

# Non-Tobacco Nicotine Dependence is Associated with Worse Outcomes after Humeral Shaft Operative Fixation

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**INTRODUCTION:** Humeral shaft fractures are common, often affecting younger populations in high-energy mechanisms. There is an increasing prevalence of nicotine dependence through non-tobacco products, including e-cigarettes, vapes, and nicotine pouches. While the deleterious relationship between tobacco use and fracture healing is well understood, the impact of non-tobacco nicotine dependence (NTND) remains unclear. This study aims to evaluate postoperative outcomes following open reduction and internal fixation (ORIF) of humeral shaft fractures among patients with NTND compared to those using traditional tobacco and those without nicotine dependence.

**METHODS:** The US collaborative network (TriNetX) was queried to identify patients aged 18 and older who underwent operative fixation of a humeral shaft fracture. Among these patients, three cohorts were created based upon nicotine status. Patients with NTND, traditional tobacco, and non-nicotine use were 1:1 propensity matched based on comorbidities and demographics, including sex, age, race, and ethnicity. Sex distribution was assessed between cohorts. Chi-squared test was used to analyze categorical variables, and an independent samples t-test was used to analyze the difference in means for continuous variables. Significance was set at  $p < 0.05$ .

**RESULTS SECTION:** A total of 16,404 patients met inclusion criteria: 1,250 with NTND, 2,515 with tobacco use, and 12,639 controls. After matching, NTND and control groups each included 1,250 patients; NTND and tobacco groups had 1,243 patients each. In the NTND group, 52.5% of patients were male compared with 44.4% of controls ( $p < 0.001$ ). No significant differences in sex were observed when comparing NTND patients with tobacco users, combined nicotine users, or other subgroups. Female representation demonstrated the inverse trend, with 44.6% of NTND patients compared to 50.1% of controls ( $p < 0.001$ ). At 90 days postoperatively, NTND patients had significantly higher rates of pneumonia (OR 2.19, 95% CI 1.44-3.31), acute blood loss anemia (OR 1.34, 95% CI 1.01-1.78), surgical site infection (SSI) (OR 1.785, 95% CI 1.04-3.07), ED visits (OR 1.56, 95% CI 1.22-1.98), and mortality (OR 1.76, 95% CI 1.08-2.87) compared to non-nicotine controls. Compared to tobacco users, NTND patients had significantly higher rates of pneumonia (OR 1.72, 95% CI 1.17-2.52), and ED visits (OR 0.73, 95% CI 0.59-0.90). At 2 years, NTND patients had significantly higher rates of nonunion or malunion (OR 1.63, 95% CI 1.07-2.49), hardware failure (OR 1.28, 95% CI 1.01-1.64), opioid dependence (OR 2.371, 95% CI 1.289-4.364), and mortality (OR 1.38, 95% CI 1.02-1.87) compared to controls. Compared to tobacco users, opioid dependence (OR 0.60, 95% CI 0.39-0.92) was significantly more likely in NTND.

**DISCUSSION:** NTND was associated with an increased risk of perioperative medical complications and long-term morbidity and mortality in patients who underwent humeral shaft operative fixation compared to both controls and traditional tobacco users. This supports the hypothesis that NTND is not a risk-free alternative to traditional tobacco use and may indicate even greater perioperative and long-term risks. Limitations include the potential underreporting of NTND, given variability in diagnostic practices across a wide range of healthcare organizations, and the inherent risk of residual confounders associated with the retrospective design. Additionally, the absence of detailed data on nicotine dose, duration, and specific product type (e.g., vaping vs. oral pouches) may limit the precision of outcome associations and trends.

**SIGNIFICANCE/CLINICAL RELEVANCE:** These findings underscore NTND as a distinct and clinically significant risk factor in patients undergoing operative fixation of humeral shaft fractures. This has direct implications for orthopedic surgeons when counseling patients regarding the risks of NTND.

**Table 1. Significant Postoperative Complications at 90 days and 2 years**

90 day complications	NTND (N = 1250)	Control (N = 1250)	OR (95% CI)	p-value	NTND (N = 1243)	Tobacco (N = 1243)	OR (95% CI)	p-value
Pneumonia	72 (5.8%)	34 (2.7%)	2.185 (1.442, 3.311)	<b>0.001</b>	72 (5.8%)	43 (3.5%)	1.716 (1.166,2.524)	<b>0.006</b>
Blood loss anemia	123 (9.8%)	94 (7.5%)	1.342 (1.013, 1.777)	<b>0.039</b>	122 (9.8%)	126 (10.1%)	.965 (0.742,1.254)	0.968
Surgical Site Infection	37 (3.0%)	21 (1.7%)	1.785 (1.039,3.067)	<b>0.034</b>	37 (3.0%)	41 (3.3%)	.899 (0.573,1.413)	0.645
ED visit	190 (15.2%)	129 (10.3%)	1.557 (1.226, 1.977)	<b>&lt;0.001</b>	189 (15.2%)	245 (19.7%)	.731 (0.593,0.9)	<b>0.003</b>
Death	45 (3.6%)	26 (2.1%)	1.758 (1.078, 2.867)	<b>0.022</b>	45 (3.6%)	28 (2.3%)	1.631 (1.01,2.63)	<b>0.044</b>
2 year complications	NTND (n = 1201)	Control (n = 1201)	OR (95% CI)	p-value	NTND (n = 1209)	Tobacco (n = 1209)	OR (95% CI)	p-value
SSI	51 (4.1%)	33 (2.6%)	1.568 (1.005,2.448)	<b>0.045</b>	51 (4.1%)	66 (5.3%)	0.765 (0.535 - 1.115)	0.173
Non-union/malunion	70 (5.6%)	42 (3.4%)	1.632 (1.071, 2.485)	<b>0.021</b>	69 (5.6%)	84 (6.8%)	.815 (0.534 - 1.136)	0.231
Hardware failure	145 (11.6%)	114 (9.1%)	1.284 (1.004,1.643)	<b>0.045</b>	157 (12.6%)	145 (11.7%)	1.015 (0.8,1.287)	0.904
Opioid dependence	35 (2.8%)	15 (1.2%)	2.371 (1.289,4.364)	<b>0.004</b>	34 (2.7%)	56 (4.5%)	.596 (0.386,0.92)	<b>0.018</b>
Death	105 (8.4%)	78 (6.2%)	1.381 (1.017,1.871)	<b>0.003</b>	107 (8.6%)	87 (7.0%)	1.252 (0.932,1.681)	0.135

All data are presented as mean ± SD or n (%) unless otherwise specified. Bold are statistically significant with  $p < 0.05$ .