HK15: Is there a role for fibrinolytic serological markers, such as fibrinogen and D-dimer, in the diagnosis of periprosthetic joint infection (PJI)?

Alisina Shahi, Ruben Arriaga Sánchez, Charles Davis, Kenneth Mathis, Saul Martinez, Laia Boadas Girones, Rocco Papalia, Aldo Riesgo, Huang Wei

Response/Recommendation:

Yes. Fibrinolytic serological markers, such as fibrinogen and D-dimer, have demonstrated utility in the diagnosis of periprosthetic joint infection (PJI). D-dimer is recognized for its sensitivity and fibrinogen for its specificity.

Level of Evidence: Strong

Delegate Vote:

Rationale:

D-dimer levels are elevated in cases of infection due to the inflammation of the synovium and the robust fibrin production. As the synovium becomes inflamed, it releases pro-inflammatory cytokines that activate the coagulation cascade, leading to increased fibrin formation and subsequent degradation. This process results in elevated circulating levels of D-dimer, which serves as a marker of systemic fibrinolysis and inflammation. Shahi et al. [1] introduced this mechanism as a key reason why D-dimer has diagnostic utility in identifying PJI. Since then, several studies have explored the utility of serum D-dimer in detecting PJI. However, their diagnostic accuracy has varied, likely due to differences in the threshold, inclusion criteria, measurement methods, and study designs. Reported pooled sensitivity of approximately 0.73 to 0.81 and specificity of 0.74 to 0.78 for D-dimer, using thresholds between 756 and 1,250 ng/mL. [2–9]

Diagnostic Performance of D-dimer: D-dimer, a fibrin degradation product, reflects the fibrinolytic activity associated with inflammation and infection. A meta-analysis of studies on D-dimer in PJI reported pooled sensitivity and specificity values of 0.81 (95% CI: 0.71–0.88) and 0.74 (95% CI: 0.61–0.84)[10], respectively. Notably, Shahi et al. [1] identified a sensitivity of 0.89 and a specificity of 0.93 for serum D-dimer when a threshold of 850 ng/mL was applied. Similarly, studies such as those by Wang et al. and Hu et al. reported consistent findings, with Wang et al. [11] demonstrating an AUC of 0.85 and Hu et al. [12] identifying a sensitivity of 0.88 and specificity of 0.89 at a threshold of 995 ng/mL. These findings suggest that D-dimer is a highly sensitive marker, making it useful for screening purposes. Furthermore, its diagnostic utility has been validated in diverse patient populations, including those with low-grade infections, where traditional markers such as CRP and ESR may fail to provide conclusive

results. In a study by Pannu et al. [13], the authors found that D-dimer has high sensitivity (97.5%) and NPV (95.4%) in PJIs caused by low virulent organisms. However, D-dimer's specificity can be limited by confounding factors such as systemic inflammatory conditions, malignancies, or recent surgical interventions. Thus, integrating D-dimer with other diagnostic markers, such as fibrinogen, CRP, and synovial fluid analysis, can enhance its overall diagnostic accuracy and clinical applicability.

Diagnostic Performance of Fibrinogen: Plasma fibrinogen, a coagulation-related protein, has emerged as a robust marker with higher specificity compared to D-dimer. Studies have reported fibrinogen's specificity to range from 0.85 to 0.90, with sensitivity values around 0.86. [2,14] Its diagnostic accuracy, reflected in an area under the curve (AUC) of 0.916, supports its use as a confirmatory test. [15] The cost-effectiveness and wide availability of fibrinogen further enhance its clinical applicability. Additionally, fibrinogen may provide added value in differentiating infectious from aseptic failure in complex cases. [16] Recent findings, such as those by Huang et al. [14], highlight the potential of fibrinogen to outperform D-dimer in diagnostic precision, particularly in distinguishing PJI from aseptic loosening. Their study noted a sensitivity of 0.78 and specificity of 0.88 for fibrinogen at a threshold of 4.01 μg/mL, which was comparable to conventional markers like CRP and ESR, but with enhanced specificity in certain clinical scenarios. The robust performance of fibrinogen underlines its utility as an adjunct in diagnosing PJI, especially in low-grade or indolent infections where traditional inflammatory markers might falter. It is crucial to recognize that fibrinogen and D-dimer share a physiological relationship, as fibrinogen is converted to fibrin, which subsequently degrades into D-dimer. This dynamic means that elevations in fibrinogen and D-dimer often occur in parallel, providing complementary insights into the coagulation and fibrinolytic processes. As such, fibrinogen should be considered following and synonymous with D-dimer, with both markers collectively reflecting the coagulation cascade's activity in inflammatory and infectious states.[17,18]

While conventional markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) remain integral to the diagnosis of PJI, both markers exhibit limitations in cases of low-grade infections or those caused by indolent organisms like *Cutibacterium* acnes. D-dimer and fibrinogen, by reflecting different pathophysiological mechanisms, complement these traditional markers and improve diagnostic yield.

Both fibrinolytic markers are minimally invasive and widely available, making them accessible tools for clinical practice. However, variations in thresholds, sampling methods (serum versus plasma), and patient comorbidities must be considered to optimize their diagnostic accuracy. Standardization of these factors will be essential for broader clinical adoption.

Several systematic reviews and meta-analyses underscore the importance of these markers. For instance, Wang et al. [8] demonstrated that D-dimer and fibrinogen are valuable additions to the

diagnostic algorithm, particularly in ambiguous cases. Prospective studies with standardized protocols will further elucidate their roles and establish robust guidelines for their application.

Conclusion:

The integration of fibrinolytic markers, such as D-dimer and fibrinogen, into the diagnostic framework for PJI enhances diagnostic accuracy and complements traditional methods. D-dimer is recommended for its high sensitivity and suitability as a screening tool, particularly excelling in the detection of low-virulence organisms, which are often challenging to diagnose with traditional markers. Fibrinogen, with its superior specificity, serves as an effective confirmatory test, especially in distinguishing infectious from aseptic failures. Both markers, being physiologically linked as fibrinogen is converted to fibrin and subsequently degrades into D-dimer, often exhibit parallel elevations, further highlighting their diagnostic synergy. These properties underline their potential to transform the diagnostic landscape for PJI. Future research should focus on standardizing thresholds, optimizing clinical algorithms, and validating these findings across diverse patient populations and clinical settings to refine their application and improve patient outcomes.

References:

[1] Shahi A, Kheir MM, Tarabichi M, Hosseinzadeh HRS, Tan TL, Parvizi J. Serum D-Dimer Test Is Promising for the Diagnosis of Periprosthetic Joint Infection and Timing of Reimplantation. J Bone Joint Surg Am 2017;99:1419–27. https://doi.org/10.2106/JBJS.16.01395.

[2] Li R, Shao H-Y, Hao L-B, Yu B-Z, Qu P-F, Zhou Y-X, et al. Plasma Fibrinogen Exhibits Better Performance Than Plasma D-Dimer in the Diagnosis of Periprosthetic Joint Infection: A Multicenter Retrospective Study. J Bone Joint Surg Am 2019;101:613–9. https://doi.org/10.2106/JBJS.18.00624.

[3] Huang J, Zhang Y, Wang Z, Dong Y, Zhao Y, Zheng J, et al. The serum level of D-Dimer is not suitable for distinguishing between prosthetic joint infection and aseptic loosening. J Orthop Surg Res 2019;14:407. https://doi.org/10.1186/s13018-019-1461-x.

[4] Qin L, Li F, Gong X, Wang J, Huang W, Hu N. Combined Measurement of D-Dimer and C-Reactive Protein Levels: Highly Accurate for Diagnosing Chronic Periprosthetic Joint Infection. J Arthroplasty 2020;35:229–34. https://doi.org/10.1016/j.arth.2019.08.012.

[5] Pannu TS, Villa JM, Patel PD, Riesgo AM, Barsoum WK, Higuera CA. The Utility of Serum d-Dimer for the Diagnosis of Periprosthetic Joint Infection in Revision Total Hip and Knee Arthroplasty. J Arthroplasty 2020;35:1692–5. https://doi.org/10.1016/j.arth.2020.01.034.

[6] Xu H, Xie J, Huang Q, Lei Y, Zhang S, Pei F. Plasma Fibrin Degradation Product and D-Dimer Are of Limited Value for Diagnosing Periprosthetic Joint Infection. J Arthroplasty 2019;34:2454–60. https://doi.org/10.1016/j.arth.2019.05.009.

[7] Xiong L, Li S, Dai M. Comparison of D-dimer with CRP and ESR for diagnosis of periprosthetic joint infection. J Orthop Surg Res 2019;14:240. https://doi.org/10.1186/s13018-019-1282-y.
[8] Wang R, Zhang H, Ding P, Jiao Q. The accuracy of D-dimer in the diagnosis of periprosthetic infections: a systematic review and meta-analysis. J Orthop Surg Res 2022;17:99. https://doi.org/10.1186/s13018-022-03001-y.
[9] Balato G, De Franco C, Balboni F, De Matteo V, Ascione T, Baldini A, et al. The role of D-dimer in periprosthetic joint infection: a systematic review and meta-analysis. Diagnosis (Berl) 2021;9:3–10. https://doi.org/10.1515/dx-2021-0032.
[10] Yan J, Xie K, Jiang X, Han X, Wang L, Yan M. D-dimer for diagnosis of periprosthetic joint infection: A meta-analysis. Journal of Orthopaedic Science 2021;26:1036–42. https://doi.org/10.1016/j.jos.2020.09.015.
[11] Wang Y, Man Z, Yuan T, Cao H, Sun S. Reliability of d-Dimer Determination in Diagnosis of Peri-Prosthetic Joint Infection: A Systematic Review and Meta-Analysis. Surg Infect (Larchmt) 2021;22:374–82. https://doi.org/10.1089/sur.2020.212.
[12] Serum D-dimer as a diagnostic index of PJI and retrospective analysis of etiology in patients with PJI - PubMed n.d. https://pubmed.ncbi.nlm.nih.gov/32178976/ (accessed January 27, 2025).
[13] Pannu TS, Villa JM, Jimenez DA, Riesgo AM, Higuera CA. Does Performance of D-Dimer for Diagnosis of Periprosthetic Joint Infection Change With the Virulence of Infecting Organism? The Journal of Arthroplasty 2023;38:S389–93. https://doi.org/10.1016/j.arth.2023.05.022.
[14] Huang J, Chen X, Qiang S, Zheng W, Zheng J, Jin Y. Exciting Performance of Plasma Fibrinogen in Periprosthetic Joint Infection Diagnosis. Orthopaedic Surgery 2021;13:812–6. https://doi.org/10.1111/os.12964.
[15] Pan L, Wu H, Liu H, Yang X, Meng Z, Cao Y. Fibrinogen performs better than D-dimer for the diagnosis of periprosthetic joint infection: a meta-analysis of diagnostic trials. J Orthop Surg Res 2021;16:30. https://doi.org/10.1186/s13018-020-02109-3.
[16] Yang F, Zhao C, Huang R, Ma H, Wang X, Wang G, et al. Plasma fibrinogen in the diagnosis of periprosthetic joint infection. Sci Rep 2021;11:677. https://doi.org/10.1038/s41598-020-80547-z.
[17] Wilde JT, Kitchen S, Kinsey S, Greaves M, Preston FE. Plasma D-dimer levels and their relationship to serum fibrinogen/fibrin degradation products in hypercoagulable states. British Journal of Haematology 1989;71:65–70. https://doi.org/10.1111/j.1365-2141.1989.tb06276.x.
[18] Moresco RN, Vargas LCR, Voegeli CF, Santos RCV. D-dimer and its relationship to fibrinogen/fibrin degradation products (FDPs) in disorders associated with activation of coagulation or fibrinolytic systems. Journal of Clinical Laboratory Analysis 2003;17:77–9. https://doi.org/10.1002/jcla.10072.