Point to Point Response to Reviewer Comments:

Reviewer #1:
Specific Comments to Authors: In this review article, the authors review the use of D-dimer in the application of the early detection and diagnosis of postoperative complications (venous thromboembolism and periprosthetic joint infection) after total joint replacements. This provides a certain basis for early detection and diagnosis of complications after total joint replacement. This review article as a whole has good clinical significance. The specific review comments:

1.Introduction The second paragraph mainly introduces the application of D-dimer in the diagnosis of periprosthetic joint infection. The first paragraph introduces too little about the application of D-dimer in the diagnosis of venous thromboembolism. Please add some content about the application of D-dimer in the diagnosis of venous thromboembolism (such as important research progress, etc.).

- More information regarding the use of D-dimer in VTE/DVT was added to the first paragraph.

2.D-DIMER It is suggested that "Utility in Medicine" be changed to "Applications in the field of medicine".

- The title of section 2.2 was changed to "Applications in the field of medicine"

3.Venous thromboembolism The authors should add some discussion about the use of D-dimer in DVT.

- A paragraph was added to the Venous Thromboembolism detailing future research into mathematical/computer based algorithm for diagnosis/prediction of VTE. We would also like to direct reviewer to the Applications in the field of medicine section (2.2), where discussion regarding the general use of D dimer in VTE detection is detailed.

4. Periprosthetic joint infection The authors should briefly analyze the reasons for the conflicting conclusions of studies on D-dimer as a biomarker for PJI.

- A summary paragraph was added to the end of section 4.1 (Chronic PJI) that summarizes the reasons for conflicting evidence and our advise in how to optimized/use D-dimer in this setting.

Reviewer #2:

Specific Comments to Authors: In the manuscript, the authors reviewed the utility of D-dimer in total joint arthroplasty. It is interesting and meaningful. I have several questions for the authors:

1.what is the mechanism of D-dimer elevated in chronic periprosthetic joint infection? Is that same to VTE or not? I would suggest the authors to explain and add it in the manuscript.

- A second paragraph detailing the specific mechanism of D-dimer elevation in VTE and in PJI was added to the "mechanism of formation" section (2.1)

2. Please explain why D-dimer can be used as a biomarker for the diagnosis of the chronic periprosthetic joint infection, but it can not used in acute PJI? What is the difference between them?

- Please refer to section 2.4 (D-dimer levels in Total Joint Arthroplasty patients), and 4.2 (Acute PJI). 2.4 details the increase in baseline D-dimer levels during the first 6 weeks after the surgery. More detail was added to section 4.2 to make this more clear. Baseline levels are very high after the surgery (within the first 6 weeks) at baseline, so current threshold for chronic PJI cannot be used.

3.As we known, procalcitonin is an important biomarker for diagnosis of infection, was there any literautre which compare D-dimer with procalcitonin? If yea, I would suggest the authors to add it in the manuscript.

- A literature search was performed, and there is no published evidence we could find comparing procalcitonin and D-dimer in the diagnosis of infection as it relates to total joint arthroplasty.

Reviewer #3:

Specific Comments to Authors: The study did not add novel things to the subject, The review did not help the reader to have a clear cut idea about usage of D-Dimer in late onset periprosthetic infection.

- Refer to our new summary paragraph at the end of section 4.1 (Chronic PJI). We believe this helps summarize the findings of the paper and provides physicians with a better idea of how to best optimize D-dimer when using it for chronic PJI diagnosis.

Name of Journal: World Journal of Orthopedics

Manuscript Type: Review (REVISION MANUSCRIPT)

The Utility of D-dimer in Total Joint Arthroplasty

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ABSTRACT:

As the number of patients receiving total joint replacements continues to rise, considerable attention has been directed towards the early detection and prevention of postoperative complications. While D-dimer has long been studied as a diagnostic tool in venous thromboembolism (VTE), this assay has recently received considerable attention in the diagnosis of periprosthetic joint infection (PJI). D-dimer values are substantially elevated in the acute postoperative period after total joint arthroplasty, with levels often exceeding the standard institutional cutoff for VTE (500 μg/L). The utility of D-dimer in detecting VTE after total joint replacement is currently limited, and more research to assess its value in the setting of contemporary prophylaxis protocols is warranted. Recent literature supports D-dimer as a good to excellent biomarker for the diagnosis of chronic PJI, especially when using serum sample technique. Providers should exercise caution when interpreting D-dimer levels in patients with inflammatory and hypercoagulability disorders, as the diagnostic value is decreased. The updated 2018 Musculoskeletal Infection Society (MSIS) criteria, which includes D-dimer levels >860 μg/L as a minor criterion, may be the most accurate for diagnosing chronic PJI to date. Larger prospective trials with transparent lab testing protocols are needed to establish best assay practices and optimal cutoff values for D-dimer in the diagnosis of PJI. This review summarizes the most current literature on the value of D-dimer in total joint arthroplasty and elucidates areas for future progress.

KEYWORDS:

D-dimer; Diagnosis; Periprosthetic joint infection; Venous thromboembolism; Deep vein thrombosis; Arthroplasty

CORE TIP:

VTE and PJI are potentially devastating complications after total joint arthroplasty. D-dimer has limited utility with current cutoff values in the detection of VTE in the acute postoperative period. The D-dimer assay is a valuable biomarker in the diagnosis of chronic periprosthetic joint infection, and its utility may be optimized by using serum sample technique. Larger prospective trials with transparent lab testing protocols are necessary to establish best assay practices and optimal cutoff values for D-dimer in the diagnosis of VTE and PJI in arthroplasty patients.

THE UTILITY OF D-DIMER IN TOTAL JOINT ARTHROPLASTY

1. INTRODUCTION

Venous thromboembolism (VTE) and periprosthetic joint infection (PJI) are serious complications of total joint arthroplasty (TJA). Deep vein thrombosis (DVT) is a leading cause of morbidity and mortality during the postoperative phase[1,2]. The early diagnosis and treatment of DVT is extremely important, as delay can result in post-thrombotic syndrome and pulmonary embolism (PE). Although D-dimer has proved to be a valuable biomarker in the detection of VTE, its interpretation after total joint arthroplasty has been controversial, as postoperative levels often exceed the common institutional cutoff of 500 μg/L. Recent literature has focused on establishing new thresholds during the immediate postoperative period, in addition to using the test in new predictive models. While D-dimer has long been studied as a diagnostic tool in thromboembolism, this assay has recently received considerable attention in the evaluation of infection.

Periprosthetic joint infection continues to be a devastating complication in orthopaedic surgery, affecting roughly 2% of patients undergoing primary total joint arthroplasty[3,4]. The development of PJI dramatically decreases a patient's quality of life and accounts for a large financial burden to the patient and national health system[5-8]. Its timely detection is important, yet establishing the diagnosis can be challenging as there is no single "gold standard" test. In 2011, the Musculoskeletal Infection Society (MSIS) introduced a diagnostic criteria

(later modified by the International Consensus Meeting (ICM) in 2013) based on a combination of clinical, serum, synovial, histologic, microbial, and operative findings[9,10]. Recently, emphasis has shifted to a large number of novel hematologic and synovial biomarkers. In a 2017 study, D-dimer demonstrated excellent performance in the diagnosis of chronic PJI, with sensitivity and specificity above both erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)[11]. As an inexpensive, rapid, and convenient hematologic test, it was quickly adopted into the 2018 MSIS and ICM criteria for PJI diagnosis as a minor criterion[12,13]. Although initial studies found D-dimer to exhibit excellent performance in determining PJI, other authors have published conflicting results[14-20]. Since its inclusion in the updated MSIS and ICM criteria, the utility of D-dimer as a biomarker for PJI has been intensely debated. The goal of this review is to summarize the most current literature on the value of D-dimer in total joint arthroplasty and elucidate areas for future progress.

2. D-DIMER

2.1 Mechanism of Formation

D-dimer is a small protein fragment produced by the breakdown of vascular thrombi through a process known as fibrinolysis [Figure I]. The creation of D-dimer begins with thrombus formation: thrombin is generated through the coagulation cascade, which in turn converts plasma fibrinogen into fibrin. Through multiple interactions, fibrin molecules are cross-linked to form a meshwork for the resulting blood clot. The degradation of this thrombus occurs through fibrinolysis, where plasmin (a fibrinolytic enzyme) cleaves the fibrin scaffolding, resulting in the creation of the D-dimer molecules. D-dimer is therefore a unique marker of both thrombus formation as well as subsequent thrombolytic activity[21].

Deep venous thrombosis occurs due to the creation of an intravascular clot as the result of three main mechanisms: hypercoagulability, vascular wall injury, and venous stasis[22]; all of which can be present in patients with recent surgery. In patients with infection, the initiation of the coagulation cascade by microorganisms and inflammatory mediators is a common and early event[23]. Although this hypercoagulable state can alone increase D-dimer levels, another mechanism appears to be at play. Ribera et al. first demonstrated significantly increased levels of synovial D-dimer within the septic joints of foals[24]. Other studies have supported that inflamed synovium secretes large amounts of fibrin, ultimately resulting in increased intra-articular concentrations of D-dimer which can efflux out of the joint and into circulation[25].

2.2 Applications in the Field of Medicine

D-dimer has been widely used as a hematogenous biomarker for the detection and exclusion of VTE, comprised of both deep vein thrombosis (DVT) and pulmonary embolism (PE), and is strongly recommended in the diagnostic algorithms of multiple medical organizations, including the American Society of Hematology[26-27]. Despite its low specificity, D-dimer has long been advocated as an effective method to screen patients for VTE, with a sensitivity up to 97%, therefore reducing expensive testing such as venography or ultrasonography. In recent years, it has also been recognized as a valuable marker for inflammation and infection. Contemporary research has found elevated D-dimer levels to be a prognostic indicator for septic shock, bacterial pneumonia, bacteremia, and COVID-19 infection[28-33]. In 2011, Saxena et al. first described an association between D-dimer and periprosthetic joint infection[34]. Since that time, a considerable amount of research evaluating the relationship between D-dimer levels and total joint-related infection has been published.

2.3 Methods of Measurement

2.3.1 Blood Sample Technique

There are two common and distinct methods to collect and prepare the blood sample for testing[35,36]:

2.3.1.1 1) Serum D-dimer: Serum is the liquid portion of the blood after coagulation has occurred. The sample tubes contain either coagulation enhancers or no additives and are exposed to room temperature for a defined time period (often 30-60 minutes). After mandatory coagulation, serum samples have significantly less fibrinogen and coagulation factors due to recent consumption.

2.3.1.2 2) Plasma D-dimer: Plasma is the liquid portion of the blood when coagulation has been prevented. The blood collection tubes contain additives (commonly citrate), which prevent coagulation and can therefore be handled much easier than serum samples. The tubes can be immediately cooled or centrifuged in order to separate plasma from blood cells.

2.3.2 Assay Methods

After the sample is collected and prepared, a variety of quantification methods can be utilized. D-dimer is most commonly detected and quantified using monoclonal antibodies that distinguish a specific epitope on the cross-linked D-dimer molecule, differentiating it from other coagulation related products such fibrinogen or fibrin monomers[21,37]. There are over thirty commercial D-dimer assays on the market, but these can be broadly divided into three categories: enzyme-linked immunosorbent assays (ELISA), immunofluorescent assays, and latex-agglutination assays. In general, ELISA-based assays are more sensitive (nearing 100%) than agglutination assays, however automated techniques such

as immunoturbidimetric detection have narrowed the gap[37,38]. Each individual assay has its own calibration standards, cutoff values, sensitivity, and specificity for the detection of VTE[39].

2.4 D-dimer Levels in Total Joint Arthroplasty Patients

Many patient conditions are known to elevate D-dimer levels, including advanced age, inflammatory disease, auto-immune disorders, cardiovascular disease, and/or a recent surgical procedure [Table 1][39-43]. As total joint patients commonly share many of these features, surgeons have difficulty interpreting elevated D-dimer levels in this population. Age-adjusted D-dimer values have helped increase the accuracy of DVT detection in elderly patients before undergoing TJA, but spiking levels in the postoperative period pose additional challenges[43,44]. Inflammatory biomarkers such as ESR and CRP are often elevated after any recent surgical procedure, so it is not surprising that D-dimer follows this trend[45,46]. In addition, D-dimer is known to be the predominant product of extravascular fibrinolysis, a process which is emerging as an essential step in wound healing and tissue regeneration after orthopaedic surgery[47-49]. D-dimer values are substantially elevated after total joint arthroplasty, and recent investigations have discovered a consistent pattern of distribution in the postoperative phase.

D-dimer levels appear to display a biphasic distribution after total joint replacement, with two distinct peaks [Figure 2]. Levels rise sharply after the operation, peaking within the first 24 hours, then sharply decrease to a trough by postoperative day 2 to 3. This is followed by a gradual increase to a second peak around the 7 to 14-day mark, with a gradual decrease thereafter[46,50-52]. Azboy et al. found the first peak to be almost 9-fold higher than baseline, with the mean levels of the two troughs, on day 3 and 45, still representing elevation of at least 3

times preoperative values[46]. D-dimer appears to maintain elevation well beyond the acute post-surgical period, with Zhang et al. reporting persistently raised values at 3 months[52]. To our knowledge, there is no literature reporting D-dimer levels beyond 90 days after an uneventful joint replacement, and the time it takes to return to baseline is currently unknown.

3. VENOUS THROMBOEMBOLISM

According to the National Quality Improvement Program (NSQIP) database, venous thromboembolism still represents one of the most common complications in patients undergoing total joint arthroplasty, affecting approximately 0.6% of patients after total hip arthroplasty (THA) and 1.4% after total knee arthroplasty (TKA)[1]. The majority of DVTs and their related complications occur within two weeks of joint replacement surgery, but can present up to 6 weeks postoperatively[2,53]. In a group of 283 symptomatic PEs, Parvizi et al. found that 89% occurred within the first postoperative week, and 94% occurred within two weeks[54]. As D-dimer remains considerably elevated during this period, it is clear that standard institutional cutoffs for VTE exclusion, most commonly 500 μg/L, are inappropriate in this population. At 6 weeks after operation, An et al. found that 92% of THA patients and 100% of TKA patients had D-dimer levels above their DVT threshold for a "positive" quantitative test[55]. The potential value of D-dimer in the detection or exclusion of DVT after total joint arthroplasty remains controversial and unclear.

Recent research has focused on establishing new D-dimer thresholds during the postoperative period after TJA. Many studies have confirmed an association between elevated D-dimer levels and the presence of DVT in total joint patients, with some establishing useful cutoffs at specific postoperative days. Shiota et. al reported a threshold of 10000 μg/L on postoperative day (POD) 7 to have the

highest sensitivity (THA- 95.5%, TKA- 94.4%) and specificity (THA- 96.9%, TKA- 90.0%) for DVT detection[56]. Other authors have determined cutoffs on POD1, POD3, and POD4 to be useful as well[57-60]. This data should be interpreted with caution, however, as none of these investigations used DVT chemoprophylaxis. Agents such as low molecular weight heparin (LMWH), Fondaparinux, Warfarin, and factor Xa inhibitors have been shown to decrease D-dimer levels and reduce its diagnostic performance in detecting DVT[60-64]. Other authors, some of whom used chemoprophylaxis and others who did not, have determined that D-dimer has limited or no value in DVT diagnosis after a recent total joint operation[65-70].

With this conflicting evidence, the role of D-dimer in the detection of VTE after TJA is undetermined. There is a lack of research assessing the value of D-dimer when the primary prophylactic agent is aspirin, which has overwhelmingly become the most popular agent used in primary joint arthroplasty according to an American Association of Hip and Knee Surgeon (AAHKS) survey in 2020[71]. In contrast to other contemporary anticoagulants, authors have shown that antiplatelet drugs such as aspirin and clopidogrel (Plavix) do not alter D-dimer levels, however these studies did not specifically evaluate arthroplasty patients[72,73]. Many previous investigations were also performed without the use of tranexamic acid (TXA), a known inhibitor of fibrinolysis, which has been shown to decrease D-dimer levels up to 3 days postoperatively [Figure 1, Figure 2] [52]. Larger trials focusing on symptomatic VTE events using contemporary prophylactic protocols are necessary. In addition, future investigations must determine when D-dimer levels finally normalize after the operation, establishing a time point for when institutional VTE cutoff values (commonly 500 μg/L) can be properly applied in this population.

Ultimately, D-dimer may be more useful as an adjunct within other diagnostic tools rather than a standalone test. In recent years, mathematical based predictive models have emerged as potentially groundbreaking tools in multiple medical fields[74]. These algorithms, which are widely used in data mining, machine learning, and artificial intelligence, can efficiently and accurately create models for the classification and prediction of adverse events based on historical case data. Chen et al. constructed an algorithm utilizing predictive indicators of VTE, including elevated D-dimer levels on POD 1, capable of accurately predicting the incidence of DVT after total knee arthroplasty[75]. Although this algorithm needs validation in larger populations, the use of D-dimer in combination with other DVT indicators in computer based models will likely form the basis of future research.

4. PERIPROSTHETIC JOINT INFECTION

4.1 Chronic Periprosthetic Joint Infection

D-dimer first emerged as a promising biomarker for PJI in 2017, when Shahi et al. demonstrated it outperformed both ESR and CRP in diagnosing chronic PJI in their cohort of 245 patients. With a cutoff of 850 μg/L, the authors found serum D-dimer to have a sensitivity of 89% and a specificity of 93% in distinguishing PJI from aseptic failure[11]. In Parvizi et al.'s 2018 evidence-based and validated criteria for the diagnosis of PJI, the authors found D-dimer, with an updated threshold of 860 μg/L, to be a valuable initial hematologic test, weighted similar to CRP and above ESR as a minor criterion in their new model[12]. This updated MSIS criteria displayed a significant increase in sensitivity compared to the prior MSIS (97.7% vs. 86.9%) and ICM (97.7% vs. 86.9%) criteria with similar specificity (99.5%). Furthermore, it has been validated in both American, German, and Chinese populations[12,76-77]. Since acceptance into the MSIS and ICM criteria, a

growing body of literature assessing D-dimer's value as a biomarker for PJI has emerged, with conflicting results and conclusions.

Investigations by Hu et al. and Qin et al. both supported the promising early findings, with D-dimer demonstrating better sensitivity, specificity, and diagnostic accuracy in detecting PJI when compared to ESR and CRP. Hu et al. found D-dimer to demonstrate a sensitivity of 87.50% and a specificity of 89.19%, superior to those of ESR (82.50% and 64.86%, respectively) and CRP (80.00% and 78.38%, respectively) [78]. Qin et al. determined D-dimer to have outstanding diagnostic accuracy with an area under the curve (AUC) of 0.915, far above that of ESR (0.719) and CRP (0.761) [79]. Other authors, however, have published less optimistic data. Xu et al. concluded that with sensitivity of 68.3% and specificity of 50.7%, D-dimer had limited value compared to traditional biomarkers[17]. Using the previously established threshold of 850 μg/L, Pannu et al. demonstrated poor accuracy (61%) and low specificity (32.3%) to discriminate PJI from aseptic loosening in their population[14]. Furthering the confusion, many studies have established different cutoffs from the recommended 860 μg/L of the new MSIS criteria, with published thresholds varying widely from 410 μg/L to 2750 μg/L[18,20].

A collection of systematic reviews and meta-analyses were recently published in an effort to eliminate confusion and draw clarity from the literature[80-87]. The overall pooled data displays that D-dimer has good diagnostic accuracy to detect PJI. Zhang et al. and Wang et al. reported D-dimer to have an overall sensitivity of 82%, a specificity of 73%, and an AUC of 0.85[84,86]. However, these studies have revealed considerable heterogeneity in the current literature. Through meta-regression and subgroup analysis, this compilation of review papers published some interesting findings that illuminate possible ways to best

optimize D-dimer as a biomarker for PJI. These conclusions are summarized as follows:

4.1.1 1) Serum Versus Plasma D-dimer

Serum D-dimer displayed better diagnostic accuracy versus plasma D-dimer

Blood sample technique was commonly found to be the number one determinant of heterogeneity among the current literature. After subgroup analysis, Li et al. found that serum D-dimer exhibited a superior pooled sensitivity and specificity (86% and 84%, respectively) versus plasma D-dimer (67% and 60%, respectively). Serum D-dimer demonstrated excellent diagnostic value with an AUC of 0.91, far above that of plasma D-dimer (AUC of 0.66) [81]. Other authors have further supported this finding[80,82-87]. Some studies have reported no difference in baseline D-dimer levels when using either of the two techniques, however, Boisclair et al. reported significant differences in sensitivity and specificity when examining serum versus plasma D-dimer in the diagnosis of disseminated intravascular coagulation (DIC), DVT, and myocardial infarction[88,89]. Large comparative trials are needed to elucidate the true value of blood sample technique in arthroplasty patients, but studies utilizing serum sampling have displayed much better accuracy in diagnosing PJI.

4.1.2 2) Inflammatory and Hypercoagulability Disorders

Exclusion of inflammatory and hypercoagulability disorders improved diagnostic accuracy

In their 2020 meta-analysis, Yan et al. found that studies which excluded patients with hypercoagulability disorders displayed higher sensitivity (85% vs. 68%) and specificity (83% vs. 62%) versus those that did not. Similarly, they reported D-dimer to demonstrate a higher sensitivity (81% vs. 75%) when patients with inflammatory arthritis were excluded[84]. These results are not unexpected, as baseline D-dimer levels are substantially elevated in patients with inflammatory joint disease, thrombosis, malignancy, pregnancy, and heart disease versus healthy controls [41,90-93]. In addition to systemic hypercoagulation, the degradation of large quantities of fibrin deposited in the synovium of rheumatoid patients has been shown to increase D-dimer levels[94]. In patients with cardiovascular disease, autoimmune disease, and malignancy, Li et al. found that plasma D-dimer had no meaningful capacity to discriminate PJI from aseptic loosening (AUC of 0.50, 0.52, and 0.58, respectively)[16]. As patients with these comorbidities also display elevated inflammatory markers such as ESR and CRP, this population presents significant challenges in regard to properly establishing a diagnosis of chronic PJI.

4.1.3 3) Race and Geography

White and Black American populations displayed increased diagnostic accuracy versus East Asian populations

In a meta-analysis of 8 studies, Lu et al. found geographic and racial differences to have a major impact on the diagnostic accuracy of D-dimer in PJI diagnosis. Caucasian and African American races demonstrated increased sensitivity (92%) and specificity (74%) versus those of East Asian populations (72% and 65%, respectively) [82]. Variances in study protocol and laboratory assay practices may confound these findings,

however racial differences in D-dimer levels are well documented in the literature, even when controlling for social factors and comorbidities[92,95]. Providers should be mindful of demographic differences when interpreting D-dimer research, and investigators should be encouraged to disclose ethnicity to increase the external validity of future studies.

4.1.4 4) Optimal D-dimer Cutoff

Current literature uses a wide range of cutoff values

There is wide variation in D-dimer threshold values used for the diagnosis of chronic PJI in the current literature. While some of the recent investigations used the previously established cutoff of 850 µg/L, others calculated their own using receiver operating characteristic (ROC) curve analysis to best optimize the diagnostic value of the biomarker[11]. Furthermore, there is a scarcity of studies utilizing the cutoff of 860 µg/L, the current threshold recommended by the MSIS and ICM[12,13]. The establishment of an appropriate threshold is essential, as any change in this value can have significant impacts on diagnostic accuracy.

This wide variation is likely due to many factors, including differences in laboratory protocols and population characteristics. In addition to blood sample technique, there is potential for substantial differences in D-dimer levels depending on each laboratory's diagnostic platform. The development of a universal reference standard for D-dimer has been infamously difficult, making standardization between assays impossible up to this point[35,38-39]. In a simulation utilizing data from 3903 laboratories, Pearson et al. calculated that given identical blood samples, the mean D-dimer value varied from 540 to 880 µg/L depending on the platform utilized. In their model, a sample with a true value of 760 µg/L

produced levels exceeding the 860 μg/L cutoff in 18% of their results. Likewise, a sample with a true value of 960 μg/L reported a level less than 860 μg/L in 24% of the samples[96]. Provided the variability in D-dimer results, the authors concluded that each site should conduct their own research to determine an optimal threshold for their unique testing platform. While this may not be practical for most institutions, a surgeon's knowledge of their center's testing protocols combined with improved transparency in the literature will help improve the reproducibility of best cutoff values.

In summary, the inclusion of inflammatory patients, population differences, and a lack of standardization of lab protocols can all be responsible for the inconsistent results and thresholds. However, the largest reason for conflicting conclusions appears to be a difference in the type of sample technique used. With current literature in mind, we advise utilizing serum D-dimer, as opposed to plasma D-dimer, to best optimize its diagnostic value in determining chronic PJI. We conclude that serum D-dimer is an excellent serological biomarker for diagnosing chronic PJI, especially when used in combination with other infectious indicators as part of diagnostic tools such as the MSIS criteria.

4.2 Acute Periprosthetic Joint Infection

Lee et al. displayed that D-dimer values fall more rapidly than ESR and CRP after total joint arthroplasty, leading to speculation it could be useful in the diagnosis of acute PJI[51]. However, persistent elevation of D-dimer levels during the acute postoperative phase (up to 6 weeks), poses issues with currently established cutoffs for chronic PJI. Azboy et al. reported that 88.7% of their uneventful TJA patients had D-dimer levels above the 860 μg/L threshold on

postoperative day 15, with 77% exceeding the cutoff on day 45[46]. As baseline D-dimer levels are already substantially inflated within the first four to six weeks due to postsurgical inflammation and fibrinolysis, D-dimer does not appear to be useful for the diagnosis of acute PJI with the currently recommended threshold. Further research is needed to determine an optimal cutoff for early PJI diagnosis, as well as establish a time point for when chronic PJI criteria can be appropriately applied.

4.3 Timing of Reimplantation in Two-stage Revision

Two-stage revision continues to be one of the most common approaches for chronic PJI treatment. There is currently no gold standard for confirmation of infection eradication prior to reimplantation, and markers such as ESR, CRP, and even alpha defensin have demonstrated limited utility in this regard[97-99]. Shahi et al. first predicted the utility of D-dimer in this setting. In 5 patients with "elevated" D-dimer at the time of reimplantation, 2 went on to experience septic failure[11]. Pannu et al. demonstrated that D-dimer had low specificity (47%) and accuracy (AUC of 0.62) to predict persistence of infection after the second stage. However, it displayed a sensitivity of 90% and a negative predictive value (NPV) of 94%, indicating promise as a biomarker to rule out residual infection and indicate safe timing for reimplantation. Furthermore, they discovered that when combined with ESR and CRP, the specificity increased to 91%[100]. Although this study is limited by a small sample size (n=10), it certainly sets the stage for future multicenter investigations and creates optimism that D-dimer can have an important role in this setting.

4.4 Plasma Fibrinogen: An Alternative to D-dimer?

Plasma fibrinogen, the precursor to fibrin, is well known for its role in the coagulation cascade and has also been found to be a promising biomarker for the diagnosis of PJI[101]. Several recent publications have found plasma fibrinogen to exhibit significantly better diagnostic performance than plasma D-dimer in identifying chronic PJI[16,18,102]. However, all of these investigations utilized plasma sampling, and to our knowledge, there are no studies comparing serum D-dimer to plasma fibrinogen. In 2021, a meta-analysis by Xu et al. reported that plasma fibrinogen had better diagnostic accuracy than D-dimer when plasma and serum data was combined. However, after subgroup analysis, D-dimer actually displayed better accuracy than plasma fibrinogen when serum sample technique was utilized (AUC 0.91 versus 0.83, respectively) [103]. The authors concluded that serum D-dimer may have better diagnostic potential than plasma fibrinogen, and that plasma D-dimer has limited diagnostic value. Regardless, plasma fibrinogen appears to be a good alternative to D-dimer, especially at sites that are limited to a plasma testing protocol.

5. LIMITATIONS

In addition to the heterogeneity of the existing literature, it is important to note additional limitations. Most studies fail to adequately describe their laboratory protocol for D-dimer testing. As Pearson et al. demonstrated, assay practices can have a large effect on D-dimer values[96]. In addition, the terms "serum" and "plasma" have incorrectly been used interchangeably in the literature, promoting fear that they may be mislabeled in other investigations[55,104]. Surgeons and researchers should appreciate which type of blood sample technique is being used at their institution, and transparency of both sample technique and assay utilized is imperative for reproducibility of future research. Lastly, although pooled data seems to confirm that serum D-dimer is superior to plasma D-dimer, no comparative studies have been performed between the two sampling

methods in the setting of chronic PJI. A prospective, paired trial comparing the diagnostic values of plasma and serum D-dimer for the diagnosis of PJI is necessary to provide more clarity.

6. CONCLUSIONS

D-dimer values are substantially elevated in the acute postoperative period after total joint arthroplasty, and standard institutional cutoffs for VTE (most commonly 500 μg/L) are inappropriate in these patients. The utility of D-dimer in detecting VTE after total joint arthroplasty is currently limited, and more research assessing its value in the face of contemporary DVT prophylaxis protocols is warranted. D-dimer appears to be a promising biomarker for the diagnosis of chronic PJI, especially when using serum sample technique. Providers should exercise caution when interpreting D-dimer levels in those with inflammatory and hypercoagulability disorders, as the diagnostic value is decreased in these patients. Larger prospective studies with transparent lab testing protocols are needed to establish best assay practices and optimal cutoff values. Despite the demand for further research to optimize the diagnostic performance of D-dimer, the current identification of PJI does not rely on a single test. More research assessing the value of combined biomarkers may be more useful, and the updated MSIS and ICM criteria, which include D-dimer levels >860 μg/L as a minor criterion, may be the most accurate for diagnosing chronic PJI to date.

ACKNOWLEDGEMENTS

We thank Mary Baldwin for her contributions to the Figures/Illustrations.

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ETHICS POLICIES/STATEMENTS:

Conflict of Interest:

Brenden Cutter, Zachary Lum, Mauro Giordani, and John Meehan declare that they have no conflict of interest. All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

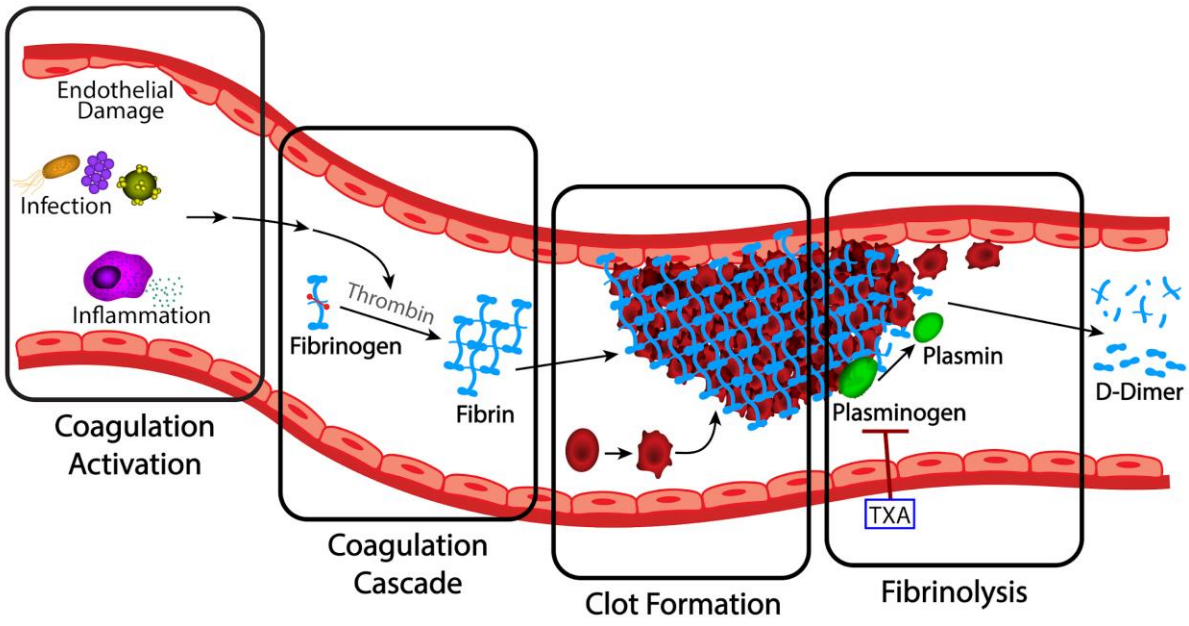
Human and Animal Rights and Informed Consent:

This article does not contain any studies with human or animal subjects performed by any of the authors.

Compliance with Ethical Standards:

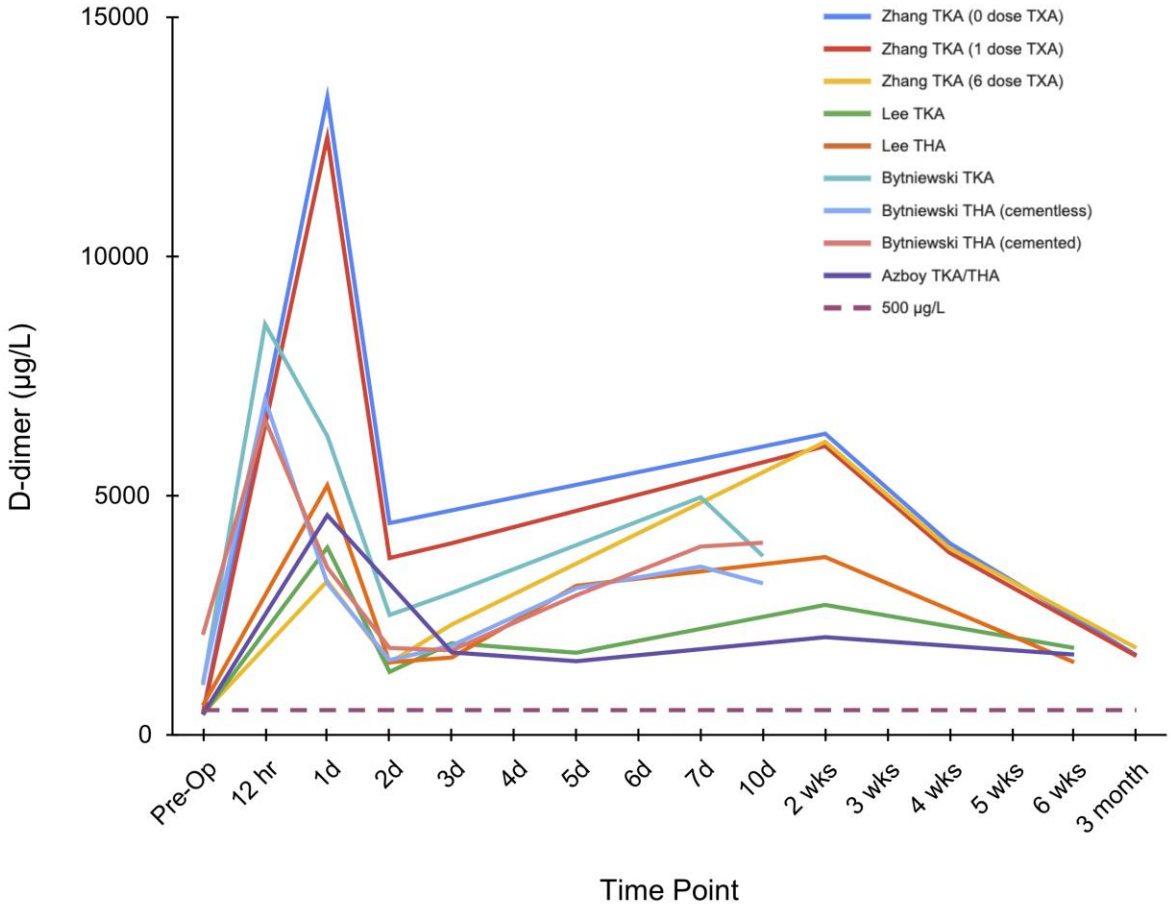
As a review paper with no involvement of human or animal subjects, no ethical approval was necessary for this research.

Figure 1. Pathophysiology of D-dimer Formation



TXA Tranexamic acid

Figure 2. D-dimer Levels After Total Joint Arthroplasty



TXA Tranexamic acid

References: Zhang et al.[52], Lee et al.[51], Bytniewski et al.[50], Azboy et al.[46]

Table 1. Conditions Associated with Elevated D-dimer Levels.

Condition
Venous Thromboembolism
Recent Surgery
Age
Trauma
Inflammation
Disseminated Intravascular Coagulation
Cancer
Infection/Sepsis
Pregnancy
Cardiovascular Disease
Liver Disease
Renal Disease

References: [21,23, 26-31,40-43]