Cervical spine deformity in patients with rheumatoid arthritis: from prevention to prediction

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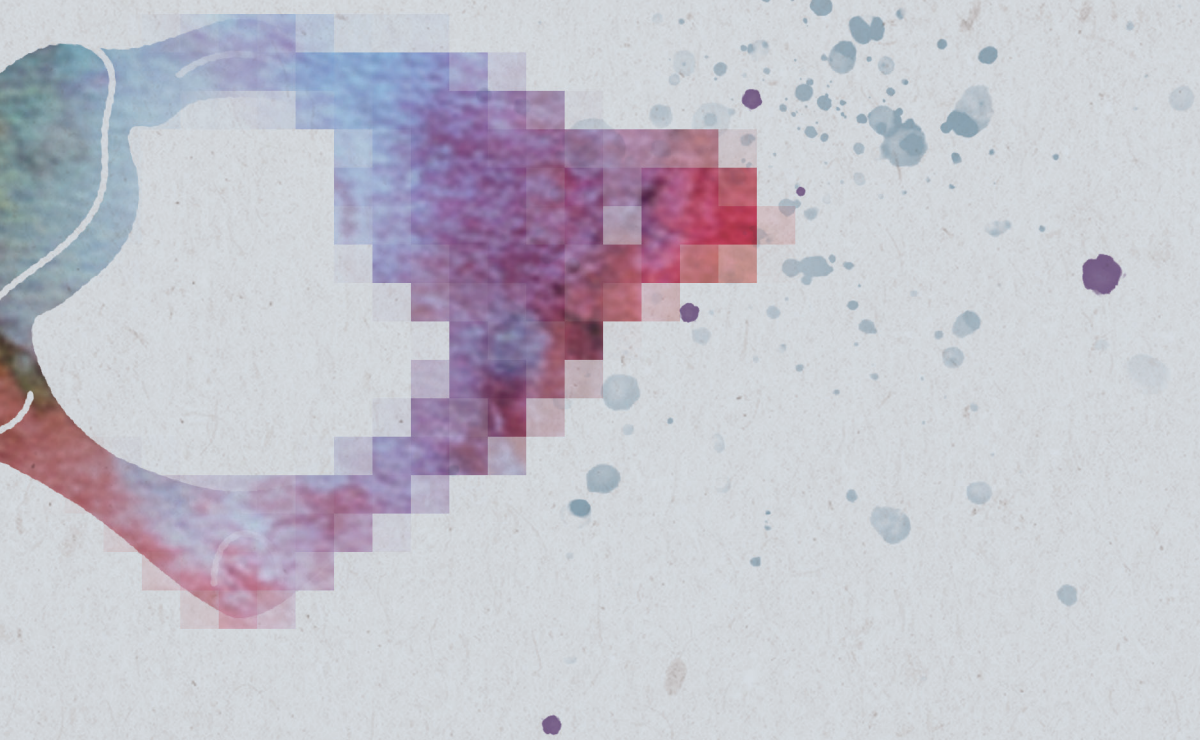

CHAPTER 9

Discussion and conclusions

In the care plan for patients with rheumatoid arthritis, the use of disease activity scores such as DAS44 play a large role in determining effectiveness of treatment and treatment strategy. This "treat to target strategy" using DAS44 has been proven to lead to higher rates of remission, defined by a low DAS44.[1] In joints such as hands and feet, literature shows that higher DAS correlates with higher prevalence of joint damage. This supports the idea of a "treat to target strategy" using DAS44. While the association between DAS and joints in hands and feet was researched extensively, the literature concerning the correlation between DAS and RA-associated deformity in the cervical spine is minimal. A systematic evaluation of literature **(Chapter 2)** did not provide us with a satisfactory answer to the question whether control of systemic disease activity in rheumatoid arthritis also prevents RA-associated cervical spine deformity, besides damage to other joints. In the scarce literature on this topic, the overall picture suggested that disease activity, represented by DAS, in RA patients with cervical deformity was higher than in those without deformities. However, reported differences were small, statistics were repeatedly lacking, and, most importantly, RA associated cervical deformity was evaluated to be correlating to DAS at one timepoint (cross-sectional) or at final follow-up. It would be much more relevant to evaluate the course of the DAS during a longer time span. Moreover, it was repeatedly reported that both groups of patients (with and without cervical deformity) had a high DAS at final follow-up. For example, in the study of Blom et al. a significant difference was observed between a mean DAS of 3.36 after 9 years of follow-up in the group without radiographic progression of cervical spine deformity, versus a mean DAS of 4.46 in the group with radiographic progression. These values are both defined as high (DAS> 2.4) and one could argue that therefore in both groups RA induced inflammation is high and that detrimental effect on the cervical spine is occurring in both groups.

Another observation from literature is that data suggest that lowering DAS values did not halt progression once cervical spine deformity was present. Three studies reported on patient groups that had been suffering from RA for more than 10 years. In the study of Kaito et al. it was shown that 81-86% of the patients with cervical spine deformity demonstrated progression although the mean DAS28 at final follow up was 2.6.[2] The other two studies showed similar results. This result is counterintuitive, since the number of patients presenting in practice with (severe) RA-associated cervical spine deformity is decreasing.[3] The observed discrepancy between clinical practice and existing literature may be attributed to the limited body of research on this topic: only very few studies evaluated progression of cervical spine deformity in RA, and those

that did studied small groups of patients, potentially inducing statistical power issues. Additionally, it is possible that cervical spine deformities are more prevalent than reported and go undetected in clinical settings, particularly if patients were screened less in case of low disease activity. Another explanation may be that patients do not present to the clinic because of an absence of clinical complaints from their cervical spine deformity. Furthermore, differentiating between hand dysfunction due to peripheral joint damage from RA and neurological deficits resulting from cervical myelopathy remains challenging, potentially leading to under recognition of cervical spine deformity. Finally, it could be true that a treat to target strategy with DAS as a determinant parameter is not the optimal strategy to prevent cervical deformity.

Das and cervical spine deformity

Since DAS is generally used as part of a treat to target strategy in the Netherlands, it was surprising that the relation between DAS values and deformity in the cervical spine was not set in stone. To further investigate the relation between DAS and radiographic cervical spine deformity, data from a Dutch randomized controlled trial (RCT), the BeSt Trial, was used. We expected that the number of patients showing deformity in the cervical spine would be very low in this group of patients, since the BeSt Trial included patients with early onset RA and randomized the patients to receive intensive treatment, targeted towards low DAS values. Medication was added, tapered or stopped based on DAS values, which were measured every three months. All with the goal of reaching remission and thereby preventing radiographic joint damage.

To assess cervical spine deformity, we first had to retrieve cut off values for AAS, VT and SAS from literature to decide what is a value that we can consider as pathological. This was, however, challenging, since there are many possible definitions known in literature. Some studies use neutral X-rays, while others prefer flexion-extension radiographs, MRI or CT scans. The severity that is 'necessary' for a radiographic distance to be deemed abnormal is ambiguous. On the one hand, we wanted to be as complete as possible and be very strict, which led to a 2 mm cut-off for AAS and SAS. On the other hand, we felt the need to distinguish between this 'mild' form of cervical spine deformity and the patients with more severe damage. Therefore, we chose to perform multiple analyses for different outcomes, specified by different definitions: any cervical spine deformity (AAS and/or SAS > 2 mm); AAS ≥ 3 mm in flexion; AAS ≥ 5 mm in

flexion or neutral. All patients who met the inclusion criteria were included in the group for any cervical spine deformity. The group for 3 mm consisted of patients who had flexion radiographs and excluded patients who only had neutral X-rays, since it would not be possible to exclude AAS of 3 mm or more in flexion only with a neutral X-ray. The group with AAS ≥ 5 mm included all patients again, since this deformity is so severe that it would be visible on both neutral and flexion X-rays. We aimed to study the subgroup with more severe deformity carefully to identify baseline characteristics of the patients prone for developing RA associated deformity. However, this group was only small and that made it difficult to reach the statistical power needed to draw conclusions. We thus chose to report outcome data in the three patient groups separately to be as complete, informative, and robust as possible.

Using these parameters, to our surprise, it was observed that 40% of the patients in the BeSt Trial had cervical spine deformity (defined as AAS and/or SAS >2 mm), and 3% even had severe cervical spine deformity (AAS 5 mm or more) (**Chapter 3**). It was remarkable that patients with well-managed DAS and intensive treatment still had RA-associated cervical spine deformity.

In addition to this variability in definitions for pathological findings on cervical spine X-rays of RA patients, the relationship between radiographic abnormalities and clinical manifestations of cervical spine involvement remains poorly understood. In the BeSt Trial, unfortunately, no clinical parameters specifically aimed to assess medullary deficits or spine related pathology were used. The only relevant clinical outcome available was the health assessment questionnaire (HAQ), which we analyzed in relation to the presence of cervical spine deformity in *chapter 3*. This analysis demonstrated that patients with cervical spine deformity had a significantly higher HAQ score (0.65 on a scale from 0-3; indicating worse function) at 10 years than patients without cervical spine deformity (0.51; p=0.04; 95% CI: -0.29 to -0.00). We would however prefer correlating the radiological abnormalities in the cervical spine to clinical outcome instruments such as the Neck Disability Index (NDI), Visual Analogue Score (VAS) for neck pain or an adjusted Japanese Orthopaedic Association (mJOA) score. These instruments would likely offer more precise insight into the functional impact of cervical spine involvement in RA.

The absence of these questionnaires from the data of the BeSt Trial illustrates the difficulty of developing and maintaining an elaborate database of patients with RA, a

task that necessitates collaboration across multiple medical specialties. It would require a collaboration between rheumatologists and spine surgeons, often including other specialists such as endocrinologists as well. Spine surgeons are very likely to combine research efforts with spine surgeons in other hospitals, but, in order to collect data on a large cohort of RA patients, every participating hospital needs a good collaboration with rheumatologists to collect large amounts of data. While this is definitely possible and would improve the quality of RA research, this is not as natural in all hospitals. The presence of a pleasant cooperation between these three medical specialties in the Leiden University Medical Center allowed us to conduct the previous studies. This enables us to have a pioneering role in establishing further studies with larger groups of patients, which would increase our statistical power and strengthen the conclusions drawn from our research.

As shown in *chapter* 3, our study found no significant differences in the mean DAS values, measured over a period of ten years' time, of the patients with and without cervical spine deformity. Given that previous literature has established a linear correlation between DAS and radiographic progression of RA associated deformity in other joints such as hands and feet[4], we hypothesized that the relationship between DAS and cervical spine deformity may not have been appropriately captured in our study. Therefore, we concluded that possibly the mean DAS was not the best way to research a possible correlation with cervical spine deformity. To address this, we also studied the DAS value at the end of follow-up and a mean DAS value, measured over 3 years' time, early in the follow-up period. A continued lack of association between DAS and cervical spine deformity led us to consider the possibility that structural damage in the cervical spine may be driven by fluctuations in disease activity over time, rather than by mean disease activity levels.

Therefore, a study was performed to report the effect of flares in DAS on the prevalence of cervical spine deformity during the 10 years of follow-up in the BeSt Trial *(chapter 4).* Flares were defined as a DAS > 1.6 after DAS had been below 1.6 for at least 6 months (sustained remission). This was an important clinical timepoint in the BeSt Trial, since medication could be tapered and stopped if sustained remission was reached. If a flare happened, medication would be restarted. In this study, in which we hypothesized that the variability in DAS in RA patients played a role in the development of cervical deformity, no unequivocal association between flares in systemic disease activity and deformity could be demonstrated either. However, there was a

trend towards a lower odds of cervical spine deformity in patients with 3 or more flares. This was remarkable and very contra-intuitive, since it would be expected that the patients with cervical spine deformity would have experienced more flares and not less.

A possible explanation was the fact that the medication regimen was intensified at every time DAS flared up. This was done with a high adherence (86%) to protocol [5] Along that line of reasoning, patients with more flares are more frequently subjected to intensified anti-rheumatic medication. We hypothesize that medication such as infliximab is very effective in preventing or halting cervical deformity and that this effect is not one-on-one represented by a response in DAS values. Even more so, we believe that treat-to-target strategy using only DAS might not be the safest option to protect the cervical spine in RA. Therefore, we switched our focus towards the reported use of medication by patients in the BeSt Trial.

The effect of medication

Immunosuppressive agents

We suspected that the trend towards less flares in patients with cervical spine deformity after 10 years, as shown in *chapter 4,* might be caused by patients use of infliximab. Infliximab was part of all treatment strategies in the BeSt Trial, only with a different place in the treatment intensification steps for all strategies. Therefore, some patients used infliximab for longer periods of time and some patients never used infliximab. This made the BeSt Trial population suitable for studying the effect of infliximab, even though we realized that the possible positive effect of infliximab could be overruled by the regimen that infliximab was particularly given to patients with the highest systemic disease activity.

In *chapter 5*, it was observed that a one-year increase in duration of infliximab was associated with a statistically significant 11% reduced odds of the presence of cervical spine deformity after 10 years (OR: 0.89; 95% CI: 0.81-0.98; p=0.02) after adjustment for the potential confounders age, gender, DAS at baseline, ACPA-status and RF-status. For patients with AAS ≥ 3 mm in flexion, the OR was 0.95 (95% CI: 0.81-1.14; p=0.64) and for patients with severe cervical spine deformity (AAS ≥ 5 mm in flexion or neutral), the OR was 0.91 (95% CI: 0.66-1.25; p=0.56). However, the number of

patients in the sub analyses was small and this may have caused underpowerment and as a consequence absence of significance. As mentioned earlier, there could be an underestimation of the true effect of infliximab use as the patients who received infliximab were patients who had higher disease activity. These results confirmed our hypothesis that infliximab use lowers the odds of cervical spine deformity after long-term follow-up. This could be part of the explanation for the decrease in surgical interventions for cervical deformity over the past decades as described in literature.[3]

It seems that biologicals such as infliximab have a great protective effect on the joints of RA patients. Therefore, one might consider giving these medications to many more patients for a long period of time. An argument against this policy is that the costs of the biologicals are very high. Literature has shown that the cost-effectiveness of biological DMARDs for improvement of quality of life (based on systemic DAS values) is questionable in comparison to conventional DMARDs.[6] However, the cost-effectiveness for patients with the worst prognoses (subgroup analysis) does meet current accepted levels.[6] The severity of the prognosis is based on DAS values, which might be a poor predictor for the presence or absence of cervical spine deformity. Therefore, in cases of cervical spine deformity where high costs of treatment are involved, the costs of biological DMARDs for prevention may be cost-effective.

Another argument against more permanent use of infliximab for a larger cohort of RA patients is the possible adverse events that come with the use of biologicals. A systematic review showed a statistically significant increase in the occurrence of any infections (20%), serious infections (40%) and tuberculosis (250%) for the use of anti-TNF biological DMARDs with moderate strength evidence.[7] In our own study, the occurrence of adverse effects was limited and did not show a statistically significant increased risk for infections in the long-term users of biological DMARDs. This was in agreement with a meta-analysis published in 2009, where no statistically significant differences were observed in adverse events, serious infections, malignancy and deaths.[8]

The concern for the risk for infection has emerged again during the COVID-19 pandemic. In a study on the COVID-19 global rheumatology alliance physician registry, it was observed that the severity of COVID-19 was worse in patients with RA who were treated with rituximab, a B-cel depleting agent, or JAK inhibitors, compared to patients on TNF-inhibitors.[9] However, a different study showed that patients who took TNF inhibitors were significantly higher at risk of COVID-19 infection than patients taking

rituximab.[10] The differences between TNF-inhibitors and other biological DMARDs such as rituximab are explained by the fact that each biological has a different target in the immune system. It might be that the inhibition of some specific 'targets' cause the immune system to be less active against infections like COVID.

Glucocorticoids

Glucocorticoids are known to cause fractures and osteoporosis, if used for long periods of time during life. Even though glucocorticoids are known to be beneficial to erosions in the hands and feet of patients with RA[11,12], we hypothesized that glucocorticoids might have a negative effect on the cervical spine. This is based on practice and on literature, where mostly negative effects of glucocorticoid use on the cervical spine were previously reported.[13-15]

We studied the glucocorticoid use of the patients in the BeSt Trial *(Chapter 6),* and observed an association between both the duration and the total cumulative dose of glucocorticoids with cervical spine deformity. After adjustment for potential confounders including age, gender, DAS at baseline, ACPA-status and RF-status, a one-year increase in duration of glucocorticoid use was associated with a statistically significant 19% increased odds for the presence of any cervical spine deformity (AAS and/or SAS > 2 mm) after 10 years (OR of 1.19; 95% CI: 1.03-1.38; p=0.02), a non-statistically significant 24% increased odds (OR: 1.24, 95% CI: 0.92-1.67; p=0.16) for the presence of moderate or severe cervical spine deformity (AAS ≥ 3 mm in flexion) and a statistically significant 57% increased odds (OR: 1.57, 95% CI: 1.09-2.28; p=0.02) for the presence of severe cervical spine deformity (AAS ≥ 5 mm in flexion or neutral).

While it was hypothesized that this was influenced by the possibility that patients with higher DAS received more glucocorticoids, while also having a more aggressive disease, adding average DAS during 10-year follow-up did not materially change the odds ratios and their 95% confidence intervals for each of the three outcomes. These results indicate that the use of glucocorticoids for prolonged periods of time is not preferable with regards to cervical spine deformity. Therefore, it is very important that caution is used in prescribing glucocorticoids for long time periods in patients at risk for developing cervical spine deformity. This conclusion is in line with the new protocol published by the American Society of Rheumatology, where they suggest that in most cases adding a new DMARD or biological is a better option than starting the use of a glucocorticoid.[16] Their advice was based on other risks of prolonged glucocorticoid

use in literature, such as osteoporosis risk, fracture risk and risk of heart disease.[17-20] Determining which patients are at risk for cervical spine deformity, however, remains a challenging task. The use of, for example, deep learning to predict cervical spine deformity early could be valuable here, which we will elaborate on further in this chapter.

This is a large shift away from previous common treatment strategies, where the place of glucocorticoids was much larger. For example, in 2010 the EULAR recommendations still advised to include a short-term treatment with glucocorticoids.[21] This in contrast to the most recent guidelines from the ACR, where it is stated that "The toxicity associated with glucocorticoids was judged to outweigh potential benefits."[16] This statement is based mostly on the status in peripheral joints, but the results in this thesis demonstrated that this statement is also true for the cervical spine. There is, however, still a place for short-term glucocorticoids as a bridge to alleviate symptoms until DMARD therapy is effective in patients with moderate to high disease activity. This is advised to be limited to the lowest effective dose for the shortest duration possible. The ACR strongly recommends against long-term glucocorticoid therapy of 3 months or longer, based on its toxicity.[16] These recommendations indicate that the place of glucocorticoids has been mostly replaced by conventional and biological DMARDs in the treatment of RA. Our results suggesting that prolonged used of glucocorticoids impacts the cervical spine negatively, strengthens this recommendation with regards to the cervical spine. Therefore, especially in patients at risk for developing cervical spine deformity, I would not suggest glucocorticoid treatment.

Screening based on X-ray images

Since it has been shown in the previous chapters of this thesis that RA-associated cervical spine deformity still exists, even in this time of biological DMARDs, it is important that patients with cervical spine deformity can be identified easily and quickly. Especially since literature indicates that once cervical spine deformity exists, it is difficult to stop progression.[22] Grading X-rays to determine presence or absence of cervical spine deformity takes extended periods of time of experts. Therefore, it would be beneficial for the early detection of RA-associated cervical spine deformity to use screening methods that use artificial intelligence. This would make it possible to screen more X-rays in a more standardized matter.

In *chapter 7,* the results of an experimental study to develop a novel automated segmentation model of the cervical spine of patients with RA was performed. The goal of this study was to automatically label the C1 and C2 vertebra using machine learning. Three experiments were performed with several types of labels and different types of convolutional neural networks (CNNs). Dice scores, which are used to express the similarity of the predicted segmentation compared to the manual segmentation provided to the model, ranged from 0.67 to 0.83. However, the best visual comparison was reached using the interstice of C1 and C2, which resembles the atlantodental interval, instead of the vertebrae themselves.

While this is one of the first studies to attempt the development of a segmentation algorithm for C1 and C2 in patients with RA, this method was not very promising. In the area where C1 and C2 are located, especially on X-ray, there is too much over projection of other structures to label the vertebrae reliably. Also, since the atlantodental space is very small, incorrect labeling of this interval would cause inaccurate classification in a model that would use the interstice of the C1 and C2 vertebrae. This would lead to a loss of its worth for screening and research purposes.

A more promising segmentation algorithm, therefore, would be of the subaxial cervical spine. In this area, over projection is less present and it is easier for an algorithm to learn to label the individual vertebrae. We have been working on a segmentation algorithm, using deep learning. In future research, this model can be further developed in a classification model to detect the difference between two adjacent vertebra and therefore to screen for SAS. Also, other factors showing deformity in the subaxial spine, such as osteophytes should be integrated in this model to provide a tool to screen for the presence of deformity. If this model could 'flag' the patients with deformity, their imaging can be further evaluated by an expert to determine the deformity present and to decide on possible interventions if necessary.

To further develop this model, more imaging is necessary in order for the model to be trained in the best way possible. This would potentially lead to an increased number of patients undergoing X-rays of the cervical spine now, while it provides us with the opportunity to practice personalized medicine once an automated segmentation algorithm is developed.

Predicting rheumatoid arthritis in the cervical spine

While early detection and screening are important goals in the management of RA, the ability to predict cervical spine deformity before its onset would represent a significant advancement in patient care. As talked about in the introduction of this thesis, deep learning can be used for this goal. In *chapter 8,* a novel deep learning-based algorithm was developed to predict the development of RA-associated cervical spine deformity form MRIs acquired at or before initial RA diagnosis.

Two hundred twenty patients were included in this study, of whom 33 patients developed cervical spine deformity. One-hundred-fifty-three patients were included for training and 67 for validation of the deep learning-based prediction model. The performance of the model was noteworthy, with an accuracy of 0.84. Of the 67 MRI scans in the test set, fifty-seven cases were predicted accurately. Seven scans were incorrectly predicted as positive, and three scans were incorrectly predicted as negative for the development of RA-associated cervical spine deformity, resulting in a sensitivity of 0.75 and a specificity of 0.87.

While this deep learning model performance is already satisfactory, it is not suitable yet to use it in a clinical setting. In order to be able to use this tool, it needs to be validated on an external dataset of MRI scans from patients of a different hospital. Future research should focus on large-scale validation of this model across diverse clinical sites.

Also, it would be very important to make the model more accessible to clinicians and make it user friendly. There is a large gap between the develop of algorithms and the practical implementation of these models. The current model needs to be operated by a computer scientist, which shows that extensive steps need to be taken towards a platform that can be used by a neurosurgeon in clinic to quickly assess the risk for an individual patient.

In this study, we used saliency maps to highlight areas of the imaging used that were most influential for the model's prediction. The saliency map is displayed as a 'heat map' covering the original MRI scan, with its color intensity indicating the 'importance' of the area for the model. Saliency maps created during the development of the deep learning algorithm showed us interesting results. While the efficacy and

trustworthiness of saliency mapping has not yet been determined[23], it was interesting to observe that the saliency maps derived from our model suggest that degeneration of the subaxial cervical spine was important for decision making of the model. The hypothesis rises that subaxial changes in the cervical spine could lead to deformities at the level of the craniocervical junction, because of increased laxity and movement in the subaxial spine. Further research on this hypothesis is granted, since it could help us understand the exact pathogenesis of cervical spine deformity in RA patients. Especially since in other studies we found no correlation between DAS and the cervical spine, it might be true that the pathogenesis of RA and its progression might be different in the cervical spine. RA causes laxity of the ligaments and causes degeneration of cartilage, but it is not clear why the cervical spine might develop and progress joint damage differently than other (peripheral) joints. It could be the case that the intricate system of ligaments and bones in the cervical spine is more sensitive to instability than other joints such as hips and fingers. However, this is something currently not fully determined in literature. It would be very helpful in terms of prediction and prevention of cervical spine deformity in RA to know what the exact pathogenesis is and why some patients develop instability and others do not.

Future research directions

Next steps in research on the cervical spine of RA patients should be focused on several aspects. First, it is important to further study the definition of cervical spine deformity. Which is a clinically relevant and significant atlanto axial distance that we should consider 'abnormal'. Of course, this will be difficult to standardize as the complaints will differ between patients and the surgical interventional threshold will defer between countries and even between surgeons. It could be useful to create a linked scale to incorporate both radiological evidence of cervical spine deformity and clinical complaints to score the severity of cervical spine involvement. This could help specialist create a more universal cut-off for surgical indications, especially since the correlation between radiological deformity and clinical complaints is not known exactly.

An important part of this is to further study the clinical complaints patients experience. Which complaints to patients have with certain types of deformity and how can we identify these early? This could be done in a recall of the patients in the BeSt Trial for example, using standardized instruments such as the mJOA or the NDI.

However, these scales might not be as trustworthy to assess cervical myelopathy in RA patients as they assess function of the extremities to grade cervical myelopathy. These functions might already be impaired in RA patients, since their peripheral joints will also be impaired by the disease. The NDI is more elaborate and also integrates pain and functioning in other terrains than the mJOA, which would make it more fitting. However, it will remain difficult to separate complaints of the extremities caused by joint damage from RA itself from neurological deficits caused by cervical myelopathy in the cervical spine of RA patients.

Aside from these clinical goals, steps should be made towards the use of automated segmentation in the clinic for increasing the speed of research and for creating the possibility to screen the cervical spine of patients with RA. In order for this to be possible, the number of X-rays available should be increased and the model should be externally validated using X-rays of other institutions. Another option might also be to decrease the use of X-rays to screen and use different imaging modalities such as MRI to screen patients early in their disease and determine their risk of cervical spine deformity and the need to screen. MRI is more suited to detect inflammation, since it captures the soft tissues better than X-ray for example. This might catch inflammation in RA earlier, before instability is visible on X-ray. However, MRI scanning is expensive and time consuming. The cost-effectiveness of MRI compared to X-ray and CT for screening should be studied further to determine the best screening modality.

With regards to prediction of cervical spine deformity, it would be interesting to externally validate the deep learning model developed in this thesis. Also a more user-friendly interface should be used for the model to be clinically applicable. This will always be a difficult point, since the integration of artificial intelligence in the decision making of medical specialists is controversial. We do expect that the implementation of artificial intelligence in medical practice will increase even more than it already has in the past years. This could lead to the integration of models like ours in medical scribe systems, which would make it worthwhile to use our model for the large number of patients with RA seen in the clinic. Aside from the need for a user friendly platform, a large amount of data is needed to be able to create a trustworthy model. Our model should be externally validated using many MRIs of patients with RA. The challenge in this case is, however, that RA develops slowly and it would take many years to collect baseline and follow-up MRIs with enough follow-up in between. This strengthens the need for international databases containing imaging and clinical data of patients

worldwide, to speed up this process and give us the ability to externally validate this model and start its implication. These databases could contain anonymized imaging of patients and their clinical information, such as treatments and disease activity scores. This model could eventually be used to better inform surgeons, rheumatologists and patients on a patients' individual risk factors and make the decision making process to decide on therapy goals and possible surgeries supported.

Conclusions

1) A systematic evaluation of literature did not provide us with a satisfactory answer to the question whether control of systemic disease activity in rheumatoid arthritis also prevents RA-associated cervical spine deformity, besides damage to other joints.
2) Many possible definitions of RA associated cervical spine deformity are known in literature. Some studies use neutral X-rays, while others prefer flexion-extension radiographs, MRI or CT scans. The severity that is 'necessary' for a radiographic distance to be deemed abnormal is ambiguous.
3) The relationship between radiographic abnormalities and clinical manifestations of cervical spine involvement remains poorly understood.
4) In the BeSt Trial, 40% of patients had cervical spine deformity (defined as AAS and/or SAS >2 mm), and 3% even had severe cervical spine deformity (AAS 5 mm or more) It was remarkable that patients with well-managed DAS and intensive treatment still had RA-associated cervical spine deformity.
5) Our study found no significant differences in the mean DAS values, measured over a period of ten years' time, of the patients with and without cervical spine deformity.
6) It was observed that a one-year increase in duration of infliximab treatment was associated with a statistically significant 11% reduced odds of the presence of cervical spine deformity after 10 years (OR: 0.89; 95% CI: 0.81-0.98; p=0.02) after adjustment for the potential confounders age, gender, DAS at baseline, ACPA-status and RF-status. For patients with AAS ≥ 3 mm in flexion, the OR was 0.95 (95% CI: 0.81-1.14; p=0.64) and for patients with severe cervical spine deformity (AAS ≥ 5 mm in flexion or neutral), the OR was 0.91 (95% CI: 0.66-1.25; p=0.56).
7) After adjustment for potential confounders including age, gender, DAS at baseline, ACPA-status and RF-status, a one-year increase in duration of glucocorticoid use

was associated with a statistically significant 19% increased odds for the presence of any cervical spine deformity (AAS and/or SAS > 2 mm) after 10 years (OR of 1.19; 95% CI: 1.03-1.38; p=0.02), a non-statistically significant 24% increased odds (OR: 1.24, 95% CI: 0.92-1.67; p=0.16) for the presence of moderate or severe cervical spine deformity (AAS ≥ 3 mm in flexion) and a statistically significant 57% increased odds (OR: 1.57, 95% CI: 1.09-2.28; p=0.02) for the presence of severe cervical spine deformity (AAS ≥ 5 mm in flexion or neutral).

8) Artificial intelligence could prove to be helpful in identifying patients at risk for cervical spine deformity after external validation on a large scale.

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