Indonesian Journal of Global Health Research
Volume 8 Number 3, June 2026
e-ISSN 2715-1972; p-ISSN 2714-9749
http://jurnal.globalhealthsciencegroup.com/index.php/IJGHR

CHRONIC INFECTION CONTRIBUTES TO THE RISK OF LIMB AMPUTATION IN PATIENTS WITH DIABETIC ULCERS: A LITERATURE REVIEW

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ABSTRACT
Diabetic foot ulcers are a chronic complication of diabetes mellitus that often leads to lower extremity amputation and significantly contributes to disability and mortality. Infections, particularly chronic and severe ones, play a significant role in accelerating ulcer progression to amputation, Nevertheless, the synthesis of scientific evidence regarding the contribution of chronic infections as a determinant of amputation is still limited. This literature review aimed to examine the role of chronic infection in the risk of amputation in patients with diabetic foot ulcers. A literature search was conducted on the Scopus, PubMed, and ScienceDirect databases for publications from 2015 to 2025 using keywords related to diabetes mellitus, diabetic foot ulcers, infection, and amputation. Articles were selected based on inclusion and exclusion criteria, 644 articles were identified. After title and abstract screening, followed by full-text review, and critical appraisal using the JBI tools, 10 selected journals were included in the literature synthesis.. The results indicated that moderate to severe infection, osteomyelitis, and pathogen characteristics, particularly Gram-negative and ESBL-producing bacteria, are the main determinants of major amputation. Peripheral artery disease, the severity of ulcers, increased inflammatory parameters, hypoalbuminemia, and certain patient factors also worsen clinical outcomes. It is concluded that chronic infection is a key determinant of amputation in diabetic foot ulcers, making early and aggressive infection prevention and control an essential strategy to reduce amputation rates.

Keywords: chronic infection; diabetic foot ulcer; diabetes mellitus; limb amputation; peripheral arterial disease

How to cite (in APA style)
Anugraini, W., Arofiati, F., & Primanda, Y. (2026). Chronic Infection Contributes to the Risk of Limb Amputation in Patients with Diabetic Ulcers: A Literature Review. *Indonesian Journal of Global Health Research*, *8*(3), 1069–1080. https://doi.org/10.37287/ijghr.v8i3.1421.

INTRODUCTION

Diabetes mellitus is one of the non-communicable diseases with a high prevalence worldwide and is a global health problem that continues to increase every year. The rise in diabetes mellitus cases is influenced by lifestyle changes, urbanization, population aging, and the epidemiological transition of diseases. According to data from the International Diabetes Federation (IDF, 2024), there are approximately 537 million adults living with diabetes worldwide. This number is projected to increase to 643 million by 2030, indicating a growing long term health burden. Indonesia ranks fifth globally with approximately 19.5 million people with diabetes in 2024, showing a significant increase compared to previous years (IDF, 2024). One of the most common chronic complications in diabetic patients is diabetic foot ulcer (DFU), which significantly impacts patients' quality of life and increases the risk of lower extremity amputation (Roy et al., 2024).

Diabetic foot ulcers are chronic wounds on the lower extremities that arise from a combination of peripheral neuropathy, angiopathy, and impaired immunity, leading to reduced tissue healing capacity (Kim, 2023). Chronic hyperglycemia creates a biological environment that supports tissue damage and the colonization of pathogenic microorganisms. Untreated ulcers become a gateway for infection, especially chronic infections that are difficult to heal. This infection can develop into serious complications such as osteomyelitis and gangrene (Matheson et al., 2021). Globally, approximately 15–25% of diabetic patients will experience foot ulcers during their lifetime, and 80% of non traumatic lower extremity amputations in diabetic patients are preceded by infected ulcers (Toledo et al., 2025). A study by Santra et al., (2020) confirms that chronic infection in

diabetic ulcers worsens tissue damage and slows wound healing, significantly increasing the risk of lower extremity amputation.

According to Armstrong et al., (2023), approximately 20% of moderate to severe diabetic foot infections result in amputation. Amputation leads to a decline in mobility function, loss of independence, and significant psychosocial disturbances in patients. The economic impact of amputation also includes increased long-term care and rehabilitation costs. Indeed, lower extremity amputations due to diabetes complications increased the burden of the disease, which has far-reaching physical, psychological, and economic impacts (Crocker et al., 2021). Therefore, more effective prevention strategies and early intervention to prevent diabetic foot ulcers and amputation by recognizing the role of chronic infections are critical.

Various studies have highlighted the strong link between chronic infection and an increased risk of amputation in patients with diabetic ulcers. Chronic infection plays a role in maintaining a continuous inflammatory process and damaging local tissues. Gong et al., (2023) found that chronic infection plays a significant role in the development of ulcers, leading to gangrene and amputation. Alay et al., (2021) reported that osteomyelitis increases the risk of amputation by 2.6 times compared to patients without bone infection involvement. Lin et al., (2020) through their meta-analysis study showed that chronic infection and gangrene each have odds ratios of 3.70 and 10.90, respectively, for the occurrence of amputation. Additionally, Hwang, (2024) research confirms that polymicrobial infections increase the risk of re-amputation by up to 8.4 times. These studies demonstrate the complexity of the relationship between chronic infection and the prognosis of DFU patients.

Most previous studies still pay insufficient attention to the temporal relationship between infection and amputation events. Some studies, such as Wukich et al., (2022), emphasize the importance of early detection of chronic infections in preventing severe complications. Another study by Mansoor & Modaweb, (2022) also highlighted the role of infection management in reducing the risk of amputation. As such, a literature review is necessary because it allows researchers to identify and summarize the key findings from various relevant studies, providing a comprehensive overview of the relationships between variables, the strength of the available evidence, and the consistency of research results. This process helps distinguish between scientifically established findings and areas that still require further exploration. In addition, the literature review serves as a scientific control mechanism to prevent unnecessary duplication of research and encourage more focused and value-added research. Therefore, literature review of quantitative research focusing on chronic infection as a determinant of amputation risk is a crucial step in strengthening clinical policies and promoting preventive interventions to reduce the rate of lower extremity amputations in diabetic patients in Indonesia and globally (Sundresh et al., 2025). Specially this literature review aims to examine the role of chronic infection in the risk of amputation in patients with diabetic foot ulcers.

METHOD

This study used a literature review method because it is suitable for integrating previous research findings, identifying patterns, gaps, and best practices in the field of evidence-based diabetic ulcers (Snyder, 2019). The data collection process was carried out by searching the scientific literature from various credible sources, especially international journal articles. The databases used in this study were Scopus, PubMed, and ScienceDirect, with search keywords including "Diabetes mellitus" AND "foot ulcer" AND "infection" AND "amputation". Inclusion criteria include open-access articles in English published between 2015 - 2025 with a subject area of nursing. Only articles presenting original research findings (primary data or independently analyzed secondary data) discussing diabetic ulcers, chronic infections, and amputations were considered. The exclusion criteria were articles published before 2015, and did not discuss diabetic ulcers, chronic infections, and amputations. Non open-access and review articles were not included in this literature review.

After entering keywords and selecting according to the inclusion and exclusion criteria, 644 articles were identified from databases. Because the content and design of the research did not align with the research objectives, 238 articles were excluded, and 406 articles were selected. From 406 articles, the articles were further screened for titles and abstracts resulted in 10 studies included in the final review. The 10 articles, then, were critically appraised using the Joanna Briggs Institute (JBI) critical appraisal tool (JBI, 2020). Each article were systematically assessed based on the methodological criteria listed in the checklist. The critical appraisal was conducted by reading the complete text and answering each item using the categories yes, no, unclear, or not applicable. Each criteria with a "yes" answer is given a score of 1 point, and other answers are given a score of 0. Then, all collected scores are calculated and summed. Literature or journals that can be considered good and valid for research material if they receive a score above 50% from that assessment.

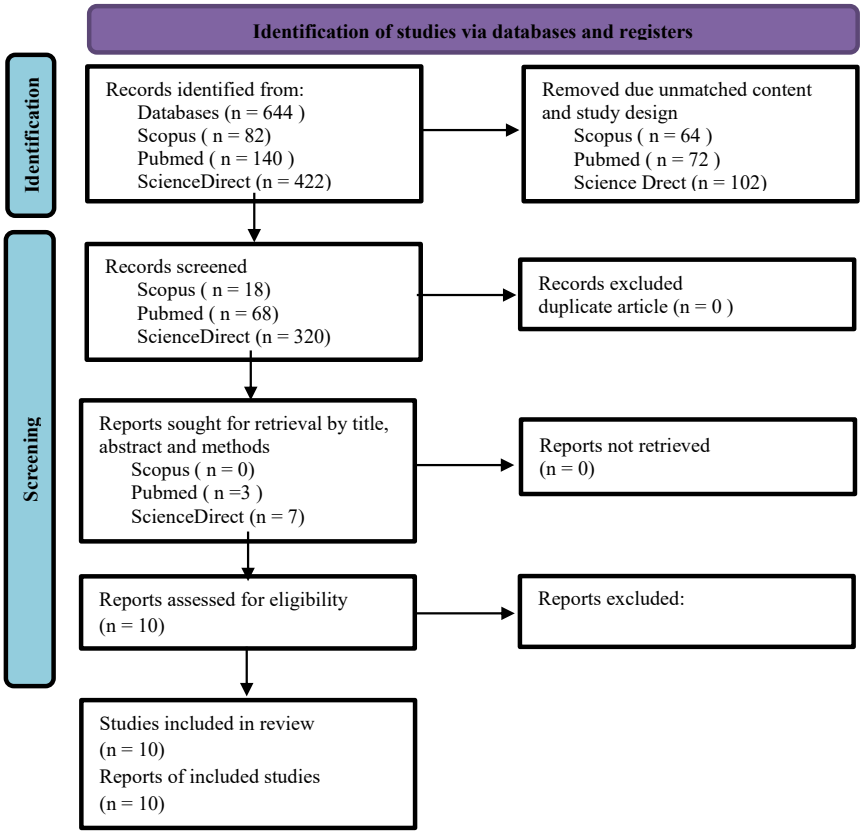

Figure 1. PRISMA Flowchart of Study Selection

RESULT

Table 1.
Critical appraisal results based on JBI

1. Cohort studies (prospective and retrospective)												
Citation	Question											Score
	1	2	3	4	5	6	7	8	9	10	11	
Chaudhary et al., (2021)	Y	U	Y	Y	Y	Y	Y	Y	Y	U	Y	81%
Zhang et al., (2025)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%
Ugwu et al., (2019)	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	90%
Saltoglu et al., (2015)	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	81%
Alvaro et al., (2024)	Y	Y	Y	Y	Y	Y	Y	Y	N	U	Y	81%
Xu et al., (2024)	Y	Y	Y	Y	Y	Y	Y	Y	U	N	Y	81%
Leibovitch et al., (2021)	Y	Y	Y	Y	Y	Y	Y	Y	U	N	Y	81%
Almohammadi et al., (2022)	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	81%
2. Cross Sectional Studies												
Citation	Question											Score

	1	2	3	4	5	6	7	8	
Sánchez Correa et al., (2025)	Y	Y	Y	Y	Y	Y	Y	Y	100%
Kilic et al., (2025)	Y	Y	Y	Y	Y	Y	Y	Y	100%

Description: Y = yes, N = no, U = unclear, atau N/A = not applicable.

Critical appraisal using JBI was performed on 10 articles, including 8 cohort studies and 2 cross-sectional studies. The appraisal results showed that all 10 articles scored > 50%, indicating that all journals were considered good and valid for research purposes.

Table 2.
Literature Review Results

No	Author, Year, Title, and Country	Study Design, Population, and Sample	Main Results	Conclusion
1	Chaudhary et al., (2021) Lower Limb Amputation Rates in Patients With Diabetes and an Infected Foot Ulcer: A Prospective Observational Study. India	Prospective observational. 81 patients aged 18–65 years with diabetes and infected foot ulcers were treated and followed until healing, minor/major amputation, or 6 months of follow up.	This study shows that factors significantly associated with major amputation are: a high score on the Perfusion-Extent-Depth-Infection-Sensation (PEDIS) classification system, high HbA1c, bacterial growth in wound cultures, and the presence of peripheral artery disease.	In diabetic patients with infected foot ulcers, lower extremity amputation, and several clinical factors such as a high PEDIS score, poor glycemic control (high HbA1c), positive wound culture, and the presence of peripheral artery disease are associated with a higher amputation rate. Early detection and intensive management of these factors are important for reducing the risk of amputation.
2	Zhang et al., (2025) The incidence of and risk factors for hospitalisations and amputations for people with diabetes-related foot ulcers in Queensland, 2011–19: an observational cohort study Australia (Queensland)	Prospective observational cohort study. 4,709 patients with diabetes-related foot ulcers (DFU) who first visited one of the 65 Diabetic Foot Service clinics in Queensland between July 1, 2011, until December 31, 2017.	DFU related hospitalization incidence: 50.8 per 100 person per years. The risk of DFU related hospitalization is higher in patients with deep ulceration, peripheral artery disease (PAD), and certain clinical factors such as smoking, cardiovascular disease, end stage renal disease, and moderate to severe infection.	This article shows that although amputation does not always occur in almost all DFU hospitalizations, clinical factors such as deeper ulcers, PAD, comorbid diseases, and smoking increase the likelihood of amputation, especially minor amputations. Early intervention in high-risk patients is necessary to prevent amputation and improve short-term outcomes.
3	Ugwu et al., (2019) Predictors of lower extremity amputation in patients with diabetic foot ulcer: findings from MEDFUN, a multi-center observational study Nigeria	Observational prospective multicenter. 336 diabetic patients with foot ulcers treated at 6 referral hospitals in Nigeria between March 2016 until April 2017.	This study shows that 119 (35.4%) patients underwent lower extremity amputation during the follow-up period. Factors correlated with amputation in univariate analysis included ulcer duration >1 month before hospitalization, PAD, Wagner grade ≥4, wound infection, proteinuria, leukocytosis, and osteomyelitis. In multivariate analysis, ulcer duration >1 month, PAD, and osteomyelitis remained independent predictors of	Ulcer duration >1 month, peripheral artery disease (PAD), and osteomyelitis are independent predictors of amputation in patients with diabetic foot ulcers. Early identification and management of these factors can reduce amputation rates in acute clinical settings.

No	Author, Year, Title, and Country	Study Design, Population, and Sample	Main Results	Conclusion
			amputation.	
4	Saltoglu et al., (2015) Predictors for limb loss among patient with diabetic foot infections: an observational retrospective multicentric study in Turkey Turkey	Observational retrospective multicentric study. There were 455 diabetic patients with diabetic foot infections.	A total of 28% of patients underwent amputation, and about a third of these were major amputations. The most common bacteria causing infection are Gram-negative rods such as Pseudomonas aeruginosa and E. coli.	Male sex, longer duration of diabetes, ulcer infection, peripheral vascular disease, retinopathy, high ESR levels, and infection with Gram-negative bacteria were independently associated with an increased risk of amputation.
5	Alvaro et al., (2024) Risk factors associated with amputations in patients with diabetic foot infection. Seven years of experience in a reference hospital in Panama. The diabetic foot study group at Chiriqui (the FOOTCHI study group) Panama	Prospective observational (prospective cohort). 351 diabetic patients treated for diabetic foot infections at referral hospitals in Panama (January 2010–December 2016)	17.4% of patients underwent lower limb amputation.	The results showed that nephrosis, osteomyelitis, and severe IDSA classification were strong predictors of amputation. In patients with diabetic foot infection, the presence of osteomyelitis, necrosis, and severe IDSA classification was significantly associated with the risk of lower limb amputation.
6	Xu et al., (2024) The Risk of and Associated Demographic and Laboratory Variables for Amputations for Inpatients with Diabetic Foot Ulcers United States	A retrospective observational study examining the medical records of adult patients hospitalized with diabetic foot ulcers. 650 inpatients with DFU from three hospitals within the same healthcare system between June 1, 2016, until May 31, 2021.	The risk of amputation during treatment is 44% among DFU patients. Factors significantly associated with amputation are male gender, low body mass index, smoking history, high erythrocyte sedimentation rate (ESR), high C-reactive protein (CRP) levels, high white blood cell (WBC) count, and low albumin levels.	The high risk of DFU-related amputation (44%) among adult patients, who were predominantly Black and/or Hispanic. Significant risk factors associated with DFU-related amputation include male sex, low body mass index, smoking, and high levels of inflammation or low albumin levels during hospitalization.
7	Sánchez Correa et al., (2025) Reamputation prevalence after minor feet amputations in patients with diabetic foot: A cross sectional study Colombia	Cross sectional study. 276 minor amputations were recorded based on medical records over a 15-year period, of which 133 cases required re-amputation.	Factors significantly associated with the risk of reamputation include a history of smoking, vascular occlusion on Doppler, revascularization, Wagner classification >3, and leukocytosis >11,000.	The prevalence of re-amputation after minor amputation in patients with diabetic foot is quite high (48%). The risk of reamputation is primarily related to factors reflecting vascular damage and infection, such as arterial occlusion, the need for revascularization, high Wagner classification, and leukocytosis.
8	Almohammadi et al., (2022) Pattern and type of amputation and mortality rate associated with diabetic foot in Jeddah, Saudi Arabia:	*R*etrospective cohort study. Patients with diabetes mellitus admitted to a tertiary center in Jeddah, Saudi Arabia between	This study shows that 84.9% of patients underwent amputation, 38.2% minor amputation, 40.1% major amputation, and 21.7% both. Infection is the most common cause of amputation (50.3%). The 7 year mortality rate was 20% (75 deaths). Low hemoglobin and high	The need to reduce the risk of amputation and mortality in diabetic foot patients thru early detection of risk factors and intervention at specialized centers with a multidisciplinary approach

No	Author, Year, Title, and Country	Study Design, Population, and Sample	Main Results	Conclusion
	A retrospective Cohort Study Saudi Arabia	January 2013 and September 2020; the sample included a review of medical records for 358 patients with diabetic foot ulcers or foot gangrene.	creatinine are significantly associated with mortality.	was emphasized.
9	Kilic et al., (2025) Prevalence, risk level and risk factors of diabetic foot ulcer among adult individuals with diabetes in the Southeastern Anatolia Region of Turkiye Turkiye	multi-centered descriptive cross-sectional research. 357 people with diabetes from 7 cities in Turkey, samples were selected using stratified and systematic sampling.	Prevalence of diabetic foot ulcers: 17.1% (13.2%-21.5%), consistent risk level: majority (86.5%) without ulcers. Significant risk factors that increase the likelihood of foot ulcers: Peripheral artery disease, history of ulcers, leg edema, fungal infections between toes.	Regular examination of risk factors such as peripheral vascular disease, history of ulcers, edema, and fungal infections is important for early detection and prevention. Early detection and personalized prevention plans are highly recommended for all diabetic patients.
10	Leibovitch et al., (2021) Predictors and outcomes of diabetic foot ulcer infection with ESBL-producing bacteria in a large tertiary center Israel	Retrospective cohort study from 2014 to 2018 Patients treated for acute diabetic foot infection (DFI) at a large tertiary hospital with 493 available cultures from DFI patients; 121 (24.5%) showed suspected ESBL-producing bacteria.	Patients treated for acute diabetic foot infection (DFI) at a large tertiary hospital with available culture samples from 493 DFI patients; 121 (24.5%) showed bacteria suspected of producing ESBL.	Infection by ESBL-producing bacteria in acute diabetic foot ulcers is common and associated with certain risk factors (older age, PVD, worse ulcer score, history of hospitalization). Although overall mortality did not increase, the presence of these bacteria was associated with a higher rate of major amputations, making this data useful in determining empirical antibiotic therapy options for DFI.

Based on a synthesis of ten analyzed journals, it was found that lower extremity amputation in diabetic foot ulcers is the result of a complex interaction between infection, vascular disorders, and the severity of the ulcer. Moderate to severe infections, osteomyelitis, and the microbiological characteristics of pathogens (especially Gram-negative and ESBL-producing bacteria) emerged as major determinants of major amputation, as consistently reported by Chaudhary et al., (2021), Ugwu et al., (2019), Alvaro et al., (2024), Saltoglu et al., (2015), and Leibovitch et al., (2021).

Peripheral artery disease plays a central role in worsening tissue perfusion, increasing the progression of infection, and is a key factor in both primary and re-amputations, as demonstrated by Chaudhary et al., (2021), Ugwu et al., (2019), Zhang et al., (2025), and Sánchez Correa et al., (2025). The severity of ulcers, measured thru the Wagner, PEDIS, and IDSA classification systems, has been proven to have high predictive value for limb amputation, confirming its role as an essential clinical risk stratification tool (Saltoglu et al., 2015; Chaudhary et al., 2021; Alvaro et al., 2024; Sánchez Correa et al., 2025).

In addition to local factors, systemic inflammatory response and nutritional status are reflected by

leukocytosis, elevated ESR and CRP, and hypoalbuminemia, which are consistently associated with poor outcomes (Ugwu et al., 2019; Xu et al., 2024; Sánchez Correa et al., 2025). Demographic and lifestyle factors, particularly male gender and smoking habits, also contribute to increased risk thru vascular and immunological mechanisms (Saltoglu et al., 2015; Xu et al., 2024; Zhang et al., 2025).

Overall, the evidence suggests that the success of preventing amputation and re-amputation in diabetic foot ulcers is highly dependent on early detection and aggressive management of infection, optimization of vascular status, assessment of ulcer severity based on clinical classification, and control of inflammation and patient risk factors, in order to improve the chances of limb salvage and reduce long-term morbidity and mortality.

DISCUSSION

Diabetic foot ulcers are one of the most serious chronic complications of diabetes mellitus and often lead to lower extremity amputation. This condition reflects the complex interaction between metabolic disorders, vascular dysfunction, peripheral neuropathy, and susceptibility to infection. Based on a synthesis of various studies, infection, especially chronic and severe infections, is a major determinant that worsens the disease course, leading to amputation. Inadequately treated infections accelerate soft tissue and bone damage, and hinder the wound healing process. The progression of infection is also closely linked to delayed diagnosis, suboptimal antibiotic therapy, and limited access to care. Therefore, infection is understood not merely as a secondary complication, but as a central component in the pathogenesis of amputation in diabetic foot ulcers.

Chronic Infection as a Major Risk Factor for Amputation

Findings by D. Wang & Jupiter, (2025) a large-scale retrospective cohort study with long-term follow-up. This study shows that infections occurring after a diagnosis of diabetic foot ulcers dramatically increase the risk of amputation, with the risk being up to 12 times higher compared to diabetic foot ulcers without infection. Time-to-event analysis showed that patients with infected diabetic foot ulcers reached a cumulative amputation rate of 50% much faster, while the non-infected group remained at low risk even over a very long observation period. These findings underscore the role of infection as an accelerator of disease progression, hastening healing failure and the transition toward amputation. A retrospective cohort study conducted by Almohammadi et al. (2022) showed that the majority of diabetic foot patients underwent amputation (84.9%), with infection being the primary cause (50.3%), and a 7-year mortality rate of 20%, which was significantly associated with anemia and impaired kidney function. This is supported by Wang et al., (2022), who confirm that prolonged infections worsen tissue damage, slow wound healing, and increase the need for surgical interventions, including amputation. Chronic infections are also often accompanied by failure of conservative therapy due to antibiotic resistance and biofilm formation. The accumulation of these pathological processes makes amputation the last therapeutic option to prevent sepsis and death. Thus, chronic infection serves as a major trigger for the clinical escalation of diabetic foot ulcers toward amputation.

Biologically, Rodríguez-Rodríguez et al., (2022) explain that the chronicity of wounds in diabetic patients is closely related to impaired immunity, persistent inflammatory response, and recurrent bacterial colonization. Chronic hyperglycemia reduces the function of neutrophils and macrophages, making them less effective at eradicating pathogens. This condition makes the infection difficult to eradicate and creates a continuous inflammatory cycle. Chronic inflammatory responses also damage the extracellular matrix and inhibit angiogenesis, which is necessary for wound healing. This combination of factors increases the risk of infection spreading to deeper tissues, including bone. Osteomyelitis that appears in this context is often clinically an indication for amputation (Rodríguez-Rodríguez et al., 2022).

Severity of Infection and Osteomyelitis

A number of observational studies have shown that the severity of infection is a strong predictor of amputation. Saltoglu et al., (2015) found that ulcer infection, particularly when accompanied by peripheral vascular disease and systemic inflammation such as elevated ESR, is independently associated with limb loss. The severity of the infection reflects the extent of tissue damage and the high bacterial load. These findings are consistent with the prospective study by Alvaro et al., (2024), which showed that osteomyelitis, tissue necrosis, and severe IDSA classification significantly increase the risk of lower limb amputation. Severe infections often indicate a failure of local and systemic defense mechanisms. Therefore, the classification of infection severity has significant prognostic value in determining the risk of amputation.

Xu et al's., (2024) research reinforces the role of systemic inflammation as an indicator of infection severity. Elevated ESR, CRP, and leukocyte levels reflect an active inflammatory response associated with progressive tissue damage. Additionally, low albumin levels indicate poor nutritional status, which hinders tissue regeneration. The combination of high inflammation and malnutrition creates a biological condition that is not conducive to wound healing. This condition also increases vulnerability to recurrent infections and systemic complications. Overall, these laboratory parameters serve as important markers for identifying diabetic foot ulcer patients at high risk of amputation.

The relationship between osteomyelitis and amputation has been consistently reported in various studies. Alay et al., (2021) showed that the presence of osteomyelitis increases the risk of amputation by up to 2.6 times in patients with diabetic foot infections. Lee et al., (2020) even reported a hazard ratio of over 6 for amputation in diabetic foot ulcer patients with osteomyelitis, confirming the strong association between chronic bone infection and limb loss. This finding is also supported by Evran et al., (2021), who showed that osteomyelitis is one of the most important clinical indicators in amputation decision-making. Meanwhile, Ugwu et al., (2019) provide a perspective from a multicenter prospective study in low and middle income countries. This study shows a high amputation rate (35.4%) and identifies delayed ulcer duration, PAD, and osteomyelitis as independent predictors of amputation.

Infection and Reamputation

Clinical issues don't end with the first amputation. Sánchez Correa et al., (2025) reported a high reamputation prevalence of 48% after minor amputation in patients with diabetic foot. The high rate of reamputation indicates that the underlying pathological processes are often not optimally addressed. Factors such as leukocytosis, a high Wagner classification, and vascular disturbances indicate that residual or recurrent infection is still ongoing after amputation. Remaining infections can spread to proximal tissues and trigger stump healing failure. This condition increases the physical, psychological, and economic burden on patients. Therefore, post-amputation infection control becomes crucial to prevent re-amputation. This aligns with Hwang, (2024), who specifically highlights that chronic polymicrobial infection is a strong predictor of re-amputation, indicating that failure to eradicate infection in the early stages has a direct impact on patients' long-term outcomes.

The Role of Pathogens and Antibiotic Resistance

Leibovitch et al., (2021) highlight that infections caused by extended-spectrum beta-lactamase (ESBL)-producing bacteria in diabetic foot ulcers are associated with an increased risk of major amputation. Drug resistant pathogens limit the choice of empirical and definitive antibiotic therapy. This often leads to delays in effective infection control. Uncontrolled infection accelerates tissue damage and expands the area of necrosis. This finding is consistent with the report by Saltoglu et al., (2015), which found a dominance of Gram-negative bacteria in amputation cases. Gram-negative bacteria are often associated with severe infections, a high inflammatory response, and poor clinical outcomes.

Infection in the Context of Multidimensional Risk Factors

A prospective observational study by Chaudhary et al., (2021) confirmed that the severity of infection and local wound conditions are major determinants of major amputation. A high PEDIS score, reflecting poor perfusion, ulcer depth, infection level, and sensory impairment, is significantly correlated with amputation. These findings indicate that amputation is not only triggered by the presence of infection, but also by the biological complexity of the wound, which is exacerbated by poor glycemic control (high HbA1c) and active bacterial colonization. The presence of peripheral artery disease (PAD) further strengthens this relationship, as tissue hypoperfusion limits immune response and the effectiveness of antibiotic therapy. Consistent with the research conducted by Zhang et al., (2025), the risk of hospitalization and amputation significantly increases in patients with deeper ulcers, peripheral artery disease (PAD), and moderate to severe infections. In addition to local wound factors, patient characteristics such as smoking habits, cardiovascular disease, and end-stage renal disease also contribute to poorer outcomes.

The study by Almohammadi et al., (2022) shows that infection is the most common cause of amputation, accounting for over 50%, in diabetic foot patients at referral centers. However, infections rarely stand alone as a single factor. Infections often interact with peripheral artery disease, anemia, and kidney disorders, which worsen tissue perfusion and healing. The combination of these factors increases vulnerability to severe and progressive infections. Kilic et al., (2025) add that even mild infections, such as interdigital fungal infections, can be a gateway to ulcers. If left untreated early, this condition can develop into a chronic infection and increase the risk of amputation.

CONCLUSION

Based on the literature reviewed, all ten journals indicate that chronic infection is the most consistent and powerful key determinant in increasing the risk of amputation in diabetic foot ulcers, especially when accompanied by a high degree of severity, osteomyelitis, antibiotic resistance, and vascular disorders. Infection not only accelerates the progression of tissue damage and wound healing failure but also plays a role in the occurrence of reamputation. Therefore, aggressive and integrated prevention, early detection, and infection control are essential strategies for reducing amputation rates in patients with diabetic foot ulcers.

REFERENCES

Alay, H., Yilmaz, S., & Can, F. K. (2021). An evaluation of risk factors affecting amputation in patients with diabetic foot infection. Journal of Health Sciences and Medicine.

Almohammadi, A. A., Alnashri, M. M., Abdulrahman T Harun, R., Alsamiri, S. M., & Alkhatieb, M. T. (2022). Pattern and type of amputation and mortality rate associated with diabetic foot in Jeddah, Saudi Arabia: A retrospective Cohort Study. Annals of Medicine and Surgery, 73, 103174. https://doi.org/https://doi.org/10.1016/j.amsu.2021.103174

Alvaro, P. B., Joaquin, M. P. A., Ana, E. D. Y., Rolando, C. A., Antonio, Q. C., & Elisa, M. (2024). Risk factors associated with amputations in patients with diabetic foot infection. Seven years of experience in a reference hospital in Panama. The diabetic foot study group at Chiriqui (the FOOTCHI study group). Endocrine and Metabolic Science, 16, 100184. https://doi.org/https://doi.org/10.1016/j.endmts.2024.100184

Armstrong, D. G., Tan, T.-W., Boulton, A. J. M., & Bus, S. A. (2023). Diabetic Foot Ulcers: A Review. JAMA, 330(1), 62–75. https://doi.org/10.1001/jama.2023.10578

Chaudhary, N., Huda, F., Roshan, R., Basu, S., Rajput, D., & Singh, S. K. (2021). Lower Limb Amputation Rates in Patients With Diabetes and an Infected Foot Ulcer: A Prospective Observational Study. Wound Management & Prevention, 67(7), 22–30.

Crocker, R. M., Palmer, K. N. B., Marrero, D. G., & Tan, T.-W. (2021). Patient perspectives on the physical, psycho-social, and financial impacts of diabetic foot ulceration and amputation.

Journal of Diabetes and Its Complications, 35(8), 107960. https://doi.org/10.1016/j.jdiacomp.2021.107960

Evran, M., Sert, M., Akkuş, G., Biçer, Ö. S., Kesiktaş, E., Kurtaran, B., Aksungur, E., & Tetiker, T. (2021). Foot Ulcer a Devastating Complication of Diabetes Mellitus: A Single-Center Experience of 400 Patients. Endocrinology Research and Practice. https://doi.org/10.25179/tjem.2021-81583

Federation, I. D. (2024). IDF Diabetes Atlas (10th ed.). International Diabetes Federation.

Gong, H., Ren, Y., Li, Z., Zha, P., Bista, R., Li, Y., Chen, D., Gao, Y., Chen, L., Ran, X., & Wang, C. (2023). Clinical characteristics and risk factors of lower extremity amputation in the diabetic inpatients with foot ulcers. Frontiers in Endocrinology, 14([not specified]), [not specified]-[not specified]. https://doi.org/10.3389/fendo.2023.1144806

Hwang, Y. (2024). Analysis of Predictor Factors and Comorbidities About Lower-Extremity Repetitive Amputation in Diabetic Foot Ulcer and Infection: A Retrospective Study. Foot & Ankle Orthopaedics. https://doi.org/10.1177/2473011424s00135

JBI. (2020). *JBI manual for evidence synthesis*. Adelaide: Joanna Briggs Institute. https://doi.org/10.46658/JBIMES-20-01

Kilic, M., Olgun, N., Dündar, M., Celik Advan, S., Kücük, F. Z., Okcuoglu, S., Sahin, S., Kır Bicer, E., Ülker, Y., Sahin, P., & Taskiran, Z. (2025). Prevalence, risk level and risk factors of diabetic foot ulcer among adult individuals with diabetes in the Southeastern Anatolia Region of Turkiye. Journal of Tissue Viability, 34(1), 100839. https://doi.org/https://doi.org/10.1016/j.jtv.2024.12.003

Kim, J. (2023). The pathophysiology of diabetic foot: a narrative review. Journal of Yeungnam Medical Science, 40(4), 328–334. https://doi.org/10.12701/jyms.2023.00731

Lee, J. H., Yoon, J. S., Lee, H. W., Won, K. C., Moon, J. S., Chung, S. M., & Lee, Y. Y. (2020). Risk factors affecting amputation in diabetic foot. Journal of Yeungnam Medical Science, 37(4), 314–320. https://doi.org/10.12701/yujm.2020.00129

Leibovitch, M., Cahn, A., Gellman, Y. N., Haze, A., Peled, S., Amit, S., Elishoov, O., & Olshtain-Pops, K. (2021). Predictors and outcomes of diabetic foot ulcer infection with ESBL-producing bacteria in a large tertiary center. International Journal of Infectious Diseases, 113, 318–324. https://doi.org/https://doi.org/10.1016/j.ijid.2021.10.016

Lin, C., Liu, J., & Sun, H. (2020). Risk factors for lower extremity amputation in patients with diabetic foot ulcers: A meta-analysis. PLOS ONE. https://doi.org/10.1371/journal.pone.0239236

Mansoor, Z., & Modaweb, A. (2022). Predicting Amputation in Patients With Diabetic Foot Ulcers: A Systematic Review. Cureus, 14(7), e27245. https://doi.org/10.7759/cureus.27245

Matheson, E. M., Bragg, S. W., & Blackwelder, R. S. (2021). Diabetes-related foot infections: diagnosis and treatment. American Family Physician, 104(4), 386–394. https://www.aafp.org/pubs/afp/issues/2021/1000/p386.html

N, J. S., Punitha, S., & Rakshana, M. (2025). Outcome Predictors for Wound Healing and Amputation Risk in Patients with Diabetic Foot Ulcer. International Journal of Innovative Science and Research Technology, 10(9), 127–134. https://doi.org/10.38124/ijisrt/25sep188

Rodríguez-Rodríguez, N., Martínez-Jiménez, I., García-Ojalvo, A., Mendoza-Mari, Y., Guillén-Nieto, G., Armstrong, D. G., & Berlanga-Acosta, J. (2022). Wound Chronicity, Impaired Immunity and Infection in Diabetic Patients. MEDICC Review, 24(1), 44–58. https://doi.org/10.37757/MR2021.V23.N3.8

Roy, R., Singh, R. K., & Shafikhani, S. H. (2024). Infection in Diabetes: Epidemiology, Immune Dysfunctions, and Therapeutics. Contemporary Diabetes.

Saltoglu, N., Yemisen, M., Ergonul, O., Kadanali, A., Karagoz, G., Batirel, A., Ak, O., Eraksoy, H., Cagatay, A., Vatan, A., Sengoz, G., Pehlivanoglu, F., Aslan, T., Akkoyunlu, Y., Engin, D., Ceran, N., Erturk, B., Mulazimoglu, L., Oncul, O., … Ozyazar, M. (2015). Predictors for limb loss among patient with diabetic foot infections: an observational retrospective multicentric

study in Turkey. Clinical Microbiology and Infection, 21(7), 659–664. https://doi.org/https://doi.org/10.1016/j.cmi.2015.03.018

Sánchez Correa, C. A., Briceño Sanín, I., Bautista Valencia, J. J., Niño, M. E., & Robledo Quijano, J. (2025). [Translated article] Reamputation prevalence after minor feet amputations in patients with diabetic foot: A cross sectional study. Revista Española de Cirugía Ortopédica y Traumatología, 69(1), T70–T76. https://doi.org/https://doi.org/10.1016/j.recot.2024.11.012

Santra, S., Rawat, A., Pattarayan, D., & Roy, S. (2020). Chapter 3 - Chronic infection and inflammation: Hallmarks of diabetic foot ulcers (D. Bagchi, A. Das, & S. B. T.-W. H. Roy Tissue Repair, and Regeneration in Diabetes (eds.); pp. 39–47). Academic Press. https://doi.org/https://doi.org/10.1016/B978-0-12-816413-6.00003-4

Snyder, H. (2019). Literature review as a research methodology: An overview and guidelines. Journal of Business Research, 104, 333–339. https://doi.org/https://doi.org/10.1016/j.jbusres.2019.07.039

Toledo, M. C. B., Soares, S., & Costa, A. M. (2025). A relação entre o "pé diabético" e amputações dos membros inferiores: uma revisão sistemática. Revista CPAQV. https://doi.org/10.36692/v17n1-19r

Ugwu, E., Adeleye, O., Gezawa, I., Okpe, I., Enamino, M., & Ezeani, I. (2019). Predictors of lower extremity amputation in patients with diabetic foot ulcer: findings from MEDFUN, a multi-center observational study. Journal of Foot and Ankle Research, 12, 34. https://doi.org/10.1186/s13047-019-0345-y

Wang, D., & Jupiter, D. C. (2025). Associations of Diabetic Foot Infection with Ulcer Prognosis and Amputation Timing in Patients with Type 2 Diabetes Mellitus. Journal of the American Podiatric Medical Association, 115(6). https://doi.org/10.7547/23-230

Wang, X., Yuan, C.-X., Xu, B., & Yu, Z. (2022). Diabetic foot ulcers: Classification, risk factors and management. World Journal of Diabetes, 13(12), 1049–1065. https://doi.org/10.4239/wjd.v13.i12.1049

Wukich, D. K., Johnson, M. J., & Raspovic, K. M. (2022). Limb Salvage in Severe Diabetic Foot Infection. Foot and Ankle Clinics, 27(3), 655–670. https://doi.org/https://doi.org/10.1016/j.fcl.2022.02.004

Xu, S., Herrera, A., Schechter, C., Tabassum, H., Milosavljevic, J., Lopez Fanas, R., Daily, J. P., & Myers, A. K. (2024). The Risk of and Associated Demographic and Laboratory Variables for Amputations for Inpatients with Diabetic Foot Ulcers. Endocrine Practice, 30(8), 758–764. https://doi.org/https://doi.org/10.1016/j.eprac.2024.04.019

Zhang, Y., Cramb, S. M., McPhail, S. M., Pacella, R., van Netten, J. J., Kinnear, E. M., & Lazzarini, P. A. (2025). The incidence of and risk factors for hospitalisations and amputations for people with diabetes-related foot ulcers in Queensland, 2011-19: an observational cohort study. The Medical Journal of Australia, 223(3), 149–158. https://doi.org/10.5694/mja2.52703