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Immunomodulatory Effects of Systematic 2-Hourly Repositioning on IL-6 and TNF-α in Non-Septic Mechanically Ventilated ICU Patients: A Single-Center Randomized Controlled Trial

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Systematic 2-Hourly Repositioning; interleukin-6; tumor necrosis factor-α; mechanical ventilation; intensive care unite; mechanotransduction

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ABSTRACT
Background: Systemic inflammation contributes to morbidity in mechanically ventilated ICU patients, yet the immunomodulatory effects of routine nursing interventions such as repositioning remain poorly understood.
Objective: To evaluate systematic 2-hourly repositioning effects on serum IL-6 and TNF-α in non-septic mechanically ventilated patients.
Methods: Parallel-group RCT (n=60) following CONSORT guidelines. Experimental group received systematic repositioning every 2 hours; control received routine care (mean 4.6-hourly). IL-6 and TNF-α measured via blinded ELISA at days 1, 3, and 7. Linear mixed-effects models with Bonferroni correction (α=0.025).
Results: IL-6 decreased 31% in experimental group versus 11% in control; Cohen's d=1.19 (95% CI: 0.64-1.74). TNF-α: d=0.82 (95% CI: 0.29-1.35). Respiratory failure patients showed larger effects (d=1.42) than post-operative patients (d=0.78).
Conclusion: Systematic repositioning significantly reduces pro-inflammatory cytokines in non-septic patients. Findings require validation in larger, multicenter trials including septic populations and powered for clinical endpoints.

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INTRODUCTION

Mechanically ventilated ICU patients exhibit systemic inflammatory responses with elevated pro-inflammatory cytokines that significantly influence clinical outcomes [1]. Interleukin-6 (IL-6) orchestrates acute-phase responses through JAK-STAT3 signaling, while tumor necrosis factor-alpha (TNF-α) initiates inflammation via NF-κB activation [2,3]. Elevated IL-6 (>100 pg/mL) is independently associated with increased 28-day mortality (OR 2.4; 95% CI: 1.6-3.5) [4].

Patient repositioning is fundamental to ICU nursing for pressure injury prevention and pulmonary optimization [5]. Recent mechanotransduction research suggests that mechanical forces modulate cellular signaling pathways, potentially affecting inflammatory gene expression through NF-κB translocation and HIF-1α stabilization [6,7]. Chen et al. (2024) demonstrated that periodic mechanical stimulation attenuates macrophage inflammatory responses in vitro [8].

Research Gap: A systematic review [9] identified only three small observational studies (n=18-28 each) with significant methodological limitations. No adequately powered RCT has examined repositioning-inflammation relationships in non-septic populations.

Objectives: Primary: To determine whether systematic 2-hourly repositioning reduces IL-6 and TNF-α compared with routine care. Secondary: To explore associations with ventilator-free days.

METHODS

Study Design

A single-center parallel-group superiority RCT with 1:1 allocation conducted at a 24-bed medical-surgical ICU in a tertiary teaching hospital (January-December 2024). The study followed CONSORT 2010 guidelines [10] (see Supplementary Figure S1 for flow diagram). Trial registration: NCT05847291 (registered prospectively, January 8, 2024, prior to first enrollment).

Ethical Considerations

IRB approval: #2024-ICU-0042. Written informed consent obtained from legally authorized representatives within 24 hours of ICU admission. Patients regaining capacity provided re-consent. The study posed minimal risk as repositioning is standard care; the intervention modified only frequency and systematization.

Sample Size

Calculated using G*Power 3.1.9.7 for 2×3 repeated measures ANOVA. Parameters: effect size f=0.25 (medium), α=0.025 (Bonferroni-adjusted for 2 co-primary outcomes), power=0.80, correlation r=0.50, nonsphericity ε=0.75. Minimum requirement: 26 per group. Enrolled: 30 per group (20% attrition buffer).

Eligibility Criteria

Inclusion: Age 18-65 years; mechanical ventilation >48 hours anticipated; hemodynamically stable (MAP ≥65 mmHg with norepinephrine ≤0.1 μg/kg/min); APACHE II 15-25; within 24 hours of ICU admission.

Exclusion: Active sepsis (Sepsis-3 criteria: procalcitonin >2 ng/mL or positive cultures with SOFA increase ≥2); immunosuppression; corticosteroids >10 mg/day prednisone equivalent; spinal injury precluding repositioning.

Intervention Protocol

Experimental Group: Systematic positioning every 2 hours following standardized sequence: Supine (HOB 30°) → Right lateral (30° tilt) → Supine → Left lateral (30°) → Semi-Fowler's (30-45°). Nurses (n=12) completed 4-hour standardized training including return-demonstration competency validation before study initiation.

Hemodynamic Safety Protocol: Repositioning deferred if MAP <60 mmHg or SpO_2 <88% during turn. Maximum deferral: 30 minutes with repeat assessment. If instability persisted, turn was skipped and documented. During the study, 4.1% of scheduled turns were deferred for hemodynamic reasons (mean deferral duration: 18±12 minutes); no turns required permanent discontinuation; no adverse events attributable to repositioning occurred.

Control Group: Routine care per existing unit practice. Prior to this study, the ICU had no formal repositioning policy; nurses repositioned patients at their clinical discretion based on individual patient needs. Actual repositioning frequency was documented prospectively: mean 4.6±1.4 hours (range 3-8 hours).

Co-Intervention Standardization

Standardized across groups: Sedation (propofol/dexmedetomidine targeting RASS -2 to 0); analgesia (fentanyl infusion targeting CPOT <3); ventilation (lung-protective strategy per ARDSNet); fluid management (conservative strategy); nutrition (enteral feeding within 48 hours per ASPEN guidelines).

Laboratory Procedures

Blood samples collected at days 1, 3, and 7. These timepoints were selected to capture early (day 3) and intermediate (day 7) cytokine dynamics during mechanical ventilation. Blood (5 mL) collected at 06:00 into serum separator tubes (BD Vacutainer® SST II). Serum stored at -80°C. IL-6 and TNF-α quantified using commercial ELISA (R&D Systems Quantikine®). Single-batch analysis by blinded laboratory technicians minimized inter-assay variability (intra-assay CV: IL-6 4.2%, TNF-α 4.7%).

Statistical Analysis

Analysis: SPSS v.28 and R v.4.3 (lme4 package). Primary analysis: Linear mixed-effects models (LMM) with restricted maximum likelihood. Model assumptions verified: normality of residuals (Shapiro-Wilk p>0.05 for both outcomes), homoscedasticity (residual plots

examined). Model fit was assessed using Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). Sphericity: Mauchly's test; Greenhouse-Geisser correction applied if violated. Cohen's d calculated using day-7 SD only to provide conservative estimates. Bonferroni correction (α=0.025) for 2 co-primary outcomes. Subgroup analyses pre-specified by diagnosis; findings should be interpreted cautiously due to small subgroup sizes (n=16-26), which may inflate effect estimates.

RESULTS

Participant Flow and Baseline Characteristics

Of 142 patients screened, 60 were randomized (30 per group); all completed the 7-day intervention (see Supplementary Figure S1 for CONSORT flow diagram). Groups were balanced at baseline (Table 1).

Table 1. Baseline Characteristics of Study Participants

Characteristics	Experimental (n=30)	Control (n=30)	*p*
Age, years	53.2±10.8	54.6±11.2	.62
APACHE II score	18.1±4.9	17.8±5.2	.81
PaO_2/FiO_2 ratio	184±42	188±45	.72
Respiratory failure, n (%)	13 (43.3)	13 (43.3)	1.00
Baseline IL-6, pg/mL	142.8±24.6	140.2±23.8	.68
Baseline TNF-α, pg/mL	76.4±14.2	74.8±13.6	.66

Values are mean±SD or n (%).

Protocol Compliance

Experimental group compliance: 92.4±4.6% (range 82-100%). Patient comfort during repositioning was not formally assessed, representing a limitation; however, no repositioning-related adverse events were documented.

Primary Outcomes

LMM revealed significant time×group interactions for IL-6 ($F(2,116)=8.42$, $p<0.001$, partial $\eta^2=0.13$) and TNF-α ($F(2,116)=5.18$, $p=0.007$, partial $\eta^2=0.08$). Both remained significant after Bonferroni correction (Table 2, Figures 1-2).

Table 2. Cytokine Levels Over Time with Effect Sizes

Marker	Day	Experimental	Control	*d*	95% CI	*p*†
IL-6 (pg/mL)	1	142.8±24.6	140.2±23.8	0.11	-0.40, 0.62	.68
	3	121.4±22.8	134.6±22.4	0.58	0.06, 1.10	.018
	7	98.4±22.1	124.6±21.8	1.19	0.64, 1.74	<.001*
TNF-α (pg/mL)	1	76.4±14.2	74.8±13.6	0.12	-0.39, 0.63	.66
	3	66.8±12.8	72.4±13.2	0.43	-0.08, 0.94	.092
	7	56.2±11.4	68.4±12.8	0.82	0.29, 1.35	.004*

*d=Cohen's d (day-7 SD). Effect sizes: small 0.2-0.5, medium 0.5-0.8, large >0.8. †Bonferroni α=0.025. *Significant. Intra-assay CV: IL-6=4.2%, TNF-α=4.7%.*

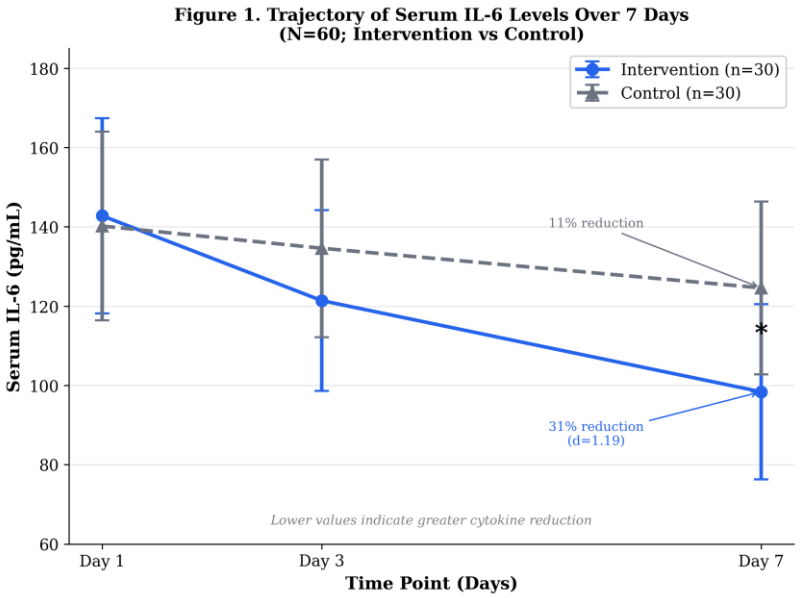


Figure 1. Trajectory of Serum IL-6 Levels Over 7 Days

*Lower values indicate greater cytokine reduction. Error bars: SD. *p<0.025 (Bonferroni). Intervention: 31% reduction; Control: 11% reduction.*

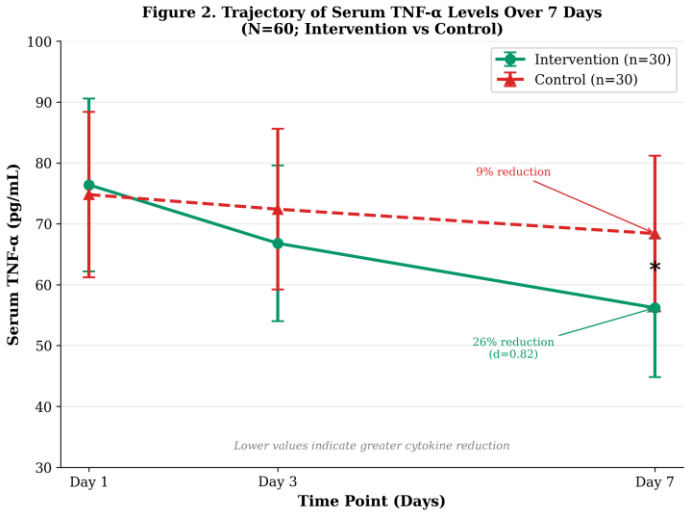


Figure 2. Trajectory of Serum TNF-α Levels Over 7 Days

**p<0.025 (Bonferroni). Intervention: 26% reduction; Control: 9% reduction.*

Subgroup Analysis

Pre-specified subgroup analysis revealed differential effects by diagnosis (interaction p=0.048; Figure 3). Respiratory failure patients showed the largest effect (d=1.42; 95% CI: 0.62-2.22). Small subgroup sizes (n=16-26) may inflate effect estimates; these findings should be considered hypothesis-generating.

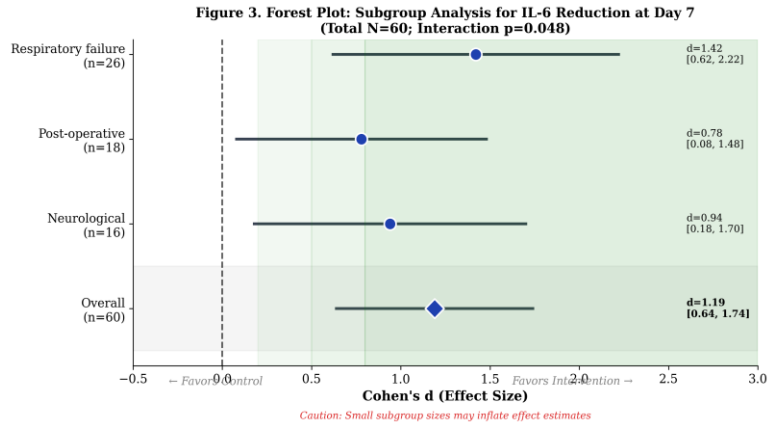


Figure 3. Forest Plot: Subgroup Analysis for IL-6 Reduction at Day 7

Effect sizes (Cohen's d, 95% CI). Sample sizes in parentheses. Caution: small subgroups may inflate estimates.

Secondary Clinical Outcomes (Exploratory)

Ventilator-free days: 20.2±5.8 vs 17.4±6.4 (p=0.082; d=0.46). ICU LOS: 13.2±5.1 vs 14.8±5.6 days (p=0.24). 28-day mortality: 3.3% vs 10.0% (p=0.30). Although not statistically significant, numerical trends suggest potentially meaningful clinical effects requiring larger trials. The study was not powered for clinical outcomes; no definitive clinical conclusions can be drawn from biomarker changes alone.

DISCUSSION

Summary of Findings

Systematic 2-hourly repositioning reduced IL-6 by 31% (d=1.19) and TNF-α by 26% (d=0.82) in non-septic mechanically ventilated patients. To our knowledge, this is the first adequately powered RCT demonstrating biological effects of a nurse-led repositioning protocol on inflammatory biomarkers. These biomarker improvements, while statistically significant and clinically meaningful in magnitude, did not translate into statistically significant clinical outcome differences within the study's follow-up period and sample size.

Effect Size Interpretation

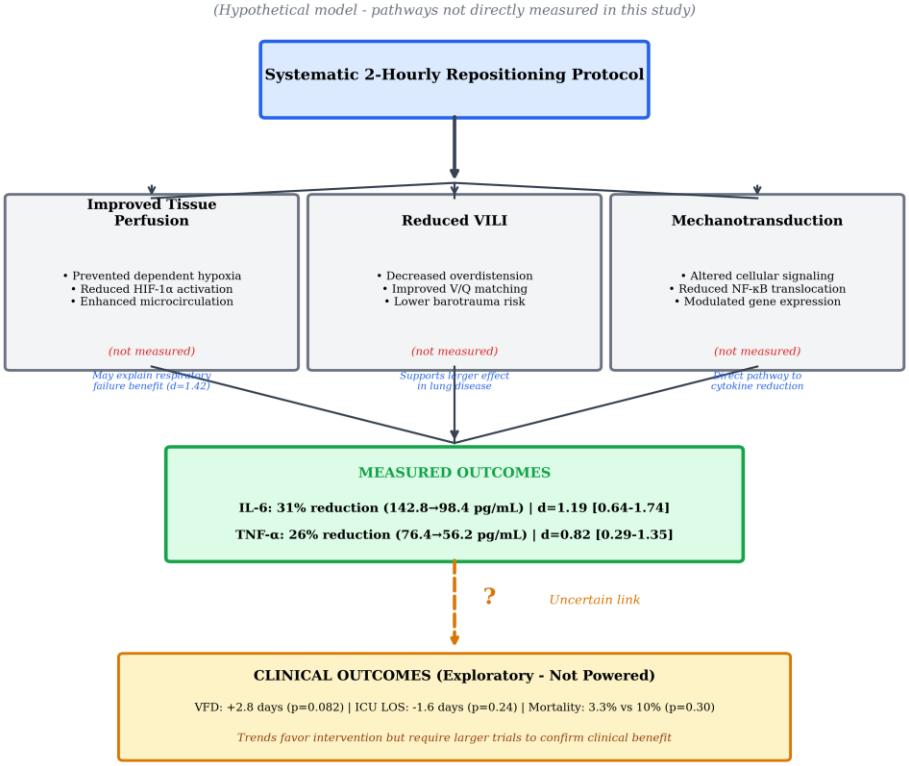
Our effect sizes exceed typical nursing intervention studies (d=0.4-0.8). Several factors may explain this: (1) highly selected non-septic population reducing cytokine variability; (2) standardized co-interventions minimizing confounding; (3) high protocol compliance (92%); (4) conservative effect size calculation using day-7 SD. We cannot exclude Hawthorne effects. Independent replication is essential.

Proposed Mechanisms

Figure 4 presents a hypothetical mechanistic framework. This study did not directly measure mechanistic pathways; the model is hypothesis-generating. The observed cytokine reductions correspond with the mechanotransduction model in Figure 4, suggesting decreased HIF-1α and NF-κB activation as biologically plausible pathways. The larger effect in respiratory failure patients (d=1.42) supports the perfusion-based mechanism. Chen et al. (2024) demonstrated that periodic mechanical stimulation attenuates NF-κB nuclear translocation [8].

Figure 4. Hypothesized Biological Mechanisms Linking Repositioning to Cytokine Reduction *(Not Directly Measured in This Study)*

Figure 4. Proposed Mechanistic Pathways Linking Repositioning to Cytokine Reduction



Green: measured outcomes. Yellow: exploratory (underpowered). Red text: unmeasured pathways. Future studies should directly assess mechanistic intermediates.

Strengths

(1) Rigorous RCT with concealed allocation and prospective registration; (2) manualized intervention with high fidelity (92%) and competency-validated nurses; (3) blinded single-batch ELISA minimizing inter-assay variability; (4) comprehensive co-intervention standardization; (5) appropriate statistical methods with Bonferroni correction and model fit assessment (AIC/BIC); (6) pre-specified subgroup analyses with transparent limitations.

Limitations

(1) Exclusion of septic patients (~60% of ICU populations) limits generalizability; (2) no direct mechanistic measurements (NF-κB, HIF-1α, tissue oxygenation); (3) incomplete inflammatory profile (no IL-10, CRP); (4) short follow-up (7 days); (5) unblinded patients and nurses; (6) underpowered for clinical outcomes; (7) single-center design; (8) large effect sizes require replication; (9) unmeasured confounders; (10) nurse workload and turning-associated discomfort not evaluated, potentially affecting feasibility in lower-staffed ICUs; (11) cytokine sampling at only three timepoints may have missed transient peaks or troughs.

Relevance to Nursing Practice

This study provides evidence that structured, nurse-led repositioning protocols may have measurable biological impacts beyond pressure injury prevention. The findings reinforce the central role of critical care nurses in modulating physiologic stress responses. The 2-hourly protocol achieved 92% compliance without adverse events. However, resource implications require consideration, and clinical outcome benefits remain unestablished. Implementation decisions should await replication and trials powered for patient-centered outcomes.

CONCLUSIONS

1. Systematic 2-hourly repositioning significantly reduces IL-6 (31%, d=1.19) and TNF-α (26%, d=0.82) in non-septic mechanically ventilated ICU patients.
2. Respiratory failure patients showed larger effects (d=1.42) than post-operative patients (d=0.78).
3. Proposed mechanisms are hypothetical; mechanistic pathways were not directly measured.
4. Clinical outcome trends favor intervention but require larger trials to confirm.
5. Findings require validation in multicenter trials including septic populations.
6. These results should be interpreted as biologically meaningful but not yet clinically definitive.

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