Diagnosis and Treatment of Femoral Head Osteonecrosis: A Protocol for Development of Evidence Based Clinical Practice Guidelines

Edward Cheng (cheng002@umn.edu)  
University of Minnesota  
https://orcid.org/0000-0001-6125-9671

Michael A. Mont  
Northwell Health Orthopaedics, Lenox Hill Hospital

Stuart B. Goodman  
Stanford University Medical Center

Rafael J Sierra  
Mayo Clinic College of Medicine and Science

Quanjun Cui  
University of Virginia

Hytham S Salem  
Northwell Health Orthopaedics, Lenox Hill Hospital

ARCO Clinical Practice Guidelines Group  
N/A

Protocol

Keywords: Osteonecrosis, Hip, Diagnosis, Treatment, Clinical practice guidelines

DOI: https://doi.org/10.21203/rs.3.rs-77450/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

Background: There are many treatment options for patients who have osteonecrosis of the femoral head (ONFH) and management strategies vary widely both among and within individual countries. Although many researchers have attempted to elucidate the optimal strategies for managing this disease, the lack of large-scale randomized control trials and the lack of agreement on disease staging have curtailed the development of clear-cut guidelines.

Methods: The Association Research Circulation Osseous (ARCO) group sought to address three questions for the management of patients who have ONFH: (1) What imaging studies are most sensitive and specific for the diagnostic evaluation of patients who have ONFH?; (2) What is the best treatment strategy for preventing disease progression in patients who have pre-collapse lesions?; and (3) What is the best treatment strategy for patients who have post-collapse disease? The PICO (Patient, Intervention, Comparison, and Outcome) format was used to formulate the search strategy for each research question. A systematic review will be performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. ARCO participants have been allocated to three groups, each representing one of the PICO questions. After qualitative and quantitative analysis of the data extracted from studies pertaining to each of the three research questions, a set of evidence-based clinical practice guidelines will be proposed for the management of patients who have ONFH.

Discussion: It is not always clear which treatment method is optimal for the management of ONFH. Thus, many surgeons have developed and performed various procedures based on various patient-specific factors. As there is no consensus on the optimal treatment for various stages of disease, it was clear that developing evidence-based clinical practice guidelines would provide more structure and uniformity to management of these patients. Therefore, the results of this systematic review will lead to the development guidelines that may improve patient-care strategies and result in better outcomes for patients who have ONFH.

Systematic Review Registration: Registration with PROSPERO has been submitted and is pending.

Background

There are many treatment options for patients who have ONFH and management strategies vary widely both among and within individual countries. Although researchers have attempted to elucidate the optimal strategies for managing this disease, the lack of large-scale randomized control trials and the lack of agreement on disease staging have limited the development of clear-cut guidelines. In addition, cultural differences in patient goals and expectations, differences in the opinions of treating surgeons, and differences in the availability and access to various implants and technologies preclude widespread international agreement on optimal treatments. At a given stage of disease, it is not always clear which treatment method is superior to another. Hence, many surgeons have developed and performed various procedures based on factors such as patient age, associated risk factors, extent of femoral head
involvement, location of the infarct within the femoral head, and degree of collapse [8]. As there is no consensus on the optimal treatment for ONFH, it was clear that developing evidence-based clinical practice guidelines (CPGs) would provide more structure and uniformity, and therefore, hopefully leading to improved patient-care strategies and outcomes.

CPGs are meant to aid clinicians and patients in determining the most appropriate diagnostic and therapeutic strategies [12]. Our CPG will follow best practice as defined by GRADE (https://www.gradeworkinggroup.org/) to satisfy the AGREE II checklist criteria [13]. Some key elements include: (1) a panel of experts from multiple disciplines; (2) a PRISMA compliant (attachment 1) systematic review of the current literature;[14] (3) consideration of important patient subgroups and patient preferences; (4) clear and transparent methodology to minimize bias and conflicts of interest; (5) description of the relationship between various treatment modalities and clinical outcomes; and (6) grading the quality of evidence used to guide each recommendation [12, 15-18].

In September 2019, the ARCO board voted to pursue the development of a CPG. Shortly thereafter, an individual with expertise in CPG methodology (C.B.) was retained to facilitate a scientifically sound process. Next, the research questions were proposed and circulated to the ARCO board for approval using a process that will be described in the following section. Registration with PROSPERO has been submitted and is pending.

The ARCO board utilized the standardized PICO (Patient, Intervention, Comparison, and Outcome) format for stating the research questions that would drive the clinical practice guideline development. The PICO formula facilitates the literature search strategy used to screen for and identify the evidence needed to answer the proposed research question. In December 2019, the ARCO board convened to develop three research questions that were then proposed and circulated among the ARCO board members for approval. These research questions are were designed to focus upon clinical questions that all physicians must contemplate when managing patients. The ARCO board approved the following PICO questions:

**PICO #1:** In patients undergoing diagnostic evaluation for ONFH, what imaging studies are most sensitive and specific for:

a) Diagnosis?

b) Detecting subchondral fracture?

c) Monitoring the effect of any intervention?

d) Correlating symptomatic versus asymptomatic disease?

**PICO #2:** In patients who have ARCO stage 1-2 ONFH (without femoral head subchondral fracture or collapse):


a) What treatment is best at preventing femoral head subchondral fracture?

b) For asymptomatic patients, does treatment versus serial observation reduce the risk of femoral head subchondral fracture?

c) For symptomatic patients, should total hip arthroplasty (THA) be performed to reduce pain?

**PICO #3:** In patients who have ARCO stage 3 ONFH (with a femoral head fracture, with or without collapse) what surgical treatment (e.g., rotational osteotomy, hemiarthroplasty, surface replacement arthroplasty, total hip arthroplasty) yields the best functional outcome for patients with:

a) lifespan less than 25 years? (Older patients)

b) lifespan greater than 25 years? (Younger patients)

In summary, this paper will describe the process and development of the guidelines for (1) the diagnosis of ONFH; (2) the treatment of pre-collapse ONFH; and (3) the treatment of post-collapse ONFH.

**Methods/design**

**Study Type**

For PICO #1, we will aim to include studies that focus on diagnostic imaging, not on a treatment outcome. For PICO #2 and #3, prospective and retrospective level of evidence I to IV studies of nontraumatic ONFH will be included. Case reports and review papers will be excluded for PICO #1, #2, and #3.

**Eligibility Criteria**

Animal studies, articles without a full text English translation, and studies in which the mean patient age is less than 16 years will be excluded from the search results of PICO #1, #2, and #3.

In order to meet eligibility criteria for PICO #2 and #3, studies must use advanced imaging (CT or MRI) in addition to x-ray to assess for the presence or absence of subchondral fracture/collapse. Uniform treatment interventions must be used across the entire treatment cohorts to qualify for inclusion. In addition, radiographic evidence of disease progression (or lack thereof) must be included as an endpoint, not just conversion to THA. Also, studies must include a minimum follow-up period of 2 years in order meet eligibility criteria (Table 1).

**Interventions, Outcomes, and Comparators of Interest**

For PICO #1, we aim to compare x-ray, CT, and MRI for diagnosing and monitoring the progression of ONFH. Specifically, we will compare sensitivities and specificities of each modality for (1) diagnosing
ONFH; (2) detecting a subchondral fracture; (3) monitoring the effect of any intervention; and (4) characterizing symptomatic versus asymptomatic disease.

For PICO #2, various modalities for the treatment of ARCO stage I-II ONFH will be compared. These treatments may include conservative methods (e.g. physical therapy, oral medication, hyperbaric oxygen), core decompression alone, core decompression with adjunctive bone grafting (vascularized and non-vascularized autologous bone grafts, allogeneic bone, synthetic bone substitutes) or core decompression with ancillary cell-based therapy. The primary outcome of interest for PICO #2 will be to determine which treatment modality is most effective in preventing femoral head subchondral fracture. In addition, we will aim to compare the rates of subchondral femoral head fracture in asymptomatic patients who undergo treatment versus serial observation. We will also attempt to determine if symptomatic patients who ARCO stage I-II ONFH should undergo THA to reduce hip pain.

For PICO #3, a comparison of surgical treatment methods for patients who have ARCO stage III ONFH will be performed. These treatment modalities will include rotational osteotomy, hemiarthroplasty, surface replacement arthroplasty, THA and others. We will aim to determine which surgical treatment yields the best functional outcome over time frames of (1) less than 25 years; and (2) greater than 25 years. In doing so, we hope to elucidate which treatment methods are most appropriate for older patient populations (< 25-year time frame) compared to their younger counterparts (> 25-year time frame).

**Information Sources and Search Strategy**

Medline (via Ovid and PubMed), EMBASE (via Ovid), Web of Science Core Collection, SCOPUS, Global Index Medicus, and The Cochrane Library (via Wiley) were utilized as databases for our literature search. The search strategies for identifying studies for each PICO question were created with the assistance of a research librarian (CB). They were then refined using the commentary from the remaining board members. Table 2 outlines the search strategies that were approved for each of the three research questions. Following the creation of these search strategies, participants were assigned to each of the three PICO groups and the agenda and goals for each research question were established.

Following the first literature screening performed by the members of each PICO group, a second virtual workshop was held to discuss full-text literature screening and data abstraction. After this workshop, in order to ensure the veracity and thoroughness of the literature search, all participants were asked to review the literature captured by the searches for any missing articles, review the search strategies, and submit any potential missing articles. This step was implemented in order to enhance the comprehensiveness and confidence of the literature searches. Furthermore, once this supplemental manual review was completed, a survey of all PICO group members was undertaken to ensure that consensus had been achieved with respect to the adequacy of the literature search.

**Screening and Full-Text Review**
A web application (Rayyan, Qatar Computing Research Institute, https://rayyan.qcri.org) was used to facilitate effective collaboration among workshop members. The members of each PICO group independently screened the titles and abstracts of all records identified in their respective literature searches. The group chairs for PICO #1 (EYC), PICO #2 (QC), and PICO #3 (SBG) resolved any discrepancies that resulted from the initial reviews.

At this point, the group chairs were confident that the best evidence to use for supporting a CPG were captured. To ensure consensus at this step in the development process, a survey of all participants was undertaken to verify that the gathered evidence and CPG development process were appropriate and acceptable. There was unanimous agreement to proceed with full-text screening, assessment of methodological quality, data abstraction, and evidence synthesis as preparation for the development of recommendations.

Handling Missing Data

In the case that any data reported in a study are unclear or not available, we will email the corresponding author to request the missing data, as well as any other unpublished data. If there is no response, an additional email will be sent 2 weeks later. If 2 weeks elapse following the second email, we will attempt to contact the first author or senior author (if not listed for correspondence). All attempts to contact these authors will be documented.

Risk of Bias in Individual Studies

Two independent reviewers from each PICO group will assess the risk of bias for each study using validated instruments to evaluate methodological quality and quantify study limitations. The instrument used will depend on the study design. For studies evaluating diagnostic accuracy (PICO #1), the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool [19, 20] will be utilized to evaluate the risk of bias. For non-randomized observational studies, the Newcastle-Ottawa Scale (NOS) [21] or the ROBINS-I scale [22] will be used for methodological quality assessment. Lastly, the risk of bias tool (RoB 2) developed by the Cochrane Collaboration will be used for risk of bias assessment for randomized control trials [23]. The risk of bias will also be assessed across multiple studies (Meta-bias) including the detection of publication bias.

Data Synthesis

Extracted data will be organized according to outcome of interest within each PICO question in order to determine if quantitative synthesis is appropriate. At least two authors will extract data from each included study and record the pertinent information in a shared spreadsheet. If any disagreement occurs in the data extracted by individual authors, the group chair will resolve the discrepancy. Heterogeneity will be assessed using the $I^2$ statistic, and an $I^2$ of above 40% will be considered significant. Should there be significant heterogeneity, no quantitative synthesis will be undertaken. If data is pooled, sensitivity analysis may be conducted to ensure that no one study has undue influence on a particular outcome. If
quantitative synthesis is inappropriate, data will be presented in a tabular and narrative format and organized to address each recommendation and its associated outcomes. The quality of evidence used to synthesize each recommendation will be assessed using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) rating system.[24]

Discussion

There are many treatment options for patients who have osteonecrosis of the femoral ONFH and management strategies vary widely both among and within individual countries. Therefore, the ARCO board sought to develop a high-quality CPG. In order to do so, they consulted with the American Academy of Orthopaedic Surgeons and other outside consultants. A research librarian (CB) with expertise in systematic reviews and CPG’s was retained to both lead and guide proper procedural development and adherence to the AGREE II instrument was undertaken to apply the required rigor to create a clinically useful and meaningful CPG free of bias [13]. Given the 3 PICO research questions, a participant group for each question was established composed of international experts drawn from within ARCO (Table 3). Each group was led by a chair, who also represented the group at the leadership level. An independent website (https://sites.google.com/umn.edu/arcocpg/home) was established to provide a central repository for the protocol, forms, and study files readily accessible by all participants at any time. The broad international representation spanning 16 time zones created logistical challenges for holding virtually based workshops. Nonetheless, over 95% of the participants attended these workshops and in addition, a video recording of the workshop, along with the slide deck, was posted on the project website. Due to the 2019 coronavirus pandemic, the first workshop was held virtually in March 2020 to review the CPG process and PICO questions, to train participants for literature screening, and to agree upon the inclusion and exclusion criteria that were used to determine the eligibility of identified articles.

Rationale for PICO #1:

ONFH frequently follows a progressive course with a majority of lesions leading to joint collapse [25, 26]. Femoral head collapse typically occurs within two years of disease onset [26, 27], but could sometimes progress more slowly in the setting of smaller asymptomatic lesions [28]. The occurrence of joint collapse necessitates THA. However, when identified in its early stages, joint preserving strategies can be employed to delay or prevent the need for THA. Because this disease tends to affect younger patients, the importance of prompt diagnosis and treatment cannot be overstated. Due to the difficulty in determining the best diagnostic and prognostic signs of ONFH, the available classification systems continue to evolve. As previously stated, ARCO recently published a newly revised iteration of their classification system [11]. Although it is hoped this system will be universally utilized, further work is needed to assess the importance of prognostic factors including lesion size, location, and acetabular involvement. In addition, it is imperative to determine the optimal imaging modalities for diagnosing ONFH, staging the extent of lesions, and monitoring the course of disease. While standard radiographs can sometimes be sufficient for the diagnosis and characterization of a given lesion, it is important to delineate when magnetic resonance (MR) or computed tomography (CT) imaging studies should be pursued. The above
concepts and issues concerned with imaging, diagnosis, and classification of the disease need to be evaluated, and are the subject of the first research question in the development of these proposed guidelines.

*Rationale for PICO #2*

Given the natural history of ONFH, it is clear that a high priority goal of treatment is to prevent subchondral collapse when lesions are diagnosed in the early stages of disease. For example, many studies support core decompression as a safe and effective treatment method that outperforms nonoperative management for pre-collapse lesions [25, 27, 29, 30]. Nevertheless, some surgeons advocate core decompression only for smaller lesions, as the results are not as favorable for larger lesions [31]. However, some smaller lesions have been shown to have a better prognosis regardless of any intervention, and at times, may even resolve spontaneously [32, 33]. This raises the question of when core decompression should be performed for a clear benefit, and recent meta-analyses and clinical trials have questioned its efficacy [30, 34, 35]. This has led to surgeons modifying either the technical procedure or augmenting the procedure biologically with grafts, growth factors, cell based therapies, or synthetic bone substitutes. While small-diameter drilling may provide the same clinical benefit as traditional core decompression [36, 37], the implications of performing one variant versus the other is not fully understood. In addition, attempts have been made to enhance the results of core decompression with various cell-based adjuncts, bone graft preparations, and bone morphogenetic proteins. When considering stand-alone bone grafting procedures, there is an assortment of techniques (e.g., vascularized and non-vascularized grafts) and harvest sites, as well as varying approaches for graft insertion [38-51]. Various other procedures including multiple types of osteotomies can also be utilized in an attempt to preserve the femoral head [52-58]. Without evidence-based CPGs, it is difficult to establish which strategy is ideal across various patient populations. Thus, these strategies are the subject of the second research question in the development of these proposed guidelines.

*Rationale for PICO #3*

For patients whose femoral head is no longer spherical due to impaction of a segment of underlying subchondral bone (collapse), THA is typically the treatment of choice for most patients. The clinical challenge is that all too often, osteonecrosis develops in a teenager or young adult. Despite the excellent pain relief afforded by hip arthroplasty, the long-term performance and durability of a current hip arthroplasty implanted in patients who have a life expectancy of over 25 years is unknown. For these patients, attempts to preserve the femoral head by performing osteotomies or bone grafting procedures might delay or prevent the need for an arthroplasty, but the degree of improvement in pain and function may be suboptimal. In contrast to traditional THA implants, short-stem femoral components are sometimes used in an attempt to preserve metaphyseal bone stock [59-64]. However, the true implications of employing these implant designs in the setting of osteonecrosis has not been confirmed. In addition, other treatment strategies including, hemiarthroplasty, and surface replacement arthroplasty may be viable options. However, the surgical treatment that yields the best pain relief and functional outcome has
not been clearly established. To this end, the ARCO has set out to establish evidence-based CPG for the treatment of ONFH.

In summary, the project methodology has progressed as follows:

- 09/2019: ARCO board votes to pursue CPG at Orlando 2020 workshop
- 10/2019: Exploratory discussions with AAOS undertaken
- 10/2019: Research services liaison joins CPG process as content expert and facilitator
- 12/2019: PICO questions proposed, circulated to board for comment and approval
- 11/2019 – 01/2020: Orlando workshop agenda for development of CPG established
- 01/2020 – 02/2020: Literature search strategy was refined in preparation for workshop; web-based platform (Rayyan) tested for usage by workshop participants
- 02/2020: Workshop participants assigned to PICO groups and agenda/goals established
- 03/2020: First workshop on CPG held virtually due to COVID-19 pandemic. PICO questions and CPG process reviewed, training given for literature screening, inclusion and exclusion criteria agreed upon by participants
- 04/2020: First literature screening completed
- 05/2020: Second workshop held virtually, full-text screening and data abstraction training.
- 05/2020 - 06/2020: Open period to submit potential missing articles and review/revise search strategy
- 06/2020: Conference of PICO group chairs and CPG expert
- 07/2020: Full text screening
- 08/2020: Assess Methodological Quality
- 09/2020 – 11/2020: Synthesize Evidence
- 12/2020 – 2/2021: Develop Recommendations

Summary

Guidelines for the optimal method of diagnosing ONFH and identifying subchondral fracture or femoral head collapse have not been clearly established. For patients who have ONFH without subchondral fracture, the best treatment method for preventing progression of disease is yet to be clearly elucidated. In addition, for patients who have ARCO stage 3 lesions with femoral head subchondral fracture, the surgical treatment that yields the best clinical outcomes is not fully understood. By pursuing the development of evidence-based CPGs for each of these three research questions, the ARCO board hopes to provide clinicians and patients guidance in determining the most appropriate diagnostic and therapeutic strategies ONFH.

List Of Abbreviations
Declarations

Ethics approval and consent to participate
Not applicable

Consent for publication
Not applicable

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests
EYC: Association Research Circulation Osseous International (ARCO): Board or committee member
Innomed: IP royalties
Journal of Bone and Joint Surgery - American: Editorial or governing board; Publishing royalties, financial or material support
Musculoskeletal Transplant Foundation: Board or committee member; Other financial or material support
Rein in Sarcoma (Research grant): Research support

Smith & Nephew: Other financial or material support

MAM:

AAOS: Board or committee member

American Association of Hip and Knee Surgeons: Board or committee member

CERAS Health: Stock or stock Options

Cymedica: Paid consultant

Flexion Therapeutics: Paid consultant

Johnson & Johnson: Paid consultant; Research support

Journal of Arthroplasty: Editorial or governing board

Journal of Knee Surgery: Editorial or governing board

Knee Society: Board or committee member

Kolon TissueGene: Paid consultant

Medicus Works LLC: Publishing royalties, financial or material support

MirrorAR: Stock or stock Options

National Institutes of Health (NIAMS & NICHD): Research support

Orthopedics: Editorial or governing board

Pacira: Paid consultant

Peerwell: Stock or stock Options

Pfizer: Paid consultant

RegenLab: Research support

Stryker: IP royalties; Paid consultant; Research support

Surgical Techniques International: Editorial or governing board

TissueGene: Research support
Up-to Date: Publishing royalties, financial or material support

USMI: Stock or stock Options

Wolters Kluwer Health - Lippincott Williams & Wilkins: Publishing royalties, financial or material support

SBG:

Accelalox: Stock or stock Options; Unpaid consultant

ARCO: Board or committee member

Arquos: Stock or stock Options

Bioengineering: Editorial or governing board

Biomaterials: Editorial or governing board; Publishing royalties, financial or material support

Bone and Joint Research: Editorial or governing board

Clinical Orthopaedics and Related Research: Editorial or governing board

Hyalex: IP royalties; Stock or stock Options

J Arthroplasty: Editorial or governing board

J Biomed Mater Res: Editorial or governing board

Journal of Orthopaedic Research: Editorial or governing board; Publishing royalties, financial or material support

Journal of Orthopaedic Translation: Editorial or governing board

Merck Manual: Publishing royalties, financial or material support

Open Orthopaedics Journal: Editorial or governing board

Orthopedics: Editorial or governing board

PLOS ONE: Editorial or governing board

Pluristem: Paid consultant

Regenerative Engineering and Translational Medicine: Editorial or governing board

Wishbone Medical: Paid consultant

RJS:
American Association of Hip and Knee Surgeons: Board or committee member

Anchor study group: Board or committee member

Biomet: Paid consultant; Paid presenter or speaker

Cytori: Research support

DePuy, A Johnson & Johnson Company: Research support

Journal of Arthroplasty: Editorial or governing board

Knee Society: Board or committee member

Link Orthopaedics: IP royalties; Paid consultant

Midamerica orthopedic society: Board or committee member

Muller Foundation: Board or committee member

Orthalign: IP royalties

Orthoalign: Paid consultant; Stock or stock Options

Springer: Publishing royalties, financial or material support

Stryker, Biomet: Research support

Think: Paid consultant

Zimmer: IP royalties; Research support

QC:

ARCO: Board or committee member

DePuy, A Johnson & Johnson Company: Research support

Exactech, Inc: Paid consultant; Research support

Journal of Arthroplasty: Editorial or governing board

Journal of Orthopaedic Research: Editorial or governing board

Saunders/Mosby-Elsevier: Publishing royalties, financial or material support

Virginia Orthopaedic Society: Board or committee member
HSS:
No competing interests to disclose

**Funding:**

This study was not funded.

**Authors' contributions**

The listed authors have drafted and edited the manuscript. All authors have approved the submitted version of the manuscript and have agreed both to be personally accountable for the work, ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and documented in the literature. The entire Clinical Practice Guideline group has reviewed, submitted edits, and approved the protocol.

**Acknowledgements**

ARCO Clinical Practice Guideline workgroup, in addition to listed authors (in alphabetical order):

Ando, Wataru; Baek, Seung-Hoon; Bakker, Caitlin J; Drescher, Wolf; Ha, Yong-Chan; Hemigou, Philippe; Jones, Lynne C; Kim, Harry; Kim, Shin-Yoon; Kim, Tae-Young; Koo, Kyung-Hoi; Lee, Mel; Reichert, Ines; Sakai, Takashi; Stronach, Ben; Sugano, Nobuo; Yamamoto, Takuaki; Yoon, Byung-Ho; and Zhao, Dewei

Institutional affiliations for ARCO CPG workgroup:
<table>
<thead>
<tr>
<th>Name</th>
<th>Email</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wataru Ando, MD, PhD</td>
<td><a href="mailto:w-ando@umin.ac.jp">w-ando@umin.ac.jp</a></td>
<td>Osaka University, Osaka, Japan</td>
</tr>
<tr>
<td>Caitlin Bakker, MLIS</td>
<td><a href="mailto:cjbakker@umn.edu">cjbakker@umn.edu</a></td>
<td>University of Minnesota, Minneapolis, USA</td>
</tr>
<tr>
<td>Seung-Hoon Baek, MD PhD</td>
<td><a href="mailto:sbaek@knu.ac.kr">sbaek@knu.ac.kr</a></td>
<td>Kyungpook National University, Daegu, South Korea</td>
</tr>
<tr>
<td>Edward Y. Cheng, MD</td>
<td><a href="mailto:cheng002@umn.edu">cheng002@umn.edu</a></td>
<td>University of Minnesota, Minneapolis, USA</td>
</tr>
<tr>
<td>Quanjun Cui, MD</td>
<td><a href="mailto:qc4q@hscmail.mcc.virginia.edu">qc4q@hscmail.mcc.virginia.edu</a></td>
<td>University of Virginia, Charlottesville, USA</td>
</tr>
<tr>
<td>Wolf Drescher, MD</td>
<td><a href="mailto:wolf.drescher@sana.de">wolf.drescher@sana.de</a></td>
<td>Department of Orthopedics, RWTH Aachen University, Aachen, Germany</td>
</tr>
<tr>
<td>Stuart Goodman, MD, PhD</td>
<td><a href="mailto:goodbone@stanford.edu">goodbone@stanford.edu</a></td>
<td>Stanford University, Palo Alto, USA</td>
</tr>
<tr>
<td>Yong-Chan Ha, MD</td>
<td><a href="mailto:hayongch@naver.com">hayongch@naver.com</a></td>
<td>Chung-Ang University, Seoul, South Korea</td>
</tr>
<tr>
<td>Philippe Hernigou, MD</td>
<td><a href="mailto:philippe.hernigou@wanadoo.fr">philippe.hernigou@wanadoo.fr</a></td>
<td>Hôpital Henri Mondo, Paris, France</td>
</tr>
<tr>
<td>Lynne C. Jones, PhD</td>
<td><a href="mailto:ljones3@jhmi.edu">ljones3@jhmi.edu</a></td>
<td>Johns Hopkins University, Baltimore, USA</td>
</tr>
<tr>
<td>Harry K. W. Kim, MD</td>
<td><a href="mailto:harry.kim@tsrh.org">harry.kim@tsrh.org</a></td>
<td>Scottish Rite for Children, Dallas, USA</td>
</tr>
<tr>
<td>Shin-Yoon Kim, MD, PhD</td>
<td><a href="mailto:syukim@knu.ac.kr">syukim@knu.ac.kr</a></td>
<td>Kyungpook National University, Daegu, South Korea</td>
</tr>
<tr>
<td>Tae-Young Kim, MD, PhD</td>
<td><a href="mailto:syty-chan@hanmail.net">syty-chan@hanmail.net</a></td>
<td>Konkuk University, Seoul, South Korea</td>
</tr>
<tr>
<td>Kyung-Hoi Koo, MD</td>
<td><a href="mailto:khkoo@snu.ac.kr">khkoo@snu.ac.kr</a></td>
<td>Seoul National University College of Medicine, Seoul, South Korea</td>
</tr>
<tr>
<td>Mel Lee, MD, PhD</td>
<td><a href="mailto:bone@doctor.com">bone@doctor.com</a></td>
<td>Chang Gung Memorial Hospital, Kaohsiung, Taiwan</td>
</tr>
<tr>
<td>Michael Mont, MD</td>
<td><a href="mailto:rhondamont@aol.com">rhondamont@aol.com</a></td>
<td>Lenox Hill Hospital, New York, USA</td>
</tr>
<tr>
<td>Ines Reichert, MD, PhD</td>
<td><a href="mailto:ines.reichert@kcl.ac.uk">ines.reichert@kcl.ac.uk</a></td>
<td>Kings College Hospital, London, United Kingdom</td>
</tr>
<tr>
<td>Takashi Sakai, MD, PhD</td>
<td><a href="mailto:cozy@yamaguchi-u.ac.jp">cozy@yamaguchi-u.ac.jp</a></td>
<td>Yamaguchi University Graduate School of Medicine, Ube, Japan</td>
</tr>
<tr>
<td>Rafael J. Sierra, MD</td>
<td><a href="mailto:sierra.rafael@mayo.edu">sierra.rafael@mayo.edu</a></td>
<td>Mayo Clinic, Rochester, USA</td>
</tr>
<tr>
<td>Benjamin M Stronach, MD</td>
<td><a href="mailto:bstronach@umc.edu">bstronach@umc.edu</a></td>
<td>University of Mississippi, Jackson, USA</td>
</tr>
<tr>
<td>Nobuhiko Sugano, MD, PhD</td>
<td><a href="mailto:n-sugano@umin.net">n-sugano@umin.net</a></td>
<td>Osaka University, Osaka, Japan</td>
</tr>
<tr>
<td>Takuaki Yamamoto, MD, PhD</td>
<td><a href="mailto:yamamotot@fukuoka-u.ac.jp">yamamotot@fukuoka-u.ac.jp</a></td>
<td>Fukuoka University, Fukuoka City, Japan</td>
</tr>
</tbody>
</table>
References


Tables

Table 1. Inclusion and Exclusion Criteria for each Research Question
### PICO #1

**Inclusion:**
- Focus of article is on imaging, not on a treatment outcome
- Humans only
- Adult population only (age $\geq 16$ years)

**Exclusion:**
- Animal studies
- Foreign language without full text English translation
- Single case reports
- Articles that do not present original data (e.g., reviews, editorials)

### PICO #2

**Inclusion:**
- Evidence level 1-4
- Case series $> 15$ patients
- Human only
- Prospective or retrospective
- Diagnosis = non-traumatic ONFH
- Treatment intervention is uniform across entire treatment cohort
- Outcome includes radiographic progression, not only conversion to total hip arthroplasty
- Follow-up: $\geq 2$ years

**Exclusion:**
- Animal studies
- Foreign language without full text English translation
- Single case reports
- No duplicate papers or patient cohorts
- Articles that do not present original data (e.g., reviews, editorials)

### PICO #3

**Inclusion:**
- Evidence level 1-4
- Case series $> 15$ patients
- Human only
- Prospective or retrospective
- Diagnosis = non-traumatic ONFH
- Staging data provided
- Treatment intervention is uniform across entire treatment cohort
- Outcome data provided
- Follow-up: $\geq 2$ years

**Exclusion:**
- Animal studies
- Foreign language without full text English translation
- Single case reports
- No duplicate papers or patient cohorts
- Articles that do not present original data (e.g., reviews, editorials)

---

**Table 2.** Search Strategies in Medline Format*
<table>
<thead>
<tr>
<th>PICO #1</th>
<th>PICO #2</th>
<th>PICO #3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. osteonecrosis/</td>
<td>1. osteonecrosis/</td>
<td>1. osteonecrosis/</td>
</tr>
<tr>
<td>2. exp Osteonecrosis/</td>
<td>2. exp Osteonecrosis/</td>
<td>3. exp Femur Head/</td>
</tr>
<tr>
<td>3. exp Femur Head/</td>
<td>3. exp Femur Head/</td>
<td>4. (1 or 2) and 3</td>
</tr>
<tr>
<td>4. (1 or 2) and 3</td>
<td>5. exp Femur Head Necrosis/</td>
<td>5. exp Femur Head Necrosis/</td>
</tr>
<tr>
<td>6. ((femur or femoral) adj2 head).tw,kw.</td>
<td>6. ((femur or femoral) adj2 head).tw,kw.</td>
<td>6. ((femur or femoral) adj2 head).tw,kw.</td>
</tr>
<tr>
<td>7. (avascular or aseptic or ischemic) adj2 (necrosis or neerces).tw,kw.</td>
<td>7. (avascular or aseptic or ischemic) adj2 (necrosis or neerces).tw,kw.</td>
<td>7. (avascular or aseptic or ischemic) adj2 (necrosis or neerces).tw,kw.</td>
</tr>
<tr>
<td>9. or/7-8</td>
<td>9. or/7-8</td>
<td>9. or/7-8</td>
</tr>
<tr>
<td>10. 6 and 9</td>
<td>10. 6 and 9</td>
<td>10. 6 and 9</td>
</tr>
<tr>
<td>11. onth.tw,kw</td>
<td>11. onth.tw,kw</td>
<td>11. onth.tw,kw</td>
</tr>
<tr>
<td>12. or/4,5,10-11</td>
<td>12. or/4,5,10-11</td>
<td>12. or/4,5,10-11</td>
</tr>
<tr>
<td>13. exp Diagnostic Imaging/</td>
<td>13. exp Diagnostic Imaging/</td>
<td>13. (ARCO adj5 &quot;3* or three or &quot;4 or four&quot;).tw,kw</td>
</tr>
<tr>
<td>14. ((diagnostic or &quot;magnetic resonance&quot; or medical) adj2 image*).tw,kw.</td>
<td>14. ((diagnostic or &quot;magnetic resonance&quot; or medical) adj2 image*).tw,kw.</td>
<td>14. (fracture* adj2 (fracture OR femoral) adj2 head*).tw,kw</td>
</tr>
<tr>
<td>15. &quot;diagnostic imaging&quot;.fs.</td>
<td>15. &quot;diagnostic imaging&quot;.fs.</td>
<td>15. exp Femur Head/</td>
</tr>
<tr>
<td>16. mri* or tomograph* or radiograph* or ultrasonograph* or x-ray).tw,kw.</td>
<td>16. mri* or tomograph* or radiograph* or ultrasonograph* or x-ray).tw,kw.</td>
<td>16. exp Hip Fractures/</td>
</tr>
<tr>
<td>17. (ct or cat) adj2 scan*).tw,kw.</td>
<td>17. (ct or cat) adj2 scan*).tw,kw.</td>
<td>17. 15 and 16</td>
</tr>
<tr>
<td>18. or/13-17</td>
<td>18. or/13-17</td>
<td>18. 13 OR 14 OR 17</td>
</tr>
<tr>
<td>20. sensitivity.tw,kw</td>
<td>20. sensitivity.tw,kw</td>
<td>20. exp Orthopedic Procedures/</td>
</tr>
<tr>
<td>22. (pre-test or pretest) adj probability).tw,kw</td>
<td>22. (pre-test or pretest) adj probability).tw,kw</td>
<td>22. (surgery* or surgical).tw,kw</td>
</tr>
<tr>
<td>24. predictive value*.tw,kw</td>
<td>24. predictive value*.tw,kw</td>
<td>24. or/19-23</td>
</tr>
<tr>
<td>25. likelihood ratio*.tw,kw</td>
<td>25. likelihood ratio*.tw,kw</td>
<td>25. 12 and 18 and 27</td>
</tr>
<tr>
<td>27. or/20-27</td>
<td>27. or/20-27</td>
<td>27. exp Animals/</td>
</tr>
<tr>
<td>28. and 12 and 18 and 27</td>
<td>28. and 12 and 18 and 27</td>
<td>28. 25 not 24</td>
</tr>
<tr>
<td>29. exp Humans/</td>
<td>29. exp Humans/</td>
<td>28. 25 not 24</td>
</tr>
<tr>
<td>30. exp Animals/</td>
<td>30. exp Animals/</td>
<td>29. 21 not 26</td>
</tr>
<tr>
<td>31. 30 not 29</td>
<td>31. 30 not 29</td>
<td>30. exp Adults/</td>
</tr>
<tr>
<td>32. 28 not 31</td>
<td>32. 28 not 31</td>
<td>31. exp Child/ or exp Infant/ or exp Adolescent/</td>
</tr>
<tr>
<td>33. exp adults/</td>
<td>33. exp adults/</td>
<td>32. 29 not 28</td>
</tr>
<tr>
<td>34. exp child/ OR exp infant/ OR exp adolescent/</td>
<td>34. exp child/ OR exp infant/ OR exp adolescent/</td>
<td>33. 31 not 34</td>
</tr>
<tr>
<td>35. 34 not 33</td>
<td>35. 34 not 33</td>
<td>34. .dedup 35</td>
</tr>
<tr>
<td>36. 32 not 35</td>
<td>36. 32 not 35</td>
<td>35. .dedup 35</td>
</tr>
<tr>
<td>38. (letter or commentary or editorial).pt</td>
<td>38. (letter or commentary or editorial).pt</td>
<td>37. .dedup 35</td>
</tr>
<tr>
<td>39. 37 or 38</td>
<td>39. 37 or 38</td>
<td>38. .dedup 37</td>
</tr>
<tr>
<td>40. 36 not 39</td>
<td>40. 36 not 39</td>
<td>39. .dedup 37</td>
</tr>
<tr>
<td>41. .dedup 40</td>
<td>41. .dedup 40</td>
<td>40. .dedup 40</td>
</tr>
</tbody>
</table>

*Italics refer to controlled vocabulary/taxonomy terms
Color-coding represents different concepts being captured in each search

Table 3. Group chairs and participants for each research question
<table>
<thead>
<tr>
<th>Group Chair:</th>
<th>PICO Group 1</th>
<th>PICO Group 2</th>
<th>PICO Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edward Y. Cheng, MD</td>
<td>Quanjun Cui, MD</td>
<td>Stuart B. Goodman, MD, PhD</td>
<td></td>
</tr>
<tr>
<td>Kyung-Hoi Koo, MD</td>
<td>Harry Kim, MD</td>
<td>Benjamin M. Stronach, MD</td>
<td></td>
</tr>
<tr>
<td>Takashi Sakai, MD</td>
<td>Michael A. Mont, MD</td>
<td>Byung-Ho Yoon, MD</td>
<td></td>
</tr>
<tr>
<td>Group Members:</td>
<td>Lynne C. Jones, MD</td>
<td>Nobuhiko Sugano, MD</td>
<td>Rafael J. Sierra, MD</td>
</tr>
<tr>
<td>Takuaki Yamamoto, MD</td>
<td>Phillipe Hernigou, MD</td>
<td>Seung-Hoon Baek, MD, PhD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wolf Drescher, MD</td>
<td>Tae-Young Kim, MD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shin-Yoon Kim, MD</td>
<td>Wataru Ando, MD, PhD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>De-Wei Zhao, MD</td>
<td>Yong-Chan Ha, MD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ines Reichert, MD, PhD</td>
<td>Mel Lee, MD, PhD</td>
<td></td>
</tr>
</tbody>
</table>

**Figures**
**PICO 1 group**
Edward Cheng MD (group chair)  
Kyung-Hoi Koo, MD  
Takashi Sakai  
Lynne Jones, PhD  
Takuaki Yamamoto  

University of Minnesota  
Seoul National University  
Yamaguchi University  
Johns Hopkins University  
yamamotot@fukuoka-u.ac.jp

**PICO 2 group**
Quanjun Cui, MD (group chair)  
Harry Kim, MD  
Michael Mont, MD  
Nobuo Sugano MD, PhD  
Philippe Hemigou, MD  
Wolf Drescher, MD  
Shin-Yoon Kim, MD  
Zhao Dewei, MD  
Ines Reichert, MD, PhD  

University of Virginia  
Texas Scottish Rite Hospital  
Northwell Health  
Osaka University  
University of Paris - Est  
RWTH Aachen University  
Kyungpook National University  
Dalian University  
King’s College Hospital

**PICO 3 group**
Stuart Goodman (group chair)  
Ben Stronach  
Byung-Ho Yoon  
Rafael Sierra  
Seung-Hoon Baek  
Tae-Young Kim  
Wataru Ando  
Yong-Chan Ha, MD  
Mel Lee, MD, PhD  

Stanford University  
University of Mississippi  
Seoul National University  
Mayo Clinic  
Kyungpook National University  
Konkuk University  
Osaka University  
Chung-Ang University  
Chang Gung Memorial Hospital

**Figure 1**

PICO study groups

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- [ONFHCPRISMAchecklist.docx](#)