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# RISK FACTORS OF PHANTOM LIMB PAIN IN PATIENTS WITH LOWER LIMB AMPUTATIONS

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Phantom pain is a common and complex complication following limb amputation. Current pharmacological, psychological, and rehabilitative approaches are only partially effective, indicating the need for further research.

This study aimed to examine risk factors associated with the occurrence of phantom pain in patients with lower limb amputations.

A cross-sectional study was conducted at the Clinic of Medical Rehabilitation of the University Clinical Center of Vojvodina in Novi Sad, including 53 patients with acquired lower limb amputation in either the pre-prosthetic or prosthetic phase of rehabilitation. Data were collected from medical records and patient history regarding age, sex, presence of cardiovascular comorbidities, diabetes mellitus, various types of pain, body mass index, level of amputation, and characteristics of the residual limb. Statistical analysis was performed using JASP software, applying descriptive statistics, the Student's t-test, the $\chi^2$ test, and binary logistic regression to examine factors associated with the occurrence of phantom limb pain. Statistical significance was set at $p < 0.05$.

Phantom limb pain was reported in 16 patients (30.18%). A statistically significant association was found between phantom pain and the level of amputation ($p = 0.046$), as well as the phase of rehabilitation ($p = 0.011$).

The level of amputation and the phase of rehabilitation represent significant risk factors for the development of phantom limb pain.

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***Key words:*** *phantom pain, lower limb amputation, diabetes mellitus*

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## Introduction

According to data from the World Health Organization from 2023, approximately 1.5 million amputations are performed worldwide each year. Limb amputation can have significant physical consequences, such as impaired gait and reduced limb mobility, as well as psychological consequences such as depression and anxiety, and socio-economic consequences (1). After limb amputation, patients often develop different types of pain, including residual limb pain, phantom limb pain, and musculoskeletal pain, which can be acute but are often chronic in nature (2). Despite innovations in surgical techniques, rehabilitation procedures, and prosthetics, literature data report the prevalence of phantom limb pain among patients after limb amputation ranging from 6.7% to 88.1% (3). The occurrence of phantom limb pain is one of the most common complications following limb amputation. Previous studies have shown that the intensity of pain prior to amputation, the presence of residual limb pain, and phantom sensations are significant predictors of phantom limb pain development in patients with lower limb amputation (4, 5). Additional risk factors include amputation due to diabetic complications, higher (proximal) level of amputation, older age, lack of preoperative counseling, and inadequate pain control before surgery (6, 7). The exact mechanism behind this phenomenon is still not fully clarified; it is considered to result from a complex combination of peripheral, central, and psychological mechanisms. Consequently, the treatment of phantom limb pain must be multidisciplinary. Since all pharmacological, psychological, and rehabilitation procedures used in the treatment of phantom limb pain are only partially effective, it is necessary to further investigate the mechanism of onset of this disorder as well as the risk factors contributing to its development (8).

**Aim**

This study aimed to investigate individual risk factors that, according to the literature, are associated with the development of phantom limb pain as a complication following lower limb amputation.

**Materials and Methods**

A cross-sectional study was conducted at the Clinic of Medical Rehabilitation of the University Clinical Center of Vojvodina (UCCV) in Novi Sad and included patients who had undergone lower limb amputation and who were evaluated as part of the pre-prosthetic phase of rehabilitation treatment or were admitted for the prosthetic phase of rehabilitation in the outpatient clinic service, day hospital, or inpatient ward of the Clinic.

The study included 53 participants with acquired lower limb loss. Based on anamnesis data and medical documentation, information was collected regarding patient age, sex, presence of cardiovascular (CVS) comorbidities (valvular diseases, episodes of heart failure, arrhythmias, cardiomyopathies, hypertension, hypotension, oedema, angina pectoris, heart and stroke history) and diabetes mellitus (DM), as well as the presence of pain (phantom limb pain, residual limb pain, or musculoskeletal pain). Clinical examination included measurement of body weight and height to calculate the body mass index (BMI), determination of amputation level, and assessment of residual limb condition, including formation and length. The study was conducted with prior approval of the Ethics Committee, approval number 00-364, issued on Oct. 15, 2024.

The collected data were entered into a specially created Microsoft Excel 2013 database. During statistical processing, descriptive statistical methods were used: measures of central tendency (arithmetic mean) and measures of variability (standard deviation). For the complete statistical analysis, JASP software was used. Student’s t-test or $\chi^2$ test was applied to determine statistically significant associations or differences. Binary logistic regression was used to examine the relationship between different factors (CVS diseases, DM, BMI, level of amputation, rehabilitation phase, residual limb formation and length) and the occurrence of phantom limb pain, which was used as a dependent variable with possible values yes/no. P-values $< 0.05$ were considered statistically significant.

**Results**

Of the total 53 participants, 39 (74.13%) were male and 14 (25.86%) were female. The mean age of participants was 64 years, with the oldest participant being 85 and the youngest 35 years old. A total of 22 (41.51%) patients had transtibial amputation, while 31 (58.49%) had transfemoral amputation. Sixteen patients experienced phantom limb pain, three reported musculoskeletal pain, and five had localized residual limb pain. Descriptive statistical measures are shown in tabular form (Table 1).

**Table 1.** Descriptive statistics are presented for all quantitative variables, including mean value, standard deviation, minimum and maximum values

| | AGE | HEIGHT | WEIGHT | BMI | LENGTH OF RESIDUAL LIMB |
|---|---|---|---|---|---|
| Number | 53 | 53 | 53 | 53 | 53 |
| Missing | 0 | 0 | 0 | 0 | 0 |
| Mean | 64.434 | 173.396 | 78.151 | 25.809 | 31.472 |
| Standard deviation | 9.912 | 9.400 | 19.671 | 5.691 | 9.758 |
| Minimum | 35.000 | 155.000 | 47.000 | 16.700 | 0.000 |
| Maximum | 85.000 | 188.000 | 143.000 | 44.100 | 49.000 |

Using the $\chi^2$ test, no statistically significant association was found between phantom limb pain and sex ($p = 0.473$) or residual limb formation ($p = 0.293$), nor with the presence of CVS comorbidities ($p = 0.692$) and DM ($p = 0.632$). On the other hand, statistically significant associations were found between phantom limb pain and amputation level ($p = 0.046$) and rehabilitation phase ($p = 0.011$). Logistic regression results also indicated that these two factors represent statistically significant predictors of phantom limb pain occurrence. For amputation level, the coefficient was -4.44, with $p = 0.019$, where the negative coefficient indicates that patients with transtibial amputation (coded as 1) have a significantly lower probability of developing phantom limb pain compared to those with transfemoral amputation (Figure 1). For the rehabilitation phase, the coefficient was -2.59, with $p = 0.031$, indicating that patients in the prosthetic phase of rehabilitation have a lower probability of developing phantom limb pain compared to those in the pre-prosthetic phase (Figure 2). Binary logistic regression did not show a statistically significant association between CVS comorbidities and DM with phantom limb pain. Stratified analyses were also performed: the group of patients with transfemoral amputation was analyzed for DM, and patients in different rehabilitation phases (prosthetic and pre-prosthetic) were analyzed for CVS comorbidities. In both stratified analyses, no statistically significant associations were found. Using Student's t-test, no statistically significant difference was found between the occurrence of phantom limb pain and age ($p = 0.146$), BMI ($p = 0.072$), or residual limb length ($p = 0.968$). No statistically significant differences were found for any of the examined parameters in relation to residual limb pain or musculoskeletal pain.

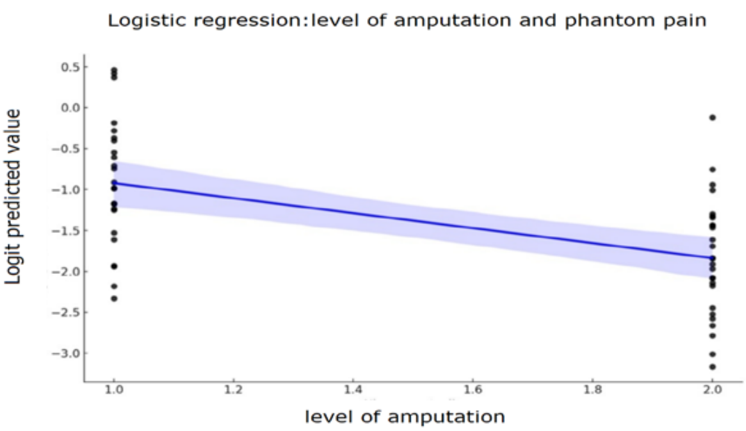


**Figure 1**. Graphical representation of the applied logistic regression, which in this case was used to examine the association between the level of amputation and the occurrence of phantom limb pain. The blue line represents the logistic regression prediction, while the shaded area corresponds to the 95% confidence interval

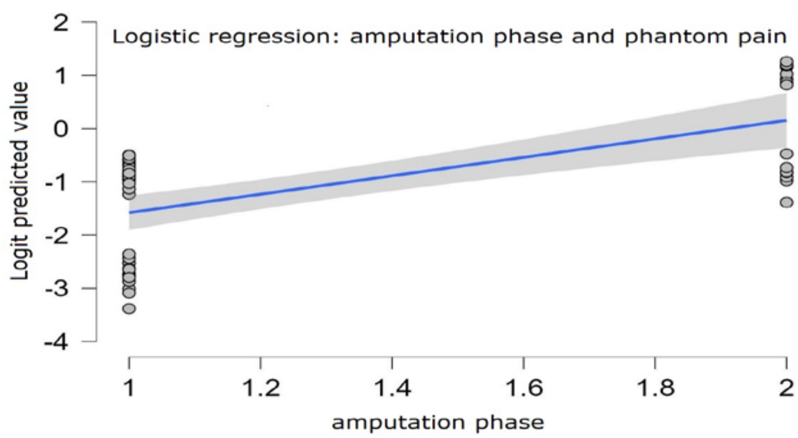


**Figure 2.** Graphical representation of the applied logistic regression, which in this case was used to examine the association between the amputation phase and the occurrence of phantom limb pain. The blue line represents the logistic regression prediction, while the shaded area corresponds to the 95% confidence interval

## Discussion

Our results indicate that there is an association between phantom limb pain and both the level of amputation and the rehabilitation phase, whereas no association was found with sex, CVS comorbidities, or DM, nor were there statistically significant differences related to patient age, residual limb length, or residual limb formation. The exact mechanism of pain persistence in the limb even after its removal is still not fully understood. The mechanisms of phantom limb pain can be divided into four sub-processes, like all pain pathways: transduction, transmission, perception, and modulation. After limb amputation, the motor cortex remains intact, and the brain continues to receive signals as if they are coming from the missing limb, creating a mismatch between motor commands and proprioceptive or somatosensory impulses from the limb (9). There is also a conflict between signals from the missing limb and efferent motor signals, which results in an incomplete somatosensory-motor feedback loop. This interaction between cortical functions and descending pain-inhibitory pathways (thalamus, periaqueductal gray matter, nucleus gigantocellularis, and raphe nucleus) leads to reduced pain inhibition and increased activation of N-methyl-D-aspartate (NMDA) receptors in the spinal cord, causing increased sensitivity (allodynia, hyperalgesia) (10). Factors reported in literature to be associated with the development of phantom limb pain include sex, age, pain before surgery, presence of peripheral nerve damage prior to surgery (diabetic polyneuropathy, etc.), higher level of amputation and shorter residual limb length, prosthetization, inadequate prostheses, etc (11). Regarding the association between sex and risk of developing phantom limb pain, study results vary. Some studies report a higher prevalence in males, with one proposed explanation being more frequent traumatic lower limb amputations among men, often of occupational nature (e.g., military service, high-risk jobs). On the other hand, several studies found no difference between sexes (12). Some studies indicate that younger individuals have an increased risk of developing phantom limb pain due to greater neuroplasticity and nervous system reactivity (13), while older patients more commonly experience chronic phantom limb pain due to more frequent vascular comorbidities and DM (14). In patients with DM, complications such as diabetic neuropathy, vascular complications, and inflammatory processes may increase the risk of developing phantom limb pain (15, 16). Other studies have shown opposite results, where the presence of diabetic neuropathy was associated with a lower incidence of phantom limb pain, explained by reduced nerve sensitivity due to severe nerve damage (17). Literature data suggest that phantom limb pain is more common in patients with transfemoral amputation compared to transtibial amputation, explained by the greater degree of nerve injury during higher-level amputations. This is linked not only to a higher risk of phantom limb pain but also residual limb pain (18, 19). Similarly, some studies have demonstrated an inverse relationship between residual limb length and phantom limb pain occurrence (20). Phantom limb pain generally occurs more frequently in the pre-prosthetic phase compared to the prosthetic phase. A simple explanation for this is that these symptoms are more common immediately after surgery, when nerve damage has just occurred, before the pain has had the opportunity to become chronic. Other explanations include the psychological component of pain and the improvement in overall patient quality of life after receiving a prosthesis, as well as better neurological integration between the residual limb and the central nervous system (21).

Our study had several limitations. Considering that this was a cross-sectional study, it was not possible to determine longitudinal relationships between different parameters or causality. Additionally, the small sample size and heterogeneity of the participants limit the ability to draw definitive conclusions.

## Conclusion

The results of this study indicate a statistically significant association between phantom limb pain and amputation level as well as rehabilitation phase. On the other hand, no association was found with sex, prevalence of CVS diseases and DM, nor were statistically significant differences found regarding age, residual limb length, or formation. Further research and a better understanding of these risk factors and the mechanisms behind phantom limb pain, as one of the most common complications following lower limb amputation, are necessary for improved prevention and adequate treatment of this condition.

## References


1. Kulkarni PG, Paudel N, Magar S, Santilli MF, Kashyap S, Baranwal AK, et al. Overcoming challenges and innovations in orthopedic prosthesis design: an interdisciplinary perspective. Biomed Mater Devices 2024; 2(1):58-69. [CrossRef] [PubMed]
2. Hsu E, Cohen SP. Postamputation pain: epidemiology, mechanisms, and treatment. J Pain Res 2013; 6: 121-36. [CrossRef] [PubMed]
3. Stankevicius A, Wallwork SB, Summers SJ, Hordacre B, Stanton TR. Prevalence and incidence of phantom limb pain, phantom limb sensations and telescoping in amputees: a systematic rapid review. Euro J Pain 2021; 25(1):23-38. [CrossRef] [PubMed]
4. Limakatso K, Bedwell GJ, Madden VJ, Parker R. The prevalence and risk factors for phantom limb pain in people with amputations: a systematic review and meta-analysis. PloS one 2020; 15(10):e0240431. [CrossRef] [PubMed]
5. Hubbard G, McNinch N, Tullington J, Merino K, Nerad R, Adams D, et al. Factors associated with phantom limb pain. JVS-VI 2023; 1:100018. [CrossRef]
6. Ishigami S, Boctor C. Epidemiology and risk factors for phantom limb pain. Front Pain Res. 2024; 5:1425544. [CrossRef] [PubMed]
7. Limakatso K, Ndhlovu F, Usenbo A, Rayamajhi S, Kloppers C, Parker R. The prevalence and risk factors for phantom limb pain: a cross-sectional survey. BMC Neurol 2024; 24(1):57. [CrossRef] [PubMed]
8. Subedi B, Grossberg GT. Phantom limb pain: mechanisms and treatment approaches. Pain Res Manag 2011; 2011:864605. [CrossRef] [PubMed]
9. Shi W, Prabhakaran B, Annaswamy T. Phantom pain: mechanisms and updates in management. Front Pain Res 2025; 6:1567956. [CrossRef] [PubMed]
10. Ahuja V, Thapa D, Ghai B. Strategies for prevention of lower limb post-amputation pain: A clinical narrative review. J Anaesthesiol Pharmacol 2018; 34(4):439-49. [CrossRef] [PubMed]
11. Jiang S, Zheng K, Wang W, Pei Y, Qiu E, Zhu G. Phantom limb pain and sensations in Chinese malignant tumor amputees: a retrospective epidemiological study. Neuropsych Dis Treat 2021;17:1579-87. [CrossRef] [PubMed]
12. Mogil JS. Sex differences in pain and pain inhibition: multiple explanations of a controversial phenomenon. Nat Rev Neurosci 2012; 13(12):859-66. [CrossRef] [PubMed]
13. Münger M, Pinto CB, Pacheco-Barrios K, Duarte D, Enes Gunduz M, Simis M, et al. Protective and risk factors for phantom limb pain and residual limb pain severity. Pain Pract 2020; 20(6):578-87. [CrossRef] [PubMed]
14. Huo X, Huang P, Di H, Ma T, Jiang S, Yao J, et al. Risk factors analysis of phantom limb pain in amputees with malignant tumors. J Pain Res 2023;16:3979-92. [CrossRef] [PubMed]
15. Collins KL, Russell HG, Schumacher PJ, Robinson-Freeman KE, O'Conor EC, Gibney KD, et al. A review of current theories and treatments for phantom limb pain. J Clin Inv 2018; 128(6):2168-76. [CrossRef] [PubMed]
16. Noguchi S, Saito J, Nakai K, Kitayama M, Hirota K. Factors affecting phantom limb pain in patients undergoing amputation: retrospective study. J Anesthes 2019; 33(2):216-20. [CrossRef] [PubMed]
17. Lans J, Groot OQ, Hazewinkel MH, Kaiser PB, Lozano-Calderón SA, Heng M, et al. Factors related to neuropathic pain following lower extremity amputation. Plast Reconst Surg 2022; 150(2):446-55. [CrossRef] [PubMed]
18. Diers M, Krumm B, Fuchs X, Bekrater-Bodmann R, Milde C, Trojan J, et al. The prevalence and characteristics of phantom limb pain and non-painful phantom phenomena in a nationwide survey of 3,374 unilateral limb amputees. J Pain 2022; 23(3):411-23. [CrossRef] [PubMed]
19. Nees TA, Matt C, Deisenhofer J, Block J, Wolf SI, Renkawitz T, et al. Pain after lower limb amputations: insights from the Heidelberg Amputation Registry. Medicina (Kaunas) 2024; 60(11):1887. [CrossRef] [PubMed]
20. Streit F, Bekrater-Bodmann R, Diers M, Reinhard I, Frank J, Wüst S, et al. Concordance of phantom and residual limb pain phenotypes in double amputees: evidence for the contribution of distinct and common individual factors. J Pain 2015; 16(12):1377-85. [CrossRef] [PubMed]
21. Bekrater-Bodmann R, Reinhard I, Diers M, Fuchs X, Flor H. Relationship of prosthesis ownership and phantom limb pain: results of a survey in 2383 limb amputees. Pain 2021; 162(2):630-40. [CrossRef] [PubMed]

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# FAKTORI RIZIKA ZA NASTANAK FANTOMSKOG BOLA KOD PACIJENATA NAKON AMPUTACIJE DONJIH EKSTREMITETA

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Fantomski bol je česta i kompleksna komplikacijakoja se može javiti nakon amputacije ekstremiteta. S obzirom na to da su postojeće farmakološke, psihološke i rehabilitacione metode samo delimično efikasne u prevazilaženju kod problema, postoji potreba za dodatnim istraživanjima. Cilj ovog rada bilo je ispitivanje faktora rizika povezanih s pojavom fantomskog bola kod pacijenata kojima je obavljena amputacija donjih ekstremiteta. Studija preseka je sprovedena u Centru za fizikalnu medicinu i rehabilitaciju Univerzitetskog kliničkog centra Vojvodine. U studiju su bila uključena 53 pacijenta (39 muškaraca, 14 žena) podvrnuta amputaciji donjih ekstremiteta ispod kolena (22) i iznad kolena (31), u pretprotetičkoj i protetičkoj fazi rehabilitacije. Podaci su sakupljeni uvidom u medicinsku dokumentaciju i kliničkim pregledom pacijenata. Fantomski bol je zabeležen kod 16 (30,18%) pacijenata. Ustanovljena je statistički značajna povezanost između pojave fantomskog bola i nivoa amputacije ($p = 0,046$), kao i između pojave fantomskog bola i faze rehabilitacije ($p = 0,011$). Nivo amputacije i faza rehabilitacije predstavljaju statistički značajne faktore rizika za razvoj fantomskog bola.

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***Ključne reči***: *fantomski bol, amputacija donjih ekstremiteta, dijabetes melitus*