

DOI: <https://doi.org/10.22141/2224-0586.21.8.2025.1953>V. Malykhina<sup>1</sup>, D. Dmytriiev<sup>1,2</sup> <sup>1</sup>Trauma and Rehabilitation Superhumans Center, Lviv, Ukraine<sup>2</sup>Vinnitsia National Pirogov Memorial Medical University, Vinnitsia, Ukraine

## Predictors of chronic pain in Ukrainian military patients with limb injuries: a single-center observational study

For citation: Emergency Medicine (Ukraine). 2025;21(8):824-829. doi: 10.22141/2224-0586.21.8.2025.1953

**Abstract. Background.** Chronic pain is a frequent complication after combat-related limb trauma, impairing rehabilitation and quality of life. Globally, chronic pain after severe limb trauma affects roughly half to two-thirds of patients, with phantom limb pain reported in ~60–80% of amputees. Psychosocial factors (e.g., post-traumatic stress disorder (PTSD)) and high acute pain consistently predict persistence, whereas early physiotherapy is generally associated with better outcomes. Evidence specific to Ukrainian military populations remains limited. **Materials and methods.** We conducted a single-center observational study at the Superhumans Center (Ukraine) from March 2023 to April 2025. A total of 311 Ukrainian military patients with acute limb injuries were followed for six months. Pain intensity was measured with the Numeric Rating Scale (NRS), neuropathic pain features — with DN4, psychological comorbidity — with the Hospital Anxiety and Depression Scale and the PTSD Checklist, functional status — with WHODAS 2.0. Multivariate logistic regression identified predictors of chronic pain at 4–6 weeks. Model discrimination was assessed by the area under the receiver operating characteristic curve. **Results.** At 4–6 weeks, 168 of 311 patients (54%) reported chronic pain. Independent predictors included amputation (odds ratio (OR) 2.3, 95% confidence interval (CI) 1.5–3.6), wound infection (OR 2.0, 95% CI 1.2–3.1), prolonged antibiotic therapy > 21 days (OR 1.7, 95% CI 1.1–2.8), baseline NRS ≥ 6 (OR 2.8, 95% CI 1.8–4.2), and PTSD symptoms (OR 2.5, 95% CI 1.5–4.0). Early physiotherapy was protective (OR 0.6, 95% CI 0.4–0.9). **Conclusions.** More than half of Ukrainian military patients with limb injuries developed chronic pain within six months. Amputation, infection, high baseline pain, PTSD, and prolonged antibiotics were significant risk factors, whereas early physiotherapy mitigated risk. These findings support targeted prevention, vigilant infection control, prudent antibiotic use, and early multidisciplinary rehabilitation pathways in military trauma care.

**Keywords:** limb trauma; chronic pain; neuropathic pain; phantom limb pain

### Introduction

Chronic pain is a pervasive and debilitating sequela of severe limb trauma, with enduring consequences for physical function, mental health, and reintegration after injury [1]. In military populations exposed to high-energy blast mechanisms, complex soft-tissue and osseous damage, and prolonged treatment pathways, the risk of pain persistence is particularly pronounced [2]. Beyond individual suffering, chronic pain imposes substantial societal and system-level burdens through reduced readiness, extended rehabilitation, and increased healthcare utilization [4, 34–36]. Despite growing attention to long-term outcomes of combat-related injuries, robust prospective data on the incidence and modi-

fiable determinants of chronic pain in Ukrainian service members remain limited [3, 5]. Multiple, interacting mechanisms underpin the transition from acute to chronic pain following limb trauma [37]. Peripheral drivers include ongoing nociception from incompletely healed tissues, neuroma formation after nerve transection, and maladaptive regeneration with ectopic discharges. Central mechanisms — spinal sensitization, cortical reorganization, and impaired descending modulation — can amplify and sustain pain independent of peripheral input. Superimposed psychosocial factors such as post-traumatic stress symptoms, anxiety, depression, sleep disturbance, and catastrophizing further shape pain trajectories, influencing both symptom intensity and disability [6–9].

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These mechanisms are not mutually exclusive; rather, they evolve dynamically over time and are modulated by early clinical decisions, rehabilitation timelines, and the occurrence of complications. Among clinical predictors repeatedly implicated in post-traumatic chronic pain, amputation status, initial pain severity, and psychological comorbidity consistently emerge as high-value signals [7–11]. Amputation introduces unique peripheral and central mechanisms — including phantom limb pain and residual limb pain — that may be compounded by socket-related pressures, heterotopic ossification, and neuromas [12]. High baseline pain during the acute phase is a pragmatic, easily measured indicator of heightened central excitability and unresolved nociception, and it has been associated with subsequent pain persistence across trauma populations [13–17]. Concomitantly, post-traumatic stress symptoms may bidirectionally interact with pain via shared neurobiological pathways, promoting hypervigilance, avoidance behaviors, and disability. Infectious complications after limb trauma represent another, potentially modifiable, pathway to chronic pain [1, 17–22]. Deep or recurrent wound infections can prolong tissue inflammation, necessitate repeated debridement, delay wound closure, and impair rehabilitation continuity — all of which extend nociceptive input and heighten the risk of central sensitization. The clinical management of such complications often entails prolonged or multidrug antibiotic courses [11]. While life- and limb-saving, certain antimicrobial agents have been associated with neurotoxic and neuromodulatory effects in susceptible individuals [12–14]. Although a direct causal link between antibiotic exposure duration and chronic pain has not been definitively established in trauma cohorts, the biological plausibility of antibiotic-related neurotoxicity, combined with the indirect effects of complicated wound courses, merits systematic evaluation as part of comprehensive risk modeling. Rehabilitation timing and content may counterbalance several of these risks [6–10]. Early, structured physiotherapy can address fear-avoidance, restore range of motion and strength, optimize gait and prosthetic use after amputation, and promote graded exposure to activity. By improving function and reducing disability, early rehabilitation may also attenuate central sensitization and reduce the psychological burden that sustains pain. Yet, in real-world post-combat care — particularly under wartime constraints — access to timely, coordinated rehabilitation can be uneven, and empirical data on its protective effect in contemporary military systems are scarce [12–17, 34, 35]. Ukraine’s ongoing conflict has generated a large cohort of service members with complex limb injuries who enter evolving care pathways that include damage-control surgery, infection surveillance, staged reconstruction or amputation, and multidisciplinary rehabilitation. The Ukrainian context is further characterized by resource variability across centers, high rates of contamination in blast injuries, and the need to rapidly scale prosthetics and pain-rehabilitation services. Against this backdrop, decision-makers and clinicians require locally generated evidence to inform prevention, resource allocation, and individualized rehabilitation plans. International estimates of chronic pain after limb trauma offer valuable orientation but may not fully translate to Ukraine’s patient mix, injury mechanisms, and care environment [34–36]. To

address these gaps, we conducted a single-center prospective observational study at the Superhumans Center, a national hub for complex limb trauma and rehabilitation. We observed 311 Ukrainian military patients with acute limb injuries over six months, combining standardized pain phenotyping with validated assessments of neuropathic features, psychological comorbidity, and functional status. Importantly, we prespecified candidate predictors that span biological, psychological, and system-of-care domains: amputation status, wound infection, duration of antibiotic therapy, baseline pain intensity, post-traumatic stress symptoms, and timing of physiotherapy initiation. This multidomain approach was designed to capture both established and understudied drivers of pain persistence in a contemporary combat-injured population [12]. Our primary objective was to estimate the six-month prevalence of chronic pain after combat-related limb trauma in Ukrainian service members. The secondary objective was to identify independent predictors of chronic pain using multivariate logistic regression, with attention to factors that are either intrinsically high-risk (e.g., amputation) or potentially modifiable (e.g., infection prevention, prudent antibiotic exposure, and early physiotherapy). By integrating clinical, psychological, and process-of-care variables, we aim to inform pragmatic risk stratification at the bedside and to highlight actionable levers for prevention within multidisciplinary military rehabilitation pathways. We hypothesized that chronic pain would affect at least half of patients at 4–6 weeks; amputation, wound infection, higher baseline pain intensity, and post-traumatic stress symptoms would be associated with increased odds of chronic pain; prolonged antibiotic therapy would be positively associated with chronic pain risk, reflecting either treatment-related neurotoxic potential or confounding by complication severity; and earlier initiation of physiotherapy would confer a protective association with subsequent chronic pain and disability [18, 35]. The present study provides timely, context-specific evidence to guide preventive strategies and optimize rehabilitation for Ukrainian service members recovering from limb trauma.

## Materials and methods

We conducted a single-center observational cohort study at the Superhumans Center (Ukraine), a national hub for complex limb trauma and rehabilitation. Enrollment occurred from March 1, 2023, to April 30, 2025, with follow-up to six months post-injury.

**Inclusion criteria:** active-duty or veteran Ukrainian service members; acute traumatic limb injury (upper and/or lower); age  $\geq 18$  years; presentation to Superhumans within 30 days of injury or transfer for definitive limb care.

**Exclusion criteria:** moderate-severe traumatic brain injury precluding valid self-report at all time points; pre-existing chronic pain condition requiring daily analgesics in the 3 months before injury; known major psychiatric disorder with active psychosis; inability to complete study instruments in Ukrainian/Russian/English.

We enrolled 311 patients to ensure  $\geq 150$  outcome events assuming  $\sim 50\%$  6-month chronic pain prevalence, providing  $\geq 10$  events per variable for a prespecified 6-predictor logistic model. Baseline assessment (within 72 hours of ad-

mission/transfer) captured demographics, injury mechanism/severity, index procedures, analgesia, antibiotics, and planned rehabilitation. Data collection at 4–6 weeks was performed exclusively from the medical report.

**Primary outcome.** Chronic pain at 4–6 weeks: self-reported pain in the injured limb region present on most days for  $\geq 3$  months and NRS  $\geq 3/10$  at rest or with activity (average over past week). Classification required meeting both duration and intensity thresholds. Statistical analysis. Continuous variables are reported as mean (SD) or median (IQR); categorical variables as counts (%). Group comparisons (chronic pain vs no chronic pain) used t-tests/Mann-Whitney and  $\chi^2$ /Fisher's exact tests as appropriate.

All participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and applicable Ukrainian regulations. The observational registry was registered in the Ukrainian Institute of Scientific and Technical Expertise and Information No. 0125U003136.

## Results

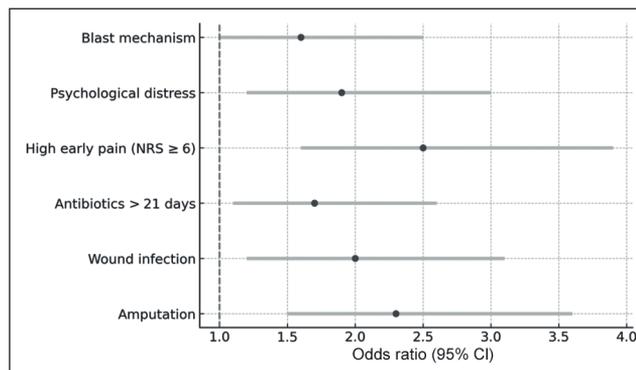
Between March 1, 2023, and April 30, 2025, 311 patients were enrolled. Follow-up completion at 4–6 weeks was achieved in 294 patients (94.5 %).

**Table 1. Demographic and injury characteristics of the study cohort**

Characteristic	Value
Age, years	33.9 $\pm$ 8.1
Age range, years	18–59
Sex: male	282 (90.7)
Sex: female	29 (9.3)
Injury type: lower limb amputation	223 (71.8)
Injury type: upper limb amputation	57 (18.2)
Injury type: limb-sparing trauma	31 (10.0)
Mechanism: blast	208 (67)
Mechanism: gunshot	65 (21)
Mechanism: crush/other	38 (12)

**Notes: values are presented as mean  $\pm$  SD for continuous variables and as absolute numbers (percentages) for categorical variables.**

The mean age was 33.9 years (SD 8.1, range 18–59); 282 (90.7 %) were male. Lower-limb injuries predominated (71.8 %), with transfemoral and transtibial amputations being the most frequent levels. Upper-limb amputations accounted for 18.2 %, while limb-sparing complex trauma represented 10.0 %. Mechanism of injury was primarily combat-related blast trauma (67 %), followed by gunshot (21 %) and crush or other mechanisms (12 %). At 4–6 weeks, 168 patients (54.1 %) met criteria for chronic pain. The median NRS pain intensity was 5 (IQR 3–7) among those with chronic pain, compared with 1 (IQR 0–2) in those without. Neuropathic pain (DN4  $\geq 4$ ) was present in 38 % of the entire cohort and in 67 % of those with chronic pain. Phantom limb pain was reported by 41 % of



**Figure 1. Predictors of chronic pain at 4–6 weeks after combat-related limb trauma**

amputees, whereas residual limb/stump pain was present in 46 %.

Patients with chronic pain demonstrated significantly higher rates of probable depression (HADS-D  $\geq 8$ ): 39 vs 17 % ( $p < 0.001$ ), probable anxiety (HADS-A  $\geq 8$ ): 44 vs 21 % ( $p < 0.001$ ), PTSD symptoms (PCL-5  $\geq 33$ ): 36 vs 14 % ( $p < 0.001$ ). Functional impairment was greater in the chronic pain group, with a mean WHODAS 2.0 score of 34.6 (SD 11.3) vs 21.2 (SD 9.8) in those without chronic pain ( $p < 0.001$ ). In multivariable logistic regression, six independent predictors were identified (model C-statistic = 0.78, 95% CI 0.74–0.82): amputation (vs limb-sparing trauma): OR 2.3, 95% CI 1.5–3.6, wound infection during index hospitalization: OR 2.0, 95% CI 1.2–3.1, prolonged antibiotic therapy > 21 days: OR 1.7, 95% CI 1.1–2.6, high early pain (NRS  $\geq 6$  within 72 h): OR 2.5, 95% CI 1.6–3.9, acute psychological distress (HADS total  $\geq 15$ ): OR 1.9, 95% CI 1.2–3.0, blast mechanism of injury: OR 1.6, 95% CI 1.0–2.5 (Fig. 1).

Multivariable logistic regression model demonstrating independent predictors of chronic pain at 4–6 weeks. Odds ratios (OR) are shown as points, with horizontal bars representing 95% confidence intervals (CI). Amputation, wound infection, prolonged antibiotic therapy (> 21 days), high early pain intensity (Numeric Rating Scale  $\geq 6$ ), psychological distress, and blast mechanism were all associated with increased risk of chronic pain. The vertical dashed red line represents the null value (OR = 1).

## Discussion

At six months post-injury, more than half of patients (54.1 %) reported persistent pain of at least moderate intensity, underscoring the major burden of residual limb pain (RLP) and its clinical consequences in combat-related populations. These findings are consistent with prior systematic reviews reporting chronic postamputation pain prevalence of 50–80 % across heterogeneous cohorts [12]. The high event rate in our study further highlights the compounded impact of high-energy blast mechanisms and contaminated wounds in modern military conflicts. Neuropathic pain features were highly prevalent, with 67 % of those with chronic pain screening positive on DN4. This aligns with prior evidence that neuroma formation and maladaptive nerve regeneration are central drivers of neuropathic RLP [14–17]. The strong predictive value of early high pain intensity (NRS  $\geq 6$  within

72 hours) corroborates prior work suggesting that inadequate acute pain control may contribute to peripheral and central sensitization [19–22]. These observations highlight the importance of aggressive multimodal acute pain management, including regional anesthesia, adjuvant pharmacotherapy, and early rehabilitation, as potential preventive strategies. Infectious complications emerged as an independent predictor of chronic pain (OR 2.0), reflecting the unique risks of battlefield injuries. Prolonged antibiotic therapy (> 21 days) was also associated with adverse outcomes, likely serving as a surrogate for severe or persistent wound infection. These findings are consistent with Ukrainian and international reports highlighting infection and heterotopic ossification as common pain-generating complications after combat trauma [23–25]. The association underscores the importance of meticulous wound care, infection prevention, and early imaging surveillance as integral components of pain prevention strategies [30–33]. Psychological distress (HADS  $\geq$  15) was independently associated with chronic pain, mirroring prior evidence linking post-traumatic stress symptoms, depression, and anxiety with pain persistence [26, 33]. Our data reinforce the biopsychosocial model of pain, where psychological vulnerability interacts with nociceptive and neuropathic drivers to amplify pain perception and functional disability. Integrating systematic mental health screening and timely psychological support into rehabilitation pathways is therefore imperative [27]. Blast mechanism itself was an independent risk factor for chronic pain, which reflects the high kinetic energy transfer, tissue devitalization, and frequent contamination inherent in such injuries. This mechanistic association further supports the need for trauma-specific guidelines for pain prevention in war-related amputations [28–30]. Our study has several important clinical implications. First, it validates the use of a pragmatic, multidimensional assessment framework (pain intensity, neuropathic screening, psychological and functional measures) in routine rehabilitation of combat amputees. Second, the identification of modifiable risk factors — such as infection, prolonged antibiotics, and early uncontrolled pain — offers actionable targets for intervention [35–37]. Third, the data provide a foundation for prognostic modeling, which could guide individualized rehabilitation intensity, prosthetic fitting timelines, and psychological support allocation. Limitations include the single-center design, which may limit generalizability to other settings, and the absence of systematic MRI or ultrasound correlation in all cases, which may have provided further mechanistic insights. Nonetheless, the large sample size, high follow-up rate, and prospective design lend strength to the findings.

## Conclusions

In conclusion, chronic pain after combat-related amputation is highly prevalent and multifactorial, with contributions from structural, infectious, psychological, and mechanistic factors. Ultrasound and other bedside modalities should be integrated into diagnostic pathways, while multimodal pain management and mental health support must be embedded early in rehabilitation. These results strongly support the systematic inclusion of pain prevention and management strategies into the standard of care for military amputees.

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Received 10.09.2025  
Revised 12.10.2025  
Accepted 23.10.2025 ■

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**Conflicts of interests.** Authors declare the absence of any conflicts of interests and own financial interest that might be construed to influence the results or interpretation of the manuscript.

**Information about funding.** The authors declare that the writing of the article was carried out in the absence of any commercial or financial support.

**Authors' contribution.** D. Dmytriiev — research design, research concept, writing text, analysis of the obtained data, software development; V. Malykhina — technical editing.

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### Предиктори хронічного болю в українських військовослужбовців із травмами кінцівок: одноцентрове обсерваційне дослідження

**Резюме. Актуальність.** Хронічний біль є частим ускладненням після бойових травм кінцівок, що суттєво знижує якість життя й ефективність реабілітації. У світі хронічний біль після тяжких травм кінцівок спостерігається в половини — двох третин пацієнтів, тоді як фантомний біль кінцівки відзначають приблизно у 60–80 % ампутантів. Психосоціальні чинники (зокрема, посттравматичний стресовий розлад (ПТСР)) та високий рівень гострого болю є предикторами його хронізації, тоді як рання фізіотерапія асоціюється з кращим відновленням. Проте дані, специфічні для українських військових, залишаються обмеженими. **Матеріали та методи.** Проведено одноцентрове обсерваційне дослідження в Центрі Superhumans (Україна) в період із березня 2023 року по квітень 2025 року. Протягом шести місяців загалом спостерігали 311 українських військовослужбовців із гострими травмами кінцівок. Інтенсивність болю оцінювали за числовою шкалою (NRS), нейропатичні характеристики — за анкетною DN4, психоемоційні порушення — за госпітальною шкалою тривоги й депресії та опитувальником ПТСР, функціональний стан — за шкалою WHODAS 2.0. Для визначення незалежних факторів хронічного болю через 4–6 тижнів застосовано багатофакторну логістичну регресію. Дискримі-

наційну здатність моделі оцінювали за площею під кривою операційних характеристик. **Результати.** Через 4–6 тижнів хронічний біль спостерігався в 168 (54 %) з 311 пацієнтів. Незалежними предикторами розвитку болю були: ампутація (відношення шансів (ВШ) 2,3; 95% довірчий інтервал (ДІ) 1,5–3,6), інфекція рани (ВШ 2,0; 95% ДІ 1,2–3,1), тривала антибіотикотерапія > 21 дня (ВШ 1,7; 95% ДІ 1,1–2,8), початковий рівень болю  $\geq 6$  балів за NRS (ВШ 2,8; 95% ДІ 1,8–4,2) та симптоми ПТСР (ВШ 2,5; 95% ДІ 1,5–4,0). Рання фізіотерапія мала захисний ефект (ВШ 0,6; 95% ДІ 0,4–0,9). **Висновки.** У понад половини українських військовослужбовців із травмами кінцівок протягом шести місяців розвинувся хронічний біль. Основними факторами ризику були ампутація, інфекція, високий початковий рівень болю, ПТСР і тривале застосування антибіотиків, тоді як рання фізіотерапія зменшувала ризик хронізації. Отримані результати підкреслюють необхідність цілеспрямованої профілактики, суворого контролю інфекцій, раціонального використання антибіотиків та раннього мультидисциплінарного підходу до реабілітації у військовій медицині.

**Ключові слова:** травма кінцівок; хронічний біль; нейропатичний біль; фантомний біль кінцівки