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Editorial

Artificial Intelligence is Pushing The Boundaries in Orthopaedic Surgery

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Three convergences of the digital world have an impact on world life, the use of artificial intelligence (AI), robotics, and autonomy. This can be seen clearly in the development of many industries in the world, whose valuation increases are companies that are able to adopt these three things. It seems to have grown quite exponentially and heavily influenced medicine. It reveals that nearly 72% of AI research within orthopedics have been published in the past 2 years.¹

Artificial intelligence (AI) is the application of algorithms that provide machines the ability to solve problems that traditionally required human intelligence. AI at its core involves machines that can perform tasks innately characteristic of human intelligence. This includes tasks like planning, understanding language, recognizing patterns, learning, and problem-solving. AI can be thought of as an umbrella term that encompasses a broad range of subfields, including machine learning (ML), which in turn contains a subfield called deep learning (DL).^{2,3}

AI can learn and improve from examples in large data sets, these algorithms serve as the fundamental AI using experience to improve performance or to make accurate predictions.⁴ The most common usage of AI research is in imaging, Thong et al. proposed optimization of 3-D spine model vectors for the automatic detection of adolescent idiopathic scoliosis.⁵ In 2019, Shah et al sought to Automatic measurement and segmentation of articular cartilage thickness in healthy knees on MRI.⁶ Another study from Chung et al. sought to apply DL to not only detect but also classify proximal humerus fractures using anterior-posterior shoulder radiographs. For detecting proximal humerus fractures, showed a high performance of 96% top-1 accuracy.⁷ AI's imaging capabilities can also play a role in preoperative planning and risk stratification. The first introduction of the patient-specific payment model is from Ramkumar et al., the model can predict the length of stay, inpatient costs, and patient disposition for lower extremity joint replacement.⁸

Advance in AI, have an interest in robotic-assisted surgery and navigational systems to limit human error in orthopedic procedures. For example, robotic arm provides tactile, visual, and auditory feedback to assist the surgeon.⁹ Seibold et al. detect drill breakthrough events and show the potential of deep learning-based acoustic sensing, they found that acoustic sensing offers a very accurate, to prevent errors in surgery.¹⁰

The future is here, it is not machine that replace human. With more research being published, AI and

medicine are merging. It is now easier than ever to push the boundaries of what is possible in orthopedic surgery.

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Literature Review

Approach to Diagnosis and Management of Osteosarcoma

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Abstract

Osteosarcoma is a primary bone malignancy of mesenchymal origin. The prevalence of osteosarcoma in Indonesia is not known with certainty. Studies have shown that Paget disease, electrical burns, trauma, beryllium exposure, exposure to alkylating agents, FBJ virus, osteo-chondromatosis, enchondromatosis, fibrous dysplasia, orthopedic prostheses, and bone fractures have been associated with the occurrence of osteosarcoma. Survival rates are expected to improve with treatment consisting of a combination or one of recently developed surgical resection, chemotherapy, and targeted immunotherapy.

Introduction

In children and adolescents, osteosarcoma is a primary bone malignancy of mesenchymal origin. Osteosarcoma also occurs in an older age spectrum (>65 years) because of its association with abnormal bone growth as seen in Paget disease. At a younger age, the incidence of osteosarcoma is associated with rapid bone growth in adolescents. Although the pathophysiology is related to several factors, the exact cause is still unknown. Survival rates are expected to improve with treatment consisting of a combination or one of recently developed surgical resection, chemotherapy, and targeted immunotherapy. In this review article, we focus on the etiology and pathogenesis associated with the diagnosis and short-term and long-term management of osteosarcoma, including newly identified agents such as targeted immunotherapy.^{1,2}

Epidemiology

The age distribution of osteosarcoma is bimodal. The first peak is in the 10 to 14 years age group, which corresponds to the pubertal growth spurt. This group accounts for the majority of primary osteosarcomas. In the age range 0-14 years, the incidence of osteosarcoma for all races and sexes is 4 cases per million people per

year (3.5-4.6, confidence interval 95%). This number increases to 5 cases per million people per year (4.6-5.6, confidence interval 95%) in the age range 0-19 years. The next peak that can be observed is in adults aged 65 years and over, where the incidence of osteosarcoma is most likely secondary cancer due to malignant degeneration of the Paget disease, location of bone infarction, etc.

The prevalence of osteosarcoma in Indonesia is not known with certainty. The incidence of bone tumors at Cipto Mangunkusumo Hospital is 1.2%, with the incidence of malignant bone tumors being 1.3%. Based on hospital information system data in 2005, osteosarcoma is included in the top five cancer cases at the age of 1-17 years. In evaluating the profile of bone tumors in children at Cipto Mangunkusumo Hospital in 1995-2004, 73.7% of cases were osteosarcoma cases. In 1991-1995, at the RSUD Dr. Soetomo found 373 cases of malignant bone tumors, with 183 cases of primary malignant bone tumors. The ratio of male: to female is 1.4:1 and the number of primary cases is 44 cases per year, especially osteosarcoma which is 62.4% of cases.⁴

Etiology & Pathogenesis

Studies have shown that Paget disease, electrical burns, trauma, beryllium exposure, exposure to

alkylating agents, FBJ virus, osteochondromatosis, enchondromatosis, fibrous dysplasia, orthopedic prostheses, and bone fractures have been associated with the occurrence of osteosarcoma. An association with secondary osteosarcoma has been identified in patients with infarction and infection. In addition, osteosarcoma has been reported to be correlated with exposure to ionizing radiation, radium, and ancient contrast agents such as Trotrast.^{3,6,7,8}

Other literature shows that the most common sites are the femur (42%, 75% tumors on the distal bone), tibia (19%, 80% tumors on the proximal bone), and humerus (10%, tumors on the proximal bone). 90% of bone proximal to bone). Other possible sites are the skull or jaw (8%) and pelvis (8%). Osteosarcoma can be divided into primary and secondary types. Primary tumors usually arise in the metaphysis of the long bones and tend to be more prominent in the knee, with nearly 60% occurring in these sites. Children and adolescents are the majority affected by this condition. Secondary tumors have a much wider distribution, reflecting the diverse nature of the underlying predisposing conditions. They most often appear in the adult population. The incidence is particularly high in the flat bones, especially in the pelvis (a commonplace Paget disease).³

Typical	Non-Typical
High-grade malignant tumor	Age >60 years
Mesenchymal cells producing osteoid and immature bone	41.3 % incidence of axial osteosarcoma in the elderly
Age 5-30 years, most often at the age of 10-20 years	High metastatic rates
Pain at night	Pathological fracture
History of minor trauma	Lymphadenopathy
Red Flag Sign <ul style="list-style-type: none"> Significant weight loss Loss of appetite Pain at night Worsening of pain on treatment Abnormal Lump 	
Local tenderness, mass, deformity	

Table 1. Typical versus atypical osteosarcoma

Diagnosis

National Comprehensive Cancer Network's 2020 Guidelines for Initial Evaluation of Osteosarcoma (Version 1.2020)

a. Clinical History and Physical Examination

Osteosarcoma symptoms can appear for a long time, sometimes weeks or months, before the patient requests an evaluation. The most common symptom is bone pain, especially with exertion. Parents often worry that their child has sprained sprain, arthritis



Figure 1. X-Ray and MRI findings in osteosarcoma of the proximal humerus

1. OS Central	a. Conventional <ul style="list-style-type: none"> i. Osteoblastic ii. From the chondroblast iii. Fibroblastic b. Epithelioid <ul style="list-style-type: none"> c. Giant cell-rich d. Osteoblastoma-like e. Small cell f. Telangiectatic g. Low-grade central
2. Multifocal	
3. Gnathic	
4. OS Surface	a. Periosteal <ul style="list-style-type: none"> b. Parosteal c. High-grade surface d. Intracortical
5. OS Secondaries	

Table 2. Types of Osteosarcoma

or growth pain/growing pains. There may or may not be a history of traumatic musculoskeletal injury reported. Swelling or a lump may or may not be reported, depending on the size and location of the tumor. Systemic symptoms, such as those seen in lymphoma (fever, night sweats, etc.), are rare. Respiratory symptoms are rare and, if present, indicate extensive pulmonary involvement. Additional symptoms are unusual because metastases to other sites are very rare.⁹

Physical examination findings are usually focused around the site of the primary tumor and may include: a palpable mass that may be tender and warm with or without overlying throbbing or bruits, although these signs are nonspecific; decreased joint involvement range of motion; local or regional lymphadenopathy (uncommon); and respiratory findings with the metastatic form.⁹

b. Laboratory Analysis

Biochemical markers such as serum alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) are assessed at baseline because they provide

evidence for diagnosis and prognosis. ALP levels will be high because of the increased osteoblastic activity associated with osteosarcoma. Very high levels have been associated with a heavy tumor burden and are generally considered a poor prognostic indicator. It is also important to assess the end of the course of treatment because biomarker levels can decrease with successful treatment and can increase with residual disease or relapse.^{10,11} ALP is increased when there is active bone formation because ALP is a by-product of osteoblast activity. Osteosarcoma is characterized by the production of immature osteoid tissue or bone so that serum ALP levels are high in osteosarcoma patients.

c. Diagnostic Imaging of Primary Tumors

1. Radiography

although MRI is the gold standard for diagnostic imaging of osteosarcoma, radiography is generally the first study obtained when a potential bone mass is identified on physical examination. Conventional radiographs of osteosarcoma may show damage to medullary bone and cortical, permeative, or cortical cortex moth-eaten, configuration "Sunburst" (due to aggressive periostitis), configuration "Codman triangle" (due to elevation of the periosteum away from the bone), bone lesion "fluffy" or "cloud-like" undefined, soft tissue mass, calcified osteoid matrix produced by the tumor.¹⁰

2. Computed Tomography

the main role of CT is primarily to assist with biopsy planning and disease staging. Unless the bone lesion is predominantly lytic in nature, CT may not make a significant contribution to direct tumor assessment after X-ray and MRI. For lytic lesions, small amounts of mineral material may not be observable on either plain film or MRI. However, chest CT is the modality of choice for evaluating metastases.¹⁰

3. Magnetic Resonance Imaging

after identifying a suspicious lesion on radiography, MRI may be required for further characterization. MRI is an indispensable tool for determining the extent of tumors inside and outside the bone. All bones involved, as well as one joint above and one joint below the tumor, should be included in the study so skip lesions not missed. MRI can accurately and precisely delineate tumor grade in adjacent soft tissues, joint involvement, whether or not the tumor traverses the physis, and proximity to the neurovascular bundle closest. Nearly every aspect of treatment can be assessed by MRI, from pre-surgical assessment of limb resection to chemotherapy response rates in the form of tumor necrosis, shrinkage, and better capsulation.¹⁰ Sequences traditionally obtained in an osteosarcoma MRI may

show the following:¹⁰

- T1 Weighted Images: Non-ossifying soft tissue component: signal intensity intermediate; Osteoid component: low signal intensity; Peritumoral edema: signal intensity intermediate; and Scattered hemorrhage foci: variable signal intensity based on chronicity.
- T2 Weighted Images: Components of soft tissue non-ossified: high signal intensity; Osteoid component: low signal intensity; and Peritumoral edema: high signal intensity.

4. Diffusion Weighted Imaging (DWI) - MRI

The most common primary malignant bone tumor is intramedullary osteosarcoma. Yakushiji et al. found that DWI may be more effective than gadolinium-enhanced MRI in differentiating chondroblastic osteosarcoma from other osteosarcomas. This is important because the large chondroid component can make it difficult to biopsy areas containing malignant tumor cells. Missing chondroblastic osteosarcoma is detrimental not only to patient management but also to the final clinical outcome. Patients with chondrosarcoma have a 5-year survival rate of 72.6% when they receive appropriate treatment whereas the 5-year survival rate for chondroblastic osteosarcoma is around 60%.¹²

5. Positron Emission Tomography

PET is a nuclear medicine imaging technique that detects severe metabolic lesions. It is an important tool for determining tumor extent and locating subtle lesions after initial imaging has identified a suspicious mass. Later in treatment, PET can help detect relapse.

Therefore, apart from conventional, well-standard anatomical imaging procedures, metabolic PET imaging is an ongoing focus of research assessing its potential usefulness in sarcoma patients, for example, to determine the metabolic rate of osteosarcoma, monitor response to neoadjuvant therapy, and differentiate sarcomas that are viable of post-treatment changes. PET scan the most widely used for osteosarcoma is 18F-FDG. PET scan Other clinical studies with reported utility for imaging osteosarcoma in patients are 18F-fluoride (18F) ion, whereas 18F-labeled monoclonal antibodies, 18F-fluoromisonidazole, RGD-labeled glycopeptides 18F, 3H-thymidine, 13N-methionine, and PET of transcriptional activity p53 in osteosarcoma has only been used in animal studies.¹³

Because of the reported overlap of 18F-FDG uptake values between different tumor grades, it is usually not possible to differentiate low-grade and occasionally high-grade osteosarcoma from benign 18F-FDG-avid lesions, such as giant cell tumors or osteomyelitis. Thus, the results made it impossible to

avoid a biopsy. PET 18F-FDG is, however, very helpful for targeting biopsies in large and heterogeneous tumors to achieve representative tumor specimens because the highest-grade area determines the histological grade and subsequent biologic behavior. This information about tumor biology cannot be provided by other radiological imaging tools. Another topic of interest that should be further evaluated in clinical studies is tumors that are highly metabolically active but histologically low-grade tumors. Within the tumor subset, histological grade did not predict the outcome. Moreover, high initial 18F-FDG uptake is predictive of poor overall and event-free survival. Clinical follow-up studies in these patients will clarify whether 18F-FDG PET is more accurate for outcome prediction than conventional clinical tumor assessment.¹³

d. Biopsy

A biopsy is necessary after a physical examination, laboratory analysis, and imaging studies confirm a lesion consistent with osteosarcoma. Definitive surgical intervention must include an excision biopsy tract. To avoid recurrence due to possible colonization of cancer cells on the biopsy tract. In this case, a tattoo should be done so that it can be easily identified. Ideally, the surgeon performing the biopsy should be the same surgeon who performed the resection, so they know the path and extent of the biopsy. Open-access biopsy previously considered the best choice because of its high accuracy. However, recent studies have found that open access is correlated with an increased risk of complications such as infection, improper wound healing, and colonization of the site by tumor cells, as previously discussed. Thus, the core biopsy has been replaced traditional open approach, not only because of the reduced risk of contamination operating room bed with tumor cells but also because of their lower cost and shorter recovery time. This is especially important for patients who are aware of potency limb-sparing surgery, whereas many local networks as possible need to be securely maintained. A core needle biopsy was performed with a single deep needle puncture through the trocar across a plane of tissue at the site included in the final resection. Multiple nuclei are needed from the representative area of the mass – the area of soft tissue around the lesion. The necrotic central region produces little viable tissue, whereas the 'Codman triangle' produces only reactive bone. Importantly, recent studies have shown that fine needle aspiration is not an effective approach for biopsy because sufficient tissue samples are not obtained for an accurate diagnosis. After the biopsy, the tissue sample must be analyzed by a pathologist in a

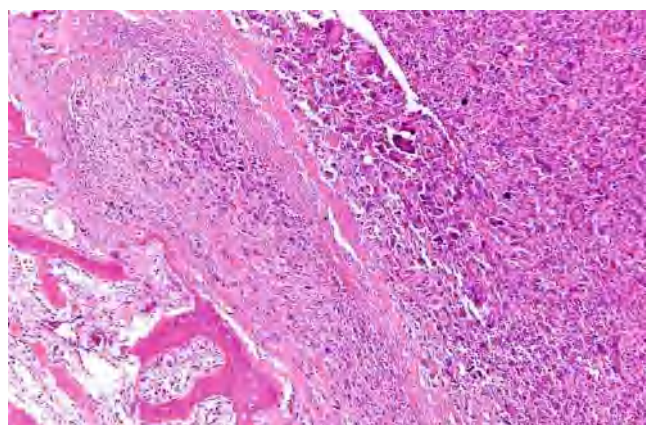


Figure 2. Medium-magnification micrograph of osteosarcoma (middle and right of image) adjacent to non-malignant bone (bottom-left of image): Top right of the image has a poorly differentiated tumor. Osteoid with a high density of malignant cells is seen between non-malignant bone and a poorly differentiated tumor (H&E stain).

biopsy format or frozen for definitive diagnosis, assessment, and histological subtype. All of these influence medical and surgical treatment strategies.¹⁴

e. Immunohistochemistry and Tumor Marker

Kaseta et al. (2007) analyzed the expression of the bax, caspase-8, and cytochrome c genes in subjects with osteosarcoma. They performed immunohistochemical analysis of 35 patients treated surgically with primary OS and 18 tissue specimens from non-malignant bone lesions. The authors suggested that neither gene had a predictive role in survival, but decreased 4-year disease-free survival in the control group, confirming that more intensive adjuvant treatment may reduce disease relapse rates.¹⁵ Contrary to previous hypotheses about c-erbB-2 and its potential role as a prognostic biologic marker, c-erbB-2 expression is not associated with metastatic risk.¹⁶

Zhao et al. (2008) assessed the distribution of ribonucleoprotein hnRNP A2/B1 in the nuclear matrix of human MG-63 osteosarcoma cells, suggesting that this nuclear matrix protein has an important role in the regulation of cell differentiation.¹⁷ Luo et al. (2008) studied the role of osteoblasts in the development of osteosarcoma. The authors confirmed that alkaline phosphatase (ALP), Runx2, OSX, and osteopontin (OPN) levels were low in the OS line because most OS cells fail to complete terminal differentiation. The results suggest that changes in the osteoprogenitor can interfere with the pathways of osteogenic differentiation. Thus, identifying potential differentiation defects in OS tumors will make it possible to reconstruct tumorigenic events in osteoprogenitors and develop rational differentiation therapies for clinical OS management.¹⁸

Staging

OS is classified based on its location, the type of cells involved, and the tumor grade. Most of the OS is located in the long medullary cavity. OS also includes preexisting periosteal, cortical, soft tissue, or bony lesions. All OS contain varying amounts of osteoid, mostly composed of cartilage and fibrous tissue. If one cell type accounts for 50% of the malignancy, the tumor is considered osteoblastic, chondroblastic, or fibroblastic, depending on its type. The prevalence of these three cell types is 50–80%, 5–25%, and 7–25%. In addition, the histological grades are low (grade 1), medium (grade 2), and high (grade 3 or 4), which are the tumor regions with the highest degeneration rates and the highest mitotic rates. Table 1 shows the different types of operating systems. In addition, it has been reported that 30% of well-differentiated chondroblasts or osteoblasts and OS usually respond poorly to chemotherapy. In addition, several studies have reported reduced metastasis-free survival in tumors with chondrocyte subtypes. It has also been reported that survival in high-grade OS is independent of the predominant cell type.^{27,29}

Cancer staging help determines the extent or likelihood of the tumor spreading throughout the body. It also provides a means of predicting the likely prognosis. As explained by Enneking, a good staging system should enable the physician to communicate the patient's condition, suggest a prognosis, guide surgical management, and suggest appropriate additional treatment.¹⁵ The two most commonly used surgical staging systems today for OS and malignant OS are the Enneking/MSTS system (Table 2) and AJCC (Table 3). Although there are slight differences between these two systems, most of the basic concepts are the same as they depend on tumor grade, size, and metastases.³⁰

Treatment

Local Control

1. Surgery - Limb-Sparing Procedure

Onco-surgery, which removes large areas of the tumor, is aimed at achieving complete resection of the disease. In this case, surgery can be done in two ways: limb-sparing and amputation. Amputation is an important therapeutic approach for cases of early OS. After ineffective adjuvant therapy, amputation is considered a necessary and effective alternative treatment for malignant bone tumors that can cause extensive cellular damage. For amputations, the osteotomy level should have a tumor-free margin of at least 5 cm. Most doctors consider the safety plane for an osteotomy to be 5 cm beyond the plane of the tumor. However, a reliable dimensional basis is required for determination based on X-ray, CT, and

MRI.³³

The goals of surgical treatment of OS have evolved from saving lives to maximizing the function of the affected limb. Limb-sparing is a surgical intervention to restore bone and joint function after extensive resection of malignant bone tumors of the extremities. The key to surgery is the selection of the right border. With the latest popularity of therapy limb-sparing comprehensive treatment combined with neoadjuvant chemotherapy, surgery limb-sparing is more widely used in clinical applications. 80-95% of patients with soft tissue sarcomas of the bones and extremities can undergo surgery limb-sparing.^{33,34}

Computer-assisted once-surgery are becoming increasingly important in the treatment of OS. Currently, there is no commercial platform that meets all the software and hardware requirements related to OS operation.³⁸

2. Radiotherapy

Local radiation therapy has been shown to have some benefit in patients who cannot be resected surgically or whose tumors remain at the edges of surgery and in patients with OS whose tumors are less responsive to chemotherapy. Preliminary results confirm that external beam radiation combined with systemic therapy may be an effective approach for local control and palliation. Following the use of effective induction chemotherapy in non-metastatic limb OS, Machak et al. regard radiation therapy as a reliable method of controlling localized disease and maintaining limb function.³³

A recent study confirmed that the combined application of ginseng polysaccharide (GPS) and ionizing radiation (IR) made OS cells sensitive to IR [85]. Although sensitizers may represent a breakthrough in radiotherapy, advances and improvements in radiotherapy technology and equipment are increasing long-term cancer survival. In the future, radiotherapy for OS is based on radiotherapy sensitization research combined with advanced techniques such as stereotactic radiosurgery, proton therapy heavy ion radiotherapy, and surgical treatment. and chemotherapy organically combined to achieve better treatment. Low dosage and high precision effect. Its role in comprehensive adjunctive limb-sparing therapy cannot be overlooked.³³

3. Cryosurgery

The use of liquid nitrogen as cryosurgery for osteosarcoma has been reported in previous studies. However, the use of cryosurgery as a method of reconstructive osteosarcoma in very young children has not been reported in previous studies. Cryosurgery is explained by applying liquid nitrogen into the tumor cavity or immersing the resected segment in liquid nitrogen. In this case,

curettage and drilling into the base and walls of the bone are performed to maximize contact between the liquid nitrogen and the deepest layers of the bone. Adequate contact with the tumor margins is important to ensure the delivery of extreme temperatures that destroy malignant cells. The efficacy of cryosurgery has been reported in 10 patients without local or systemic recurrence in all subjects and a functional score of 82.4%. Another study by Tsuchiya et al. with similar cryosurgery techniques showed excellent limb function in the majority of subjects and high rates of bone fusion. In this case, we found a radiology unit at 6 months follow-up with a musculoskeletal community tumor score of 76.6%. However, complications were reported in 25% of subjects with infection (10.5%), fracture (7.5%), and local recurrence (7.5%). Apart from the complications mentioned, cryosurgery can be an option for the biological reconstruction of osteosarcoma.³⁹

Systemic Control

1. Chemotherapy

Research on the effects of chemotherapy on OS began in the 1970s. At that time, chemotherapy was used as an adjunctive therapy after surgery to eliminate the formation of lesions and metastases that could not be removed completely by surgery alone. In the late 1970s, innovative preoperative chemotherapy was boldly and successfully applied in the clinic to eliminate tumor asymptomaticity before surgery, reduce the reaction zone around it, and create conditions suitable for limb-sparing surgery. This approach has become known as neoadjuvant chemotherapy.⁴⁰

The importance of neoadjuvant chemotherapy is to allow early systemic treatment that eliminates potential micro-metastases. Preoperative chemotherapy can be evaluated and postoperative chemotherapy can be guided based on the degree of tumor necrosis. Reduce tumor edema bands. Increase the limb salvage rate. This reduces the recurrence rate.⁴¹ This concept is widely accepted and widely used in clinical practice, with the gradual establishment of comprehensive limb-sparing therapy complementing neoadjuvant chemotherapy, limb-sparing surgery being the mainstay of OS, and OS leading to a significant 5-year survival rate.⁴²

2. Targeted Therapy

Given that genetic mutations are the most fundamental cause of OS, it is important to involve genetic research in OS prevention and treatment strategies. Gene therapy involves the introduction of normal or therapeutic genes into human target cells via vectors to correct genetic defects or provide a therapeutic effect sufficient to achieve a therapeutic

outcome. This is a medical method.³³

OS mainly focuses on tumor suppressor genes, suicide genes, combination gene therapy, antisense genes, immune genes, and anti-angiogenic genes. The p53, p16, p21, and Rb tumor suppressor genes are currently being tested for therapy. Of these, p53 has been studied in detail. These studies show that patients with OS frequently have mutations in p53.³³ Wu et al. noted that p53-expressed protein may be a prognostic biomarker for predicting overall survival from OS, further enhancing the status of p53 as an entry point for gene therapy in OS. I pay attention. leaves et al.²⁹ reported that overexpression of wild-type p53 sensitizes a multidrug-resistant OS cell line to chemotherapy, which may provide new clues for the resolution of chemotherapy resistance. I have. For suicide gene therapy, the thymidine kinase (TK)/propoxyguanosine (GCV) system is preferred. Zhang et al.⁴⁴

Based on combination gene therapy, the effect of other combination therapies is more significant, not only by creating a synergistic effect but also by reducing the side effects caused by the use of a single drug. Combining gene therapy with other therapies to treat OS patients is expected to be recognized as a useful approach for gene therapy in the future⁴⁶, especially genetically modified T-cell therapy. This has shown promise in preclinical studies. Gene therapy has made great strides in recent years and offers valuable prospects, but it is still in the experimental stage and far from having a true clinical application.

3. Immunotherapy

Immunotherapy is carried out to modulate the body's immune function which allows, among other things, the killing tumor cells, regulating and balancing the body's immune function, as well as differentiation and suppression of tumor growth. This therapeutic approach is important in adjuvant oncology because it provides specific and effective outcomes for cancer patients, especially by providing novel and effective treatments for sex enhancement of advanced, metastatic, and recurrent OS. As the most basic components of immunotherapy, cytokines regulate the activation, proliferation, and functional activity of immune cells.³³

Checkpoint inhibitors are also an interesting area of research. However, an increased understanding of tumor immunity has confirmed that tumor cells are poorly immunogenic and cannot be expressed strongly in the immune system. Therefore, the introduction and expression of immunogen-related molecules into tumor cells enhances the immunogenicity of tumor cells and provides strong immune stimulation of the immune system. This

line of thinking has led to the new topic of tumor immunotherapy. There is still a lot of work to be done, but it is hoped that immunotherapy will provide a breakthrough and revolutionize the treatment of OS.¹⁷

Conclusion

Osteosarcoma is a malignant tumor that arises in mesenchymal tissue. Advances in chemotherapy and surgery have made it possible to transform OS from a nearly universally fatal disease to one in which the majority of patients survive. Accurate and effective diagnosis, preoperative chemotherapy, surgical resection, postoperative chemotherapy, and lifelong surveillance are key components in the successful management of this complex and potentially fatal disease.

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Review Article

Functional Outcomes in the Management of ACL Rupture by ACL Reconstruction with Lateral Extra-articular Tenodesis Lemaire Procedure Versus MacIntosh Procedure: A Systematic Review

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Abstract

The purpose of this study was to systematically review the functional outcomes between lateral extraarticular tenodesis (LET) Modified Lemaire procedure and MacIntosh modified by Cocker-Arnold procedure other than ACL reconstruction (ACLR) alone in studies with high levels of evidence.

We performed a literature search for clinical studies comparing the LET Modified Lemaire procedure and MacIntosh modified by Cocker-Arnold procedure as an augmentation to ACLR with ACLR alone. The primary outcomes were the International Knee Documentation Committee (IKDC) score, the Lysholm score, and graft failures.

A systematic search on the literature was performed online from the inception dates to July 2022. Based on the screening of abstracts and titles, a total of 123 records were excluded. The authors independently based on the extracted full text. This selection process resulted in the final 6 articles for inclusion in the systematic review. The remaining 6 studies were eventually included, consisting of 2 randomized controlled trials, 2 retrospective studies and 2 prospective studies. ACLR with the LET provides better functional outcomes than ACLR alone, whereas between the two LET i.e. Lemaire and MacIntosh in the ACLR action do not give different functional outcomes.

ACLR with the LET provides better functional results than ACLR without the LET, the LET provides better rotational stability than ACLR alone, and also lower graft failures than ACLR alone. Meanwhile, between the two LET, namely the Lemaire and MacIntosh in ACLR, do not give different functional results because they can maintain rotational stability to reduce the incidence of graft failure and later will provide better functional outcomes.

Introduction

Despite a long history of differing surgical procedures, controlling anterolateral rotational laxity of the knee after anterior cruciate ligament (ACL) rupture remains a challenge. The results of a primary intraarticular anterior cruciate ligament reconstruction (ACLR) are excellent, with approximately 90% of patients achieving normal or near-normal knee function.

However, these results are not universal. Studies have reported 11%–30% recurrent and persistent instability.¹

Traditional, single-bundle anterior cruciate ligament reconstruction (ACLR) techniques have been demonstrated to provide good subjective results; however, multiple studies have shown that many patients continue to have complications related to the procedure. Failure of ACLR might be caused by anterolateral rotational instability due to the

inadequacy of the intraarticular graft to recreate normal knee kinematics. One of the proposed solutions is to use lateral-based soft-tissue reconstructive techniques in addition to ACLR.²

The structures that stabilize the lateral aspect of the knee are in a complex arrangement. Understanding the anatomy of this area may be crucial in determining whether any extra-articular reconstruction is likely to be desirable at the time of ACL reconstruction.³

David et al describe about advantage of the lateral extraarticular tenodesis (LET) procedure (1) Offers additional anterolateral rotary instability when used in conjunction with anterior cruciate ligament reconstruction. (2) Does not use soft tissue autografts that are commonly used for other knee ligament reconstructions. The disadvantage of the LET procedure is (1) Potentially overconstrains knee internal rotation. (2) Requires additional lateral incision and dissection.⁴

MacIntosh modified by Cocker-Arnold procedure. After the intraarticular reconstruction was fixed, the incision on the lateral side was extended to 10 to 12 cm in a hockey-stick fashion, extending from the Gerdy tubercle proximally to just inferior to the lateral epicondyle while the knee was flexed to 90°. The proximal extent of this incision parallels the midportion of the iliotibial tract. The fascia lata was exposed and incised along its fibers about 3 cm from the posterior border. With 1 cm of the iliotibial tract left intact posteriorly, a 1 cm-wide and 13-cm long strip of the iliotibial tract was detached proximally, leaving intact its distal attachment on the Gerdy tubercle. The lateral collateral ligament was identified, and the proximal part of the strip was passed under the ligament; the band was then reflected on itself and sutured under tension with periosteal absorbable stitches to the Gerdy tubercle while the tibia was held in maximal external rotation. Since we started using the described technique, we have always successfully used absorbable stitches (Vicryl) with no complication. Therefore, we consider their use suitable for the described procedure. The strip was also sutured to the fibular collateral ligament for additional stability. A combined reconstruction required an additional surgical time of 15 minutes.⁵

Modified Lemaire procedure. To begin, with the patient positioned supine and the knee in 90° of flexion, a lateral incision is performed beginning at the level of the femoral insertion of the lateral collateral ligament (LCL) and extended proximally for 5 cm. Dissection is taken through sub-cutaneous tissues to the ITB. A central 8-cm x 1-cm strip of ITB is harvested and left attached distally to Gerdy's tubercle. Care is taken to avoid the important Kaplan's fibers posteriorly. The ITB graft is then whipped and stitched. After the LCL is identified, the graft is passed deep (medial) to the LCL. Intraoperative fluoroscopy (mini c-arm) is recommended to confirm the positioning of a drill guide directed distally to the distal femoral physis

with an anterior trajectory (to avoid convergence with the femoral socket of the ACLR) and just proximal and posterior to the femoral insertion of the LCL. In 30° of flexion and neutral rotation, the ITB graft is secured with an all-suture anchor. We currently prefer fixation with an all-suture anchor; however, PEEK (polyether ether ketone) or biocomposite suture anchors also may be used at the surgeon's discretion. The ITB graft is then passed lateral to the LCL and secured to itself using a nonabsorbable suture to complete the tenodesis. The ITB donor defect is then closed using nonabsorbable sutures in an interrupted simple fashion to complete the LET.⁶

Methods

Search Strategy

Focused literature searches were primarily conducted using Google Scholar and PubMed/MEDLINE, from their inception dates to July 2022. To optimize the sensitivity and specificity of the search method and identify all research, use the keywords listed below in combination with Boolean "AND" and "OR" phrases. Search terms: "Anterior Cruciate Ligament Rupture", "Anterior Cruciate Ligament Reconstruction", "Lemaire procedure", "MacIntosh procedure", and "outcomes".

Inclusion Criteria

One reviewer screened the search results. Operative management of patients with ACL rupture and planned to undergo ACL reconstruction with arthroscopy and combination with lateral extra-articular tenodesis Modified Lemaire procedure or MacIntosh Modified by Cocker-Arnold procedure and evaluation functional outcome in this systematic review. Patients with ACLR with ALL reconstruction, pharmacological treatment, nutrition treatment, and physical therapy or rehabilitation which stands alone were excluded. Patient ACL rupture with concomitant PCL was excluded in this systematic review. Other than studies using English were excluded in this systematic review.

Quality Evaluation

This was done, and based on inclusion criteria the authors filtered eligible studies through titles and abstracts. Then, the authors screened the complete studies from all the studies that were collected. The author is looking for publications that are very relevant to be included in this research. The author also assessed the quality of the study.

Result

The electronic search returned 123 records, after removing duplicate results. Based on duplicate records, screening of abstracts and titles, a total of 117 records were excluded. The authors independently based on the extracted full text. This selection process resulted in the final 6 articles for inclusion in the systematic review

Study Component	Inclusion	Exclusion
Population	Patients aged >18 years or older with primary ACL rupture and planned to undergo ACL reconstruction with arthroscopy.	<ul style="list-style-type: none"> • Animal studies. • Revision cases of ACL reconstruction. • Concomitant PCL. • Underlying congenital condition or neoplasm.
Intervention and Comparison	ACL reconstruction with lateral extra-articular tenodesis (Modified Lemaire procedure, MacIntosh Modified by Cocker-Arnold procedure)	<ul style="list-style-type: none"> • ACLR with (ALL) reconstruction. • Pharmacologic treatment. • Nutrition treatment. • Physical therapy or rehabilitation which stands alone.
Control	ACL Reconstruction alone	
Outcome	Measures clinical outcomes including the IKDC score, Lysholm score, report of graft failure	<ul style="list-style-type: none"> • Study is ongoing, and no results have been reported. • Outcome measures not reported in completion. • Other than a study using English
Publication	Studies published in English Listed in PubMed or Google Scholar Archives	Proceedings, Presentations Abstracts, Editorials, Letters Duplicate publications of the same study Studies published in languages other than English
Study Design	Retrospective study Prospective study Randomized control trial	Case reports, review articles

Abbreviations: PICO, Population-Intervention-Comparison-Outcome

Table 1. PICO Table Describing Inclusion and Exclusion Criteria

and is depicted in Figure 1. The remaining 6 studies were eventually included, consisting of 2 randomized controlled trials, 2 retrospective studies and 2 prospective studies. The details of this study are listed in Table 2.

According to a study by Castoldi et al. (2020) they used the modified Lemaire procedure for lateral extraarticular tenodesis (LET). The research conducted with a total sample of 61 samples for the ACLR alone group and 60 samples for the ACLR group with lateral extraarticular tenodesis. Functional outcomes obtained from the 2 groups were followed up for 19.4 years (19–20.2 years) of follow-up for each group, for the IKDC score 81.1 (42.5–100) for the ACLR group alone, 82.4 (55.2–100) for the ACLR group with LET. Meanwhile, the Lysholm score was 86.6 (42–100) for the ACLR alone group, 90.3 (67–100) for the ACLR group with LET, as well as graft failure which was reported as 47.54% in the ACLR alone group, and 21.67% in the ACLR group with LET.⁷

Getgood et al. (2020) also explained in their research that were comparing 2 groups. The first group was ACLR alone and the second group was ACLR with modified Lemaire. From this study, the IKDC score for the first group was 86.6 ± 0.8, and for the second group 87.3 ± 0.8. The Lysholm score was not described in the study. As for graft failure, it obtained as much as 11.37% for the first group and 3.7% for the second group.⁸

Research conducted by Porter et al. (2020) also explained the same thing with the functional outcomes obtained from each group, namely the IKDC score with a value of 90.9 ± 10.7 for ACLR alone and 94.2 ± 11.2 for the ACLR group with the LET procedure. The Lysholm score was reported as 92.5 ± 4.8 for the ACLR alone group and 96.8 ± 8.0 for the ACLR group with LET. According to graft failure, it was reported that 14.8% occurred in ACLR alone and 0% in ACLR with LET. The LET procedure used in the study conducted by Porter et al. was MacIntosh modified by Cocker-Arnold.⁹

Rowan et al. (2019) also conducted a study using a prospective design study, using 171 total samples and followed up for 2 years. Lysholm score for the ACLR alone group was 90 (70–100) and for the ACLR group with LET procedure using Modified Lemaire was 98 (75–100) and 5.9% for graft failure for the ACLR group alone and 0% for the ACLR group with the Modified Lemaire procedure.¹⁰

Based on research by Ferretti et al. (2016) which compared 2 groups, namely the ACLR group alone with the ACLR group with the LET procedure (MacIntosh modified by Cocker-Arnold). In a study conducted by Ferretti et al, was followed up for 10 years and 5 months (121–128 months) for each group with a total sample of 140. From the evaluated functional outcome, the IKDC score was 93.77 ± 6.63 for

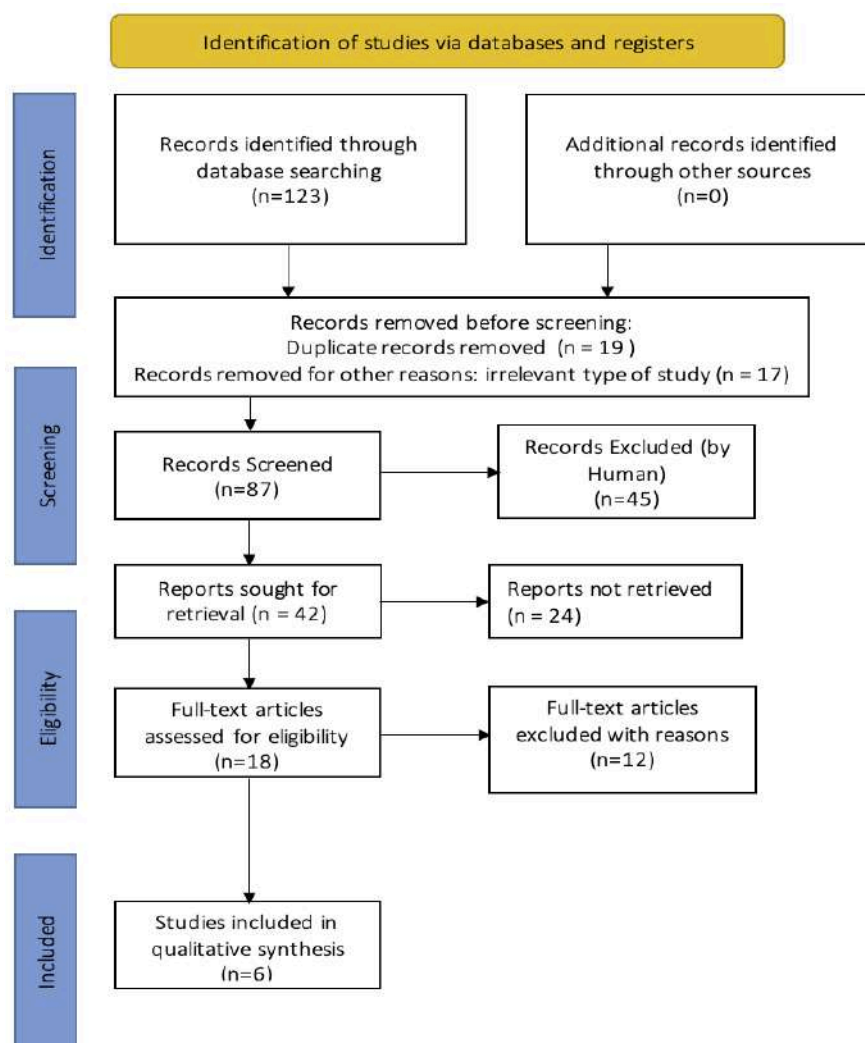


Figure 1. Flow chart showing article selection

the ACLR alone group and 96.19 ± 3.3 for the ACLR group with LET. Meanwhile, the Lysholm score was 95.46 ± 5.68 for the ACLR group alone and 96.24 ± 3.5 for the ACLR group with the LET procedure. From the graft evaluation, it was found that graft failure was 11.1% for the ACLR alone group and 0% for the ACLR group with the LET procedure.⁵

From the research conducted by Antonio et al. (2012) used a prospective study design comparing anterior cruciate ligament reconstruction (ACLR) alone with ACLR with lateral extraarticular tenodesis (LET) procedure. The LET procedure used is the MacIntosh modified by Cocker-Arnold. From the research conducted, the functional outcome of total samples was 55 patients, with an IKDC score of 87 ± 1.8 for the ACLR alone group, and 89 ± 1.5 for the ACLR group with LET. Meanwhile, the Lysholm score was 94.5 ± 6.65 for the ACLR group alone, and 95.8 ± 3.99 for the ACLR group with LET. The reported graft failure percentage was 6.2% for the ACLR alone group and 0% for the ACLR group with LET.¹¹

Discussion

Based on several studies that compared the ACLR procedure alone with the ACLR accompanied by the LET procedure, namely the Lemaire procedure and MacIntosh procedure, there was an increase in functional outcome between the ACLR alone group and the ACLR with the LET procedure assessed based on the IKDC score and Lysholm score, as well as the most graft failures, occurs in ACLR alone. Meanwhile, the Lemaire and MacIntosh procedure did not show any difference, they both produced better functional results compared to ACLR alone in ACL injury.

Residual instability, notch impingement, and graft re-tear in ACL-reconstructed knees is commonly associated with failure to return to sports. The residual pivot-shift phenomenon may lead to secondary meniscal injury or osteoarthritis development. Hence, controlling pivot shifts is one of the critical factors for improving outcomes after ACLR. The combined ACLR and LET reconstruction in patients with ACL injury is

No	Reference	Journal	Study Design	Level of Evidence
1.	Castoldi et al, 2020	The American Journal of Sports Medicine	Randomized Controlled Trial	II
2.	Getgood, et al, 2020	The American Journal of Sports Medicine	Randomized Controlled Trial	II
3.	Porter et al, 2020	The American Journal of Sports Medicine	Retrospective study	III
4.	Rowan et al, 2019	Archives of Orthopedic and Trauma Surgery; Springer	Prospective study	II
5.	Ferretti et al, 2016	Arthroscopy: The Journal of Arthroscopic and Related Surgery	Retrospective study	III

Table 2. Studies included in the analysis

Validity	Castoldi et al. (2020)	Getgood et al. (2020)	Porter et al. (2020)	Rowan et al. (2019)	Ferretti et al. (2016)	Antonio et al. (2012)
Same Population	●	●	●	●	●	●
Similar exposure	●	●	●	●	●	●
Exposure measurement	●	●	●	●	●	●
Confounding factors	●	●	●	●	●	●
Strategies to deal with confounding factors	●	●	●	●	●	●
Free of the outcome at the start	●	●	●	●	●	●
Outcome measurement	●	●	●	●	●	●
Follow up time	●	●	●	●	●	●
Follow up completeness	●	●	●	●	●	●
Strategies to address incomplete follow up	●	●	●	●	●	●
Statistical analysis	●	●	●	●	●	●

Note: Green, clearly stated; Blue, unclearly stated; Red, not stated.

Table 3. Eligibility Assessment of Included Studies

an effective and safe solution and leads to good functional outcomes with no increase in complications and aids in early return to preinjury activities with a surviving healthy graft. We recommend its application in indicated cases, especially when MRI documents ALL injuries.¹²

The most important finding of the present study is that the combination of LET. to ACLR is a safe and effective surgical option in young patients with ACL rupture. Clinical scores at follow-up were satisfactory in the study group, and 86% of patients could return to their pre-injury sports level. Furthermore, in this study, no case of graft failure occurred. The most common complication of ACLR in skeletally immature patients is graft failure, observed in up to 25% of patients undergoing ACLR. The absence of graft failure cases in

our series could be attributable to the combination of LET to ACLR. Indeed, extra-articular augmentation between the tibia and femur on the lateral side of the knee could prevent internal rotation of the tibia, stabilize the knee, and protect the reconstructed ligament.¹³

In their metanalysis, Rezende et al found no significant differences in functional outcome between ACL reconstruction with or without LET, though there was a clear reduction in high-grade pivot-shift test in the LET-treated groups. This observation is shared in a systematic review by Song et al, which noted that isolated ACL reconstruction is sufficient to handle only low-grade pivot shift. Dutton et al, found that, besides improving rotational control of the knee, LET, also reduced by more than 40% the stress of intra-articular reconstruction, which is especially useful in ACL revision. Noyes and Barber²¹ reported a significantly lower re-rupture rate when ACL reconstruction was combined with LET.¹⁴

The rationale of combining intra and extra-articular procedures in ACL reconstruction is to restrict the internal rotation of the reconstructed knee, thus providing more stability in the knee in the rotational axis and preventing the ACL graft from undergoing further excessive stress. Many studies have already investigated the role of such extra-articular procedures. Anderson et al, as well as Roth et al, showed no improvement with the addition of an extra-articular procedure. Completely different conclusions were shown by Lerat et al. and Noyes et al., which showed the results of two prospective studies with significantly better results in patients with an extra-articular procedure. In conclusion study Vadala et al., the combination of an extra-articular MacIntosh procedure modified by Cocker-Arnold with ACL reconstruction seems to significantly reduce the rotational instability of the knee.¹¹

David et al. also describe when performed in addition to an ACL reconstruction, LET procedures have been demonstrated to significantly reduce anterior tibial translation and anterolateral rotary instability in addition to reducing the force experienced by the graft when an anteriorly directed load was applied. This does come at the cost of over-constraint of the knee, with decreased tibial internal rotation across various flexion angles from 0° to 90°. However, persistent anterolateral rotary instability occurring after ACL reconstruction leads to poor patient outcomes and increased risk of graft failure; thus, LET procedures may be able to help improve patient outcomes when used as an adjunct to ACL reconstruction by helping to restore normal rotational stability.⁴

Finally, this study has several limitations: (1) The studies included are of level II and III evidence; (2) The heterogeneity of some analyses is high; (3) Due to the

No	Study (year)	LET Technique	LET Graft	ACL Technique	ACL Graft	Age		Gender		Sample		Mean follow up	
						ACL alone	ACL + LET	ACL alone	ACL + LET	ACL alone	ACL + LET	ACL alone	ACL + LET
1.	Castoldi et al. (2020)	Modified Lemaire	Gracilis	N/A	Bone patellar tendon bone graft	26 years (15–40 years)	26 years (15–40 years)	Male: 43(70%) Female: 18(30%)	Male: 47 (78%) Female: 13 (22%)	61	60	19.4 years (19–20.2 years) follow up	19.4 years (19–20.2 years) follow up
2.	Getgood et al. (2020)	Modified Lemaire	Iliotibial band	Various	Semitendinosus and/or gracilis.	26 years (15–40 years)	18.9 years (14–25 years)	Male: 151 (48%) Female: 161(52%)	Male: 151 (49%) Female: 155 (51%)	312	306	24 months follow up	24 months follow up
3.	Porter et al. (2020)	MacIntosh modified by Cocker-Arnold	Iliotibial band	Standard knee arthroscopy surgery	Doubled autologous hamstring tendon graft	22.3 ± 3.7 years	21.8 ± 4.1 years	Male: 12(44.4%) Female: 15(55.6%)	Male: 11 (39.2%) Female: 17 (60.8%)	27	28	2 years follow up	2 years follow up
4.	Rowan et al. (2019)	Modified Lemaire	Iliotibial band	Single bundle	Doubled gracilis and semitendinosus hamstring graft	29 years (15–56 years)	27 years (16–64 years)	Male: 67 (54%) Female: 58 (46%)	Male: 27 (59%) Female: 19 (41%)	125	46	2 years follow up	2 years follow up
5.	Ferretti et al. (2016)	MacIntosh modified by Cocker-Arnold	Iliotibial band	Single Bundle	Semitendinosus and gracilis	27.3 years (18–50 years)	25.7 years (18–46 years)	Male: 51 (71%) Female: 21 (29%)	Male: 56 (82%) Female: 12 (18%)	72	68	10 years 5 months (121–128 months) follow up	10 years 5 months (121–128 months) follow up
6.	Antonio et al. (2012)	MacIntosh modified by Cocker-Arnold	Iliotibial band	Anatomical Out-In technique,	Hamstring tendon graft	28 years (15–40 years)	27 years (15–40 years)	N/A	N/A	28	27	44.6 months (36–50) follow up	44.6 months (36–50) follow up

Abbreviations: LET, Lateral Extraarticular Tenodesis; ACLR, Anterior Cruciate Ligament Reconstruction; N/A, Not Available

Table 4. Sample characteristics of included studies

No	Study (year)	IKDC			Lysholm			Graft failure (%)		
		ACLR alone	ACLR + Modified Lemaire Technique	ACLR + MacIntosh Modified by Cocker-Arnold Technique	ACLR alone	ACLR + Modified Lemaire Technique	ACLR + MacIntosh Modified by Cocker-Arnold Technique	ACLR alone	ACLR + Modified Lemaire Technique	ACLR + MacIntosh Modified by Cocker-Arnold Technique
1.	Castoldi et al. (2020)	81.1 (42.5–100)	82.4 (55.2–100)	N/A	86.6 (42–100)	90.3 (67–100)	N/A	47.54%	21.67%	N/A
2.	Getgood et al. (2020)	86.6 ± 0.8	87.3 ± 0.8	N/A	N/A	N/A	N/A	11,37%	3,7%	N/A
3.	Porter et al. (2020)	90.9 ± 10.7	N/A	94.2 ± 11.2	92.5 ± 4.8	N/A	96.8 ± 8.0	14,8%	N/A	0%
4.	Rowan et al. (2019)	N/A	N/A	N/A	90 (70–100)	98 (75–100)	N/A	5,9%	0%	N/A
5.	Ferretti et al. (2016)	93.77 ± 6.63	N/A	96.19 ± 3.3	95.46 ± 5.68	N/A	96.24 ± 3.5	11,1%	NA	0%
6.	Antonio et al, (2012)	87 ± 1.8	N/A	89 ± 1.5	94.5 ± 6.65	NA	95.8 ± 3.99	6,2%	NA	0%

Abbreviations: IKDC, International Knee Documentation Committee; ACLR, Anterior Cruciate Ligament Reconstruction; N/A, Not Available

Table 5. Outcomes discussed in included studies

scarcity of studies, single and multilevel pathologies were all included into the analysis, where this may cause bias in the overall analysis; (4) there is no study comparison between Lemaire and MacIntosh procedure the study just comparison between ACLR alone with ACLR with LET procedure (Lemaire and MacIntosh procedure). However, to our knowledge, this study is the first to formulate a systematic review on this matter thoroughly. It is hoped that this study might be beneficial as a guideline in choosing appropriate methods of treatment for patients with anterior cruciate ligament rupture, while further inspiring other researchers to conduct well-designed trials with a bigger number of samples and performing subgroup analysis.

Conclusion

ACLR with the LET procedure provides better functional results than ACLR without the LET procedure, the LET procedure provides better rotational stability than ACLR alone and also lower graft failures than ACLR alone. Meanwhile, between the two LET procedures, namely the Lemaire and MacIntosh procedures in ACL reconstruction, they do not give different functional results because they can maintain rotational stability to reduce the incidence of graft failure and later will provide better functional outcomes.

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Review Article

Comparison of Peroneus Longus Tendon Autograft and Hamstring Tendon Autograft for Anterior Cruciate Ligament Reconstruction: A Systematic Review

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Abstract

Purpose: The aim of this study is to compare the outcomes between peroneus longus tendon autograft versus hamstring tendon autograft for anterior cruciate ligament reconstruction such as International Knee Documentation Committee (IKDC), Lysholm score, Modified Cincinnati score, Tegner activity scale, and donor site morbidity.

Methods: This systematic review uses Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Multiple databases were searched for studies that compared functional outcomes of ACL reconstruction with peroneus longus tendon autograft versus hamstring tendon autografts with a minimum 1 year follow-up.

Result: We analyzed 5 studies that included direct comparison of the peroneus longus tendon (106 patients) versus the hamstring tendon (137 patients). There was no significant difference comparison of the outcome such as Modified Cincinnati, Tegner scale activity, and Lysholm score. On IKDC score, 1 study reported there was a significant difference between peroneus longus tendon autograft 87.4 (67.8-100) versus hamstring tendon autograft 78.2 (35.6-95.6) with $p=0$. Two studies reported donor site morbidity mostly occurred in hamstring tendon autograft (11.4 ± 3.6) were higher than peroneus longus tendon (2.5 ± 0.5) ($P=0.002$). The knee flexion of donor site morbidity in the peroneus longus tendon group (41.97 ± 1.98) is higher than the hamstring tendon group (40.65 ± 1.74) ($P=0.02$).

Conclusion: This study concluded there was no significant difference of comparison between the peroneus longus group and the hamstring group after ACL reconstruction but the IKDC score after a reconstruction could be affected by gender and graft size. Donor site morbidity most occurred in hamstring group than peroneus longus group after ACL reconstruction

Introduction

The anterior cruciate ligament (ACL) is a ligament that functions to stabilize the knee joint. The anterior cruciate ligament consists of two bundles, the posterolateral and the anteromedial bundle.^{1,2,3,4} Anterior cruciate ligament tears are the most common ligament injuries.^{1,5,6} In the United States the incidence of anterior cruciate ligament tears is around 100,000-

200,000 per year and about 53% occur in athletes, especially football players.⁷

Anterior cruciate ligament tears consist of partial and complete tears (appley, netter). Partial tears usually cause symptoms of unlimited joint movement but are painful, while complete tears complain of limited joint movement without pain. Apart from that, other symptoms that can arise from an ACL tear are hemarthrosis, a sound popping as a tissue is snapped,

and swelling around the joint is heard. The typical physical examination of an ACL tear is positive on the Lachman test and anterior drawer test.^{3,5,8}

One of the surgical procedures that can be performed on an ACL tear is anterior cruciate ligament reconstruction (ACLR). The hamstring tendon or patella tendon is the most frequently used graft method for ACLR because the hamstring tendon is easy to harvest with minimal donor site morbidity.^{9,10} Several recent cases reported that the peroneus longus tendon is used as the main choice of autograft in ACL reconstruction and is often used in several orthopedic procedures because it has good outcome results with minimal donor site morbidity.^{11,12}

The purpose of this study was to compare the outcomes between the peroneus longus tendon and hamstring tendon as autografts in ACL reconstruction by looking at several indicators such as the International Knee Documentation Committee (IKDC), Modified Cincinnati, Lysholm score, Tegner activity scale, and donor site morbidity.

Methods

Search Strategy

This study was designed with a systematic review. We evaluated and interpreted the qualified studies using the Preferred Reporting Items for Systematic

Reviews and Meta-Analysis (PRISMA). A literature search was performed comprehensively to gather a full-length, peer-reviewed paper in English on the evaluation of Peroneus Longus Tendon vs Hamstring Tendon on ACL reconstruction. The literature was searched through PubMed, Google Scholar, Science Direct, and Cochrane Library using Boolean operators with the following keywords:

- "Anterior Cruciate Ligament Reconstruction" or "ACL Reconstruction"
- "PLT" or "Autograft" or "Peroneus Longus Tendon" or "HT" or "Hamstring Tendon" or "Groups" and
- "Randomized Controlled Trial" or "Prospective Cohort" or "Retrospective Cohort"

We screened the literature to report relevant results based on inclusion and exclusion criteria which were downloaded full articles that met the criteria to be evaluated for quality assessment and underwent data extraction. A total of 1074 studies were obtained upon executing the search strategy, 910 were excluded based on duplication and 746 were excluded based on title screening. Further 145 articles were excluded after reading the abstract. The full text of the remaining 19 articles was reviewed. Out of these, 14 articles were excluded upon full-text review. The final number of included studies in this systematic review was 5 studies (Figure 1).

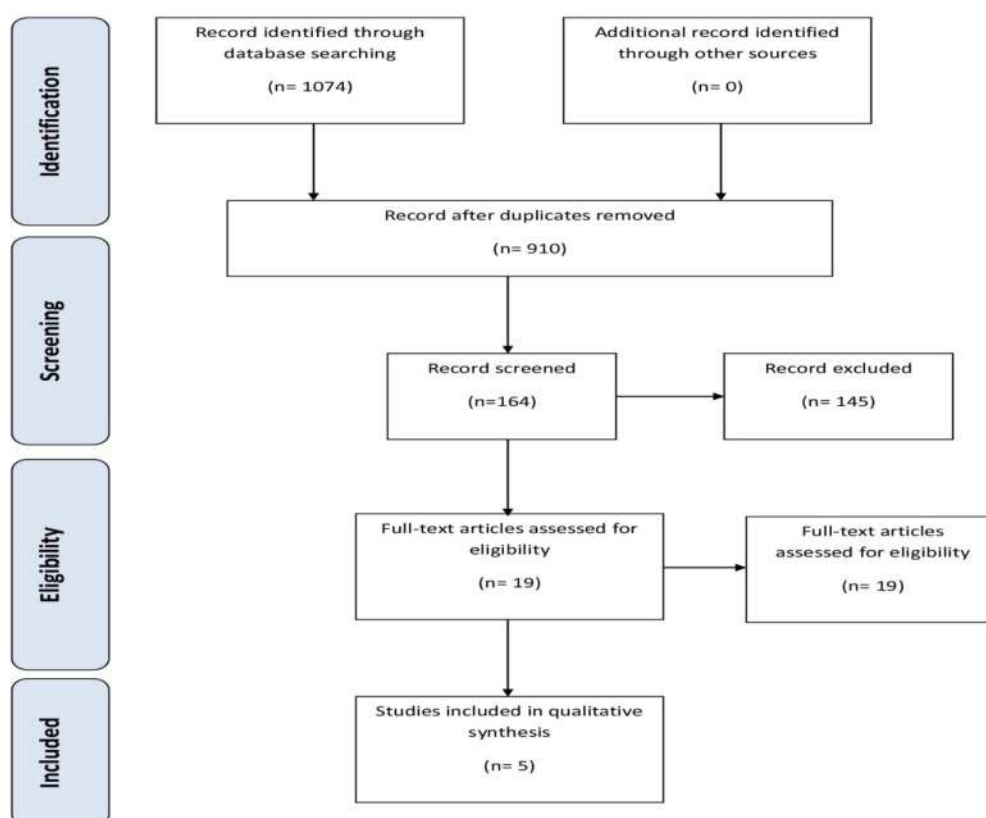


Figure 1. The diagram flow of PRISMA

Inclusion Criteria

The author uses a logic grid method with the PICO approach to search for suitable keywords. Any studies that evaluated peroneus longus tendon vs hamstring tendon in ACL reconstruction published in English were included in this review. The clinical outcomes were assessed by the subjective International Knee Documentation Committee (IKDC) score, Modified Cincinnati score, Lysholm score, Tegner, and donor site morbidity. Due to a limited number of research comparing both procedures, there was no limitation in patient demographics. Any study that was not in English was excluded.

Quality Evaluation

The class of evidence in each study was categorized into class I, II, III, and IV, each for good quality RCT, moderate to poor quality RCT and cohort study, moderate to poor quality cohorts and case-control studies and case series, respectively. Risk of bias assessed using the Cochrane Risk of Bias Tool: i) random sequencing, ii) allocation concealment, iii) blinding of participants and personnel, iv) blinding of outcome assessment, v) incomplete outcome data, vi) selective reporting, and vii) other biases (Figure 2). Then, from these components, we label them into three groups: low-risk, moderate, and high-risk bias. A total of 5 studies have the low-quality risk of bias.

Result

Key characteristics of the included studies and their level of evidence are depicted in Tables 1 and 2. Among these five studies, one is retrospective cohort study, two are prospective cohort studies and two are

randomized control trials. A total of 243 patients from five studies were included, with 106 patients undergoing peroneus longus tendon autograft and the rest 137 patients having hamstring tendon autograft, as shown in Table 2. The summary of outcomes assessed and the outcomes in each study are presented in Table 3 and 4, respectively. The outcome was assessed by IKDC, Modified Cincinnati score, Lysholm score, Tegner activity scale, and donor site morbidity.

Discussion

The ACL is one of the most common injuries to the knee. The hamstring tendon has recently been known as a frequently used graft method for ACLR. Several studies have confirmed that the peroneus longus tendon graft can be used as an alternative graft in ACL reconstruction.

IKDC scores were obtained in 4 studies conducted by Rhatomy S., et al, Gunadham U., et al, Seed U., et al and Shi F et al. There was no significant results were obtained in 3 studies and significant results were obtained in 1 study. Results that were not significant on the IKDC score were obtained in the study of Rhatomy S., et al on the peroneus longus group and hamstring group with mean 92.5 ± 6.2 and 88.8 ± 9.7 ($P > 0.05$). Nonsignificant results were also found in a study conducted by Saeed., et al with a result of 91.4 ± 1 in the peroneus longus group and 92.7 ± 3 in the hamstring group ($P > 0.05$). In a study conducted by Shi., et al, the results were not significant in IKDC after 24 months with a mean of 90.13 ± 3.01 in the peroneus longus group and 89.22 ± 3.83 for the hamstring group ($P = 0.4298$). Meanwhile, a study conducted by

	Vijay 2022	Shi 2017	Seed 2021	Rhatomy 2019	Gunadham 2022	
	?	?	?	+	+	Random sequence generation (selection bias)
	?	+	+	?	+	Allocation concealment (selection bias)
	+	+	+	+	+	Blinding of participants and personnel (performance bias)
	?	?	?	?	?	Blinding of outcome assessment (detection bias)
	?	?	?	+	?	Incomplete outcome data (attrition bias)
	+	+	+	+	+	Selective reporting (reporting bias)
	?	-	-	?	-	Other bias

Figure 2. Risk of Bias Assessment using Cochrane Risk of BIAS tools

No.	Reference	Year	Country	Journal	Study design	Level of evidence
1.	Rhatomy S., et al	2019	Indonesia	Knee surgery, Sports Traumatology, Arthroscopy	Prospective Cohort	II
2.	Gunadham U., et al	2022	Thailand	Journal of Orthopaedics, Trauma, and Rehabilitation	Retrospective Cohort	II
3.	Vijay C., et al	2022	India	Journal of Orthopaedics, Trauma, and Rehabilitation	Prospective cohort	II
4.	Seed U., et al	2021	Pakistan	Journal of Pakistan Orthopedic Association	RCT	I
5.	Shi F., et al	2017	China	The Journal of Knee Surgery	RCT	I

Table 1. List of included studies

No	Reference	Total Sample	Mean age (Age range in a year)	Male	Female
1.	Rhatomy S., et al, 2019	52 PL: 24 HT: 28	PL: 23.4±8.1 HT: 26.4 ± 8.6	44	8
2.	Gunadham U., et al, 2022	52 PL: 13 HT: 39	PL: 27.6 ± 9.4 HT: 31.1 ± 10.7	48	4
3.	Vijay C., et al, 2022	45 PL: 23 HT: 22	PL: 33.57 ± 9.54 HT: 31.82 ± 9.62	35	10
4.	Seed U., et al, 2021	56 PL: 28 HT: 28	PL: 39.4±6 HT: 39.6±2	53	3
5.	Shi F., et al, 2017	38 PL: 18 HT: 20	PL: 42 (19-58) HT: 40 (19-58)	N/A	N/A

Table 2. Characteristic Patient of included studies

No	Reference	Study Comparison	Follow-up duration (Year)	Outcome
1.	Rhatomy S., et al, 2019	Peroneus Longus Tendon versus Hamstring Tendon	1 year	IKDC, Modified Cincinnati, Donor site morbidity, Lysholm score
2.	Gunadham U., et al, 2022	Anterior Half Peroneus Longus Tendon versus Hamstring Tendon	3 year	IKDC, Tegner activity scale
3.	Vijay C., et al, 2022	Peroneus Longus Tendon versus Hamstring Tendon	1 Year	Modified Cincinnati, Lysholm score, Donor site morbidity (knee flexion and knee extension)
4.	Saeed U., et al, 2021	Peroneus Longus Tendon versus Hamstring Tendon	1 year	IKDC, Lysholm score
5.	Shi F., et al, 2017	Peroneus Longus Tendon versus Hamstring Tendon	2 year	Tegner activity scale, IKDC, Lysholm score

Table 3. Summary of outcome

No.	Reference	Outcome Measure			
		IKDC	Modified Cincinnati	Donor site morbidity	Lysholm score
1.	Rhatomy S., et al, 2019	PL: 92.5 ± 6.2 HT: 88.8 ± 9.7	PL: 92.7 ± 5.9 HT: 88.1 ± 8.5	PL: 2.5 ± 0.5 HT: 11.4 ± 3.6	PL: 94.9 ± 5.6 HT: 93.1 ± 7.3
	P Value	P>0.05	P>0.05	P=0.02	P>0.05
No.	Reference	Outcome Measure			
		IKDC	Tegner activity scale		
2.	Gunadham U., et al, 2022	PL: 78.2 (35.6-96.6) HT: 87.4 (67.8-100)	PL: 92.7 ± 5.9 HT: 88.1 ± 8.5		
	P Value	P=0.015		P=0.157	
No.	Reference	Outcome Measure			
		Modified Cincinnati	Lysholm score	Donor site morbidity	
3	Vijay C., et al, 2022	PL: 89.83 ± 3.47 HT: 86.45 ±3.31	PL: 88.39 ± 4.60 HT: 86.55 ± 2.74	Knee flexion PL: 41.97 ± 1.98 HT: 40.65 ± 1.74	Knee extension PL: 51.37 ±3.41 HT: 51.92 ±2.47
	P Value	P=0.002	P=0.1	P: 0.02	P: 0.5
No.	Reference	Outcome Measure			
		Tegner-Lysholm		IKDC	
4.	Saeed U., et al	PL: 92.2 ± 2.5 HT: 91.4 ±1.7		PL: 91.4 ± 1 HT: 92.7 ± 3	
	P Value	P>0.05		P>0.05	
No.	Reference	Outcome Measure			
		Tegner	IKDC	Lysholm	
5.	Shi F., et al, 2017	PL: 5 ± 0.89 HT: 6 ± 0.12	PL: 90.13 ± 3.01 HT: 89.22 ± 3.83	PL: 94 ± 6.81 HT: 93 ± 5.22	
	P Value	P=0.41	P=0.429	P=0.427	

Table 4. Characteristics of Outcome Studies

Gunadham showed significant results in which hamstring group higher than the peroneus longus group with mean 87.4 and 78.2 ($p<0.05$) but there was significant factors that affected postoperative IKDC scores such as graft type and gender because smaller graft size which less than 8 mm associated with re-rupture after ACL reconstruction that was reported femoral graft size 8.1 ± 0.6 mm in hamstring group larger than peroneus longus group is 7.6 ± 0.6 mm ($P=0.023$) and tibial graft size in hamstring tendon group is 8.1 ± 0.6 mm larger than 7.8 ± 0.8 mm in peroneus longus tendon group ($P=0.0006$). Females were shorter and had a smaller graft size than males with p -value is 0.009.^{9,11,13,14}

The modified Cincinnati score was only done by Rhatomy, et al. The modified Cincinnati score was not significant with a mean of 92.7 ± 5.9 for the peroneus longus tendon and 88.1 ± 8.5 for the hamstring tendon ($P>0.05$).⁷

The Lysholm score that compared the peroneus longus tendon and hamstring tendon after ACL reconstruction was obtained in four studies conducted by Rhatomy, et al, Vijay C., et al, Saeed U., et al, and Shi F., et al had a non significant result with $P>0.05$.^{11,13,14,15}

The donor site morbidity score was obtained in 2 studies conducted by Rhatomy, et al and Vijay C., et al. Rhatomy, et al explained that thigh hypotrophy, hypoesthesia, or anaesthesia most occurs in the hamstring tendon group and there was a significant result of donor site morbidity when used hamstring tendon with a mean was 11.4 ± 3.6 were higher than peroneus longus tendon was 2.5 ± 0.5 ($P=0.002$). That

study also reported an excellent result after harvesting peroneus longus tendon namely AOFAS was 97.3 ± 4.2 (range 88–100) and FADI score was 98 ± 3.4 (85.6–100) because the peroneus brevis is still intact in the donor's ankle for maintain eversion function of the ankle. The study conducted by Vijay C., et al explained the strength of knee flexion after 1 year of follow up was reduced in the hamstring tendon group than normal contralateral knee because the hamstring tendon had to contribute as component for normal knee flexion. Meanwhile, there was normal strength of knee flexion in the peroneus longus tendon group but instead improved after one year follow up which donor site morbidity of knee flexion with a mean 41.97 ± 1.98 in the peroneus longus tendon group higher than hamstring tendon group with mean 40.65 ± 1.74 ($P=0.02$). There was no difference in the strength of plantar flexion and eversion at the donor side ankle compared with normal contralateral ankle after 1 year follow-up. That study also reported 27% of patients had knee pain in the hamstring group but there was no patients who had ankle pain, numbness and limitation of movement at the ankle joint in the peroneus longus group with AOFAS had an excellent improvement after 1 year with mean 96.43 ± 3.13 .^{13,15}

The Tegner activity scale showed non-significant results which compared the peroneus longus tendon and hamstring tendon after ACL reconstruction conducted by Gundham U., et al and Shi F., et al with 0.157 and 0.41 respectively with $P>0.05$.^{9,11}

Conclusion

ACL tears are one of the most common ligament injuries in orthopedics. The autograft method for ACL reconstruction can be used such as hamstring tendon autograft or peroneus longus tendon autograft. In this systematic review, we reviewed several studies that used the two autograft methods and focused on functional outcomes. We concluded that the IKDC score after ACL reconstruction with hamstring tendon and peroneus longus tendon had an equally excellent result but some factors affected post operative IKDC score such as graft size and gender. Meanwhile, peroneus longus tendon autograft showed better donor site morbidity than hamstring tendon for ACL reconstruction.

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Literature Review

Principles Treatment Of Septic Arthritis Of The Knee: A Brief Review

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Septic arthritis is an emergency condition in which infection occurs in the synovial joints, resulting in the formation of pus in the synovial spaces. The incidence of septic arthritis increases in patients with an increased risk such as rheumatoid arthritis. The etiology of septic arthritis is mainly bacterial. Risk factors include iatrogenic procedures (surgery, implant placement, joint puncture) and systemic conditions (diabetes mellitus, rheumatoid arthritis receiving immunosuppressants, etc). Pathophysiology of septic arthritis is due to blood flow stasis in metaphyseal areas especially in children and intraarticular minimal blood circulation. Clinical pictures include sudden onset of fever, malaise, localized pain in the infected joint, joint swelling, and reduced range of motion. Examination for septic arthritis is a physical examination carried out are inspection (see), palpation (touch), and movement. supporting examinations include bloteststest, PCR, radiological and joint fluid tests. Treatments include non-pharmacological such as rest and physical therapy, pharmacological the form of antibiotics, and surgical therapy such as drainage incision. This study is a brief review of the current Principles Treatment Of Septic Arthritis Of The Knee. The reference to this review was taken from the latest journal up to 5 years and the latest book up to 10 years.

Background

Septic arthritis (also known as pyogenic arthritis or suppurative arthritis) is an emergency condition in which infection occurs in the synovial joints, resulting in the formation of pus in the synovial spaces.¹ The etiology of septic arthritis is mainly bacterial, other etiologies are fungi and viruses. Septic arthritis due to bacterial infection is a serious disease that rapidly destroys the articular hyaline cartilage and irreversible loss of joint function. Early diagnosis followed by appropriate therapy can prevent joint damage and joint deformity.¹

The incidence of septic arthritis in the general population varies from 2-10 cases per 100,000 people per year.² This incidence increases in patients with an increased risk such as rheumatoid arthritis 28-38 cases

per 100,000 per year, patients with joint prostheses 40-68 cases/100,000/year (30-70%). The peak incidence in the age group was children aged less than 5 years (5 per 100,000/year) and adults aged more than 64 years (8.4 cases/100,000 population/year). Most septic arthritis occurs in a single joint, whereas polyarticular involvement occurs in 10-15% of cases. The knee joint is the most commonly affected joint at 48-56%, followed by the hip joint at 16-21%, and the ankle at 8%.¹

Patients with acute septic arthritis are characterized by severe joint pain, joint swelling, stiffness, and impaired function, in addition to various other systemic symptoms such as fever and general weakness. The knee joint is subject to frequent and usually indolent monoarthritis (See Figure 1). Several risk factors include; knee and hip prosthesis with skin infection, skin infection without prosthesis, hip and



Figure 1. The Difference Between a Healthy Knee Joint And a Septic Arthritis Knee Joint

knee prosthesis without knee and skin infection, age more than 80 years, diabetes mellitus, rheumatoid arthritis receiving immunosuppressive treatment, and joint surgery.³ In the Philippines it was reported that Systemic Lupus Erythematosus (SLE) patients were the fifth-order risk factor for septic arthritis.⁴

Septic arthritis is closely related to systemic infection because it is difficult for germs to enter directly intra-articularly if not through the spread of hematogenous bacteria or direct inoculation due to intra-articular injection. Systemic infections originate from wounds around the joints or infections in other organs. Most AS is caused by a bacterial infection. The main sources of infection are infections of the tissues around the joints, and bacteremia originating from infections of the respiratory, gastrointestinal, and urinary tracts. Germs that are often found are; *Staphylococcus aureus* and *Streptococci*. In all age groups, 80% of cases are caused by aerobic Gram-positives (60% *Staphylococcus aureus*, 15% β -hemolytic *Streptococci*, 5% *Streptococcus Pneumonia*), and approximately 20% of cases are caused by Gram-negative anaerobes.²

Types of Septic Arthritis

Several joint disorders that need to be considered as a differential diagnosis of septic arthritis such as infection in previously affected joints, crystal-induced arthritis, reactive arthritis, traumatic arthritis, and viral arthritis.⁵

1. Crystal-induced arthritis

Gout and pseudogout mimic the signs and symptoms of septic arthritis. So that the joint fluid must be examined using a polarized light microscope for the presence of negative birefringent crystals (uric acid) or positive birefringence (calcium pyrophosphate dihyd-

rate) to rule out crystal disease in the joints. However, it should be remembered that there have been reports of concomitant arthritis with crystal-induced joint disease.²

2. Reactive arthritis

The existence of a joint inflammatory response to the presence of a bacterial infection process outside the joint is known as reactive arthritis. Often the patient has a history of infections in the distal parts such as the gastrointestinal tract (eg *Shigella* spp., *Salmonella* spp., *Campylobacter* spp., or *Yersinia* spp.), genitourinary tract (eg chlamydia and mycoplasma), and respiratory tract (eg *Streptococcus pyogenes*). The joint is inflamed but sterile. The PCR examination detected microbial antigens in the joints. The presence of these microbial antigens reflects the natural filtering response of the synovium and increasing numbers of these bacterial antigens will stimulate inflammation. Patients also often experience enteropathies or uveitis, skin lesions, or mucous membranes.²

Pre-existing joint infection. Patients with underlying chronic joint diseases such as rheumatoid arthritis, osteoarthritis, and other connective tissue diseases experience flares and give a picture resembling septic arthritis or have an infection that gives a poor prognosis because there is often a delay in the diagnosis of septic arthritis. Often the patient has no fever and an indolent clinical picture. Thus the diagnosis of septic arthritis should always be considered if there is a sudden inflammation of one or both joints in this patient.²

3. Traumatic arthritis

Traumatic arthritis is arthritis caused by trauma either blunt trauma, penetration, or repeated trauma or trauma from inappropriate movement of the joints which in turn causes avascular necrosis. Avascular necrosis occurs due to the cessation of blood flow to the femoral head and then the bones become brittle. The surrounding cartilage becomes damaged and causes complaints and symptoms in the form of swelling, pain, joint instability, and internal bleeding. The joint fluid analysis found a lot of red blood cells.²

4. Viral arthritis

Patients with viral arthritis are usually manifested by polyarthritis generally involving symmetrical small joints, fever, lymphadenopathy, and a characteristic rash. On examination of the joint fluid, there were many mononuclear cells and normal glucose levels.²

Pathogenesis

The pathogenesis of septic arthritis is multifactorial and depends on the interaction of the bacterial pathogen and the host immune response. The processes that occur in natural joints can be divided into three stages: bacterial colonization, infection, and induction of a host inflammatory response.⁶

1) Bacterial colonization

The tissue tropism of bacteria is very important for the occurrence of joint infection. *S. aureus* has a variety of receptors (adhesins) that mediate effective adhesion to a variety of joint tissues. These adhesins are tightly regulated by genetic factors, including accessory gene regulators (*agr*), staphylococcal accessory regulators (SAR), and sortase A.⁹

2) Bacterial virulence factor

Apart from adhesin, other materials of the bacterial cell wall are peptidoglycan and polysaccharide microcapsules which play a role in regulating the virulence of *S. aureus* through their influence on opsonization and phagocytosis. Microcapsules (thin capsules) are important at the start of bacterial colonization in the joint space which allows staphylococcal adhesin factors to bind to host proteins and further capsule production will be increased to form thicker capsules that are more resistant to host immune clearance. So the role of microcapsules here is resistance to phagocytosis and opsonization and allows bacteria to survive intracellularly.⁶

3) Host immune response

Once colonized in the joint space, bacteria rapidly proliferate and activate an acute inflammatory response. Synovial cells initially release pro-inflammatory cytokines including interleukin-1 β (IL-1 β), and IL6. These cytokines activate the release of acute-phase proteins from the liver and also activate the complement system.⁷

In septic arthritis organisms could enter joints through *direct inoculation*, via deployment from network periarticular or through Genre blood which is the route infection most common. Normal joints have component protective to prevent the process of infection, namely: cells synovial own ability to phagocytize and fluid synovial own ability bactericidal.⁸

In rheumatoid arthritis and SLE disease occur decline function immune the Bacteria could enter the room joints through several method that is, entering through the operating process are joint, through action aspirations joints, injections corticosteroids, or other traumas. Successful bacteria enter the cavity joints in a few hours raising reaction inflammation of the membranes synovial form hyperplasia and proliferation and occur release factors inflammation as *cytokines* and *proteases* that cause degradation from cartilage joints (See Figure 2).⁶

In Rheumatoid arthritis has happened to damage joints, this makes it easy to happen something infection membrane synovial, in joints, this happens neovascularization and occur enhancement factor appearance later adhesion causing happening bacteremia and continued Becomes infection of joints. The consequence of infection joints is damage to

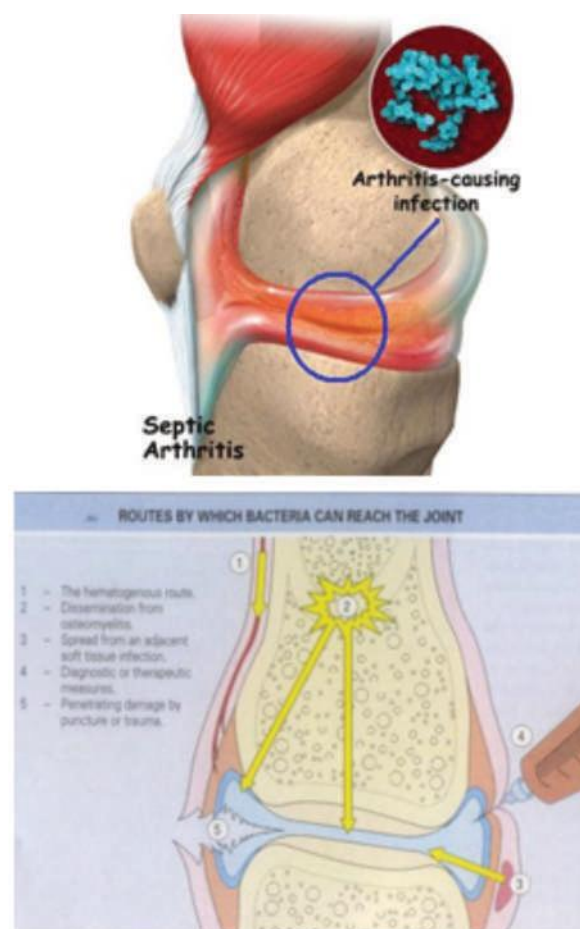


Figure 2. Pathogenesis of Septic Arthritis of The Knee

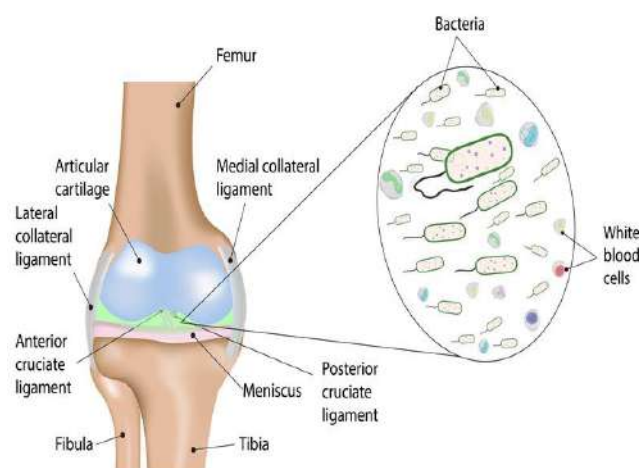


Figure 3. Septic Arthritis of The Knee

articular cartilage. On *S aureus* chondrocyte proteases germs that could react with later host polymorphonuclear leukocytes activate synthesis cytokines and various product inflammation other causes hydrolysis from collagen and proteoglycans.⁹

In infection Due to *N. gonorrhea* there is an influx of white blood cells into the joint causing only minimal joint damage compared to *S aureus*. then cause

interference with the flow of blood vessels and cause aseptic necrosis of the bone. This breakdown process could happen 3 days early in patients who experience infected joints without treatment.⁶

Viral infection can happen through method invasion direct (rubella) or through antibody-antigen product complex for example, in hepatitis B virus infection, *parvovirus B19* and *lymphocytic choriomeningitis viruses*. In addition, septic arthritis can also occur due to local processes other, most often in the gastrointestinal, with germs most common namely: *Salmonella enteritidis*, *Salmonella typhimurium*, *Yersinia enterocolitica*, *Campylobacter jejuni*, *Clostridium difficile*, *Shigella sonnei*, *Entamoeba histolytica*, *Cryptosporidium*. The most common second infection on genitourinary is *Chlamydia trachomatis* (See Figure 3).⁹

The morbidity that can occur is in the form of joint dysfunction and the incidence of mortality depends on the causative agent, in N gonorrhea the mortality rate is low, whereas in A aureus it can reach 50%. 56% occur in men, 45% of septic arthritis occurs over the age of 65.⁶

Clinical Symptoms

The classic symptoms of septic arthritis are sudden onset of fever, malaise, localized pain in the infected joint, joint swelling, and reduced range of motion. Several patients only complain of mild fever. Fever is reported in 60-80% of cases, usually mild fever and high fever occurs in 30-40% of cases up to more than 39 0C. Pain in septic arthritis is typically severe and occurs at rest as well as with active or passive movement.¹⁰

In addition, a history of rheumatoid arthritis, a history of injections in the joint area, and a history of diarrhea should be explored. Are there extra-articular symptoms, a history of intravenous drug use, or a history of blood vessel catheterization? Is there a history of venereal diseases, are there other diseases that cause a decrease in the immune system such as liver disease, diabetes mellitus lymphoma, and use of immunosuppressive drugs?⁴

The clinical symptoms of septic arthritis in non-gonococcal infections are sudden onset of joint swelling, feeling warm and very painful, most commonly occurring in the knee joint (50% of cases), whereas in children it most often occurs in the hip joint, the hip joint is usually in the position of flexion and external rotation and is very painful when moved. Approximately 10-20% of polyarticular infection occurs, usually 2 or 3 joints. Polyarticular septic arthritis usually occurs in patients with rheumatoid arthritis, patients with soft tissue infections, or in patients with severe sepsis.⁸

The initial evaluation includes a detailed history taking including predisposing factors, looking for transient or persistent sources of bacteremia (skin

infections, pneumonia, urinary tract infections, presence of invasive procedures, injecting drug users, etc.), identifying any systemic disease affecting the joints or the presence of joint trauma.⁵

The knee joint is the most frequently affected in both adults and children, ranging from 45%-56%, followed by the hip joint, 16-38%. Polyarticular septic arthritis, which typically involves two or three joints, occurs in 10%-20% of cases and is frequently associated with rheumatoid arthritis. If there is a fever and flare in rheumatoid arthritis, the possibility of septic arthritis needs to be considered.⁹

Examination

Physical

The physical examination carried out is inspection (see), palpation (touch), and movement. Movement ones. The first is that we look at the behavior (how it behaves (how is the position of the joint/part which is the joint/part affected), swelling, deformity, wasting of the muscles around the joint, and redness of the overlying skin. Determine the pattern of joint disease, for example, small or large joints. And also we see whether it is attacked monoarticularly or polyarticularly.¹¹

After inspection (seeing) we can feel/feel heat or not and determine swelling in the form of bone (osteoarthritis), fluid (effusion, synovitis), and tissue (rheumatoid nodules). When touched, whether there is pain or not.¹¹

After inspection and palpation, the patient is asked to perform movements such as flexion, extension, abduction, adduction, internal rotation, and external rotation. We see if the patient can perform the above movements or if there is pain while doing so.¹¹

On physical examination of the joint, signs of erythema, swelling (90% of cases), warmth, and tenderness are found which are important signs for diagnosing infection. The effusion is usually very large and is associated with a limited range of motion of the joint, both active and passive. But this sign becomes less obvious when the infection affects the spine, hip, and shoulder joints.¹⁰

Support

1. Peripheral blood examination

There was an increase in leukocytes with a predominance of segmental neutrophils, increased sedimentation rate, and C-reactive Protein (CRP). This test is not specific but is often used as an additional marker in the diagnosis, especially in suspected septic arthritis of the joint. Blood culture is positive in 50-70% of cases.¹²

2. Examination of joint fluid

Joint fluid aspiration should be carried out immediately if septic arthritis is suspected, if it is

difficult to reach, such as in the hip and shoulder joints, use a radiological guide. Joint fluid looks cloudy, or purulent, joint fluid leukocytes more than 50,000 cells/mm³ predominantly PMN, often reaching 75% -80%. In patients with malignancy, receiving corticosteroid therapy, and frequent injecting drug users with leukocytes less than 30,000 cells/mm³. Joint fluid leukocytes of more than 50,000 cells/mm³ also occur in inflammation due to crystal buildup or other inflammations such as rheumatoid arthritis. For this reason, it is necessary to examine the joint fluid using a polarized light microscope to look for crystals. The presence of crystals in the joint fluid also does not rule out concomitant septic arthritis.¹²

Synovial fluid gram stain should be performed, and it is positive in 75% of cases of staphylococcal culture-positive arthritis and 50% of gram-negative bacilli culture-positive arthritis. This gram stain can guide initial antibiotic therapy pending culture and sensitivity test results. Joint fluid cultures are performed for aerobic, anaerobic, and if indicated for fungi and mycobacteria. Synovial fluid cultures are positive in 90% of nongonococcal septic arthritis.²

3. Polymerase Chain Reaction (PCR) examination

Bacterial polymerase chain reaction (PCR) examination can detect the presence of bacterial nucleic acid in small amounts with almost 100% sensitivity and specificity. Some of the advantages of using PCR in detecting an infection include:

- Detect bacterial quickly
- Can detect slow-growing bacteria
- Detect non-culturable bacteria
- Detecting bacteria in patients receiving therapy
- Identify new bacteria as causative

But PCR also has weaknesses, namely false positive results if the material or reagent is contaminated during the inspection process.²

4. Radiological examination

Radiological examination on the first day usually shows a normal picture or an underlying joint disorder. Initial findings include swelling of the joint capsule and affected joint soft tissue, displacement of the fat pad, and widening of the joint space. Periarticular osteoporosis occurs in the first week of septic arthritis. Within 7 to 14 days, diffuse joint space narrowing and erosion due to cartilage destruction. In advanced stages that do not receive adequate therapy, radiological features show joint destruction, osteomyelitis, ankylosis, calcification of the periarticular tissue, or loss of subchondral bone followed by reactive sclerosis.²

Ultrasound examination can show abnormalities both intra and extra-articular which are not visible on radiographic examination. Highly sensitive for detecting minimal joint effusion (1-2 mL), including

deep joints such as the hip joint. Hyperechoic synovial fluid and joint capsule thickening are characteristic features of septic arthritis.¹¹

Another examination used in septic arthritis where the joint is difficult to evaluate clinically or determine the extent of bone and tissue infection is CT, MRI, or radiology.¹⁰

Management

The main goals of treating septic arthritis are joint decompression, joint sterilization, and restoration of joint function. Treatment of septic arthritis includes non-pharmacological, pharmacological, and joint fluid drainage.¹³

1) Non-pharmacological therapy

The patient is advised to rest the affected joint in the acute phase. Rehabilitation is important to maintain joint function and reduce the morbidity of septic arthritis. Rehabilitation should be initiated at the onset of arthritis to reduce loss of function. In the acute, suppurative phase, the patient must maintain a slightly to moderately flexed position which tends to contracture. Splinting is sometimes necessary to maintain a position with optimal function; knee joint in extension position, hip joint in neutral extension and rotation position, elbow flexed 90°, and wrist in a neutral position until slightly extended. Even in the acute phase, isotonic exercises must be performed immediately to prevent muscle atrophy. Joint movement, both active and passive, must be carried out no later than 24 hours after the complaint improves.⁸

2) Pharmacological therapy

Once septic arthritis is suspected, samples are immediately collected for examination and appropriate antibiotic therapy is performed and joint fluid drainage is performed immediately. The choice of antibiotic should be based on several considerations including clinical condition, age, pattern and local bacterial resistance, and the results of gram staining of joint fluid.⁸

Antibiotic modification is carried out when there are culture results and bacterial sensitivity. It should be noted that vancomycin should not be continued in patients with B lactam-sensitive staphylococcal or streptococcal infections. The clinical course of the patient also needs to be taken into consideration because the correlation between in vitro and in vivo bacterial sensitivity tests is not absolute. In general, the recommendation is to administer intravenous antibiotics for at least 2 weeks, followed by oral antibiotics for 1-4 weeks. Longer administration of intravenous antibiotics is indicated for bacterial infections that are difficult to eradicate such as *P aerogenosa* or *Enterobacter* spp. In cases of *S aureus* bacteremia and

secondary *S aureus* arthritis, 4 weeks of parenteral antibiotics were given to prevent recurrent infections. Intra-articular administration of antibiotics is ineffective and can cause chemical synovitis.¹²

a) Antibiotic

The choice of antibiotic should be based on the results of the joint fluid culture. Before the culture results are available, you can be given a choice of antibiotics such as penicillin G/clindamycin/cloxacillin if it is caused by *Staphylococcus aureus*. Whereas for gram-positive can be given vancomycin. For gram negatives with a decreased immune system, aminoglycosides/antipseudomonal/penicillin/3rd generation cephalosporins can be given. And for gram negatives with a good immune system, penicillin/ceftriaxone can be given. Meanwhile, in old age can be given antibiotics with a broad spectrum.¹³

b) Joint drainage

The technique of drainage depends on the joint involved, the stage of infection, and the patient's response. Although an infected joint can be drained with satisfactory results through repeated aspiration, the hip joint and possibly other joints that are difficult to drain should be performed arthrotomy as soon as possible after identification of septic arthritis.¹³

c) Surgical action

Considered in conditions such as coxal infection in children, joints that are difficult to drain, together with osteomyelitis, and also an infection that develops into the surrounding soft tissue.²

interaction of the pathogenic bacteria and the host's immune response. The processes occurring in natural joints can be divided into three stages: bacterial colonization, infection, and induction of a host inflammatory response.

The clinical symptoms of septic arthritis in non-gonococcal infections are sudden joint swelling, feeling warm, and very painful, most commonly occurring in the knee joint, for those occurring in the hip joint usually in a flexion and external rotation position and are very painful when moved. The physical examination carried out is inspection (see), palpation (touch), and movement. While the supporting examinations include peripheral blood examination, joint fluid examination, polymerase chain reaction (PCR) examination, and radiological examination. Management includes non-pharmacology such as rest and physiotherapy, pharmacology in the form of antibiotics, and surgical therapy such as drainage incisions.

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Conclusion

Septic arthritis is an emergency condition in which an infection occurs in the synovial joint resulting in the formation of pus in the synovial space. The etiologies include bacteria, fungi, and viruses. The peak incidence in the age group is children aged less than 5 years and adults aged more than 64 years. The joints affected include the knees, hips, and ankles. Risk factors for septic arthritis include knee and hip prostheses with skin infection, skin infection without prosthesis, hip and knee prosthesis without knee and skin infection, age over 80 years, diabetes mellitus, rheumatoid arthritis receiving immunosuppressive treatment, and joint surgery. Septic arthritis is closely related to systemic infection because it is difficult for germs to enter directly intra-articular if not through hematogenous bacterial spread or direct inoculation due to intra-articular injection. Several joint disorders need to be considered in the differential diagnosis of septic arthritis such as infection in previously affected joints, crystal-induced arthritis, reactive arthritis, traumatic arthritis, and viral arthritis. The pathogenesis of septic arthritis is multifactorial and depends on the

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Case Report

Acute Limb Ischemia Rutherford Classification III and COVID-19: A Case Report

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Abstract

Background: COVID-19 is caused by SARS-CoV-2 infections, which are responsible for the recent pandemic. COVID-19 infection increases thromboembolic events, including Acute Limb Ischemia (ALI) by causing elevated cytokine levels, systemic inflammation, hypercoagulation state, and hyperinflammation responses. This complication might cause loss of limbs.

Case description: We report a case of a 61-year-old male with COVID-19 who developed an ALI. He presented to the emergency department with acute left leg pain since a day before admission and shortness of breath three days before admission. His left foot was bluish-discolored, cold to the touch, and mottled in appearance. Chest x-ray showed bilateral inhomogeneous consolidation. Left lower limb X-ray revealed a gangrenous appearance. CT-Angiography suggested severe distal stenosis of the left femoral artery with complete occlusion of its distal aspect. COVID-19 was diagnosed based on RT-PCR testing. He received antibiotics and anticoagulation. Unfortunately, he underwent an amputation procedure.

Conclusion: A high index of suspicion should be maintained for ALI in COVID-19 patients, which is a vascular emergency. Some patients can achieve revascularization with observation or medical and/or surgical intervention, but other patients succumb to either amputation or death.

Introduction

COVID-19 is a pathological condition caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection. Since the first case was reported in Wuhan, the symptoms of the infection have not been specific and are frequently associated with pulmonary complications.¹

Various extrapulmonary manifestations of COVID-19 have been described and associated with acute thromboembolic phenomena, including systemic inflammation, endothelial injury, and platelet dysfunction at the cardiopulmonary, cerebrovascular, and peripheral venous and arterial levels. These manifestations affect at least 49% of patients and overshadow the patient's prognosis. Recent publications have reported a sudden increase in cases of arterial

thrombosis in patients with COVID-19, impacting the incidence of ALI and surgical emergencies.¹ Although most cases are asymptomatic, further primary prevention is urgently needed. Primary health care facilitators play an essential role in early diagnosing and managing patients who present with symptoms of ALI or who have risk factors for developing ALI, particularly in populations with a history of COVID-19. An adequate management strategy will improve the patient's quality of life. Herein, we report a case of a 61-year-old male with Rutherford Class III Acute Limb Ischemia associated with COVID-19.

Case Report

A 61-year-old male came to the Emergency Department in Karawang General Hospital with chief



Figure 1. Patient's condition on admission

complaints of pain in his left leg a day before admission. The pain was sudden, especially in the knee area. Along with the pain, he felt tingles, cold, and bluish discoloration in his leg. He also complained of shortness of breath, cough, and fever since three days ago. He had hypertension and congestive heart failure and underwent a stent angioplasty in 2017. History of diabetes mellitus and COVID-19 vaccination was denied.

From a general physical examination, the patient looks weak. From the primary survey, his airway, breathing, and circulation were within normal limits, and he is fully conscious (*compos mentis*). His blood pressure was 170/100 mmHg; the respiratory rate was 26 breaths/minute; pulse rate was 120 beats per minute; the temperature was 36.8°C, and oxygen saturation was 97% in the room air. From the secondary survey, his left foot was bluish-discolored, cold to the touch, and mottled in appearance. The left lower limb's dorsalis pedis artery and posterior tibial artery were absent on palpation, and capillary refill time could not be detected.

Laboratory examination revealed hemoglobin 13.7 g/dL, hematocrit 41.2%, erythrocyte 4700000 cells/mm³, total leukocyte count 14930 cells/mm³, platelets 507000 cells/mm³, urea 58.6 mg/dL, creatinine 1.58 mg/dL, NLR 5.205, ALC 2.245, and ESR 99 mm/h at the time of presentation. His random blood sugar was 150 mg/dL, CRP was reactive, and HIV was negative. The SARS-CoV-2 real-time PCR examination showed positive results. Chest x-ray showed inhomogeneous consolidation in bilateral pulmonary inferior zones, suspecting viral pneumonia. X-ray of his left foot and leg suggested a gangrenous appearance. CT-Angiography suggested severe distal stenosis of the left femoral artery with complete occlusion of its distal aspect.

According to the patient's history, physical examination, and additional tests, he was diagnosed with Acute Limb Ischemia Rutherford category III and COVID-19. In the ED, he was given intravenous fluid with NaCl 0.9%, Ceftriaxone, Heparin 3000 units bolus next 600 units per hour, Atorvastatin, Aspirin, Clopidogrel, Captopril, Paracetamol, Bicnat, Avigan, Azithromycin, Vitamin D, N-acetylcysteine. He was planned to be referred to a hospital with an isolation

operating room for COVID-19, but he refused therefore we managed the patient with debridement and left leg amputation.

Discussion

Coronavirus disease 2019 (COVID-19) is caused by the virus Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which is very contagious and caused a pandemic recently. The primary manifestation involves the respiratory system. Up to July 13th, 2021, the Indonesian Government reported 2.615.529 confirmed cases, 68.219 deaths, and 2.139.601 recovered from COVID-19.^{2,3}



Figure 2. Chest X-Ray



Figure 3. CT-Angiography



Figure 4. Post-amputation condition

The exact pathogenesis is still debatable and has yet to be explored in detail. Nevertheless, SARS-CoV-2 mainly infects airway cells lining the alveoli and binds with receptors, specifically ACE-2 into the host cell. Glycoprotein within the spike envelope will bind with a cellular receptor in ACE2, duplicate its genetic material then synthesize proteins essential for generating new virions. Dysregulation of the immune system plays a role in tissue damage during infection. On the other hand, excessive immune response might cause tissue damage.⁴

This virus mainly attacks the respiratory system. Diagnosis is made based on clinical manifestation. Typical signs and symptoms of COVID-19 are acute respiratory problems, fever ($>38^{\circ}\text{C}$), cough, and breathing difficulty. Additionally, patients might have ageusia, anosmia, nausea, and vomiting. About half of the cases suffer from dyspnea within a week. The mean incubation time is 5-6 days, with the longest reaching 14 days. A severe form of COVID-19 might provoke sepsis, extreme pneumonia, ARDS, kidney failure, and even death. An X-ray examination might show ground-glass opacity and diffuse pneumonic infiltrate in both lung fields.^{5,6}

A recent study reported clinical characteristics and overall results of COVID-19 with its effects on the healthcare system. Two studies highlight coagulopathy and its association with a higher mortality rate. Tang et al. found abnormal coagulation profiles, marked with spiking D-dimer and fibrin degradation products, commonly found in deceased patients due to COVID-19 pneumonia. Han et al. showed that coagulation function was significantly disturbed compared to healthy individuals, and monitoring coagulation parameters potentially supported identifying severe

cases earlier. COVID-19 infection is associated with increased thromboembolic events, including ALI. Acute limb ischemia might develop even in young and healthy adults with anticoagulation prophylaxis. Before COVID-19, studies had found that the overall incidence of ALI had decreased significantly, and hypercoagulation was the unusual cause in a broad population with ALI.^{7,8}

Acute limb ischemia is a vascular emergency associated with a high risk of limb loss and death. Most cases result from in situ thrombosis in patients with pre-existing peripheral arterial disease or those undergoing vascular procedures, including stenting and bypass grafts. The other common source is cardioembolic.⁹

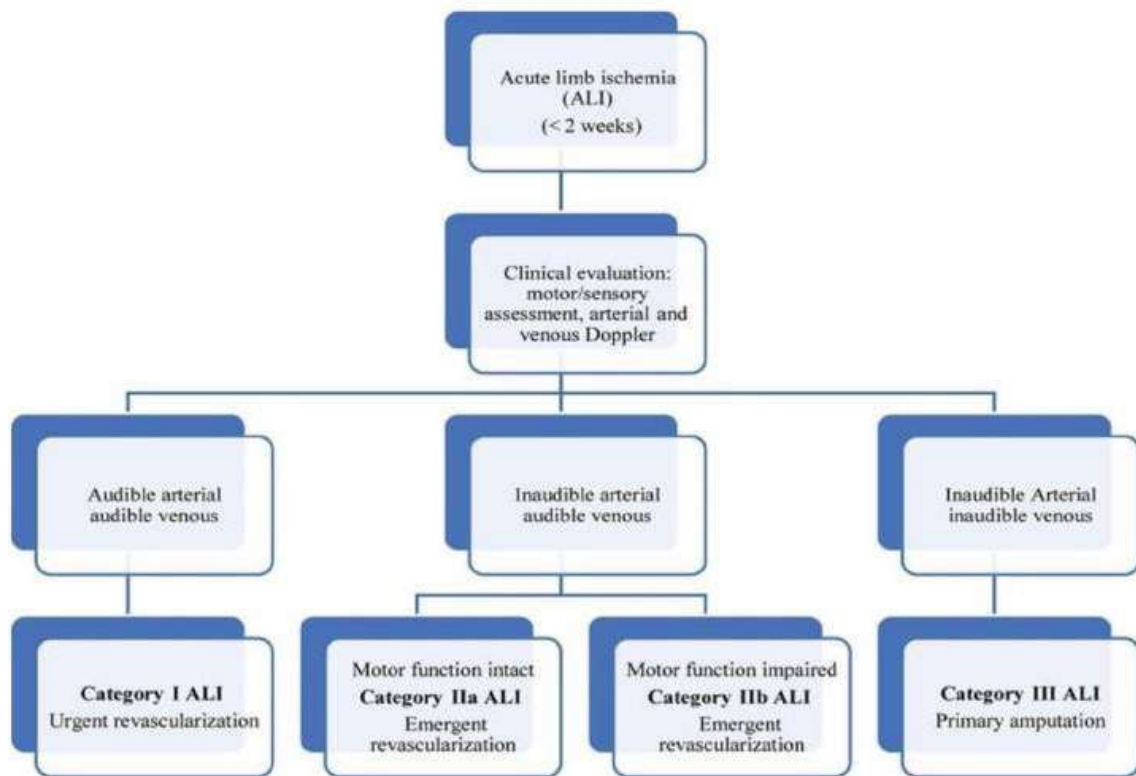
The causative mechanism for ALI is a systematic inflammatory process triggered by a massive activation of macrophages that generate a cytokine storm. COVID-19 causes elevated cytokine levels, including but not limited to tumor necrosis factor- α , IL-1 β , IL-6, procalcitonin, and interferon γ . The coupling of inflammation and coagulation has also been described in the literature, sharing common molecular pathways.¹⁰ The typical clinical presentation of ALI is encompassed by "the rule of P's": pain, pulselessness, pallor, poikilothermia (cool extremity), paresthesia, and finally, the onset of paralysis.⁹

The clinical classification for ALI, as proposed by Rutherford et al. and subsequently adopted by the Society of Vascular Surgery and the International Society of Cardiovascular Surgery, considers the clinical findings such as sensory and muscle weakness and the Doppler indices of the arterial and venous systems. This classification helps to determine urgency, prognosticate the success of limb salvage, and guide decision-making in terms of therapy (Table 1).¹⁰

Due to hypercoagulation, ALI management in COVID-19 might be more challenging than expected. The patient might benefit from *unfractionated heparin* (UFH) after prolonged surgery. Bellosta et al. described 20 patients (18 male) with ALI associated with COVID-19 for three months. Seventeen patients underwent surgical care with revascularisation, and only 12 succeeded (70,6%). The lower success rate than expected might be due to a hypercoagulable state. Previous studies have proven that the pathogenesis of arterial thrombotic disease in COVID-19 was different from classic arterial thrombosis.⁸

COVID-19 patients might present with acute non-atherosclerotic thrombosis. Several mechanisms have been suggested to explain those phenomena. Hyperinflammation response was expected to be responsible for both arterial and venous thromboembolic events in COVID-19 patients. Increased D-dimer, fibrinogen, coagulation factors, acquired antiphospholipid antibody, decreased protein C, protein S, antithrombin, and platelet and neutrophil

Category	Description	Clinical finding		Doppler signals		Prognosis
		Sensory Loss	Muscle weakness	Arterial	Venous	
I	Viable	None	None	Audible	Audible	Not immediately threatened, can attempt revascularization
II	Threatened					
Ila	Marginally threatened	Minimal (toes) or none	None	Often inaudible	Audible	Salvageable with prompt revascularization
Ilb	Immediately threatened	More than toes, associated with rest pain	Mild or moderate	Usually inaudible	Audible	Salvageable with immediate revascularization
III	Irreversible	Profound, anesthetic	Profound, paralysis (rigor)	Inaudible	Inaudible	Major tissue loss or permanent nerve damage is inevitable, consider amputation

Table 1. Rutherford clinical classification.¹⁰Table 5. Diagnosis and management of acute limb ischemia.⁹

hyperactivation had been observed. There was also speculation that direct viral infection from endothelial cells through ACE-2 might be the cause of arterial thrombosis in COVID-19.⁸

Rutherford's class, duration of ischemia, comorbidities, and therapy-related risks and outcomes. Fig. 5 outlines the initial assessment and recommended

revascularization strategies endorsed by professional societies.⁹ The main goals of CLI (Critical Limb Ischemia) treatments are to preserve limbs. Revascularization is the fundamental strategy to preserve extremities; however, in several patients, this measure did not improve both function and mobility of the limbs. When revascularization is considered,

arterial imaging helps identify the target and mode of revascularization. Due to the limitation of distal artery imaging non-invasively, the invasive angiography view regarding the management selection should be considered before amputation. Revascularization might not be suitable for all patients; therefore, requiring major amputation, including for patients with severe arterial, is commonly done to provide a better disease, infection, or tissue loss that is impossible to be preserved. Major amputation is a definitive therapy for those cases. Application of a grading system might help identify those with a high risk of undergoing major amputation.¹¹

Conclusion

COVID-19 is an exceptionally infectious disease that yielded a pandemic recently. COVID-19 infection is associated with an increased incidence of thromboembolic events, related to the increased mortality rate. Acute limb ischemia is the most severe peripheral arterial disease associated with an increased risk of limb loss. The primary purpose of therapy was to preserve the functionality of the affected body parts. Although revascularization had known to provide a good outcome; unfortunately, not all patients could be managed with revascularization; therefore had to undergo major amputation. Major amputation is a crucial treatment choice for managing the third category of ALI classification by Rutherford. A rational and wise approach is needed to choose between revascularization and amputation for high-risk patients.

Conflict of interest

The author has no conflict of interest related to this article.

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