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Research Article

Delayed displacement of minimally displaced clavicle fractures in polytrauma patients: a retrospective cohort study

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ABSTRACT

Objective: This study aimed to investigate the incidence and potential predictors of delayed displacement in minimally displaced clavicle fractures associated with polytrauma. It was hypothesized that polytrauma-related factors may reduce the risk of delayed displacement by limiting early patient mobilization.

Methods: Between 2018 and 2021, a cohort study was conducted on 79 patients with minimally displaced clavicle fractures who had an injury severity score (ISS) of 16 or greater and were initially treated conservatively. The patients underwent regular radiographic examinations and those who exhibited displacement of more than 100% during follow-up were classified as having delayed displacement and subsequently underwent surgical intervention. Univariate and multivariate logistic regression analyses were used for statistical analysis to evaluate the risk factors for delayed displacement. The factors included polytrauma-related factors, such as the ISS, accompanying upper extremity injury, scapular fracture, rib fracture, level of consciousness, traumatic central nervous system injury, intensive care unit admission, use of a ventilator, duration of intubation, and fracture-specific factors, which were the location of the fracture and the presence of comminution.

Results: Overall, 31 patients (39.2%) had delayed displacement. The univariate and multivariate logistic regression analyses showed that the statistically significant risk factors for delayed displacement of clavicle fractures were the presence of comminuted fractures and fractures located in the middle third of the clavicle shaft (odds ratio = 5.954 and 4.423, respectively; $P = .003$ and .018, respectively), while polytrauma-related factors were not associated.

Conclusion: Polytrauma-related factors were not significantly associated with delayed displacement in minimally displaced clavicle fractures accompanied by polytrauma. Instead, fracture-specific characteristics, such as midshaft location and comminution, emerged as important predictors of delayed displacement, even when the initial displacement was minimal. These findings highlight the need for regular radiographic monitoring for at least 5 weeks in patients with polytrauma, particularly when such fracture characteristics are present.

Level of Evidence: Level III, Retrospective Cohort Study.

Introduction

Polytrauma is generally defined as an injury severity score (ISS) of 16 or higher in combination with injuries involving at least 2 different body regions.[1,2] It is the leading cause of mortality among individuals younger than 40 years.[3-6] Approximately 70% of patients with polytrauma experience musculoskeletal injuries, such as clavicle or rib fractures, which may require differentiated treatment strategies compared to isolated fractures. Although most rib fractures in polytrauma cases are managed conservatively, the optimal treatment for clavicle fractures, which are prevalent in approximately 10% of polytrauma cases, remains unkown.[7,8]

Some experts prefer conservative treatment for clavicle fractures in the context of polytrauma, given the relatively lower risk of further fracture displacement associated with sedation and general inactivity.[9] However, other studies have reported better outcomes with prompt surgical intervention than with conservative management regarding complication rates and length of stay in the intensive care unit (ICU).[8,10,11] Nevertheless, there is limited evidence specifically addressing the management of minimally displaced clavicle fractures in polytrauma patients. In particular, whether polytrauma-related factors influence the occurrence of delayed displacement has not been clearly investigated. This gap in the literature provided the rationale for the study.

Therefore, the aim of this study was to investigate the incidence and potential predictors of delayed displacement in minimally displaced clavicle fractures associated with polytrauma, evaluating both polytrauma-related variables and fracture-specific factors. It wase hypothesized that polytrauma-related factors, which were expected to restrict early patient movement, might decrease the risk of delayed displacement.

Material and methods

This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Institutional Review Board of Ajou Univeristy Hospital (Approval No. AJIRB-MED-MDB-19-556).

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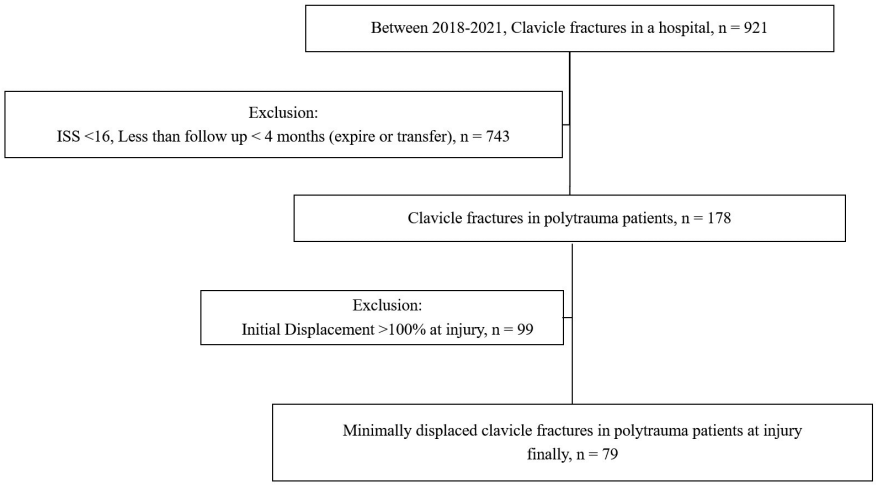

Figure 1. Flowchart showing the criteria for inclusion and exclusion of patients in this study.

Informed consent was waived due to the retrospective nature of the study, as approved by the institutional review board.

Medical records of patients treated for clavicle fractures between January 2018 and April 2021 were retrospectively reviewed. Patients with an ISS of less than 16 or those with a follow-up duration of less than 4 months because of transfer out or expiration were excluded (n=743). In this study, the classical ISS was used. Patients with >100% displacement on initial radiologic imaging were also excluded, as they underwent early operative treatment (n=99). Finally, 79 patients with minimally displaced clavicle fractures caused by polytrauma were included in the cohort (Figure 1). These patients underwent conservative treatment with the use of an arm sling, and immobilization was maintained for at least 5 weeks. In conscious patients, continuous use of the arm sling was strictly recommended for at least 5 weeks, regardless of posture. In unconscious patients under ventilator care, sling compliance was generally maintained because involuntary movement was minimal. In irritable patients, restraints were occasionally applied with guardian consent to prevent accidental removal of medical lines, which also helped to ensure sling retention.

A dedicated upright clavicle radiographic series consisting of an anteroposterior (AP) radiograph of the clavicle, a 45° cephalic tilt radiograph, and an acromioclavicular radiograph was obtained initially. Among these, the 45° cephalic tilt view was performed, albeit with limitations, to assess displacement in the axial plane. Radiographs of the dedicated upright clavicle series were obtained at 1-week intervals for at least 5 weeks after the injury. In cases where polytrauma patients were unable to assume the upright position due to their general condition in the early post-injury period, radiographs were obtained in the supine position. At that time, when patients were unstable and equipped with various devices including ventilators, it was not always possible to obtain all radiographic views, resulting in some omissions. In such cases, shoulder or chest computed tomography (CT) scans obtained as part of trauma assessment were used to determine the initial degree of fracture displacement. During follow-up, every effort was made to obtain all 3 radiographic views whenever possible. Quantitative displacement measurements were obtained by calculating the distance between adjacent cortices at the fracture site on the radiograph, demonstrating the greatest degree of fracture displacement. Fractures showing less than 100% translation were considered minimally displaced, while those with 100% or greater translation, including fractures with overlap, were deemed failures of conservative treatment. Similarly, fracture site shortening, which results from overlap following ≥100% displacement, was also excluded from conservative treatment. However, in this study, failure of conservative treatment was defined purely based on this radiographic threshold and did not necessarily represent a clinical indication for surgical intervention in polytrauma patients. Because clavicle series radiographs were obtained at relatively long intervals (1 week), the exact timing of delayed displacement was estimated by reviewing the daily chest AP radiographs that are routinely obtained in ICU patients. The Arbeitsgemeinschaft für Osteosynthesefragen/Orthopaedic Trauma Association classification was employed to identify the location of the fracture. A mid-shaft fracture was determined if it was positioned laterally to a vertical line drawn upward from the center of the first rib and medially to a vertical line drawn upward from the center of the base of the coracoid process. The degree of displacement, fracture location, and comminution in the dedicated clavicle series were independently assessed by 2 observers (DHL and WSC). Inter-observer reliability was evaluated using the intraclass correlation coefficient (ICC),[12] and intra-observer reliability was determined by having 1 observer (WSC) re-evaluate all radiographs at a different time point. In cases of disagreement, the 2 observers jointly reviewed the radiographs and reached a consensus through discussion.

All patients were analyzed for the following polytrauma-related factors: ISS, accompanying upper extremity injury, scapular fracture, rib fracture, level of consciousness, traumatic central nervous system (CNS) injury, ICU admission, ventilator use, and duration of intubation. The level of consciousness was evaluated using the Glasgow Coma Scale, and the worst level was recorded. In addition, fracture-specific factors such as the location of the fracture and the presence

HIGHLIGHTS

- In patients with polytrauma and minimally displaced clavicle fractures, delayed displacement (>100%) occurred in approximately 40% of cases during conservative treatment.
- Fracture-specific factors, particularly midshaft location and comminution were significantly associated with delayed displacement, while polytrauma-related factors showed no significant impact.
- These findings suggest that conservative treatment should be accompanied by regular radiographic monitoring for at least 5 weeks in patients with these fracture characteristics.

Table 1. Characteristics of demographic factors in a cohort of 79 cases with minimally displaced clavicle fractures in polytrauma

	n=79
Sex, n	
Male : female	58 : 21
Age, years (SD)	49.5 (17.5)
Fracture specific factors	
Comminution of fractures, n (%)	23 (29)
Location of clavicle fracture, n (%)	
Medial (AO/OTA type 15.1)	8 (10)
Middle (AO/OTA type 15.2)	43 (54)
Lateral (AO/OTA type 15.3)	28 (36)
Polytrauma-related factors	
Injury severity score (SD)	24.9 (7.8)
Accompanying upper extremity injury except scapula, n (%)	17 (21.5)
Scapular fracture, n (%)	19 (24.1)
Rib fractures, n (%)	61 (77.2)
Glasgow coma scale (SD) Mild (12-15), Moderate (9-12), Severe (3-8)	11.4 (4.3) Mild: 42, Moderate: 16, Severe: 21
Traumatic CNS injury, n (%)	43 (54.3)
ICU admission, days (SD)	15.1 (19)
Use of ventilator, n (%)	40 (50.6)
Duration of intubation, days (SD)	10 (14.9)

CNS, central nervous system; ICU, intensive care unit.

of comminution were assessed, as these characteristics were considered potential predictors of delayed displacement.

Furthermore, for statistical analysis, a regression analysis was performed to determine the risk factors associated with delayed displacement of >100% of the fracture during conservative treatment. Initially, a univariate logistic regression analysis was performed to analyze individual factors, while a multivariate logistic regression analysis was conducted to analyze the factors related to delayed displacement with a *P* value of <.25, following established recommendations to minimize the risk of overfitting while retaining clinically relevant predictors. Odds ratios (ORs) and 95% CIs of each factor were calculated. To assess potential multicollinearity, collinearity diagnostics were performed using the Variance Inflation Factor (VIF). IBM SPSS Statistics version 20.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis, and a *P* value of <.05 was considered statistically significant.

Results

Overall, 79 patients (58 men and 21 women) who had sustained polytrauma with minimally displaced clavicle fractures, as identified on initial radiography, were included in the cohort. The demographic characteristics of the cohort are summarized in Table 1.

A total of 31 patients (39.2%) experienced delayed displacement, determined by >100% displacement of the fracture. The remaining 48 patients (60.8%) consistently exhibited <100% displacement with conservative treatment during the follow-up (Figure 2). Among the patients who experienced delayed displacement, 18 (58.1%) underwent surgery for fixation (Figure 3), whereas 13 (41.9%) continued with conservative treatment because of their inability to achieve medical optimization owing to hemodynamic instability. The average time to delayed displacement was 10.1 ± 8.1 days (range: 2-33 days) after the initial injury. In 1 patient in whom delayed displacement was identified on day 2, initial assessment of the clavicle fracture was performed using chest CT because a dedicated clavicle radiographic series could not be obtained at presentation. On the following day, when a clavicle radiographic series became feasible, displacement greater than 100% was identified on the acromioclavicular view. Overall, 25 patients did not undergo an initial dedicated clavicle radiographic series, and delayed displacement subsequently occurred in 8 of these patients.

The assessment of displacement demonstrated good inter-observer reliability, with an ICC of 0.85, and excellent intra-observer reliability, with an ICC of 0.91.

Univariate logistic regression analysis for delayed displacement revealed fracture-specific factors, such as mid-shaft fracture location and the presence of comminution, as significant risk factors (OR=4.2 (1.427-12.460) and 6.2 (2.149-18.161), respectively; *P* = .009 and .001, respectively). However, all polytrauma-related factors, including the ISS, accompanying upper extremity injury, scapular fracture, rib fractures, level of consciousness, traumatic CNS injury, ICU admission, ventilator use, and duration of intubation, demonstrated no significance (all, *P* > .05) (Table 2). A multivariate logistic regression analysis was performed to analyze factors with a *P* value of < .25 in the univariate analysis, such as the location of the fracture, presence of comminuted fractures, rib fracture, and ventilator use. The result of the multivariate analysis also identified mid-shaft location and the presence of comminution as significant risk factors (*P* = .018 and .003, respectively) (Table 3). Collinearity diagnostics demonstrated that all included variables had VIF values <2.0, indicating no significant multicollinearity. The overall explanatory power of the multivariate model was moderate, with a Nagelkerke R^2 of 0.352.

With regard to scapular fractures, the association with specific subgroups was additionally examined. The displacement rates were 0% for glenoid fractures (1/1), 28.6% for acromion fractures (2/7), 50.0% for coracoid fractures (1/2), and 25.0% for body fractures (3/12), compared with 41.7% in patients without scapular fractures. Logistic regression analysis demonstrated no significant association between any scapular subgroup and clavicle displacement (all *P* > .05).

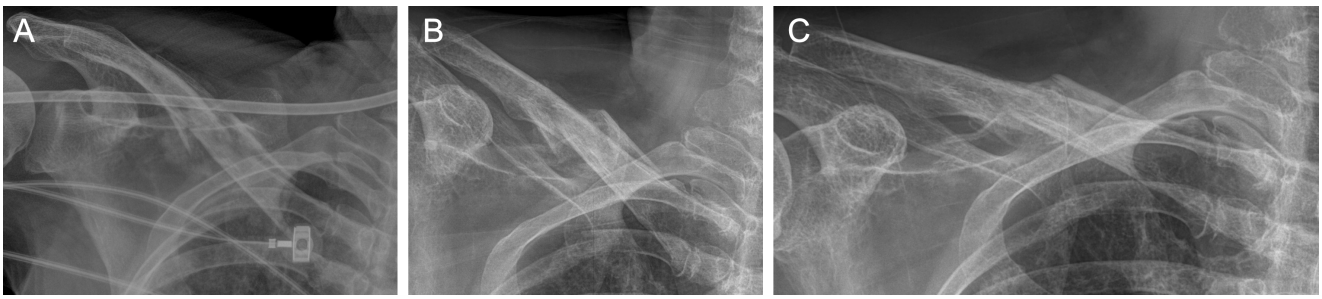

Figure 2. (A) A 57-year-old female patient with a minimally displaced midshaft clavicle fracture treated conservatively. (B) At 6 weeks post-injury, the fracture remained stable without further displacement. (C) At 3 months, bony union was achieved.

Figure 3. (A) A 20-year-old female patient with a minimally displaced midshaft clavicle fracture had initially undergone conservative treatment; (B) Delayed displacement occurred 13 days after injury; (C) She eventually underwent surgery with plate and screws.

Discussion

The aim of this study was to evaluate the incidence and predictors of delayed displacement in minimally displaced clavicle fractures associated with polytrauma. Midshaft location and fracture comminution were identified as significant risk factors. Contrary to the initial hypothesis, polytrauma-related factors such as the ISS, associated extremity injury, level of consciousness, traumatic CNS injury, ICU admission, use of mechanical ventilation, and duration of intubation were not significantly associated with the occurrence of delayed displacement. Notably, rib fractures showed a tendency to increase the risk of delayed displacement (OR=2.730, *P*=.157), while ventilator use tended to reduce the risk (OR=0.433, *P*=.142); however, neither reached statistical significance. Although these findings suggest that the effect of polytrauma-related factors was not strong enough to demonstrate statistical significance in this cohort, this lack of significance should be interpreted with caution. Given the relatively small number of events in relation to the number of variables included in the regression analysis, the possibility of a Type 2 error cannot be excluded, and the absence of statistical significance does not necessarily indicate a definitive lack of influence of systemic injury severity on delayed displacement.

A multidisciplinary approach is essential for the management of patients with polytrauma, allowing fracture treatment decisions to be made based on the patient's overall systemic condition.[13-18] Surgical indications in polytrauma patients may differ from those in isolated fractures, and conservative management is often preferred during the acute phase because of poor general condition or delayed diagnosis.[7,19-21] Nevertheless, appropriate fracture stabilization, when feasible, may facilitate recovery, prevent complications, and improve functional outcomes.[15]

Clavicle fractures are the most common musculoskeletal injuries in patients with polytrauma. However, few studies have investigated the proper treatment of these injuries in such patients. Many studies have reported better outcomes in patients with clavicle fractures who underwent surgical treatment, which is attributed to higher rates of bone union and faster functional recovery.[22-29] However, many of these studies evaluated patients with isolated clavicle fractures, and whether their results can be extrapolated to polytrauma patients with clavicle fractures remains controversial. Ferree et al suggested that a wait-and-see approach might be appropriate for patients with polytrauma with displaced midshaft clavicle fractures, given that the rates of non-union or delayed union following delayed fixation are comparable to those seen in patients with isolated displaced clavicle fractures.[30] Nevertheless, in their polytrauma cohort, non-union or delayed union was observed in approximately 15% of patients, and there were no surgical guidelines regarding early or delayed fixation for the remaining 85% of patients. Delayed fixation at 4 months after injury carries a higher risk of complications, such as a neurovascular injury, than that by an early surgery.[31-34] Callus formation and soft tissue contractures around the fracture site can also make it difficult to treat displaced fractures and additional bone grafts may be required. In this study, surgical guidelines were established for patients in whom displacement was observed to be greater than 100%. In comparison, patients with an initial displacement of less than 100% were initially treated conservatively and monitored by performing radiographies weekly. Although there is no evidence indicating that conservative treatment with figure-of-eight bandages is better than conservative treatment with arm slings, the use of figure-of-eight bandages is associated with more pain and increased risk of neurovascular injury and pressure sores.[21,35-37] Therefore, only arm slings were used for the initial conservative treatment.

For patients in whom delayed displacement occurs during conservative management, surgical intervention may be considered

Table 2. Univariable logistic regression analysis to determine the risk factors associated with delayed displacement >100%

	OR (95% CI)	Wald χ^2	*P*
Gender (male compared to female)	1.412 (0.496-4.022)	0.417	.519
Age	0.988 (0.962-1.014)	0.831	.362
Fracture specific factors			
Comminution of fracture	6.248 (2.149-18.161)	11.325	.001
Location of clavicle fracture			.022
Medial compared lateral	1.222 (0.195-7.675)	0.011	.830
Middle compared lateral	4.217 (1.427-12.460)	4.896	.009
Polytrauma-related factors			
Injury severity score	1.015 (0.958-1.075)	0.244	.621
Accompanying upper extremity fracture	1.108 (0.372-3.306)	0.034	.854
Scapular fracture	0.646 (0.216-1.932)	0.611	.434
Rib fractures	2.779 (0.820-9.421)	2.694	.101
Glasgow coma scale	0.995 (0.894-1.107)	0.009	.925
Traumatic CNS injury	1.027 (0.415-2.545)	0.003	.953
Use of ventilator	0.562 (0.225-1.400)	1.532	.216
Duration of ICU care	0.990 (0.965-1.015)	0.625	.429
Duration of intubation	0.994 (0.964-1.026)	0.140	.709

CNS, central nervous system; ICU, intensive care unit; OR, odds ratio.

Table 3. Multivariable logistic regression analysis to determine the risk factors associated with delayed displacement

	OR (95% CI)	Wald χ^2	*P*
Fracture specific factors			
Comminution of fracture	5.954 (1.852-19.145)	8.962	.003
Location of clavicle fracture			
Medial compared to lateral	0.752 (0.091-6.228)	0.070	.792
Middle compared to lateral	4.423 (1.295-15.106)	5.631	.018
Polytrauma-related factors			
Rib fractures	2.730 (0.680-10.953)	2.007	.157
Use of ventilator	0.433 (0.142-1.324)	2.153	.142

ICU, intensive care unit; OR, odds ratio.

depending on the patient's overall clinical condition. Previous studies have shown that both locked intramedullary nailing and anatomical locking plate fixation provide favorable clinical and radiological outcomes for displaced midshaft clavicle fractures. In particular, Zehir et al reported comparable results between these 2 techniques, supporting the feasibility of surgical treatment when delayed displacement occurs during follow-up.[38] Similarly, recent studies have reported favorable clinical outcomes with various surgical techniques for clavicle-related injuries, including distal clavicle fractures and acromioclavicular joint instability. Lin et al demonstrated good clinical efficacy using an Endobutton combined with a mini-plate for Neer type IIB distal clavicle fractures,[39] while Bascı et al reported satisfactory clinical and radiological outcomes following combined coracoclavicular ligament and transacromial capsule reconstruction for chronic acromioclavicular joint instability.[40]

In some cases, patients underwent surgical treatment for concomitant extremity fractures, raising the question of why clavicle fixation was not performed during the same operative session. In the cohort, the decision for surgical intervention of the clavicle was based solely on the degree of initial displacement (≥100% of the clavicle diameter), irrespective of the presence or surgical requirement of other fractures. Moreover, in polytrauma patients with multiple extremity injuries, each fracture was managed by subspecialty orthopedic surgeons according to their field of expertise, and thus the surgical indication for the clavicle was determined independently. Finally, there was concern about the risks associated with prolonged operative time in severely injured patients. Although recent multidisciplinary approaches have enabled more proactive early management, limiting surgical procedures to essential interventions within a shorter operative duration is still considered beneficial for reducing mortality and morbidity in polytrauma patients.

The cohort study revealed that 39.2% of patients showed delayed displacement during follow-up. Another study reported that 60.0% of patients with minimal displacement in high-energy injuries showed delayed displacement. It was concluded that radiologic studies should be repeated over 2 weeks to ensure that the occurrence of delayed displacement is not overlooked.[9] Given that the time to delayed displacement ranged from 2 days to a maximum of 33 days in the study, it is recommended that cases of minimally displaced fractures in patients with polytrauma should be regularly monitored radiologically for at least 5 weeks.

Furthermore, this study found that polytrauma-related factors did not significantly impact the risk of delayed displacement of clavicular fractures. Stahl et al previously identified concurrent rib fracture as a significant factor inducing delayed displacement of clavicle fractures, whereas ipsilateral scapular fractures did not.[41] It is unclear whether the study included patients with polytrauma. Among the patients with clavicular fractures and concurrent rib fractures, 72% experienced delayed displacement, whereas among patients with clavicular fractures alone, 54% experienced delayed displacement. In contrast, the study did not identify concurrent rib fracture as a significant predictor of delayed displacement, although the OR suggested a tendency toward increased risk (OR = 2.730, $P = .157$). Furthermore, the presence of ipsilateral scapular fractures with clavicular fractures, which would create a floating shoulder associated with increased displacement, was found to be insignificant. Comminution at the time of injury or midshaft fracture location, which are fracture-specific characteristics, emerged as risk factors in multiple and single regression analyses. These findings are consistent with recent evidence emphasizing the biomechanical instability associated with comminuted fracture patterns. Baysal et al reported inferior outcomes and a higher risk of failure in conservatively treated midshaft clavicle fractures with a butterfly fragment, demonstrating that comminution itself predisposes fractures to secondary displacement despite initially minimal radiographic displacement.[42] A study reported that delayed displacement occurred in 32.3% of cases of high-energy clavicle fractures with an initial displacement of 3 mm or less, as observed on radiography, compared with that in 73.4% of cases with an initial displacement greater than 3 mm.[9] Additionally, isolated midshaft clavicle fractures with comminution and >100% displacement were identified as risk factors for non-union following conservative treatment.[43] Consistent with findings from studies of isolated fractures, local fracture biomechanics—particularly comminution and midshaft location—appear to play a dominant role in delayed displacement, even within the complex clinical context of polytrauma. Taken together, these findings suggest that surgical intervention is not mandatory for minimally displaced clavicle fractures in patients with polytrauma; however, careful and regular radiographic follow-up for at least 5 weeks is warranted to detect delayed displacement, particularly in fractures involving the midshaft or comminution.

This study has several limitations. First, it was a retrospective cohort study. However, consistent treatment was provided because physicians from a single institution shared crucial treatment guidelines, such as the decision-making process for surgical interventions. Second, the large reduction from the initially screened population to the final study cohort may raise concerns regarding potential selection bias. Third, instead of evaluating fracture healing, >100% displacement was adopted as the criterion for the failure of conservative treatment. This was because many patients with polytrauma required surgery but could not undergo the procedure due to an overall worsening condition. Another study reported >100% displacement as a predictor of non-union. Other studies investigating clavicle fractures in patients with polytrauma also defined displacement greater than 100% as the limit for conservative treatment.[43,44] Fourth, displacement was assessed using plain radiographs, which are less accurate than CT scans in evaluating axial or rotational deformities. Nevertheless, plain radiographs were the only feasible modality for frequent follow-up in polytrauma patients. Although chest CT was often performed during the initial trauma evaluation for associated injuries, initial fracture displacement was preferentially assessed using plain radiographs whenever feasible to maintain consistency with subsequent follow-up imaging. To mitigate the inherent limitations of plain radiographs, a dedicated clavicle series (AP, cephalic tilt, and acromioclavicular views) was used to assess displacement from multiple angles. In addition, 2 observers independently evaluated the radiographs, and intra- and inter-observer reliability was confirmed using the ICC, which showed good-to-excellent agreement. Fifth, the exact timing of displacement may not always have been precisely determined. Follow-up imaging consisted primarily of weekly dedicated clavicle radiographs supplemented by routine ICU chest AP radiographs, which are not optimized for evaluating clavicle alignment and may therefore have introduced some inaccuracy in identifying the precise timing of displacement. Sixth, the number of events (n = 31) was relatively small compared with the number of variables included in the regression analysis, resulting in a lower events-per-variable ratio than the generally recommended threshold of 10. Although the study attempted to minimize the risk of overfitting by applying a stricter inclusion threshold ($P < .25$) and

confirming the absence of significant collinearity (all VIF values <2.0), this limitation may have affected the robustness of the regression results. In line with this, some CIs in the regression models were relatively wide, reflecting the limited sample size and reducing the precision of the estimates; these results should therefore be interpreted with caution. Last, not all radiographs could be obtained upright because patients with severe overall conditions could not assume this posture.

In conclusion, delayed displacement was observed in 39.2% of patients with minimally displaced clavicle fractures associated with polytrauma. Polytrauma-related factors did not affect delayed displacement for minimally displaced clavicle fractures. However, delayed displacement was more likely to occur in cases where the fracture was located at the mid-shaft or involved comminution, even if the displacement was not severe at the time of injury. Therefore, regular weekly radiographic examinations of patients with polytrauma are necessary to detect delayed displacement, particularly in patients with these risk factors.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Artificial Intelligence Usage Statement: This study used ChatGPT (OpenAI) to improve language clarity, edit grammar, and refine wording during the preparation of the manuscript.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Ajou University Hospital (Approval no: AJIRB-MED-MDB-19-566, Date: 03.10.2020).

Informed Consent: N/A.

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