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The 2018 Definition of Periprosthetic Hip and Knee Infection: An Evidence-Based and Validated Criteria

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ABSTRACT

Background: The introduction of the Musculoskeletal Infection Society (MSIS) criteria for periprosthetic joint infection (PJI) in 2011 resulted in improvements in diagnostic confidence and research collaboration. The emergence of new diagnostic tests and the lessons we have learned from the past 7 years using the MSIS definition, prompted us to develop an evidence-based and validated updated version of the criteria.
Methods: This multi-institutional study of patients undergoing revision total joint arthroplasty was conducted at 3 academic centers. For the development of the new diagnostic criteria, PJI and aseptic patient cohorts were stringently defined: PJI cases were defined using only major criteria from the MSIS definition (n = 684) and aseptic cases underwent one-stage revision for a noninfective indication and did not fail within 2 years (n = 820). Serum C-reactive protein (CRP), D-dimer, erythrocyte sedimentation rate were investigated, as well as synovial white blood cell count, polymorphonuclear percentage, leukocyte esterase, alpha-defensin, and synovial CRP. Intraoperative findings included frozen section, presence of purulence, and isolation of a pathogen by culture. A stepwise approach using random forest analysis and multivariate regression was used to generate relative weights for each diagnostic marker. Preoperative and intraoperative definitions were created based on beta coefficients. The new definition was then validated on an external cohort of 222 patients with PJI who subsequently failed with reinfection and 200 aseptic patients. The performance of the new criteria was compared to the established MSIS and the prior International Consensus Meeting definitions.
Results: Two positive cultures or the presence of a sinus tract were considered as major criteria and diagnostic of PJI. The calculated weights of an elevated serum CRP (>1 mg/dL), D-dimer (>860 ng/mL), and erythrocyte sedimentation rate (>30 mm/h) were 2, 2, and 1 points, respectively. Furthermore, elevated synovial fluid white blood cell count (>3000 cells/μL), alpha-defensin (signal-to-cutoff ratio >1), leukocyte esterase (++), polymorphonuclear percentage (>80%), and synovial CRP (>6.9 mg/L) received 3, 3, 3, 2, and 1 points, respectively. Patients with an aggregate score of greater than or equal to 6 were considered infected, while a score between 2 and 5 required the inclusion of intraoperative findings for confirming or refuting the diagnosis. Intraoperative findings of positive histology, purulence, and single positive culture were assigned 3, 3, and 2 points, respectively. Combined with the preoperative score, a total of greater than or equal to 6 was considered infected, a score between 4 and 5 was inconclusive, and a score of 3 or less was not infected. The new criteria demonstrated a higher sensitivity of 97.7% compared to the MSIS (79.3%) and International Consensus Meeting definition (86.9%), with a similar specificity of 99.5%.
Conclusion: This study offers an evidence-based definition for diagnosing hip and knee PJI, which has shown excellent performance on formal external validation.

Diagnosing periprosthetic joint infection (PJI) of the hip and knee remains a major challenge as there is no test with absolute accuracy [1,2]. The diagnosis of PJI is based on a combination of clinical findings, laboratory results from peripheral blood and synovial fluid, microbiological culture, histological evaluation of periprosthetic tissue, and intraoperative findings.

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The Musculoskeletal Infection Society (MSIS) and the Infectious Diseases Society (IDSA) have previously developed criteria to standardize the definition of PJI [3,4]. A further consensus meeting in 2013 endorsed the MSIS definition of PJI and modified it slightly [5]. These definitions have become widely accepted among surgeons worldwide and have dramatically improved diagnostic confidence and facilitated treatment. Moreover, their use in research allowed for consistency in definition between studies and enhanced the potential for collaboration and the overall quality of literature. However, existing guidelines were largely generated by expert opinions and have not been validated. Furthermore, while relatively specific, there is concern about the sensitivity of the current definitions [6].

Although definite evidence or major criteria for infection are identical between the different definitions, the supportive evidence or minor criteria differ and are less agreed upon. In the recent years, numerous markers have been evaluated and become available [7–9], including serum D-dimer [10], synovial leukocyte esterase (LE) [11–13], synovial alpha-defensin [14,15], synovial C-reactive protein (CRP) [16,17], and molecular techniques such as next-generation sequencing [18]. Moreover, publications in the recent years have shown different weights (sensitivity and specificity) for the various tests used [9,19] and highlight the value of a high pretest probability in the overall diagnosis [14,20,21].

These advancements in the field of PJI diagnosis call for the modification of current diagnostic criteria to an evidence-based one that is inclusive of the recent tests and considers the relative weights of the different tests. The purpose of this multi-institutional study was, thus, to: (1) generate an evidence-based, weight-adjusted scoring system for the definition of PJI of hip and knee, (2) validate it on an external cohort, and (3) compare its performance against currently available definitions.

Materials and Methods

After the institutional review board approval, we conducted a retrospective review of the medical records of all patients undergoing revision total hip arthroplasty (THA) and total knee arthroplasty (TKA) arthroplasty from 3 academic centers between January 2001 and July 2016. We excluded patients without serum erythrocyte sedimentation rate (ESR) or serum CRP, as well as those without a joint aspiration or an attempt at aspiration. Patients in whom the aspiration or serum testing was performed more than 8 weeks before surgery were also excluded.

Patient Population

Developmental Model

Patients were classified as having a PJI if they met major diagnostic criteria of MSIS and International Consensus Meeting (ICM) [3–5], namely the presence of a sinus tract (with evidence of communication to the joint or visualization of the prosthesis) or 2 positive cultures isolating the same pathogen from the periprosthetic tissue or synovial fluid samples. Patients coded as infected who did not meet these definitions and those with megaprosthesis or missing surgical data were excluded from the study. In addition, we excluded acute PJI cases, defined as occurring less than 3 months from the index arthroplasty, and acute hematogenous PJI, defined as acute symptoms occurring for less than 6 weeks but more than 3 months from index surgery. Aseptic revisions were defined as cases undergoing single-stage revision for a diagnosis other than infection (loosening, wear, instability, malalignment, adverse local tissue reactions, or other aseptic causes) who did not fail with infection, nor had any further reoperation on the same joint.

Validation of the New Criteria

We performed external validation on separate patients from the same 3 institutions, who were not included in the initial developmental model. This validation was performed on a group of PJI and aseptic patients.

PJI Cases. As there is no "gold standard" for PJI, we chose a representative sample of infected cases that was independent from any intrinsic bias from the commonly used definitions for infection. This group composed of patients who were treated as PJI cases (undergoing 2-stage revision THA and TKA) and failed with a reinfection within 1 year. All these patients were coded as infected (based on the International Classification of Diseases, Ninth Revision codes for PJI: 996.6, 996.66, 996.67, 998.5, 100, and 998.59). Data from the first infection were documented.

Aseptic Cases. A randomly selected holdout sample of 200 aseptic revisions was excluded from the developmental model for validation purposes. These patients met the same aforementioned criteria for aseptic revision and did not fail with infection within 1 year after surgery.

Data Collection

Patient characteristics, comorbidities, laboratory results (serum, synovial, and microbial), and intraoperative findings (purulence and histopathology) were documented (see Appendix A). Laboratory values and histopathology results were dichotomized as elevated or not based on the ICM cutoffs.[5] For markers not present in the ICM definition (serum D-dimer, synovial CRP), a cutoff was determined using the Gini index [22].

Statistical Analysis

To maximize applicability to clinical practice, diagnostic markers were evaluated in a stepwise classification model based on the American Academy of Orthopaedic Surgeons guidelines accounting for simplicity and invasiveness [23]. This stepwise approach allowed us to take into account the pretest probability for infection and minimize missing data and the use of imputed data [24]. Missing data were filled by 10 imputations using multiple imputation by chained equations [25]. The probability for infection was evaluated independently for each step; progression from one step to another was determined to minimize false positive and negatives. The discriminatory capability of each step was then assessed by receiver-operating characteristic curve analysis. Area under the curve (AUC) scores were typically considered acceptable if the AUC exceeded 0.7, with an AUC of 0.5 representing a poor test (toss of a coin) and an AUC of 1.0 signifying a perfect test. The first step included serum markers (CRP, D-dimer, and ESR). Subjects with an extremely low probability for PJI would not proceed to step 2. Step 2 included testing of synovial markers which requires more invasive testing (synovial fluid white blood cell [WBC] count, polymorphonuclear percentage, CRP, LE, and alpha-defensin). Subjects with an extremely low and high probability for infection would not proceed to step 3. The evaluation of intraoperative findings (histology, purulence, and single positive culture) was performed in step 3. Single culture was evaluated in step 3 (and not in step 2) as patients reaching this point already have a high index of suspicion (pretest probability) for infection, thus minimizing the chance for false positive cultures and increasing its overall performance.

For each step, a random forest analysis was performed to evaluate the relative weight and importance of each examined variable. Random forest is a robust method for ranking the prediction ability