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Optimizing treatment for odontoid fractures in the elderly: a balancing act with the patient at center stage

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Citation
Huybregts, J. G. J. (2025, November 21). *Optimizing treatment for odontoid fractures in the elderly: a balancing act with the patient at center stage*. Retrieved from https://hdl.handle.net/1887/4283689

Version:	Publisher's Version
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Note: To cite this publication please use the final published version (if applicable).

CHAPTER

5

HOUNSFIELD UNIT MEASUREMENTS TO PREDICT ODONTOID FRACTURE UNION IN ELDERLY PATIENTS: POST-HOC SUBGROUP ANALYSIS FROM AN INTERNATIONAL PROSPECTIVE COMPARATIVE STUDY

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Spine J. 2025 May 7:S1529-9430(25)00235-9.

ABSTRACT

Introduction

Decreased bone mineral density (BMD) has been associated with impaired fracture healing in vertebral fractures. In the absence of dual-energy X-ray absorptiometry (DXA) scans, CT-derived Hounsfield units (HU) may serve as a surrogate marker for BMD. This study evaluated whether baseline HU measurements in the C2 and C3 vertebrae could predict odontoid fracture union in elderly patients.

Methods

A post-hoc subgroup analysis was performed within an international prospective study involving 142 patients aged ≥55 years with acute (<2 weeks) type II/III odontoid fractures. Standardized HU measurements were obtained from baseline CT scans in both mid-sagittal and mid-axial planes of C2 and C3. Fracture union at 52 weeks was compared between patients with and without union. Multivariable regression analyses adjusted for age, gender, fracture type, fracture displacement, other C1-C2 fractures, and treatment modality.

Results

There were no relevant differences in HU values between the union and non-union groups. Mean (SE) C2 HU was 246 (6.3) in the union group vs. 282 (33) in the non-union group (p=0.29), and mean C3 HU was 260 (6.5) vs. 251 (15), respectively (p=0.56). No association was found between baseline HU and fracture union (p=0.34 for C2; p=0.86 for C3). None of the baseline characteristics were significant predictors of union at 52 weeks. Compared to control patients in the literature, both the union and non-union groups had reduced HU (<300), indicating osteopenia.

Conclusion

Baseline HU measurements in C2 and C3 did not predict fracture union at 52 weeks. Given that both groups exhibited decreased BMD, all elderly patients with odontoid fractures should be referred for osteoporosis screening and appropriate treatment.

INTRODUCTION

Odontoid fractures are the most common cervical spine fractures in the elderly and are associated with osteoporosis.[1, 2] Impaired fracture healing is common after both surgical and conservative treatments, making the identification of predictive factors for fracture union valuable for guiding treatment decisions.

Decreased bone mineral density (BMD) has been linked to poorer fracture healing in animal and some clinical studies, though data on odontoid fractures remain limited.[3, 4] While dual-energy X-ray absorptiometry (DXA) is the gold standard for measuring BMD, it is often unavailable at the time of fracture diagnosis. Measuring Hounsfield units (HU) on computed tomography (CT) scans offers an opportunistic method to assess BMD at the time of injury.[5] Prior studies have demonstrated the feasibility of HU measurements on lumbar spine CT scans to predict BMD.[6, 7] However, the correlation between HU and BMD in cervical spine CT remains unclear due to its unique anatomical characteristics.

Currently, there is limited literature on HU measurements in cervical spine CT, and no established reference values exist for classifying BMD in this region. One study reported mean HU of 232 (95% CI 214, 250) for osteoporosis, 284 (95% CI 272, 296) for osteopenia, and 360 (95% CI 351, 368) for normal BMD, but noted gaps between 95% confidence intervals.[5] Another study identified a HU cutoff of 308 to distinguish high and low bone quality with a 90% specificity.[8] A third study proposed a HU cutoff of 300 to differentiate normal bone quality from osteopenia/osteoporosis with a 77% specificity.[9] These studies suggest HU measurements, particularly in the C2 and C3 vertebral bodies, may serve as surrogates for BMD.[5, 8] However, the relationship between cervical spine BMD and fracture healing remains unclear, and studies specifically addressing this association in odontoid fractures are scarce, particularly in elderly patients.[10]

This study aimed to investigate the association between BMD and odontoid fracture healing in elderly patients. HU measurements in C2 and C3 were used to quantify BMD and were assessed as predictors of fracture union at 52 weeks in patients with type II/III odontoid fractures. It was hypothesized that HU would be lower in patients with persistent non-union.

METHODS

Patient selection

Patients were selected from the INNOVATE trial (INterNational study on Odontoid frActure Treatment in the Elderly), an international prospective comparative study evaluating surgical versus conservative treatment for odontoid fractures. The study included 279 patients aged ≥55 years with CT-confirmed type II/III fractures between 2012 and 2022, and the results were published in 2024.[11] For the present study, a subgroup was included consisting of all patients from the five centers that provided baseline CT scans for re-evaluation at the coordinating center.

Treatment and follow-up

The treatment modality was determined through shared decision-making between the attending surgeon and the patient. Follow-up appointments were scheduled at 6, 12, 26, 52, and 104 weeks, during which the surgeon completed questionnaires regarding fracture healing and the patients' recovery. Follow-up could be terminated prematurely by the surgeon if a patient had achieved fracture union and/or stability, along with (nearly) complete clinical recovery.

Data collection

Baseline CT scans were collected, and the following variables were assessed: age, gender, fracture type, fracture displacement, other C1-C2 fractures, applied treatment, and union status at 52 weeks. Union was defined on CT by the attending surgeon and radiologist as the presence of bone trabeculae crossing the fracture site and the absence of adjacent sclerotic borders.[12] Patients were classified into two groups: a union group, demonstrating union at 52 weeks, and a non-union group, with persistent non-union at this time point.

HU measurements

Standardized mean HU measurements in the C2 and C3 vertebral bodies were performed on baseline non-contrast CT scans using Picture Archiving and

Communication System (PACS) software. C2 and C3 were selected due to their demonstrated correlation with DXA scan outcomes, providing the most accurate reflection of BMD.[5] Different methods of HU measurements were applied to C2 and C3 to evaluate the effectiveness of these individual approaches (**Figure 1**).

For C2, mean HU were measured using a region of interest (ROI) adapted to the shape of the vertebra, excluding the fracture line, cortical bone, degenerative sclerosis, subchondral cysts, bone islands, and artefacts. For C3, mean HU were measured using a circle of interest (COI) of 50 mm^2, again avoiding potential anomalies. Measurements for both vertebrae were taken in mid-sagittal and mid-axial planes using the localizer tool. The mean of these mid-sagittal and mid-axial measurements was then calculated to provide the most representative values.[5]

ROI measurements in C2 were independently done by two reviewers (LH, ER). Repeated measurements in C2 were conducted by both reviewers to assess intra- and interobserver variability. COI measurements in C3 were done by one reviewer (LH).

Statistical analysis

Age and baseline HU were treated as continuous variables and analyzed univariably by union status using independent samples T-tests. Other baseline characteristics and treatment modality were categorical variables, analyzed univariably with χ^2-tests. Multivariable logistic regression was used to assess the association between mean HU in C2 and C3 and union status. Variables generally presumed to relate to the outcome were adjusted for in the regression analyses: age (continuous), gender (male, female), fracture type (II, III), fracture displacement (≤2 mm, >2 mm), concomitant C1-C2 fractures (no, yes), and treatment modality (surgical, conservative).

The associations of individual variables were studied separately. Sensitivity analyses were performed by successively adding HU for mid-sagittal and mid-axial planes to the regression model (instead of the mean of these two), to assess the appropriateness of the applied concept. The Pearson correlation coefficient was used to examine the correlation between mid-sagittal and mid-axial measurements.[13] Intra- and interobserver variability of HU measurements were evaluated using intraclass correlation coefficients.[14]

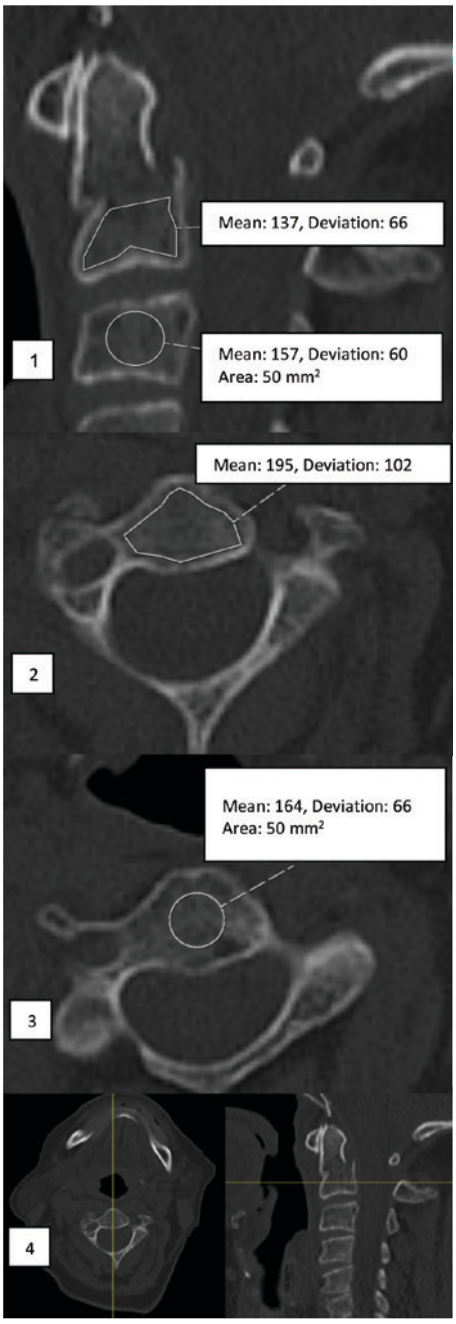

Figure 1. Example of HU measurements in a 70-years old female patient. Region-of-interest measurements were performed in C2 on mid-sagittal (1) and mid-axial (2) planes. Circle-of-interest measurements were performed in C3 on mid-sagittal (1) and mid-axial (3) planes. The localizer tool was used (4). The mean of mid-sagittal and mid-axial values was analyzed.

Radiological follow-up was concluded before 52 weeks in cases of positive outcomes (i.e., fracture union/stability and (nearly) complete clinical recovery), resulting in missing data beyond the last follow-up. Two rules were applied to complete data on union status: union implies later union, and non-union implies prior non-union. Union data were completely available for 105 (74%) patients. Missing data were multiply imputed using predictive mean matching (m=10), assuming data were missing at random. Multiple imputation results for union were adjusted to adhere to the two rules. A two-tailed p-value <0.05 was considered statistically significant. Analyses were conducted using IBM SPSS, version 29.

RESULTS

Patient selection

Of the original 279 patients in the INNOVATE trial, a total of 142 patients from five participating centers met the selection criteria (**Figure 2**). Patients were included from the Leiden University Medical Center (n=45), Haaglanden Medical Center (n=42), Academic Hospital Feldkirch (n=32), University Medical Center Utrecht (n=18), and St. Olavs Hospital Trondheim (n=5).

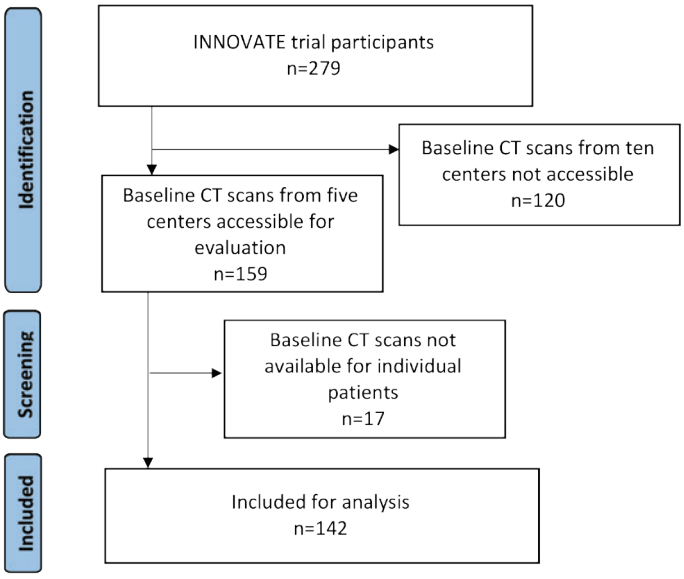

Figure 2. Flowchart depicting the inclusion process

Patient characteristics

At 52 weeks, fracture union was achieved by 115 (81%) patients, while the remaining 27 (19%) patients exhibited persistent non-union. In univariable analyses, patients with union were younger than patients with persistent non-union (mean age (SD) 76 (9.9) vs. 82 (7.7), p=0.007), fractures displaced ≤2 mm showed less union than fractures displaced >2 mm (73% vs. 93%, OR 0.20 (95% CI 0.04, 0.90)), and surgical patients had a higher union rate than conservative patients (92% vs. 73%, OR 4.1 (95% CI 1.3, 12), **Table 1**). Importantly, these variables were among the covariates adjusted for in the multivariable analyses.

Table 1. Patient characteristics by union status at 52 weeks (n=142)

	Outcome		
	Union (n=115)	**Non-union (n=27)**	**Univariable analysis**
Age, mean (SD)	76.1 (9.9)	82.1 (7.7)	***p*=0.007**
Gender			
Male	62 (85%)	11 (15%)	OR 1.8 (CI 0.56, 5.8)
Female	53 (77%)	16 (23%)	
Fracture type			
Type II	74 (76%)	24 (24%)	OR 0.16 (CI 0.02, 1.2)
Type III	41 (93%)	3 (7%)	
Fracture displacement			
≤2 mm	62 (73%)	23 (27%)	**OR 0.20 (CI 0.04, 0.90)**
>2 mm	53 (93%)	4 (7%)	
Other C1-C2 fractures			
No	83 (81%)	20 (19%)	OR 0.86 (CI 0.31, 2.4)
Yes	32 (82%)	7 (18%)	
Applied treatment			
Surgical	57 (92%)	5 (8%)	**OR 4.1 (CI 1.3, 12)**
Conservative	58 (73%)	22 (27%)	

Abbreviations: SD, standard deviation. OR, pooled odds ratio. CI, confidence interval. Values in bold represent statistical significance.

Baseline HU

The mean baseline HU (SE) in C2 was 246 (6.3) for patients with union and 282 (33) for patients with non-union (p=0.29). The mean baseline HU (SE) in C3 was 260 (6.5) for patients with union and 251 (15) for patients with non-union (p=0.56, **Table 2**).

In multivariable analysis, baseline HU in C2 and C3 were not significant predictors for union at 52 weeks (p=0.34 and p=0.86, respectively, **Table 3**).

Measurement correlations

The Pearson correlation coefficients between mid-sagittal and mid-axial planes were 0.80 for C2 and 0.90 for C3, indicating (very) strong correlations between measurements in different planes (both p<0.001).[13]

The intraobserver variability between repeated measurements was 0.95 for C2 and 0.96 for C3, both indicating excellent correlation (both p<0.001).[14]

Additionally, the interobserver variability for repeated C2 measurements was 0.97, also indicating excellent correlation (p<0.001).

Table 2. HU values by union status at 52 weeks

	Outcome		
	Union (n=115)	**Non-union (n=27)**	**Univariable analysis**
Baseline HU in C2, mean (SE)	246 (6.3)	282 (33)	p=0.29
Baseline HU in C3, mean (SE)	260 (6.5)	251 (15)	p=0.56

Abbreviations: SE, standard error.

Table 3. Results of logistic regression analysis

Independent variable	B	SE	Multivariable analysis	
			aOR (95% CI)	*p*-value
Baseline C2 HU (continuous, per HU increase)	0.004	0.004	1.00 (0.99, 1.01)	0.34
Baseline C3 HU (continuous, per HU increase)	−0.001	0.005	1.00 (0.99, 1.01)	0.86
Age (continuous)	0.05	0.03	1.05 (0.99, 1.1)	0.12
Gender (male vs. female)	0.42	0.74	1.5 (0.34, 6.9)	0.58
Fracture type (II vs. III)	−2.1	1.1	0.12 (0.01, 1.1)	0.06
Fracture displacement (≤2 mm vs. >2mm)	−1.3	0.83	0.29 (0.05, 1.5)	0.14
Other C1-C2 fractures (no vs. yes)	−0.04	0.61	0.96 (0.29, 3.2)	0.95
Applied treatment (surgical vs. conservative)	1.3	0.67	3.6 (0.97, 14)	0.06

Abbreviations: B, regression coefficients. SE, standard errors. aOR, adjusted odds ratios. CI, confidence intervals.
Regression analysis was done with union status as dependent variable (union: 0, non-union: 1), and age, gender, fracture type, fracture displacement, other C1-C2 fractures and applied treatment as covariates.

Additional analyses

In multivariable analysis, none of the baseline characteristics—age, gender, fracture type, fracture displacement, other C1-C2 fractures, and applied treatment—were significantly associated with union at 52 weeks (**Table 3**). These findings are in agreement with the more extensive analyses of the original (larger) cohort from which this subgroup was derived.[11]

No significant association was found when mid-sagittal or mid-axial HU measurements (instead of their mean) were successively added to the multivariable logistic regression model:

- For C2: mid-sagittal p=0.93, aOR 1.00 (95% CI 0.99, 1.01) per unit increase in HU; mid-axial p=0.44, aOR 1.00 (95% CI 0.99, 1.01) per unit increase in HU.
- For C3: mid-sagittal p=0.94, aOR 1.00 (95% CI 0.99, 1.01) per unit increase in HU; mid-axial p=0.88, aOR 1.00 (95% CI 0.99, 1.01) per unit increase in HU.

DISCUSSION

In this prospective study involving elderly patients treated for odontoid fractures, no relevant differences were found in baseline HU measurements in C2 and C3 between those with and without fracture union at 52 weeks. Therefore, these measurements did not predict the likelihood of achieving union in this patient group. Compared to control patients in the literature, both the union and non-union groups exhibited decreased BMD, with mean cervical HU <300 in both groups, indicating osteopenia/osteoporosis.[5, 8, 9] This highlights the need for elderly patients with odontoid fractures to be referred for osteoporosis screening and appropriate treatment. While low BMD is recognized as a risk factor for odontoid fractures, BMD status at baseline did not significantly influence fracture union in this study.

The primary analysis was conducted using the mean of mid-sagittal and mid-axial HU measurements. Both ROI measurements for C2 and COI measurements for C3 showed largely similar results. While measurements in these two planes typically exhibited different values and wide deviations, three additional analyses were performed to validate the methods: First, correlation between mid-sagittal and mid-axial values was found to be (very) strong. Second, intraobserver and interobserver variability were examined, demonstrating excellent correlations. Third, sensitivity analysis by adding mid-sagittal and mid-axial measurements (instead of their mean) to the regression model yielded similar results. These findings confirmed the appropriateness of the applied measurement model.

In multivariable analysis, none of the baseline characteristics (age, gender, fracture type, fracture displacement, other C1-C2 fractures, and applied treatment) were found to serve as predictors for union at 52 weeks. These results contradict previously published studies that suggested superior union rates for type III fractures and surgical treatments.[4, 15] However, prior studies often had retrospective designs, lacked controls, and relied on univariable analysis, often with considerable heterogeneity in treatment allocation, outcome assessment, and follow-up duration. Illustratively, the univariable analyses in the present study demonstrated a significant influence of fracture displacement and applied treatment, which was not observed in multivariable analyses. The prospective INNOVATE trial, from which the data in this study were derived, is the first study to use multivariable analysis

to adjust for baseline differences. The outcomes at 52 weeks showed no significant influence of any of the patient or fracture characteristics or applied treatments on clinical and radiological results.[11]

Perspective

This is the first study to investigate the relationship between baseline HU and fracture union in elderly patients treated for odontoid fractures. A previous study retrospectively analyzed 45 patients with C2 fractures treated by anterior odontoid screw fixation and demonstrated higher HU in patients that achieved union. However, that study did not focus on elderly patients specifically and included individuals aged 19-95 years.[10] This suggests that HU measurements may be useful in other age groups.

HU in C2 and C3 were remarkably high compared to previous findings in the lumbar spine (typically HU <150), despite patients in this study having decreased BMD compared to other cervical studies (cervical HU <300 in both the union and non-union groups).[1, 5, 16] Further studies aimed at establishing reference values for the cervical spine could offer valuable insights into general BMD, and may prove useful in future research. However, the clinical significance of these values in predicting radiological outcomes in elderly patients remains uncertain, as this study did not demonstrate an association. Future research may explore volume-of-interest measurements and artificial intelligence for more accurate measurements, potentially surpassing manual assessments.[17]

Limitations

This study has several limitations. First, it focused on elderly patients with fractures, who generally have poorer bone quality.[1, 2] This may explain the lack of differences between groups and also limits the generalizability of the findings to other populations. Additionally, it was not recorded whether the patients had been diagnosed with or treated for osteoporosis in the past. Second, the primary focus was on fracture union, and the association with clinical outcome was not explored. The clinical implications of non-unions in asymptomatic elderly patients remain debated, as does whether they should be considered treatment failures at all. Third, this was a non-randomized study. Despite adjusting for

age, gender, various fracture characteristics, and applied treatment, the results may still have been influenced by residual confounding and observer bias.

CONCLUSION

Baseline HU measurements in C2 and C3 were not associated with fracture union at 52 weeks and, therefore, failed as predictors of union in elderly patients with odontoid fractures. Since both the union and non-union groups exhibited reduced BMD compared to control patients in the literature, all elderly patients with odontoid fractures should undergo osteoporosis screening and receive appropriate treatment.

LIST OF ABBREVIATIONS

aOR — Adjusted odds ratio
B — Regression coefficient
BMD — Bone mineral density
CI — Confidence interval
COI — Circle of Interest
CT — Computed tomography
DXA — Dual-energy X-ray absorptiometry
HU — Hounsfield units
OR — Odds ratio
PACS — Picture archiving and communication system
ROI — Region of Interest
SE — Standard error

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