristics. To improve our understanding of biological efficacy and to promote repeatability, stricter adherence to the MIBO guidelines is necessary. We propose that the checklist limitations be addressed and that modification of the MIBO guidelines be considered to improve the reporting of individual components within certain categories.

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