

# The Timing of Femur Fracture Fixation is an Important Factor for Prolonged Mechanical Ventilation

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**Purpose:** Mechanical ventilation (MV) is an essential life-saving modality for severely injured patients. However, the long-term use of MV is a major risk factor for late mortality. The surgical correction of long bone fractures plays a critical role not only in improving functional outcomes, but also in reducing physiological derangements, including MV duration. This study investigated the factors affecting prolonged MV (PMV) in severely injured patients with femur fractures.

**Methods:** We retrospectively evaluated all severely injured patients (injury severity score >15) with femur fractures who were taken to the emergency department within 12 hours of the causative accidents between January 2016 and December 2018. PMV was defined as MV lasting for  $\geq 7$  days. We analyzed the factors affecting PMV.

**Results:** In total, 35 patients were enrolled and 21 (33.3%) were included in the PMV group. The PMV group required more red blood cell (RBC) transfusions within 7 days RBC (7dRBC) (12.8 vs. 6.8 units;  $p=0.03$ ) and the time to femur fracture fixation (TFFF) was longer (7.9 vs. 2.7 days;  $p=0.018$ ). The area under the curve (AUC) for TFFF was 0.740 (95% confidence interval [CI]: 0.572–0.908;  $p=0.018$ ) and the AUC for 7dRBC was 0.718 (95% CI: 0.546–0.889;  $p=0.031$ ).

**Conclusions:** This study indicates that TFFF is an independent risk factor for PMV. Early fixation of femur fractures might prevent PMV and its associated complications.

**Keywords:** Mechanical ventilation; Fracture of long bone; Fixation of femoral fracture

## INTRODUCTION

Since Trunkey described a trimodal distribution of trauma deaths in 1983 [1], this pattern has changed to a bimodal curve as a result of subsequent developments of trauma care systems [2,3]. Notwithstanding the improvements that have taken place in trauma deaths, the causes of death at various times elapsed from the injury have not changed. Late mortality has been reported to vary from 8% to 16.4% [3,4] and the major causes of trauma deaths remain the same; namely, sepsis and multiple organ dysfunction syndrome (MODS) attributable to the consequences of the initial insults, aggressive resuscitation, and treatment [5,6]. Mechanical ventilation (MV) is an essential life-saving modality for severely injured patients. However, the long-term use of MV is also a major risk factor, increasing the late mortality rate to 24.2–35.6% [7,8].

A longer MV duration is correlated with a higher risk of pulmonary complications, and prolonged MV (PMV) increases the risk of mortality by 4.89-fold [9]. The reported risk factors for PMV include a low Glasgow Coma Scale score, flail chest, a high abbreviated injury scale (AIS) score of the thorax, the amount of resuscitation fluid, and facial fracture [10,11]. Although numerous modalities have been proposed as ways to minimize complications, researchers have primarily focused on medical treatments. The surgical correction of long bone fractures also plays a critical role not only in improving functional outcomes, but also in reducing physiological derangements, including the duration of MV [12]. The timing of long bone fixation may be considered to be an important factor, as it is a physiological parameter that affects patients' clinical course and outcomes. Therefore, this study investigated the factors affecting PMV in severely injured patients with femur fractures.

## METHODS

### Data collection and exclusion criteria

The present study was approved by the Institutional Review Board, which waived informed consent because no additional intervention was performed (IRB No. 2019-

09-017). We retrospectively evaluated all severely injured patients (injury severity score [ISS] >15) with femur fractures who were taken to the emergency department within 12 hours of the causative accidents between January 2016 and December 2018.

We excluded patients aged <18 or ≥80 years, those who died or were transferred to another hospital within 7 days, those who did not need MV, and those with femur fractures that did not need fixation due to amputation or lesions affecting areas such as the trochanter or condyle. To prevent bias from influencing the outcomes, we also excluded patients with end-stage renal disease on dialysis and those with critical injuries (AIS ≥5) on any other part of the body.

### Measurement of variables

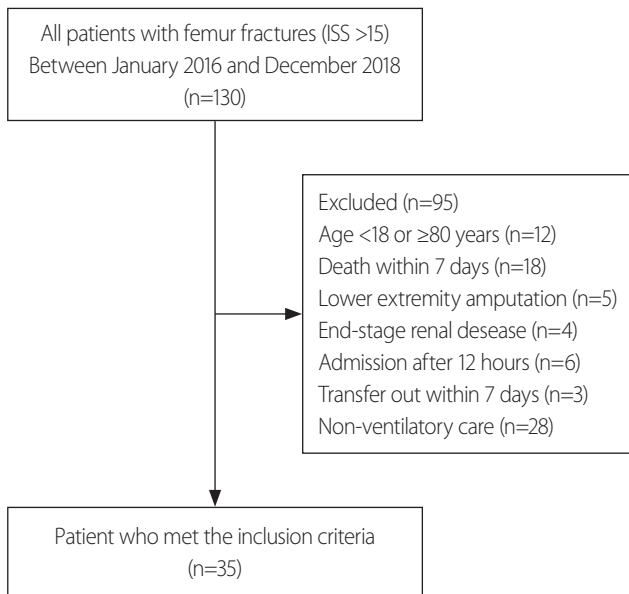
The patients were divided into the following two groups based on MV duration: less than 7 days and 7 or more days, and PMV was defined as MV lasting for ≥7 days. To analyze the factors affecting the MV duration, the following information was collected: age, sex, injury mechanism, revised trauma score (RTS), the AIS of all body regions, the amount of transfusion, and the time to femur fracture fixation (TFFF) after the accident.

### Statistical analysis

Continuous variables were presented as mean±standard deviation and compared using the Mann–Whitney *U* test. Categorical variables were presented as n (%) and compared using the chi-square and Fisher exact tests. Variables with  $p < 0.05$  in the univariate analysis were included in the multivariable logistic regression analysis to identify predictors of PMV. We calculated the adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for independent predictors of PMV. All statistical tests were two-sided, with significance set to 0.05. All statistical analyses were performed using SPSS for Windows, version 21.0 (IBM Corp., Armonk, NY, USA).

## RESULTS

In total, 35 patients met the inclusion criteria (Fig. 1). All patients were injured by blunt mechanisms and 21 (60.0%)



**Fig. 1.** Flow diagram showing patient enrollment.

experienced PMV. There were no significant differences between the PMV and non-PMV groups in age, sex, timing of arrival to the trauma center, AIS, ISS, or emergency surgery. The PMV group had a higher RTS ( $10.4 \pm 1.6$  vs.  $11.5 \pm 0.9$ ,  $p=0.022$ ) and significantly more red blood cells (RBCs) transfused within 7 days (7dRBC) ( $6.8 \pm 2.5$  vs.  $12.8 \pm 9.1$  units,  $p=0.03$ ). The PMV group also had a longer TFFF ( $2.7 \pm 2.9$  vs.  $7.9 \pm 11.2$  days,  $p=0.018$ ). One patient in the PMV group died, but there was no significant difference in mortality between the groups (Table 1).

The receiver operating characteristic curves for RTS, TFFF, and 7dRBC showed significant predictive values. The area under the curve (AUC) of RTS was 0.716 (95% CI: 0.110–0.458,  $p=0.033$ ) and the AUC of 7dRBC was 0.718 (95% CI: 0.546–0.889,  $p=0.031$ ). The AUC of TFFF was 0.740 (95% CI: 0.572–0.908,  $p=0.018$ ); the cut-off value of 3.1 days had a sensitivity of 66.7% and specificity of

**Table 1.** Comparisons of demographic factors and clinical course according to the duration of mechanical ventilation

Variable (n=35)	Non-PMV	PMV	p-value
Number	14 (40.0)	21 (60.0)	
Age (years)	56.2±17.3	51.6±17.7	0.490
Male	12 (85.7)	20 (95.2)	0.551
Direct transport	5 (35.7)	8 (38.1)	0.886
Scene to trauma center (minutes)	180.4±164.1	160.9±112.1	0.946
Revised trauma score	11.5±0.9	10.4±1.6	0.022
Injury severity score	26.9±5.7	26.81±7.3	0.708
Abbreviated injury score			
Head and neck	1.3±1.6	1.4±1.8	0.909
Face	0.6±0.9	0.7±1.1	0.936
Thorax and thoracic spine	2.5±1.4	2.2±1.5	0.610
Abdomen and lumbar spine	1.4±1.6	1.5±1.6	0.842
Pelvis and extremities	3.1±0.3	3.1±0.3	0.808
External	0.4±0.5	0.7±0.6	0.198
Emergency surgery for CNS injury	0 (0)	3 (14.3)	0.259
Emergency surgery for thoracoabdominal injury	3 (21.4)	4 (19.0)	0.594
Time to femur fracture fixation (days)	2.7±2.9	7.9±11.2	0.018
Ventilator days	2.1±1.8	20.8±23.7	<0.001
ICU days	9.2±4.3	30.9±23.8	<0.001
RBC transfusion within 7days (units)	6.8±2.5	12.8±9.1	0.030
Mortality	0 (0)	1 (4.8)	1.000

Values are presented as mean±standard deviation or number (%).

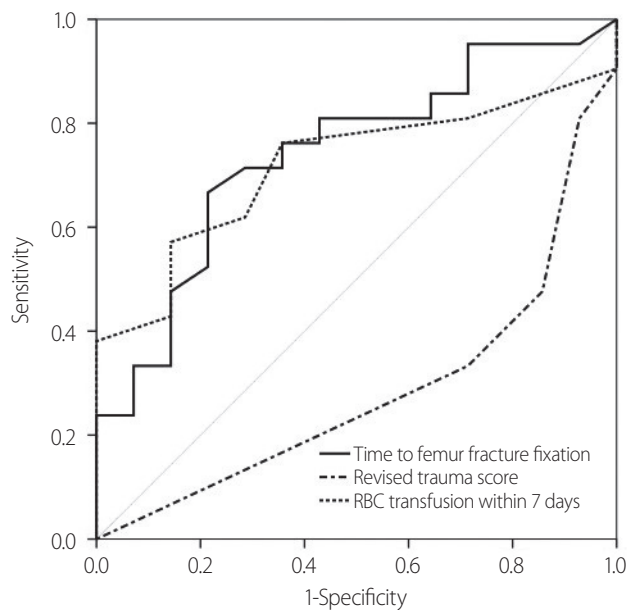
PMV: prolonged mechanical ventilation, CNS: central nervous system, ICU: intensive care unit, RBC: red blood cell.

78.6% (Fig. 2).

To identify the risk factors, variables with  $p < 0.05$  in the univariate analysis were analyzed by multivariate logistic regression, and TFFF was categorized using the cut-off of 3 days derived from the above-presented results of this study. RTS (OR: 0.578, 95% CI: 0.285–1.170,  $p = 0.128$ ) and the amount of 7dRBC (OR: 1.212, 95% CI: 0.987–1.490,  $p = 0.067$ ) did not reach statistical significance, but a TFFF  $\geq 3$  days (OR: 11.873, 95% CI: 1.644–85.767,  $p = 0.014$ ) was identified as a significant predictive factor for PMV (Table 2).

## DISCUSSION

The numerous complications of multiple trauma are



**Fig. 2.** Receiver operating characteristic curves of the risk factors for prolonged mechanical ventilation.

related to the sequelae of resuscitation and life-saving procedures, in combination with the severity of the injury. Massive transfusion is associated with the lethal triad, electrolyte abnormalities, MODS, infection, and acute lung injury [13,14]. Though transfusion is a well-known major risk factor for MV and PMV [15,16], many trauma patients cannot avoid transfusion. In addition to efforts to decrease transfusions, therapeutic approaches should also be developed to reduce the duration of MV.

The timing of skeletal fixation remains controversial. Reconstructive secondary surgery is performed in survivors after damage control surgery or resuscitation. Secondary surgery promotes proinflammatory cytokines and aggravates organ dysfunction, imposing an additional burden due to the second-hit effect [17,18]. Contrary to emphasizing the risk of the second hit, recent studies have demonstrated the beneficial effects of early fixation, especially femur fracture. These studies reported that early stabilization of fractures reduced pulmonary complications, infections, hospital stay, and mortality [19-21]. Although the consensus on the advantages of early femur fixation has been widely accepted, the definition of “early” varies from within 12 hours to 4 days [17,20,21]. Furthermore, most studies did not explain the mechanisms by which early fixation decreases complications.

Moderate exercise upregulates antioxidants [22], and even passive physical activity improves levels of proinflammatory cytokines such as interleukin (IL)-6 and IL-10 [23]. Accordingly, although early mobilization is negatively associated with MV duration, it is problematic not to mobilize patients and even to change their position because of skeletal traction and concerns about additional injuries in patients with femur fractures [24]. Thus, early fixation of femur fractures followed by early mobilization may be more beneficial despite the risk of the second hit.

Pape et al. [25] reported an increased occurrence of

**Table 2.** Multivariate analysis of the risk factors for prolonged mechanical ventilation

Variable (n=35)	OR	95% CI	p-value
Revised trauma score	0.578	0.285-1.170	0.128
Time to femur fracture fixation, $\geq 3$ days	11.873	1.644-85.767	0.014
RBC transfusion within 7 days (units)	1.212	0.987-1.490	0.067

OR: odds ratio, CI: confidence interval, RBC: red blood cell.

organ dysfunction when secondary surgery for major fractures was performed within less than 5 days, using IL-6 levels to assess the additional inflammatory burden caused by secondary surgery. They recommended that major skeletal surgery be delayed until after 5 days for safety [17]. Similarly to this, Cantu et al. [21] reported delaying surgery for femur fractures until at least 48 hours in all patients; moreover, severely injured patients ( $ISS \geq 26$ ) also had higher mortality due to insufficient resuscitation when femur fracture fixation was performed within 12 hours. These differences can be interpreted in light of the clinical course of trauma. Proinflammatory cytokines are released immediately after injury and return to the normal range in about 5 days [25]. MODS develops concomitant with the course of systemic inflammation and peaks within 3–5 days [26]. Therefore, the better outcomes for early or delayed surgery result from avoiding the peak period of systemic inflammation. Although a detailed subgroup analysis was not performed in this study, the TFFF cut-off of 3.1 days for PMV seemed to result from the avoidance of peak systemic inflammation and organ dysfunction, combined with the effects of early mobilization.

The current study has some limitations. First, there was no correlation between PMV and ISS, which is one of the most important prognostic factors in trauma patients. We excluded patients with an AIS  $\geq 5$  to eliminate bias caused by critical injuries to specific body regions; thus, the results might have been influenced by this narrow range of ISS. Second, we did not analyze specific conditions influencing MV or outcomes such as infection, delirium, and organ dysfunction. Despite these limitations, our findings suggest that early fixation of femur fractures might improve outcomes in patients with severe trauma.

## CONCLUSION

This study indicates that TFFF is an independent risk factor for PMV. Early fixation of femur fractures might prevent PMV and its associated complications.

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