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REVIEW

Utility of D-dimer in total joint arthroplasty

Brenden Cutter, Zachary C Lum, Mauro Giordani, John P Meehan

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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 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.

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

Core Tip: Venous thromboembolism (VTE) and periprosthetic joint infection (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.

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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.

D-DIMER

Mechanism of formation

D-dimer is a small protein fragment produced by the breakdown of vascular thrombi through a process known as fibrinolysis (Figure 1). 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*[24] first demonstrated significantly increased levels of synovial D-dimer within the septic joints of foals.

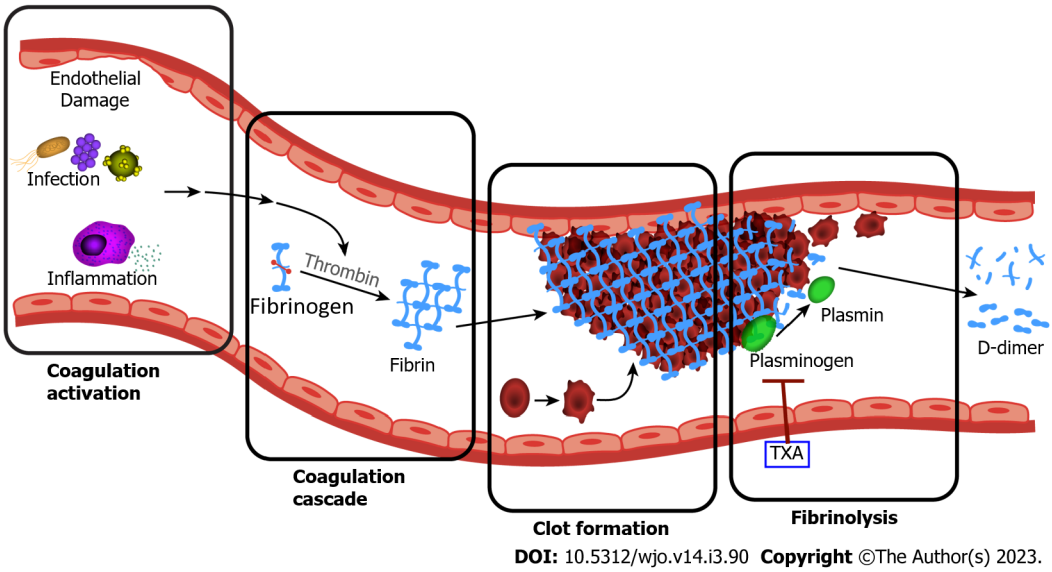

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Figure 1 Pathophysiology of D-dimer formation. TXA: Tranexamic acid.

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].

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 DVT and 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*[34] first described an association between D-dimer and periprosthetic joint infection. Since that time, a considerable amount of research evaluating the relationship between D-dimer levels and total joint-related infection has been published.

Methods of measurement

Blood sample technique: There are two common and distinct methods to collect and prepare the blood sample for testing[35,36]: (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 min). After mandatory coagulation, serum samples have significantly less fibrinogen and coagulation factors due to recent consumption; and (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.

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].

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)

Table 1 Conditions associated with elevated D-dimer levels

Venous thromboembolism
Surgery
Age
Trauma
Inflammation
Disseminated intravascular coagulation
Cancer
Infection/sepsis
Pregnancy
Cardiovascular disease
Liver disease
Renal disease

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

[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 h, 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-d mark, with a gradual decrease thereafter[46,50-52]. Azboy *et al*[46] 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. D-dimer appears to maintain elevation well beyond the acute post-surgical period, with Zhang *et al*[52] reporting persistently raised values at 3 mo. To our knowledge, there is no literature reporting D-dimer levels beyond 90 d after an uneventful joint replacement, and the time it takes to return to baseline is currently unknown.

VENOUS THROMBOEMBOLISM

According to the National Quality Improvement Program 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 wk postoperatively[2,53]. In a group of 283 symptomatic PEs, Parvizi *et al*[54] found that 89% occurred within the first postoperative week, and 94% occurred within two weeks. 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 wk after operation, An *et al*[55] found that 92% of THA patients and 100% of TKA patients had D-dimer levels above their DVT threshold for a "positive" quantitative test. 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*[56] 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

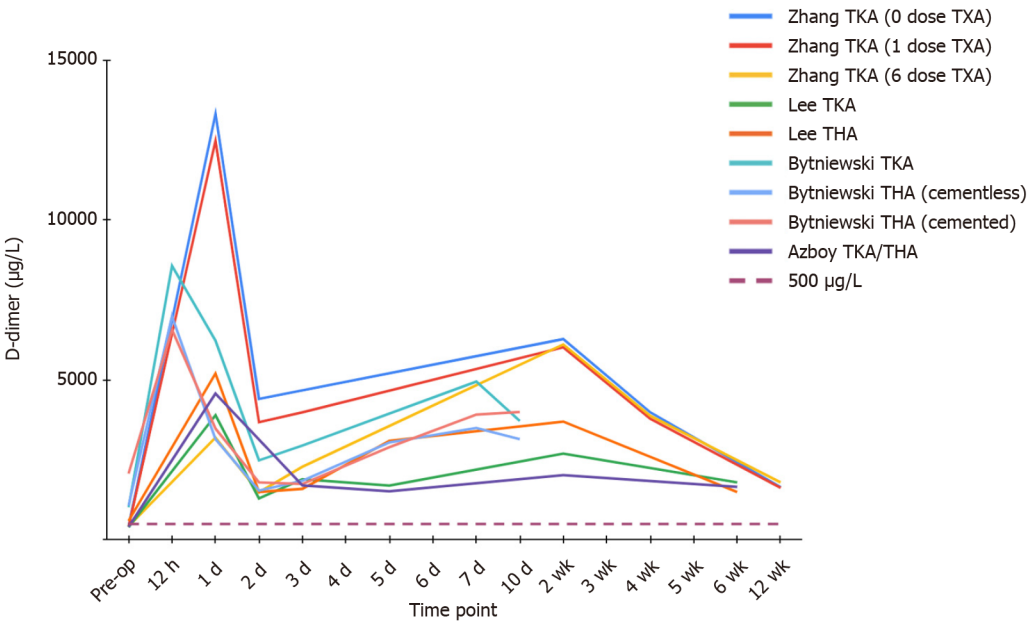

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Figure 2 D-dimer levels after total joint arthroplasty. TXA: Tranexamic acid. References: Zhang *et al*[52], Lee *et al*[51], Bytniewski *et al*[50], Azboy *et al*[46].

detection. 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, 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 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, a known inhibitor of fibrinolysis, which has been shown to decrease D-dimer levels up to 3 days postoperatively (Figures 1 and 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*[75] 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. 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.

PERIPROSTHETIC JOINT INFECTION

Chronic periprosthetic joint infection

D-dimer first emerged as a promising biomarker for PJI in 2017, when Shahi *et al*[11] 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. 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*[78] and Qin *et al*[79] 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*[78] 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). Qin *et al*[79] 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). Other authors, however, have published less optimistic data. Xu *et al*[17] concluded that with sensitivity of 68.3% and specificity of 50.7%, D-dimer had limited value compared to traditional biomarkers. Using the previously established threshold of 850 μg/L, Pannu *et al*[14] demonstrated poor accuracy (61%) and low specificity (32.3%) to discriminate PJI from aseptic loosening in their population. 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*[86] and Wang *et al*[84] reported D-dimer to have an overall sensitivity of 82%, a specificity of 73%, and an AUC of 0.85. 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.

Serum versus plasma D-dimer: Serum D-dimer displayed better diagnostic accuracy *vs* 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*[81] found that serum D-dimer exhibited a superior pooled sensitivity and specificity (86% and 84%, respectively) *vs* 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). 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*[89] reported significant differences in sensitivity and specificity when examining serum *vs* plasma D-dimer in the diagnosis of disseminated intravascular coagulation, 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.

Inflammatory and hypercoagulability disorders: Exclusion of inflammatory and hypercoagulability disorders improved diagnostic accuracy: In their 2020 meta-analysis, Yan *et al*[85] found that studies which excluded patients with hypercoagulability disorders displayed higher sensitivity (85% *vs* 68%) and specificity (83% *vs* 62%) *vs* 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 *vs* 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*[16] 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). 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.

Race and geography: White and black american populations displayed increased diagnostic accuracy *vs* east asian populations: In a meta-analysis of 8 studies, Lu *et al*[82] 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%) *vs* those of East Asian populations (72% and 65%, respectively). 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.

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 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*[96] 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. 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.

Acute periprosthetic joint infection

Lee *et al*[51] 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. However, persistent elevation of D-dimer levels during the acute postoperative phase (up to 6 wk), poses issues with currently established cutoffs for chronic PJI. Azboy *et al*[46] 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. 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.

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*[11] 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. Pannu *et al*[100] 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 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%. 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.

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*[103] 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 *vs* 0.83, respectively). 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.

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* [96] demonstrated, assay practices can have a large effect on D-dimer values. 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.

CONCLUSION

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.

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FOOTNOTES

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MINIREVIEWS

Advances in wrist arthroscopic surgery in Indonesia

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Abstract

Since the 1990s, new insights in wrist arthroscopy have led to the introduction of numerous treatment methods. Consequently, therapeutic procedures are no longer limited to resection as more specialized repair and functional reconstruction methods, involving tissue replacement and essential structural augmentation, have been shown to be beneficial. This article discusses the most prevalent reasons and uses for wrist arthroscopy, with an emphasis on Indonesia's most recent and major advances in reconstructive arthroscopic surgery. Joint debridement, synovectomy, ganglionectomy, capsular release, and osteotomies are frequent resection operations. Ligament repair and arthroscopy-aided reduction and fixation for fractures and nonunion are all examples of reconstructive surgery.

Key Words: Arthroscopy; Synovectomy; Ganglionectomy; Arthrolysis; Arthroscopic-assisted reduction and internal fixation; Scaphoid fractures; Carpal nonunion; Triangular fibro cartilage complex injury

Core Tip: Several novel procedures with specific surgical indications have been developed over the past 15 years. More difficult and precise procedures can now be performed with fewer complications as both techniques and instrumentation improve. Debridement and resection are no longer the only therapeutic treatment available. Functional reconstruction treatments involving the repair of tissue defects and augmentation of important structures with graft material as well as more particular anatomical structure fixing procedures have been performed with established clinical benefit. This article covers current arthroscopic techniques used in clinical practice in Indonesia, some of which represent cutting-edge breakthroughs in therapeutic arthroscopy.

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INTRODUCTION

The constant development of numerous treatment methods since the 1990s has triggered significant advancements in wrist arthroscopy. Due to the simultaneous development of tailored instruments adapted for small joints, most techniques used in large joint arthroscopy are either transferred or inspired from already established methods. The increase of popularity in therapeutic arthroscopy has increased the usage and role of arthroscopy in the treatment of wrist disorders including acute and elective settings. Wrist arthroscopy has become a new standard for evaluation and treatment in specific clinical disorders, such as chronic ulnar wrist pain. Similarly, in an increasing variety of clinical illnesses, such as scaphoid fractures, carpal nonunion, ganglion, and triangular fibro cartilage complex (TFCC) lesions, novel therapeutic strategies are challenging traditional surgical treatment methods, thinking, and long-term outcomes. Consequently, wrist arthroscopy could eventually reach the same level of popularity as other arthroscopy surgery.

Several novel procedures with specific surgical indications have been developed over the past 15 years. More difficult and precise procedures can now be performed with fewer complications as both techniques and instrumentation improve. Debridement and resection are no longer the only therapeutic treatment available. Functional reconstruction treatments involving the repair of tissue defects and augmentation of important structures with graft material as well as more particular anatomical structure fixing procedures have been performed with established clinical benefit. This article covered current arthroscopic techniques used in clinical practice in Indonesia on a regular basis, some of which represent cutting-edge breakthroughs in therapeutic arthroscopy.

DEBRIDEMENT

This method is used when the accumulated debris in the joint contributes either directly or indirectly to the manifestation of symptoms. Degenerative arthritis, gout, central TFCC tear[1], Kinbock disease[2], and partial interosseous ligament tear[3] are all examples. In the partial excision of a central TFCC tear, several devices such as suction punches, motorized shavers, arthroscopic knives, and more recently radiofrequency devices can all be used. In the absence of carpal dissociation, debridement can provide clinical alleviation in partial intraosseous ligament rupture[4]. If the ulnar variance of the wrist is neutral or minus[5,6], clinical improvement should be expected after partial excision of a central TFCC rupture. Wafer procedure[7], or formal ulnar shortening[8] is frequently needed for definitive treatment in patients with ulnar positive (Figure 1A and B).

SYNOVECTOMY

Rheumatoid arthritis and other systemic diseases affecting the wrist joint are the best candidates for this operation. Arthroscopic synovectomy can reduce surgical trauma while allowing simple access to different wrist compartments. The first series of arthroscopic synovectomy on 18 wrists of 16 patients was reported by Adolfsson and Nylander[9] in 1997, and the results showed a significant improvement in pain intensity and range of motion in all patients. At a mean follow-up of 7.9 years, Lee *et al*[10] revealed the long-term results of arthroscopic synovectomy in 49 subjects with 56 wrists. The mean Mayo wrist score increased from 48 to 76; the mean of wrist pain calculated using visual analogue score reduced from 6.3 to 1.7. Synovitis was successfully managed in 42 wrists (75%) but recurred in the

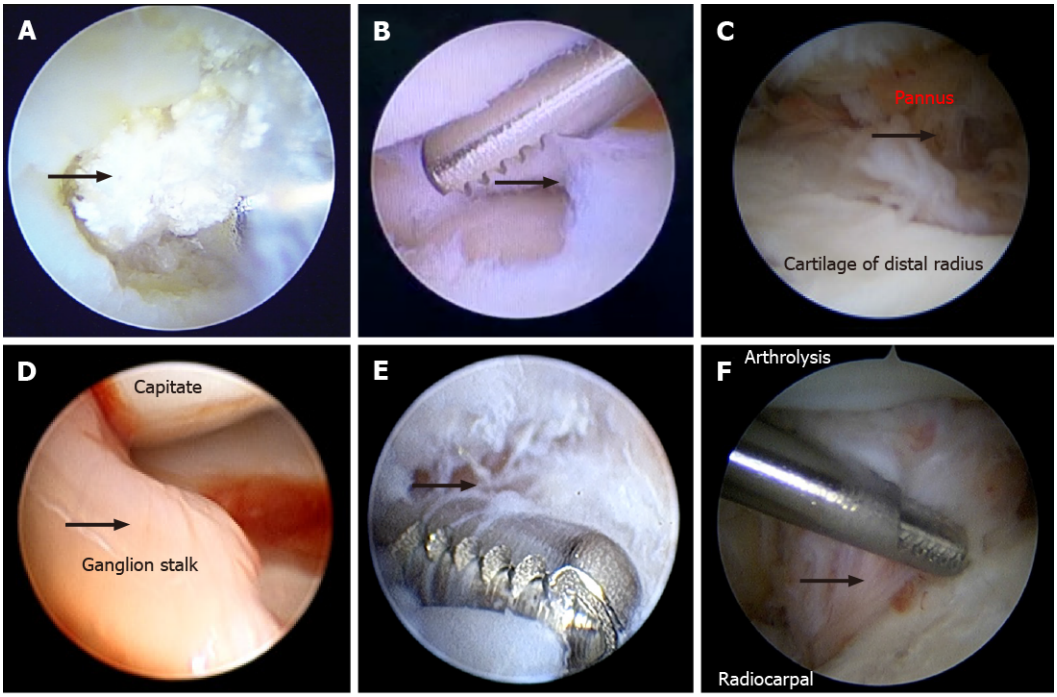

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Figure 1 Image of the radiocarpal joint. A: The crystals seen are destructing the lunate; B: Debridement of a central triangular fibro cartilage complex tear; C: The pannus seen are destructing the cartilage of distal radius; D: Ganglion stalk seen protruding into the joint; E: Resection of the ganglion stalk; F: Arthrolysis was performed by shaving the fibrous tissue inside the radiocarpal joint.

remaining 14 wrists at the final follow-up[10] (Figure 1C).

GANGLIONECTOMY

Ganglionectomy is better described as marsupialization of the ganglion because the ganglion cyst is not anatomically removed. This method is based on the idea of eliminating the "check valve" effect by producing a capsular defect at the stalk section of the ganglion cyst, where it communicates with the wrist joint, allowing the ganglion to drain, diminish, and resolve spontaneously. The approach for the usual dorsal wrist ganglion originating proximal to the scapholunate joint was first published by Osterman[11] in 1995; 6R was the viewing portal. To resect a 1-cm defect in the dorsal capsule, a full-radius resector can be introduced *via* the 3-4 portal. The goal of this process is to induce a flood of mucinous fluid drain into the joint, which allow the ganglion to entirely vanish outwardly. All 18 cases in the Osterman series had full resection and no recurrence (Figure 1D and E).

ARTHROLYSIS AND RELEASE

In 2 cases of significant post-traumatic capsular fibrosis and stiff wrist[12], Verhellen and Bain[12] used combined volar and dorsal portals to accomplish arthroscopic release. Except for the ulno-carpal ligament complex and the volar radio-ulnar ligament, all volar capsular ligaments were entirely separated with a shaver, RF probe, or arthroscopic knife and then gently manipulated under anesthesia (Figure 1F).

Ligament repair

The TFCC is prone to damage because it is subjected to significant axial loading and shear stresses[13, 14]. Palmer[15] demonstrated and classified tears concerning the TFCC in 1989. This laid the foundation for current ulnar-sided wrist pain diagnosis and treatment. Thiru *et al*[16] and Bednar *et al*[17] found that the outside 10%-40% of the articular disc was highly perfused, implying that these wounded areas could heal if they were repaired. Consequently, there has been a lot of effort directed to preserve and repair peripheral TFCC lesions. In 1991, Hermansdorfer and Kleinman[18] reported that open TFCC repair produced good results, with 8 of 11 patients able to go back to regular activities. Using open repairs, Cooney *et al*[19] reported 26 good to excellent results in 33 operated wrists. With the introduction of wrist arthroscopy, surgeons have been able to duplicate, if not exceed, the results of

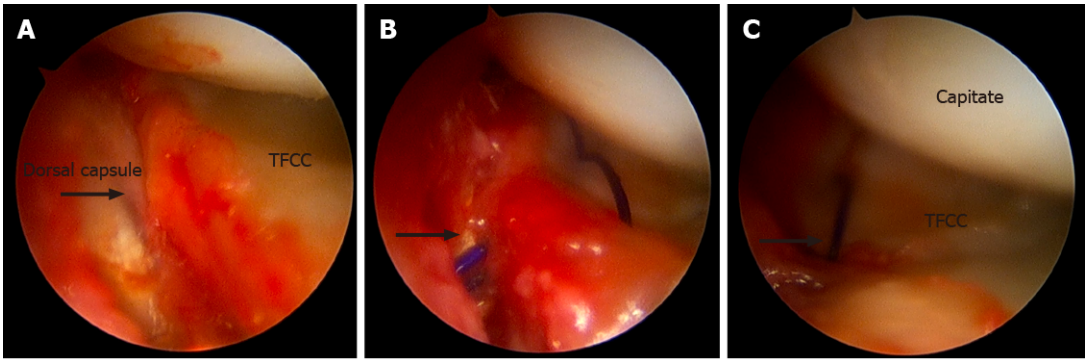

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Figure 2 Repair of triangular fibro cartilage complex tear. A: Tear seen on the dorsal aspect of the triangular fibro cartilage complex (TFCC); B: Suture of TFCC; C: Suture tightened.

open repairs[20-24]. The majority of research focused on palmar 1B tear healing, with types 1C and 1D tears reported less frequently. The inside-out and outside-in approaches to arthroscopic repair have been advocated. Simple hypodermic needles[25], epidural Tuohy needles, meniscal needles, and zone-specific repair kits[26] were among the instruments used.

In terms of clinical outcomes, the open group had a higher rate of postoperative superficial ulnar nerve discomfort and reoperation. There has been no recent study comparing the outcomes of various arthroscopic repair procedures. To promote healing and induce fibrovascular in growth, it is critical to debride the rim of the torn ligament down to healthy vascular tissue in all TFCC mending procedures. To ensure healing, the torn peripheral rim of the TFCC is positioned against the fovea or the capsular tissue (Figure 2).

Ligament reconstruction with tendon graft

The optimum surgical reconstruction for painful distal radioulnar joint (DRUJ) instability induced by TFCC disruption has been a source of debate until recently. The dorsal and palmar of radio-ulnar marginal ligaments, which are linked during various stages of prono-supination, are now recognized as the most important stabilizers of the DRUJ. During forearm rotational movement, damage to one or both of these ligaments resulted in pain and instability. Adams *et al*[27] and Adams[28] conducted a thorough biomechanical analysis and advocated anatomical repair of the distal radio-ulnar ligaments as the optimal treatment option for this complex problem. The authors found good results from open reconstruction with graft from palmaris longus tendon in 12 patients with post-traumatic DRUJ instability with 1-4 years of follow-up evaluation[28].

ARTHROSCOPIC-ASSISTED REDUCTION AND INTERNAL FIXATION

For proper reduction and fixing, arthroscopic-assisted reduction and internal fixation is still necessary. Furthermore, arthroscopy can be used to treat related soft tissue injuries in the same setting, with success rates ranging from 40%-75% in distal radius fracture and up to 50% in scaphoid fracture. Intra-articular fracture with comminution and displacement is the best indication for arthroscopic intervention in distal radius fractures, and the target of articular reduction is within 2 mm of step or gap [29]. Percutaneous access to and assessment of depressed intra-articular fragments is notoriously difficult. In terms of measuring joint surface reduction, arthroscopy has been proven to be superior to intraoperative fluoroscopy and plain radiograph[30]. When compared to the conventional reduction method with fluoroscopy alone, patients that underwent arthroscopically-assisted reduction of intra-articular distal radius fractures had better clinical outcomes, improved radiologic variable regarding displacement and angulation, and greater range of motion[31,32].

Through arthroscopic portals, the misplaced fragments can be attacked, elevated, and reduced using a fine bone or a probe under direct visualization. When volar plating is being considered, both dorsal and volar ports can be utilized. While the articular reduction is monitored and regulated arthroscopically, the fragments can also be elevated with an osteotome or a bone spike injected through the metaphyseal region. Subchondral screws or pins are used to repair the decreased fracture. Dry arthroscopy has grown in favor in recent years, especially for fracture reduction and fixation because it allows for easier fracture manipulation and reduces the possibility of fluid extravasation, which can lead to compartment syndrome[33]. Arthroscopy can also detect and treat unnoticed soft tissue and cartilage injuries.

In the treatment of acute scaphoid fractures, percutaneous screw fixation is gaining popularity. The majority of series had a high rate of union and a positive functional outcome. Arthroscopy can become a useful adjuvant to a minimally invasive method for treating tricky cases, such as misplaced fractures, fracture comminution, and delayed presentation, and can often eliminate the need for open reduction. It causes minimum vascular and soft tissue disruption, promoting fracture union. In most cases, including proximal third fractures, we undertake reduction and percutaneous fixation using the volar route. In many series, the volar approach not only has a higher union rate and lower complication rate but also provides safer and easier screw entry, maintains and corrects fracture deformity in the extended wrist, does not disrupt the load bearing proximal scaphoid cartilage, has minimum hardware issues, and gives no harm to the tendons and dorsal wrist structures, which have been expressed in dorsal approach surgeries[34] (Figures 3 and 4).

NONUNION OF SCAPHOID

The complete intra-articular position of scaphoid nonunion favor an arthroscopic approach for diagnostic and therapeutic interventions while preserving as much blood supply and ligamentous architecture as possible, which favors union and functional restoration.

Between 2019 and 2021, we used arthroscopic bone grafting to treat osseous abnormalities in 6 cases of scaphoid nonunion. In all situations, we obtained union within 4 mo on average. Minimal disruption to complex ligamentous structures, maximum preservation of carpal bone vascularity, holistic assessment of wrist joint allowed prior to surgical intervention, minimum scar and pain, unnecessary tourniquet, stitch-less surgery, and faster healing process were all potential benefits of this approach (Figures 5-7).

OSTEOTOMY

Radial styloidectomy for post-traumatic arthritis secondary to scaphoid nonunion and rheumatoid or carpal instability, as well as the Wafer operation for ulnar impaction syndrome, are two of the most common indications for osseous resection plasty. The advantage of arthroscopic radial styloidectomy is that it allows for improved vision and conserves the radio-scapho-capitate ligament that acts as a crucial stabilizing structure of the wrist.

Furthermore, the Wafer method is a well-established therapy for the ulnar impaction syndrome. A completely perforated TFCC is required for an arthroscopic operation, which is usually only possible for degenerative TFCC tears of Palmer stage 2C or higher. In cases of distal radius malunion, osteotomy may also be used for reconstruction. A challenging intra-articular distal radius malunion can be restored using osteotomy assisted by arthroscopy in conjunction with a three-dimensional-printed surgical guide (Figure 8).

CONCLUSION

When surgeons began debating whether meniscal surgery of the knee could be done arthroscopically 40 years ago, the phrase "open meniscectomy" was likely only used in the dictionary. If the result can be shown to be equivalent or superior to open surgery, then minimally invasive arthroscopic surgery would be the optimum and preferred therapy. Because it has only been in development since 1986, wrist arthroscopy will still benefit from improvements. In fact, we learned from the literature that most traditional open wrist surgery has been attempted arthroscopically with varying degrees of success over the last 15 years. While diagnostic arthroscopy has established itself as the gold standard, most novel therapeutic studies had small numbers of clinical subjects and insufficient controlled randomized prospective study methods and lacked long-term evaluation. Well-designed clinical trials confirm the therapeutic significance in diverse wrist ailments. Wrist arthroscopy as an office diagnostic technique may become a reality in the future, with a considerably broader clinical applicability. Future advancements will most likely be restricted only by surgeons' imaginations and skill. Nonetheless, further controlled randomized prospective studies are needed to determine the genuine efficacy of each arthroscopy treatment approach in the future.

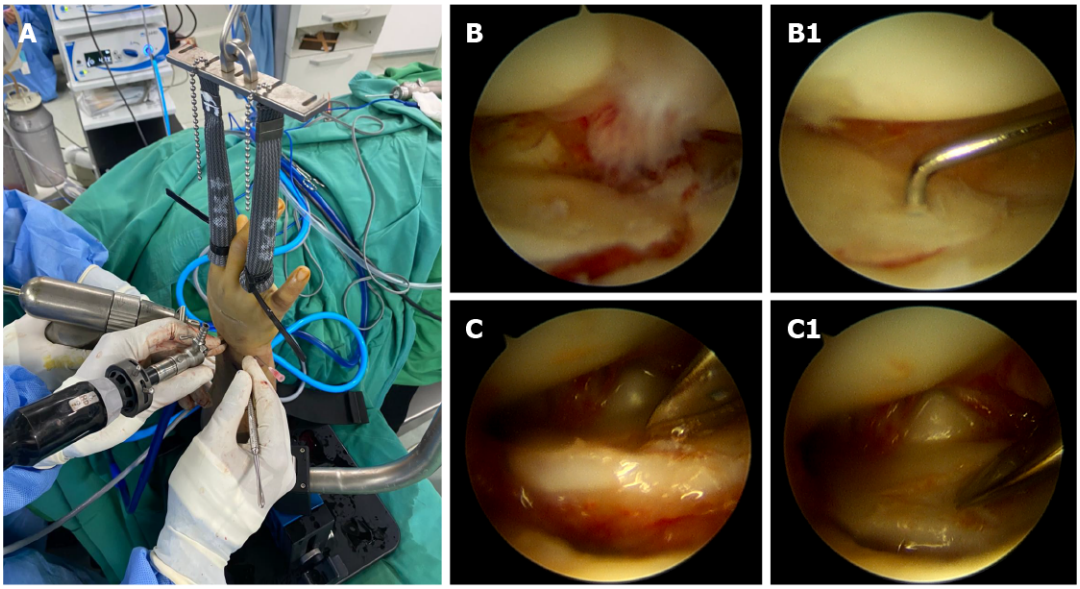

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Figure 3 Arthroscopic-assisted intra-articular reduction of a distal radius fracture. A: Finger traction was applied to the wrist; B and C: Image of intraarticular step before reduction, B1 and C1: After intraarticular reduction.

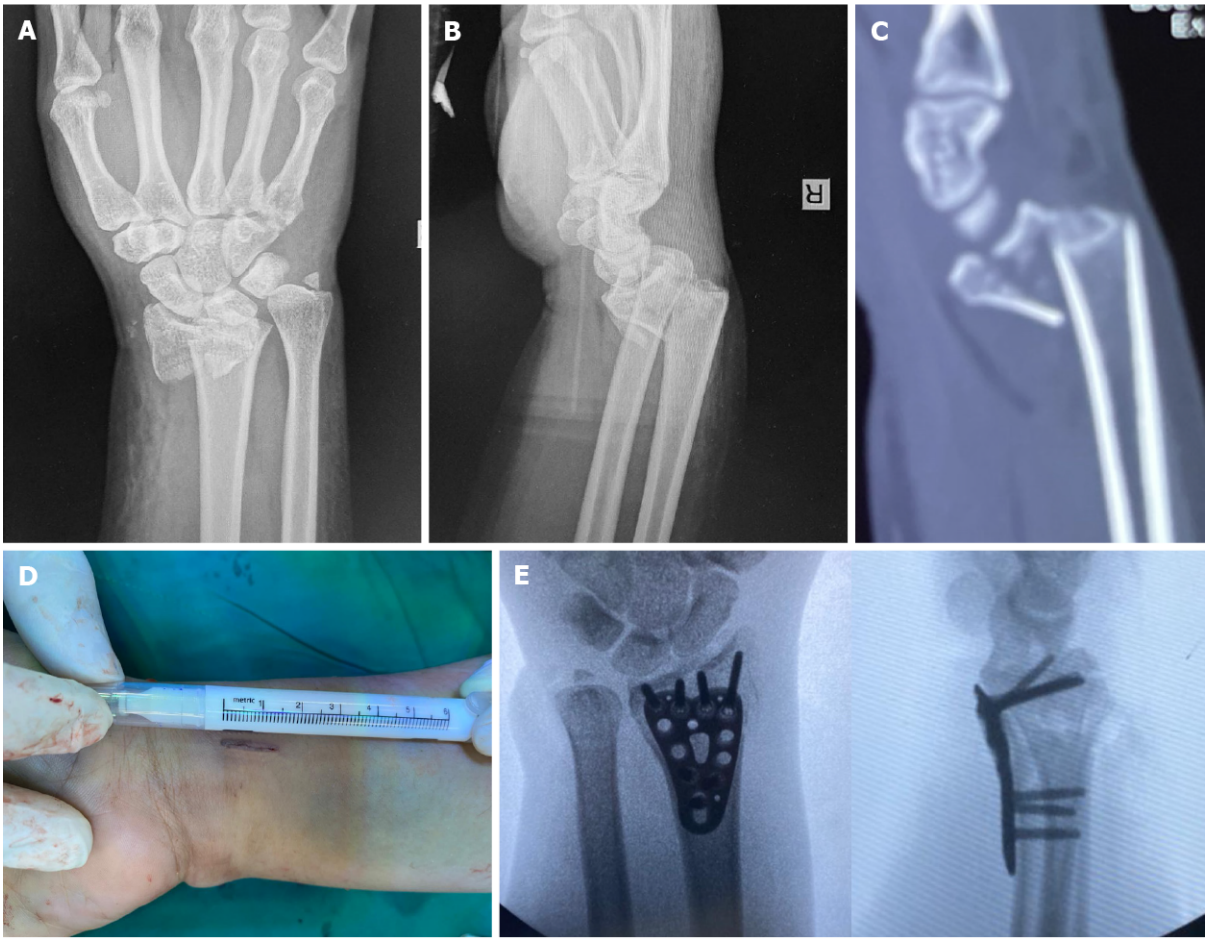

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Figure 4 Preoperative X-ray and computed tomography scan showed intra-articular fragment of a distal radius fracture and postoperative X-ray of the minimally invasive plate osteosynthesis technique with a 15 mm incision. A: Postero-anterior plain X-ray of the right wrist; B: Lateral plain X-ray of the right wrist; C: Sagittal view of computed tomography scan showed displaced intra-articular fracture of the right wrist; D: A 15 mm incision was used for the procedure; E: Postero-anterior and lateral views showed the result after plate and screw fixation.

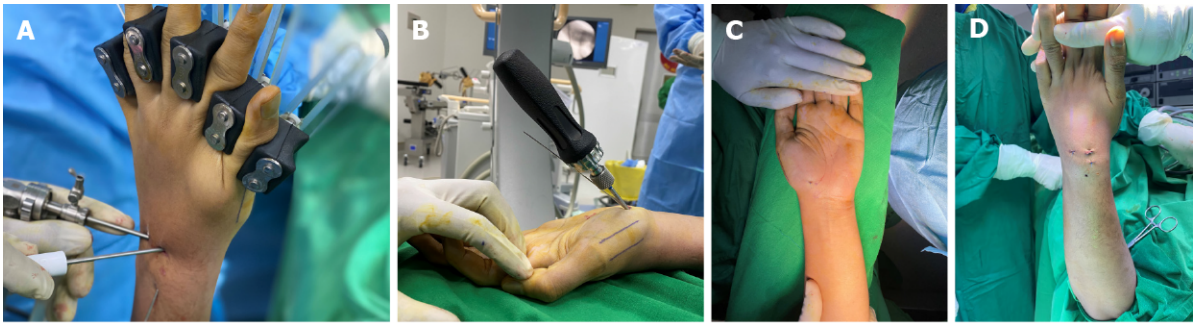

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Figure 5 Intraoperative technique of arthroscopic treatment of scaphoid nonunion. A: Arthroscopic procedure in scaphoid nonunion graft and fixation; B: Headless screw insertion through volar percutaneous approach; C and D: Minimal wound from the arthroscopic procedure.

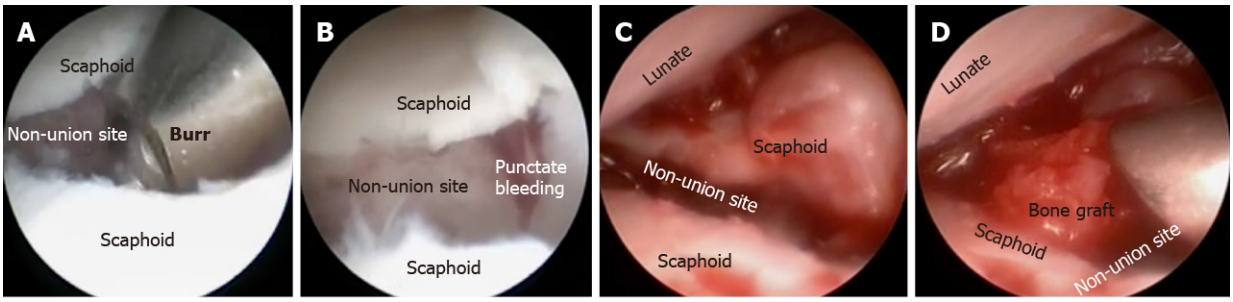

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Figure 6 Arthroscopic view of nonunion scaphoid treatment. A: The nonunion site was debrided; B: Debridement continued until punctate bleeding was observed; C: Nonunion site was clearly visible; D: The nonunion site was packed with bone graft.

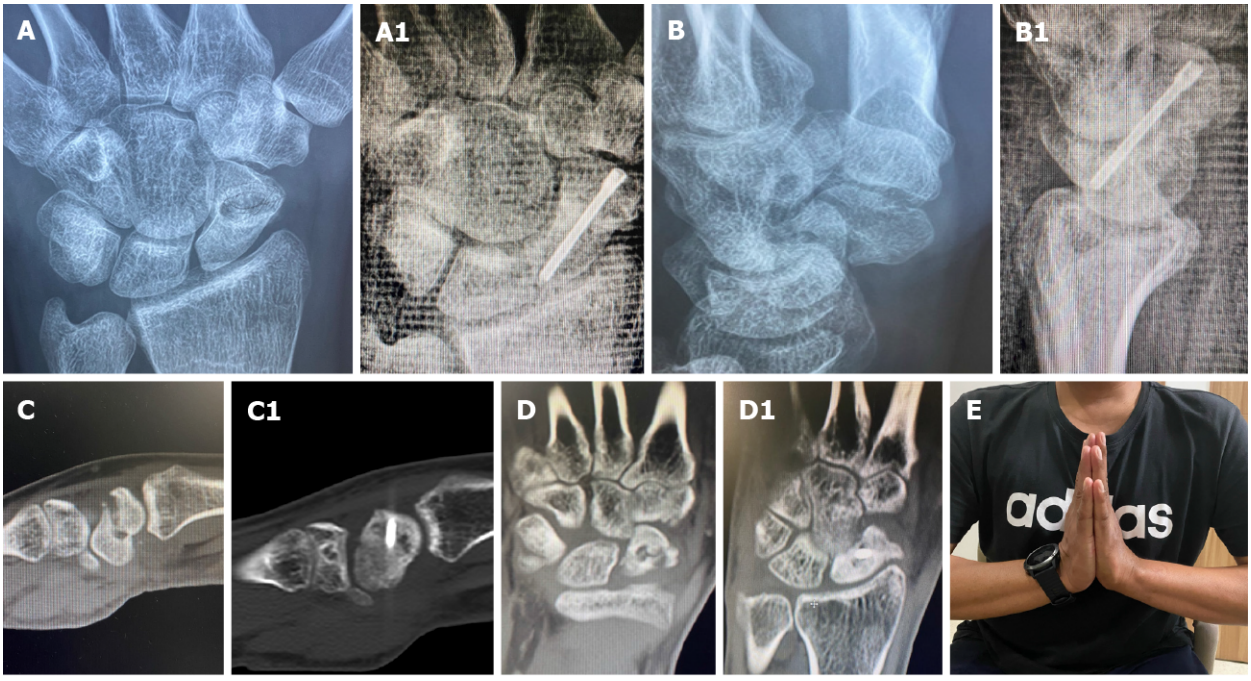

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Figure 7 Arthroscopic fixation and bone grafting in scaphoid non-union. A and B: Pre-operative X-rays; C and D: Computed tomography scans of nonunion scaphoid, showing no bony bridge and humpback deformity. The nonunion and humpback deformity was successfully healed and corrected (A1, B1, C1 and D1); E: Post-operative clinical image after five months demonstrating good and painless range of motion.

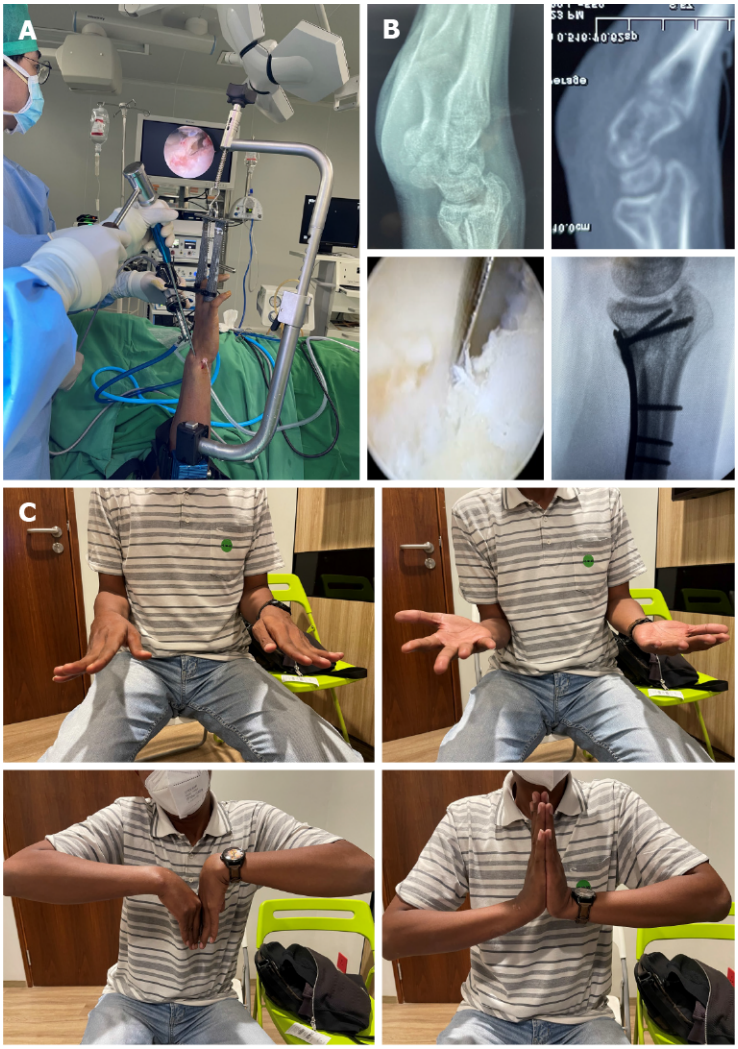

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Figure 8 Arthroscopic assisted osteotomy of distal radius intra-articular malunion. A: Arthroscopic-assisted intra-articular osteotomy; B: Pre-operative X-ray, showing volar shear intra-articular malunion with arthroscopic-assisted intra-articular osteotomy through the fracture line, and post-operative X-ray showing anatomical reduction; C: Post-operative clinical image after five months showing good and painless range of motion.

FOOTNOTES

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MINIREVIEWS

Two-stage revision in periprosthetic knee joint infections

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Abstract

Periprosthetic joint infection (PJI) following total knee arthroplasty is one of the most catastrophic and costly complications that carries significant patient wellness as well as economic burdens. The road to efficiently diagnosing and treating PJI is challenging, as there is still no gold standard method to reach the diagnosis as early as desired. There are also international controversies with respect to the best approach to manage PJI cases. In this review, we highlight recent advances in managing PJI following knee arthroplasty surgery and discuss in depth the two-stage revision method.

Key Words: Periprosthetic joint infection; Knee arthroplasty; Two-stage revision; Spacer; Reimplantation

Core Tip: Two-stage revision for management of periprosthetic joint infection (PJI) following total knee arthroplasty has been widely used with satisfactory outcomes. In this review, we provide comprehensive discussion of the treatment of knee PJI with the two-stage revision method.

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INTRODUCTION

Owing to recent advancements in medicine, the life expectancy of the general population has increased. With changes in modern lifestyle, there is an increased expectation for retention of physical activity and mobility; therefore, the number of joint replacement surgeries has surged[1,2]. Around 1 million knee and hip arthroplasty procedures are performed annually in the United States, and this number is anticipated to double by 2030[3]. In addition to this increase in the number of surgeries, the incidence of PJI also continues to rise[2]. Currently PJI occurs in 1% to 2% of primary and 4% of revision arthroplasties[1,2,4,5]. Kurtz *et al*[1] suggest that there will be over 260,000 revision total knee arthroplasties (TKAs) performed in the United States by 2030. Compared to hip arthroplasty, the risk of PJI is higher after knee arthroplasty[6,7]. For example, the rate of PJI reported after TKA varies from 0.5%-2%, while a range of 0.5%-1.0% is reported after total hip arthroplasty. A higher risk of PJI following TKA may be attributed to less protective soft tissue coverage and higher joint mobility in the knee[8,9]. Delanois *et al* [10] report that PJI alone accounted for 20.4% of all revisions after TKA, and this is considered the most common etiology leading to revision surgery. A number of risk factors are associated with developing PJI including the operative setting, patient comorbidities, and implant-related factors[2]. Additionally, the longer the implanted prosthesis is expected to last, the greater the cumulative risk is for developing infection. Diagnosing PJI early can reduce the significant physical and emotional burden on the patient and the financial pressures on society. However, early diagnosis is still challenging due to the lack of tests that are highly sensitive and specific for this complication. However, early clinical suspicion in parallel to the use of existing serological markers, radiological examination, joint aspirate evaluation, and biopsy continues to be the mainstay for diagnosing PJI[11,12]. The management of PJI remains controversial and requires a complex therapeutic approach, prolonged antimicrobial therapy, and the use of a variety of surgical techniques. Selecting the optimal treatment strategy to eradicate the infection requires proper diagnosis of the infecting microorganisms and identification of their antibiotic susceptibilities. When PJI is missed or inadequately treated, the patient will likely need to endure several operations due to the persistence of infection, negatively impacting function and quality of life[13]. An interdisciplinary approach is crucial to reaching the best patient outcome, and this requires the involvement of orthopedic and plastic surgeons, infectious disease physicians, and microbiologists[2, 14]. The greatest difficulty in managing PJI is the formation of the so-called biofilm, which enables the responsible pathogens to remain on the implant surface, making them resistant to most systemic intravenous antibiotics. Understanding this phenomenon helps in diagnosing and treating PJI[2]. For example, the use of modern diagnostic methods such as sonication for biofilm detection increases the sensitivity for diagnosing PJI, especially in chronic infections caused by low-virulence pathogens[2].

In this review, we provide an updated summary of the current concepts surrounding the two-stage revision procedure in the management of periprosthetic knee joint infections.

DEFINITION & CLASSIFICATION OF PJI

As there currently exists no single test that is capable of diagnosing PJI with complete accuracy, this surgical complication continues to be extremely challenging to tackle[15-17]. The Musculoskeletal Infection Society (MSIS) and the Infectious Diseases Society (IDSA) have proposed criteria to help physicians diagnose PJI[18,19]. In 2018, a second consensus meeting validated the MSIS definition of PJI, but made a few minor modifications[20]. Whilst the major criteria for PJI are the same across all definitions, the minor criteria and supporting evidence are less universally agreed upon. Lately, new tests and biomarkers have evolved and become increasingly available[21-23], including serum D-dimer [24], synovial leukocyte esterase[25], synovial alpha-defensin[26], synovial C-reactive protein (CRP) [27], and molecular techniques such as next-generation sequencing[28]. However, recent research has demonstrated the variability in the sensitivity and specificity of these tests[29]. Therefore, such advancements in PJI diagnosis demanded revision of the existing diagnostic criteria to incorporate the new testing and take into account the relative importance of the different tests included. Thus, a multi-institutional study was published in 2018 in the Journal of Arthroplasty and included new diagnostic criteria[17]. This new PJI scoring system outperformed the IDSA and MSIS criteria in terms of sensitivity and specificity.

The timing in which infection occurs can aid the identification of the infecting organism. Toms *et al* [30] propose a classification consisting of four modes of presentation of PJI: Stage 1 - acute infections occurring within 6 wk; Stage 2 - late onset with chronic indolent infection; Stage 3: sudden-onset in an otherwise well-functioning prosthesis with an acute presentation of infection secondary to hematogenous spread; Stage 4 (proposed by Tsukayama, Estrada, and Gustilo[31]) - positive culture at the time of surgery without previous evidence of infection.

PATHOPHYSIOLOGY OF PERIPROSTHETIC JOINT INFECTION

Most PJI cases are iatrogenic due to inoculation of microorganisms intraoperatively[13]. Based on the virulence of the infecting microorganisms, PJI could either have an early presentation (during the 1st 4-6 wk postoperative) or be delayed (usually 3 mo to 3 years). Early infection usually presents with distinct local and systemic signs of inflammation and is typically caused by highly virulent microorganisms (*e.g.*, *Staphylococcus aureus, Streptococci spp., Enterococci spp.*). On the other hand, less virulent organisms (*e.g.*, coagulase-negative *Staphylococci* or *Cutibacterium spp.*) are the culprits of most delayed infections, which usually present with milder signs and symptoms[2,13] (Figure 1). The presence of foreign bodies such as orthopedic implants increases the infection risk, largely owing to the establishment of the so-called biofilm on prosthetic surfaces[32]. The biofilm formation process consists of several steps: (1) Adherence of the microorganisms to the implant; (2) Multiplication and elaboration of exopolysaccharides ("glycocalyx"); and (3) Coalescence of microcolonies encased in the glycocalyx to form a film [33]. Near the biofilm's surface, microorganisms are generally metabolically active and have free access to nutrients. However, deep within the biofilm, microorganisms have less nutrient access and become metabolically inactive or exist in different states of dormancy, making them more immune to host defenses[34]. Hence, the success of antimicrobial therapy may be negatively impacted by the microenvironment within a biofilm, as diffusion of drugs through the biofilm may be limited[33]. Furthermore, due to the high vascularity of periprosthetic tissue, all implants are at high risk of hematogenous seeding from a distant primary focus. While the risk of this is high during the life of the implant, the highest risk of hematogenous infection occurs in the first few years after implantation[2,35].

TREATMENT PLAN

The management of PJI remains controversial; therefore treatment plans should be tailored for each patient individually. Eradication of the infection, reduction of pain, and restoration of joint function are the primary goals of treatment[12]. In general, management of PJI consists of antimicrobial therapy alone or antimicrobial therapy combined with single or staged surgeries. The approach depends on several factors, including the timing and microbiology of infection, condition of the joint and implant, and the individual patient circumstance. Surgical options include debridement and retention of the prosthesis, resection arthroplasty with reimplantation in a single or staged procedure, resection arthroplasty alone, or in extreme cases, amputation[36]. Two-stage revision remains the favorite surgical option, with overall higher rates of eradicating PJI in comparison to single-stage revision. For example, Elson *et al*[37] report 3.5% failure rates with two-stage revision *vs* 12.4% using a single-stage strategy. Similarly, Garvin *et al*[38] report a failure rate of 5.6% *vs* 10.1%, respectively. For the purposes of this review article, we will focus mainly on the two-stage revision method.

TWO-STAGE REVISION

The two-stage revision procedure is considered to be the gold standard for the management of PJI[12]. This method was described in 1983 by Insall *et al*[39] and in 1995, Garvin *et al*[40] conducted a literature review that highlighted the success associated with this approach. The first stage of the procedure includes the removal of the in-situ prosthesis, thorough debridement of the infected bone and soft tissue, and the implantation of antibiotic-loaded cement (ALC) spacers for temporary fixation. The interim period between the two stages includes administration of intravenous antibiotics and close monitoring of the patient clinically and serologically for resolution of infection. Once the infection has resolved, the second stage, which comprises the use of antibiotic-loaded cement for reimplantation of the definitive prosthesis[12,41]. The time between stages can range from 6 wk to several months. Both stages necessitate aggressive debridement of all infected and necrotic tissue[41]. The following are indications for using a two-stage rather than a single-stage revision procedure[12]: (1) Systemic infection (sepsis) with signs of infection but an unidentified causative microorganism; (2) Antibiotic-resistant microorganisms identified by preoperative cultures; (3) Presence of a sinus tract; and (4) Insufficient soft tissue coverage to allow a single-stage procedure.

1st stage

The first stage of the procedure entails a thorough and vigorous debridement of the whole effective joint space after the removal of all implanted materials and cement[41] (Figure 2). Whenever possible, the use of antibiotics is postponed until all microbiological samples have been collected. To increase the likelihood of arriving at a conclusive diagnosis, it is recommended to obtain both aerobic and anaerobic cultures; at least three and as many as six intraoperative periprosthetic tissue samples or the explanted prosthesis itself may be sent for testing[42]. The sensitivity, specificity, positive predictive value, and negative predictive value with a minimum of two positive samples have been reported to be 94%, 97%,

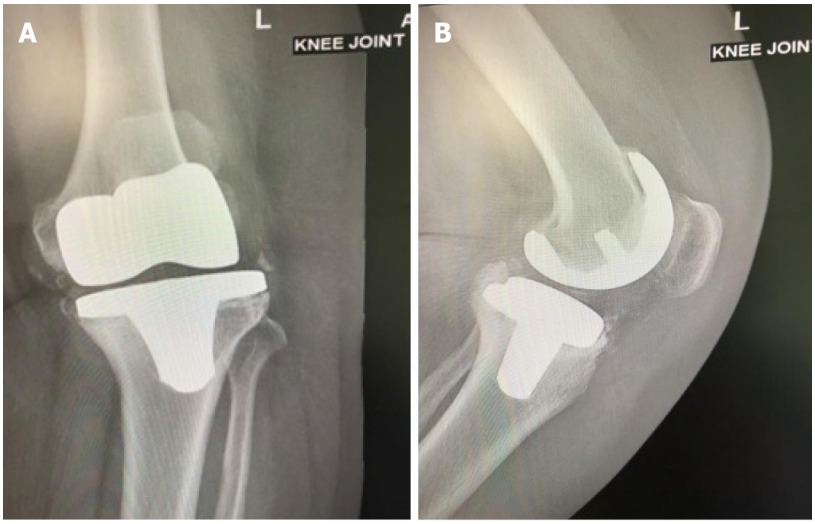

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Figure 1 Anteroposterior and lateral plain radiographs showing septic loosening of a left total knee arthroplasty in a 65-year-old female patient who underwent the primary procedure 5 years previously. A: Anteroposterior view; B: Lateral view. Preoperative aspiration confirmed *Staphylococcus aureus* infection and serum and synovial fluid inflammatory markers were elevated.

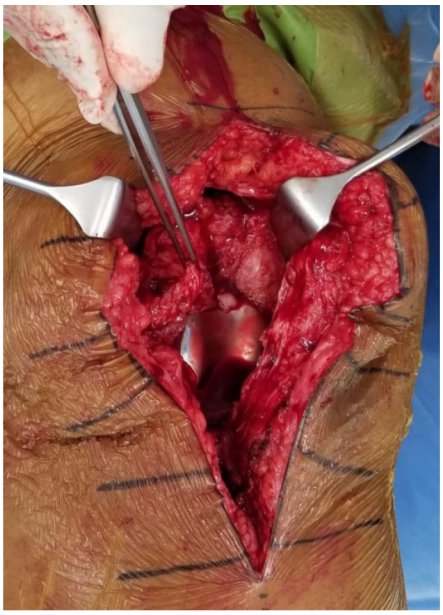

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Figure 2 First stage revision of the case shown in Figure 1. Synovial tissue surrounds the prosthesis. Total synovectomy was performed and samples sent for culture confirmed the growth of *Staphylococcus aureus*.

77%, and 99.9%, respectively[43]. It is advised to excise the old scar and the sinus tract if present. Sending the prosthetic parts for sonification is an option, but this should be planned prior to surgery as it requires special packaging[41]. It is crucial to remove any cement, even if it is firmly affixed to the underlying bone, in addition to any soft tissue that is grossly involved by the infection[44]. Osteotomes, specialized chisels, drills, and taps, as well as various methods that make use of ultrasound-based extraction instruments, can all be used to remove the cement[45]. During this stage, the surgeon must proceed cautiously, since iatrogenic bone injury is possible[44] (Figure 3A). It is important to perform extensive lavage with a high-pressure pulsatile lavage system using at least 6 L of fluid. Normal saline is usually favored, and lavage provides a significant mechanical action that eliminates sequestra, necrotic tissue, and microorganisms. Several studies have investigated adding antibiotics to the normal saline, but no therapeutic advantage over plain lavage solution has been shown[41]. Following the removal of the implants and thorough debridement, new sterile drapes are applied followed by a spacer with ALC (Figure 3B and C). Spacers are either static or dynamic, prefabricated or handcrafted and hemiarthroplasty spacers can replace both sides of the joint. Preoperative culture and sensitivity testing of the

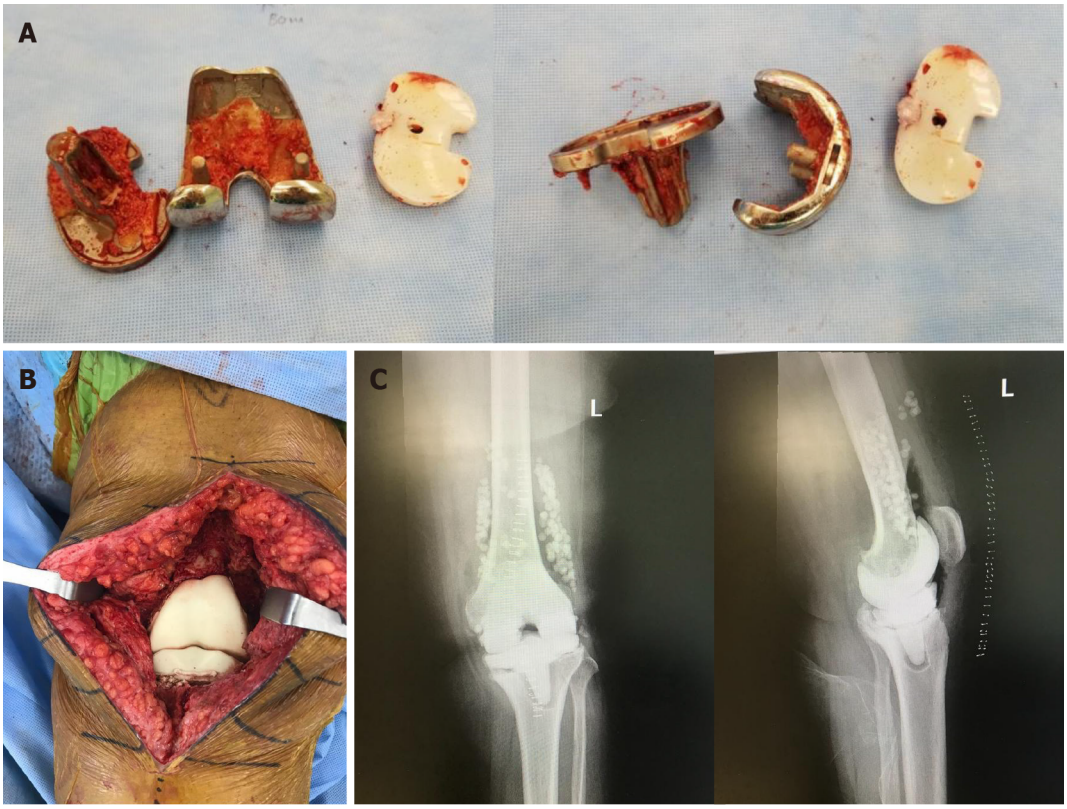

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Figure 3 First stage revision. A: Explanted prosthesis with minimal bone loss; B: Articulating spacer implantation at the end of the procedure containing vancomycin and tobramycin; C: Anteroposterior and lateral plain radiographs of the left knee after the first stage showing the spacer in situ with antibiotic beads.

infecting microorganisms helps to decide the best antibiotics to be added preoperatively to the cement used for construction of the spacer. A discussion with a microbiologist is also necessary to agree on the best choice of antibiotics[41].

Interim period

At this point, antibiotic therapy is the cornerstone and should be tailored depending on the microorganism's antimicrobial sensitivity. With the help of a microbiologist, empiric therapy should be started if the organism or sensitivities are unknown. To identify an organism, all reasonable efforts should be made[41]. The most popular regimen is intravenous antibiotics for 4-6 wk followed by discontinuation of the antibiotics for a period of 2-8 wk prior to the second stage, as this results in a high rate of infection control[46,47]. The best results are usually obtained when the infecting microorganism is sensitive and systemic antibiotics are used in the interim period[48,49]. Prolonging the interim period has been linked with suboptimal infection control rates and poor function restoration[12]. However, a single study concluded that there were no differences in functional outcome in patients who had undergone a two-stage revision with an interim period of less than 6 mo *vs* those with more than 6 mo between resection and reimplantation[12,19]. Deciding to move forward with prosthesis reimplantation depends on clinical, serological testing, and joint aspirate assessment. Residual infection requires further debridement and a new spacer insertion[41]. Normalization of the CRP and erythrocyte sedimentation rate (ESR) alone does not guarantee eradication of the infection, especially in coagulase-negative staphylococcal infections, as these may not trigger a significant inflammatory response[12]. Kusuma *et al* [50] reported that synovial white blood cell (WBC) count is the most reliable predictor of infection control, and a decision to proceed to the second stage depends on attaining a WBC count of less than 3000/μL with less than 80% polymorphonuclear cells from the joint aspirate. Negative intraoperative frozen sections and tissues grossly appearing noninfected are other criteria which are utilized in the second stage to support the decision of proceeding with reimplantation, as there is a high risk of false positive or false negative preoperative cultures. The joint aspirate is mainly used for cell count assessment[50].

Spacer

Spacers are categorized as articulating (dynamic) or non-articulating (static). Between staged procedures, dynamic spacers maintain ambulation and joint range of motion, which protect against muscle wasting; evidence has shown them to be as or more effective at eliminating infection as static

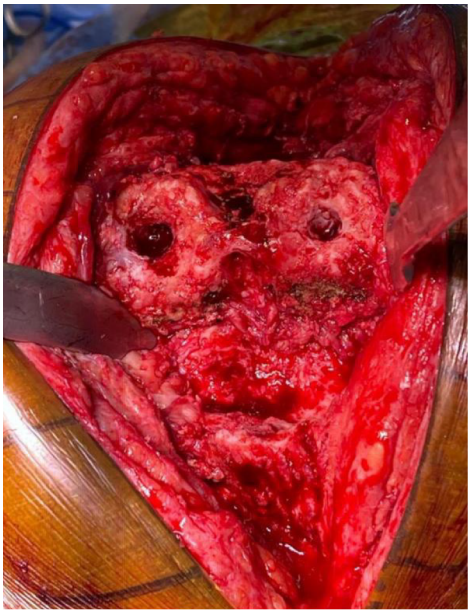

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Figure 4 Second stage revision. After the removal of the spacer, the joint is prepared for reimplantation of the prosthesis. This joint shows minimal bone loss.

spacers[51]. Being able to maintain a range of motion also prevents against the formation of soft tissue and muscle contractures, which facilitates the reimplantation procedure[12,52,53]. Brunnekreef *et al*[54] found a better and quicker recovery of knee function with dynamic spacers, resulting in shorter operation times. Furthermore, compared to static spacers, the use of a dynamic spacer appears to increase the rate of infection eradication (91.2% *vs* 87%)[55]. Moreover, using a static spacer may result in bone loss due to migration of the spacer[56,57]. Despite the above, static spacers may be preferrable in certain circumstances, such as massive bony and soft tissues loss, ligament laxity in the knee, and deficiency of the abductor muscles of the hips[41,44]. Prosthesis with Antibiotic-Loaded Acrylic Cement (PROSTALAC) is an example of an articulating spacer that delivers high concentration of broad-spectrum antibiotics locally. A common regimen used with PROSTALACs is the inclusion of 3 g of vancomycin and 2 g of gentamicin in each sachet of Palacos R cement (Schering Plough Ltd, Labo nv, Belgium). However, antibiotics in spacers may also be prepared according to the sensitivities of the infecting micro-organisms if detected preoperatively[12]. Spacers are usually augmented with a post-operative course of intravenous antibiotics until the definitive antibiotic sensitivities of the infective micro-organisms are detected from the intraoperative cultures taken at the first stage procedure[12]. However, spacers are not complication-free. Faschingbauer *et al*[58] reported that out of 138 patients, 27 (19.6%) developed complications, including spacer fractures in 12 cases (8.7%), dislocation in 12 cases (8.7%), 1 case of a periprosthetic femoral fracture with a spacer in situ, 1 case of a dislocation with simultaneous spacer fracture, and 1 case of protrusion into the pelvis.

2nd stage

The second stage consists of removal of the spacer, further debridement, and collection of tissue samples followed by definitive reimplantation of a new prosthesis (Figure 4). The decision to proceed with the definitive reimplantation must be made after the resolution of all infection-related symptoms and signs and improvement of laboratory results (a declining trend of CRP and ESR may be accepted as opposed to complete normalization of the values as stated earlier)[41,44]. During the second stage, the existing scar is usually utilized to approach the joint[59]. Once the joint is appropriately exposed, further samples are obtained for cultures. It is crucial to remove the cement spacer with the pseudo-synovial cavity that develops around the spacer without compromising the surrounding bone. Necrotic tissue is removed, and pulse lavage is used for extensive irrigation of the joint. This ensures the removal of any residual cement debris, which potentially can cause third body wear if left at the spacer site. If necessary, bone allografts may be utilized at this point to reconstruct any bony deficiencies followed by reimplantation of the definitive prosthesis in accordance with the preoperative plan. The use of bone allografts in revision surgery after PJI has drawn some controversy in the past[60]. Latest evidence, however, has not been able to demonstrate a substantial difference in the rate of reinfection following the use of allografts in this context. Therefore, when there is considerable bone loss, bone grafts may still be used safely[61]. Both cemented and uncemented prostheses may be utilized for the definitive implant. Modern antibiotic delivery methods like defensive antibacterial coating may also be utilized at this stage[62]. Similar reinfection rates and aseptic loosening have been reported when using cemented or uncemented prostheses in TKA revisions for infection[63]. Following surgery, antibiotics may be

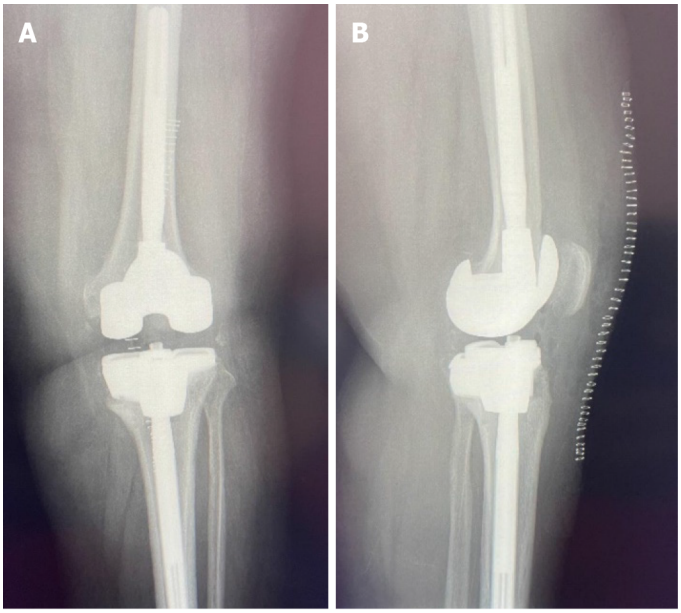

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Figure 5 Postoperative anteroposterior and lateral plain radiographs. A: Postoperative anteroposterior view of the left knee after completion of the second stage revision; B: Lateral view of the left knee after completion of the second stage revision.

administered until the bacteriology results are revealed[12]. If any suspicion remains regarding infection during the second stage, a synovial leukocyte esterase strip test, synovial alpha-defensin test, or a frozen section intraoperative tissue analysis may be used to confirm. If the tests are suggestive of residual infection, aggressive debridement followed by a cemented spacer reimplantation (a repetition of the first stage) is necessary[41,44] (Figure 5).

CONCLUSION

PJI is challenging to manage, but recent advancements in laboratory testing have helped to facilitate early diagnosis when used collectively under the internationally agreed upon definition of this surgical complication. A multidisciplinary team approach is crucial when dealing with such cases. Efforts should be made to diagnose the causative microorganism as early as possible in order to start appropriate antimicrobial therapy and plan surgical intervention accordingly. In terms of surgical options, the two-stage revision procedure remains the gold standard approach in chronic cases and yields the highest PJI eradication rates.

FOOTNOTES

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ORIGINAL ARTICLE

Case Control Study

Rural implementation of the perioperative surgical home: A case-control study

Srinivasan Sridhar, Amy Mouat-Hunter, Bernadette McCrory

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Abstract

BACKGROUND

Perioperative surgical home (PSH) is a novel patient-centric surgical system developed by American Society of Anesthesiologist to improve outcomes and patient satisfaction. PSH has proven success in large urban health centers by reducing surgery cancellation, operating room time, length of stay (LOS), and readmission rates. Yet, only limited studies have assessed the impact of PSH on surgical outcomes in rural areas.

AIM

To evaluate the newly implemented PSH system at a community hospital by comparing the surgical outcomes using a longitudinal case-control study.

METHODS

The research study was conducted at an 83-bed, licensed level-III trauma rural community hospital. A total of 3096 TJR procedures were collected retrospectively between January 2016 and December 2021 and were categorized as PSH and non-PSH cohorts (n = 2305). To evaluate the importance of PSH in the rural surgical system, a case-control study was performed to compare TJR surgical outcomes (LOS, discharge disposition, and 90-d readmission) of the PSH cohort against two control cohorts [Control-1 PSH (C1-PSH) (n = 1413) and Control-2 PSH (C2-PSH) (n = 892)]. Statistical tests including Chi-square test or Fischer's exact test were performed for categorical variables and Mann-Whitney test or Student's t-test were performed for continuous variables. The general linear models (Poisson regression and binomial logistic regression) were performed to fit adjusted models.

RESULTS

The LOS was significantly shorter in PSH cohort compared to two control cohorts (median PSH = 34 h, C1-PSH = 53 h, C2-PSH = 35 h) (P value < 0.05). Similarly, the PSH cohort had lower percentages of discharges to other facilities (PSH = 3.5%, C1-PSH = 15.5%, C2-PSH = 6.7%) (P value < 0.05). There was no statistical difference observed in 90-d readmission between control and PSH cohorts. However, the PSH implementation reduced the 90-d readmission percentage (PSH = 4.7%, C1-PSH = 6.1%, C2-PSH = 3.6%) lower than the national average 30-d readmission percentage which is 5.5%. The PSH system was effectively established at the rural community hospital with the help of team-based coordinated multi-disciplinary clinicians or physician co-management. The elements of PSH including preoperative assessment, patient education and optimization, and longitudinal digital engagement were vital for improving the TJR surgical outcomes at the community hospital.

CONCLUSION

Implementation of the PSH system in a rural community hospital reduced LOS, increased direct-to-home discharge, and reduced 90-d readmission percentages.

Key Words: Perioperative surgical home; Rural medicine; Case-control study; Total joint replacements; Health equity

Core Tip: The study evaluated the newly implemented perioperative surgical home (PSH) at a rural community hospital using a case-control design. With limited supporting microsystems, team-based physician co-management was vital to establish the PSH system and following protocols including preoperative assessment, patient education, and longitudinal digital engagement. The surgical outcomes - length of stay, discharge disposition, and 90-d readmission - were compared between the PSH cohort and the control cohorts. The results from this study highlighted the effectiveness of PSH in improving total joint replacement surgical outcomes, especially for high-risk patients who are older and have one or more medical complications.

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INTRODUCTION

The demand for orthopedic surgeries including total joint replacement (TJR), which are primarily performed on hips, knees, and shoulders, are drastically increasing each year[1]. Yet, delivering quality surgical care to large volumes of TJR patients is a challenge to many hospitals, specifically those hospitals located in rural areas[2,3]. Rural and frontier health systems have siloed perioperative care that is spread across many disciplines and institutions, which contributes to inadequate communication, high cost, poor care continuity, and preventable complications[4]. On average, TJR patients are 65 years or older, and have one or more health conditions (*e.g.*, comorbidities). Due to generally higher risk of surgery in these populations, there is a 1% to 50% chance of adverse events in TJR surgeries including major cardiac incidents, healthcare-acquired conditions, extended length of stay (LOS), readmission to inpatient facilities, improper pain management, and side effects[4,5].

To improve surgical outcomes and patient experience, the perioperative surgical home (PSH) model of care was created by the leaders within American Society of Anesthesiologists (ASA)[6,7]. Compared to a traditional surgical system, the PSH is a coordinated interdisciplinary team providing all surgical care to patients from the preoperative phase (30 d before surgery) to recovery phase (90 d after surgery) (Figure 1)[7-11].

The components of PSH also included patient-centered coordination programs and enhanced recovery after surgery[12,13]. The implementation of PSH in larger healthcare systems and academic medical institutions has shown promising results in surgical outcomes, especially in orthopedic procedures[9]. For example, Qiu *et al*[14] and Alvis *et al*[15] observed that the PSH cohort had a day shorter LOS than the control cohort when examining hip and knee procedures. Kim *et al*[16] analyzed 1194 TJR procedures and found that the PSH cohort had higher discharges to home by 8.1% compared

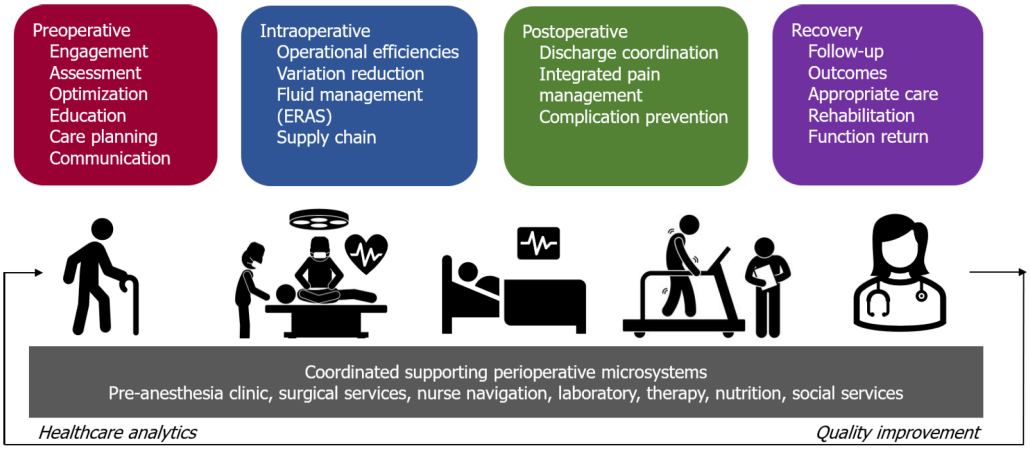

Figure 1 Perioperative surgical model (adapted from[4]).

to the non-PSH cohort. The authors also noticed the surgical cost in the non-PSH cohort was 14.9% greater cost than the PSH cohort. Yajnik *et al*[17] retrospectively analyzed 40 knee procedures and demonstrated that the PSH cohort experienced optimized post-surgical pain management with less consumption of opioids than the non-PSH cohort. Likewise, past researchers found that PSH contributed to improved surgical outcomes including, lower readmission rates, faster postoperative recovery, improved operational efficiency, and higher patient satisfaction[15,18-21].

Despite these successes, some researchers found no change in surgical outcomes with PSH in similar size urban health centers. For example, Vetter *et al*[22] and Powell *et al*[23] found no significant difference in LOS after implementing PSH for orthopedic surgeries. Qui *et al*[14] and Vetter *et al*[22] found no difference in readmission rates using the PSH system. In terms of surgery cost, Leahy *et al*[24] found there was no significant reduction for pediatric patients. These examples exhibit that there is no standard PSH program to achieve a standardized surgical outcome[9]. These PSH studies were performed in urban healthcare systems and academic-affiliated medical centers. To authors' knowledge only our pilot study has explored PSH systems in rural or frontier healthcare service area[4]. This current study addresses this gap by assessing TJR outcomes at a rural hospital with a newly implemented PSH system using a case-control study design.

Surgical care inequality is greater within rural community hospitals due to limited resources, socioeconomic differences, and poor access to healthcare[25-27]. Compared to urban hospitals, rural surgical outcomes have higher odds of in-hospital mortality and higher hospitalization cost[28]. One of the reasons for this is many rural patients are uninsured, older, and have one or more medical complications[29,30]. Rural hospitals in the United States can often be overwhelmed by the growing demand for TJR surgeries and factors such as poor coordination among clinicians, lack of patient education, poor patient care transitions, limited patient engagement (pre-operative and post-operative), and inconsistent/non-standardized care delivery affect rural orthopedic surgical care negatively[1,5].

A newly implemented PSH at a community hospital in rural Montana was created to address the factors mentioned above, which have plagued the rural orthopedic surgery system. With limited resources and supporting microsystems, the PSH was successfully initiated with the help of strong team-based coordination amongst clinicians. The PSH multi-disciplinary team consisted of the patient's selected surgeon, anesthesiologist, hospitalist, physician assistant, registered nurse, and the patient's primary care manager. This collaboration focused on improving surgical care and enhancing patient engagement perioperatively. Effective communication between clinicians was established for communal decision-making for patient-centric - "physician co-management"[31].

This research study's primary objective was to evaluate the newly implemented PSH system at a local rural, community hospital by comparing TJR surgical outcomes using a longitudinal case-control study design. Based on our preliminary study[32], it was hypothesized that the implementation of the PSH in the rural community hospital would positively impact patients' TJR outcomes (*i.e.*, shorter LOS, reduced readmissions, and increased rate of home discharge) across three distinct cohorts for the case-control design.

MATERIALS AND METHODS

The PSH clinic affiliated with the local community hospital began seeing TJR patients in November 2018. The hospital was an 83-bed, licensed level-III trauma center primarily serving three counties. However, based on initial analyses, the hospital was serving patients from more than 10 surrounding counties covering 9000 square miles and approximately 136000 residents. The research team (health

systems engineers and clinicians) retrospectively collected and analyzed all TJR data from January 2016 to December 2021. The observational timeframes were reviewed, and three distinct cohorts were determined for the case-control study design.

Data collection and pre-processing

Data were extracted from the electronic medical record for a total of 6685 orthopedic procedures that were performed on knees, hips, and shoulders between January 2016 and December 2021 (Figure 2). Six hundred and forty-eight (n = 648) procedures were included that had CPT codes - 27447 (total knee), 27130 (total hip), and 23472 (total shoulder). The remaining 6037 did not have CPT codes and were filtered for TJR procedures by searching for keywords 'arthroplasty', 'total', 'THA' (*i.e.*, Total Hip Arthroplasty), 'TKA' (*i.e.*, Total Knee Arthroplasty), and 'TSA' (*i.e.*, Total Shoulder Arthroplasty). During this filtering process, a total of 3420 procedures were excluded because they were identified as non-TJR procedures, (*e.g.*, arthroscopic procedures, reductions, nailing hip). A total of 82 TJR procedures were also excluded from the analysis because they were either duplicate records (n = 1) or missing key outcomes and demographic values (n = 81) of the patients.

A total of 3183 TJR procedures were considered for the analysis and were categorized into: the PSH cohort (case) and non-PSH cohort (control). The PSH pathway begins with visiting PSH clinic for preoperative assessment. Most patients visited the PSH clinic between 30 to 60 d before surgery for their preoperative assessment. Very few medically complicated patients needed more time for optimization and postponed their surgery 6-9 mo (not more than a year) after their preoperative assessment. Therefore, the inclusion criteria for the PSH cohort (n = 791) included if the patient visited the PSH clinic for optimization between 1 and 364 d before surgery. Those patients who visited the PSH clinic but failed to meet the inclusion criteria (*i.e.*, visited the PSH clinic a year before their surgery or after their surgery), were excluded from the analysis (n = 87). The inclusion criteria for the non-PSH cohort included the patients who did not visit the PSH clinic during their surgical process at all. The non-PSH cohort was further subcategorized based on the timeframes: Control-1 PSH (C1-PSH) cohort (before PSH implementation between January 2016 and October 2018, n = 1413) and Control-2 PSH (C2-PSH) cohort (after PSH implementation between November 2018 and December 2021, n = 892).

The study utilized two control cohorts to evaluate the importance of the PSH system in two timeframes - before and after PSH implementation. In the first evaluation, the PSH cohort was compared with C1-PSH cohort. In the second evaluation, the PSH cohort was compared with C2-PSH cohort. The baseline characteristics were compared with variables including patient age, gender, body mass index (BMI), ASA score (Class 1, 2, 3, or 4), procedure type (THA, TKA, and TSA) and insurance type (private or public payer). These variables were included in the baseline characteristics and in the analysis, as they were found to be potential confounders at PSH implemented hospitals with the surgical outcomes LOS, discharge disposition, and 90-d readmission[14,16,24,33,34].

Statistical analysis

Either the Fischer's exact test or Chi-square test for association were used to compare the categorical variables between non-PSH and PSH cohorts. The continuous variables between two cohorts were analyzed using the Mann-Whitney test or Student's t test, as appropriate. The LOS was found to be right skewed and was not normally distributed using the Shapiro-Wilk test (P value < 0.01). Therefore, a Poisson regression was performed to fit an adjusted model[14,35]. For dichotomous variables, *i.e.*, discharge disposition and 90-d readmission, the binomial logistic regression was used to fit an adjusted model. All data handling, visualization, and statistical analyses were performed using R (V4.0.3, Vienna, Austria). The statistical analyses were performed with an alpha (α) value of 0.05. All data were encrypted and were accessed only by the authors and clinicians working at the hospital.

RESULTS

Evaluation 1: Comparison of C1-PSH cohort and PSH cohort

There were no significant differences observed in the baseline characteristics for the variables gender, BMI, and procedure type (P value > 0.05) (Table 1). However, a difference was observed between cohorts for the variables age, ASA class, and insurance type (P value < 0.05). On average, patients in the PSH cohort were two years older than in the C1-PSH cohort. The PSH cohort also included more medically complex patients with a higher proportion of ASA class 3 (42%) compared to the C1-PSH cohort (36%). For insurance, there were more public insurance payers in the PSH cohort (82%) compared to the C1-PSH cohort (71%).

The LOS was lower in the PSH cohort compared to the C1-PSH cohort (median 34 *vs* 53 h, P value < 0.01) (Figure 3). Based on the Poisson regression results, the PSH clinic had a positive effect on LOS (P value < 0.01). On average, the LOS was 10% shorter in the PSH cohort compared to the C1-PSH cohort (Table 1). Other variables that also had a significant effect on patients' LOS were age, gender, BMI, procedure type, and insurance type (P value < 0.05) (Supplementary Table 1).

Table 1 Comparison of baseline characteristics between Control-1 perioperative surgical home and perioperative surgical home cohorts

Characteristics	C1-PSH (*n* = 1413)	PSH (*n* = 791)	*P* value
	mean (SD) [min, max] or *n* (%)	mean (SD) [min, max] or *n* (%)	
Age	67.3 (10) [18, 95]	69.2 (8.6) [31, 90]	< 0.01[1]
Gender			0.19[2]
Male	629 (45)	379 (47.5)	
BMI	29.7 (6.2) [17.3, 68.5]	29 (6.09) [14.67, 55.3]	0.86[1]
ASA			0.009[3]
Class 1	67 (4.7)	20 (2.5)	
Class 2	817 (57.8)	434 (54.9)	
Class 3	517 (36.6)	332 (42)	
Class 4	12 (0.8)	5 (0.6)	
Procedure			0.08[2]
THA	489 (35)	311 (39.3)	
TKA	686 (49)	356 (45)	
TSA	238 (17)	124 (15.7)	
Insurance			< 0.01[2]
Private	415 (29)	145 (18)	
Public	998 (71)	646 (82)	

[1]Mann-Whitney test.
[2]Chi-square test.
[3]Ficher's exact test.
C1-PSH: Control-1 perioperative surgical home; BMI: Body mass index; ASA: American Society of Anesthesiologist Score; THA: Total hip arthroplasty; TKA: Total knee arthroplasty; TSA: Total shoulder arthroplasty.

Discharge disposition was classified into two types: patient discharged to home or discharged to other facilities such as skilled nurse facilities, inpatient rehabilitation facilities, or other hospitals' swing beds. Discharge disposition was significantly different between the PSH and C1-PSH cohort (χ^2 = 72, *P* value < 0.01) (Figure 4). The unadjusted odds for the PSH cohort discharged to other facilities was 80% lower than the C1-PSH cohort (*P* value < 0.01) (Table 2). Using logistic regression, the adjusted odds for the PSH cohort discharged to other facilities were 91% lower than the C1-PSH cohort (*P* value < 0.01) (Table 2). Age, gender, procedure type, insurance type, and LOS were also associated with the patient's discharge type (*P* < 0.05) (Supplementary Table 1).

Readmission was categorized by if a patient was readmitted to any inpatient within 90 d post-surgery or not. The Chi-square test had no strong evidence for a difference in the readmission rates between the PSH and C1-PSH cohort (χ^2 = 1.65, *P* = 0.2) (Figure 4). The unadjusted odds for the PSH cohort readmitted after surgery was 24% lower than the C1-PSH cohort (*P* = 0.17) (Table 2). The adjusted odds for the PSH cohort readmitted after surgery was 28% lower than the C1-PSH cohort (*P* = 0.17) (Table 2). In this adjusted analysis, no variable had a significant effect on patient readmission (Supplementary Table 1).

Evaluation 2: Comparison of PSH and C2-PSH cohort

Except for variables ASA and procedure type, there was no significant difference observed between cohorts in the baseline characteristics (*P* = 0.046) (Table 3). Similar to evaluation 1, the PSH cohort had more medically complex patients with a higher proportion of ASA class 3 (42%) compared to the C2-PSH cohort (36%). For procedure types, there were more knee procedures in the PSH cohort and there were more hip and shoulder procedures in the C2-PSH cohort.

There was no significant difference between LOS in the PSH cohort and C2-PSH cohort in the unadjusted analysis (median 34 *vs* 35 h, *P* = 0.5) (Figure 5). However, in the adjusted analysis using Poisson regression, the LOS was found to be lower in the PSH cohort compared to the C2-PSH cohort (*P* value < 0.01). On average, the LOS was 10% shorter in the PSH cohort compared to the C2-PSH cohort (Table 4). Other variables that also had significant effect on patients' LOS were age, gender, BMI, procedure type, and insurance type (*P* value < 0.05) (Supplementary Table 2).

Table 2 Surgical outcomes of perioperative surgical home cohort relative to Control-1 perioperative surgical home cohort

Outcomes	Unadjusted odds ratio (95%CI)	Unadjusted, *P* value	Adjusted risk (95%CI)	Adjusted, *P* value
Length of stay	-	-	0.90 (0.88, 0.91)[1]	< 0.01
Discharge disposition	0.20 (0.13, 0.30)	< 0.01	0.09 (0.05, 0.14)[2]	< 0.01
Readmission	0.76 (0.51, 1.12)	0.17	0.72 (0.47, 1.09)[3]	0.11

[1]Poisson regression adjusted with age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA), procedure type, and insurance type.
[2]Binomial logistic regression adjusted with LOS, age, gender, BMI, ASA, procedure type, and insurance type.
[3]Binomial logistic regression adjusted with LOS, discharge disposition, age, gender, BMI, ASA, procedure type, and insurance type.

Table 3 Comparison of baseline characteristics between the Control-2 perioperative surgical home and perioperative surgical home cohorts

Characteristics	C2-PSH (*n* = 892)	PSH (*n* = 791)	*P* value
	mean (SD) [min, max] or *n* (%)	mean (SD) [min, max] or *n* (%)	
Age	69 (8.5) [37, 98]	69.2 (8.6) [31, 90]	0.2[1]
Gender			0.52[2]
Male	439 (49.2)	376 (47.5)	
BMI	30 (6.2) [17, 57.8]	30 (6.1) [14.67, 55.3]	0.76[1]
ASA			0.046[3]
Class 1	24 (2.7)	16 (3.4)	
Class 2	546 (61.2)	434 (54.9)	
Class 3	319 (35.8)	332 (42)	
Class 4	3 (0.3)	5 (0.6)	
Procedure			< 0.01[2]
THA	294 (33)	311 (39.3)	
TKA	355 (39.8)	356 (45)	
TSA	243 (27.2)	124 (15.7)	
Insurance			0.4[2]
Private	179 (20)	145 (18)	
Public	713 (80)	646 (82)	

[1]Mann-Whitney test.
[2]Chi-square test.
[3]Ficher's exact test.
C2-PSH: Control-2 perioperative surgical home; BMI: Body mass index; ASA: American Society of Anesthesiologist Score; THA: Total hip arthroplasty; TKA: Total knee arthroplasty; TSA: Total shoulder arthroplasty.

Similar to evaluation 1, the discharge disposition was found to be significantly different between the PSH and C2-PSH cohorts (χ^2 = 8, *P* value < 0.01) (Figure 6). The unadjusted odds for the PSH cohort discharged to other facilities was 49% lower than the C2-PSH cohort (*P* value < 0.01) (Table 4). Using logistic regression, the adjusted odds for the PSH cohort discharged to other facilities was 62% lower than the C2-PSH cohort (*P* value < 0.01) (Table 4). Age, gender, procedure type, insurance type, and LOS were also associated with patient discharge type (*P* value < 0.05) (Supplementary Table 2).

Similar to evaluation 1, the Chi-square test had no strong evidence for a difference in the readmission rates between the PSH and C2-PSH cohort (χ^2 = 1, *P* = 0.31) (Figure 6). However, atypical results were observed in the unadjusted analysis, where the odds of the PSH cohort readmitted after surgery was 31% higher than the C2-PSH cohort (*P* = 0.26) (Table 4). Atypical results were also observed in the adjusted analysis, where the odds for the PSH cohort readmitted after surgery was 29% higher than the C2-PSH cohort (*P* = 0.26) (Table 4). In the adjusted analysis, no variable had a significant effect on patient readmission (*P* value > 0.05) (Supplementary Table 2).

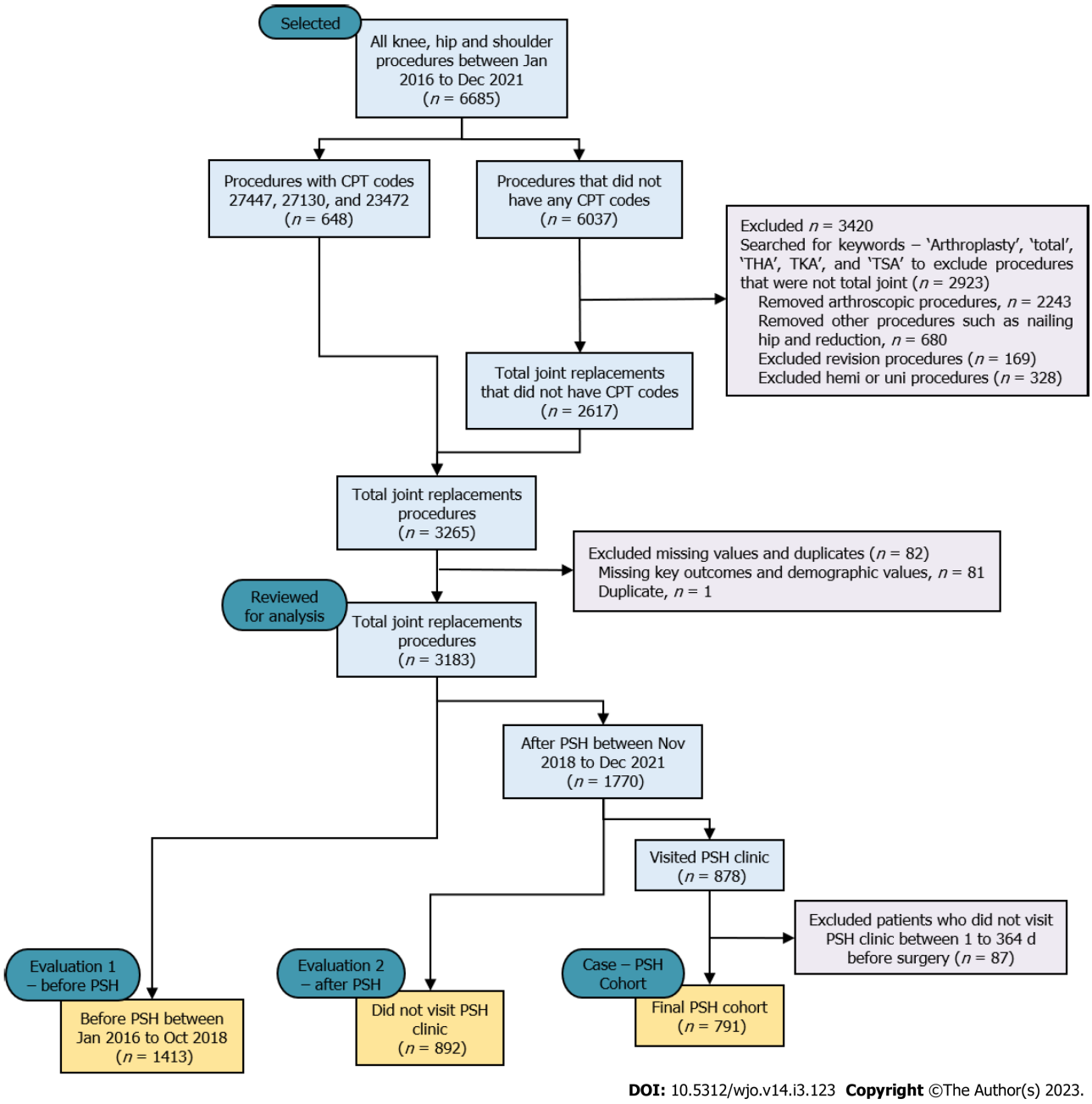

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Figure 2 CONSORT diagram for perioperative surgical home case-control study. PSH: Perioperative surgical home.

DISCUSSION

This study evaluated the importance of PSH at a rural community hospital by comparing the PSH cohort with two control cohorts. In the first evaluation, the PSH cohort was compared with the C1-PSH cohort and for the second evaluation, the PSH cohort was compared with the C2-PSH cohort. The C1-PSH cohort included patients who had TJR surgeries before the PSH was implemented. The C2-PSH cohort consists of patients, who had TJR surgeries after PSH was implemented but did not visit the PSH clinic or followed the PSH-pathway.

In both evaluations, the LOS was shorter in the PSH cohort compared to the control cohorts (median PSH = 34 h, C1-PSH = 53 h, C2-PSH = 35 h)[14,33,34]. Although there was no statistical difference in LOS between the PSH and the C2-PSH cohort in the unadjusted analysis, the LOS was significantly shorter in the PSH cohort (10% shorter) in the adjusted analysis. This is because the PSH cohort had older and more medically complicated patients than the control cohorts. Therefore, when adjusted for the variables age, BMI, ASA, *etc.*, the PSH had a significant effect in reducing LOS. Correspondingly, the PSH cohort had lower percentage of discharges to other facilities compared to the control cohorts (PSH = 3.5%, C1-PSH = 15.5%, C2-PSH = 6.7%).

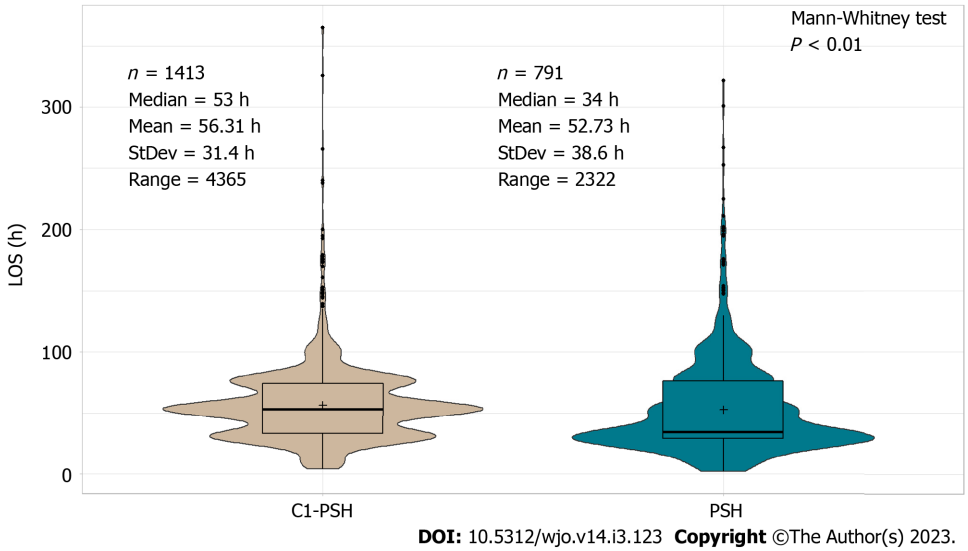

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Figure 3 Length of stay distributional difference between the Control-1 perioperative surgical home and perioperative surgical home cohort. PSH: Perioperative surgical home; C1-PSH: Control-1 PSH.

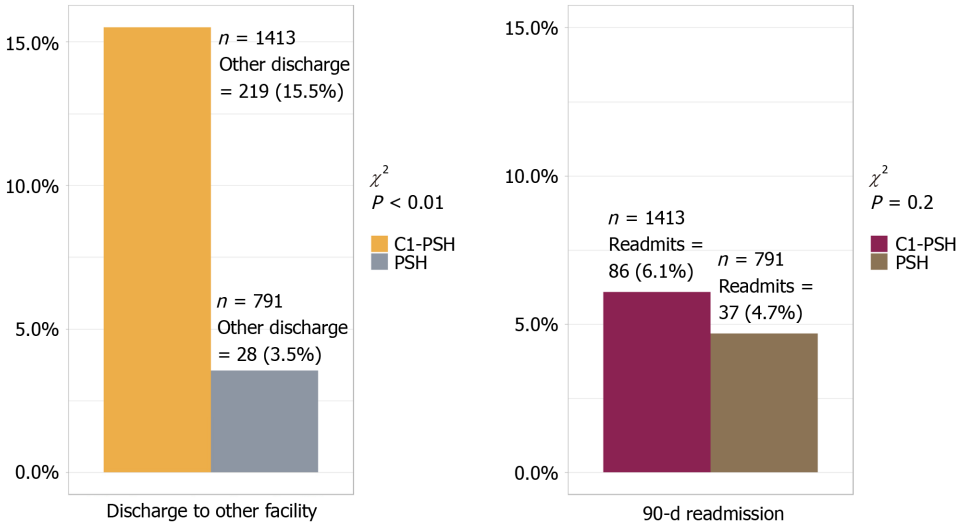

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Figure 4 Discharge disposition and readmission between the Control-1 perioperative surgical home cohort and perioperative surgical home cohort. PSH: Perioperative surgical home; C1-PSH: Control-1 PSH; C2-PSH: Control-2 PSH.

There was no statistical significance in adjusted and unadjusted analysis for 90-d readmission. The readmission percentage was lower in the PSH cohort (4.7%) than the C1-PSH cohort (6.1%). Conversely, the PSH cohort (4.7%) had slightly higher percentage of 90-d readmission than the C2-PSH cohort (3.6%). Despite a marginal increase in the PSH cohort, the 90-d readmission percentage was still lower than the national average 30-d readmission which is 5.5%[36-38]. Past studies also demonstrated similar results where despite no statistical significance, the implementation of PSH helped to lower the readmission rates after surgery[33,38,39].

Akin to other studies of urban health systems[6,9], implementing PSH at a community hospital helped to improve the TJR surgical outcomes. With only limited resources and siloed supporting microsystems, physician co-management was vital to effectively establish the PSH system at the rural community hospital. The PSH preoperative process utilized patient assessment and patient education approximately 30 d before surgery. The assessment helped clinicians identify patients with high-risk factors such as diabetes, high or low blood pressure, sleep apnea, obesity, and heart or respiratory complications[7,40]. Based on these risks, the patients were 'optimized' and received treatment to improve the overall care by minimizing existing conditions or controlling undiagnosed conditions. In addition, the total joint education class hosted by the PSH clinicians educated patients on how to prepare for surgery, manage pain, plan for postoperative discharge, and reach clinicians for postoperative assistance[6,41]. Finally, a digital platform was initiated in the recovery phase to improve

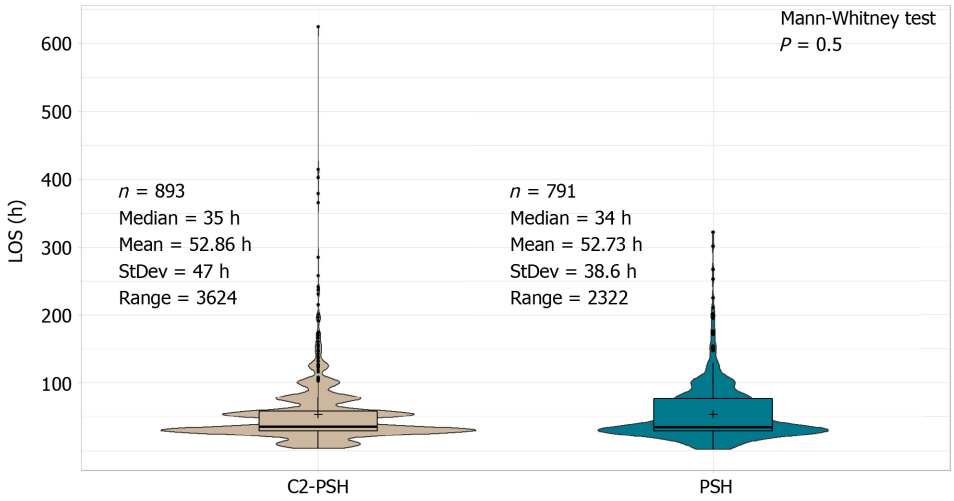

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Figure 5 Length of stay distributional difference between Control-2 perioperative surgical home and perioperative surgical home cohort. PSH: Perioperative surgical home; C2-PSH: Control-2 PSH.

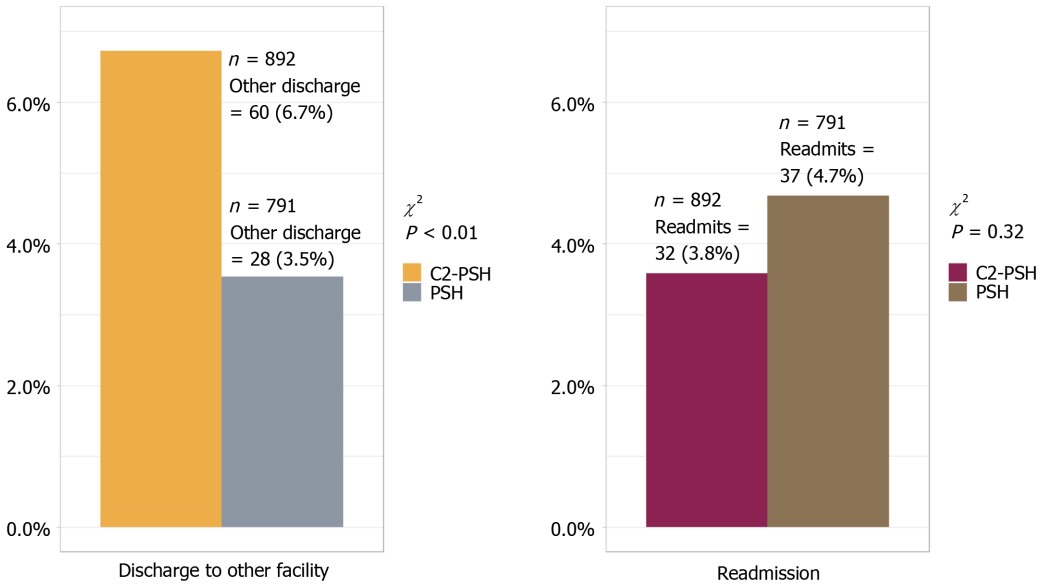

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Figure 6 Discharge disposition and readmission between the Control-2 perioperative surgical home cohort and perioperative surgical home cohort. PSH: Perioperative surgical home; C2-PSH: Control-2 PSH.

patient-clinician coordination and communication after surgery. The digital platform was used to engage and assess longitudinal patient-reported outcomes (post and pre-surgical pain, satisfaction, sleep, *etc.*) from 30 d preoperative to 90 d postoperative. These factors were conducive to improving patient satisfaction, shortening the LOS, increasing discharge to home, and reducing readmission after the surgery[6,24,42].

The PSH clinic majorly saw patients who were high risk (older, high ASA score, high BMI, one or more medical complications such as diabetes, hypertension), which left the C2-PSH cohort with low to medium-risk patients. This explained why the C2-PSH had improved surgical outcomes for LOS, discharge disposition, and 90-readmission compared to the C1-PSH cohort. The PSH system was effective in optimizing medically complicated patients, delivering similar or improved surgical outcomes compared to the C2-PSH cohort. The results from this study support that more patients (especially high and medium risk) should follow the PSH pathway for an effective and improved surgical experience.

Unlike the majority of the PSH studies that were performed at hospitals or health institutions located in metropolitical areas, this research examined the dissemination of PSH system and its effectiveness at a community hospital located in a micro-statistical area (population between 10000 to 50000). According to the United States Census Bureau, 27.2 million people (8.4% of the United States population) live in

Table 4 Surgical outcomes of perioperative surgical home cohort relative to Control-2 non-perioperative surgical home cohort

Outcomes	Unadjusted odds ratio (95%CI)	Unadjusted, *P* value	Adjusted risk (95%CI)	Adjusted, *P* value
Length of stay	-	-	0.91 (0.90, 0.94)[1]	< 0.01
Discharge disposition	0.51 (0.32, 0.80)	< 0.01	0.38 (0.17, 0.77)[2]	< 0.01
Readmission	0.48 (0.22, 0.99)	0.04	0.43 (0.21, 0.93)[3]	0.03

[1]Poisson regression adjusted with age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA), procedure type, and insurance type.
[2]Binomial logistic regression adjusted with LOS, age, gender, BMI, ASA, procedure type, and insurance type.
[3]Binomial logistic regression adjusted with LOS, discharge disposition, age, gender, BMI, ASA, procedure type, and insurance type.

micro-statistical areas encompassing 660 counties[43]. Compared to metropolitical areas, patients living in micro-statistical areas are often prone to experiencing health equity issues and access to health services, including surgical care[44]. This study contributes to improving surgical outcomes using PSH system for community hospitals that are specifically located in micro-statistical areas. The authors envision that these study results will immensely help researchers and clinicians who are working to enhance surgical care in states similar to Montana demographics and social factors, including Alaska, Idaho, Wyoming, North Dakota, and South Dakota.

The limitations of this study include being a retrospective which may contain data collection biases that could alter the results and key findings[45]. Instead, a prospective clinical trial study can minimize these biases and provide better evidence-based results[46]. Second, this study was performed at a community hospital located in a rural micro-statistical area (with a population greater than 10000). The results from this study may not be generalizable to more rural places (*e.g.*, with a population of less than 5000).

CONCLUSION

To the author's knowledge, this study is first of its kind to evaluate the effectiveness of a PSH in a rural surgical system using a case-control study design. Implementing PSH at a community hospital was primarily successful because of patient-centric physician co-management to ensure continuity of care across all perioperative surgical phases. The PSH elements including preoperative assessment, patient education, and longitudinal digital engagement were imperative for improving the TJR surgical outcomes at the community hospital. Future research should include analysis of outcomes including same-day surgery cancellation, surgical cost, postoperative recovery measures, and postoperative opioid consumption. Other future research should also include advanced analytics and predictive modeling such as machine learning and deep learning to predict patient risk and improve the performance of surgical systems at rural and frontier hospitals[47].

ARTICLE HIGHLIGHTS

Research background

With increasing demand for total joint replacement (TJR) procedures, delivering quality surgical care is a challenge to many hospitals, specifically those hospitals located in rural areas. The perioperative surgical home (PSH) developed by American Society of Anesthesiologists has proven successful in large urban health centers by reducing surgery cancellation, operating room time, length of stay (LOS), and readmission rates. Yet, only limited studies have assessed the impact of PSH on surgical outcomes in rural areas.

Research motivation

Compared to urban hospitals, rural hospitals in the United States can often be overwhelmed by the growing demand for TJR surgeries and factors such as poor coordination among clinicians, lack of patient education, poor patient care transition, and inconsistent care delivery that affect rural orthopedic surgical care negatively. A new PSH system was implemented at a community hospital located in rural Montana to address these issues, which have plagued the rural orthopedic surgery system.

Research objectives

The objective of this research was to evaluate the newly implemented PSH system at a local rural, community hospital by comparing TJR surgical outcomes using a longitudinal case-control study.

Research methods

A case-control study was performed to compare the PSH and non-PSH cohorts of TJR surgical outcomes performed at a rural community hospital. Statistical tests including the Chi-square test or Fischer's exact test were performed to compare the categorical variables between non-PSH and PSH cohorts. Similarly, for continuous variables, student's *t* test or Mann-Whitney test was performed, as appropriate. The adjusted analysis was performed using general linear models; Poisson regression for the LOS, and binomial logistic regression for discharge disposition and 90-d readmission.

Research results

The LOS was shorter in PSH cohort compared to the control cohorts [median PSH = 34 h, Control-1 PSH (C1-PSH) = 53 h, Control-2 PSH (C2-PSH) = 35 h]. Correspondingly, the PSH cohort had a lower percentage of discharges to other facilities than the control cohorts (PSH = 3.5%, C1-PSH = 15.5%, C2-PSH = 6.7%). No statistically significant difference was observed in 90-d readmission between PSH and control cohorts. However, the implementation of PSH helped to lower the readmission rates after surgery.

Research conclusions

Implementing PSH at a community hospital helped to improve the TJR surgical outcomes. The patient-centric physician co-management to ensure continuity of care across all perioperative surgical phases was vital for establishing PSH system at a rural community hospital. The PSH elements including preoperative assessment, patient education, and longitudinal digital engagement were imperative for improving patient satisfaction, shortening the LOS, increasing discharge to home, and reducing readmission after the surgery.

Research perspectives

This study contributes to improving surgical outcomes using PSH system for community hospitals that are specifically located in micro-statistical areas. The authors envision that these study results will immensely help researchers and clinicians who are working to enhance surgical care in states similar to Montana demographics and social factors, including Alaska, Idaho, Wyoming, North Dakota, and South Dakota. In the long term, this research will contribute to reducing socio-economic and socio-demographic differences in delivering high-quality surgical care to patients in the United States.

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ORIGINAL ARTICLE

Retrospective Study

Inflammatory response in confirmed non-diabetic foot and ankle infections: A case series with normal inflammatory markers

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Abstract

BACKGROUND

The distinction between foot and ankle wound healing complications as opposed to infection is crucial for the appropriate and efficacious allocation of antibiotic therapy. Multiple reports have focused on the diagnostic accuracy of different inflammatory markers, however, mainly in the diabetic population.

AIM

To evaluate the diagnostic accuracy of white cell count (WCC) and C-reactive protein (CRP) as diagnostic tools for this distinction in the non-diabetic cohort.

METHODS

Data was reviewed from a prospectively maintained Infectious Diseases Unit database of 216 patients admitted at Leicester University Hospitals–United Kingdom with musculoskeletal infections over the period between July 2014 and February 2020 (68 mo). All patients with confirmed diagnosis of diabetes were excluded while only those with confirmed microbiological or clinical diagnosis of foot or ankle infection were included in our study. For the included patients, we retrospectively retrieved the inflammatory markers (WCCs and CRP) at the time of presentation. Values of CRP 0-10 mg/L and WCC 4.0-11.0 × 10^9/L were considered normal.

RESULTS

After exclusion of patients with confirmed diabetes, 25 patients with confirmed foot or ankle infections were included. All infections were confirmed microbiologically with positive intra-operative culture results. 7 (28%) patients with

osteomyelitis (OM) of the foot, 11 (44%) with OM of the ankle, 5 (20%) with ankle septic arthritis and 2 (8%) patients with post-surgical wound infection were identified. Previous bony surgery was identified in 13 (52%) patients, either a corrective osteotomy or an open reduction and internal fixation for a foot or ankle fracture with the infection developing on top of the existing metalwork. 21 (84%) patients did have raised inflammatory markers while 4 (16%) patients failed to mount an inflammatory response even with subsequent debridement and removal of metal work. CRP sensitivity was 84%, while WCC sensitivity was only 28%.

CONCLUSION

CRP has a relatively good sensitivity in the diagnosis of foot and ankle infections in non-diabetic patients, whereas WCC is a poor inflammatory marker in the detection of such cases. In presence of clinically high level of suspicion of foot or ankle infection, a normal CRP should not rule out the diagnosis of OM.

Key Words: Osteomyelitis; Septic arthritis; Surgical site infection; Inflammatory markers; C-reactive protein; White cell count

Core Tip: Distinction between foot and ankle wound healing complications as opposed to infection is crucial for appropriate and efficacious allocation of antibiotic therapy. Multiple reports have focused on diagnostic accuracy of different inflammatory markers, however, mainly in the diabetic population. Our aim was to evaluate the diagnostic accuracy of white cell count and C-reactive protein as diagnostic tools for this distinction in the non-diabetic cohort.

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INTRODUCTION

Early stages of infection are difficult to discern from non-infected wound healing complications which warrants a different course of management and appropriate allocation of antibiotic treatment. Antibiotic treatment for non-infected wound dehiscence would kill commensal flora and may impair healing as well as possibly leading to an ensued infection with emergence of multi-drug resistance[1,2]. Conversely, delayed diagnosis of infection will lead to potentially avoidable complications which might culminate in amputation. It is therefore of paramount importance to assess strategies for differentiating non-infected from infected wounds at an early stage to begin advanced testing and treatment in high-risk patients.

Most of the literature addressing osteomyelitis (OM) of the foot and ankle focuses on patients with diabetes mellitus (DM) owing to the significantly higher rates of infection in this cohort of patients. It was established by a retrospective review on 1000 foot and ankle orthopedic surgical related infections that diabetic patients were five times more likely to experience a severe infection requiring hospitalization compared with non-diabetic patients[3]. That being said, it was further affirmed by another retrospective review on 1465 consecutive foot and ankle surgical cases that it was more specifically complicated diabetes (in terms of peripheral neuropathy and foot ulceration) that was incriminated in this significantly higher rate of infection rather than diabetes itself[4].

Diagnosis of foot and ankle OM relies on a thorough clinical examination and history taking further validated with laboratory evaluation, microbiological assessment, and diagnostic imaging. As previously mentioned, complicated diabetes adds significantly to the risk of post-operative infections and should be excluded through examination for peripheral neuropathy and ankle brachial index or other vascular examination if warranted. Plain radiographs are the initial imaging modalities to be considered and can be 67% specific and 60% sensitive for OM[5]. In equivocal cases, an advanced imaging such as a magnetic resonance imaging (MRI) especially new functional MRI modalities, including Dixon imaging, diffusion-weighted imaging and dynamic contrast-enhanced MRI or even Bone scans, such as the white blood cell labelled Indium-111 or Sulphur colloid marrow scan, may prove beneficial in distinguishing infections from other non-infective etiologies such as Charcot's

arthropathy or non-infected wound healing complications[6].

In terms of laboratory workup, acute phase reactants such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white cell count (WCC) as well as less commonly utilised surrogates for infection such as serum albumin levels, pro-calcitonin (PCT) and interleukin (IL)-6 have all been described for surgical foot and ankle infections[7].

Increased serum inflammatory markers such as CRP and ESR have been used for the diagnosis of OM with a sensitivity and specificity of > 0.70[8,9]. From the immunological perspective, a raised CRP heralds a mounting response to tumour necrosis factor-α-, IL-6- and IL-1-mediated insult. CRP should be interpreted carefully as it is routinely elevated postoperatively peaking at the second to third post-operative day and plummeting back to normal within three weeks. Therefore, any second peak in CRP level after the third postoperative day may be a sign of infection[10]. Another consideration is that CRP levels might not be elevated in a subset of patients with low virulent pathogens specifically coagulase negative Staphylococcus as well as fungal infections. This was established by diagnostic studies on shoulder and hip prosthetic joint infections showing low sensitivity for serum CRP when low-virulent organisms such as Propionibacterium acnes, coagulase negative Staphylococci and Enterococcus faecalis when compared to Streptococcal and Staphylococcal highly virulent culture diagnosis[11-14]. Leucocytosis may or may not be present and should not be used as an absolute indicator of OM. In the acute stage, elevation of the WCC may be seen. However, this condition is not true in all patients, in immunocompromised individuals, the normality of systemic temperature and WCC may be misleading in the face of an infection, making other diagnostic modalities essential[15,16].

Our study aimed to assess the diagnostic accuracy of simple and readily available inflammatory markers such as WCC and CRP as an aid to making this distinction in confirming suspected foot and ankle infections in the non-diabetic population thereby reducing morbidity and associated healthcare costs.

MATERIALS AND METHODS

A prospectively managed database for all patients discharged home on intravenous antibiotics through the University Hospitals of Leicester NHS Trust Outpatient Parenteral Antimicrobial Therapy (OPAT) service was interrogated, to identify patients who had been treated for musculoskeletal infections. The period of inclusion was from July 1, 2014 (inception of the database) until February 28, 2020 over a period of 68 mo. Patient with infections at sites other than foot and/or ankle and those with preceding confirmed diagnosis of DM were excluded. We subsequently retrieved the inflammatory markers for included patients at the time of presentation and during the perioperative period. Values of CRP 0-10 mg/L and WCC 4.0-11.0 × 10^9/L were considered normal.

The diagnosis was based on the clinical picture and confirmed by imaging and laboratory investigations. All patients presented with pain, stiffness, swelling, and erythema of the affected area. Plain radiographs were the first imaging modality requested in the investigation work-up. If no radiographic evidence was present, but clinical suspicion was high, other modalities of diagnostic studies were considered *i.e.*, ultrasonography, computed tomography and/or MRI. Laboratory investigations included WCC, CRP and blood cultures. ESR, procalcitonin and IL-6 were not routinely assessed in our hospital. Wound swabs were requested for infected surgical wounds, ulcers, or sinuses. Arthrocentesis with microscopic examination, gram staining, culture and sensitivity was performed for patients with septic arthritis. Intra-operative tissue and bone samples from OM patients acquired at the time of surgical debridement were sent to the microbiology laboratory to confirm the diagnosis, identify the causative organism and to tailor the antibiotic regimen. At least 5 samples were taken for each patient for microbiological and histological analysis.

RESULTS

A total of 216 patients were identified. Only 37 patients were identified as having foot and/or ankle infection, of those 12 had a diagnosis of DM. After exclusion of those with a confirmed diagnosis of DM at the time of the diagnosis or infections other than foot or ankle, 25 patients remained. The mean age at presentation was 48 years (range = 26–74) and 14 (56%) were males while 11 (44%) were females.

Of those 25 patients, 11 (44%) were admitted for foot OM, 7 (28%) for ankle OM, 5 (20%) patients with septic arthritis of the ankle joint, and 2 (8%) cases were diagnosed of having surgical site infection (SSI). A history of previous bony surgery, whether an elective osteotomy for deformity correction or fracture fixation was identified in 13 patients (52%) while 12 patients (48%) had non-surgical infections. The clinical summary of these patients is shown in Table 1.

Of those 21 patients (84%) showed raised inflammatory markers at the time of presentation. CRP was elevated in 21 patients with a sensitivity of 84% (range = 13–417, median = 108), whereas WCC was raised only in 7 patients with a poor sensitivity of 28% (range = 10.8–20, median = 16.5). Four patients (16%) did not mount an inflammatory response: 2 with foot OM and 2 with ankle OM. All of them

Table 1 Distribution of included patients as regards different presentations and preceding history of surgical risk factor

Diagnosis	No	Surgery related	Not surgery related
OM foot	7	1	6
OM ankle	11	10	1
Septic arthritis ankle	5	0	5
Postsurgical wound infection	2	2	0

OM: Osteomyelitis.

showed normal inflammatory markers at the time of presentation and during the perioperative period. None of these patients had a history of DM and all had normal blood glucose levels (BGL) at the time of presentation (random BGL < 11.1 mmol/L). All these patients had a history of previous bony surgery, either a corrective osteotomy (25%, n = 1) or an open reduction and internal fixation (ORIF) (75%, n = 3) for a foot or ankle fracture with the infection developing on top of the existing metalwork. Methicillin sensitive Staphylococcus aureus (MSSA) was isolated in all 4 patients. Even after implant removal and subsequent debridement for those patients, their inflammatory markers remained normal and their response to treatment was monitored clinically by successful control of local signs of infection. No significant systemic illness was noted in any of those patients and no immunosuppressive aetiology was identified. Recurrence of infection was noted in only 1 patient of those 4 (25%). The demographics of these 4 patients, their clinical and microbiological data are shown in Table 2. A more detailed history for each of those 4 presentations is described below.

Case 1: A 46-year-old female patient was admitted for debridement of a-4-week-old ulceration on right big toe, complicated by septic 1st metatarsophalangeal joint on a background history of arthrodesis 2 years prior with uneventful postoperative period. She had normal inflammatory markers with CRP and WCC values of 7 and 6.9 respectively. MSSA and Corynebacterium were isolated from all surgical specimens. Post debridement and implant removal, postoperative inflammatory markers remained within normal range, with CRP of < 5 and WCC of 7.7. One year later, she was admitted with recurrent OM, and underwent multiple procedures with the aim of infection eradication and achieving union (Figure 1). Throughout all these procedures, CRP and WCC remained within the normal range.

Case 2: A 54-year-old female patient diagnosed with OM of the right distal fibula 5 mo following ORIF for closed Weber-B lateral malleolus fracture. This infection did not mount an inflammatory response with normal values of CRP and WCC at time of presentation (CRP < 5 and WCC 6.3), and even after metalwork removal and debridement (CRP < 5 and WCC 5.4). The diagnosis was based on clinical findings, radiographs, and MRI scans (Figures 2 and 3). Tissue specimens grew MSSA and Coagulase –ve Staphylococcus.

Case 3: A 56-year-old female patient presented with infected left medial malleolus metal work and OM 5 mo after the index procedure. Pus was draining from the medial wound on presentation; however, with normal inflammatory markers (CRP 6, WCC 6.6). She was admitted for IV antibiotics with repeated inflammatory markers 3 d later still within the normal range (CRP 6 and WCC 4.3). Removal of all metalwork was done a week later with tissue and pus samples growing MSSA.

Case 4: A 48–year-old male patient presented with OM of right 5th metatarsal 2 mo following a closed fracture to the right 5th metatarsal bone managed with ORIF. On presentation, his WCC and CRP were normal with values of 8.4 and < 5 respectively. The clinical diagnosis was confirmed by MRI showing sinus tract extending from the head of the fifth metatarsal to the skin. He underwent washout and debridement with excision of the distal right 5th metatarsal followed by 5th ray amputation. Intra-operative bone and tissue samples grew MSSA. His CRP and WCC results were within the normal values from the date of presentation till the date of his last operation.

DISCUSSION

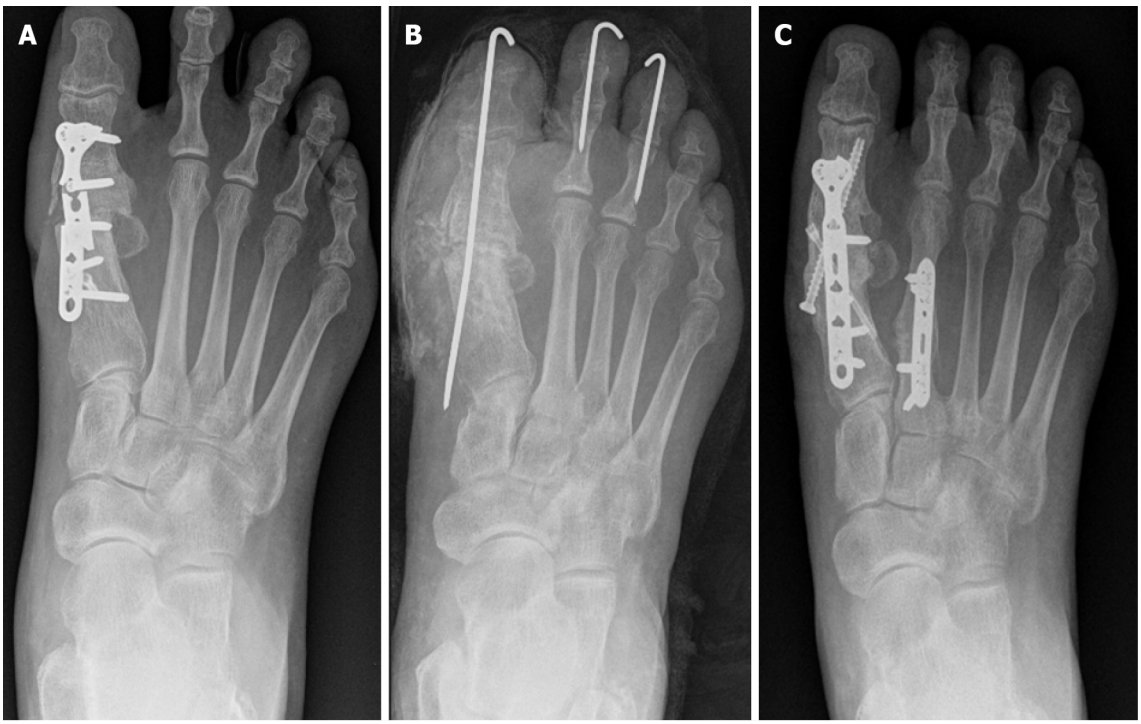
SSI following ankle surgery is one of the most common complications usually with substantial sequalae on both the patient such as permanent disability and eventually amputation if not addressed promptly, and the healthcare costs with estimated increase more than 300% for subsequent procedures[17-19].

Despite that surgical foot and ankle infections in diabetic patients is significantly higher than in their non-diabetic counterparts, OM in non-diabetics is not uncommon[2,3]. The population-based study by Kremers *et al*[20] reported the incidence of OM during a 41-year period; there was a 15% incidence of OM of the foot in patients without diabetes. Similarly, Haji Zaine *et al*[21] reported an 18.8% incidence of OM among non-diabetic patients. Although advanced imaging such as MRI and leucocyte-labelled bone scans can provide high sensitivity and specificity in diagnosing these infections, they are expensive and

Table 2 Patient demographics, index procedures and microbiological diagnosis for those 4 patients with normal inflammatory markers

No.	Diagnosis	Procedure	Gender	Age (years)	Surgery-infection interval (months)	Isolated organism
Case 1	OM 1st metatarsal	SCARF and Akin osteotomy for hallux valgus	Female	46	22	MSSA and *corynebacterium*
Case 2	OM distal fibula	ORIF lateral malleolus fracture	Female	54	5	MSSA and Coagulase-ve Staphylococcus
Case 3	OM ankle	ORIF medial malleolus fracture	Female	56	5	MSSA
Case 4	OM 5th metatarsal	ORIF 5th metatarsal fracture	Male	48	2	MSSA

OM: Osteomyelitis; ORIF: Open reduction and internal fixation; MSSA: Methicillin sensitive Staphylococcus aureus.



DOI: 10.5312/wjo.v14.i3.136

Figure 1 Foot radiographs of case 1. A: Anteroposterior radiographs showing metalwork failure, non-union and medial ulceration soft tissue shadow; B: Removal of infected metalwork, placement of anti-biotic laden calcium beads and temporary fixation; C: Two years later with union at the fracture site and no recurrence of infection. Throughout all these procedures, C-reactive protein and white cell count were within normal range.

might not be readily available in some centres[22,23] That warranted better understanding of the reliability and sensitivity of different readily available surrogate markers for infection in that population for early diagnosis and mitigation of associated healthcare costs.

A readily available and cost-effective laboratory tests for OM diagnosis are WCCs and CRP[24]. In the presence of infection, bone marrow accelerates white blood cells production with resultant increases in WCC which is used to signify severity of infection[25]. CRP is an acute phase reactant produced by hepatocytes that increases significantly in concentration in response to infection particularly bacterial infections[26,27].

In our case series, we found that CRP > 10 mg/L had a sensitivity of 84% in the diagnosis of non-diabetic foot and ankle infections, whereas WCC had a poor sensitivity of 28% in the diagnosis of such cases. Other authors have shown similar high sensitivity of CRP diagnosis of OM. Fleischer *et al*[28] showed in their diagnostic study that CRP > 32 mg/L has a sensitivity of 0.85 and specificity of 0.65 for the diagnosis of OM. In another retrospective cohort study on 102 surgical foot and ankle infections, it was shown that CRP had a sensitivity of 71% in differentiating between superficial wound infection and OM[29].

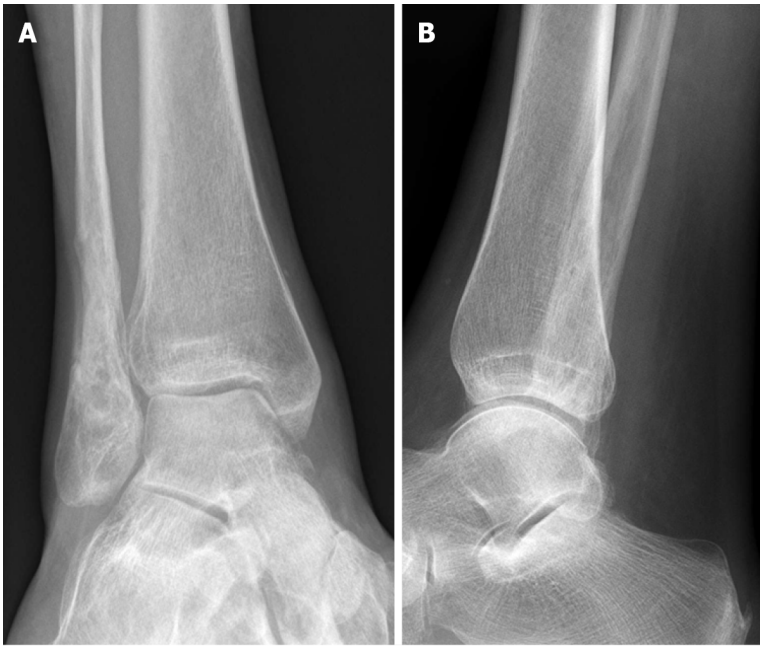


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Figure 2 Ankle radiographs of case 2. A: Anteroposterior; B: Lateral radiographs of ankle after removal of metalwork for infected Weber-B fracture.

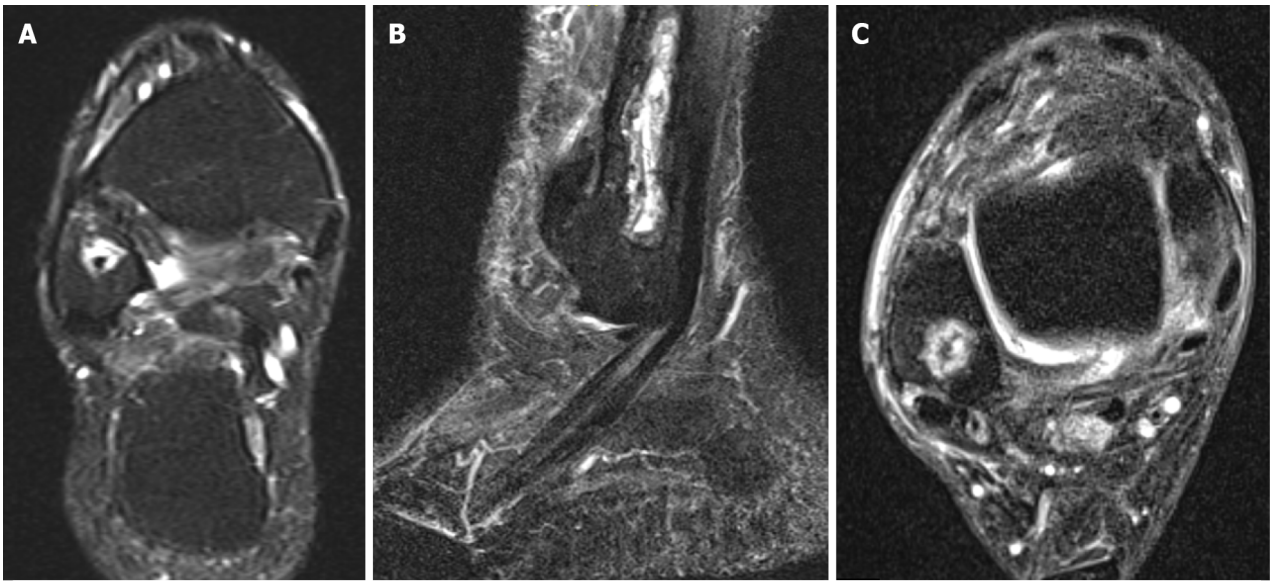

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Figure 3 Ankle magnetic resonance imaging of case 2 showing a Broadie's abscess. A: Coronal; B: Sagittal; C: Axial T2-magnetic resonance imaging images showing a hyperintense intra-osseous collection consistent with Broadie's abscess. The patient did not show any elevated inflammatory markers throughout the treatment.

In our cohort, a small subset of confirmed infections (16%, n = 4) did not seem to mount any inflammatory systemic reaction with resultant normal CRP and WCC levels. In their review article, Harris *et al* [30] concluded that for patients with risk factors for OM or a clinically high level of suspicion, values of ESR < 30 mm/h or CRP < 10 mg/L should not rule out the diagnosis of OM, especially in patients with puncture wounds or foot ulcers/infections. This finding has been corroborated by our results with 16% of radiologically/microbiologically confirmed infections having a CRP < 10 mg/L on presentation. In a study by Armstrong and colleagues[31], 54% of the patients with acute OM presented with normal WCC. Our series reported even higher percentage with 72% of confirmed infections presenting with normal WCC. Thus, we recommend corroborating the results with different radiological investigations as well as also considering other emerging biochemical markers for diagnosis of infection.

Those other biochemical markers are increasingly being embedded in the diagnostic panel of investigations. PCT was found in a meta-analysis to be more sensitive than CRP for differentiating bacterial from non-infective causes of inflammation (88% *vs* 75%)[32]. In another study on 93 diabetic foot ulcers, a CRP cut-off value of 17 mg/dL was found to be the single most sensitive marker for confirming infection with sensitivity 0.727, specificity 1.000, positive predictive value 1.000, and negative predictive value 0.793 while total leucocytic neutrophil count was found to be non-predictive[33]. Moreover, combining CRP with PCT yielded higher diagnostic accuracy than solely relying on only one parameter. Serum IL-6 has been described as a more sensitive marker of acute periprosthetic infection particularly in hips and knees with high accuracy, sensitivity, and specificity (97%, 100% and 95% respectively) but has not been specifically investigated in foot and ankle infections[34-36]. Measurement of bacterial load with a critical level of bacteria ≥ 10^4 to 10^6 colony-forming units per g of tissue has been also described to objectively confirm an infective aetiology[37,38].

The retrospective nature of our study has inherent limitations. It may not have included all patients with foot and ankle infections, since not all patients may have been discharged on OPAT and therefore would not have been captured by the database. The proportion of deep infections preceded by a superficial infection was not recorded however eventually all deep infections in our series were identified and reported. Our data relied on different biochemical markers but no attempt to identify a cut-off value or to quantify bacterial load was done. We agree that bacterial load is a reliable indicator of infection in acute infections but has been shown to be less reliable in early subacute or chronic infections as well as in healing wounds[39,40].

Our case series also lacked the assessment of the diagnostic sensitivity of other inflammatory markers for the diagnosis of foot and ankle infections *e.g.*, ESR, PCT and IL-6 as they are not routinely performed in our hospital. Further evaluation of these biochemical markers is recommended.

CONCLUSION

In conclusion, CRP has good sensitivity in the diagnosis these non-diabetic infections, whereas WCC is a poor inflammatory marker in the detection of such cases and should not be used as an absolute indicator of OM. In a subset of patients, relying on these inflammatory markers solely can delay diagnosis as they can be normal, and no inflammatory response mounted. We recommend incorporating other inflammatory markers such as PCT, IL-6 and bacterial load as well as radiological diagnosis when there is a high index of suspicion despite negative CRP and WCC in this subset of patients. A noteworthy finding in our study is that CRP is a readily available, cost-effective, and reliable indicator for ankle and foot infections, directing appropriate antibiotic therapy for those likely to benefit from it.

ARTICLE HIGHLIGHTS

Research background

Non-diabetic foot and ankle infections are not uncommon. Despite this, there is a paucity of the literature investigating the diagnostic accuracy of different inflammatory markers in the diagnosis of these infections as opposed to the diabetic population.

Research motivation

Defining the reliability of inflammatory markers in the diagnosis of non-diabetic foot and ankle infections can aid in early diagnosis and mitigate associated healthcare costs for delayed treatments.

Research objectives

Our aim was to define the reliability of the commonly utilized inflammatory markers such as white cell count (WCC) and C-reactive protein (CRP) in the diagnosis of non-diabetic foot and ankle infections as well as to highlight the shortcomings of those markers in a small subset of patients with normal inflammatory markers despite a microbiologically confirmed diagnosis of infection.

Research methods

This was a retrospective cohort study looking into microbiologically confirmed foot and ankle infections in the non-diabetic population presenting to our hospital (University Hospitals Leicester-United Kingdom) over the period of 6 years (2014-2020).

Research results

A total of 25 non-diabetic patients with confirmed foot or ankle infections were identified. Previous bony surgery was identified in 13 (52%) patients. Inflammatory markers were raised in 21 (84%) patients

while 4 (16%) patients did not mount an inflammatory response even with subsequent surgical procedures. CRP sensitivity was shown to be 84%, while WCC sensitivity was only 28%.

Research conclusions

CRP had a relatively good sensitivity whereas WCC is a poor inflammatory marker in the detection of non-diabetic foot and ankle infections. In a subset of non-diabetic foot and ankle infections, inflammatory markers will not be raised, and a normal CRP should not rule out the diagnosis of osteomyelitis. In these cases where a high level of suspicion persists despite normal CRP, further advanced radiological and laboratory investigations should be performed.

Research perspectives

Further evaluation of different inflammatory markers in the non-diabetic foot and ankle infections (erythrocyte sedimentation rate, pro-calcitonin and interleukin-6) could improve diagnostic accuracy and avoid more expensive investigative procedures.

FOOTNOTES

Author contributions: Mangwani J and White H conceptualized the study design and aim; Ahmed AH and Ahmed S completed data collection and statistical analysis; Barakat A drafted the manuscript and reviewed it for final submission.

Institutional review board statement: This study was reviewed by the Leicester University Hospitals-NHS Trust research ethics committee. No ethical approval was required due to the de-identified anonymous retrospective nature of the published laboratory data.

Informed consent statement: There was no direct or even indirect contact between researchers and patients, with no necessity for "Signed Informed Consent Form" to carry out our study.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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ORIGINAL ARTICLE

Retrospective Study

Identifying sex-specific injury predictors as a key factor in maintaining optimal physical activity levels

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Abstract

BACKGROUND

Optimal physical activity is known to reduce cardiovascular, respiratory and endocrine system diseases and, as a consequence, improve quality of life. An important risk factor for reinjuries during normal exercise is the initial connective tissue pathology. The variety of clinical dysplastic manifestations significantly complicate the timely diagnosis of this comorbidity.

AIM

To establish pathognomonic sex-specific dysplasia phenotypes that indicate a particular sensitivity to physical exertion.

METHODS

The study involved 117 participants with recurrent musculoskeletal injuries that occurred during normal exercise. There were 67 women (57.26%) and 50 men (42.74%), which made it possible to compare the presence of the identified signs between sexes. A validated questionnaire was used to screen their connective tissue status.

RESULTS

Ranking the most commonly revealed dysplasia signs depending on their clinical significance made it possible to establish pathognomonic sex-specific phenotypes that indicated a particular susceptibility to injuries. Individualized programs of optimal physical activity are necessary for men with chest deformities, flat-valgus feet, dolichostenomelia, arachnodactylia, hemorrhoids, abdominal muscle diastasis and recurrent hernias. In women, special sensitivity to physical exertion was associated with a combination of signs such as asthenic body, joint hypermobility, overly soft auricles, thin hyperelastic skin, atrophic striae, telangiectasias and varicose veins. Of particular importance were universal signs such as gothic palate, scoliosis, kyphosis, leg deformities, temporomandibular joint crunching, and moderate to high myopia.

CONCLUSION

Participants' connective tissue condition should be considered when designing optimal physical activity programs. Identifying the established sex-specific dysplasia phenotypes will allow timely optimization of training loads, thus reducing the risk of injury.

Key Words: Injury risk; Physical activity; Connective tissue condition; Sex-specific dysplasia phenotypes; Clinical dysplastic manifestations

Core Tip: Ranking the most commonly revealed dysplasia signs depending on their clinical significance made it possible to establish pathognomonic sex-specific phenotypes that indicate a particular susceptibility to injuries. Individualized programs of optimal physical activity are necessary for men with chest deformities, flat-valgus feet, dolichostenomelia, arachnodactylia, hemorrhoids, abdominal muscle diastasis and recurrent hernias. In women, special sensitivity to physical exertion was associated with a combination of signs such as asthenic body, joint hypermobility, overly soft auricles, thin hyperelastic skin, atrophic striae, telangiectasias and varicose veins. Identifying the established sex-specific dysplasia phenotypes will allow timely optimization of training loads and prescription of therapeutic measures aimed at connective tissue strengthening that will reduce the injury risk during physical activity and improve public health.

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INTRODUCTION

Increasing physical activity in the population and promoting a healthy lifestyle are among the priorities of preventive measures in the health-care system[1-4]. Optimal and regular exercise is known to reduce cardiovascular, respiratory and endocrine system diseases and, as a consequence, improve the quality and duration of life[5-7]. A healthy lifestyle and the desire to maintain an optimal body functional state through increased physical activity and sports are becoming an integral part of the modern person's life, even during the coronavirus disease 2019 pandemic[8-12]. However, physical activity is invariably associated with injury risk, and professional sports are associated with the possible occurrence of musculoskeletal posttraumatic chronic conditions as a result of reinjuries[13-15].

Recently, there has been an increase in the number of cases involving sprains and ruptures of the joint ligament apparatus, dislocations and tendon injuries occurring during normal physical activity[15-19]. An important risk factor for this kind of reinjury is connective tissue pathology, the prevalence of which reaches 85.4% in the population[20-24]. Connective tissue changes caused by impaired synthesis or increased degradation of its components result in its inability to withstand full mechanical load[24,25]. The clinico-morphological manifestations of this pathology are quite variable and exhibit significant differences between sexes[22,23]. In this regard, an individualized approach to connective tissue assessment and optimal physical activity program design, taking into account sex-specific features of the dysplastic signs set, becomes relevant. Therefore, the purpose of this study was to establish pathognomonic sex-specific injury phenotypes for consideration when designing exercise programs that support optimal physical activity in men and women.

A

$$N_1 = \left\{ z_{1-\alpha/2} * \sqrt{\bar{p} * \bar{q} * (1 + \frac{1}{k})} + z_{1-\beta} * \sqrt{p_1 * q_1 + (\frac{p_2 * q_2}{k})} \right\}^2 / \Delta^2$$

$$q_1 = 1 - p_1$$

$$q_2 = 1 - p_2$$

$$\bar{p} = \frac{p_1 + kp_2}{1 + K}$$

$$\bar{q} = 1 - \bar{p}$$

B

$$N_1 = \left\{ 1.96 * \sqrt{0.68 * 0.32 * (1 + \frac{1}{1})} + 1.04 * \sqrt{0.889 * 0.111 + (\frac{0.471 * 0.529}{1})} \right\}^2 / 0.418^2$$

$$N_1 = 21$$

$$N_2 = K * N_1 = 21$$

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Figure 1 Minimum sample size calculation. A: Formula; B: Calculation process for this study. p1, p2: Proportion (incidence) of groups #1 and #2; Δ = |p2-p1| = absolute difference between two proportions; n1: Sample size for group #1; n2: Sample size for group #2; α: Probability of type I error; β: Probability of type II error; z: Critical *Z* value for a given α or β; K: Ratio of sample size for group #2 to group #1.

MATERIALS AND METHODS

Study design and participants

The study, conducted at Sechenov University and European Osteopathic Clinical Center and in accordance with STROBE guidelines, involved 117 participants with recurrent musculoskeletal injuries that occurred during normal physical activity in the absence of a pronounced traumatic factor. Musculoskeletal injuries of varying severity included sprains and ruptures of the joint ligament apparatus, dislocations and tendon tears. All participants, aged 26 to 47 years (average 36.4 ± 6.0 years), underwent a complete clinico-instrumental examination in the period from 2019 to 2022. There were 67 women (57.4%) and 50 men (42.6%), which made it possible to compare the identified dysplasia signs between sexes. Using the statistical package G* (EM) Power (Christian Albrechts-Universität, Olshausenstr, Germany)[26], it was determined that 21 was the minimum sample size required for each group for a statistical power of 85% and alpha criterion of 0.05. The formula and the calculations are shown in Figure 1.

Clinico-instrumental examination

The standard clinico-instrumental therapeutic examination was supplemented with an assessment of anthropometric parameters, such as body height and weight, chest volume, arm span, lower body segment, zygomatic width, face height, and hand and foot length. The facial index (the ratio of the facial height to the zygomatic diameter) was calculated to evaluate the facial skeleton. The Verveck (the ratio of height to the sum of twice the body weight and chest circumference) and Pignet (the difference in height and the sum of body weight and chest circumference) indices were calculated to assess body proportionality. The Varga (the difference between the ratio of body weight to height and age to 100) and Quetelet (the ratio of body weight to squared height) indices were calculated to reveal body weight deficiency. The indices of hand length/height ratios, foot length/height ratios, arm span/height ratios, and upper body/lower body ratios made it possible to diagnose dolichostenomelia features[20,21]. Middle finger length and thumb and wrist tests were used to detect arachnodactyly, and Bayton's criteria were used to establish joint hypermobility[27-29]. Examinations also included ophthalmic consultation, fibrogastroduodenoscopy, ultrasound, and radiography. The revealed dysplasia signs were registered in a specially developed validated questionnaire[21] based on the Kadurina and Abbakumova[29] scale, in which each sign is assessed from 0 to 4 points.

Ethical considerations

The study complied with the Helsinki Declaration norms and was fully approved by the Local Ethics Committee of the I.M. Sechenov First Moscow State Medical University under protocol No. 08-19 on 05.06.2019. All participants gave informed consent before the study.

Statistical analysis

Comparative analysis and ranking of the revealed signs of dysplasia were carried out using RStudio Desktop (RStudio, Boston, MA, United States). The minimum sample size required for this study was calculated by power analysis. Intergroup qualitative indicators were compared using Pearson's χ-square test and Fisher's exact test. Differences were considered to be significant when $P < 0.05$. The results were counted twice by two independent researchers.

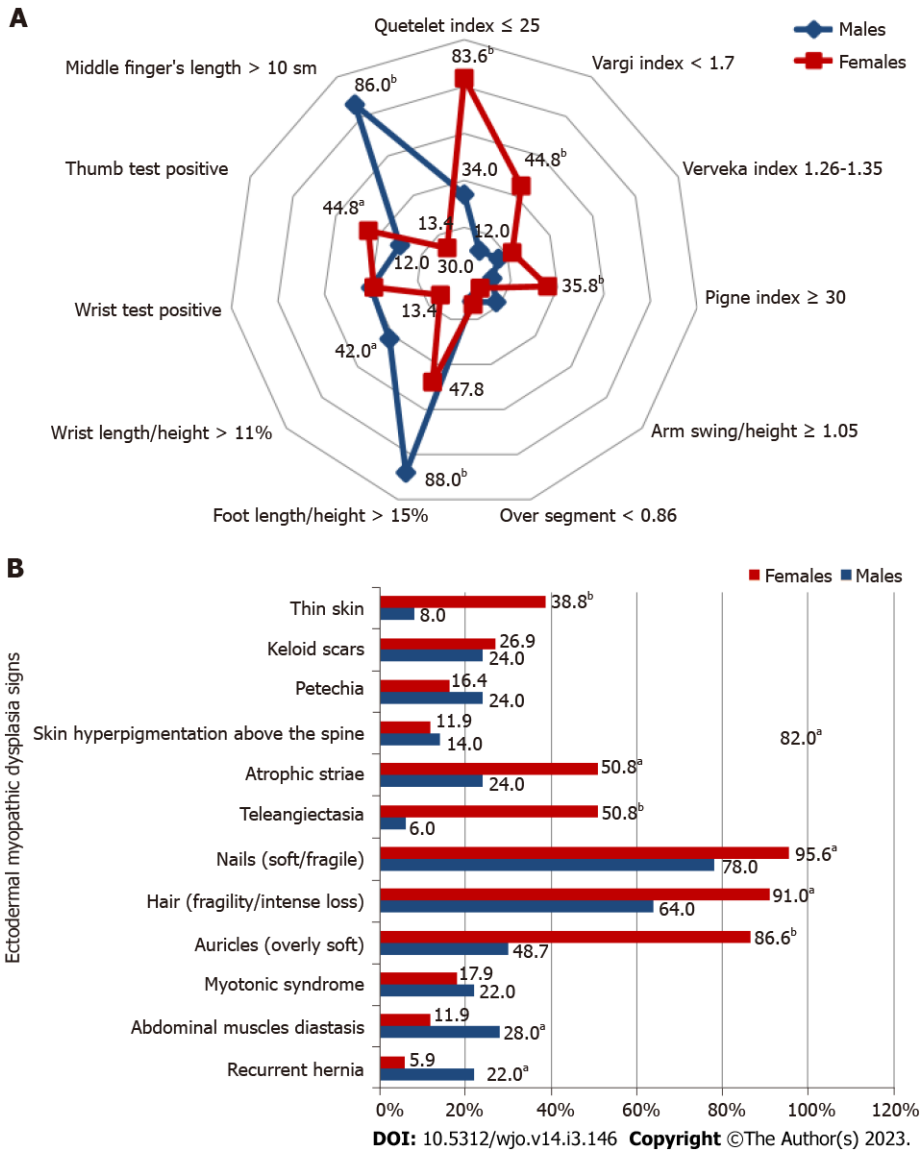

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Figure 2 Body proportionality assessment, ectodermal and myopathic sign assessment in persons with musculoskeletal reinjuries. A: Body proportionality assessment; B: Ectodermal and myopathic sign assessment. [a]*P* < 0.05, the differences are significant; [b]*P* < 0.001, the differences are highly significant.

RESULTS

Body proportionality assessment

One of the leading clinico-morphological manifestations of connective tissue pathology is the asthenic body type identified by calculating special indices (Verveck, Pignet, Varga, and Quetelet indices) and characterized by significant longitudinal size predominance and mass deficit. This constitutional type was reliably more common among women with musculoskeletal reinjuries (Figure 2A).

The data presented in the chart show that men with musculoskeletal disorders were significantly more likely than women to have disproportionately long hands and feet, indicating the presence of dolichostenomelia. Arachnodactyly manifested by long, thin, "spider" fingers was also significantly more common in men in terms of middle finger length. Notably, there was a higher rate of positive thumb tests in women with musculoskeletal reinjuries.

Osteoarticular dysplasia sign assessment

The results of this study are summarized in Figure 3A. Skeletal connective tissue damage in most persons with musculoskeletal reinjuries manifests sex-independent changes such as gothic palate, scoliosis, kyphosis, and X- and O-shaped legs. Spinal pathology, altered leg shapes and, as a consequence, incorrect motor patterns caused pronounced biomechanical disorders and led to shoulder and shoulder blade asymmetry in most subjects regardless of sex. The majority of women, in contrast to men, also had pelvic bone asymmetry. Over half of the participants reported joint crunching during

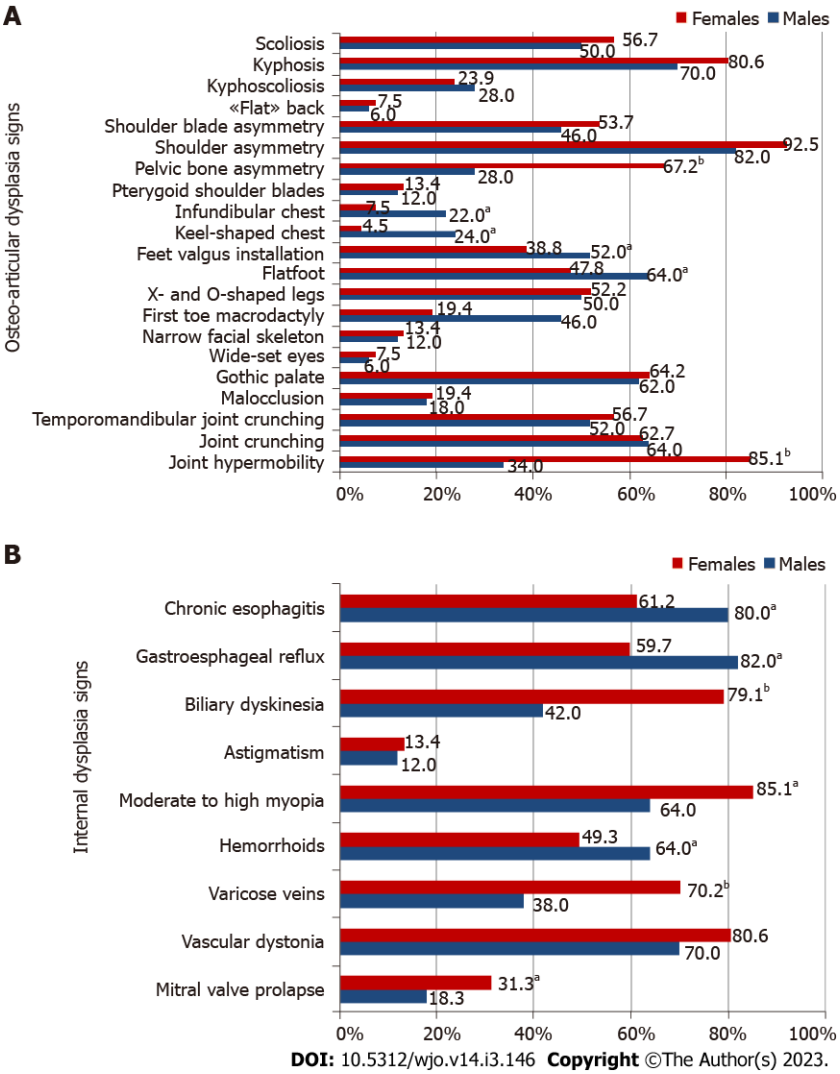

Figure 3 Assessment of osteoarticular dysplasia signs and internal dysplasia signs in persons with musculoskeletal reinjuries. A: Assessment of osteoarticular dysplasia signs; B: Assessment of internal dysplasia signs. [a]*P* < 0.05, the differences are significant; [b]*P* < 0.001, the differences are highly significant.

their movements, and half of the patients were affected by TMJ crunching. Compared to that in women, the external phenotype in men with musculoskeletal postexercise disorders was significantly more often formed by chest deformities, first toe macrodactyly, and flat feet in combination with valgus foot placement. Women, in turn, were more likely to have joint hypermobility.

Assessment of ectodermal and myopathic dysplasia signs

Ectodermal dysplasia signs such as thin hyperelastic skin with a well-visible vessel network, overly soft auricles, atrophic striae, telangiectasias, and nail and hair pathology were more prevalent in women. In addition, abdominal muscle diastasis and recurrent hernia were more typical for men (Figure 2B).

Internal dysplasia sign assessment

The results indicated that most participants with musculoskeletal reinjuries presented vascular dystonia, the incidence of which was shown to have a sex-independent distribution. Mitral valve prolapse, varicose veins and biliary dyskinesia were more common in women, while hemorrhoids, gastroesophageal reflux and chronic esophagitis were often observed in men. A specific sign of connective tissue pathology is moderate to high myopia, which was diagnosed in most men and women with postexercise musculoskeletal disorders, with a significant prevalence in the second subgroup (Figure 3B).

Ranking clinical significance of revealed dysplasia signs

Ranking the most common revealed dysplasia signs depending on their clinical significance made it possible to establish pathognomonic sex-specific phenotypes that indicate a particular susceptibility to injuries. Individual programs of optimal physical activity are necessary for men with chest deformities,

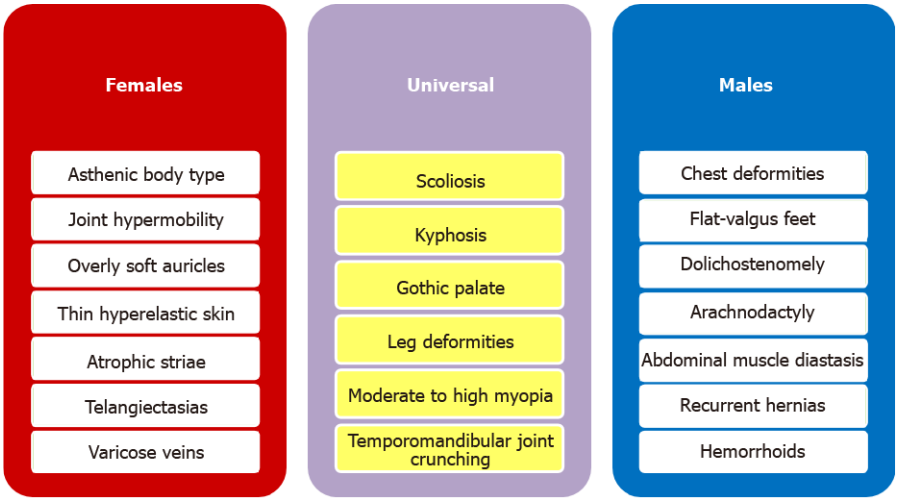

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Figure 4 Pathognomonic sex-specific and universal injury predictors.

flat-valgus feet, dolichostenomelia, arachnodactylia, hemorrhoids, abdominal muscle diastasis and recurrent hernias. In women, special sensitivity to physical exertion was associated with a combination of such signs as asthenic body, joint hypermobility, overly soft auricles, thin hyperelastic skin, atrophic striae, telangiectasias and varicose veins. Of particular importance are universal signs such as gothic palate, scoliosis, kyphosis, leg deformities, temporomandibular joint crunching, and moderate to high myopia (Figure 4).

DISCUSSION

At present, sports medicine is of particular importance in the regular medical-biological support of people engaged in physical exercise and sports[30-33]. The main tasks of sports physicians and physical education specialists are a reasonable choice of sports activities, timely correction of training load, and prevention of injuries and posttraumatic conditions[34-37]. The optimal physical activity program is individually designed for each person and primarily depends on their initial health state. Of particular importance is the detection of connective tissue pathology, which determines the increased sensitivity to mechanical stress, creates injury predisposition and impairs connective tissue recovery in the posttraumatic period, causing further injury recurrence[20,21].

For the first time, significant sex differences in the prevalence of certain connective dysplasia signs were revealed in persons with musculoskeletal reinjuries. Indeed, while bone and myopathic dysplasia signs were significantly more common in men, the prevalence of skin dysplasia signs and joint hypermobility was noted in women. There is evidence that sex differences in dysplastic phenotypes are largely due to exposure to sex hormones: If testosterone gives greater strength to the connective tissue by stimulating fibroplastic reactions, then estrogen causes its excessive elasticity and extensibility, contributing to the appearance of deformity. This explains the greater percentage of overly soft auricles, thin hyperelastic skin, and atrophic striae in women. Vascular wall failure is manifested by telangiectasias and varicose veins. Overstretching of the most powerful ligaments connecting the lumbar spine and the pelvic bones leads to their inability to firmly fix articular surfaces and form pelvic bone asymmetry, which is more common in women.

The influence of female sex hormones is also responsible for the higher incidence of joint hypermobility in the female population, as confirmed by other studies[25]. Increased amplitude of movement in the carpometacarpal and metacarpophalangeal joints in women causes more frequent positive wrist tests in them. The presence of pathological mobility in the joints naturally leads to the appearance of unnatural movements in most loaded joints during increased physical activity and chronic injury[36].

The pathogenetic mechanism of musculoskeletal reinjury in men with connective tissue dysplasia is more associated with skeletal system involvement in the dysplastic process and pathological motor stereotype formation, leading to degenerative-dystrophic changes in the joints and a tendency toward chronic injuries. Significant changes in the composition of glycosaminoglycans and type I and III collagen of the anterior abdominal wall cause an increase in the proportion of muscle diastasis and recurrent hernias[25].

The obtained data necessitate the development of a differentiated approach to dysplasia sign assessment and connective tissue pathology diagnosis in men and women engaged in physical exercise

and sports. At the same time, the current recommendations for identifying dysplastic phenotypes do not take into account the sex of the examined subject[22,37].

One of our study limitations was the relatively small number of participants, which may affect the reliability level of the results. In future studies, we will recruit more subjects. Another limitation is that the study was conducted in one clinical center and among individuals with a large age range. For this reason, this study and its results must be understood as the initial stage of multicenter research for developing measures to prevent sports injuries.

CONCLUSION

The connective tissue condition should be taken into account when attempting to design an optimal physical activity program. It is advisable to develop a differentiated approach to dysplasia sign assessment and connective tissue pathology diagnosis in men and women engaged in physical exercise and sports. Identifying the established sex-specific dysplasia phenotypes will allow timely optimization of training loads and prescription of therapeutic measures aimed at connective tissue strengthening that will reduce injury risk during physical activity and improve public health.

ARTICLE HIGHLIGHTS

Research background

At present, sports medicine is of particular importance in the regular medical-biological support of people engaged in physical exercise and sports. Of particular importance is the detection of connective tissue pathology, which determines the increased sensitivity to mechanical stress, creates injury predisposition and impairs connective tissue recovery in the posttraumatic period, causing further injury recurrence.

Research motivation

This study was created because existing methods often do not take into account differentiated approaches to dysplasia sign assessment and connective tissue pathology diagnosis in men and women and is therefore aimed at filling this gap and creating approaches that complement existing ones.

Research objectives

The purpose of this work was to establish pathognomonic sex-specific injury phenotypes for consideration when designing exercise programs that support optimal physical activity in men and women. The results of the study were conceived as an addition to the existing methods of assessing the risk of further injury recurrence.

Research methods

In our study, we measured 117 participants with recurrent musculoskeletal injuries that occurred during normal physical activity in the absence of a pronounced traumatic factor. Musculoskeletal injuries of varying severity included sprains and ruptures of the joint ligament apparatus, dislocations and tendon tears. Anthropometric parameters and indices indicating the presence of signs of connective tissue dysplasia were studied. An analysis was also performed to identify differences in the presence of signs between sexes. A validated questionnaire was used to screen the connective tissue state.

Research results

In our research, we studied the ranking of the most commonly revealed dysplasia signs depending on their clinical significance, making it possible to establish pathognomonic sex-specific phenotypes that indicate a particular susceptibility to injuries.

Research conclusions

The study results are of particular importance in the context of physical culture and sport safety and emphasize the importance of a differentiated approach of medico- biological support of sports activities in men and women.

Research perspectives

To further develop these findings, it is possible to conduct a larger-scale study with a larger number of participants. Further refinement of the sex-specific dysplasia phenotypes is needed for clarification and, possibly, expansion of these findings. With satisfactorily refined results, it is possible to introduce the proposed methodology into practice for a clinical trial.

FOOTNOTES

Author contributions: Sankova MV, Oganesyan MV, and Vovkogon AD involved in the conceptualization of the manuscript; Sankova MV, Nikolenko VN, Oganesyan MV, Vovkogon AD, and Zharikov YO contributed to the methodology of this article; Sankova MV, Oganesyan MV, Vovkogon AD, and Gadzhiakhmedova AN participated to the resources; Sankova MV analysed data; Sankova MV and Oganesyan MV wrote the original draft preparation; Sankova MV, Oganesyan MV, Zharikova TS and Zharikov YO wrote the review and editing; Nikolenko VN, Oganesyan MV, Vovkogon AD and Zharikov YO involved in the project administration; and all authors have read and agreed to the published manuscript version.

Institutional review board statement: The current research study was approved by the Ethics Committee of I.M. Sechenov First Moscow State Medical University (Sechenov University) under protocol No. 08-19 on 05.06.2019.

Informed consent statement: Informed consent was obtained from the participants included in this study.

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SYSTEMATIC REVIEWS

Prenatal radiographic evaluation of congenital transverse limb deficiencies: A scoping review

Neeraj Vij, Luis F Goncalves, Aaron Llanes, Sean Youn, Mohan V Belthur

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Abstract

BACKGROUND

Congenital transverse deficiencies are horizontal deficiencies of the long bones that occur with a reported incidence as high 0.38%. They can occur alone or represent a manifestation of a various clinical syndromes. Diagnosis has traditionally comprised of conventional radiography and prenatal imaging studies. There has been much advancement regarding prenatal imaging modalities to allow for early diagnosis and appropriate treatment.

AIM

To summarize the current state of knowledge on congenital transverse limb deficiencies and to provide an update regarding the radiographic evaluation of congenital transverse limb deficiencies.

METHODS

This IRB-exempt scoping review followed the PRISMA-ScR checklist for scoping reviews strictly. Five search engines were searched for a total of 265 publications. Four authors reviewed these during the screening process. Of these, 51 studies were included in our article. Prenatal magnetic resonance imaging (MRI), 3D Ultrasound, and multidetector Computed tomography (CT) exist are emerging modalities that have the potential to improve diagnosis.

RESULTS

Use of the appropriate classification system, three-dimensional ultrasonography with a maximum intensity projection, and appropriate use of prenatal MRI and prenatal CT can improve diagnosis and inter-provider communication.

CONCLUSION

Further scholarly efforts are required to develop improve standardized guidelines regarding the pre-natal radiographic evaluation of congenital limb deficiencies.

Key Words: Terminal deficiencies; Roentgenographic evaluation; Pediatric skeletal deficiencies; Early diagnosis; Patient-centered care; Prenatal imaging

Core Tip: Early diagnosis can lead to early, appropriate, family-centered care strategies with the current literature supporting both non-operative and surgical management.

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INTRODUCTION

Congenital transverse deficiencies are horizontal deficiencies involving the long bones. The incidence of congenital limb abnormalities is reported between 0.035%[1] and 0.38%[2], of which transverse limb deficiencies account for approximately half[3]. Congenital transverse limb deficiencies can occur in isolation or as a part of a clinical syndrome. These include femoral and fibular deficiencies[4], Adams-Oliver syndrome[5], Dandy-Walker syndrome[6], and Opitz trigonocephaly[7]. Congenital transverse limb deficiencies can occur in any long bones of the body, though an upper limb and left sided predominance have been demonstrated[8,9]. In the upper extremity, the most common deficiency is the transverse terminal deficiency at the upper third forearm[10].

Diagnosis of congenital transverse limb deficiencies is traditionally thought to be largely supported by conventional radiography[11]. In recent years there has been advancement regarding the use of prenatal imaging to assist in early diagnosis. This includes two-dimensional ultrasound (2D US) (Figure 1A and B, Figure 2A), three-dimensional ultrasound (3D US) (Figure 1C and Figure 2B), fetal magnetic resonance imaging (fetal MRI) (Figure 1C and E, Figure 3A) and low-dose multidetector computerized tomography with 3D reconstruction (3D-CT). The purpose of this scoping review article is to summarize the current state of knowledge on congenital transverse limb deficiencies and to provide an update regarding the radiographic evaluation of congenital transverse limb deficiencies.

MATERIALS AND METHODS

General

This was an IRB-exempt scoping review. The scoping review checklist available at the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews Checklist was followed strictly. The International prospective register of systematic reviews (PROPSERO) was contacted regarding our intention of this article and advised that scoping views do not require registration with PROSPERO.

Search strategy

The following search engines were used: Medline, PubMed Advanced Search, Cochrane library, Embase, and Scopus. Cochrane Reviews was also searched per the recommendations of Pautasso *et al* [12]. The following search items were used: 'Pediatric Transverse Limb Deficiencies', 'Radiography transverse limb deficiencies', 'radiographic evaluation' AND 'pediatric transverse limb defects', 'transverse' AND 'limb' AND 'defects', '*radiographic* AND *evaluation*' AND '*transverse*' AND '*limb*' AND '*deficiencies*', 'MRI' AND 'transverse limb deficiencies', and 'prenatal diagnosis' AND 'transverse limb deficiencies.' This resulted in a total of 265 articles.

Study Screening and Selection

Four of the authors (Neeraj Vij, Aaron Llanes, Sean Youn, MV Belthur) screened the article by title and abstract. A preliminary decision to include or exclude an article was made based on relevance of the information within the abstract as determined by our inclusion/exclusion criteria (Table 1) This resulted in a preliminary list of 112 articles. This preliminary list of articles was organized into the following

Table 1 Our inclusion and exclusion criteria as applied independently by 3 of the authors during the initial title/abstract review

Inclusion criteria	Exclusion criteria
Pediatric population (ages 0 – 18)	Absence of etiologic, classification system, radiographic, or outcome data in the abstract
Date of publication 1950 – 2022[1]	
Mention of the diagnosis of terminal transverse or intercalary transverse limb deficiencies	Insufficient description of patient characteristics to reasonably draw inferences

[1]The date of publication was chosen per the recommendations of Pautasso *et al*[12].

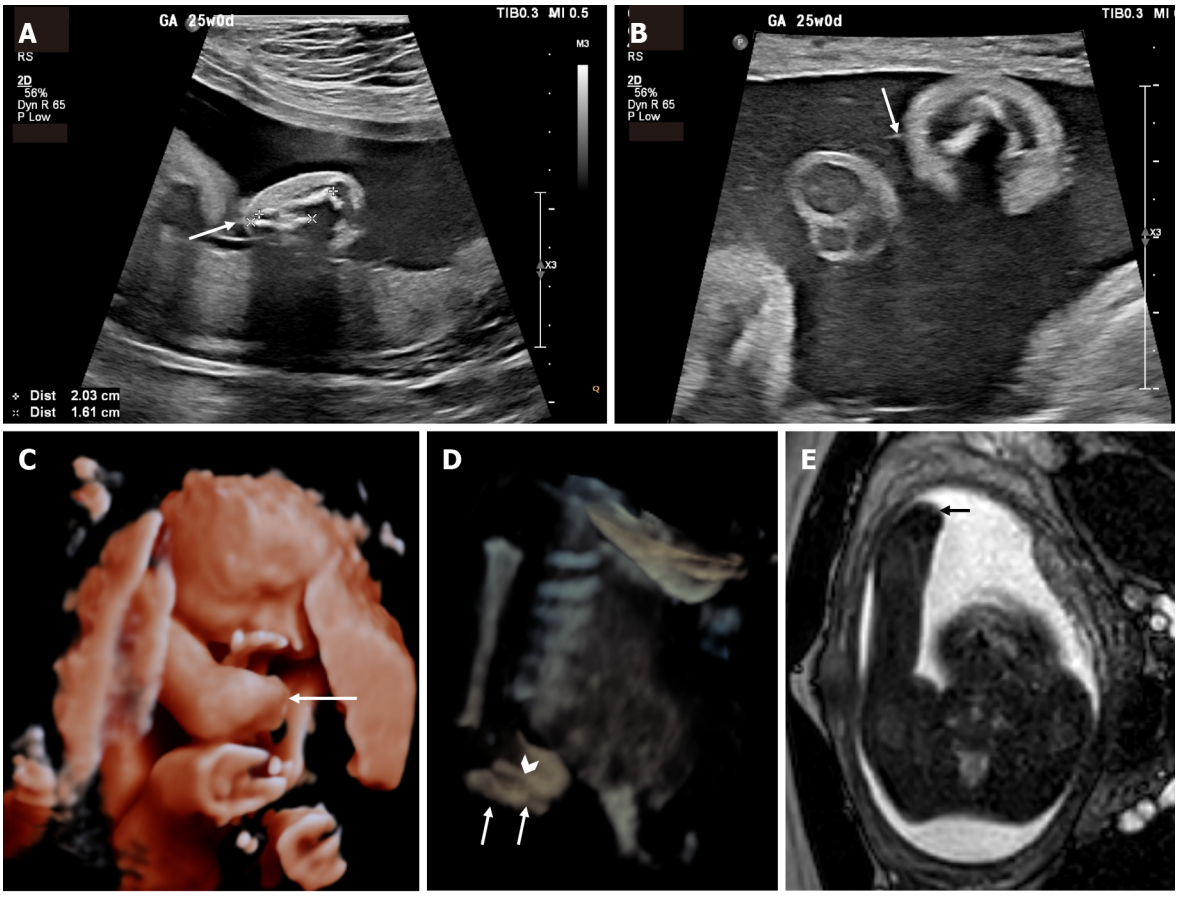

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Figure 1 Prenatal imaging at 24 wk and 5 d demonstrating a transverse limb deficiency of the right forearm. A: Two-dimensional ultrasound (2D US) showing markedly shortened right ulna (bone between "+" crosshairs) and radius (bone between "x" crosshairs) secondary to a transverse limb reduction defect (arrow); B: High-resolution 2D ultrasound with high-frequency 4-18 Megahertz probe demonstrating a hyperechogenic thin line (arrow) representing a visualized amniotic band attached to the forearm defect; C: 3D US rendered image showing the terminal transverse limb defect below the elbow (arrow); D: 3D US reconstructed image using the maximum intensity projection to demonstrate the markedly short ulna (arrows) and radius (arrowhead). The advantage of 3D US in this case is that the normal humerus and elbow (which are not in the same plane of section in Figure 1A) as well as their relationship with the amputated distal forearm can be appreciated in a single image. The 3D rendered images (Figure 1C and D) are easier to understand for both the referring providers and parents; E: Axial balanced turbo field echo fetal magnetic resonance imaging slice showing the deficiency (arrow).

subheadings: Embryology, Etiology, Natural History, Classification Systems, Prenatal Imaging, Non-surgical treatment, and Surgical treatment.

Full-Text Screening

These articles then underwent a full-text screening process by the same four authors (Neeraj Vij, Aaron Llanes, Sean Youn, MV Belthur). The primary purpose of the full-text screening was final inclusion based on the inclusion/exclusion criteria, and placement of the article in a given section. This resulted in a total of 51 included articles. The references of the selected articles were also hand-searched to identify any missing articles. This did not reveal any additional articles. The include articles were then imported and stored into the most up-to-date stable release Mendeley (v2.57.0)[12].

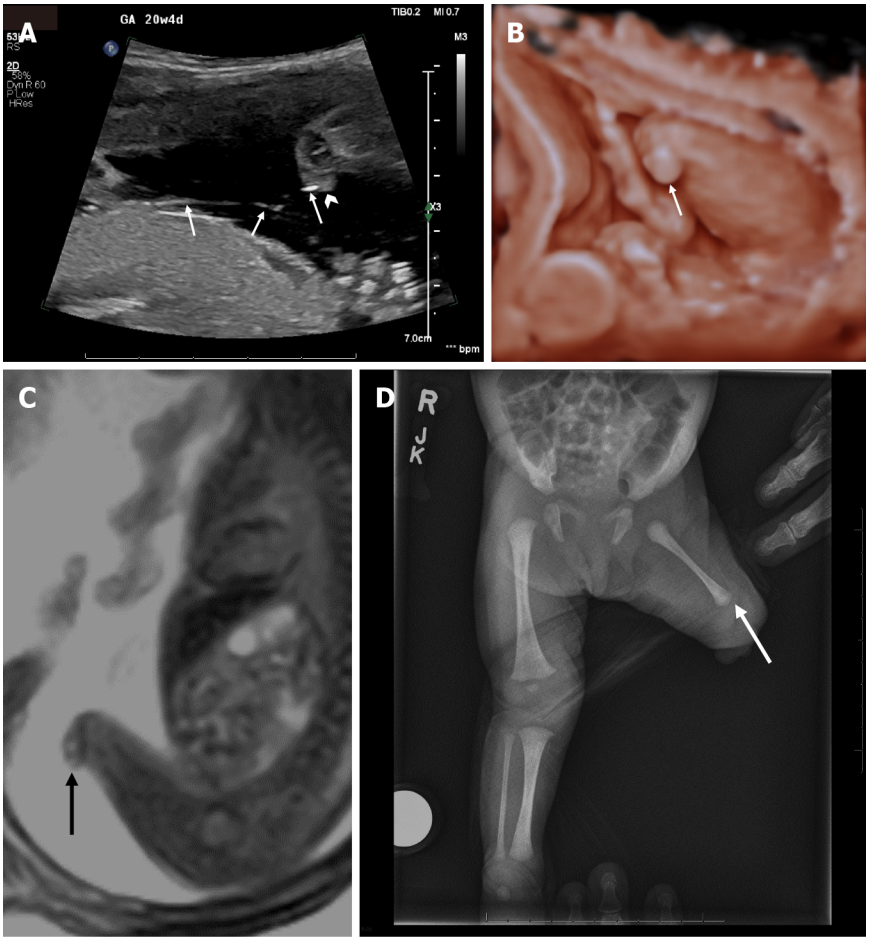

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Figure 2 Prenatal images at 20 wk and 4 d and postnatal images demonstrating a congenital transverse limb deficiency below the left knee. A: Two-dimensional (2D) ultrasound demonstrating the amniotic bands (arrows) that attach to the residual nubbin (arrowhead); B: 3D ultrasound rendered image showing the transverse reduction defect at the level of the knee (arrow); C: Sagittal balanced turbo field echo slice on prenatal MRI of the left lower extremity showing a terminal transverse limb defect (arrow); D: Postnatal AP x-rays of the lower extremities demonstrating the left transverse reduction defect at the left of the knee, residual nubbin (arrow) and shorter left femur compared to right.

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RESULTS

Etiology & embryology

Limb development begins through paired primordial limb buds at 4 wk of intrauterine development. This is enabled by the undifferentiated mesenchymal cells that underlay the ectoderm on both the forelimb and hindlimb[13]. This structure is referred to as the apical ectodermal ridge and permits both proximodistal development through fibroblastic growth factor, anteroposterior development through the sonic hedgehog protein, and dorsoventral development through the Engrailed-1 protein[14]. The main mechanism of the etiology and embryological level is the disruption of growth of the Apical Epidermal Ridge (AER) along the proximodistal plane[14]. The subsequent result is that the interaxial signaling that is responsible for normal limb development is disrupted and causes a deficiency in the plane orthogonal to the developing limb bud, that is, transversely.

There are several proposed causes for this disruption of the AER. The leading theory includes hypoperfusion, which leads to apoptosis of the AER. This is generally thought to be due to a vasoocclusive event[15] including and other vascular etiologies including thrombosis, vasospasm, and embolism[5,16-18]. Decongestants, non-aspirin non-steroidal anti-inflammatory drugs, and smoking are significantly associated with terminal transverse limb deficiencies[16]. Other etiologies include maternal thrombophilias[9], alpha-thalassemias[19], and amniotic band sequence[16] (Figure 1).

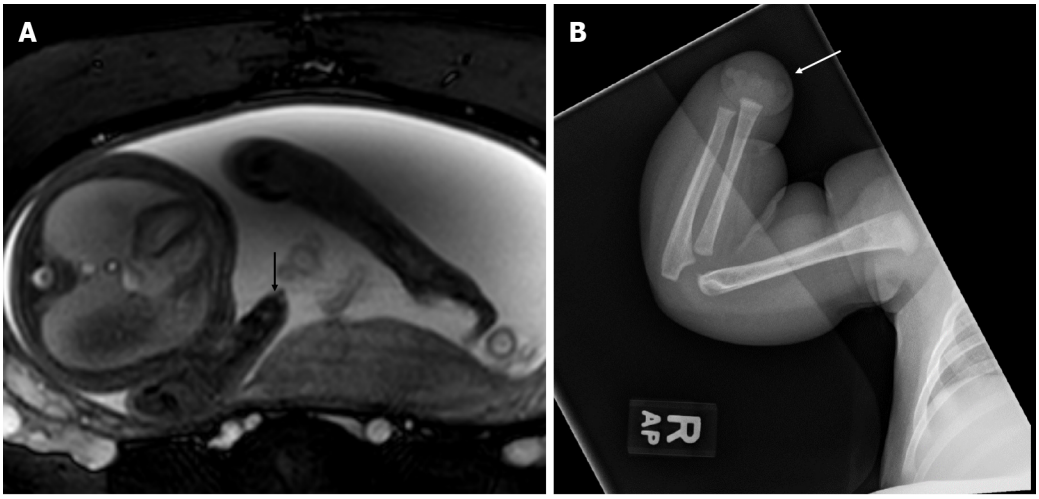

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Figure 3 Prenatal and post natal images of a transverse limb deficiency at the level of the right wrist. A: Axial balanced turbo field echo slice on fetal MRI at 28 wk and 5 d demonstrating a terminal transverse limb defect (arrow); B: Postnatal radiographs confirming the diagnosis (arrow).

Natural history

Congenital transverse limb deficiencies are non-progressive disorders. These disorders result from apoptosis failure (usually secondary to a vascular insult). Thus, the condition is of maximum severity at its presentation and does not progress. Though congenital transverse limb deficiencies are characterized by decreased mobility and function, the symptoms do not worsen as the child grows older.

While the deformity itself cannot worsen, there are malformations associated with limb defects that need to be monitored. Preaxial limb defects were shown to occur more frequently with esophageal atresia, heart defects, and unilateral kidney dysgenesis; postaxial defects with hypospadias; transverse defects with craniofacial defects and ring constrictions; and amelia with anorectal atresia, omphalocele, gastroschises, and ring constriction[20]. Therefore, close attention to associated congenital anomalies is necessary to ensure the health and proper growth of the child.

In a significant proportion of congenital transverse limb deficiency cases, surgery and prosthetics are unnecessary and sometimes contraindicated due to the possibility of complications and the lack of functional gain. Therefore, supportive treatment along with aid from occupational therapists can be a viable option[21].

Classification systems

The first classification of congenital limb deficiencies was described in 1961 by Frantz *et al*[22] The International Society for Prosthetics and Orthotics anatomical classification for congenital limb deficiencies represented a significant expansion of the originally published classification[23]. In this system, congenital limb deficiencies are first described as either longitudinal or transverse. Longitudinal limb deficiencies refer to the complete absence or reduction of the long axis of a limb, whereas transverse limb deficiencies refer to the abrupt absence of an otherwise normally developing limb. Limb deficiencies can be described to specify the affected limb and the extent to which it is affected. By convention, longitudinal limb deficiencies name the bone that is affected such as the ulna or tibia whereas transverse limb deficiencies name the anatomical location that is affected such as the shoulder or leg. The degree of deficiency for both longitudinal and transverse deficiencies can be described as total or partial.

More recent classification systems have expounded upon the anatomy and etiology of congenital limb deficiencies. For instance, McGuirk *et al*[24] considered an additional category of limb deficiency termed intercalary defects, which refers specifically to the absence or hypoplasia of the middle portion of a long bone with intact distal features.

The most recent classification includes both an anatomic and etiologic component[25]. This greatly expands on that of Day *et al*[23] and McGuirk *et al*[24] to include an etiologic component that includes chromosomal abnormalities, Mendelian inheritance, syndromes, teratogenic exposures, vascular disruption defects, or unknown causes[25]. This classification also includes other congenital limb deficiencies, can be used to succinctly describe the location, and allows modification for the presence of nubbins. By allowing subclassification by syndromic, teratogenic, vascular, or other etiologies and by distinguishing between phenotypes within the family of transverse limb deficiencies, the classification proposed by Gold *et al*[25] can provide improved communication between providers and guide genetic testing[26].

Prenatal imaging findings

Prenatal 2D US has become the mainstay of the diagnosis of transverse limb deficiencies (Figures 1A and B, 2A) In much of the developed world, prenatal evaluation involves the mid-trimester scan[1,27]. However, a comprehensive cross-sectional study in 12 European countries for a total of 7758 cases found a prenatal detection rate of 22.7% for isolated terminal transverse deficiencies[1]. Another large study from England, demonstrates a second trimester detection rate of 25%[27]. These large studies in the developed world demonstrate a significant barrier to early intervention and counseling for patients' families.

Of note, is the potential utility of the first-trimester ultrasound scan that has shown to be useful in the detection of transverse limb deficiencies. Liao *et al*[2] demonstrated a detection rate of 77.8% for all fetal limb abnormalities through the first trimester scan. The first trimester scan may have greater role in diagnosis of these limb deficiencies than previously thought.

Fetal MRI is also used as a secondary diagnostic modality (Figures 1C and E, 3A) It is particularly useful in cases that do not image well by ultrasound including cases of maternal obesity, advanced gestational age, oligohydramnios, and unfavorable fetal position[11]. MRI may uncover other associated soft tissue anomalies that may not otherwise be diagnosed prenatally. 3D US (Figures 1C and D, 2B) and multidetector computed tomography are also emerging as modalities to improve diagnosis and lead to earlier treatment[28]; however, low-dose 3D CT is, in general, more useful in cases of suspected skeletal dysplasias. A set of radiographic pearls have been developed by our institutional experts for the reader (Table 2). However, no standardized algorithm incorporating their use is available.

DISCUSSION

Caring for individuals with congenital transverse limb deficiencies

Non-surgical therapies: Non-surgical management of congenital limb deficiencies is comprised of physical therapy, orthoses, and prostheses (Figure 4). Quality of life, functionality, and the degree of limb deficit should all be considered in deciding an appropriate non-surgical strategy[29-31]. Timely implementation of a multidisciplinary strategy is required for reducing pain, function loss, and improving quality of life[32-36].

While there are no clinical guidelines regarding the timeline of treatment, most studies recommend prosthetic fitting before the age of 2 years as the prosthetic rejection rate increases drastically after the age of two[37,38]. It is important to note that children who have treatment can achieve satisfactory degrees of movement and function.

An important facet to treatment is appropriate counseling of the family. This begins with a thorough conversation about the diagnosis, prognosis, natural history, treatment options, and alternatives. Providing an opportunity for the family to meet the family of another affected child has been shown to be very helpful. Doing so can reduce parental anxiety and improve compliance with treatment recommendations[39,40].

Special considerations in upper extremity defects – prosthesis timing and choice

Location of the defect is a very important determinant in the treatment strategy (Figure 3B). While lower extremity prosthetic intervention is widely used, the treatment strategy around upper extremity defects is more nuanced[21]. Upper extremity defects are more common and the choice and fit of prosthesis is rapidly evolving[41].

The ideal time range for prosthesis fitting for trans-forearm and trans-humeral deficiencies is between six and twenty-four months of age[42]. This improves the performance of activities of daily living (ADL's) and minimizes prosthetic rejection. Generally, the outcome of prosthesis use in patients with proximal upper limb deficiencies is good[43]. There is evidence to suggest that early myoelectric prosthesis devices between 2.5 and 4 years of age may have potential therapeutic benefit[42]. However, it is important to consider that prosthesis choice and fit needs to be individualized based on the level of amputation and stump choice to prevent the nerve entrapment syndromes associated with prosthesis overuse[44].

There is a reported underuse of upper limb prosthesis in children with congenital transverse reductions[45]. Children tend to use their prostheses for specific activities and not others[45]. A recent study has shown that there is a direct correlation between the number of activities that children perform and daily use of the upper extremity prosthesis[46]. Addressing the issue of sporadic use may lead to better performance on activities of daily living and increased independence[38].

Though the current literature supports the use of prostheses, there are no long-term reports that compare the outcomes of prosthetic treatment in terms of patient-reported or functional outcomes. Further studies are needed to determine the functional outcome for upper extremity prosthesis users and non-users and thus allow clinicians to make evidence-based recommendations.

Table 2 The radiographic pearls and pitfalls as identified by our literature search and our institutional musculoskeletal radiology experts

Pearl or pitfall	Reasoning and evidence
Use the appropriate classification system	Many classification systems exist[25,26]. However, the most recent classification system by Gold *et al*[27] provides improved communication. When these fail, description of the location and use of modifiers can be helpful to radiologists and non-radiologists, alike
Prenatal ultrasound pearl	Three-dimensional ultrasonography using both maximum intensity projection (MIP), thick slabs with MIP, or surface rendering greatly complements the examination using two-dimensional ultrasound. Scanning with new generation high-frequency broad band probes (up to 22 MHz in some cases) allows greater confidence in the identification of amniotic bands compared to standard obstetrical probes[11]
Prenatal fetal MRI pearl	MRI is not superior to ultrasound for imaging fetal bones. However, it may prove useful in cases where ultrasonography windows are limited, such as maternal obesity, advanced gestational age, oligohydramnios, and unfavorable fetal position. It also provides an additional opportunity to diagnose associated congenital anomalies for which MRI is more sensitive than ultrasound (*i.e.*, CNS anomalies)
Prenatal CT	Current literature supports the use of low-dose CT with 3D reconstruction for the evaluation of skeletal dysplasias[30]. The use of CT for the evaluation of transverse limb deficiencies has not been fully evaluated. The use of CT may be considered when both ultrasound and MRI failed to characterize the phenotype and only after thorough evaluation of benefits versus risks in individual cases

MRI: Magnetic resonance imaging; CT: Computed tomography.

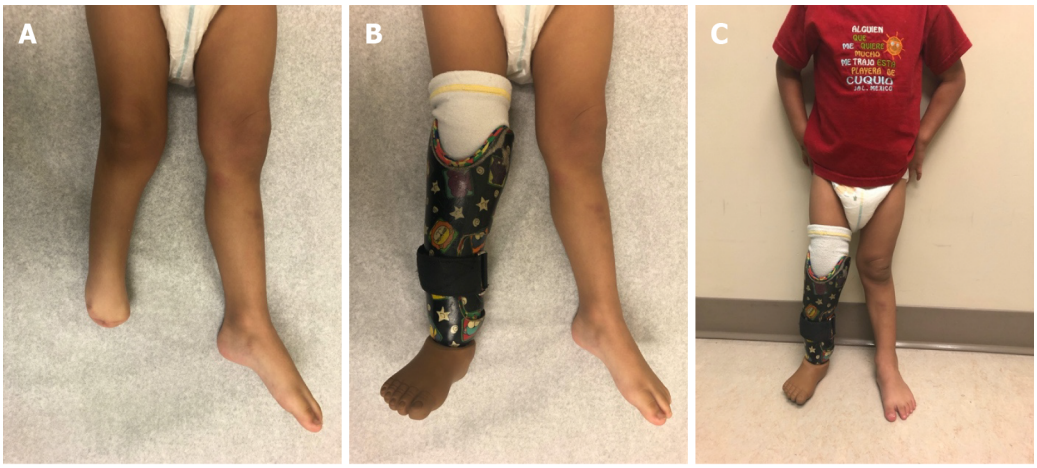

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Figure 4 Clinical photographs of a terminal transverse deficiency of the right leg. A: Supine photograph of the transverse deficiency below the right knee; B: Supine photograph demonstrating proper prosthesis fit; C: Standing photograph demonstrating comfortable standing with the prosthesis.

Social resources

An important topic of discussion is rehabilitation options for young adults. These management resources are often underutilized. A low rate of referral to the affected child and an interdisciplinary management team has been noted from the Regional Disablement Service in Northern Ireland[47].

Ultimately, this has led to progressive social strains that further worsen the quality of life of individuals with transverse limb deficiencies. Many young adults with transverse upper limb deficiencies have difficulty in finding suitable housing and employment[48]. Further, most young adults with upper limb transversal deficiencies are unaware of available resources and have perceived limited benefit of said resources[49]. Increased focus on age-relevant information as well as dedicated training programs could increase benefit to young adults with upper limb transverse limb defects[49]. These findings suggest that an emphasis on the availability and use of these resources could have a great impact on the quality of life of individuals with transverse limb deficiencies. It remains unclear as to what the ideal age, modality of education, and the role of the physician would be to better utilize these options. More research is required to identify what measures can be taken to increase both awareness and use of available resources.

Surgical treatment

Surgical treatment is reserved for a minority of patients and ranges from 16.9%[50] to 25%[3] of patients. Generally, surgical treatment involves intermediary correction for prosthesis placement[42]. However, there is a role in corrective surgeries[3] and lengthening procedures[42,51-52] for some patients.

Surgical treatment pursued varies based on the location of the deficiency[3]. An epidemiological study in Japan noted that in both the upper and lower extremity, surgical treatment was more commonly pursued than prosthesis and orthosis combined in the setting of transverse deficiencies at or distal to the level of distal to the carpals. However, in proximal upper and lower extremity defects, surgery was rarely pursued.

When considering surgical options, they can be broadly classified as one of the following: amputation/constriction ring procedures[3], lengthening procedures[42,51], joint reconstructions[52], and digit transfer surgeries[53]. The literature on outcomes in lower extremity transverse limb surgery is sparse; however, the outcomes for upper limb defects in the hand and wrist are summarized below.

Hand and wrist upper limb deficiencies

To treat upper limb deficiencies at the level of the metacarpal or distal to the metacarpal, finger resurfacing procedures are performed. Amputation and constriction ring release procedures are also performed in preparation for the complete articulation of the limb and prosthetic[3]. However, there are a few surgical options that have been described around the topic of improving orthotic use and increasing functional ability without the need for prostheses.

Reconstruction of the wrist articulation with an iliac crest autograft has been described in the setting of terminal deficiencies. In two patients, these were shown to have cartilage formation on MRI and improved functional abilities[52].

Microsurgical toe-to-hand transfers have also been described with good radiographic outcomes at a mean follow-up of 21 months; however, no patient-reported outcomes have been noted with this surgical option. In the setting of cleft hand, transverse limb deficiencies respond well to cleft hand reconstruction with both radiographic and functional outcomes[53]. Importantly, 4 out of the 11 cleft hands due to underlying transverse limb deficiencies did require additional surgery[54]. Lengthening with either an on-top resurfacing procedure or distraction lengthening has been described with good radiographic outcomes and improved inch function[51].

Though there is some good data regarding radiographic outcomes, the literature is sparse for success rates and re-operation rates when considering these surgical options. Overall, when considering upper extremity transverse deficiencies, a re-operation rate of 5%-20% has been reported. More studies with long-term clinical and functional outcomes of these surgical options and studies investigating causes for re-operation are needed to assist in surgical decision-making.

Limitations

As a scoping review, this manuscript is limited by the quality of the evidence of the studies included. The lowest quality of evidence included was level IV. Further as a scoping review, this article uses summary date to draw conclusions about the current state of a topic. As such, it is vulnerable to selection bias. This may also result in the inability of our search findings to be completely generalizable.

CONCLUSION

Transverse limb deficiencies are rare and display an upper limb predominance. Conventionally, the diagnosis was made through radiography; however, 2D US emerged as a prevalent technology with the potential to improve our diagnostic capabilities. Prenatal 3D US, fetal MRI, and low-dose 3D CT are newly emerging modalities that could also potentially improve diagnosis; however, are not routinely employed in diagnosis. To date, there are no standardized international guidelines regarding the pre-natal radiographic evaluation of congenital limb deficiencies. A systematic method would allow for enhanced interdisciplinary communication, early diagnosis, and integration of family values into treatment plans. Management with prosthesis is commonly pursued, especially in the upper extremity, with highly variable use rates. Surgical treatment is less commonly sought out. Though some studies demonstrate good radiographic and clinical outcomes for hand/wrist surgical options, these are limited by the number of patients and quality of evidence. Further long-term studies are needed for both the conservative and operative treatment options to assist in clinical decision-making.

ARTICLE HIGHLIGHTS

Research background

Congenital transverse deficiencies are horizontal deficiencies of the long bones that occur with a reported incidence as high 0.38%.

Research motivation

There has been much advancement regarding prenatal imaging modalities to allow for early diagnosis

and appropriate treatment.

Research objectives
The purpose of this scoping review article is to summarize the current state of knowledge on congenital transverse limb deficiencies and to provide an update regarding the radiographic evaluation of congenital transverse limb deficiencies.

Research methods
This IRB-exempt scoping review followed the PRISMA-ScR checklist for scoping reviews strictly. Five search engines were searched for a total of 265 publications.

Research results
Of these, 51 studies were included in our article.

Research conclusions
Prenatal magnetic resonance imaging (MRI), 3D Ultrasound, and multidetector computed tomography (CT) exist are emerging modalities that have the potential to improve diagnosis. Use of the appropriate classification system, three-dimensional ultrasonography with a maximum intensity projection, and appropriate use of prenatal MRI and prenatal CT can improve diagnosis and inter-provider communication.

Research perspectives
Further scholarly efforts are required to develop improve standardized guidelines regarding the prenatal radiographic evaluation of congenital limb deficiencies.

FOOTNOTES

Author contributions: Vij N, Belthur M, Llanes A, Youn S, Goncalves LF contributed equally to his work. Vij N, Belthur M, Goncalves LF designed research. Vij N, Belthur M, Llanes A, Youn S, Goncalves LF performed research. Vij N, Belthur M, Llanes A, Youn S, Goncalves LF contributed to the analytic tools. Vij N, Belthur M, Llanes A, Youn S, Goncalves LF analyzed data. Vij N, Belthur M, Llanes A, Youn S, Goncalves LF wrote the paper.

Conflict-of-interest statement: None of the authors have any conflicts of interest.

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CASE REPORT

Can we suppress excessive post-surgical scar formation: A case report

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Abstract

BACKGROUND

Hypertrophic scars (HSs) formation is a complication that occurs after wounds heal with secondary intention and sometimes after clean surgical incisions. Many treatments are in vogue now with varying successes. Although the mechanism or mechanisms that cause a HS to form are not clearly understood, one thing that is clear is that once scar tissue matures, any intervention will not be successful. In this paper, we report on a case where a patient who was known to develop HS was treated with a new combination of ingredients (Phyto-chemicals + Silicone JUMI) to suppress HS formation.

CASE SUMMARY

A 68-year-old female of African descent presented a severe HS post total knee replacement (TKR), which the patient describes as itchy and painful. Due to complications caused by the scar, she was apprehensive about undergoing TKR on her other knee. However, after the TKR of the contralateral side post-removal of skin clips, JUMI anti-scar cream (JASC) was used to suppress excessive scar formation.

CONCLUSION

JASC appears potent and efficacious at suppressing excessive scar formation. We believe that this warrants further studies on larger patient groups and on different surgical sites.

Key Words: Hypertrophic scars; Photo-chemicals; JUMI; Keloid; Case report

Core Tip: Hypertrophic scars are common after surgery and often result in social, emotional, and psychological effects. Many treatments have been tested and the most prominent one is silicone gel. However, this form of treatment has complications related to hot weather. JUMI anti-scar cream is a phyto-chemical based silicone gel that was found to be quite efficacious in reducing post-surgery scars.

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INTRODUCTION

Hypertrophic and excessive scars are common occurrences that often result in social, emotional, and psychological effects[1], in addition to exorbitant costs to manage such complications[2,3].

Hypertrophic scars (HSs) develop due to excessive collagen formation, which can regress slowly[4], but in certain circumstances may continue to deposit collagen, causing HSs[5]. We observed that scarring post joint arthroplasty occurs commonly and that scars in these areas are devoid of hair follicles and sweat glands; excessive scarring can even feel itchy and uncomfortable. Occasionally, HSs result in keloid formations, indicating that there is a dysregulation of the normal healing process, which results in excessive production of collagen, elastin, proteoglycans, and extracellular matrix proteins[6]. This demonstrates that early HS prevention could prevent keloid formation.

In this paper, we report on a case where a patient who was prone to hypertrophic scarring was treated with JUMI cream, which successfully suppressed the post-surgical scar.

CASE PRESENTATION

Chief complaints

Excessive scar formation post total knee arthroplasty of the left knee.

History of present illness

A 68-year-old female of African descent presented with pain in left knee, difficulty to walk due to severe osteoarthritis of left knee. Total knee replacement (TKR) was recommended. She was very apprehensive that the post-surgical scar will become hypertrophic and painful as the right side.

History of past illness

She had undergone TKR of her right knee 12 mo earlier and experience HS post-surgery (Figure 1A). She complained of persistent itching and pain in around the scar and sometimes depressed her became depressed because of it. She had many treatments, including using silicone gel to reduce the scar, which all failed. The patient insisted that she needed to delay surgery on her other knee because she was afraid of another scar forming with the same outcome.

Physical examination

Nothing abnormal except she had 15 degrees of varus deformity of the left knee.

Laboratory examinations

All values within normal range.

Imaging examinations

X-rays show Grade IV Kellgren-Lawrence osteoarthritis in left knee.

FINAL DIAGNOSIS

Suppression of the scar formation post TKR.

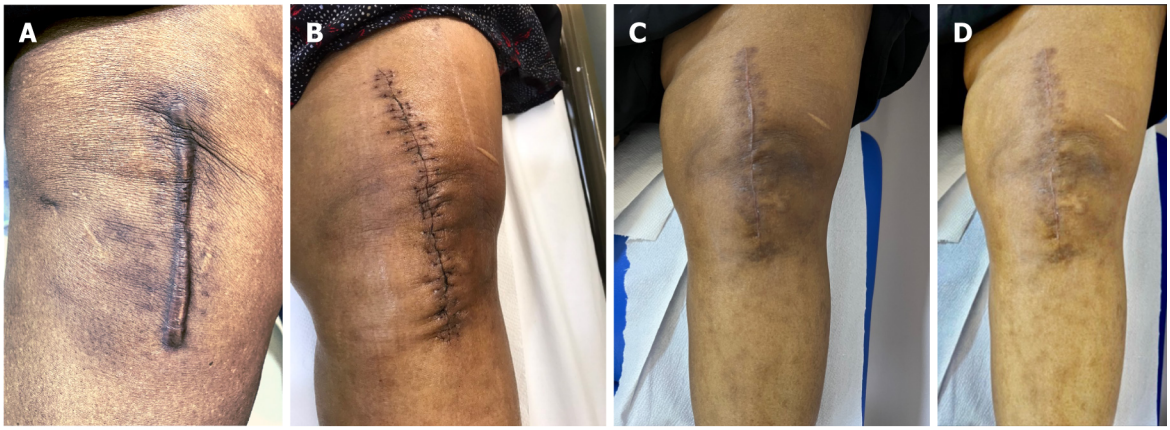

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Figure 1 Post operative picture. A: Post operative scar after 12 mo of total knee replacement (TKR); B: Post operative picture after removal of surgical clips on the other knee after TKR; C: Post surgery clinical picture after six weeks of use of JUMI anti-scar cream (JASC); D: Post surgery clinical picture after 12 wk of use of JASC.

TREATMENT

As her pain grew and her mobility deteriorated, she decided to undergo total knee arthroplasty on her left side. During the second surgery, the same procedure and closure methods from the first surgery were used again (*i.e.*, the subcutaneous layer was closed using 2-0 vicryl sutures and the Covidien Appose Single Use Skin Stapler 710 from Medtronic Parkway Minneapolis, MN 55432 United States). Standard rehabilitation hospital protocol for post-TKR was followed after both surgeries.

Two weeks post-surgery, the surgical clips were removed (Figure 1B). The patient was advised to apply JUMI anti-scar cream (JASC) twice a day for 3 mo, which she did regularly.

OUTCOME AND FOLLOW-UP

After 6 wk of applying JASC, the patient was quite happy with the effect on her scar (Figure 1C). Figure 1D shows the scar at 12 wk post suture removal, which is when she expressed having no pain or itchiness in the scar.

DISCUSSION

This case report shows that JASC [a combination of silicone gel and Phyto-Extracts (*e.g.*, Centella asiatica extract, Curcuma Longa, lavender oil, marshmallows, Musa Paradisiaca, pineapple extract, and tea tree oil)] was quite effective at suppressing scar formation. After an extensive review, Hsu *et al*[6] reported that the majority of studies that evaluated silicone gel's ability to prevent HS and keloids were poor quality with high risk of biases. Kong *et al*[7] performed a randomized study of scars after TKR and reported that silicone gel had no beneficial effects on scar pain and itching. In addition, when silicone gel was exposed to hot weather, the researchers observed incessant pruritus (80%), skin rash and maceration, and poor patient compliance[8]. HS and keloid management has improved over the years, but has not achieved the zenith of success; therefore, more trials and more effective drugs are required.

Phyto-chemicals from medicinal plants that can be used to treat HSs have been studied and found to be highly effective[9-11]. Centella asiatica extract is an important phyto-chemical used in JASC that has been proven to contain bioactive constituents, such as triterpenoid saponins, flavonoids, phenolic acids, triterpenic steroids, and amino acids. These improve skin health by increasing hydration and decreasing transepidermal water loss with anti-inflammatory effects[12-14]. JASC is a combination of optimum phyto-chemicals and silicone gel, which has been proven to be efficacious at suppressing post-operative scars.

HSs cause great discontentment and psychological and emotional issues when the scars are close to the joint. Our patient was so depressed because of the scar from the previous surgery that she decided to live with the intolerable pain rather than risk another ugly scar. Our case report demonstrates that there are many ways to suppress post-operative scars, and JASC is one of them. We believe more studies are necessary to confirm the efficacy of JASC for all types of post-operative scars.

CONCLUSION

JASC appears potent and efficacious at suppressing excessive scar formation. We believe that this finding warrants further studies on larger patient groups and different surgical sites.

FOOTNOTES

Author contributions: All authors contributed equally in the work; The literature search, writing was performed by Sadat-Ali M and Al-Mousa SA; Operated by Al-Anii FM and Al-Tabash KW; The patient was followed by Abotaleb MM, Abotaleb MM was blinded what was used for the wound after sutures were removed; All authors have read and approve the final manuscript.

Informed consent statement: Informed consent has been taken prior to surgery and publication of data and pictures thereof.

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