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Platelet-rich plasma injections for the management of knee osteoarthritis: The ESSKA-ICRS consensus. Recommendations using the RAND/UCLA appropriateness method for different clinical scenarios

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Abstract

Purpose: The aim of this consensus was to develop evidence- and expert-based patient-focused recommendations on the appropriateness of intra-articular platelet-rich plasma (PRP) injections in different clinical scenarios of patients with knee osteoarthritis (OA).

Methods: The RAND/UCLA Appropriateness Method was used by the European Society of Sports Traumatology, Knee Surgery, and Arthroscopy (ESSKA), as well as the International Cartilage Regeneration and Joint Preservation Society (ICRS) to reach a consensus and produce recommendations for specific patient categories combining best available scientific evidence with the collective judgement of a panel of experts.

Results: Scenarios were defined based on first treatment vs first injective treatment vs second injective treatment, age (<50/50–65/66–80/>80), tibiofemoral vs patellofemoral involvement, OA level (Kellgren–Lawrence/KL 0–I/II–III/IV), and joint effusion (dry knee, minor-mild or major effusion). Out of 216 scenarios, in 84 (38.9%) the indication was considered

For affiliations refer to page 9.

Abbreviations: BMI, body mass index; CFA, Concerted Action on Appropriateness; ESSKA, European Society of Sports Traumatology, Knee Surgery and Arthroscopy; HA, hyaluronic acid; ICRS, International Cartilage Regeneration and Joint Preservation Society; IPR, interpercentile range; IPRAS, interpercentile range adjusted for symmetry; KL, Kellgren–Lawrence; OA, osteoarthritis; ORBIT, orthobiologic initiative; PRP, platelet-rich plasma; RAM, RAND/UCLA Appropriateness Method; RCT, randomized controlled trial; TKA, total knee arthroplasty.

appropriate, in 9 (4.2%) inappropriate and in 123 (56.9%) uncertain. The parameters associated with the highest consensus were PRP use after failed injective treatments (62.5%), followed by PRP after failed conservative treatments and KL 0–III scenarios (58.3%), while the highest uncertainty was found for PRP use as first treatment and KL IV OA (91.7% and 87.5% of uncertain scenarios, respectively).

Conclusion: This ESSKA-ICRS consensus established recommendations on the appropriateness or inappropriateness of PRP injections for the treatment of knee OA, providing a useful reference for clinical practice. PRP injections are considered appropriate in patients aged ≤80 years with knee KL 0–III OA grade after failed conservative non-injective or injective treatments, while they are not considered appropriate as first treatment nor in KL IV OA grade.

Level of Evidence: Level I.

KEYWORDS

consensus, knee, OA, osteoarthritis, platelet-rich plasma

INTRODUCTION

Platelet-rich plasma (PRP) has emerged as an injective treatment option for the management of early to moderate knee osteoarthritis (OA) [9]. It showed a good safety record and a simple preparation technique to obtain its biologically active content [15]. This orthobiologic product relies on the high concentration of platelets, enriched with growth factors, cytokines and bioactive molecules, which are associated with the homoeostasis of joint tissues, being involved in both healing processes and immunoregulation and inflammation modulation [5, 33]. The use of PRP injections to address knee OA is increasing in clinical practice, and its efficacy in improving pain and function is supported by several randomized controlled trials (RCTs) and meta-analyses demonstrating higher benefits than placebo, corticosteroids and hyaluronic acid (HA) [7, 10, 16, 21, 32], although other studies reported less favourable results [3, 23, 29]. In fact, literature results are heterogeneous, and different studies suggest that some patient factors and OA features may be responsible for the variable treatment response [4, 22, 26, 30]. In this scenario, while some high-level studies may demonstrate the overall potential of this biological approach, a multidimensional approach is needed to translate the scientific evidence into clinical practice by combining the literature results with the judgements of experts [2].

An expert consensus based on the modified Delphi method has recently been conducted by the Orthobiologic Initiative (ORBIT) of the European Society of Sports Traumatology, Knee Surgery, and Arthroscopy (ESSKA) to produce recommendations on the use of PRP for the treatment of knee OA [24]. Building on the valuable guidelines offered by this consensus, ESSKA and the International Cartilage Regeneration and Joint Preservation Society (ICRS) joined efforts to define more specific and practical clinical indications through the RAND/UCLA Appropriateness Method (RAM). The RAM consensus is a structured approach used to reach a consensus on complex or controversial issues to produce patient-specific recommendations combining the best available scientific evidence with the collective judgement of a panel of experts [17, 25]. The experts work through a series of iterations where they assess the appropriateness of a treatment for different clinical indications, investigating patients with different characteristics and disease features. Thus, this expert consensus could be of clinical relevance by helping to clarify the clinical scenarios in which the use of intra-articular PRP may or may not be appropriate, giving indications for its application in clinical practice.

The aim of this ESSKA-ICRS consensus was to develop evidence- and expert-based patient-focused recommendations on the appropriateness of intra-articular PRP injections in different clinical scenarios of patients with knee OA.

MATERIALS AND METHODS

Consensus design

The RAM was used to develop recommendations on the appropriateness of PRP injections in patients affected by knee OA. The RAM process involved three interdependent groups: a core panel, an expert panel, and a discussion panel. The core panel defined the scenarios of the RAM and guided the expert panel through the RAM tasks. The expert panel, composed of

15 voting members selected based on their expertise in the conservative treatment of knee OA and PRP while ensuring geographical representation, used the data provided by the core panel to come to a consensus. The expert panel was the only one voting the scenarios. The discussion helped in providing a multi-specialty point of view to the discussions. The members were selected based on their scientific and clinical expertise in knee OA and PRP injections while ensuring the geographical representation of ESSKA and ICRS European members (Table 1).

Clinical scenarios development

The RAM process was preceded by an extensive literature review undertaken by the steering group of the 'Formal Consensus Project', set up by the ORBIT Initiative of ESSKA on PRP in knee OA [24]. This literature review ensured that panellists had access to the body of evidence for the rating procedure and was used by the core panel to develop the consensus scenarios. These clinical scenarios were presented in the form of a matrix detailing demographic data, characteristics of the joint and clinical features. These factors were based on literature evidence and clinical experience of the core panel, selected to potentially influence the appropriateness of the procedure:

1. Treatment (first treatment vs. first injection treatment vs. second injection treatment).
2. Age (<50 years old vs. 50–65 years old vs. 66-80 years old vs. >80 years old).
3. Joint involvement (Tibiofemoral vs. Patellofemoral).
4. OA level (Kellgren–Lawrence/KL grade 0–I vs grade II–III vs. grade IV).
5. Joint effusion (dry knee vs. minor-mild effusion vs. major effusion).

The first parameter was included in the equation to define the appropriateness based on the other treatment options for managing patients affected by knee OA, who may come to the physician's attention for the first time or after having performed without sufficient benefit other than non-surgical treatments, conservative or injective. In this light, three categories have been identified. In the first one, the patient comes to the physician with knee OA-related symptoms, but without having performed any treatment. In the second case, the patient exhausted a conservative treatment cycle (excluding injections) without sufficient benefit. Finally, the last case refers to patients who also tried corticosteroid and/or HA injections without sufficient benefit.

With regard to age, the category <50 years old has been chosen to identify the appropriateness of the indications in patients in the age where there are high activity expectations and where the literature shows the worst results of total knee arthroplasty (TKA) in terms of risk of revision [1]. The age category 50–65 is the category where most of the evidence are published on PRP [24]. This is also a category where there is an increasing number of TKA performed, although TKA failures are double that in older patients [27]. In the category 66–80, PRP showed lower results, while this represents the main age range for performing TKA. Finally, lower results can be expected from PRP in older patients, but the category >80 years old has been identified as also TKA is often contraindicated for higher

TABLE 1 Members involved in the consensus process.

Core panel	Laura de Girolamo (IT) Elizaveta Kon (IT) Lior Laver (IL) Mikel Sánchez (ES) Kristof Sas (BE) Giuseppe Filardo (IT) – *Moderator*	
Consensus participants	Isabel Andia (ES) – *Discusser* Jérémy Magalon (FR) – *Discusser* Lucienne Vonk (NL) – *Discusser* Luca Andriolo (IT) – *Project management* Angelo Boffa (IT) – *Project management* Philippe Beaufils (FR) – *Consensus advisor*	
Voting panel	Ricardo Bastos (PT) Leela Biant (UK) Bertè Boe (NOR) Ramon Cugat (ES) Alessandro Di Martino (IT) Christoph Erggelet (CH) Michael Iosifidis (GR)	Baris Kocaoglu (TUR) Rodica Marinescu (RO) Stefan Nehrer (AUT) Philipp Niemeyer (DE) Marko Ostojic (BIH) Thomas Piontek (PL) Georges Skarpas (GR) Thomas Tischer (DE)

morbidity and mortality rates [28], thus leaving less alternatives to address these patients.

The third parameter focused on the prevalent joint involvement. Although it is common not to have exclusively tibio-femoral or patello-femoral OA, this category refers to OA manifestation mainly presenting to one site or the other, to account for the different aetiology, symptomatology, as well as the different evidence, being most studies on PRP focused on tibio-femoral OA, while evidence is limited for patello-femoral joint [24].

The extent of OA disease within the joint is another key parameter, which has been studied and showed to influence the treatment results. OA has been divided into three levels, early, mild/moderate, and advanced (KL 0–I vs. II, III vs. IV), to account for the different severity of the disease, and the different results reported in the literature based on OA grades, showing PRP effect mainly in mild and moderate cases of knee OA [24].

Finally, the last parameter considered to build the scenarios' matrix is the level of effusion (dry knee vs. minor/mild effusion vs. major effusion). While it is difficult to quantify the effusion level, a practical definition has been chosen to distinguish the presence of minor/mild effusion versus the major one, the latter one being the effusion requiring aspiration. This consensus considered PRP injection being performed in the same session after joint aspiration.

Further considerations have been taken into account to interpret the scenarios developed: No gross osseous malalignment (indicatively varus/valgus within 5°), neither ligamentous injury requiring treatment; knee OA affecting patients' quality of life, and patients wishing to go back to their previous activities (professional players were not considered); no osteochondritis dissecans/focal lesions; no SIFK/SONK; no major flexion contracture; no BMI distinction. Moreover, neither the subchondral application nor the preventive use of PRP were considered. Finally, since no evidence clearly supports the advantage of specific PRP types or protocols [24], no distinction was made considering these aspects.

Based on the five clinical variables selected by the core expert panel, a set of 216 clinical scenarios was produced. The scenarios were grouped into four 'chapters' based on patient age (Figure 1). Panellists were asked to individually assess the appropriateness

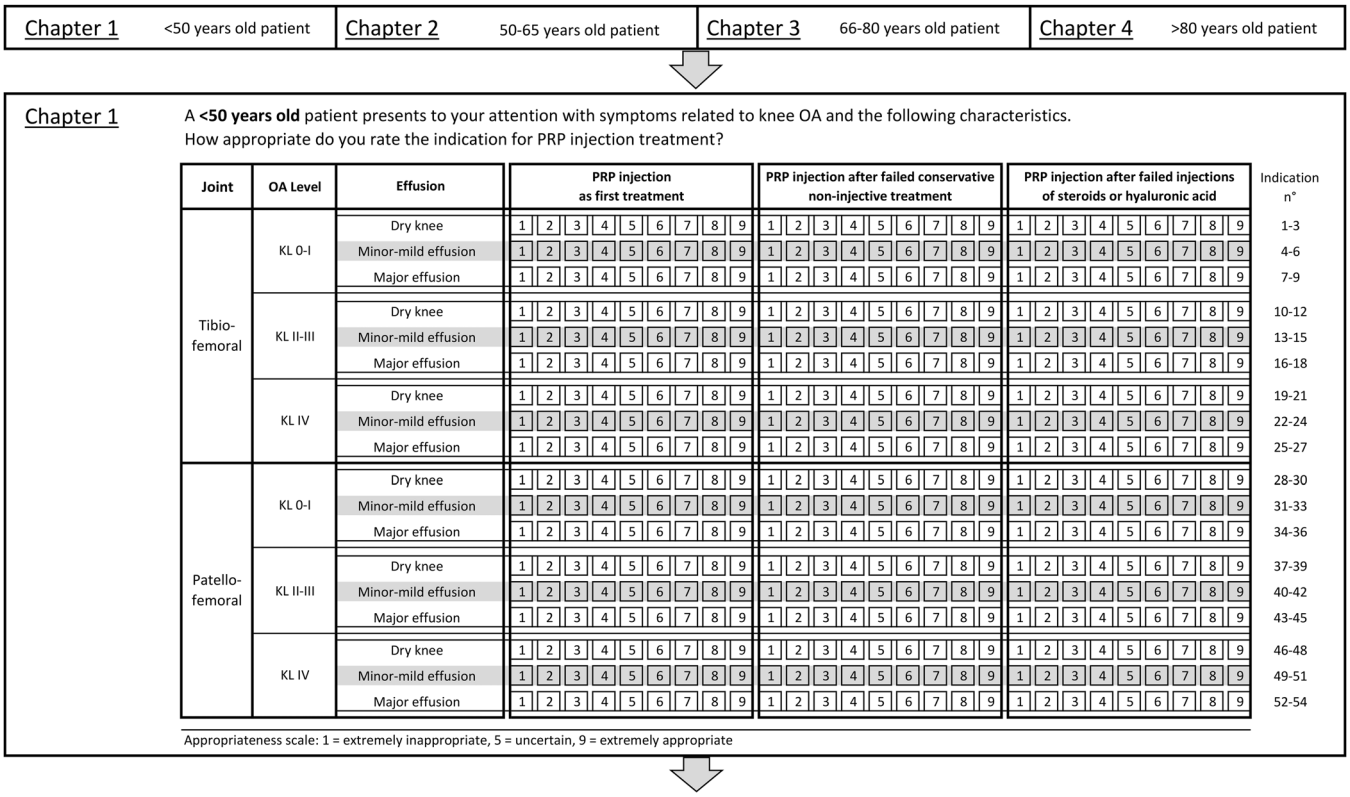

FIGURE 1 Example of the clinical scenarios presented to the voting panellists. Chapter 1 (<50 years old patients). Two specific scenarios are shown in detail.

of the indication for PRP injection treatment for each of the scenarios. The scenarios were presented to the voting experts in the form of a question: 'A … years old patient presents to your attention with symptoms related to knee OA and the following characteristics. How appropriate do you rate the indication for PRP injection treatment?'.

Consensus process

The appropriateness of the indication for injective PRP treatment in each of the different scenarios was rated in two rounds. The two-round RAM process is designed to identify whether discrepant ratings are due to real clinical disagreement over the use of the procedure ('real' disagreement) or to fatigue or misunderstanding ('artefactual' disagreement) [17]. In the first round, the expert panel received the clinical scenarios by email and was asked to rate the appropriateness of PRP indication. According to the methodology [17], each panellist ranked, independently from the other panellists, the appropriateness for each scenario. A 9-point Likert scale was used with the range 1–3 considered 'inappropriate', 4–6 'uncertain', and 7–9 'appropriate'. They were invited to consider the synthesized literature review evidence provided by the ORBIT ESSKA 'Formal Consensus Project' on PRP in knee OA. The expert panellists were asked to base their ratings on an 'average patient' presenting to an 'average physician' practising in an 'average healthcare setting', and to discount the cost of the procedure in rating the appropriateness of the scenarios.

In the second round, the experts and core panels met under the leadership of a moderator. Each panellist received an individualized document showing their round-one rating and the distribution of the entire expert group's first rating round. During the meeting, panellists discussed the ratings, focusing on areas of disagreement. The opportunity was given to modify the original list of indications and/or definitions, if desired. The expert panel was not forced to reach a consensus towards appropriateness or inappropriateness and, after discussing each chapter, experts individually re-rated the appropriateness of the indication for PRP for each scenario [17].

Data analysis and statistical method

The final scores of the 9-point Likert scale of each expert were then pooled to generate a median appropriateness score for each scenario. The presence of voting dispersion was calculated by statistical analysis based on the Interpercentile Range Adjusted for Symmetry (IPRAS), according to BIOMED Concerted Action on Appropriateness (CFA) [17] to define the presence of 'disagreement' among votes in each scenario. In detail, IPRAS is calculated as follows: IPRr + (AI * CFA), where IPRr is the Interpercentile Range required for disagreement when perfect symmetry exists; AI is the Asymmetry Index; and CFA is the Correction Factor for Asymmetry. An indication is rated with disagreement if IPR > IPRAS for that specific indication. Finally, the use of PRP for each scenario was classified:

- 'Appropriate': median score of ≥7 without disagreement
- 'Inappropriate': median vote of ≤3 without disagreement

A scenario receiving a score between 4 and 6 or a scenario with disagreement was classified as 'uncertain'. An 'uncertain' recommendation can reflect either the ambiguous state of current evidence or equivocal appropriateness either due to a moderately unfavourable risk profile or to limited efficacy. The 'uncertain' classification is not intended to be a negative recommendation or to preclude a priori the use of the treatment for the specific scenario, relying instead on the physician–patient interaction in determining treatment decisions in the context of the individual characteristics, comorbidities, and preferences.

RESULTS

Details of experts' ratings with median, agreement value, and recommendation for each clinical scenario are reported in the Supporting Information S1. Following the voting rounds, there was agreement for 93 (43.1%) of the scenarios: in 84 scenarios (38.9%) the indication for PRP was considered appropriate without disagreement, in 9 (4.2%) inappropriate without disagreement. In the other 123 (56.9%) scenarios, no agreement was reached amongst the experts towards appropriateness or inappropriateness, and the indication was deemed uncertain.

Appropriateness, inappropriateness and uncertain areas

Experts considered PRP injections appropriate in all scenarios, including patients aged ≤80 years with OA grade 0–III after failed conservative non-injective or injective treatment (with steroids or HA), regardless of effusion and of tibio-femoral or patello-femoral joint involvement [α].

Conversely, PRP injections were never considered appropriate as first treatment (i.e. before conservative treatment as exercise and weight control according to international guidelines), being inappropriate in case of KL IV OA grade with patello-femoral joint involvement, with major effusion or over 80 years old [β] and uncertain in all the other scenarios [γ].

Focusing on the appropriateness of PRP injections after failed conservative non-injective or injective

treatment, the main areas of uncertainty included all the scenarios regarding patients under 80 years old with OA grade IV, regardless of effusion and tibio-femoral or patello-femoral joint involvement [δ].

A variability in the appropriateness of PRP injections after failed conservative non-injective or injective treatment was obtained in the 36 scenarios including patients over 80 years old, with 12 (33.3%) scenarios considered appropriate, 3 (8.3%) inappropriate, and (58.4%) 21 uncertain. In detail, PRP was considered appropriate after failed conservative non-injective treatment for OA grade 0–III with tibio-femoral involvement and dry knee or minor-mild effusion (scenarios nos.: 164, 167, 173 and 176) but uncertain with major effusion (scenarios nos.: 170 and 179) or patello-femoral involvement [ε]. After failed injective treatment and tibio-femoral involvement, PRP was considered appropriate for OA grade 0–III (scenarios nos.: 165, 168, 171, 174 and 177), with the exception of KL II–III with major effusion (scenario no: 180) which was uncertain. In case of patello-femoral involvement after failed injective treatment, it was appropriate in KL 0–I and II–III dry knees (scenarios nos.: 192 and 201) and KL II–III knees with mild effusion (scenario no: 204), uncertain in KL 0–I knees with minor and major effusion (scenarios nos.: 195 and 198) or KL II–III knees with major effusion (scenario no: 207). On the other hand, PRP injections were considered inappropriate for patients with OA grade IV with patello-femoral involvement and major effusion (scenarios nos.: 215 and 216) or minor-mild effusion after failed conservative non-injective treatment (scenario no.: 212). All the other scenarios regarding patients over 80 years old with PRP injections after failed conservative non-injective or injective treatment and KL IV knees were considered uncertain [ζ].

Changes of appropriateness within parameters

The appropriateness of PRP injections changed differently according to the influence of each parameter:

1) The OA grade influenced 108 out of 216 possible treatment indication changes (50.0%). In particular, while KL 0–I presented very similar results to KL II–III, 51 out of 72 treatment indications changed passing from KL II–III to KL IV (70.8%).
2) PRP injection as the first treatment or after failed conservative non-injective or injective treatment influenced 98 out of 216 possible treatment indication changes (45.4%). In particular, while scenarios after failed injective treatment presented very similar results to those after failed conservative non-injective treatment, 44 out of 72 indications changed passing from the first treatment to scenarios after failed conservative non-injective treatment (61.1%).
3) Age influenced 36 out of 216 possible treatment indication changes (16.7%); but taking into account that no indication changed among the three parameters under 80 years old (<50, 50–65 and 66–80), thus reducing the age parameters from 4 to 2, age influenced 17 out of 54 possible treatment indication changes passing from ≤80 to >80 years old (31.5%).
4) The tibio-femoral or patello-femoral joint involvement influenced 15 out of 108 possible treatment indication changes (13.9%).
5) Effusion influenced 20 out of 216 possible treatment indication changes (9.3%). In particular, while dry knee presented very similar results to minor-mild effusion, 8 out of 72 treatment indications changed passing from minor-mild to major effusion (11.1%).

Appropriateness for each parameter

The parameters evaluated in the clinical scenarios had different appropriateness results for the indication of PRP use (Figure 2).

The parameters with the highest appropriateness were the use of PRP after failed injective treatment with steroids or HA (61.1% of appropriate scenarios), its use after failed non-injective conservative treatment (55.5% of appropriate scenarios), and an OA grade KL 0–I and II–III (both 58.3% of appropriate scenarios). Conversely, the parameters with the highest inappropriateness were KL IV (12.5% of inappropriate scenarios), age over 80 years old (11.1% of inappropriate scenarios), and patello-femoral joint, major effusion, and the use of PRP as first treatment (all with 8.3% of inappropriate scenarios).

The parameters associated with the highest consensus were the use of PRP after failed injective treatments (62.5%), followed by PRP after failed conservative treatments and KL 0–I/II–III scenarios (all with 58.3% consensus). The parameters associated with the highest uncertainty were the use of PRP as the first treatment (91.7% of uncertain scenarios) and KL IV (87.5% of uncertain scenarios). No scenario characterized by one of these two parameters was considered appropriate (0% of appropriate scenarios for both of them).

A graphic representation of the overall consensus results is found in Figure 3.

DISCUSSION

The main finding of this ESSKA-ICRS consensus with the RAM approach is that PRP injections are considered an appropriate option in patients aged ≤80 years with knee KL 0–III OA grade after failed

		A	U	I	CONSENSUS
TREATMENT	First treatment	0%	91.7%	8.3%	8.3%
	After failed conservative	55.5%	41.7%	2.8%	58.3%
	After failed injections	61.1%	37.5%	1.4%	62.5%
JOINT	Tibio-femoral	41.7%	58.3%	0%	41.7%
	Patello-femoral	36.1%	55.6%	8.3%	44.4%
OA GRADE	KL 0-I	58.3%	41.7%	0%	58.3%
	KL II-III	58.3%	41.7%	0%	58.3%
	KL IV	0%	87.5%	12.5%	12.5%
EFFUSION	Dry knee	41.7%	56.9%	1.4%	43.1%
	Minor-mild	40.3%	56.9%	2.8%	43.1%
	Major	34.7%	56.9%	8.3%	43.1%
AGE	<50	44.4%	53.7%	1.9%	46.3%
	50-65	44.4%	53.7%	1.9%	46.3%
	66-80	44.4%	53.7%	1.9%	46.3%
	>80	22.2%	66.7%	11.1%	33.3%

FIGURE 2 Rating of scenarios evaluated as Appropriate, Uncertain, or Inappropriate, for each parameter considered. Green indicates the highest rates of appropriateness, yellow the most uncertain parameters and red the highest rate of inappropriateness when considering the indication for PRP based on the different parameters evaluated. The last column refers to the overall consensus reached, by including both consensus on appropriateness and inappropriateness. A, appropriate; KL Kellgren–Lawrence; I, inappropriate; OA, osteoarthritis; U, uncertain.

conservative non-injective or injective treatment, while they are not considered appropriate as first treatment nor in KL IV OA grade.

The use of PRP as injective treatment for knee OA remains a subject of debate in the orthopaedic field. Previous attempts have been made to reach a consensus on PRP to determine whether this treatment is suitable or not for managing knee OA [19, 24, 31]. However, their overall conclusions on PRP potential do not help in understanding when physicians should use PRP in clinical practice, also considering the possible treatment alternatives. Therefore, the purpose of this consensus using the RAM approach was to assess, based on the available evidence and expert-based recommendations, the appropriateness of using PRP injections in different clinical scenarios. In this regard, experts reached the highest agreement in recommending the use of PRP when other injective alternatives have already failed. Moreover, appropriateness was also found for the use of PRP as a first-line injective treatment. This aligns with the results of the ORBIT PRP consensus using the 'Formal Consensus' ESSKA approach, which supported PRP benefits over steroids and HA for the treatment of knee OA [24].

The RAM process allowed experts to identify patient characteristics influencing the appropriateness of PRP use for knee OA. Amongst these, the OA level represented the factor influencing the most expert judgement. The use of PRP is recommended primarily in mild and moderate OA, while it is not considered appropriate for severe OA (KL IV), where it appears to be less effective [12, 13, 18, 34, 35]. Nevertheless, as in the previous 'Formal Consensus' of ESSKA, PRP treatment could be considered in selected severe knee OA cases, for example, in patients who decline or are not suitable for arthroplasty surgery due to comorbidities, although lower results could be expected [24].

Other factors influenced PRP indications based on age, experts provided similar recommendations for the categories of patients under the age of 80, where they considered appropriate the use of PRP, while PRP was considered less appropriate for those over 80 years of age. Another distinction in the indications for PRP treatment has been made concerning the involvement of the tibio-femoral or patello-femoral joint. For the latter, the evidence in the literature is limited, being primarily focused on tibio-femoral OA [8, 20]. Nevertheless, overall, the experts recommended the use of

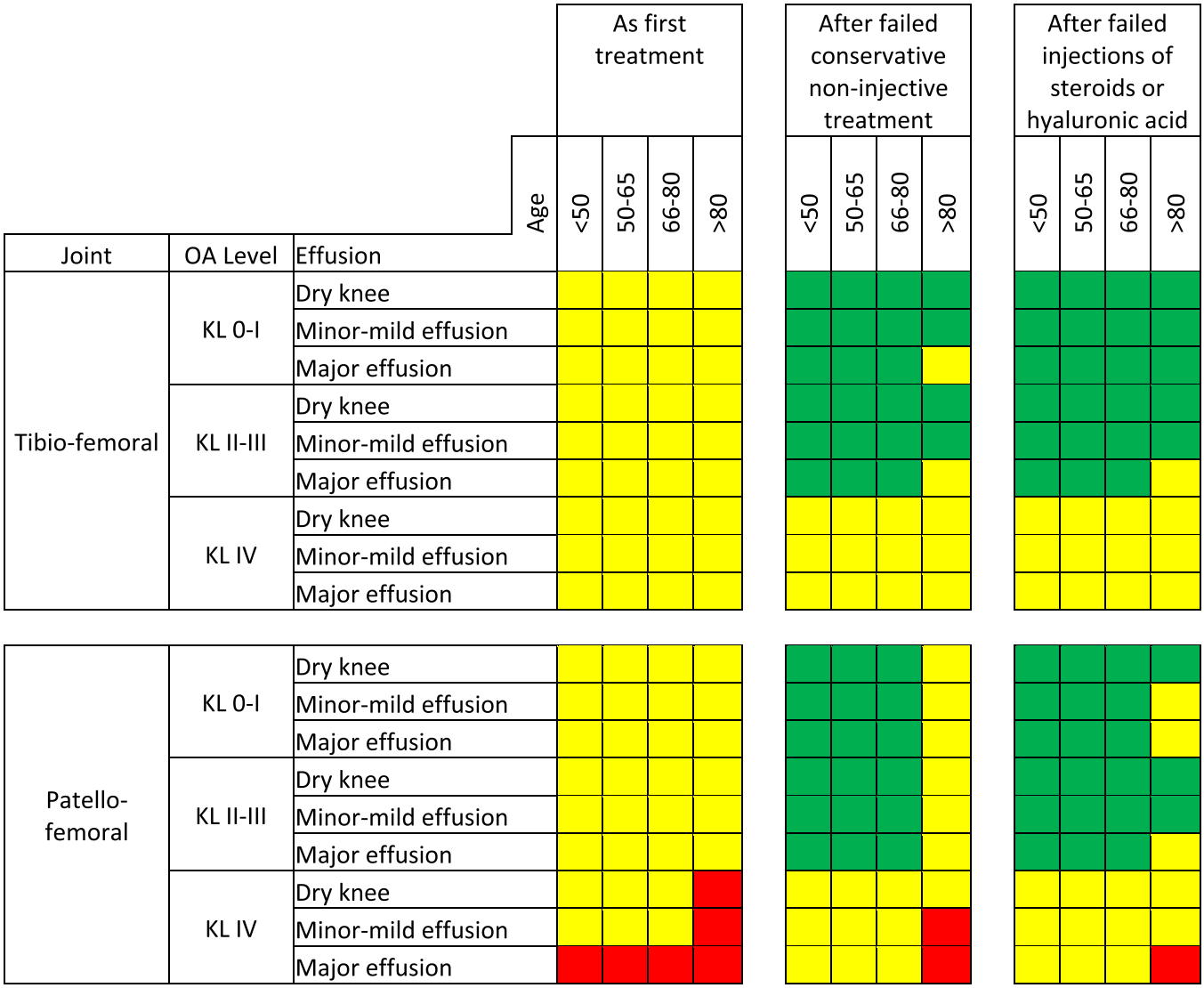

FIGURE 3 Graphic representation of the overall RAM consensus results on the appropriateness of platelet-rich plasma injections for the management of knee osteoarthritis (green: appropriate; yellow: uncertain; red: inappropriate). KL, Kellgren–Lawrence; OA, osteoarthritis.

PRP also for patello-femoral OA, although with a lower number of appropriate scenarios.

Effusion is another parameter that has been evaluated in this consensus. Although current clinical evidence is lacking regarding the injection of PRP based on different levels of joint swelling, the experts agreed that the indication for PRP use is less appropriate when there is a major effusion. As concluded by the previous 'Formal Consensus' of ESSKA [24], in case of effusion, an aspiration should be performed to avoid the dilution of the injected PRP. Future studies should investigate whether the use of different PRP formulations may have different benefits in OA knees with more or less effusion. In OA knees with effusion, indicating a higher inflammation level, the use of leucocyte-poor PRP (LP-PRP) could be more suitable having shown less pro-inflammatory features compared to LR-PRP in preclinical and clinical studies [6, 14]. However, this could mainly affect the immediate post-injective phase, as the clinical effectiveness has been confirmed for both PRP types, with and without leucocytes, with a recent double-blind RCT demonstrating no significant difference between LP-PRP and LR-PRP in terms of clinical outcomes over time [11].

This study has some limitations. First, the RAM consensus considered all PRP formulations without discriminating amongst the product types, in line with the conclusions of the 'Formal Consensus' of ESSKA on PRP, where experts could not support different recommendations between PRP with and without leucocytes, as well as for platelet concentration, as currently, it is not possible to determine whether PRP with a high platelet concentration is more or less effective than PRP with a low platelet concentration. Considering the lack of evidence on these and other factors, including the volume of PRP injected, the

number of injections, or PRP activation, experts voted based on their experience with the type of PRP used, resulting in an overall judgement on the broad PRP approach, which represents a limitation of this consensus. Moreover, even though the RAM process developed and investigated many scenarios, the consensus still considered scenarios regarding average patients affected by knee OA, which represents an oversimplification of the patients, without accounting for all specific patient characteristics, for all possible PRP application modalities. Thus, the results of this consensus have to be considered as broad recommendations on the different factors which should be taken into account when deciding on the use of PRP injections for individual patients, rather than strict indications. Another limitation could be represented by the panel composition, which included clinicians experienced in PRP injections, and may consequently be biased in favour of PRP use. However, the aim was not to define a yes vs no answer for PRP use, but to give more complex answers. In this regard, PRP users were needed to answer questions pertaining to the clinical indications in different scenarios, as per RAM methodology, where the literature evidence should be combined with the experience of the voters. Moreover, this group of experts considered PRP appropriate in only 38.9% of the evaluated scenarios, thus confirming for the majority of scenarios a large uncertainty driven by the insufficient current evidence, and offering important indications for the clinical practice in a field where guidance is needed, being PRP already largely used. Finally, as per RAM process, this consensus did not consider the costs of PRP in relation to the other products, since the costs of the orthobiologic can differ in different countries around the world and could change over time, although costs are an important factor for both patients and the healthcare system that could influence the treatment choice in the clinical practice. Nonetheless, the focus of this consensus was on the patient benefits and the consensus process, starting from the available evidence and based on expert recommendations, identified indications where PRP could provide benefits to patients affected by knee OA.

CONCLUSIONS

This ESSKA-ICRS RAM expert consensus established recommendations on the appropriateness of PRP injections for the treatment of knee OA, providing a useful reference for the clinical practice in terms of treatment indications in specific patient categories. PRP injections are considered appropriate in patients aged ≤80 years with knee KL 0–III OA grade after failed conservative non-injective or injective treatments, while they are not considered appropriate as the first treatment nor in KL IV OA grade.

Scenarios groups

[α]: 2, 3, 5, 6, 8, 9, 11, 12, 14, 15, 17, 18, 29, 30, 32, 33, 35, 36, 38, 39, 41, 42, 44, 45, 56, 57, 59, 60, 62, 63, 65, 66, 68, 69, 71, 72, 83, 84, 86, 87, 89, 90, 92, 93, 95, 96, 98, 99, 110, 111, 113, 114, 116, 117, 119, 120, 122, 123, 125, 126, 137, 138, 140, 141, 143, 144, 146, 147, 149, 150, 152 and 153.

[β]: 52, 106, 160, 208, 211 and 214.

[γ]: 1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 55, 58, 61, 64, 67, 70, 73, 76, 79, 82, 85, 88, 91, 94, 97, 100, 103, 109, 112, 115, 118, 121, 124, 127, 130, 133, 136, 139, 142, 145, 148, 151, 154, 157, 163, 166, 169, 172, 175, 178, 181, 184, 187, 190, 193, 196, 199, 202 and 205.

[δ]: 20, 21, 23, 24, 26, 27, 47, 48, 50, 51, 53, 54, 74, 75, 77, 78, 80, 81, 101, 102, 104, 105, 107, 108, 128, 129, 131, 132, 134, 135, 155, 156, 158, 159, 161 and 162.

[ε]: 191, 194, 197, 200, 203 and 206.

[ζ]: 182, 183, 185, 186, 188, 189, 209, 210 and 213.

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AUTHOR CONTRIBUTIONS

All authors actively participated in the consensus process. Laura de Girolamo, Elizaveta Kon, Lior Laver, Mikel Sánchez, Kristof Sas and Giuseppe Filardo were part of the core panel. Isabel Andia, Jérémy Magalon, Lucienne Vonk, Luca Andriolo, Angelo Boffa and Philippe Beaufils were part of the consensus participants. Ricardo Bastos, Leela Biant, Berte Bøe, Ramon Cugat, Alessandro Di Martino, Christoph Erggelet, Michael Iosifidis, Baris Kocaoglu, Rodica Marinescu, Stefan Nehrer, Philipp Niemeyer, Marko Ostojić, Tomasz Piontek, Georges Skarpas and Thomas Tischer were part of the voting panel. The manuscript was written by Luca Andriolo and Angelo Boffa, and supervision was provided by Giuseppe Filardo. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST STATEMENT

Elizaveta Kon reports consulting for Cartiheal ldt, Green Bone, Geistlich and Bioveex and speaking for Zimmer Biomet and Fidia Farmaceutici SPA. Isabel Andia reports scientific Advisory Board of SPRY BIO, INC. Leela Biant reports research funding by Medacta International, Educational speaker for Medacta International, Consultancy for Pfizer, Bioventus and Contura. Berte Bøe reports being paid for lectures in educational courses from Smith + Nephew and Ortomedic. Lucienne Vonk reports employed by Xintela AB, senior and social media associate editor of the Journal of Cartilage & Joint Preservation, deputy co-chair of the Translational Research Committee of the ICRS. The other authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data not available for this study.

ETHICS STATEMENT

The ethics statement is not available.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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