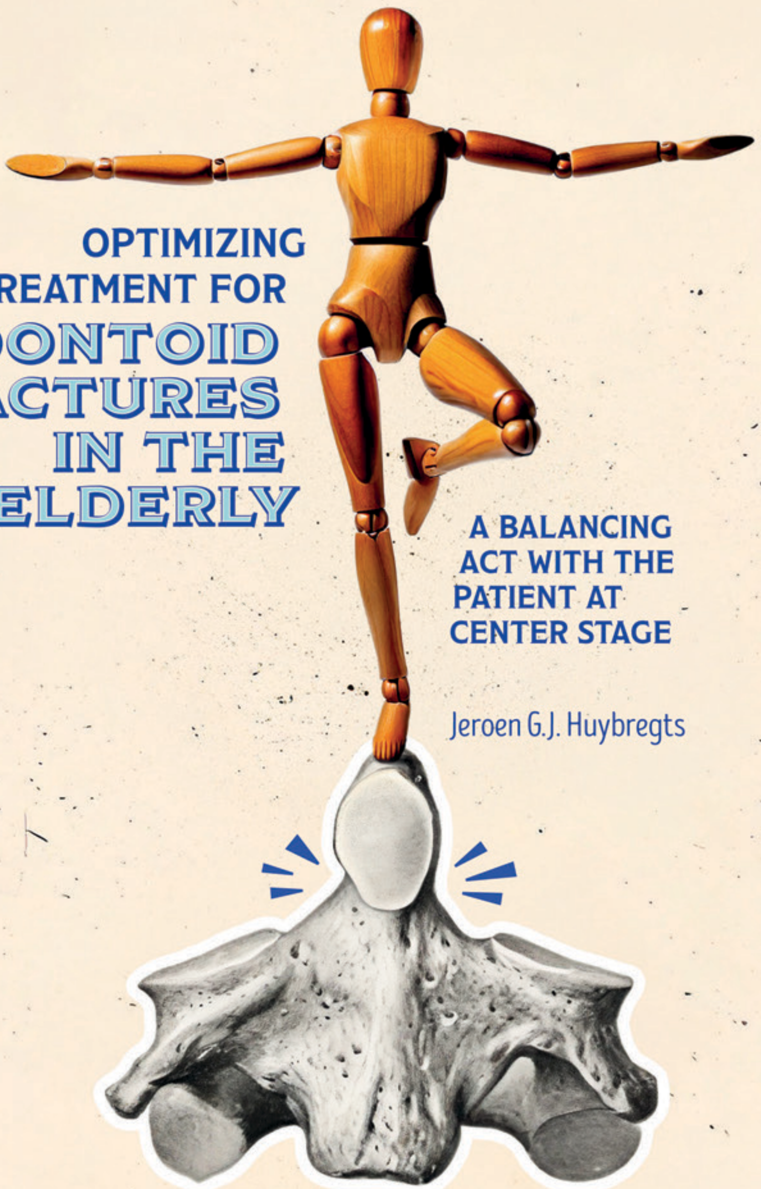
Optimizing treatment for odontoid fractures in the elderly: a balancing act with the patient at center stage
Huybregts, J.G.J.

OPTIMIZING TREATMENT FOR ODONTOID FRACTURES IN THE ELDERLY



A BALANCING ACT WITH THE PATIENT AT CENTER STAGE

Jeroen G.J. Huybregts

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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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1

GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

GENERAL INTRODUCTION

The odontoid process

The odontoid process is a bony projection extending from the superior aspect of the second cervical vertebra (the axis, or C2). Due to its shape, it is also referred to as the dens, derived from the Latin word for tooth. The odontoid process extends upwards into a recess in the anterior arch of the first cervical vertebra (the atlas, or C1), where it serves as a pivot point around which the atlas rotates (**Figure 1**).[1] It is encased by the transverse ligament posteriorly, and attaches to the skull base cranially through the apical and alar ligaments.[2] Rotational movements of the head (shaking 'no') primarily occur along the vertical axis defined by the odontoid process (**Figure 2**). The atlanto-axial joints form the most flexible spinal segment for axial rotation, accounting for over half of all cervical rotation movements.[2]

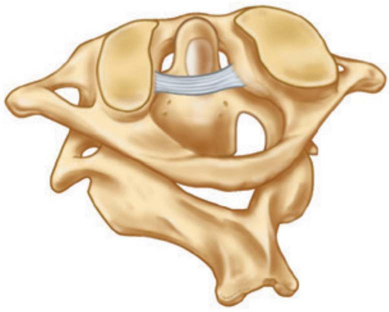

Figure 1. Left posterior-superior view of the atlas (above) and axis (below) vertebrae, showing the odontoid process on the superior aspect of the axis and the transverse ligament. Custom image by S. Blankevoort, 2024.

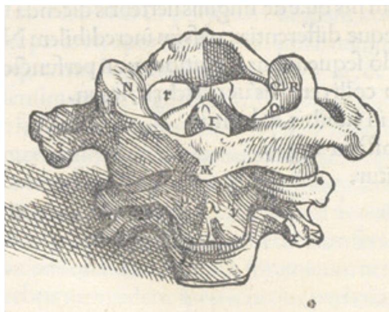

Figure 2. Likely the earliest anatomical description of the atlanto-axial region, based on direct observation and dissection, was published by Andreas Vesalius in 1543 in *De humani corporis fabrica libri septem*. Anterior-superior view. The accompanying descriptions demonstrate a profound understanding of anatomy and function. Reprinted with permission from Ghent University Library.

Odontoid fractures

Fractures of the odontoid process are the most common cervical spine fractures, typically resulting from (minor) hyperextension or hyperflexion trauma.[3] Odontoid fractures may cause neck pain and atlanto-axial instability, though associated neurological deficits from spinal cord injury are rare (**Figure 3**).[4, 5] These fractures are particularly prevalent among elderly patients and have been associated with osteoporosis.[6] More than 70% of patients are aged 65 years or older, with over 40% aged 80 years or older.[7] Furthermore, elderly patients face an increased risk of complications and mortality. Overall one-year mortality rates as high as 30 percent have been reported in patients aged 65 and above, similar to those of hip fractures.[8]

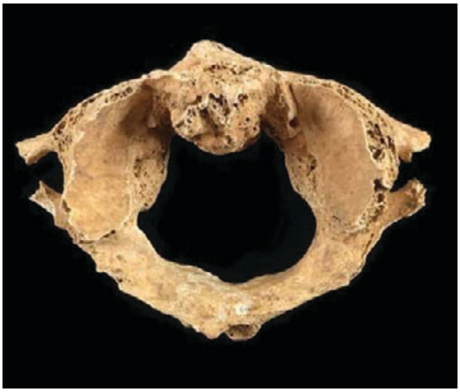

Figure 3. Presumably the oldest recorded odontoid fracture. Male, aged 50–60, medieval necropolis of Maro, Spain, 10th–11th CE. Superior view showing union of the odontoid process and the atlas, indicating long-term survival. Reprinted with publisher permission.

The older population is projected to grow by 50% between 2016 and 2030.[9] As a result, the incidence and healthcare burden of odontoid fractures are also expected to rise.[7] From 2000 to 2010, the incidence of these fractures increased across all age groups in the United States, with the most rapid rise observed among patients over 84 years, reaching 9,77 hospitalizations per 10,000 individuals annually. During this period, estimated annual charges for inpatient care of patients with axis fractures increased 4.7-fold, surpassing 1.5 billion dollars in 2010 in the United States alone.[10] Both the rising incidence and higher costs per treatment contribute to an increase in healthcare expenses.[11]

Fracture classifications

The most commonly used classification for odontoid fractures was published by Anderson and d'Alonzo in 1974 (**Figure 4**).[12] In this classification, type I fractures occur at the upper part of the odontoid process itself, type II fractures occur at the junction of the odontoid process and the body of the axis, and type III fractures are essentially fractures through the body of the axis. Type I fractures are relatively rare, usually considered avulsion fractures involving the alar ligaments, have a favorable clinical course, and are therefore typically outside the scope of clinical research.[4] Type II fractures are generally considered the most unstable.[13]

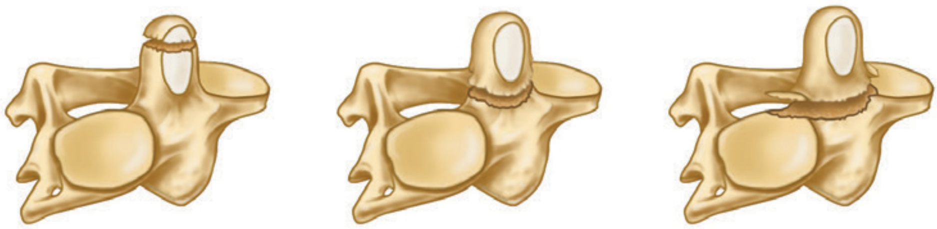

Figure 4. Right anterior-superior view of the axis depicting the Anderson and d'Alonzo classification. Fracture type I (left), type II (middle), and type III (right). Custom image by S. Blankevoort, 2024.

An alternative, though less commonly used, classification was proposed by Grauer et al. in 2005.[14] This classification aimed to provide a more precise distinction between type II and III fractures based on the presence or absence of facet joint involvement, and to aid treatment decisions. In this classification, type IIA fractures are horizontal non-displaced fractures, type IIB fractures follow an anterior-superior to posterior-inferior course or are displaced transverse fractures, type IIC fractures follow an anterior-inferior to posterior-superior course or are comminuted fractures, and type III fractures include at least one of the superior articular facets of the axis. A nearly identical classification was published in German by Eysel and Roosen in 1993.[15]

Besides the Anderson and D'Alonzo and Grauer classifications, up to nine other classification systems have been described in the literature. However, existing systems do not consider osteoporosis and the medical frailty of elderly patients, who represent a significant proportion of cases. Recommendations have been made for future classification systems to address these factors to better guide treatment for this population.[16]

Treatment options

The treatment for odontoid fractures aims to achieve fracture healing and a favorable clinical outcome while minimizing complications. Treatment approaches can be either surgical or conservative in nature.

The most common surgical treatments include posterior atlanto-axial fusion and anterior odontoid screw fixation. Conservative treatment involves the use of a cervical collar or halo vest to immobilize the cervical spine, promoting fracture healing and preventing secondary fracture displacement.

Surgical treatment

Posterior atlanto-axial fusion

Posterior atlanto-axial (C1-C2) fusion provides immediate stabilization, although thereby limiting its rotational capacity. There are various methods for performing C1-C2 fusions.

In the commonly applied method described by Harms and Melcher in 2001, polyaxial screws are bilaterally inserted into the lateral masses (or arch) of the atlas and into the pars interarticularis of the axis. This can be done under X-ray guidance or intraoperative navigation. The screws are then connected by two rods (**Figure 5**).[17] A largely similar method using plating was previously described by Goel and Laheri in 1994.[18]

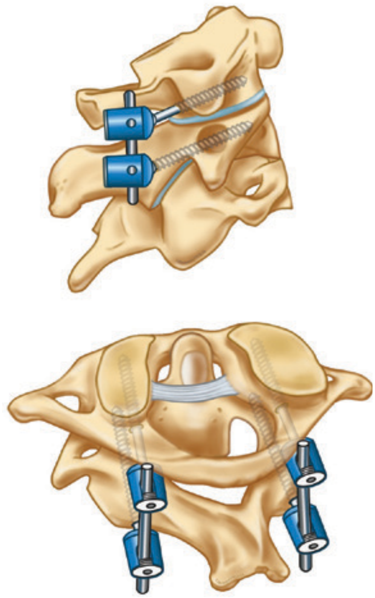

Figure 5. Right lateral view (above) and left posterior-superior view (below) illustrating posterior C1-C2 fusion as described by Harms and Melcher. Custom image by S. Blankevoort, 2024.

Transarticular C1-C2 fusion was described by Magerl and Seeman in 1986.[19] This technique is still used today, although it can be technically challenging and is not always feasible due to anatomical variations, such as a high-riding vertebral artery. Posterior interlaminar wiring with bone graft application was described by Gallie in 1939, and by Brooks and Jenkins in 1978.[20, 21] These wiring methods are still occasionally employed to facilitate osseous union, usually in conjunction with other fusion techniques.

Depending on the indication, C1-C2 fusion can be extended cranially to include the occiput or caudally to encompass the subaxial region. In elderly patients, posterior fusion has been associated with an increased risk of complications.[22]

Anterior odontoid screw fixation

Direct stabilization of odontoid fractures can be achieved by anterior odontoid screw fixation (**Figure 6**). This method was first described in 1980 by Nakanishi et al. in Japanese, although this paper did not receive widespread international recognition.[23, 24] Instead, a paper published by Böhler in 1982 gained international acclaim for this method.[25] During this procedure, a guided K-wire is first inserted into the inferior edge of the body of the axis. The screw trajectory is then drilled and tapped under X-ray guidance or intraoperative navigation. Finally, one or two screws are placed though the axis's body into the odontoid process to bridge the fracture.[26] These screws can be fully or partially threaded.[27] This procedure is particularly suitable for fracture lines perpendicular to the screw trajectory and preserves atlanto-axial movement. However, it has been associated with increased risk of complications in the elderly.[28, 29]

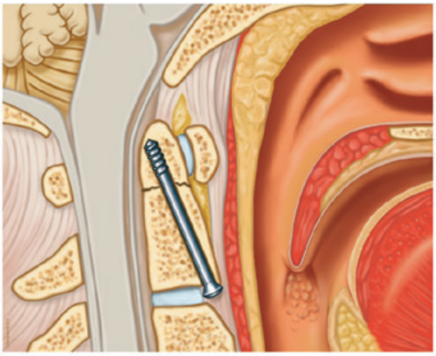

Figure 6. Right lateral view illustrating direct stabilization through anterior odontoid screw fixation. Custom image by S. Blankevoort, 2024.

Conservative treatment

Cervical collar

A cervical collar is applied upon presentation to externally stabilize the neck (**Figure 7**). The collar restricts movement in the cervical spine, limiting flexion, extension, lateral bending, and rotation. Multiple manufacturers offer cervical collars, each featuring distinct designs, yet serving the same fundamental purpose. Regular follow-up visits throughout treatment are used to monitor clinical and radiological progress.

Figure 7. Left-anterior view depicting a patient wearing a cervical collar. Custom image by S. Blankevoort, 2024.

Cervical spine immobilization protocols are not standardized.[30] Some centers prescribe cervical collars for continuous wear, while others recommend their removal during bed rest to prevent pressure ulcers. The duration of collar immobilization varies between centers, but typically falls within the range of six to twelve weeks.[31] Recently, there has been growing discussion about whether collar treatment is necessary at all in elderly patients, with a current study comparing collar use to no immobilization in this population.[32]

Halo vest

A halo vest is applied upon presentation and provides rigid stabilization of the cervical spine by restricting movement in all directions (**Figure 8**). The halo ring, made of lightweight metal, is positioned around the head. Metal pins are inserted into the outer layer of the skull under local anesthesia, serving as anchor points for attaching the halo ring. The ring is then connected to a vest made of rigid material, secured tightly around the torso to provide additional support and stability. Similar to cervical collar treatment, the duration of immobilization varies between centers. Regular follow-up visits are conducted during treatment to monitor clinical and radiological progress. The use of the halo vest in treatment has decreased over the last decades.[10] In elderly patients, it has been associated with an increased risk of complications and mortality.[33]

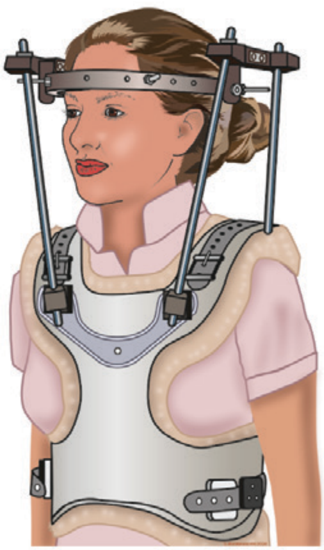

Figure 8. Left anterior view depicting a patient with a halo vest. Custom image by S. Blankevoort, 2024.

THESIS OUTLINE

Elderly patients with odontoid fractures have a higher risk of impaired fracture healing and complications with both surgical and conservative treatments. Each treatment option presents its own perceived advantages and disadvantages. The most relevant outcome parameters remain uncertain, as there is insufficient evidence of a direct association between fracture healing and more favorable clinical outcomes. Additionally, it remains unclear whether historical concerns about secondary fracture displacement leading to spinal cord injury are justified. As a result, the optimal treatment remains a topic of debate.

This thesis aims to compare clinical and radiological outcomes of surgical and conservative treatments for odontoid fractures in the elderly:

- **Chapter 2** provides a systematic review and meta-analysis of the available literature.
- **Chapter 3** compares the outcomes of a low-threshold-for-surgery versus a primarily-conservative treatment strategy, utilizing historical practice variation in the Netherlands in a natural experimental design.
- **Chapter 4** presents the findings from an international prospective study comparing surgical and initial conservative treatments, representing the largest cohort available.
- **Chapter 5** explores the usability of Hounsfield unit measurements on baseline computed tomography scans to predict odontoid fracture union.
- **Chapter 6** provides a general discussion, also addressing the limitations, future perspectives, and direct clinical implications.
- **Chapter 7** provides an English summary.
- **Chapter 8** includes a Dutch summary.
- The **Appendices** contain a list of publications, acknowledgements, and author information.

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CHAPTER 2

THE OPTIMAL TREATMENT OF TYPE II AND III ODONTOID FRACTURES IN THE ELDERLY: AN UPDATED META-ANALYSIS

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Eur Spine J. 2023;32(10):3434-3449.

Also based on:

The optimal treatment of type II and III odontoid fractures in the elderly: a systematic review

Jeroen G.J. Huybregts, Wilco C.H. Jacobs, Carmen L.A. Vleggeert-Lankamp

Eur Spine J. 2013 Jan;22(1):1-13.

ABSTRACT

Purpose

Odontoid fractures are the most common cervical spine fractures in the elderly, with a controversial optimal treatment. The objective of this review was to compare the outcome of surgical and conservative treatments in elderly (≥65 years), by updating a systematic review published by the authors in 2013.

Methods

A comprehensive search was conducted in seven databases. Clinical outcome was the primary outcome. Fracture union- and stability were secondary outcomes. Pooled point estimates and their respective 95% confidence intervals (CIs) were derived using the random-effects model. A random-effects multivariable meta-regression model was used to correct for baseline co-variates when sufficiently reported.

Results

Forty-one studies met the inclusion criteria, of which forty were case series and one a cohort study. No clinical differences in outcomes including the Neck Disability Index (NDI, 700 patients), Visual Analogue Scale pain (VAS, 180 patients), and Smiley Webster Scale (SWS, 231 patients) scores were identified between surgical and conservative treatments. However, fracture union was higher in surgically-treated patients (pooled incidence 72.7%, 95% CI 66.1%, 78.5%, 31 studies, 988 patients) than in conservatively-treated patients (40.2%, 95% CI 32.0%, 49.0%, 22 studies, 912 patients). This difference remained after correcting for age and fracture type. Fracture stability (41 studies, 1917 patients), although numerically favoring surgery, did not appear to differ between treatment groups.

Conclusion

While surgically-treated patients showed higher union rates than conservatively-treated patients, no clinically relevant differences were observed in NDI, VAS pain, and SWS scores and stability rates. These results need to be further confirmed in well-designed comparative studies with proper adjustment for confounding, such as age, fracture characteristics, and osteoporosis degree.

INTRODUCTION

Odontoid fractures account for 9 to 18% of all cervical spine fractures and are most frequently caused by either hyperextension or hyperflexion.[1-4] In the elderly, odontoid fractures are the most common cervical spine fractures.[5, 6] Moreover, as the population ages, these fractures will become increasingly relevant to clinical practice.[4] The optimal treatment of odontoid fractures in the elderly is, however, still subject to controversy. This age group typically suffers from an increased risk of operative complications when treated surgically but is also at a higher risk of non-union and prolonged treatment duration when treated conservatively.

The treatment for odontoid fractures is typically based on fracture pattern (such as defined by Anderson and d'Alonzo), patient age, neurological deficits and the patient's medical condition, in an effort to weigh fracture healing versus treatment complications.[2, 4, 7] The general presumption is that a surgical intervention, i.e. either anterior odontoid screw fixation or posterior atlantoaxial fusion, leads to a stable cervical spine. However, the condition of the patient may deteriorate by undergoing (major) cervical spine surgery. Surgical intervention carries significant risks particularly in a very old patient (≥80 years). An alternative to surgical stabilization is conservative treatment, involving rigid or non-rigid immobilization. This treatment, however, can also fail and prolong fracture instability, requiring secondary surgery, which unnecessarily lengthens treatment duration. Additionally, conservative treatment can cause immobilization-related complications, e.g. pneumonia, pressure sores.

The objective of this review was to summarize and compare the outcomes of surgical and conservative treatments for type II and III odontoid fractures in the elderly (≥65 years), focusing primarily on clinical outcomes and secondarily on fracture union and -stability rates. This review is an update of a systematic review published by the authors in 2013.[8]

METHODS

Search methods for identification of studies

The PRISMA checklist was used for this review. A systematic search was conducted in seven databases of medical literature: MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Web of Science, Emcare, Academic Search Premier, and PEDro to update the author's previously published systematic review in 2013 (Supplementary Material). The updated search spanned between April 2012 and January 2022. The search strategy was adapted for the other databases. No restriction was made with regard to language or date. 'Os odontoideum' was included in the search, as this term is sometimes incorrectly used to describe odontoid fractures. Duplicate references were removed. References from the included studies were also screened in order to identify additional primary studies not previously identified. Two review authors (JH, CV) working independently examined titles and abstracts from the electronic search. Full texts were obtained for titles and abstracts that were approved by pairs of reviewers. A third review author was consulted, if consensus was not reached.

Criteria for considering studies for this review

Studies were included if the following criteria were met: 1-Studies described one or more outcomes of at least ten patients treated for acute type II or III odontoid fractures, with or without associated fractures or dislocation. 2-Participants were at least 65 years old, and their data could be extracted separately from studies that also involved younger subjects. 3-Inclusion criteria were explicit and the follow-up period was at least two weeks. 4-The study evaluated any surgical and/or conservative treatment and results were given for each distinct treatment. 5-Patients were not treated for odontoid fractures in the past. 6-Patients did not suffer from systemic comorbidity expected to influence outcome (e.g. rheumatoid arthritis). 7-The paper was published in a peer-reviewed journal. Case reports were excluded.

Clinical outcome was the primary outcome. The Neck Disability Index (NDI) was the most commonly used instrument to assess clinical outcome. The NDI is a 50-point scale, in which a higher score represents a higher degree of disability. The minimal clinically important change/difference

(MCID) for the NDI was determined to be 7.5.[9-12] The Visual Analogue Scale (VAS) pain score was also commonly reported. The VAS is a 10-point scale (derived from a 100 mm scale), in which a higher score represents a higher degree of pain, and of which the MCID was determined to be 1 (10 mm).[13, 14] The Smiley-Webster Scale (SWS) was the third commonly used instrument. The SWS is an ordinal scale from 1 to 4, in which 1 represents excellent functioning and 4 represents poor functioning. Fracture union- and stability rates were the secondary outcomes. Fracture union was defined as presence of bony consolidation of the fracture. Fracture stability was defined as presence of either bony consolidation or fibrous union of the fracture.

Data collection and analysis

Two review authors (KB, CR) working independently conducted the data extraction. From each study, both demographic/descriptive data (e.g. study population, sample size, number of patients followed-up, fracture types, age, gender, applied treatment) and quantitative data regarding outcomes and complications were extracted. Outcomes were extracted at 52 weeks when available, and, if missing, outcomes at the last follow-up moment were extracted. Outcomes reported over wide and equally spaced intervals, such as NDI and VAS pain scores, were treated as continuous variables, and means and standard deviations were extracted and meta-analyzed. Unless otherwise specified, a random-effects model was used to calculate pooled point estimates with 95% confidence intervals for the NDI, fracture union, and fracture stability. A fixed-effect model was used for VAS scores to avoid negative values for the lower bound of the 95% CI. Outcomes reported over narrow or unequally spaced intervals, such as the SWS score, were treated as categorical ordinal variables, of which medians and their respective ranges were extracted. Given that medians cannot be meta-analyzed, weighted medians were calculated by multiplying the sample size in each study by its respective median, divided by the total number of patients in all studies, of which the result was rounded off. This was similar to the fixed-effect model using sample size as the weighting method. Forest plots were generated to summarize the results. *P*-values for heterogeneity (<0.10) and I-squared were computed. I-squared values for heterogeneity were categorized as low (0-25%), moderate (25-50%) and substantial (>50%). A random-effects multivariable meta-regression model was used to correct for baseline co-variates when sufficiently reported. Both baseline co-variates and clinical outcomes were heterogeneously and sparsely reported. Correction in the meta-regression analysis was therefore only feasible for mean age and fracture type (II, II/III) in relation to the radiological outcomes. The heterogenous reporting of clinical outcomes made further analyses of these outcomes infeasible. Three meta-regression analyses were done for fracture union and fracture stability. The first model included treatment type, age and fracture type. The other models were for each treatment type separately: one for surgical and one for conservative treatment, including only age and fracture type to the model. A two-tailed p-value < 0.05 was considered statistically significant, unless otherwise indicated. Analyses were performed using Comprehensive Meta-Analysis Software (CMA), version 4.

Assessment of risk-of-bias for the included studies

Two review authors (KB, CR) working independently conducted the risk-of-bias assessment. Studies were classified as cohort studies if confounding variables were corrected for; otherwise, studies were treated as two separate case series extracted from one original study even if these studies were labelled as cohort studies by the authors. Risk-of-bias of the individual studies was assessed with methodology scores based on the type of study: Newcastle-Ottawa Quality Assessment Scale (NOS) for cohort studies and a self-designed appraisal form for uncontrolled case series based on three other studies (Supplemtary Material).[15-18] For the NOS, cohort selection, comparability and outcome assessment were scored on a 0 to 9 range. Items were scored as positive if they fulfilled the criterion, negative when bias was likely or marked as inconclusive if there was insufficient information. If an item was scored positive, one point was awarded. The number of positively scored items was summed per study, adding up to a score between 0 and 22 points for this instrument. Differences in the scoring of the risk-of-bias assessment were discussed during a consensus meeting. For outcomes reported in at least ten studies, the potential for small study bias was assessed using funnel plots, along with Begg's test for categorical outcomes and Egger's test for continuous outcomes.[19, 20] Because of high heterogeneity in the results, the trim-and-fill method was not used to address the potential publication bias if an asymmetry was found in the funnel plot.[21] Instead, the classic fail safe n, which is the number of missing studies that would bring p-value to > alpha, was conducted and reported for each outcome.

RESULTS

Search and selection results

The initial search yielded 1,337 unique references, after removal of duplicates also identified in the search for the previous review.[8] After screening studies based on title and abstract, 127 studies were selected for full-text screening. Additionally, reference and citation tracking were carried out, yielding no further references. A total of thirty-one studies were initially identified. The seventeen unique studies from the previous review were also included, adding up to a total of forty-eight. Seven studies were subsequently excluded, all because they were believed to (partially) describe the same patient cohorts as other studies included in this review.[22-28] These studies were excluded in favor of studies (partially) reporting on the same patients, but that reported on larger samples and/or more appropriate clinical/radiological outcomes. A total of 41 studies were eventually included (**Figure 1** and **Table 1**). Four studies were carried out prospectively. Thirty-nine studies were published in English, one in French and one in German. Twenty-four studies systematically reported clinical outcome and hence were primarily included, as this review's primary focus was on clinical outcome. The other seventeen systematically reported union- and/or stability rates only and were consequently secondarily included. Overall, forty studies reported fracture union, and all forty-one reported fracture stability.

Risk-of-bias assessment

Only one study corrected for confounding variables and was hence classified as cohort study, while the remaining studies were classified as case series (Supplementary Material). All but four studies were retrospective case series. Quality scores for case series ranged between 10 and 20 on a 22-point scale. For the case series, baseline demographics and results were mostly adequately reported, whereas baseline clinical status was generally poorly and heterogeneously reported. Funnel plots were only feasible for the outcomes of fracture union and fracture stability, as clinical outcomes were reported in fewer than ten studies (Supplementary Material). Begg's test showed a significant small study effect for the surgically treated group for both fracture union and fracture stability (p=0.048 and p=0.049, respectively). Of note, the source of asymmetry in a funnel plot could be due to other reasons than publication bias (e.g. true heterogeneity, data irregularities, selection bias).[20] Given the source of asymmetry was driven by publication bias, the classic fail safe n showed a very large number of missing studies that would be needed to bring the pooled results to become non-significant. This reinforced that the results were robust to any potential publication bias.

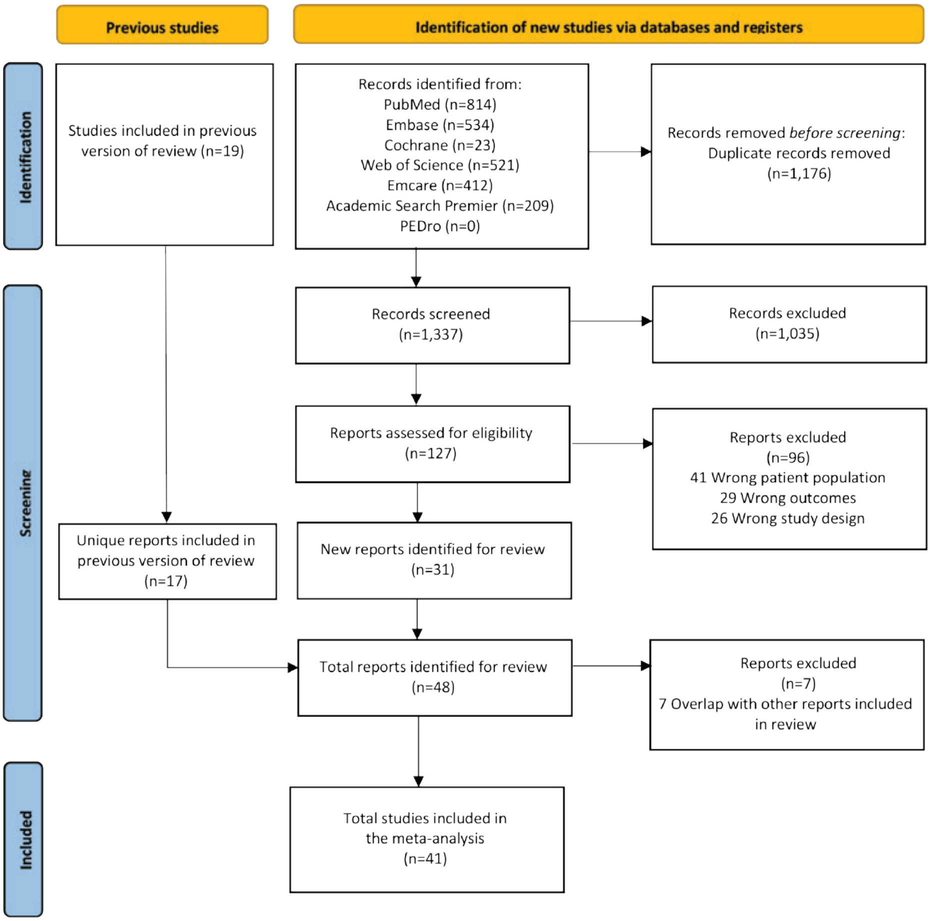


Figure 1. Modified PRISMA flow diagram depicting the study selection process

Table 1. Characteristics of included studies

	Study timing	Study's inclusion criteria	Treat-ment	Sample size	Patients followed-up	µ Age (range or ±SD)	Male n (%)	µ Follow-up weeks (range)	Risk-of-bias score Case series: 0-22 Cohort (NOS): 0-9
Primary included									
Chibbaro S, 2021 [31]	Prospective	Type II, ≥75 years, (non)rigid collar	C	260	260	84.3 (75-96)	83 (32)	min: 24 (?-?)	14 / 22
Moscolo F, 2021 [32]	Retrospective	Type II, ≥65 years, various treatments	S & C	34	31	73.5 (65-88)	26 (76)	? (13-52)	17 / 22
McIlroy S, 2020 [33]	Retrospective	Type II, ≥65 years, semi-rigid collar	C	125	125	83.7±7.3	49 (39)	33 (9-76)	16 / 22
Gembruch O, 2019 [34]	Retrospective	Type II, ≥80 years, various treatments	S & C	125	95	85,7±4.2	30 (24)	? (?-52)	14 / 22
Girardo M, 2019 [35]	Retrospective	Type II, ≥65 years, OSF or halo vest	S & C	57	57	77 (65-68)	40 (70)	38 (24-68)	20 / 22
Lofrese G, 2019 [36]	Retrospective	Type II, ≥65 years, rigid collar	C	60	50	82.7±6.9	20 (40)‡	69 (52-117)	13 / 22
Alhashash M, 2018 [37]	Prospective	Type II, ≥65 years, percutaneous transarticular fusion	S	20	20	81 (65-98)	9 (45)	97 (78-130)	14 / 22
Aquila F, 2018 [38]	Retrospective	Type II, ≥75 years, collar	C	25	24	83.3 (75-94)	9 (36)	78 (78-104)	16 / 22
Scholz C, 2018 [39]	Retrospective	Type II/III, ≥70 years, C1-C2 fusion	S	17	17	86 (72-91)	?	38 (12-73)*	15 / 22
Ishak B, 2017 [40]	Retrospective	Type II, ≥80 year, C1-C2 fusion	S	35	30	86.5 (80-96)	17 (49)	22 (6-72)	17 / 22

	Study timing	Study's inclusion criteria	Treat-ment	Sample size	Patients followed-up	μ Age (range or ±SD)	Male n (%)	μ Follow-up weeks (range)	Risk-of-bias score Case series: 0–22 Cohort (NOS): 0–9
Dobran M, 2016 [41]	Retrospective	Type II, geriatric patients, C1–C2 fixation	S	21	21	76 (68–85)	15 (71)	53 (38–91)	18 / 22
Joestl J, 2016 [42]	Retrospective	Type II, ≥65 years, OSF or halo vest	S & C	80	73	73 (65–96)	33 (41)	? (?–104)	17 / 22
Josten C, 2016 [43]	Retrospective	Type II, ≥70 years, anterior transarticular fusion and OSF	S	83	63	84.7 (70–101)	26 (31)	? (6–52)	14 / 22
Molinari W, 2013 [30]	Retrospective	Type II, ≥65 years, posterior fusion or collar	S & C	58	47	81 (65–99)	31 (53)	60 (1–208)	17 / 22
Vaccaro A, 2013 [29]†	Prospective	Type II, ≥65 years, various treatments	S & C	159	130	S 80.3±7.3, C 81.2±8.0	63 (40)	? (?–52)	9 / 9†
Hénaux P, 2011 [44]	Retrospective	Type IIB, ≥80 years, OSF	S	11	9	85.4 (82–93)	4 (36)	32 (2–116)	16 / 22
Hou Y, 2011 [45]	Retrospective	Type II, ≥65 year, OSF	S	43	42	80.6 (65–92)	24 (56)	21.3 (18–24)	16 / 22
Osti M, 2011 [46]	Retrospective	Type II, ≥65 year, OSF	S	35	33	79.6 (65–94)	18 (51)	74 (9.6–128)	16 / 22
Butler J, 2010 [47]	Retrospective	Type II, halo and collar	C	14	14	? (?–80)	?	66 (?–?)*	14 / 22

	Study timing	Study's inclusion criteria	Treat-ment	Sample size	Patients followed-up	µ Age (range or ±SD)	Male n (%)	µ Follow-up weeks (range)	Risk-of-bias score Case series: 0–22 Cohort (NOS): 0–9
Lefranc M, 2009 [French] [48]	Retrospective	Type II/III, ≥70 years, various treatments	S & C	27	22	80.7 (70–97)	13 (48)	52 (?–?)	18 / 22
Kaminski A, 2008 [German] [49]	Retrospective	Type II/III, ≥70 years, transarticular C1–C2 fusion	S	36	28	80.1 (70–93)	14 (39)	100 (52–312)	13 / 22
Koech F, 2008 [50]	Retrospective	Type II, ≥65 years, collar and halo	C	57	42	80 (67–91)	9 (21)‡	86 (39–104)	15 / 22
Platzer P, 2007 [51]	Retrospective	Type II/III, ≥65 years, anterior or posterior fixation	S	62	56	71.4 (66–83)	25 (45)‡	? (?–104)	16 / 22
Seybold E, 1998 [52]	Retrospective	Type II–III, posterior fusion, collar, halo	S & C	22	17	77.9 (65–93)	10 (45)	91 (0–470)	16 / 22
Secondary included									
Traynelis V, 2021 [53]	Retrospective	Type II, ≥65 years, C1–C2 fusion	S	93	93	78 (65–95)	47 (51)	14 (1–75)	10 / 22
Allia J, 2020 [54]	Retrospective	Type II, ≥70 years, various treatments	S & C	79	79	84.5 (70–105)	32 (41)	? (13–52)	14 / 22
Hong J, 2018 [55]	Retrospective	Type II, ≥65 years, collar and halo	C	50	50	80 (67–97)	26 (52)	54 (2–158)	15 / 22
Perry A, 2018 [56]	Retrospective	Type II, ≥80 years, surgery or collar	S & C	19	19	83.5 (80–98)	7 (37)	60 (36–83)	16 / 22

	Study timing	Study's inclusion criteria	Treat-ment	Sample size	Patients followed-up	µ Age (range or ±SD)	Male n (%)	µ Follow-up weeks (range)	Risk-of-bias score Case series: 0–22 Cohort (NOS): 0–9
Schwarz F, 2018 [57]	Retrospective	Type II, ≥65 years, OSF	S	52	52	84 (73–94)	11 (21)	43 (30–52)	14 / 22
Faure A, 2017 [58]	Retrospective	Type II–III, ≥75 years, anterior/posterior surgery	S	70	70	85.1 (75–104)	24 (34)	23 (0.2–91)	15 / 22
Waschke A, 2016 [59]	Prospective	Type II, ≥65 years, OSF	S	11	10	84.6 (73–89)	3 (27)	15 (6–34)	13 / 22
Bisson E, 2015 [60]	Retrospective	Type II, C1–C2 fusion	S	10	10	81.5 (68–87)	2 (20)	16 (5–36)	12 / 22
Scheyerer M, 2013 [61]	Retrospective	Type II, ≥65 years, various treatments	S & C	47	47	81 (?–?)	22 (47)	31.1 (1–77)	15 / 22
Dailey A, 2010 [62]	Retrospective	Type II–III, ≥70 years, OSF	S	57	42	81.2 (70–96)	27 (47)	65 (13–269)	13 / 22
Koivikko M, 2004 [63]	Retrospective	Type II, halo vest	C	25	25	? (65–94)	?	52 (9–356)*	13 / 22
Börm W, 2003 [64]	Retrospective	Type II, ≥70 years, OSF	S	15	15	81 (70–?)	?	72 (?–?)*	15 / 22
Andersson S, 2000 [65]	Retrospective	Type II–III, ≥65 years, various treatments	S & C	29	27	78 (66–99)	11 (38)	51 (24–89)	14 / 22
Kuntz C, 2000 [66]	Retrospective	Type II, ≥65 year, various treatments	S & C	20	20	80 (66–92)	12 (60)	S 73 (?–?), C 56 (0–143)	13 / 22
Berlemann U, 1997 [67]	Retrospective	Type II, ≥65 years, OSF	S	19	19	75 (65–87)	10 (53)	30 (3.6–132)	14 / 22

	Study timing	Study's inclusion criteria	Treat-ment	Sample size	Patients followed-up	μ Age (range or ±SD)	Male n (%)	μ Follow-up weeks (range)	Risk-of-bias score Case series: 0–22 Cohort (NOS): 0–9
Hanigan W, 1993 [68]	Retrospective	Type II–III, ≥80 years, various treatments	S & C	19	19	86.2 (80–99)	9 (47)	S 45 (24–72), C 20 (5–51)	16 / 22
Hanssen A, 1987 [69]	Retrospective	Type II–III, ≥65 years, various treatments	C	18	11	76.5 (65–87)	10 (56)	30 (6–60)	13 /22
			Total	2099	1914				

†: All studies were case series, except for Vaccaro 2013, which was a cohort study. S: surgical, C: conservative, ?: cannot tell or not retrievable, ‡: for number followed-up, *: for entire patient group studied (i.e. including <65 years), NOS: Newcastle-Ottawa Quality Assessment Scale.

2

Baseline characteristics

A total of 2099 patients were included, of which 1104 (53%) were treated surgically. A total of 1917 patients were followed-up clinically and/or radiologically, representing a 91% follow-up rate. The pooled mean age was 80.6 (95% CI 79.0, 82.1) for surgically-treated patients and 81.7 (95% CI 79.7, 83.7) for conservatively-treated patients. A total of 1742 (83%) patients were treated for type II fractures, while the remaining 357 patients were enrolled in studies describing both type II and III fractures, in which outcomes were not typically split out by fracture type. The pooled mean follow-up time was 47.9 (95% CI 39.3, 56.4) weeks for surgically treated patients and 55.9 (95% CI 45.3, 66.5) for conservatively treated patients. ASA scores were most frequently used to report baseline functioning, yet were still only provided in fourteen studies. Mean fracture displacement could be derived from only nine studies. Analysis of a difference in baseline functioning and fracture displacement between treatment groups was not feasible.

Clinical outcomes

Analysis of clinical outcome was only feasible for the three most commonly used instruments (**Table 2**, **Table 3** and **Figure 2**). The remaining studies used other tools that were reported too sparsely to be compared.

Neck Disability Index (NDI)

Seven studies reported NDI scores, of which four for both surgically and conservatively treated patients. NDI scores were available for 700 patients, of which 156 (22%) were treated surgically. The pooled mean NDI score was 14.2 (95% CI 8.79, 19.5) for surgically-treated patients and 16.0 (95% CI 12.0, 19.9) for conservatively-treated patients. The difference was not clinically relevant (< 7.5), and the data were substantially heterogeneous (p-heterogeneity surgical <0.001, I-squared 97.4%; p-heterogeneity conservative <0.001, I-squared 98.9%).

Visual Analogue Scale (VAS) pain

Five studies reported VAS pain scores, of which one for both surgically and conservatively treated patients. VAS scores were available for 180 patients, of which 150 (83%) were treated surgically. The pooled mean VAS score was 1.53

(95% CI 1.35, 1.72) for surgically-treated patients and 0.73 (95% CI 0.30, 1.16) for conservatively-treated patients. The difference was not clinically relevant (<1), and the data were substantially heterogeneous (p-heterogeneity surgical <0.001, I-squared 98.2%).

Smiley-Webster Scale (SWS)

Six studies reported the SWS, of which two for both surgically- and conservatively-treated patients. Median SWS scores were available for 231 patients, of which 98 (42%) were treated surgically. Weighted median SWS score was 1 (range 1 - 4) for surgically-treated patients, which was not clinically different from the median of 2 (range 1 - 4) for conservatively-treated patients. Of note, both a SWS score of 1 and 2 represents return to full-time work/activity, the difference being no consumption of pain medication for 1 and occasional consumption of pain medication for 2.

Table 2. Results of random effects analyses for clinical and radiological outcomes

	Number of studies	Number of patients	Pooled point estimate	95% CI	*p*-heterogeneity	*I*-squared
Primary outcomes (clinical)						
Neck Disability Index (0 no – 50 severest)			**Mean**			
Surgical	4	156	14.2	8.79, 19.5	<0.001	97.4%
Conservative	7	544	16.0	12.0, 19.9	<0.001	98.9%
Visual Analogue Scale pain score (0 no – 10 severest)‡						
Surgical	5	170	1.53	1.35, 1.72	<0.001	98.2%
Conservative	1	30	0.73	0.30, 1.16	NA	NA
Secondary outcomes (radiological)						
Fracture union (%)			**Incidence**			
Surgical	31	988	72.7%	66.1%, 78.5%	<0.001	75.1%
Conservative	22	912	40.2%	32.0%, 49.0%	<0.001	74.3%
Fracture stability (%)						
Surgical	32	1104	82.6%	74.9 %, 88.3%	<0.001	75.7%
Conservative	23	995	70.1%	57.7%, 80.1%	<0.001	88.3%

CI: confidence interval, NA: not applicable, ‡: Fixed effect model was used to avoid negative values for the lower bounds of the 95% CI.

Table 3. Median and range for the ordinal clinical outcome as reported by original studies

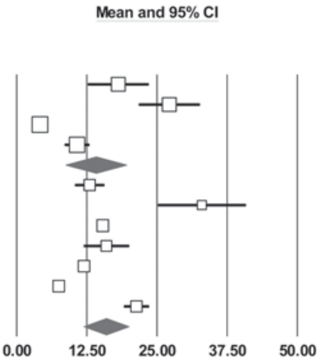
	Number of patients	Median	Range 1, 4
Smiley Webster scale (1 excellent – 4 poor)			
Surgical			
Girardo, M. 2019	27	1	1, 4
Hénaux, P. 2011	9	2	1, 4
Platzer, P. 2007	56	1	1, 4
Seybold, E. 1998	6	2	1, 3
Weighted median‡	*98*	*1*	*1, 4*
Conservative			
Girardo, M. 2019	30	2	1, 4
Lofrese, G. 2019	50	2	1, 4
Koech, F. 2008	42	2	1, 4
Seybold, E. 1998	11	2	1, 4
Weighted median‡	*133*	*2*	*1, 4*

‡: Medians and ranges cannot meta-analyzed. Hence, a sample-size weighted calculation was conducted as such (number of patients in each study (x) median in each study) / total number of patients in all studies, rounded off, under the fixed effect model assumption.

2

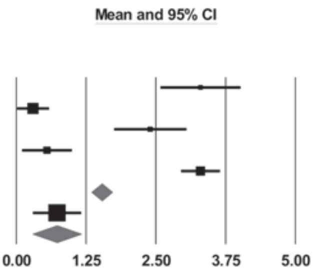
Figure 2. Forest plots showing the pooled average reported outcome (for continuous data) or pooled incidence (for discrete data) stratified by treatment type, surgery and conservative. The squares represent the point estimate of each study with the horizontal lines denoting the 95% CI. The size of the square is proportional to the weight of each study. The center of the grey diamond is the pooled point estimate for each subgroup using a random effects model and its width reflects the 95% CI.

Group by Treatment type	Study name	Statistics for each study: Mean	Standard error	Lower limit	Upper limit
1-Surgery	Molinari, W. 2013a	18.10	2.75	12.70	23.50
1-Surgery	Vaccaro, A. 2013a	27.20	2.77	21.78	32.62
1-Surgery	Girardo, M. 2019a	4.15	0.45	3.27	5.03
1-Surgery	Moscolo, F. 2021a	10.76	1.11	8.59	12.93
1-Surgery	Pooled	14.15	2.74	8.79	19.51
2-Conservative	Molinari, W. 2013b	13.00	1.32	10.41	15.59
2-Conservative	Vaccaro, A. 2013b	33.00	3.98	25.20	40.80
2-Conservative	Girardo, M. 2019b	15.33	0.46	14.43	16.23
2-Conservative	Lofrese, G. 2019	16.00	2.05	11.98	20.02
2-Conservative	McIlroy, S. 2020	12.00	0.38	11.25	12.75
2-Conservative	Chibbaro, S. 2021	7.50	0.16	7.20	7.80
2-Conservative	Moscolo, F. 2021b	21.35	1.13	19.14	23.56
2-Conservative	Pooled	15.96	2.03	11.98	19.94



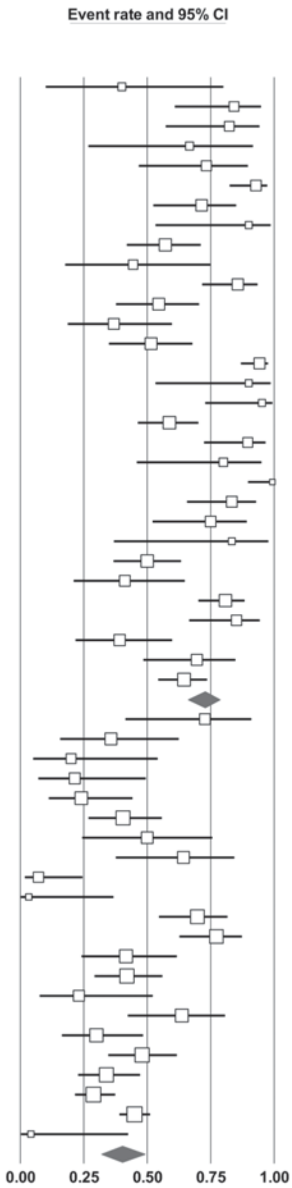
2.1 Neck Disability Index

Group by Treatment type	Study name	Statistics for each study: Mean	Standard error	Lower limit	Upper limit
1-Surgery	Moscolo, F. 2021a	3.30	0.36	2.58	4.02
1-Surgery	Girardo, M. 2019a	0.30	0.14	0.02	0.58
1-Surgery	Alhashash, M. 2018	2.40	0.33	1.76	3.04
1-Surgery	Scholz, C. 2018	0.55	0.23	0.11	0.99
1-Surgery	Josten, C. 2016	3.30	0.18	2.96	3.64
1-Surgery	Pooled	1.53	0.09	1.35	1.71
2-Conservative	Girardo, M. 2019b	0.73	0.22	0.30	1.16
2-Conservative	Pooled	0.73	0.22	0.30	1.16



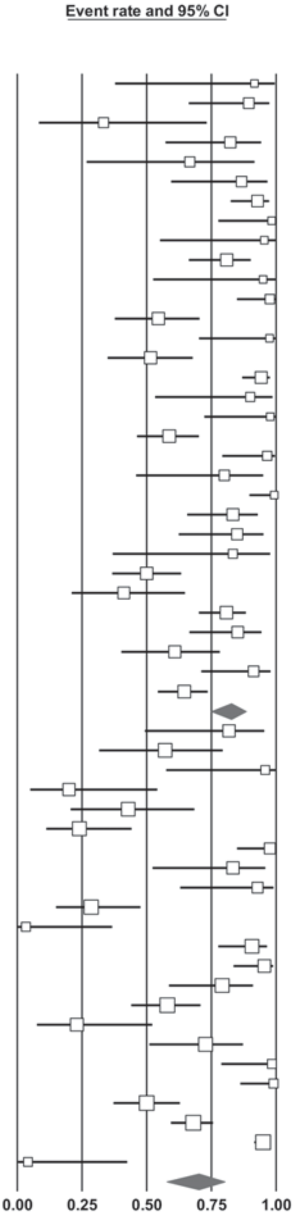
2.2 VAS pain scores

Group by Treatment type	Study name	Event rate	Lower limit	Upper limit
1-Surgery	Hanigan, W. 1993a	0.40	0.10	0.80
1-Surgery	Berlemann, U. 1997	0.84	0.61	0.95
1-Surgery	Andersson, S. 2000a	0.82	0.57	0.94
1-Surgery	Kuntz, C. 2000a	0.67	0.27	0.92
1-Surgery	Börm, W. 2003	0.73	0.47	0.90
1-Surgery	Platzer, P. 2007	0.93	0.82	0.97
1-Surgery	Kaminski, A. 2008	0.71	0.52	0.85
1-Surgery	Lefranc, M. 2009a	0.90	0.53	0.99
1-Surgery	Dailey, A. 2010	0.57	0.42	0.71
1-Surgery	Hénaux, P. 2011	0.44	0.18	0.75
1-Surgery	Hou, Y. 2011	0.86	0.72	0.93
1-Surgery	Osti, M. 2011	0.55	0.38	0.70
1-Surgery	Molinari, W. 2013a	0.37	0.19	0.60
1-Surgery	Scheyerer, M. 2013a	0.52	0.35	0.68
1-Surgery	Vaccaro, A. 2013a	0.94	0.87	0.98
1-Surgery	Bisson, E. 2015	0.90	0.53	0.99
1-Surgery	Dobran, M. 2016	0.95	0.73	0.99
1-Surgery	Josten, C. 2016	0.59	0.46	0.70
1-Surgery	Joestl, J. 2016a	0.90	0.72	0.97
1-Surgery	Waschke, A. 2016	0.80	0.46	0.95
1-Surgery	Faure, A. 2017	0.99	0.90	1.00
1-Surgery	Ishak, B. 2017	0.83	0.66	0.93
1-Surgery	Alhashash, M. 2018	0.75	0.52	0.89
1-Surgery	Perry, A. 2018a	0.83	0.37	0.98
1-Surgery	Schwarz, F. 2018	0.50	0.37	0.63
1-Surgery	Scholz, C. 2018	0.41	0.21	0.65
1-Surgery	Gembruch, O. 2019a	0.81	0.70	0.88
1-Surgery	Girardo, M. 2019a	0.85	0.67	0.94
1-Surgery	Allia, J. 2020a	0.39	0.22	0.60
1-Surgery	Moscolo, F. 2021a	0.70	0.48	0.85
1-Surgery	Traynelis, V. 2021	0.65	0.54	0.74
1-Surgery	Pooled	0.73	0.66	0.78
2-Conservative	Hanssen, A. 1987	0.73	0.41	0.91
2-Conservative	Hanigan, W. 1993b	0.36	0.16	0.62
2-Conservative	Andersson, S. 2000b	0.20	0.05	0.54
2-Conservative	Kuntz, C. 2000b	0.21	0.07	0.49
2-Conservative	Koivikko, M. 2004	0.24	0.11	0.44
2-Conservative	Koech, F. 2008	0.40	0.27	0.56
2-Conservative	Lefranc, M. 2009b	0.50	0.24	0.76
2-Conservative	Butler, J. 2010	0.64	0.38	0.84
2-Conservative	Molinari, W. 2013b	0.07	0.02	0.24
2-Conservative	Scheyerer, M. 2013b	0.03	0.00	0.37
2-Conservative	Vaccaro, A. 2013b	0.70	0.55	0.82
2-Conservative	Joestl, J. 2016b	0.77	0.63	0.87
2-Conservative	Aquila, F. 2018	0.42	0.24	0.62
2-Conservative	Hong, J. 2018	0.42	0.29	0.56
2-Conservative	Perry, A. 2018b	0.23	0.08	0.52
2-Conservative	Gembruch, O. 2019b	0.64	0.42	0.81
2-Conservative	Girardo, M. 2019b	0.30	0.16	0.48
2-Conservative	Lofrese, G. 2019	0.48	0.35	0.62
2-Conservative	Allia, J. 2020b	0.34	0.23	0.47
2-Conservative	McIlroy, S. 2020	0.29	0.22	0.37
2-Conservative	Chibbaro, S. 2021	0.45	0.39	0.51
2-Conservative	Moscolo, F. 2021b	0.04	0.00	0.42
2-Conservative	Pooled	0.40	0.32	0.49



2.3 Fracture union

Group by Treatment type	Study name	Event rate	Lower limit	Upper limit
1-Surgery	Hanigan, W. 1993a	0.92	0.38	0.99
1-Surgery	Berlemann, U. 1997	0.89	0.66	0.97
1-Surgery	Seybold, E. 1998a	0.33	0.08	0.73
1-Surgery	Andersson, S. 2000a	0.82	0.57	0.94
1-Surgery	Kuntz, C. 2000a	0.67	0.27	0.92
1-Surgery	Börm, W. 2003	0.87	0.59	0.97
1-Surgery	Platzer, P. 2007	0.93	0.82	0.97
1-Surgery	Kaminski, A. 2008	0.98	0.78	1.00
1-Surgery	Lefranc, M. 2009a	0.95	0.55	1.00
1-Surgery	Dailey, A. 2010	0.81	0.66	0.90
1-Surgery	Hénaux, P. 2011	0.95	0.53	1.00
1-Surgery	Hou, Y. 2011	0.98	0.85	1.00
1-Surgery	Osti, M. 2011	0.55	0.38	0.70
1-Surgery	Molinari, W. 2013a	0.98	0.70	1.00
1-Surgery	Scheyerer, M. 2013a	0.52	0.35	0.68
1-Surgery	Vaccaro, A. 2013a	0.94	0.87	0.98
1-Surgery	Bisson, E. 2015	0.90	0.53	0.99
1-Surgery	Dobran, M. 2016	0.98	0.72	1.00
1-Surgery	Josten, C. 2016	0.59	0.46	0.70
1-Surgery	Joestl, J. 2016a	0.97	0.79	1.00
1-Surgery	Waschke, A. 2016	0.80	0.46	0.95
1-Surgery	Faure, A. 2017	0.99	0.90	1.00
1-Surgery	Ishak, B. 2017	0.83	0.66	0.93
1-Surgery	Alhashash, M. 2018	0.85	0.62	0.95
1-Surgery	Perry, A. 2018a	0.83	0.37	0.98
1-Surgery	Schwarz, F. 2018	0.50	0.37	0.63
1-Surgery	Scholz, C. 2018	0.41	0.21	0.65
1-Surgery	Gembruch, O. 2019a	0.81	0.70	0.88
1-Surgery	Girardo, M. 2019a	0.85	0.67	0.94
1-Surgery	Allia, J. 2020a	0.61	0.40	0.78
1-Surgery	Moscolo, F. 2021a	0.91	0.71	0.98
1-Surgery	Traynelis, V. 2021	0.65	0.54	0.74
1-Surgery	Pooled	0.83	0.75	0.88
2-Conservative	Hanssen, A. 1987	0.82	0.49	0.95
2-Conservative	Hanigan, W. 1993b	0.57	0.32	0.79
2-Conservative	Seybold, E. 1998b	0.96	0.58	1.00
2-Conservative	Andersson, S. 2000b	0.20	0.05	0.54
2-Conservative	Kuntz, C. 2000b	0.43	0.21	0.68
2-Conservative	Koivikko, M. 2004	0.24	0.11	0.44
2-Conservative	Koech, F. 2008	0.98	0.85	1.00
2-Conservative	Lefranc, M. 2009b	0.83	0.52	0.96
2-Conservative	Butler, J. 2010	0.93	0.63	0.99
2-Conservative	Molinari, W. 2013b	0.29	0.15	0.48
2-Conservative	Scheyerer, M. 2013b	0.03	0.00	0.37
2-Conservative	Vaccaro, A. 2013b	0.91	0.78	0.96
2-Conservative	Joestl, J. 2016b	0.95	0.84	0.99
2-Conservative	Aquila, F. 2018	0.79	0.59	0.91
2-Conservative	Hong, J. 2018	0.58	0.44	0.71
2-Conservative	Perry, A. 2018b	0.23	0.08	0.52
2-Conservative	Gembruch, O. 2019b	0.73	0.51	0.87
2-Conservative	Girardo, M. 2019b	0.98	0.79	1.00
2-Conservative	Lofrese, G. 2019	0.99	0.86	1.00
2-Conservative	Allia, J. 2020b	0.50	0.37	0.63
2-Conservative	McIlroy, S. 2020	0.68	0.59	0.76
2-Conservative	Chibbaro, S. 2021	0.95	0.92	0.97
2-Conservative	Moscolo, F. 2021b	0.04	0.00	0.42
2-Conservative	Pooled	0.70	0.58	0.80



2.4 Fracture stability

Radiological outcome

Fracture union

Forty studies reported extractable fracture union rates, including thirteen that reported union rates for surgical and conservative groups (**Table 2** and **Figure 2**). Union data were available for 1900 patients, of which 988 (52%) were treated surgically. Union was achieved in 72.7% (95% CI 66.1%, 78.5%) of surgically-treated patients and in 40.2% (95% CI 32.0%, 49.0%) of conservatively-treated patients. This difference was clinically significant, although the data were substantially heterogeneous (p-heterogeneity surgical <0.001, I-squared 75.1%; p-heterogeneity conservative <0.001, I-squared 74.3%).

Fracture stability

Forty-one studies reported extractable fracture stability rates, including fourteen that reported stability rates for surgical and conservative groups (**Table 2** and **Figure 2**). Stability data were available for 1917 patients, of which 994 (52%) were treated surgically. Stability was achieved in 82.6% (95% CI 74.9%, 88.3%) of surgically-treated patients and in 70.1% (95% CI 57.7%, 80.1%) of conservatively-treated patients. Data were substantially heterogeneous (p-heterogeneity surgical <0.001, I-squared 75.7%; p-heterogeneity conservative <0.001, I-squared 88.3%).

Complications and mortality

Complications and mortality were heterogeneously reported across studies. Complications in the surgical group were mostly related to the operation, whether intraoperative (e.g. screw malposition) or postoperative (e.g. wound infections). Complications in the conservative group were mostly immobilization-related, such as pressure ulcerations and pneumonia. Analysis of a difference in complications and mortality between treatment groups was not feasible.

Meta-regression analysis

Meta-regression analysis: Fracture union

In the model including treatment type, surgically treated patients showed significantly more union than conservative treated patients when corrected for age and fracture type (p<0.001), although data were still substantially heterogeneous (new I-squared 75.6%). Individually, increased age and fracture type were not identified to significantly influence fracture union (**Table 4**).

Meta-regression analysis: Fracture stability

In the model including treatment type, no significant difference in stability rates were identified between surgically and conservatively treated patients when corrected for age and fracture type (*p*=0.09). Data were substantially heterogeneous (new I-squared 83.8%). Individually, increased age and fracture type were not identified to significantly influence fracture stability (**Table 4**).

Table 4. Results of random effects multivariable meta-regression analysis for fracture union and stability

	Regression coefficient	95% CI	*p*-value	New *I*-squared
Fracture union				
For all 40 studies (treatment included in model)†				75.6%
Treatment (surgical vs. conservative)	1.42	**0.83, 2.00**	**<0.001**	
Age	-0.02	-0.08, 0.03	0.40	
Fracture type (II/III vs. II)	0.19	-0.54, 0.92	0.61	
For the 31 surgical studies subgroup				74.2%
Age	-0.09	-0.18, 0.01	0.06	
Fracture type (II/III vs. II)	0.12	-0.79, 1.03	0.79	
For the 22 conservative studies subgroup				77.2%
Age	0.01	-0.06, 0.09	0.71	
Fracture type (II/III vs. II)	0.24	-1.05, 1.53	0.70	
Fracture stability				
For all 41 studies (treatment included in model)‡				83.8%

	Regression coefficient	95% CI	*p*-value	New *I*-squared
Treatment (surgical vs. conservative)	0.77	-0.13, 1.66	0.09	
Age	0.01	-0.08, 0.09	0.84	
Fracture type (II/III vs. II)	0.12	-0.92, 1.16	0.82	
For the 32 surgical studies subgroup				74.0%
Age	-0.10	-0.20, 0.02	0.10	
Fracture type (II/III vs. II)	0.12	-0.09, 1.18	0.81	
For the 23 conservative studies subgroup				88.8%
Age	0.07	-0.07, 0.21	0.33	
Fracture type (II/III vs. II)	-0.06	-2.26, 2.14	0.95	

2

DISCUSSION

Multiple studies describing treatment outcomes for odontoid fractures in the elderly have been published since publication of the previous systematic review by the authors in 2013.[8] Although these studies typically reported larger samples, only four studies included in this updated review were performed prospectively. Only one study corrected for confounding variables and was therefore classified as cohort study. The other studies were classified as case series. Reported data suffered from substantial heterogeneity. These factors limited the analyses that could be executed. As a result, no strong recommendations can be made regarding the optimal treatment for odontoid fractures in the elderly, even though interesting observations were made.

Evaluation of outcomes of odontoid fractures usually focused on the radiological outcome. Clinical outcome was less often described, but can be considered the most relevant. Focusing primarily on clinical outcomes in the current literature review, no clinically relevant differences were observed between surgically and conservatively treated patients for the NDI and VAS pain scores. Median SWS score was 1 for surgically treated patients and 2 for conservatively treated patients, although both a SWS score of 1 and 2 represents return to full-time work/activity, the difference being no consumption of pain medication for 1 and occasional consumption of pain medication for 2. This difference was also not considered clinically relevant. The clinical outcome measures that were reported in the remaining studies varied widely and could not be used for generalized conclusions.

Fracture union was achieved more often in surgically treated patients than in conservatively treated patients. This difference remained after correction for age and fracture type (II/III vs. II) in the meta-regression analysis. A similar difference in fracture stability was not identified between the treatment groups. Multiple studies used fracture union and/or stability as primary outcome, but the correlation with clinical outcome was not properly studied. It remains unclear whether patients indeed benefit clinically from favorable radiological outcomes. Consequently, debate remains as to what the exact goal of treatment should be (e.g. favorable clinical outcome, osseous union and/or fracture stability), and as to how outcome should be measured.

Patient age in the included studies was comparable between treatment groups. However, different age criteria were applied amongst studies, describing patients ≥65, ≥70, ≥75 or ≥80 years. Moreover, surgically and conservatively treated groups described in the included studies may not be comparable with respect to other patient characteristics (e.g. co-morbidity, osteoporosis, severity of comminution). Outcome diversification per age group amongst the elderly was mostly absent and needs further study. Furthermore, it is often postulated that treatment outcome depends on patient age. Other factors must, however, play some role, as different studies have shown different outcomes for the same treatment, which cannot be explained by patient age alone.

Complications and mortality were common in both treatment groups, although not uniformly reported and therefore not reliably analyzable. Complications relating to the operation, both intraoperatively (e.g. screw malposition) and postoperatively (e.g. wound infections), were the most common complications in surgically treated patients. Immobilization-related complications, such as pressure ulcerations and pneumonia, were the most prevalent complications in patients treated conservatively.

Vaccaro et al. published the only prospective cohort study included in this review that directly compared surgical to conservative treatment.[29] In this study involving 159 patients, of which 101 treated surgically, higher union rates after surgical treatment were reported. This study reported an NDI increase (clinical worsening) between baseline and 52 weeks after both surgical and conservative treatment. This increase was only significant for conservatively treated patients, even though selection bias and residual confounding may have influenced these findings (e.g. no correction for osteoporosis, no adjusted odds ratios reported). Of note, the outcomes presented in this systematic review were not comparisons between baseline and 52 weeks, but rather the pooled point estimates at 52 weeks specifically. In that respect, Vaccaro et al. reported a mean NDI at one year follow-up of 28.0 (SE 2.49) for surgically treated patients and 31.6 (SE 3.34) for conservatively treated patients, also not reaching a minimally clinically important difference (>7.5), similar to the findings in this systematic review. As already mentioned, the most relevant outcome parameter remains debated.

Strengths and limitations

This meta-analysis had a few limitations. The studies were mostly case series with their associated limitations, such as missing data, confounding bias and variability in outcome assessment. Outcomes were not uniformly reported at 52 weeks, and, when missing, were extracted for the last available follow-up time point. As a result, data collected for this review suffered from substantial heterogeneity throughout the dataset. Meta-regression analyses were feasible for the radiological outcomes only, where only mean age and fracture type could be corrected for. Outcomes should therefore be interpreted with caution. Results were certainly affected by residual confounding. Illustrative in this respect is the study by Molinari et al, in which patients with <50% fracture displacement were treated conservatively and patients with ≥50% fracture displacement were treated surgically, introducing heterogeneity between treatment groups even within one study.[30] For the primary analysis, type II and III fractures were analyzed as one group. It is plausible that type II fractures were more often treated surgically, whereas conservative management was preferred for type III fractures. This may have influenced the findings. In studies describing patients with both type II and III fractures (n=10), results were not typically sub-grouped by fracture type. Consequently, adjustment for fracture type was only possible for type II/III vs. type II (the other studies, n=31) fractures, not for type II vs. type III fractures as would ideally have been the case. Additionally, bone quality was only scarcely described, even when it is known to be an important factor in bone healing. Finally, a variety of both surgical and conservative treatments were analyzed in only two groups. Further diversification of outcomes for different surgical (e.g. anterior, posterior approach) and conservative (e.g. collar, halo vest) treatments was not deemed feasible due to the data limitations. Nevertheless, this study had some strengths. No restriction was made with regard to language or date, which led to a substantially large number of studies to be meta-analyzed for some outcomes. Consequently, this enabled the authors to conduct a multivariable meta-regression analysis to control for confounding as much as the reported data allowed. Lastly, the classic fail safe n conducted gave reassurance that publication bias was unlikely to be the reason of the asymmetry observed in a few funnel plots.

CONCLUSION

Implications for clinical practice

No clinically relevant differences between surgically and conservatively treated patients were identified in term of the NDI, VAS pain and SWS scores. When corrected for age and fracture type, surgically treated patients showed higher union rates than conservatively treated patients, although selection mechanisms might (partially) explain this difference. When corrected for age and fracture type, no difference in stability rates were observed between surgically and conservatively treated patients. Data were substantially heterogeneous, limiting the possibilities for analysis and strengths of the recommendations derived from these results.

Implications for research

These results need to be further confirmed in well-designed comparative studies with proper adjustment for confounding, such as age, fracture characteristics, and degree of osteoporosis. The correlation between clinical and radiological outcomes needs to be further explored.

SUPPLEMENTARY MATERIAL

Supplementary material can be accessed at https://link.springer.com/article/10.1007/s00586-023-07779-1.

LIST OF ABBREVIATIONS

CI — 95% Confidence Interval
MCID — Minimal clinically important difference
NDI — Neck Disability Index
NOS — Newcastle-Ottawa Quality Assessment Scale
SD — Standard deviation
SE — Standard error
SWS — Smiley-Webster Scale
VAS — Visual Analogue Scale

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CHAPTER

3

LOW-THRESHOLD-FOR-SURGERY VERSUS PRIMARILY-CONSERVATIVE TREATMENT FOR ODONTOID FRACTURES IN THE ELDERLY: EVALUATING PRACTICE VARIATION IN THE NETHERLANDS

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ABSTRACT

Study design

Retrospective cohort study.

Objectives

Odontoid fractures are the most common cervical spine fractures in the elderly. The optimal treatment remains controversial. The aim of this study was to compare results of a low-threshold-for-surgery strategy (surgery for dislocated fractures in relatively healthy patients) to a primarily-conservative strategy (for all patients).

Methods

Patient records from five medical centers were reviewed for patients who met the selection criteria (e.g. age ≥55 years, type II/III odontoid fractures). Demographics, fracture types/characteristics, fracture union/stability, clinical outcome and mortality were compared. The influence of age on outcome was studied (≥55-80 vs. ≥80 years).

Results

A total of 173 patients were included: 120 treated with low-threshold-for-surgery (of which 22 primarily operated, and 23 secondarily) vs. 53 treated primarily-conservative. No differences in demographics and fracture characteristics between the groups were identified. Fracture union (53% vs. 43%) and fracture stability (90% vs. 85%) at last follow-up did not differ between groups. The majority of patients (56%) achieved clinical improvement compared to baseline. Analysis of differences in clinical outcome between groups was infeasible due to data limitations. In both strategies, patients ≥80 years achieved worse union (64% vs. 30%), worse stability (97% vs. 77%), and—as to be expected—increased mortality <104 weeks (2% vs. 22%).

Conclusions

Union and stability rates did not differ between the treatment strategies. Advanced age (≥80 years) negatively influenced both radiological outcome and mortality. No cases of secondary neurological deficits were identified, suggesting that concerns for the consequences of under-treatment may be unjustified.

INTRODUCTION

Odontoid fractures are the most common cervical spine fractures in the elderly, and their incidence is expected to further increase due to aging of the population.[1–3] Treatment for odontoid fractures is either surgical or conservative in nature. Surgical treatment involves anterior odontoid screw fixation or (extended) posterior atlanto-axial fusion. Conservative treatment involves immobilization devices, e.g. cervical collar or halo vest. Particularly in the elderly, controversy exists about the optimal treatment as well as about the goal of treatment.

Surgical treatment carries increased risks related to the intervention and general anesthesia. Conservative treatment involves risks of prolonged fracture instability, prolonged treatment duration and complications related to immobilization. Finding a balance between fracture healing and the risk of treatment complications is challenging.[4–6] Recent literature reviews on this topic were inconclusive, due to limited quantity and quality of the available data.[7–9] Debate also remains as to what the treatment goal should be, because there is no convincing evidence that fracture healing clearly contributes to a more favorable clinical outcome.[10–12] Furthermore, recent clinical studies focused on type II fractures only, while the distinction between type II and III fractures can be challenging.[13]

In the absence of high-quality evidence, the applied treatment strategies often differ between centers. The goal of this multicenter, retrospective study was to utilize this practice variation to compare the results of two treatment strategies: A low-threshold-for-surgery strategy (surgery for displaced fractures in relatively healthy patients, low-threshold for secondary surgery in case of prolonged instability) was compared to a primarily-conservative strategy (conservative treatment irrespective of patient/fracture characteristics). The radiological and clinical outcomes of these strategies were compared, rather than the specific treatment modalities. This approach was assumed to limit heterogeneity between groups, as no subgroups had to be selected based on applied treatment modalities. Particular focus was on the impact of age on treatment outcome (55-80 versus ≥80 years) and on cases with secondary neurological deficits. Potential prognostic factors were evaluated. Finally, the interobserver variability of the Anderson and d'Alonzo classification was studied to test the reliability of the caretakers' distinction between type II and III fractures, and to evaluate whether differences in treatment modalities derived from this distinction are—in general—appropriate.

METHODS

Participating centers

The authors selected two regions in the Netherlands with similar populations but different treatment strategies for odontoid fractures. These regions used these different strategies consistently throughout the study period.

A low-threshold-for-surgery strategy was followed in the Leiden University Medical Center (LUMC), Haaglanden Medical Center (HMC), Maastricht University Medical Center (MUMC) and Zuyderland Medical Center (ZMC). Surgical treatment was applied for dislocated fractures in relatively healthy patients, whereas conservative treatment was applied for non-dislocated fractures and patients in weak medical condition. Also, there was a low threshold for secondary surgery in case of prolonged instability or clinical symptoms (neck pain).

A primarily-conservative strategy, on the other hand, is less common and was followed in the University Medical Center Utrecht (UMCU). Conservative treatment was applied always, irrespective of fracture characteristics and the patient's condition. Surgery was only applied as secondary treatment, in case of failure of conservative treatment.

Patient selection

All patients who met the selection criteria were included: 1-Patients suffered from acute (<2 weeks) type II or III odontoid fractures.[14] 2-Patients were at least 55 years old. 3-Patients were not previously treated for odontoid fractures. 4-Patients did not suffer from systemic comorbidity expected to influence outcome (e.g. rheumatoid arthritis). 5-Surgical or conservative treatment had taken place with at least two weeks follow-up.

The data manager working for the LUMC and HMC conducted a sensitive search of the electronic patient files between 2000 and 2012. The data manager working for the MUMC and ZMC conducted a similar search between 2000 and 2019. The UMCU had two prospectively acquired databases of patients treated for spinal injuries between 2001 and 2012, from which only patients with odontoid fractures were selected. Patients from LUMC/HMC/UMCU admitted after 2012 were not included, as they were enrolled in a prospective study on odontoid fractures treatment.[15] Patients from MUMC/ZMC were also considered for inclusion if they were admitted after 2012, as these centers were not involved in the prospective study.

The Institutional Review Boards (IRB) of MUMC and ZMC declared that the medical research involving human subjects act (WMO in Dutch) did not apply to this study (Medisch-Ethische Toetsingscommissie van het azM en Maastricht University, 2019-1280, and Medisch Ethische Toetsings Commissie van Zuyderland en Zuyd Hogeschool Zuderland, METCZ20190096, respectively). Written informed consent was obtained from all MUMC/ZMC patients. Data from LUMC/HMC/UMCU were collected in 2013, at which time IRB declarations and informed consent were not required for non-WMO studies, and data were anonymously stored since then.

Data collection and analysis

Demographic parameters and fracture types from the patient files, as scored by the caretakers, were collected. Additionally, a set of review authors scored fracture types/characteristics, treatment data and outcome parameters based on a predefined data collection protocol (JH/CV for LUMC, JH/MA for HMC, JH/WS for UMCU, IH/AS/HS for MUMC/ZMC). Union was defined as evidence of bone trabeculae crossing the fracture site and absence of sclerotic borders adjacent to the fracture site on computed tomography (CT) scans. In cases of absent follow-up CT scans, union was defined as complete absence of a visible fracture line on the last follow-up X-ray. Fracture stability was defined as either presence of union or a maximum of 2 mm movement at fracture site on dynamic X-ray.[16] Union and stability were assessed at the last follow-up moment. Clinical outcome was retrieved from the patient files and classified as ‘clinical improvement compared to baseline’, ‘no change compared to baseline’ or ‘deterioration compared to baseline’. Fracture displacement was defined as >2 mm displacement at the fracture site. Cases of secondary neurological deficits, secondary surgery (after failed initial treatment) and death by any cause within 104 weeks were collected.

Statistical analysis

Baseline characteristics were presented using means and standard deviation (SD) for continuous outcomes (age), and numbers and percentages for categorical variables. T-tests were done for continuous variables (age). χ^2-tests were done for categorical variables (such as union and stability). Mann-Whitney U tests were done in case of skewed distributions (follow-up duration), of which medians and interquartile ranges (IQR) were presented. Statistical analysis of baseline American Society of Anesthesiologists (ASA) scores and clinical outcome was infeasible due to heterogeneous reporting, so they are presented descriptively. The fracture types as listed in the patient files (II/III) were used for the analysis. A Kappa (κ) value was calculated to classify the interobserver variability of the Anderson and d'Alonzo classification by comparing the original fracture score in the patient files to the independently reviewed scoring by the authors.[17] A two-tailed p-value <0.05 was considered statistically significant. Odds ratios (OR) and their respective 95% confidence intervals (CI) were calculated. Intention-to-treat analyses were performed using IBM SPSS, version 25.

RESULTS

Patient selection

The initial search identified 261 patients diagnosed with odontoid fractures. Of these, 88 patients did not meet the selection criteria and were excluded. The most common reasons for exclusion were age <55 years and insufficient follow-up data. A total of 173 patients were included, of whom 120 were treated with a low-threshold-for-surgery strategy and 53 with a primarily-conservative strategy (**Figure 1**).

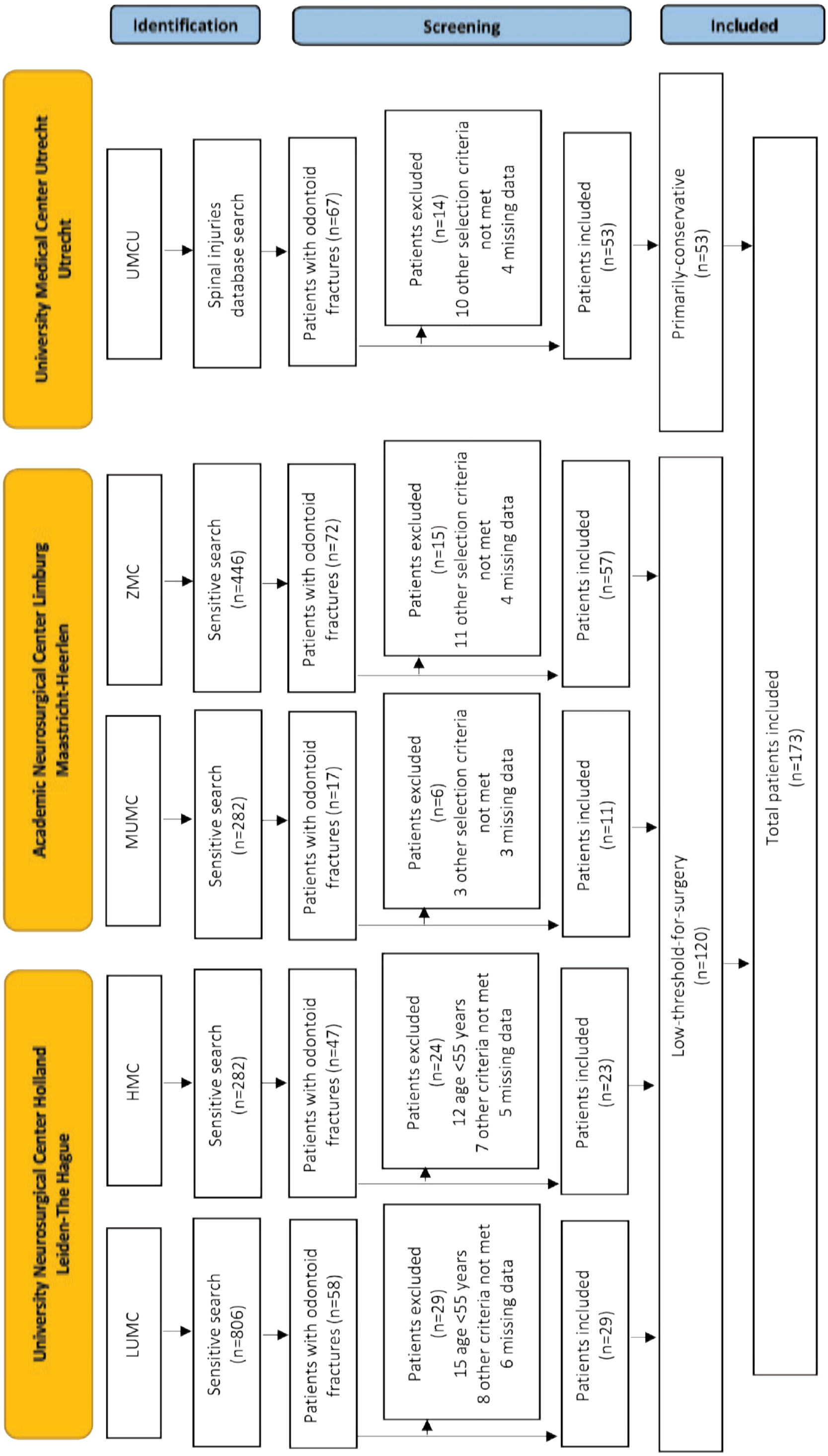

Figure 1. Flow diagram depicting the patient selection process

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Table 1. Summary of demographic and baseline data

	Low-threshold-for-surgery (n=120)	Primarily-conservative (n=53)	*p*-value
Mean age ± SD	76.6 ± 10.7	73.9 ± 9.5	0.11
Age groups			
55-80 years	66 (55%)	34 (64%)	0.32
≥80 years	54 (45%)	19 (36%)	
Gender			
Male	47 (39%)	19 (36%)	0.74
Female	73 (61%)	34 (64%)	
Fracture type (patient files)			
Type II	69 (57%)	27 (51%)	0.51
Type III	51 (43%)	26 (49%)	
Fracture displacement			
≤ 2 mm	72 (60%)	27 (51%)	0.32
> 2 mm	48 (40%)	26 (49%)	
Other C1/C2 fractures			
No	94 (78%)	45 (85%)	0.41
Yes	26 (22%)	8 (15%)	

SD: standard deviation.

Demographic and baseline data

Analysis of the demographic and baseline data showed no differences between groups (**Table 1**). For the total cohort, mean age was 75.8 ± 10.4 years, 73 patients (42%) were ≥80 years, and 107 patients (62%) were females. Type II fractures were present in 96 patients (55%), fracture displacement was observed in 74 patients (43%), and other concomitant C1-C2 fractures were recorded in 34 patients (20%). The baseline ASA scores could be retrieved for 118 (68%) patients. Of these, 8 (7%) were ASA 1, 51 (43%) were ASA 2, 49 (42%) were ASA 3, 9 (8%) were ASA 4, and 1 (1%) was ASA 5.

Treatment strategy

Of the 120 patients treated with the *low-threshold-for-surgery strategy*, 22 (18%) patients received primary surgical treatment: 11 (9%) underwent odontoid screw fixation and 11 (9%) underwent posterior C1-C2 fusion. The majority was primarily treated conservatively: 68 (57%) patients were treated with cervical collar and 30 (25%) with halo vest. Of the 54 patients ≥80 years (45%) in the low-threshold-for-surgery group, 8 (15%) were treated surgically.

Of the 53 patients treated with the *primarily-conservative treatment strategy*, 52 (98%) patients were treated initially conservative: 44 (83%) with halo vest and 8 (15%) with cervical collar. The remaining patient (2%) refused to undergo external immobilization and therefore primarily underwent odontoid screw fixation. None of the 19 octogenarians in the primarily-conservative group were operated.

Median follow-up duration was similar for both groups: 17 (IQR 12, 34) weeks for the low-threshold-for-surgery group and 19 (IQR 14, 37) weeks for the primarily-conservative group (Mann-Whitney $U = 2852$, $p = 0.28$). Secondary surgery was applied in 24 patients (20%) in the low-threshold-for-surgery group: 1 was initially treated with odontoid screw fixation, 14 initially with halo vest, and 9 initially with cervical collar. Secondary surgery was applied in 5 patients (9%) of the primarily-conservative group: 4 were initially treated with halo vest, and 1 initially with cervical collar. The mean moment for secondary surgery was 14.0 ± 12.3 weeks after start of the initial treatment.

Including cases of secondary surgery, a total of 45 (38%) patients were eventually surgically treated in the low-threshold-for-surgery group, as opposed to 6 (11%) patients in the primarily-conservative group.

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Fracture union and stability

No differences in fracture union and stability were found between the two groups (**Table 2**). Union was achieved in 63 (53%) patients in the low-threshold-for-surgery group and in 23 (43%) patients in the primarily-conservative group (OR 1.44; 95% CI 0.75, 2.76). Stability was achieved in 108 (90%) patients in the low-threshold-for-surgery group and in 45 (85%) patients in the primarily-conservative group (OR 1.60; 95% CI 0.61, 4.18). Patients aged 55-80 years achieved more union (64% vs. 30%, OR 4.12; 95% CI 2.16, 7.86)) and stability (97% vs. 77%, OR 9.82; 95% CI 2.76, 35.0) than patients ≥80 years.

Union and stability were additionally evaluated separately for the two age groups (**Table 3**). For patients aged 55-80 years, union (68% vs. 56%) and stability (97% vs. 97%) did not differ between treatment strategy groups (OR 1.69; 95% CI 0.72, 3.97 and OR 0.97; 95% CI 0.09, 11.1, respectively). For patients aged ≥80 years, union (33% vs. 21%) and stability (81% vs. 63%) similarly did not differ between treatment strategy groups (OR 1.88; 95% CI 0.54, 6.48 and OR 2.57; 95% CI 0.81, 8.17, respectively). Median follow-up was longer for younger patients: 22 (IQR 15, 39) weeks for patients aged 55-80 years and 14 (IQR 12, 29) weeks for patients aged ≥80 years (Mann-Whitney $U = 2661$, $p = 0.002$).

Table 2. Summary of the main results

	Union	Stability
Overall	86 / 173 (50%)	153 / 173 (88%)
Treatment strategy		
Low-threshold-for-surgery	63 / 120 (53%)	108 / 120 (90%)
Primarily-conservative	23 / 53 (43%)	45 / 53 (85%)
OR (95% CI)	1.44 (0.75, 2.76)	1.60 (0.61, 4.18)
Initially applied treatment		
Surgical	15 / 23 (65%)	21 / 23 (91%)
Conservative	71 / 150 (47%)	132 / 150 (88%)
OR (95% CI)	2.38 (0.92, 6.18)	1.43 (0.31, 6.62)
Patient age		
55-80 years	64 / 100 (64%)	97 / 100 (97%)
≥80 years	22 / 73 (30%)	56 / 73 (77%)
OR (95% CI)	4.12 (2.16, 7.86)	9.82 (2.76, 35.0)
Gender		
Male	37 / 66 (56%)	60 / 66 (91%)
Female	49 / 107 (46%)	93 / 107 (87%)
OR (95% CI)	1.51 (0.82, 2.80)	1.51 (0.55, 4.13)
Fracture type		
Type II	41 / 96 (43%)	84 / 96 (88%)
Type III	45 / 77 (58%)	69 / 77 (90%)
OR (95% CI)	0.53 (0.29, 0.97)	0.81 (0.31, 2.10)
Fracture displacement		
≤ 2 mm	51 / 99 (52%)	86 / 99 (87%)
> 2 mm	35 / 74 (47%)	67 / 74 (91%)
OR (95% CI)	1.18 (0.65, 2.16)	0.69 (0.26, 1.83)
Other C1/C2 fractures		
No	72 / 139 (52%)	122 / 139 (88%)
Yes	14 / 34 (41%)	31 / 34 (91%)
OR (95% CI)	1.56 (0.72, 3.28)	0.69 (0.19, 2.52)

OR: odds ratio, CI: confidence interval.

Table 3. Main radiological outcome by age group

		Union	Stability
55-80 years	Low-threshold-for-surgery	45 / 66 (68%)	64 / 66 (97%)
	Primarily-conservative	19 / 34 (56%)	33 / 34 (97%)
	OR (95% CI)	1.69 (0.72, 3.97)	0.97 (0.09, 11.1)
≥80 years	Low-threshold-for-surgery	18 / 54 (33%)	44 / 54 (81%)
	Primarily-conservative	4 / 19 (21%)	12 / 19 (63%)
	OR (95% CI)	1.88 (0.54, 6.48)	2.57 (0.81, 8.17)

OR: odds ratio, CI: confidence interval.

Clinical outcome

Clinical outcome could be extracted from patient files for 109 patients (63%). Sixty-one (56%) patients exhibited clinical improvement compared to baseline, 25 (23%) exhibited unchanged symptoms compared to baseline, and 23 (21%) exhibited clinical deterioration compared to baseline. No cases of secondary neurological deficits were identified. Clinical outcome data were scarce in the primarily-conservative group (11%), due to the design of the database available for this group. Hence, analysis of clinical outcomes between the treatment strategies was infeasible. For the 22 surgically treated patients in the low-threshold-for-surgery group, 9 (41%) experienced clinical improvement, 2 (9%) remained the same as at baseline, and 6 (27%) experienced clinical deterioration (of which 5 aged ≥80 years), and clinical outcome could not be determined in 5 (23%) patients. Clinical outcome could be extracted in 56 (77%) patients ≥80 years. In this subgroup, 29 (52%) showed clinical improvement, 12 (21%) remained the same, and 15 (27%) showed clinical deterioration compared to baseline.

Mortality and complications

Death by any cause <104 weeks occurred in 12 (10%) patients in the low-threshold-for-surgery group and in 6 (11%) patients in the primarily-conservative group (OR 0.87; 95% CI 0.35, 2.46). None of these deaths could be directly related to the treatment strategy. For the 18 (10%) patients who died, mean moment of death was at 16.7 ± 14.8 weeks. Death occurred more often in the patient group aged ≥80 years: 2 (2%) patients aged 55-80 years died as opposed to 16 (22%) patients aged ≥80 years (OR 0.07; 95% CI 0.02, 0.33). Secondary surgery was applied in 20 (20%) patients aged 55-80 years and in 9 (12%) patients aged ≥80 years (OR 1.78;

95% CI 0.76, 4.17). Two patients died after secondary surgery of unrelated cause (3 and 26 weeks later, respectively). No complications were recorded in 85 (71%) patients in the low-threshold-for-surgery group and in 43 (81%) patients in the primarily-conservative group (OR 0.57; 95% CI 0.26, 1.25). No complications were recorded in 78 (78%) patients aged 55-80 years and in 50 (68%) patients aged ≥80 years (OR 1.63; 95% CI 0.82, 3.23).

Prognostic factors

Baseline functioning

The baseline ASA scores could be extracted from the patient files in 118 patients (68%). Like the clinical outcome data, ASA score data were scarce in the primarily-conservative group (17%), and analysis of difference in ASA scores between groups was thus infeasible. For the 22 surgically treated patients in the low-threshold-for-surgery group, 2 (9%) were ASA 1, 11 (50%) were ASA 2, 4 (18%) were ASA 3, 3 (14%) were ASA 4, and in 2 (9%) ASA scores were missing.

Fracture type

For the total cohort, less patients with type II fractures achieved union compared to patients with type III fractures (43% vs. 58%, OR 0.53; 95% CI 0.29, 0.97). No difference was found between type II and III fractures in terms of the achievement of stability (88% vs. 90%, OR 0.81; 95% CI 0.31, 2.10).

Fracture displacement

For the total cohort, no influence of the presence of fracture displacement (> 2 mm) was demonstrated on the achievement of union (OR 1.18; 95% CI 0.65, 2.16) and stability (OR 0.69; 95% CI 0.26, 1.83).

Other C1-C2 fractures

For the total cohort, no influence of the presence of other C1/C2 fractures was found on the achievement of union (OR 1.54; 95% CI 0.72, 3.28) and stability (OR 0.69; 95% CI 0.19, 2.52).

Interobserver variability of fracture type-scoring

Blinded to the original scoring in the patient files, the authors identified 100 type II fractures and 73 type III fractures using baseline CT scans. These findings were compared to the scorings listed in the patient files. This comparison showed discrepancies in 26 (15%) of fractures. The agreement was substantial (κ=0.69), indicative of the reliability of the Anderson and d'Alonzo classification (**Table 4**).[17]

Table 4. Interobserver variability of Anderson and d'Alonzo classification

Kappa (κ)=0.69		**Fracture type according to authors (blinded scoring)**	
Fracture type according to patient files		Type II	Type III
	Type II	85	11
	Type III	15	62

DISCUSSION

No differences in union and stability rates were observed between the low-threshold-for-surgery and primarily-conservative treatment strategies. The majority of patients showed clinical improvement compared to baseline. Analysis of differences in clinical outcome between treatment strategy groups or between radiological outcome groups was infeasible due to data limitations. Interestingly, no cases of secondary neurological deficits were identified, suggesting that concerns for consequences of unstable non-unions or under-treatment may be unjustified.

Patients aged 55-80 years achieved more union and stability compared to patients ≥80 years, regardless of the applied treatment strategy. In the low-threshold-for-surgery group, 18% of the total group underwent primary surgery, as opposed to 15% of patients ≥80 years. This indicates that age alone was not the decisive factor in the choice for a particular treatment modality. In both groups, mortality rates in octogenarians were higher than in non-octogenarians, which is to be expected due to life expectancy in this population. Although the common hypothesis is that treatment outcome deteriorates with advancing age, no worse clinical outcome was demonstrated for patients ≥80 years in this study.[18]

Patients with type II fractures achieved lower union rates, but similar stability rates compared to patients with type III fractures. Even though previous studies have often focused on type II fractures, the distinction between type II and III fractures is sometimes difficult to make.[1,13] Illustratively, the interobserver analysis of fracture scoring in this study showed discrepancies in 15% of fractures. Especially for this group of fractures that does not obviously classify as either type II or III, the authors recommend caution in labeling these fractures and consequently treating them as different entities based on a sometimes debatable fracture type.

Contrary to the common presumption, the presence of odontoid fracture displacement (> 2 mm) or concomitant C1/C2 fractures did not negatively influence radiological outcome. The grade of displacement may be impactful, but finding a reliable grading system is challenging in the variety of upper cervical spine fractures. Different treatment strategies were compared in this study, in which the grade of displacement was evenly distributed between both groups. These results indicate that the presence of fracture displacement or multiple fractures may be less influential on outcome than commonly thought.

Strengths and limitations

This patient cohort is one of the largest available so far and thereby adds to the knowledge on the topic.[7-10] To the author's knowledge, this is the first study to compare the results of different treatment *strategies between centers*—rather than comparing treatment *modalities within centers*—using a natural experimental design. This approach was used to improve comparability between groups, as considerable heterogeneity is often introduced when outcomes of surgical and conservative treatment are compared (e.g. surgery for patients in relatively good condition, conservative treatment for frail patients). The retrospective nature of this study has its associated limitations. Data was often interpreted by non-direct observers. Potential confounding variables could not be corrected for. Despite describing a relatively large cohort, this study might have been underpowered to identify potential small differences between treatment strategies (type 2 error). It can, however, be concluded that such difference, if existent, would be small and of questionable clinical relevance. Union rates may be an underestimation, as CT scans were not routinely made in all centers when (dynamic) X-rays showed no instability in asymptomatic patients. In such cases, to avoid false positive findings, union was only scored to be present in case of complete absence of a visible fracture line on the last X-ray. This assessment was considered less reliable than CT assessments but superior to no analysis at all. Data limitations restricted the possibilities for analysis, especially regarding clinical outcome and baseline functioning. The relatively long inclusion period was not considered influential, as treatments have not changed considerably in the last decades. Finally, in the centers that used a low-threshold-for-surgery strategy, 18% of patients were primarily operated, and another 20% underwent secondary surgery. Despite this more aggressive approach, this may still be considered relatively conservative compared to centers that may follow a primarily-surgical strategy.

Perspective

The strategy approach used for this study allowed for a comparison between centers without need for patient sub-selection based on treatment modalities. This multicenter study examined the possible advantage of a low-threshold-for-surgery strategy (surgery for displaced fractures in relatively healthy patients, low-threshold for secondary surgery), as opposed to a primarily-conservative strategy. No evidence was demonstrated for the superiority of either one of these strategies. Prospective studies with proper adjustment for confounding and systematical evaluation of clinical outcome are needed to identify the best treatment strategy for this challenging pathology. To minimize heterogeneity introduced by patient sub-selection based on actual treatment modalities, future multicenter studies should also consider comparisons between centers, ideally comparing centers with a primarily-surgical to a primarily-conservative treatment strategy in otherwise relatively equal cohorts.

CONCLUSION

This study identified no differences in union and stability rates at last follow-up between low-threshold-for-surgery and primarily-conservative treatment strategies. Advanced age (≥80 years) negatively influenced radiological outcome and mortality in both treatment groups. Type II fractures resulted in lower union but comparable stability rates compared to type III fractures, even though the distinction between these entities can be difficult. No evidence was found for worse outcomes in case of dislocated or concomitant fractures. No cases of secondary neurological deficits were identified, suggesting that concerns for the consequences of unstable non-unions or under-treatment may be unjustified.

LIST OF ABBREVIATIONS

ASA — American Society of Anesthesiologists
CI — Confidence interval
CT — Computed tomography
HMC — Haaglanden Medical Center
IRB — Institutional review board
IQR — Interquartile range
κ — Kappa
LUMC — Leiden University Medical Center
MUMC — Maastricht University Medical Center
NA — Not applicable
OR — Odds ratio
SD — Standard deviation
UMCU — University Medical Center Utrecht
UNCH — University Neurosurgical Center Holland
WMO — Medical research involving human subjects Act (Dutch: Wet Medisch-wetenschappelijk Onderzoek met mensen)
ZMC — Zuyderland Medical Center

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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CHAPTER

4

SURGICAL VERSUS CONSERVATIVE TREATMENT FOR ODONTOID FRACTURES IN THE ELDERLY: AN INTERNATIONAL PROSPECTIVE COMPARATIVE STUDY

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ABSTRACT

Background

The optimal treatment for odontoid fractures in older people remains debated. Odontoid fractures are increasingly relevant to clinical practice due to ageing of the population.

Methods

An international prospective comparative study was conducted in fifteen European centers, involving patients aged ≥55 years with type II/III odontoid fractures. The surgeon and patient jointly decided on the applied treatment. Surgical and conservative treatments were compared. Primary outcomes were Neck Disability Index (NDI) improvement, fracture union and stability at 52 weeks. Secondary outcomes were Visual Analogue Scale neck pain, Likert patient-perceived recovery, and EuroQol-5D-3L at 52 weeks. Subgroup analyses considered age, type II and displaced fractures. Multivariable regression analyses adjusted for age, gender and fracture characteristics.

Results

The study included 276 patients, of which 144 (52%) were treated surgically and 132 (48%) conservatively (mean (SD) age 77.3 (9.1) vs. 76.6 (9.7), p=0.56). NDI improvement was largely similar between surgical and conservative treatments (mean (SE) -11 (2.4) vs. -14 (1.8), p=0.08), as were union (86% vs. 78%, aOR 2.3, 95% CI 0.97-5.7), and stability (99% vs. 98%, aOR NA). NDI improvement did not differ between patients with union and persistent non-union (mean (SE) -13 (2.0) vs. -12 (2.8), p=0.78). There was no difference for any of the secondary outcomes or subgroups.

Conclusions

Clinical outcome and fracture healing at 52 weeks were similar between treatments. Clinical outcome and fracture union were not associated. Treatments should prioritize favorable clinical over radiological outcomes.

INTRODUCTION

Odontoid fractures are the most common cervical spine fractures in older people.[1, 2] The incidence and health care burden are expected to further increase in the ageing population. Between 2000 and 2010, the incidence of C2 fracture hospitalizations in patients >84 years in the United States increased more than 3-fold to 9.77 per 10,000 individuals per year.[3] From 2003 to 2017, surgical treatment rates in the United States doubled to 86%, with operative treatments costing twice as much as conservative treatments.[4]

The optimal treatment for odontoid fractures is debated. Historically, treatments focused on achieving fracture union to prevent dreaded complications like secondary spinal cord injury.[5] More recently, studies have focused on favorable clinical rather than radiological outcomes.[6, 7] Literature reviews on the optimal treatment were inconclusive, mainly due to heterogeneity between groups, and studies showing superior union after surgery may have been biased.[8–11] There is no convincing evidence that clinical outcome and fracture union are associated.[6, 12] In the absence of high-quality evidence, treatment is often based on local treatment culture and the surgeon's preference, leading to considerable (inter)national practice variation.

The INNOVATE (INterNational study on Odontoid frActure Treatment in the Elderly) trial aimed to prospectively compare effects of surgery with initial conservative treatment on clinical outcome (including NDI improvement), fracture union, and fracture stability at 52 weeks in patients ≥55 years with type II/III odontoid fractures.

METHODS

Study design

This prospective comparative study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[13] Fifteen centers from eight European countries participated. Patient inclusion started in September 2012, with seven centers starting later, and the last patient was enrolled in February 2022. All institutional review boards approved the study. Patients provided written

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informed consent. The study protocol was published previously.[14] The study was registered in the Dutch Trial Register (NTR3630).[15]

Patient selection

Selection criteria were age ≥55 years, acute (<2 weeks) type II/III odontoid fracture diagnosed using computed tomography (CT), no rheumatoid arthritis/ankylosing spondylitis, no previous odontoid fracture treatment, and no language barrier/cognitive impairment. Patients admitted to the participating centers were asked to participate if they met these criteria.

Treatment

The attending surgeon and patient made a shared decision on the applied treatment modality. All centers were able to facilitate both surgical and conservative treatments.

Data collection

Surgeons and patients completed baseline questionnaires focusing on patient and fracture characteristics, symptoms, and treatment modality. Follow-up was at 6, 12, 26, 52 and 104 weeks. Follow-up visits could be concluded earlier by the surgeon in case of (nearly) complete clinical recovery and fracture union and/or stability. Patients were asked to complete questionnaires at home at all follow-up moments.

Outcomes

The co-primary outcomes were (1) clinical outcome in terms of Neck Disability Index (NDI) improvement, (2) fracture union and (3) fracture stability, at 52 weeks. NDI improvement was defined as the score difference between baseline and 52 weeks. The NDI is a validated 50-point instrument, with higher scores indicating greater disability.[16] Baseline NDI scores were determined by patients evaluating their current post-injury status, assuming no mobility restrictions were imposed. Union was assessed using CT and defined as evidence of bone trabeculae crossing the fracture site and absence of adjacent sclerotic borders. Stability was assessed with dynamic X-rays, where ≤2mm movement indicated stability.[17] If union was achieved, the fracture was also classified stable. Secondary outcomes included Visual Analogue Scale (VAS, 0-100 mm) neck pain, 7-point Likert patient-perceived recovery scales for symptoms and neck pain (good results were defined as (nearly) complete recovery) and EuroQol-5D-3L (EQ5D, 0-1 point, 0-100 mm), at 52 weeks.[18-20] Complications included rates of secondary neurological deficits, secondary treatment (repeated surgery or surgery/halo after conservative treatment), and mortality within 52 and 104 weeks. Subgroup analyses were done for age (55-79 and ≥80 years), type II fractures and fractures displaced >2 mm. Post-hoc treatment subtype analyses were done for odontoid screw fixation vs. C1-C2 fusion and cervical collar vs. halo vest.

Statistical analysis

NDI improvement between baseline and 52 weeks was univariably analyzed as continuous outcome with independent sample T-tests, with lower NDI scores indicating clinical improvement. The predetermined minimal clinically important difference (MCID) in NDI was 7.5.[21, 22] Union and stability were dichotomous outcomes univariably analyzed with $\chi 2$-tests. Multivariable analyses were done using regression models. Linear regression assessed NDI improvement, also adjusting for baseline NDI. Logistic regression assessed union and stability. To address baseline differences between treatments, variables generally presumed to influence outcome were added: age (continuous), gender (male, female), fracture type (II, III), fracture displacement (≤2, >2mm), concomitant C1-C2 fractures (no, yes), degree of osteoporosis in C2 (none/mild, moderate/severe), and degree of C0-C2 facet joints degeneration (none/mild, moderate/severe).[23] Similar analyses were done for the secondary outcomes and subgroups. The influence of individual variables in the models was studied. Linear regression analyzed the association between NDI improvement and union, with union status as predictor and baseline NDI as covariate. For missing items in individual NDI scores, the mean value of available items was inserted for a maximum of two missing items.[24] Radiological follow-up concluded before 52 weeks in case of positive outcomes, resulting in missing data beyond the last follow-up. Five rules were hence applied to complete union and stability data: (1) Union implies later union (e.g., if union was achieved at 26 weeks and the patient was discharged, union was also scored at 52 and 104 weeks); (2) Stability implies later stability (similar to rule 1); (3) Union implies stability (union cases were also scored as stable); (4) Non-union implies prior non-union (e.g., in case of non-union at 26 weeks and absence of earlier CT scans, non-union was scored at earlier points); (5) Instability implies prior instability (similar to rule 4). NDI improvement was completely available for 135 (49%) patients, union for 170 (62%) and stability for 201 (73%). The extent of missing data was largely similar across all outcomes between treatments. Missing data were multiply imputed using predictive mean matching (m=10), assuming data to be missing-at-random. Multiple imputation results for union and stability were adjusted to adhere to the five rules. Primary analyses were done with the resulting dataset. Sensitivity analyses were done with the original, non-imputed dataset. Line graphs displayed the proportion of patients achieving outcomes at different timepoints between treatments. Two-tailed p-values <0.05 were considered statistically significant. Intention-to-treat analyses were done using IBM SPSS, version 29, and R, version 4.3.1 in RStudio version 2022.12.0.

RESULTS

Patient characteristics

A total of 279 patients were included, of which 146 (52%) were treated surgically and 133 (48%) conservatively. Two surgical patients and one conservative patient withdrew from the study. Hence, 276 patients were included for analysis (**Figure 1**, Supplementary-Table 1).

Baseline characteristics were largely similar across treatments, except for two variables. Firstly, surgical patients had more type II fractures than conservative patients (81% vs. 56%, $p<0.001$). Secondly, surgical patients more often had fracture displacement >2 mm (47% vs. 27%, p=0.001, **Table 1**). Both these variables were among the covariates adjusted for in the multivariable analyses.

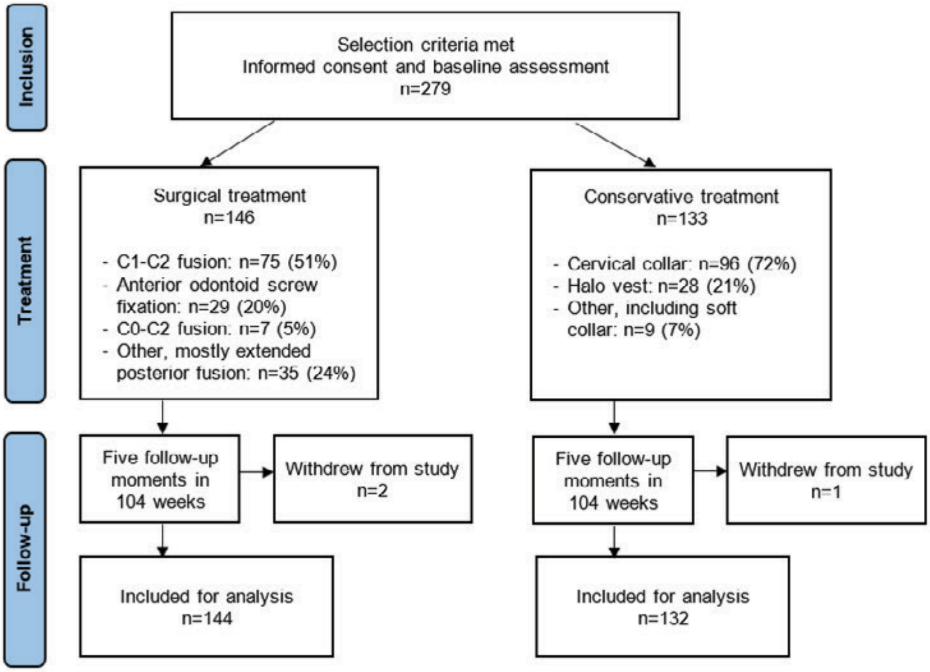

Figure 1. Flowchart depicting the applied treatments and follow-up period for patients with odontoid fractures

Table 1. Baseline characteristics of included patients

	No (%)		Univariable analysis
	Surgical (n=144)	Conservative (n=132)	*p*-value
Demographic data			
Age, mean (SD), y	77.3 (9.1)	76.6 (9.7)	0.56
Age groups			
55-79 years	81 (56)	72 (55)	0.78
≥80 years	63 (44)	60 (45)	
Male gender	72 (50)	53 (40)	0.10
Fracture characteristics			
Type II fractures (vs. III)	116 (81)	74 (56)	**<0.001**
Fracture displacement >2 mm (vs. ≤2 mm)	67 (47)	36 (27)	**0.001**
Other C1-C2 fractures present	35 (24)	30 (23)	0.76
Moderate/severe osteoporosis in C2 (vs. none/mild)	76 (53)	62 (47)	0.34
Moderate/severe degeneration C0-C2 facet joints (vs. none/mild)	39 (27)	33 (25)	0.69
Neurological deficits			
Medullary-induced	5 (3)	4 (3)	0.84
Radicular-induced	5 (3)	1 (1)	0.16

Abbreviations: SD, standard deviation
Values in bold represent statistical significance.

Primary outcomes

NDI improvement at 52 weeks did not differ significantly between surgical and conservative patients (mean (SE) decrease -11 (2.4) vs. -14 (1.8), *p*=0.08, <7.5 MCID). Union rates at 52 weeks did not differ between surgical and conservative patients (86% vs. 78%, aOR 2.3, 95% CI 0.97-5.7), nor did stability rates (99% vs. 98%, aOR NA, **Table 2**).

Table 2. Results for primary and secondary outcomes

	No. (%)			
	Surgical (n=144)	**Conservative (n=132)**	**Univariable analysis**	**Multivariable analysis**
Primary outcomes				
NDI improvement (decrease) baseline-52 weeks, mean (SE)	-11 (2.4)	-14 (1.8)	*p*=0.13	*p*=0.08
NDI at baseline, mean (SE)	27 (0.9)	29 (0.8)	*p*=0.10	*p*=0.07
NDI at 52 weeks, mean (SE)	16 (2.4)	15 (1.7)	*p*=0.47	*p*=0.43
Union at 52 weeks	124 (86)	103 (78)	OR 1.8 (CI 0.93-3.3)	aOR 2.3 (CI 0.97- 5.7)
Stability at 52 weeks	143 (99)	130 (98)	OR 2.2 (CI 0.20-25)	aOR NA
Secondary outcomes				
VAS neck pain				
VAS at baseline, mean (SE)	48 (2.2)	50 (2.8)	*p*=0.66	*p*=0.67
VAS at 52 weeks, mean (SE)	28 (7.3)	25 (5.7)	*p*=0.47	*p*=0.22
Likert patient-perceived recovery				
(Nearly) complete recovery of symptoms	39 (27)	48 (36)	OR 0.65 (CI 0.39-1.1)	aOR 1.0 (CI 0.29-3.5)
(Nearly) complete recovery of neck pain	50 (35)	55 (42)	OR 0.74 (CI 0.46-1.2)	aOR 1.0 (CI 0.40-2.7)
EQ5D				
EQ5D at baseline, mean (SE)	0.40 (0.03)	0.34 (0.03)	*p*=0.22	*p*=0.15
VAS health at baseline, mean (SE)	51 (2.1)	42 (2.5)	***p*=0.02**	***p*=0.01**
EQ5D at 52 weeks, mean (SE)	0.53 (0.06)	0.62 (0.06)	*p*=0.10	*p*=0.40
VAS health at 52 weeks, mean (SE)	57 (8.2)	61 (6.6)	*p*=0.44	*p*=0.48

Abbreviations: SE, standard error. OR, odds ratio. CI, 95% confidence interval. aOR, adjusted odds ratio.
Values in bold represent statistical significance. Odds ratios affected by non-convergence are reported as not available (NA).

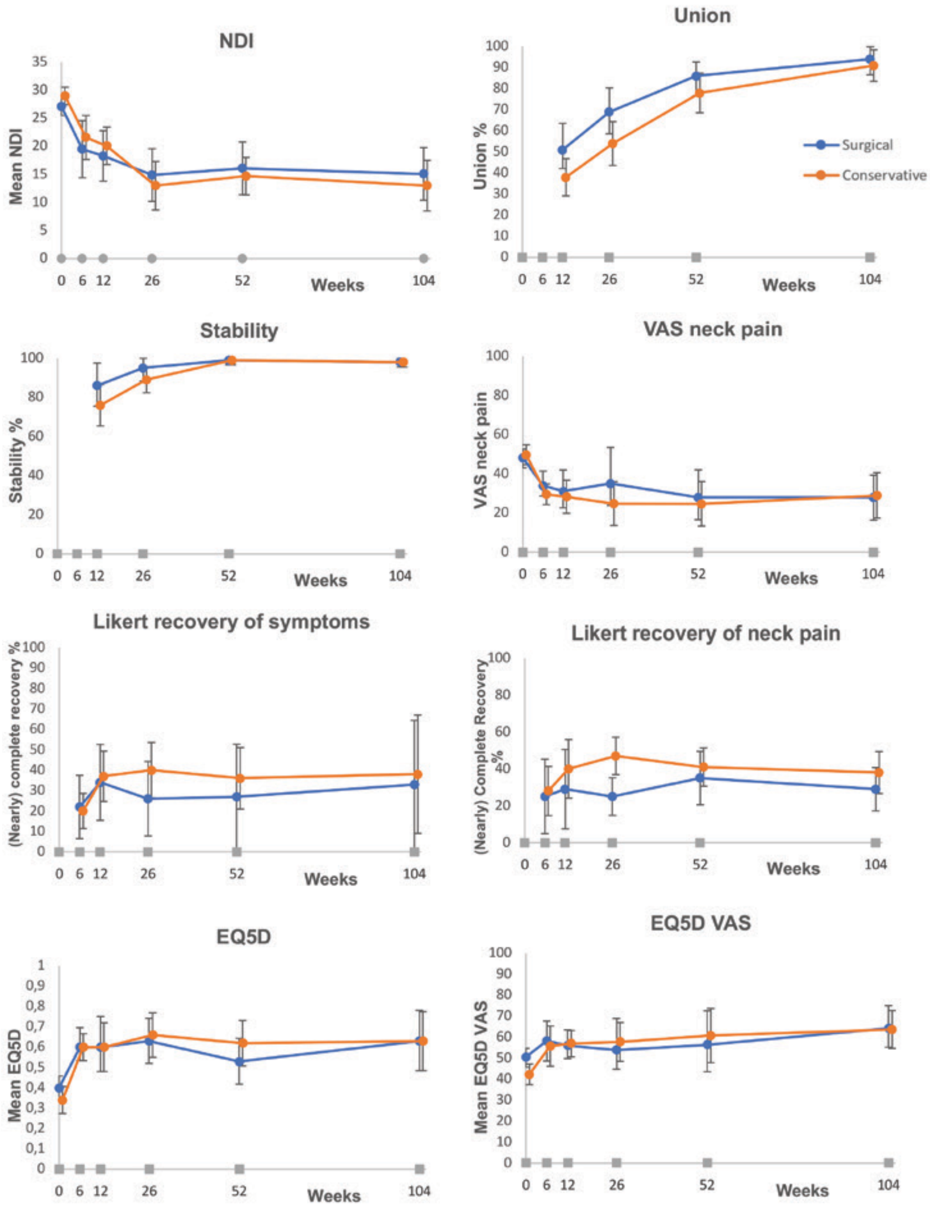

Figure 2. Line graphs displaying outcomes with 95% confidence intervals at various timepoints between treatments

Secondary outcomes

VAS neck pain at 52 weeks was similar between surgical and conservative patients (mean (SE) 28 (7.3) vs. 25 (5.7), p=0.22). The rate of patients reporting (nearly) complete recovery of symptoms did not differ (27% vs. 36%, aOR 1.0, 95% CI 0.29-3.5), nor did the rate of patients reporting (nearly) complete recovery of neck pain (35% vs. 42%, aOR 1.0, 95% CI 0.40-2.7). EQ5D-VAS health at baseline was higher for surgical patients (mean (SE) 50 (2.1) vs. 42 (2.5), p=0.01). EQ5D at 52 weeks did not differ between treatments (mean (SE) 0.53 (0.1) vs. 0.62 (0.1), p=0.40), nor did VAS health at 52 weeks (mean (SE) 57 (8.2) vs. 61 (6.6), p=0.48, **Table 2**).

Association NDI improvement and union

NDI improvement did not differ between patients with union and non-union at 52 weeks (mean (SE) -13 (2.0) vs. -12 (2.8), p=0.78). NDI improvement similarly did not differ between patients with union and non-union when analyzed separately for each treatment (mean (SE) -11 (2.3) vs. -10 (4.3), p=0.78 for surgical treatment; -15 (2.0) vs. -14 (3.3), p=0.82 for conservative treatment).

Outcomes throughout follow-up

NDI improvement, union and stability were largely similar between treatments throughout the follow-up period, as were the secondary outcomes (**Figure 2**). NDI improvement between baseline and 104 weeks did not differ between surgical and conservative patients (mean (SE) -12 (2.5) vs. -16 (2.4), p=0.06, <7.5 MCID). NDI did hence not clearly improve further between 52 and 104 weeks. Union at 104 weeks did not differ between treatments (94% vs. 91%, aOR 1.9, 95% CI 0.34-11), nor did stability (99% vs. 98%, aOR NA).

Complications

No secondary neurological deficits were identified in either treatment groups. Secondary treatment was applied less often after surgical than conservative treatment (OR 0.32, 95% CI 0.14-0.72). Nine (6%) surgically treated patients required secondary surgery: C1-C2 fusion (n=2), odontoid screw fixation (n=1), extended posterior fusion (n=3), hardware removal (n=2), and wound revision (n=1).

Of these 9 patients, 3 were ≥80 years. Twenty-three (19%) conservatively treated patients required secondary treatment: C1-C2 fusion (n=10), odontoid screw fixation (n=2), extended posterior fusion (n=10), and halo vest placement (n=1). Of these 23 patients, 7 were ≥80 years. Reasons for secondary treatment were prolonged fracture instability (n=2 surgical, n=11 conservative), prolonged non-union (n=3 surgical, n=8 conservative), persistent symptoms (n=4 conservative), collar non-compliance (n=1 conservative), and various other reasons (n=5 surgical, n=8 conservative). Time to secondary treatment did not differ between treatments (median (IQR) 12 (3-23) vs. 6 (3.5-16) weeks, Mann-Whitney U=84, p=0.41). Mortality within 52 and 104 weeks did not differ between treatments. Twelve (8%) surgical and 15 (11%) conservative patients died within 52 weeks (OR 0.71, 95% CI 0.32-1.6). Of these 27 patients, 17 were ≥80 years, of which 5 treated surgically. Fourteen (10%) surgical and 18 (14%) conservative patients died within 104 weeks (OR 0.68, 95% CI 0.33-1.4). Of these 32 patients, 21 were ≥80 years, of which 6 treated surgically. Time to death did not differ between treatments (median (IQR) 7 (3.9-20) vs. 26 (6.5-55) weeks, Mann-Whitney U=105, p=0.13, Supplementary-Figure 1).

Subgroup analyses

In patients aged 55-79 years, NDI improved less after surgical than conservative treatment (mean (SE) -11 (2.7) vs. -17 (2.2), p=0.04), although the difference was not clinically relevant (<7.5 MCID). Union and stability did not differ between treatments in this age group. In patients ≥80 years, NDI improvement, union and stability similarly did not differ between treatments. Union rates for type II fractures were higher after surgery in univariable analysis, but not in multivariable analysis (84% vs. 65%, aOR 2.4, 95% CI 0.93-6.2), and again NDI improvement and stability did not differ between treatments. NDI improvement, union and stability did not differ between treatments for fractures displaced >2 mm (**Table 3**).

Table 3. Results for primary outcomes for age subgroups, type II fractures and displaced fractures

	No. (%)			
	Surgical (n=144)	**Conservative (n=132)**	**Univariable analysis**	**Multivariable analysis**
NDI improvement (decrease) baseline-52 weeks, mean (SE)				
55-79 years	-11 (2.7)	-17 (2.2)	***p*=0.03**	***p*=0.04**
≥80 years	-11 (2.9)	-11 (2.2)	*p*=0.83	*p*=0.74
Type II fractures	-11 (2.5)	-13 (2.4)	*p*=0.35	*p*=0.22
Fractures displaced >2 mm	-11 (3.0)	-15 (2.7)	*p*=0.19	*p*=0.14
Union at 52 weeks				
55-79 years	72 / 81 (89)	61 / 72 (85)	OR 1.4 (CI 0.56-3.7)	aOR 2.1 (CI 0.38-12)
≥80 years	52 / 63 (83)	42 / 60 (70)	OR 2.0 (CI 0.86-4.8)	aOR 2.7 (CI 0.80-9.2)
Type II fractures	97 / 116 (84)	48 / 74 (65)	**OR 2.8 (CI 1.4-5.5)**	aOR 2.4 (CI 0.93-6.2)
Fractures displaced >2 mm	62 / 67 (93)	32 / 36 (89)	OR 1.6 (CI 0.39-6.2)	aOR 3.1 (CI 0.47-20)
Stability at 52 weeks				
55-79 years	80 / 81 (99)	72 / 72 (100)	OR 0.37 (CI 0.01-9.2)	aOR NA
≥80 years	63 / 63 (100)	58 / 60 (97)	OR NA	aOR NA
Type II fractures	115 / 116 (99)	72 / 74 (97)	OR 1.6 (CI 0.22-12)	aOR NA
Fractures displaced >2 mm	67 / 67 (100)	36 / 36 (100)	OR NA	aOR NA

Abbreviations: SE, standard error. OR, odds ratio. CI, 95% confidence interval. aOR, adjusted odds ratio.
Values in bold represent statistical significance. Odds ratios affected by non-convergence are reported as not available (NA).

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Treatment subtypes

NDI improvement did not differ between patients treated by odontoid screw fixation and C1-C2 fusion (mean (SE) -13 (2.9) vs. -9 (2.6), p=0.22), nor did union (76% vs. 88%, aOR 0.35, 95% CI 0.06-2.1) and stability (100% vs. 99%, aOR NA). Similarly, NDI improvement did not differ between patients treated with cervical collar and halo vest (mean (SE) -13 (2.1) vs. -20 (2.6), p=0.13), nor did union (76% vs. 86%, aOR 1.03, 95% CI 0.21-4.9) and stability (99% vs. 100%, aOR NA, Supplementary-Table 2).

Influence of baseline characteristics

Type III fractures showed substantially more union than type II fractures (aOR 11, 95% CI 1.7-76), while NDI improvement and stability were similar. None of the other baseline characteristics (age, gender, fracture displacement, other C1-C2 fractures, osteoporosis in C2, C0-C2 facet joints degeneration) were relevant predictors for the primary outcomes at 52 weeks (Supplementary-Table 3).

Sensitivity analysis

The sensitivity analysis using non-imputed data showed less NDI improvement for surgical patients (mean (SE) -13 (1.6) vs. -18 (1.3), p=0.004), although the difference was not clinically relevant (<7.5 MCID). Union rates were higher after surgery (92% vs. 84%, aOR 4.8, 95% CI 1.5-16), but NDI improvement for patients with union and non-union was similar. Stability did not differ between treatments (100% vs. 99%, aOR NA). Baseline NDI was higher in conservative patients, although the difference between means was 2 (<7.5 MCID, Supplementary-Table 4-5). NDI improvement, union and stability were largely similar between treatments throughout the follow-up period, as were the secondary outcomes (Supplementary-Figure 2). NDI improvement at 104 weeks was greater after conservative treatment, although the difference between means was 5 (<7.5 MCID). Union and stability at 104 weeks did not differ between treatments (Supplementary-Table 6). NDI improvement for patients aged 55-79 years and with displaced fractures was greater after conservative treatment, although the differences between means were 6.5 and 7.4 (<7.5 MCID). For type II fractures, union rates were superior after surgical treatment, but NDI improvement and stability were similar between treatments (Supplementary-Table 7). NDI improvement was greater after odontoid screw fixation than C1-C2 fusion, although the difference was not clinically relevant, and union and stability did not differ. The primary outcomes did not differ between treatments with cervical collar and halo vest (Supplementary-Table 8).

DISCUSSION

This multicenter prospective comparative study of older patients with odontoid fractures represents the most extensive comparison of outcomes between surgical and conservative treatments. At 52 weeks, outcomes between treatments did not differ in terms of NDI improvement, union and stability, nor for any of the secondary outcomes, also after adjusting for patient- and fracture characteristics. Furthermore, NDI improvement did not differ between patients with union and non-union, providing evidence that clinical outcome and union status are not clearly associated, and that a favorable clinical rather than radiological outcome should be the aim of treatment. Nevertheless, the proportion of (nearly) complete patient-perceived recoveries was disappointingly low in both groups.

No cases of secondary neurological deficit were identified, indicating that historical fears for undertreatment are unjustified. As expected, secondary surgery was more common after initial conservative treatment. No difference in mortality between treatments was identified. In patients aged 55-79 years, NDI improved more in conservative patients, although the difference was not clinically relevant, and union and stability were similar. Primary outcomes were similar between treatments of patients ≥80 years, type II fractures and fractures displaced >2 mm.

The authors conclude that initial conservative treatment is justified, and that surgery can be reserved as secondary treatment in relatively rare cases of persistent symptomatic non-union.

Perspective

In recent decades, the treatment approach for odontoid fractures has shifted. In the 1990s, case series reported in-hospital mortality following rigid immobilization and flat bed rest of over 25%.[25] Since then, rigid immobilization (halo-vest) gradually waned in popularity.[26, 27] Advancements in surgical care, like improved implants and intraoperative imaging, have made surgery on older people more common.[28-30] This was assumed to enhance union rates, but the clinical benefit remained unclear. In more recent years, the focus has shifted to prioritize favorable clinical outcomes.

In 2013, the only other prospective study comparing surgical and conservative treatments involved 159 patients, of which 101 were treated surgically.[31] Union rates were higher after surgery (95% vs. 79%). Surgical patients had less NDI deterioration compared to conservative patients, in contrast to the NDI improvement observed in both treatments in the present study. This difference is (partially) explained by the former study using pre-injury status for NDI scores, whereas the present study used post-injury status assuming no mobility restrictions were imposed. NDI scores at 52 weeks did not differ between treatments in both prospective studies, despite variations in the scores between the studies.

In 2021, a prospective uncontrolled study reported on 260 patients treated conservatively by semi-rigid collar for 6 weeks, followed by 6 weeks by soft collar.[32] Short Form 12 (SF-12) health survey showed excellent functional outcome in 95%. NDI and SF-12 did not differ between patients with union and pseudo-arthrosis (stability). Interestingly, 36% of patients did not follow the prescribed treatment by discontinuing or not wearing the collar, yet still achieved good functional outcomes. Building on this, a current randomized controlled trial is comparing outcomes of 12-week collar treatment with no immobilization at all.[33]

Limitations

This study has several limitations, mainly being a non-randomized study. Even after adjusting for age, gender, and various fracture characteristics, results may still have been influenced by residual confounding. A randomized controlled trial was deemed impracticable due to differences in treatment culture among participating centers. At the time of designing this study, there was a widespread belief that surgery was necessary for many odontoid fractures, rendering conservative treatment ethically questionable. The present study was therefore proposed, and many of Europe's major spine centers were keen to participate.

The involvement of older people, the multicenter nature, and the relatively frequent five follow-up moments unavoidably led to considerable missing data, impacting the data's reliability. Missing data posed challenges for the statistical analysis. A simple last observation carried forward approach was avoided because it would underestimate the treatment effect at 52 weeks, merely reflecting outcome at last follow-up. Sensitivity analyses using non-imputed data showed greater, albeit not clinically relevant, NDI improvement after conservative treatment, superior union after surgery, and similar NDI improvement for patients with union and non-union. These findings further affirm the robustness of the presented results.

Unlike the common focus on type II fractures, this study included type II and III fractures, for which was accounted in multivariable analyses and type II subgroup analysis. Different forms of surgical (anterior/posterior) and conservative (collar/halo) treatments were analyzed in their respective groups, which may have influenced outcomes, although outcomes of post-hoc analyses for treatment subtypes showed no evidence for a difference. The inclusion period of over nine years, although relatively lengthy, did not introduce methodological issues since treatment modalities have not changed considerably during this period. No standardized assessment was done for baseline health status, likely favoring generally healthier surgical patients.[4] Notably, the study included patients ≥55 years, rather than the more common ≥65 years. This difference should be taken into account in future study comparisons.

CONCLUSIONS

Conservative treatment yielded similar clinical outcome and fracture healing to surgical treatment in older patients with odontoid fractures. Clinical outcome was not clearly associated with fracture union. No cases of secondary neurological deficits were identified, indicating that historical fears for undertreatment are unjustified. Treatments should prioritize favorable clinical over radiological outcomes.

SUPPLEMENTARY MATERIAL

Supplementary material can be accessed at https://academic.oup.com/ageing/article/53/8/afae189/7742919.

LIST OF ABBREVIATIONS

aOR — Adjusted odds ratio
CI — Confidence interval
CT — Computed tomography
EQ5D — EuroQol-5D-3L
IQR — Interquartile range
MCID — Minimal clinically important difference
NA — Not available
NDI — Neck Disability Index
OR — Odds ratio
SD — Standard deviation
SE — Standard error
SF-12 — Short Form 12
STROBE — Strengthening the reporting of observational studies in epidemiology
VAS — Visual Analogue Scale

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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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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]

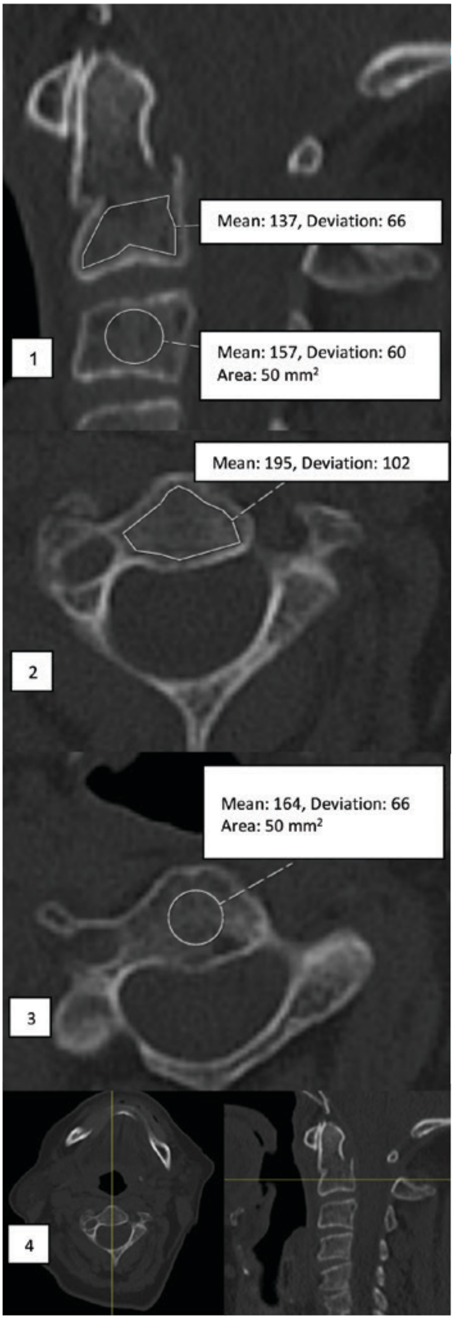

Figure 1. Example of HU measurements in a 70-years old female patient. Region-of-interest measurements were performed in C2 on mid-sagittal (1) and mid-axial (2) planes. Circle-of-interest measurements were performed in C3 on mid-sagittal (1) and mid-axial (3) planes. The localizer tool was used (4).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

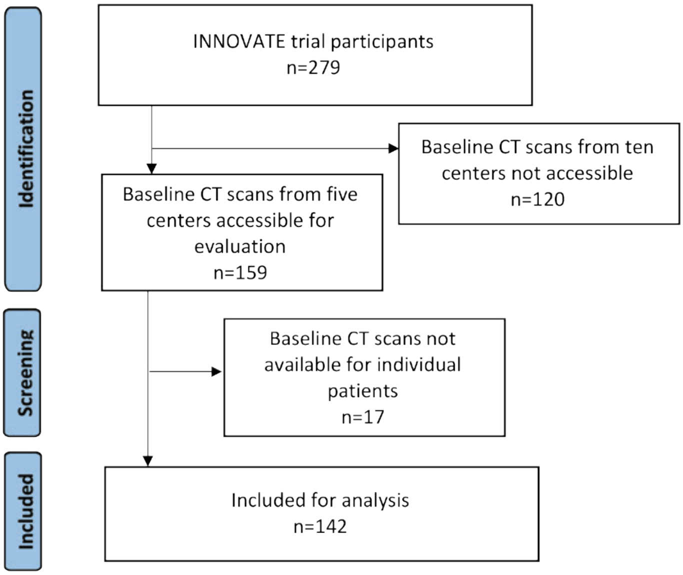

Figure 2. Flowchart depicting the inclusion process

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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CHAPTER 6

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

GENERAL DISCUSSION

The best treatment for odontoid fractures in elderly patients has been a subject of intense debate for decades. In the absence of high-quality evidence, treatment decisions have historically been based on local treatment cultures, as well as the surgeon's training and experience. This has led to considerable national and international practice variation, with some centers advocating for primary surgery, others favoring primary conservative treatment, and still others adopting a fracture- or patient-specific approach.

This thesis aimed to strengthen the quality of the available evidence and support future clinical decision-making by comparing clinical and radiological outcomes of surgical and initial conservative treatments for odontoid fractures in elderly patients. This chapter will provide a general discussion, also addressing the limitations, future perspectives, and direct clinical implications.

Appraisal of historical literature and clinical practice

The existing literature was systematically reviewed and subjected to meta-analysis in the study presented in Chapter 2. The review revealed that historical studies were generally of limited quality and had small sample sizes. Among the 41 studies included, only four studies were prospective, and just one adjusted for confounding variables—qualifying it as a cohort study—while the rest were case series. These designs suffered from inherent limitations such as variability in outcome assessments, missing data, and confounding bias (e.g. surgery for relatively healthy patients and conservative treatment for the most frail).[1] Moreover, outcome parameters varied, with older studies focusing exclusively on fracture healing rather than clinical outcomes. Together, these limitations resulted in substantial heterogeneity in the data. Meta-analyses were feasible only for radiological outcomes, with adjustments limited to baseline differences in mean age and fracture type. Collectively, these factors significantly constrained both the depth of analysis and the strength of the recommendations that could be drawn from historical literature.

In historical literature, patients treated surgically demonstrated higher union rates than those treated conservatively, although this difference may be—at least partly—attributed to the limitations mentioned above.

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Furthermore, no clinically relevant differences were observed in Neck Disability Index (NDI), Visual Analogue Scale (VAS) pain, or Smiley-Webster Scale scores, nor fracture stability rates. Other clinical outcome parameters were reported too inconsistently to allow for even univariable analysis. Additionally, the association between clinical outcome and fracture union remained unexplored. It must, therefore, be concluded that historical treatments were not based on robust research.

Despite the limitations discussed, some observations are noteworthy. The treatment approach for odontoid fractures has evolved over recent decades. In the 1990s, case series reported in-hospital mortality rates of over 25% following rigid immobilization and flat bed rest.[2] It is now likely that, at the time, patients died as a result of the treatment rather than from the fracture itself. Since then, the popularity of rigid immobilization methods, such as the halo vest, has gradually declined.[3, 4] Advancements in surgical techniques, including improved implants and intraoperative imaging, have increased the prevalence of surgery among older patients, with surgical treatment rates reaching up to 86% in the United States in 2017.[1, 5–7] These changes were believed to improve union rates, although the clinical benefits for the patient remained unclear. In recent years, the focus has shifted toward prioritizing favorable clinical outcomes.

New insights from the clinical studies in this thesis

The most comprehensive comparison of treatment outcomes to date was presented in Chapter 4. This international prospective comparative study involved 276 patients, with 144 undergoing surgical treatment and 132 receiving conservative treatment. The results provide valuable new insights, particularly regarding clinical outcome, fracture union, fracture stability, and the association between clinical outcome and fracture union.

Clinical outcome

Clinical outcome is now widely considered the most relevant, especially in elderly patients. The primary clinical outcome was assessed using NDI improvement compared to baseline. At the primary assessment at 52 weeks, there was no significant difference in NDI improvement between the surgical and conservative treatment groups. This trend continued throughout the entire 104-week follow-up, with largely similar NDI improvements observed across both groups. Additionally, NDI improvement was most noticeable between baseline and 26 weeks, with no clear further improvement between 26 and 104 weeks.

Moreover, no relevant differences were found between surgical or conservative treatments in any of the secondary clinical outcome parameters assessed in this thesis. These parameters included VAS neck pain scores, Likert patient-perceived recovery of symptoms, Likert patient-perceived recovery of neck pain, and EuroQol-5D-3L (EQ5D) scores.

Fracture union

Fracture union remains a key objective of treatment and, for some, is still considered the most important outcome parameter. At the primary outcome assessment at 52 weeks, there was no significant difference in fracture union rates between surgical and conservative patients (86% vs. 78%). This similarity in fracture union rates remained consistent throughout the entire 104-week follow-up.

These findings contrast with earlier, lower-quality studies that reported higher union rates following surgery. Those studies had smaller sample sizes, typically relied on univariable analyses, and may have been (more) biased—for instance, by selecting healthier patients for surgery or due to differences in follow-up duration between treatment groups.[1] Illustratively, the univariable analyses in Chapter 5 demonstrated a significant influence of fracture displacement and applied treatment, which was not observed in multivariable analyses.

Fracture stability

Fracture stability, sometimes referred to as fibrous union, has received increasing attention in recent decades. When accompanied by a favorable clinical outcome, it can be considered a successful treatment result in elderly patients. At the primary outcome assessment at 52 weeks, fracture stability was nearly identical between the surgical and conservative groups (99% vs. 98%). This similarity remained consistent throughout the 104-week follow-up.

Association between clinical outcome and fracture union

The association between clinical outcome and fracture union—specifically whether non-union leads to symptoms—has long been uncertain. In the study presented, there was no relevant difference in NDI improvement between patients with union and those with persistent non-union at the 52-week mark. This lack of difference remained consistent when analyzed separately for each treatment group. In other words, there was no evidence that achieving fracture union resulted in better clinical outcomes for patients compared to persistent non-union.

Complications

Historically, prolonged non-union leading to secondary fracture displacement and potential upper spinal cord injury has been a feared complication, often used as justification for aggressive treatment of odontoid fractures. However, whether this was a likely outcome or merely a theoretical concern has remained unclear, given that reports of secondary deficits are very rare and typically associated with high-impact trauma in previously undiagnosed fractures in non-geriatric patients.[8-10] In the studies included in this thesis, no secondary neurological deficits were identified in any patient—not even in centers with the most liberal collar treatment policies. This suggests that historical concerns about the dangers of undertreatment are unfounded.

As expected, secondary treatment was applied less frequently after surgical treatment than after conservative treatment (6% vs. 19%). This is unsurprising and can be viewed as a logical consequence of the initial conservative approach. Moreover, radiological findings, rather than patient complaints, have primarily driven secondary treatments. In the future, these numbers may decrease as patient complaints become the primary focus, given that only four of the twenty-three patients in the conservative group underwent secondary treatment based on their complaints.

There were no relevant differences between treatment groups in terms of time to secondary treatment, mortality within 52 and 104 weeks, or time to death.

Residual confounding and study design limitations

Despite adjusting for various baseline characteristics in the prospective study in Chapter 4, residual confounding may still have influenced the results. A randomized controlled trial, considered the gold standard, was deemed infeasible at the time of study design due to variations in local treatment practices and may not even be necessary.[11, 12] An alternative study design—comparing treatment *strategies between centers* in otherwise similar patient populations rather than comparing treatment *modalities within centers*—potentially reduces confounding. This design, also referred to as natural experiment or pseudo-randomization, was applied in the study presented in Chapter 3.[13, 14]

Low-threshold-for-surgery vs. initially-conservative treatment strategy

The retrospective study presented in Chapter 3 compared two distinct treatment strategies between regions in the Netherlands. One region employed a low-threshold-for-surgery approach, performing primary surgery for dislocated fractures in relatively healthy patients, while the other primarily applied a conservative approach for all patients.

Among the 173 patients included (120 in the low-threshold-for-surgery group and 53 in the initially-conservative group), fracture union (53% vs. 43%) and fracture stability (90% vs. 85%) were largely similar between the groups at the last follow-up. These percentages are lower than those in the prospective study, likely due—at least to a large extent—to outcome assessments being conducted at the last available follow-up, which was generally much earlier than the 52-week mark used in the prospective study.

As expected, patients aged 80 and older had worse outcomes in terms of union, stability, and mortality compared to those aged 55–80, regardless of treatment strategy. No cases of secondary neurological deficits were identified, further challenging concerns about the potential consequences of undertreatment.

Interobserver variability in the Anderson and d'Alonzo fracture classification

In the study presented in Chapter 3, all fractures were reassessed using baseline computed tomography (CT) scans, with evaluators blinded to the original scoring. Discrepancies were identified in 26 (15%) fractures, with only substantial agreement (κ=0.69) between the new and original scores. This underscores the limitations of the Anderson and d'Alonzo classification, particularly for fractures that do not clearly classify as type II or III.[15] Therefore, caution should be exercised when using this classification to guide treatment decisions.

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Hounsfield unit measurements to predict fracture union

Decreased bone mineral density (BMD) is associated with poorer fracture healing.[16] The role of BMD in odontoid fractures in the elderly had not been previously studied, although it may have influenced study findings. In Chapter 5, Hounsfield units (HU) on baseline CT scans were analyzed as a proxy for BMD in 142 patients from the prospective study in Chapter 4.

There was no relevant difference in baseline HU values between patients who achieved union and those who did not at 52 weeks. Patients in both groups showed decreased HU (cervical HU <300), indicating osteopenia, and HU measurements failed to predict fracture union. These findings suggest that all elderly patients with odontoid fractures should undergo osteoporosis screening and receive appropriate treatment.

Differences in prescribed treatment regimens

There remains considerable variation in how treatment regimens are applied across different centers. For instance, there are no standardized immobilization protocols and practices vary regarding the use of collars—some centers prescribe them only during mobilization, while others mandate continuous use. The duration of collar treatment also varies, with centers prescribing a fixed 6-week period and others continuing until favorable radiological outcomes are achieved, occasionally extending beyond 12 weeks.[17, 18] In some centers, postoperative collar immobilization is routine, while others avoid it altogether.[19, 20]

These variations, although unlikely to affect the overall conclusions, may have influenced the data due to the observational nature of the studies in this thesis. Importantly, there is no evidence that more aggressive treatment regimens improve patient outcomes and, in fact, they may cause unnecessary harm, such as pressure ulcers requiring secondary surgery. Surgeons should therefore remain aware that the prescribed treatment regimen may harm the patient more than the fracture itself.

LIMITATIONS

The studies presented in this thesis have several limitations. None were randomized, and despite adjustments for variables such as age, gender, and fracture characteristics, residual confounding may still have influenced the results. At the time of the study design, randomization was deemed impracticable due to variations in local treatment practices.

Additionally, no standardized assessments were conducted for baseline health status in the clinical studies. If this influenced the outcome, it most likely favored generally healthier surgical patients.[1] Missing data—largely due to the involvement of older patients, the multicenter nature of the studies, and the relatively frequent follow-up moments—posed challenges for the statistical analyses. In the prospective study, sensitivity analyses using non-imputed data yielded similar overall clinical conclusions, further confirming the robustness of the results.

Unlike the common focus on type II fractures, this thesis examined both type II and III fractures, which was accounted for in the multivariable analyses and type II subgroup analysis. Various surgical (anterior, posterior) and conservative (collar, halo) treatments were analyzed within their respective groups. While these treatment variations may have influenced outcomes, post-hoc analyses in the prospective study found no evidence of differences between treatment subtypes.

The inclusion period spanned over ten years for the retrospective study and over nine years for the prospective study. Although relatively long, this was not expected to introduce methodological issues, as treatment modalities remained largely unchanged throughout the study period.

Lastly, the clinical studies included patients aged 55 and older, a slightly younger cohort than the commonly studied population (≥65 years), which should be considered in future study comparisons.

FUTURE PERSPECTIVES

None of the studies in this thesis found relevant differences between surgical and conservative treatment outcomes. Future research could replicate these findings and address the questions that arise from the presented studies.

Based on the results of this thesis, randomization is now justified in future studies, and preparations for a such study have commenced.[21] Alternatively, future research could evaluate outcomes across centers with varying treatment approaches in similar patient populations, employing a natural experimental design, as demonstrated in Chapter 3. Ideally, this would involve comparing centers that follow a primary surgical strategy with those that follow a primary conservative approach.

More invasive treatments (surgery, rigid immobilization) did not yield superior outcomes in the studies presented. Given the comparable treatment results, future research should focus on minimizing patient-perceived treatment burden. Future studies may also investigate the long-term (>104 weeks) clinical outcomes of patients with persistent asymptomatic non-union.

Moreover, the natural history of odontoid fractures may be more favorable than previously presumed. Fractures are often diagnosed more than a week after injury, with no clear clinical consequences, and patients can achieve good functional outcomes even if they do not use the prescribed collar.[17, 22] Therefore, further studies should evaluate whether treatment is necessary at all for elderly patients. A current randomized controlled trial is comparing the outcomes of 12-week collar treatment versus no immobilization, which may help answer this important clinical question.[23] Such studies should also take frailty status into account—such as by using the modified 5-Item Frailty Index—to predict complications and mortality.[24] Fracture classifications may be updated to incorporate these factors accordingly to better guide treatment decisions.[25]

From a societal perspective—given the projected increase in the aging population and its associated healthcare burden—future research should also focus on evaluating cost-effectiveness and reducing treatment-related costs without compromising patient care.[26] The findings of this thesis indicate that more aggressive—and presumably more costly—treatment strategies may not be warranted, and future research might even suggest that primary interventions may be unnecessary.

DIRECT CLINICAL IMPLICATIONS

Surgical and initially conservative treatments for odontoid fractures in elderly patients lead to similar clinical and radiological outcomes. Therefore, initial conservative management is justified, with surgery reserved for the relatively rare cases of persistent symptomatic non-union. The primary focus should be on achieving favorable clinical outcomes rather than radiological results.

Historical concerns about undertreatment, such as the risk of secondary fracture displacement leading to upper spinal cord injury, are now considered unwarranted. Asymptomatic non-union can be considered an acceptable treatment outcome and should not automatically prompt secondary surgical intervention. Furthermore, elderly patients with odontoid fractures likely have decreased bone mineral density and should be routinely referred for osteoporosis screening and management.

Primum non nocere—first, do no harm. Although surgeons might interpret these results as a rationale for maintaining their usual treatment practices, they should recognize that similar outcomes can be achieved with treatments that impose a lower burden on the patient and may be less costly. Therefore, surgeons should prioritize minimizing this burden by avoiding overly aggressive treatments that do not improve outcomes and may introduce additional risks. The prescribed treatment regimen could ultimately harm the patient more than the fracture itself.

LIST OF ABBREVIATIONS

BMD — Bone mineral density
CT — Computed tomography
EQ5D — EuroQol-5D-3L
HU — Hounsfield units
K — Kappa
NDI — Neck Disability Index
VAS — Visual Analogue Scale

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CHAPTER 7

SUMMARY

SUMMARY

This thesis addresses the complexities of treating odontoid fractures in elderly patients. These fractures affect the odontoid process of the second cervical vertebra (C2) and present unique treatment challenges. The optimal treatment approach remains controversial.

Chapter 1 provides a general introduction and outline of the thesis. Odontoid fractures are the most common cervical spine injuries among the elderly, who have an increased risk of complications and mortality. More than 70% of patients with odontoid fractures are older than 65 years, with many being over 80 years old. These fractures are largely caused by minor trauma, such as falls, and are often exacerbated by osteoporosis, a condition prevalent in the elderly. Odontoid fractures are classified into three types, with type II and type III being the most prevalent and clinically relevant. Treatment may be surgical or conservative, each with its own risks and benefits, particularly for elderly patients. The main objective of this thesis was to explore the clinical and radiological outcomes of both surgical and conservative treatment approaches, with the aim of optimizing care for this patient group.

Chapter 2 presents a systematic review and meta-analysis of the historical literature. This review aimed to compare outcomes of surgical and conservative treatments for type II and III odontoid fractures in patients aged 65 and older, focusing on clinical outcomes, fracture union, and fracture stability. A comprehensive search was conducted across seven databases, yielding 41 studies with a total of 2099 patients, most of which were retrospective case series. The review found no clinically relevant differences in Neck Disability Index (NDI) and Visual Analogue Scale (VAS) pain scores between treatment methods. Surgically treated patients had higher fracture union rates at last follow-up (72.7% vs. 40.2%), but stability rates were not significantly different from those of patients treated conservatively. Data were of limited quality and showed substantial heterogeneity, severely limiting the strength of conclusions, and studies were likely biased. Complications were common in both groups, with surgical complications related mainly to the operation itself, and conservative treatment leading to immobilization-related issues. This review suggested the need for well-designed studies to better understand the correlation between clinical and radiological outcomes and to adjust for differences in factors such as age and fracture characteristics.

Chapter 3 examines practice variation in the Netherlands regarding the treatment of odontoid fractures in elderly patients. This study retrospectively explored differences in treatment strategies across centers, rather than treatment modalities within centers. Some centers adopted a low-threshold-for-surgery approach, recommending surgery for relatively healthy patients with dislocated fractures. In contrast, another center employed an initially-conservative approach for all patients. Outcomes of these two treatment philosophies were compared in a natural experiment—or pseudo-randomized design—to reduce confounding. Fracture union (53% vs. 43%) and fracture stability (90% vs. 85%) at last follow-up did not differ between groups. Analyzing differences in clinical outcomes between the groups was infeasible due to data limitations. As expected, patients aged ≥80 years in both strategies exhibited less union (64% vs. 30%), less stability (97% vs. 77%), and higher mortality within 104 weeks (2% vs. 22%) compared to patients aged 55-80 years. When the fractures were reassessed blinded for the original scoring in the patient files, discrepancies were found in 26 cases (15%), indicating only substantial agreement (κ=0.69) between the new and original scores. Caution should therefore be exercised when using this classification to guide treatment decisions.

Chapter 4 presents the results of an international prospective comparative study—the largest available study on odontoid fractures in the elderly. Fifteen centers in eight European countries participated in comparing outcomes between surgical and conservative treatments. At 52 weeks, improvement (decrease) in NDI was largely similar between surgical and conservative treatments (-11 vs. -14), as were union (86% vs. 78%), and stability (99% vs. 98%). NDI improvement did not differ between patients with union and those with persistent non-union (-13 vs. -12), indicating that clinical outcomes and fracture union are not clearly associated. There were no differences in any of the secondary outcomes (including VAS neck pain, Likert patient-perceived recovery, and EuroQol-5D-3L) or among subgroups (including type II and displaced fractures). No cases of secondary neurological deficits were identified. As expected, secondary treatment was less common after surgical treatment than after initial conservative treatment (6% vs. 19%). Mortality within 52 weeks (8% vs. 11%) and 104 weeks (10% vs. 14%) did not differ between the treatment groups. It can therefore be concluded that treatment should prioritize favorable clinical outcomes over radiological findings.

Chapter 5 explores the usability of Hounsfield unit (HU) measurements as a predictor of fracture union in elderly patients with odontoid fractures. HUs are a quantitative measure of bone mineral density (BMD) obtained from CT scans. Decreased BMD has been associated with poorer fracture healing in animal and some clinical studies, although it had not yet been studied in odontoid fractures in the elderly. This study examined whether baseline HU measurements in the bodies of C2 and C3 can predict fracture union at 52 weeks. Baseline HUs in C2 (HU 246 vs. 282) and C3 (HU 260 vs. 251) did not differ between patients with and without union. Compared to control patients in the literature, both patients with and without union exhibited lowered HUs, suggesting osteopenia (cervical HUs <300). It can be concluded that baseline HU measurements in C2 and C3 are not associated with fracture union at 52 weeks, and therefore fail to serve as predictors of union in elderly patients with odontoid fractures. Since both the union and non-union groups exhibited decreased BMD, all elderly patients with odontoid fractures should be referred for osteoporosis screening and appropriate treatment.

Chapter 6 presents a general discussion, also addressing the limitations, future perspectives, and direct clinical implications. The findings of this thesis support initial conservative treatment for odontoid fractures in elderly patients, with surgical intervention reserved for the relatively rare cases of persistent symptomatic non-union. Prioritizing clinical outcomes over radiological results is important, since clinical outcomes and fracture union are not clearly associated. Asymptomatic non-union can be viewed as an acceptable treatment outcome and should not automatically prompt secondary surgical treatment. Additionally, given the prevalence of decreased bone mineral density in this population, routine osteoporosis screening is recommended to enhance care for elderly patients with odontoid fractures. Historical fears regarding the dangers of undertreatment—such as secondary fracture displacement leading to spinal cord injury—are now considered unfounded, as none of the patients in this thesis experienced these complications. Although surgeons might interpret these results as a rationale for maintaining their usual treatment practices, they should recognize that similar outcomes can be achieved with treatments that impose a lower burden on the patient and may be less costly. Therefore, surgeons should prioritize minimizing this burden by avoiding overly aggressive treatments that do not improve outcomes and may introduce additional risks. The prescribed treatment regimen could ultimately harm the patient more than the fracture itself.

CHAPTER 8

SAMENVATTING (DUTCH)

SAMENVATTING

Dit proefschrift behandelt de complexiteit van de behandeling van densfracturen bij ouderen. Deze fracturen treffen de dens op de bovenzijde van de tweede halswervel (C2) en brengen unieke behandeluitdagingen met zich mee. De optimale behandelstrategie blijft controversieel.

Hoofdstuk 1 biedt een algemene inleiding en overzicht van het proefschrift. Densfracturen zijn de meest voorkomende nekwervelletsels bij ouderen, die bovendien een verhoogd risico op complicaties en mortaliteit hebben. Meer dan 70% van de patiënten met densfracturen is ouder dan 65 jaar, waarbij velen ouder zijn dan 80 jaar. Deze fracturen worden grotendeels veroorzaakt door lichte trauma's, zoals valpartijen, en worden vaak verergerd door osteoporose, een veel voorkomende aandoening bij ouderen. Densfracturen worden ingedeeld in drie types, waarbij type II en type III de meest voorkomende en klinisch relevante vormen zijn. De behandeling kan chirurgisch of conservatief van aard zijn, waarbij elke methode zijn eigen risico's en voordelen heeft, in het bijzonder voor oudere patiënten. Het voornaamste doel van dit proefschrift was om de klinische en radiologische uitkomsten van zowel chirurgische als conservatieve behandelmethoden te onderzoeken, met als doel de zorg voor deze patiëntengroep te optimaliseren.

Hoofdstuk 2 presenteert een systematisch review en meta-analyse van de historische literatuur. Dit review had tot doel de uitkomsten van chirurgische en conservatieve behandelingen van type II en III densfracturen bij patiënten van 65 jaar en ouder te vergelijken, met een focus op klinische uitkomsten, botdoorbouw en fractuurstabiliteit. Er werd een uitgebreide zoekactie uitgevoerd in zeven databanken, waaruit 41 studies werden geselecteerd met in totaal 2099 patiënten, waarvan de meeste retrospectieve case series waren. Het review vond geen klinisch relevante verschillen in de scores op de Neck Disability Index (NDI) en de Visual Analogue Scale (VAS) voor pijn tussen de behandelmethoden. Patiënten die chirurgisch werden behandeld, hadden vaker botdoorbouw bij het laatste follow-up moment (72,7% versus 40,2%), maar de fractuurstabiliteit verschilde niet significant van die bij patiënten die conservatief werden behandeld. De data waren van beperkte kwaliteit en vertoonden een aanzienlijke heterogeniteit, wat de sterkte van de conclusies ernstig beperkte. Bovendien was bias in de studies aannemelijk. Complicaties kwamen in beide groepen vaak voor, waarbij de chirurgische complicaties voornamelijk verband hielden met de ingreep zelf en de conservatieve behandeling leidde tot immobilisatie-gerelateerde problemen. Dit review suggereerde dat er behoefte was aan goed ontworpen studies om de correlatie tussen klinische en radiologische uitkomsten beter te begrijpen en om te corrigeren voor factoren zoals leeftijd en fractuureigenschappen.

Hoofdstuk 3 onderzoekt praktijkvariatie in Nederland met betrekking tot de behandeling van densfracturen bij oudere patiënten. Deze studie onderzocht retrospectief de verschillen in behandelstrategieën tussen centra, in plaats van behandelmodaliteiten binnen centra. Sommige centra hanteerden een laagdrempelig-chirurgische aanpak en adviseerden een operatie voor relatief gezonde patiënten met gedisloceerde fracturen. Daarentegen paste een ander centrum een initieel-conservatieve benadering toe voor alle patiënten. De uitkomsten van deze twee behandelstrategieën werden vergeleken in een natuurlijk experiment – of pseudo-gerandomiseerde studie – om confouding te verminderen. De botdoorbouw (53% vs. 43%) en de fractuurstabiliteit (90% versus 85%) bij het laatste follow-up moment verschilden niet tussen de groepen. Het analyseren van verschillen in klinische uitkomsten tussen de groepen bleek onmogelijk vanwege databeperkingen. Zoals verwacht vertoonden patiënten van ≥80 jaar in beide strategieën minder botdoorbouw (64% vs. 30%), minder fractuurstabiliteit (97% versus 77%) en een hogere mortaliteit binnen 104 weken (2% vs. 22%) vergeleken met patiënten van 55–80 jaar. Wanneer de fracturen, geblindeerd voor de oorspronkelijke score in de patiëntendossiers, opnieuw werden beoordeeld, werden discrepanties gevonden in 26 gevallen (15%), wat wijst op slechts substantiële overeenstemming (κ=0,69) tussen de nieuwe en de oorspronkelijke scores. Daarom dient voorzichtigheid te worden betracht bij het gebruik van deze classificatie om behandelbeslissingen te ondersteunen.

Hoofdstuk 4 presenteert de resultaten van een internationale prospectieve vergelijkende studie – de grootste beschikbare studie naar densfracturen bij ouderen. Vijftien centra in acht Europese landen namen deel aan het vergelijken van de uitkomsten van chirurgische en conservatieve behandelingen. Na 52 weken was de verbetering (daling) in de NDI grotendeels vergelijkbaar tussen de chirurgische en de conservatieve behandeling (−11 vs. −14), evenals de botdoorbouw (86% vs. 78%) en de fractuurstabiliteit (99% vs. 98%). De verbetering in NDI verschilde niet tussen patiënten met en zonder botdoorbouw (−13 vs. −12), wat aangeeft dat de klinische uitkomsten en de botdoorbouw niet duidelijk met elkaar samenhangen. Er waren ook geen verschillen in de secundaire uitkomsten (inclusief VAS nekpijn, Likert patiënt-ervaren herstel en EuroQol-5D-3L) noch tussen subgroepen (inclusief type II en verplaatste fracturen). Er werden geen gevallen van secundaire neurologische uitval vastgesteld. Zoals verwacht was secundaire behandeling minder gebruikelijk na chirurgische behandeling dan na een aanvankelijke conservatieve behandeling (6% vs. 19%). De mortaliteit binnen 52 weken (8% vs. 11%) en binnen 104 weken (10% vs. 14%) verschilden niet tussen de behandelingsgroepen. Hieruit kan worden geconcludeerd dat de behandeling moet zijn gericht op gunstige klinische uitkomsten boven radiologische bevindingen.

Hoofdstuk 5 onderzoekt de bruikbaarheid van Hounsfield-eenheden (HU) als voorspeller van botdoorbouw bij oudere patiënten met densfracturen. Hounsfield-eenheden vormen een kwantitatieve maat voor de botmineraaldichtheid (BMD) die verkregen wordt uit CT-scans. Een verminderde BMD is in dierstudies en sommige klinische studies in verband gebracht met een slechtere fractuurgenezing, hoewel dit nog niet was bestudeerd bij densfracturen bij ouderen. Deze studie onderzocht of de baseline HU-metingen in de corpora van C2 en C3 de botdoorbouw na 52 weken kunnen voorspellen. De baseline HU's in C2 (HU 246 vs. 282) en in C3 (HU 260 vs. 251) verschilden niet tussen patiënten met en zonder botdoorbouw. In vergelijking met controle patiënten uit de literatuur vertoonden zowel patiënten met als zonder botdoorbouw verlaagde HU-waarden, wat duidt op osteopenie (cervicale HU's <300). Hieruit kan worden geconcludeerd dat de baseline HU-metingen in C2 en C3 niet geassocieerd zijn met de botdoorbouw na 52 weken en daarom niet als voorspellers van botdoorbouw kunnen dienen bij oudere patiënten met densfracturen. Aangezien zowel patiënten met als zonder botdoorbouw een verminderde BMD vertoonden, moeten alle oudere patiënten met densfracturen worden doorverwezen voor osteoporosescreening en passende behandeling.

Hoofdstuk 6 presenteert een algemene discussie, waarin ook de beperkingen, toekomstige perspectieven en de directe klinische implicaties aan bod komen. De bevindingen van dit proefschrift ondersteunen een initieel conservatieve behandeling van densfracturen in oudere patiënten, waarbij chirurgie voorbehouden kan blijven aan relatief zeldzame gevallen van symptomatisch uitblijvende botdoorbouw. Het is belangrijk om de klinische uitkomsten boven de radiologische resultaten te stellen, aangezien er geen duidelijke samenhang bestaat tussen de klinische uitkomsten en botdoorbouw. Een asymptomatisch uitblijvende botdoorbouw kan als een acceptabele behandeluitkomst worden beschouwd en zou niet automatisch moeten leiden tot een secundaire chirurgische behandeling. Bovendien wordt, gezien de prevalentie van een verminderde botmineraaldichtheid in deze populatie, aangeraden om routinematig osteoporose-screening uit te voeren om de zorg voor oudere patiënten met densfracturen te verbeteren. Historische zorgen voor de gevaren van onderbehandeling – zoals secundaire fractuurverschuiving met als gevolg ruggenmergletsel – kunnen als ongegrond worden beschouwd, aangezien geen van de patiënten in dit proefschrift dergelijke complicaties heeft ondervonden. Hoewel chirurgen deze resultaten mogelijk als rechtvaardiging zien om hun gebruikelijke behandelwijze voort te zetten, moeten zij zich ervan bewust zijn dat vergelijkbare resultaten kunnen worden bereikt met behandelmethoden die minder belastend zijn voor de patiënt en mogelijk minder kostbaar zijn. Daarom moeten chirurgen prioriteit geven aan het minimaliseren van deze belasting door het vermijden van agressievere behandelingen die de uitkomsten niet verbeteren en mogelijk extra risico's introduceren. Het voorgeschreven behandelregime zou de patiënt zelfs meer kunnen schaden dan de fractuur zelf.

APPENDICES

LIST OF PUBLICATIONS

Peer-reviewed articles

Huybregts JGJ, Jacobs WCH, Van Haaster LWF, Ruitenbeek EK, Arts MP, Osti M, Slooff WBM, Öner FC, Gulati S, Appelman-Dijkstra NM, Steyerberg EW, Lycklama à Nijeholt GJ, Peul WC, Vleggeert-Lankamp CLA. Hounsfield unit measurements to predict odontoid fracture union in elderly patients: a subgroup analysis from an international prospective comparative study. *Spine J. 2025 May 7:S1529-9430(25)00235-9.*

Omara C, Lebouille-Veldman AB, Yearley AG, Withers J, Karimi H, Steinbuchel EJ, Arora H, Kilgallon JL, Johnston BR; Gerstl JVE, Kryzanski JT, Mekary RA, Groff MW, Riesenburger RI, **Huybregts JGJ**, Smith TR, Vleggeert-Lankamp CLA, Florman JE. Safety of non-osseous union of type II odontoid fractures – a multi-institutional cohort study. *Spine J. 2025 Mar 26:S1529-9430(25)00166-4.*

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Polak SB, **Huybregts JGJ**, Zwartbol MHT, Hammer S, Lycklama à Nijeholt GJ, Broekman MLD. Uw diagnose? *Tijdschr Neurol Neurochir 2021;122(2):84.*

Geers NC, Zegel M, **Huybregts JGJ**, Niessen FB. The influence of preoperative interventions on postoperative surgical wound healing in patients without risk factors: a systematic review. *Aesthet Surg J. 2018 Oct, 15;38(11): 1237-1249.*

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Huybregts JGJ, Jacobs WCH, Vleggeert-Lankamp CLAM. The optimal treatment of type II and III odontoid fractures: a systematic review. *Eur Spine J. 2013 Jan, 22(1):1-13.*

Awards related to this thesis

- Dutch Spine Society (DSS) Award 2024
- Best Abstract Award in Spinal Neurosurgery at European Association of Neurosurgical Societies (EANS) Sofia 2024
- 3rd Best Abstract Award at Cervical Spine Research Society (CSRS) Chicago 2024

Invited lectures related to this thesis

- Dutch Society for Neurosurgery Annual Meeting 2024, Den Bosch, The Netherlands
- Norwegian Society for Neurosurgery Annual Meeting 2024, Oslo, Norway
- German Society for Neurosurgery 75th Annual Joint Meeting 2024, Göttingen, Germany
- EANS Webinar, March 2024
- EUROSPINE Spine Tuesday Webinar, March 2022

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Jeroen Huybregts was born on November 30, 1988, in Willemstad. He obtained his high school gymnasium diploma from Norbertuscollege in 2007. After studying Liberal Arts and Sciences for one year at University College Roosevelt, he commenced medical school at Leiden University in 2008.

In 2011, driven by a combined interest in surgery and neurology, Jeroen started working as a student researcher in the department of neurosurgery at the Leiden University Medical Center (LUMC). His research on treating odontoid fractures in the elderly led to several national and international studies, culminating in this PhD thesis.

During medical school, he organized national medical conferences as a board member of the Medisch Interfacultair Congres (Jaarbeurs Utrecht, 2011) and the Symposium Experimenteel Onderzoek Heelkundige Specialismen (Stadsgehoorzaal Leiden, 2015). He also completed clinical internships in Dhaka, Bangladesh, and Paramaribo, Suriname.

After graduating from medical school in 2015, Jeroen participated in a transatlantic sailing voyage from Sint Maarten to the Netherlands, as both a sailor and the ship's doctor. He subsequently began his neurosurgery residency at Haaglanden Medical Center (HMC) and LUMC, where he continued his scientific work alongside clinical training until completing his residency in 2023. From 2020 to 2023, he served as a resident board member of the Dutch Spine Society.

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