Impaired spinal stability in fractures and metastases of the thoracolumbar spine

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Therapeutic and prognostic aspects for decision making and management of fractures and metastases of the thoracolumbar spine.

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Verminderde spinale stabiliteit bij fracturen en metastasen van de thoracolumbale wervelkolom

Therapeutische en prognostische aspecten in de besluitvorming en behandeling van fracturen en metastasen van de thoracolumbale wervelkolom.

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit van Maastricht op gezag van de Rector Magnificus, Prof. dr. Habibovic, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op 24 april 2023 des middags te 13 uur.

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Content

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CHAPTER I

Introduction and Outline

General Introduction

The spinal column comprises the vertebral column and the spinal cord and consists of 33 vertebrae with typical lordotic curves in the cervical and lumbar regions and a kyphotic curve in the thoracic region, thus forming a 'double S' shape [1]. Each vertebra has an anterior part, the vertebral body, and a posterior part, the vertebral arch. All successive vertebral arches constitute the spinal canal, which encloses the spinal cord and nerve roots (cauda equina). Each vertebral arch supports seven processes: One spinous process, a dorsal midline structure arising between the lamina, a place for attachment of muscles and ligaments. Two transverse processes, laterally at the junction of the lamina and the pedicles. Four articular processes: two superior, projecting upwards,and two inferior, projecting downwards, that participate in each zygapophyseal or facet joint above and below. The pedicles of two adjacent vertebrae form the intervertebral neuroforamina on each side, through which nerve roots exit the spinal column.

The major functions of the vertebral column are to protect the spinal cord and to form the central axis of weight-bearing and transmit body weight in walking and standing. The jointed structure of the spine allows rotation and bending. In the thoracic region, the spine provides attachment sites for ribs. The spine serves as the attachment site for multiple muscles that, help to stabilize the spine and allow spinal motion.

The definition of spinal stability by the American Academy of Orthopedic Surgeons is the capacity of the vertebrae remain cohesive in all physiological body movements [1]. Panjabi et al. defined stability as the ability of the spine under physiological loads to limit patterns of displacement that damage or irritate the spinal cord and nerve roots and to prevent incapacitating deformity or pain caused by structural changes [2-5]. According to Panjabi et al. stability of the spine is maintained by three mechanisms: (1) the active subsystem (musculoskeletal system); (2) the passive subsystem (the spinal column); (3) the neural subsystem (activation of the active system through neurological control). Mechanical stability is normally maintained by the three subsystems, while the spinal column translates and rotates around the anatomical axes, thus allowing for spinal flexion/extension, lateroflexion and axial rotation. The passive subsystem is dependent on: the vertebral morphology and bony architecture, bone mineral density (BMD), the intervertebral discs, facet joints, ligaments and physiological spinal curves.

The trabecular bone in the vertebral body plays a crucial role in strength and elasticity [6]. Vertical trabecular columns transmit forces between the endplates. The tendency of isolated vertical columns to bow is restrained by horizontal lamellae, which tension

favours the radial dispersion of forces conferring elasticity to the vertebral body. The resistance of vertebral spongiosa depends on both trabecular architecture and bone density. The spongiosa of any vertebra contains four main trabecular systems having a relative constant orientation: the vertical system between endplates which transmits axial loads, the curved system running in the neural arch, two curved systems joining the endplates with the articular and spinous processes which anchor the neural arch to vertebral body resisting shearing forces. Exponentional reduction of resistance occurs in bone loss in osteoporosis [7]. In the early stages of osteoporosis, the elective reabsorption of transverse connections leads to a progressive relative elongation of vertical columns, whose resistance decreases by the square of the length. In a later period thinning of columns contributes to a quadratic loss of strength with a summation of both effects. The bone loss in early osteoporosis is mainly trabecular bone loss in origin. With increasing age, cortical bone becomes porous and, therefore, its endocortical surface increases. The largest loss of absolute bone mass due to osteoporosis occurs in cortical bone by intracortical rather than endocortical or trabecular remodelling [8].

Part 1: Impaired spinal stability due to (osteoporotic) vertebral fractures

As a result of the aging process, bone deteriorates in composition, structure and function, which predisposes to osteoporosis. In 1994 WHO published a report in which by "Gaussian" criteria, women were classified as healthy or ill according to their bone mineral density (BMD) value, when compared with the average 30-year-old woman (T-score) as measured by Dual Energy X-ray Absorptiometry (DEXA), as the gold standard [9]. The definition of osteoporosis has changed over the years and nowadays osteoporosis is defined as "a skeletal disease characterized by decreased bone strength that predisposes a person to an increased risk of fracture". Bone strength is thereby a reflection of the integration of bone density and quality. Bone density is defined by peak bone mass and quantity of bone loss. Bone quality refers to architecture, replacement, accumulation of lesions (microfractures) and mineralization. Currently, osteoporosis cannot be defined by BMD value only, since many aspects related to trabecular microarchitecture, bone remodeling, genetic, pharmacological and other factors related to the risk of falls would be omitted [10].

Osteoporosis is a multifactorial disease of which the prevalence is steadily increasing in the general aging population, and is a major cause of mortality, morbidity and medical expenditures world-wide. Osteoporosis has been called "the silent epidemic", because its progressive bone loss develops over many decades without any obvious signs and affects about one-tenth of women aged 60, one-fifth of women aged 70, two-fifths

of women aged 80, and two-thirds of women aged 90 who are all at increased risk of fragility fractures [11]. Fractures at the wrist, hip and vertebrae are the most common sites of osteoporotic fracture. Furthermore, a previous low-trauma fracture, at any site, increases the risk of a subsequent fracture by approximately two fold in women and men [11-12].

Worldwide, approximately 200 million women have osteoporosis defined as a value for femoral neck and lumbar spine BMD that is more than 2.5 times the standard deviation (SD) below the mean value of 30 year old females (T-score less than or equal to – 2.5) as assessed on a DEXA scan[12]. Note that the BMD threshold applies to men as well as women. The T-score represents the number of standard deviations above or below the mean for a healthy 30-year-old adult of the same sex and ethnicity as the patient. In 2015, there were an estimated 20 million individuals defined with osteoporosis in the European Union (EU) [13]. Of those, 15.8 million were women and 4.2 million were men. The number of women with osteoporosis increases markedly with age. The prevalence of osteoporosis at the age of 50 years or more, as judged by femoral neck BMD, was 6.8% in men and 22.5% in women.

Age-related loss of bone and muscle mass are signs of frailty and are associated with an increased risk of falls and consecutive vertebral fractures. The clinical relevance of osteoporosis lies in the associated fragility fractures; until such an event occurs, there are usually no symptoms. Fractures at the wrist, hip and vertebrae are the most common sites of osteoporotic fracture [12-14].

Due to this high risk of subsequent fractures Fracture liaison services (FLS) are initiated. FLS have been initiated. FLS are coordinator-based models of secondary fracture prevention services, designed to identify patients who are at increased risk of secondary fractures and, following a comprehensive assessment, to ensure that patients initiate appropriate treatment via improved care coordination and communication. The provision of FLS services is recommended in guidelines for the prophylaxis of secondary bone fractures issued by the American Society for Bone and Mineral Research (ASBMR) and European League Against Rheumatism (EULAR)/European Federation of National Associations of Orthopaedics and Traumatology (EFFORT) [15-16]. However, it should be acknowledged that treatment gaps remain , and pharmacological prevention remains suboptimal. In 2013, the International Osteoporosis Foundation (IOF) initiated the promotion of FLS programs to be implemented worldwide, although their outcomes show wide variability [17].

The Spinal Section of the German Orthopedic and Trauma Society (DGOU) developed an osteoporotic fracture (OF) Classification, which is adopted by AO Spine (AO

Spine-DGOU Osteoporotic Fracture Classification System) [18]. This is a recently developed morphologic classification of the different types of OVF. The OF classification grades thoracolumbar OVFs according to morphologic and deformity components into 5 types, in progressive severity. The 5 degrees of severity range from no deformation with vertebral body edema (OF 1), deformation of 1 endplate without or with minimal minor posterior wall involvement (OF 2), deformation of 1 endplate with distinct posterior wall involvement (OF 3), deformation of both endplates with/without posterior wall involvement (OF 4), and injuries with anterior or posterior tension band injuries (OF 5). The proposed OF classification is an attempt to group the most common osteoporotic fracture types from a clinical point of view and aid in therapeutic decision making.

The majority of patients with a symptomatic osteoporotic vertebral fracture (OVF) is treated with pain medication, preventive medication, physical therapy, bracing, and occasionally pain intervention [19]. Prolonged bed rest should not be prescribed in order to avoid the hazards of further deconditioning, accelerated bone loss, and the risk of deep venous thrombosis, pneumonia, decubitus ulcers, disorientation, and depression. Although OVFs can have a detrimental impact on health and quality of life in elderly people, there is still a lack of awareness among physicians, as well as health care agencies, which results in suboptimal care with the risk of more fragility fractures and subsequent worsening of health status. The need for an algorithm in the treatment of painful OVFs is based on the often disappointing results of conservative treatment and the lack of consensus regarding pain intervention and surgery. Specifically, the debate concerning the use of percutaneous cement augmentation techniques of the fractured vertebral body is ongoing. Although in many countries percutaneous vertebroplasty (VP), balloon kyphoplasty (KP) or vertebral body stenting (VBS) are widely used in current practice their role is still controversial [20-21]. Patients affected by an OVF generally suffer from multiple morbidity and are often subjected to polymedication. Vertebral cement augmentation aims to restore the stiffness and strength of an injured painful vertebral body, normalizing pressure in the adjacent disc and load-sharing between vertebral body and arch [22]. Therefore, after proper patient selection, minimally invasive, preferably percutaneous techniques, can be considered. Vertebral cement augmentation is not only proposed in painful osteoporotic vertebral fractures but can also be combined with spinal instrumentation in high energy traumatic fractures.

Part 2: Impaired spinal stability due to spinal metastases

An increasingly encountered problem in Western society are spinal metastases in patients affected by cancer [23-25]. Primary tumors that most often lead to bone metastasis are in the order of incidence: prostate, breast, kidney, lung, and thyroid cancer. The incidence of skeletal metastasis from autopsy studies is 73% (range of 47–85%) in breast cancer, 68% (range of 33–85%) in prostate cancer, 42% (range of 28–60%) in thyroid cancer, 36% (range of 30–55%) in lung cancer, 35% (range of 33–40%) in kidney cancer, 6% (range of of 5–7%) in esophageal cancer, 5% (range of 3–11%) in gastrointestinal tract cancers, 11% (range of 8–13%) in rectal cancer. Given the high prevalence of breast, prostate, and lung cancer, they are responsible for more than 80% of cases of metastatic bone disease [26-27]. The probability that an elderly patient (60–79 years old) is affected by bony metastases compared to a middle-aged patient (40–59 years old) is four times higher in men and three times higher in women [25]. While pain is the most frequent symptom, 10% of spinal metastases patients develops weakness, sensory disturbances, bowel or bladder dysfunction, and gait disturbance [28-29]. Spinal instability may cause severe disability and neurological deficit that have major impact on patients quality of life and eventually impact on patients' survival. The Spine Oncology Study Group defined spinal instability as a "loss of spinal integrity as a result of a neoplastic process that is associated with movement-related pain, symptomatic or progressive deformity, and/or neural compromise under physiologic loads" [30]. Metastases compromise the mechanical integrity of the vertebra and make it susceptible to fracture. Patients with pathological vertebral fractures are often symptomatic, with pain deteriorating at night. Moreover, mechanical pain generally due to spinal instability or fracture may cause spinal cord compression and neurological deficits.

As the prevalence of spinal metastases has increased over the course of the last two decades because of the aging population as well as longer survival after primary tumors, spine care practitioners are increasingly confronted with the need to treat patients with this challenging medical condition. It is now estimated that as many as 70% of patients diagnosed with cancer will eventually develop metastatic spread to the spinal column [31]. The care of patients with spinal metastases is associated with high morbidity and is reported to incur high costs in the range of $40,000 to $60,000 per hospital admission [32]. In this context, clinicians must balance the individual patient's chance to benefit from an expensive and invasive intervention, against the potential of morbidity and mortality in the early post-treatment period.

Radiotherapy, either alone or following decompressive and/or stabilisation surgery, is the most frequently used treatment to control symptoms and prevent complications.

In order to provide a treatment that is optimally tailored to a patient's individual situation, it is important to estimate remaining life expectancy as accurately as possible. This can be facilitated with prediction models that constitute of diverse patient characteristics. In the ideal situation, a prognostication would compare different management options, evaluating the outcome of surgical intervention based on survival, toxicity and cost-effectiveness, and propose a more rational, objective, safe and reproducible management.

Several prediction models were published in the past years [33-37]. The Tokuhashi prediction model was introduced in 1989 and was revised in 2005 [33-34]. Tomita et al, introduced an alternative scoring system in 2001 [35]. Both Tokuhashi and Tomita address the type of primary tumor, the burden of bone secondary lesions and the presence of visceral metastases as critical prognostic factors. Tokuhashi acknowledges significance of functional parameters like ambulation, while Tomita score completely overlooks paralysis as factor for poor prognosis. Over the following years, more prediction models followed like: Van der Linden, Rades scores [36-37]. Their prognostic value and clinical relevance have been assessed in several studies, but the results have been inconsistent [38-40]. Classically, prediction models for spinal metastasis have been developed using logistic or proportional hazards regression analyses. Like in other fields of medicine, evolving computational methodologies, including machine-learning algorithms, should be assessed extensively in terms of their potential in the management of spinal metastasis. There is a need for more up-to-date prediction models to aid personalized medicine in the current era of metastatic spinal tumor treatment.

Biopsies have limitations like the inherent tumor heterogeneity and the invasive character of biopsies for patients. Radiomics has emerged as a potential solution to provide non-invasive imaging biomarkers from available routine pre-treatment images. Radiomics is a booming field in medical image analysis [41]. Radiomics is a process to extract high throughput data from medical images by using advanced mathematical and statistical algorithms. It involves various steps like image generation, segmentation of region of interest (e.g. a tumor), image preprocessing, radiomic feature extraction, feature analysis and selection and finally prediction model development. Radiomics process explores the heterogeneity, irregularity and size parameters of the tumor to calculate thousands of advanced features. The resulting features can be mined, similarly to other -omics domains, in order to identify the relevant ones. One advantage of radiomics is that it exploits diagnostic images that are available already, so it does not require additional exams (imaging or biological). Several radiomics based prediction models have been developed and reported in the literature to predict various prediction endpoints like; overall survival, progression-free survival and recur-

rence in various cancer such as brain tumor, head and neck cancer, lung cancer and several other cancer types. Radiomics based digital phenotypes have shown promising results in diagnosis and treatment outcome prediction in oncology. In the coming years, radiomics is going to play a significant role in precision oncology.

Specific research questions and thesis outline

1. Can a Fracture Liaison Service (FLS) aid in reducing subsequent fracture risk in the elderly patients (>85 years of age)?

Osteoporotic fractures and an aging population are a significant public health challenge worldwide. Our study hypothesis was formed based upon the clinical observation in our FLS Maastricht UMC, that elderly patients frequently decline the proposition of screening for osteoporosis and fall-related risk factors, but that these patients do not have more subsequent fractures than patients who participate in the screening program. The aim of this prospective cohort-study was to evaluate the subsequent fracture risk in all patients > 85 years old, comparing FLS attenders and non-attenders. The relevance of this study lies in the increased proportion of patients with a fall-related fracture in the extreme elderly.

2. What is the effect of vertebral cement augmentation in the treatment algorithm for elderly patients with symptomatic osteoporotic vertebral fractures (OVFs)?

A recent Cochrane review concluded that there is a lack of high-quality evidence to support the benefit of any minimal invasive surgical technique and even noticed a potential for harm in the treatment of OVFs. Our aim is to provide an updated comprehensive systematic review on the use of percutaneous cement augmentation, with a special focus on the frail elderly with symptomatic OVFs, using data from RCTs and prospective non-RCTs comparing percutaneous vertebroplasty (PV) or percutaneous kyphoplasty (PKP) with conservative treatment or sham procedures.

3. Does less invasive operative stabilization lead to comparable clinical outcome in the isolated and the multi-injured patient with spine fractures?

At present, the evolution of less invasive stabilization systems (LISSs) may allow surgeons to improve pain and neurologic deficit with a reduction of approach-related morbidity, thus enhancing the quality of life (QOL) for their patients. To date, several studies have described the multiple advantages of posterior pedicle screw fixation techniques in thoracolumbar fractures. However, QOL outcome data are limited for

spine trauma patients. Additionally, the role of LISSs remains unclear in treating spine fractures in polytrauma patients. The aim of this study is to describe the QOL and radiological outcome of posterior percutaneous pedicle screw fixation in the treatment of traumatic thoracolumbar fractures.

4. Is the performance of current prediction models for spinal bone metastases (SBM) good enough to be used in clinical practice?

Prediction of survival is not only crucial in counseling patients or appropriate allocation of health care resources, but also in selecting the most adequate treatment. Patients with a short expected survival (< 3-6 months) are likely to benefit most from supportive care (e.g., a short radiotherapy course), whereas patients with a relatively long expected survival may benefit from minimal invasive surgery or even more extensive surgical interventions, followed by high-dose radiotherapy including stereotactic ablative radiotherapy. Over- or undertreatment due to inadequate prognostication may have a large impact on a patient's activities of daily living, dependency and quality of remaining lifespan. Several prediction models all with their respective pitfalls, have been developed and are widely used in clinical practice. Because the performance of a prediction model is generally overestimated in the sample in which it has been developed, external validation of a model in an independent sample is crucial to broadly evaluate the performance and thus the potential utility of the model in different populations and settings. The primary aim was to externally validate two currently used prediction models. Our secondary aim was to identify additional factors predicting survival in patients with SBM.

5. Can radiomics identify textural and intensity-based features and associate them with patient survival probability or disease progression in spinal bone metastases (SBM)?

Existing prediction models lack precision, particularly in predicting which patients will survive for more than a period of 3 to 6 months and become a potential candidate for surgical treatment. Therefore, there's a significant need for new prognostic biomarkers. Radiomics offers a broad palette of imaging biomarkers that could give us more information in e.g. assessment of prognosis, prediction of response to treatment, or even monitoring of disease status. In this study we aim to compare clinical prognostic variables with SBM tumor characteristics by the use of Radiomics analysis, to analyze both clinical and radiomics scores as independent predictors in discriminating the survival of SBM patients.

6. Is it possible to create a user friendly digital prediction tool to estimate individualised survival probability for patients with spinal metastatic disease?

Many algorithms prognosticate survival for spinal bone metastases patients, although one cannot predict individual survival times from these algorithms. Furthermore, many of these algorithms are inaccurate, or are not tested in external patient samples. This is the first study aimed at developing a prediction tool with a user-friendly digital interface that could be used to reliably estimate the 1, 3, and 6-months overall probabilities of survival for patients with SBM and possibly guide in individualised patient management decisions.

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CHAPTER II

The role of the Fracture Liaison Service (FLS) in subsequent fracture prevention in the extreme elderly.

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Aging Clin Exp Res. 2019;31(8):1105-1111. doi: 10.1007/s40520-018-1054-2.

Abstract

Background: Several guidelines recommend a bone and fall-related osteoporosis risk assessment in all patients with fracture and age >50 years. In practice, however, there is no consensus whether screening >85 years is useful.

Aim: To evaluate the subsequent fracture risk in all patient >85 years, comparing the two populations of Fracture Liaison Service (FLS) attenders and non-attenders.

Methods: All patients >85 years that presented at the FLS with a non-vertebral fracture were included in the study during a 5-year period (September 2004 and December 2009). Excluded were pathologic fractures, death<30 days, or patients on osteoporosis treatment. In patients that attended the FLS, assessment of bone mineral density and fall-risk factors were screened. In both the attenders and non-attenders groups, mortality and subsequent fracture rates were scored during a follow-up of 2 years.

Results: 282 patients fulfilled inclusion criteria for screening, of which 160 (57%) patients did not attend the FLS. 122 patients were screened for osteoporosis and fall-related risk of whom 72 were diagnosed with osteoporosis. Subsequent fracture risk in both groups was 19%. Medical treatment was started in 51 patients, of which 15 patients developed a subsequent fracture. Cox-regression analysis indicated a significantly lower mortality rate, but not a diminished subsequent fracture rate in the FLS screened population compared to the non-attenders.

Conclusion: The advantage of a FLS in reducing subsequent fracture risk in patients >85 years seems to be limited. In practice a large proportion of these patients are not screened.

Introduction

Osteoporosis-related fractures are common in older patients and lead to a reduced quality of life, increased morbidity and mortality and high health costs. Untreated osteoporosis can cause fragility fractures, also termed a 'fracture cascade' or named the 'osteoporotic career' [1, 2]. Several studies indicate that having a fracture >50 years of age is associated with an increased relative risk of developing a subsequent fracture, both in men and in women. Johnell et al. found the relative risk in their population to be the highest during the first years after the event [3]. Van Helden et al. showed an absolute new fracture risk of 10.8% for any clinical fracture and the observation that 60% of these new fractures occurred within 1 year [4]. Several guidelines concerning osteoporosis have been published worldwide [5–9]. The latest update of the evidence-based guideline on osteoporosis of the Dutch Institute for Healthcare Improvement (CBO) published in 2011 recommends performing a bone densitometry and validated bone-related and fall-related questionnaires in all patients who experience a non-vertebral fracture older than 50 years of age to evaluate osteoporosis and related subsequent fracture risk [9]. The age at which a Fracture Liaison Service (FLS) no longer offers significant benefit is unknown. There's lack of evidence regarding osteoporosis treatment for patients over the age of 85. Osteoporotic fracture risk in the extreme elderly is multifactorial, and involves osteoporotic bone with poor biomechanical characteristics, side effect of medications, poor balance, difficulty mobilizing around environmental hazards with higher likelihood of falls [10–12]. The uniform approach for success is a FLS. In several countries a FLS has reduced subsequent fractures by integrating fracture care with secondary fracture prevention through management of fracture risk and low bone mass. Successful secondary prevention measures not only depend on investigation and initiation of treatment, but also on adherence and compliance of treatment, which may pose additional challenges in the very old [8]. Our study hypothesis was formed based upon the clinical observation in our FLS that elderly patients at the extreme of ages frequently decline the proposition of screening for osteoporosis and fall-related risk factor, but that these patients do not have more subsequent fractures than patients who participate in the screening program. Decreased life-expectancy and low physical demand may be potential reasons for this. Therefore, our hypothesis is that patients of extreme age (>85 years) not screened and treated for osteoporosis and fall-related risks do not have a higher subsequent fracture risk than patients screened at an age >85 years. The aim of this prospective cohort-study is to evaluate the subsequent fracture risk in all patient>85 years old comparing the two populations of FLS attenders and non-attenders. The importance of this study comes from the increased proportion of patients with fall-related fracture in the extreme elderly [10].

Methods

Study design and participants

The fracture and osteoporosis outpatient clinic was initiated in September 2004 for fracture patients aged 50 years and older treated at Maastricht University Hospital. All patients aged over 85 years with a clinical fracture, who were treated in this European level-one trauma center during a 5 year period (September 2004 and December 2009) were eligible for the study. Patients who died within 30 days were excluded, as were patients already treated for osteoporosis, patients with vertebral fractures, pathological fractures, as well as patients not currently living in the Netherlands or living in the Belgian boarder adjacent to Maastricht. Fractures were classified according to Center et al., into major fractures which include pelvis, hip, humerus, proximal tibia, distal femur and multiple rib fractures, and minor fractures which comprise all other fractures [13].

Follow-up and outcome assessment

All study subjects were followed prospectively until death or the latest clinical contact, with a maximum follow-up of 2 years. Subsequent fractures were investigated by a prospective registration and verified by examination of the radiograph reports in the 2 years after the baseline fracture. Patients refusing or not complying with the screening program were asked for the reason and follow-up was performed in this group for subsequent fracture and/or death for 2 years as standard care. In patients willing to participate a written informed consent was signed and patients received oral and written information about osteoporosis and the prevention of fall-related fractures. The assessment involved the use of a dual energy X-ray absorptiometry (DXA) scan measuring bone mineral density (BMD) in the left or right hip and the lumbar spine and a fall risk assessment. Fall risk assessment was done by measuring mobility, balance, handgrip strength, lower limb muscle strength, visual impairment, cognitive state, activities of daily living and general health measurement (blood pressure, BMI), as described previously [14]. The medical ethical committee of the Maastricht University Medical Center has approved the study and the study is conducted according to the revised version of the Declaration of Helsinki (October 2008, Seoul).

Statistical analysis

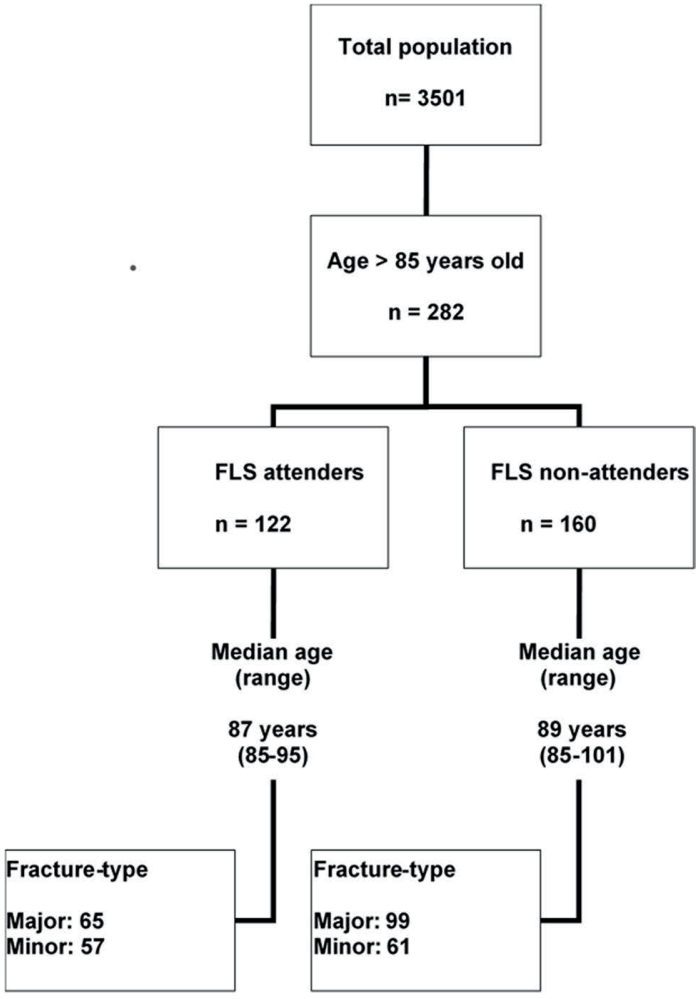
Statistical Package for the Social Sciences (IBM SPSS Statistics 20.0, Somers, NY, USA) software was used for statistical analysis. Data are presented as mean (standard deviation) if not stated otherwise. A Student's t test for continuous variables in case of Gaussian distribution and Chi-square test for categorical variables was used for comparisons of two groups. Univariate analyses of parameters were applied to identify the risk factors of subsequent fracture and mortality. Parameters with $p<0.2$ in

univariate analysis were entered stepwise into a multiple logistic regression model to identify independent risk factors for mortality. Correlated variables were entered into a Cox-regression to detect difference in subsequent fracture or mortality incidence comparing the non-screening and screening group corrected for age, gender, and fracture type as confounders. Kaplan–Meier curves and log-rank tests were used for comparison of subsequent fracture and mortality rate.

Results

Within the cohort of 3501 patients with a fracture at an age above 50 years, 282 patients sustained a fracture at an age>85 years. Of these 282 patients, 122 patients (43%) underwent post-fracture assessment by the FLS. Of the patients aged 50–85 years, compliance with the screening and treatment program was 72%. ($p<0.05$). In 160 patients (57%) aged 85 years and older no screening was performed because of dementia (32%), at the request of patients or relatives (37%), for age-related reasons ('too old') (9%), immobility (1%), other reasons (4%) and 17% did not attend their scheduled appointment without explanation. Gender (predominated by women) and the median age of patients did not differ significantly in the FLS attenders and non-attenders group. Hip-fractures and radius/ulna fractures predominated in both groups. (Fig. 1).

Fig. 1 Flowchart of patients included in the study



Risk factors for osteoporotic fractures in the screened population were multifactorial, with a high percentage of patients having risk factors. (Table 1)

Table 1 Risk factors for osteoporotic subsequent fractures in the population FLS attenders aged above 85 years.

Risk factors	*N* (%)
Bone mineral density	
Osteoporosis	72 (59)
Osteopenia	40 (33)
Normal	10 (8)
Bone-related	
Low body weight (<60 kg)	44 (36)
Severe immobility	44 (36)
Presence of a vertebral fracture	13 (11)
Positive family history	8 (7)
Use of corticosteroids	3 (2)
Fall-related	
Impaired ADL	55 (45)
Psychiatric drugs	40 (33)
>1 fall in the past year	39 (32)
Urinary incontinence	34 (28)
Impaired vision	17 (14)
Rheumatoid arthritis	1 (1)

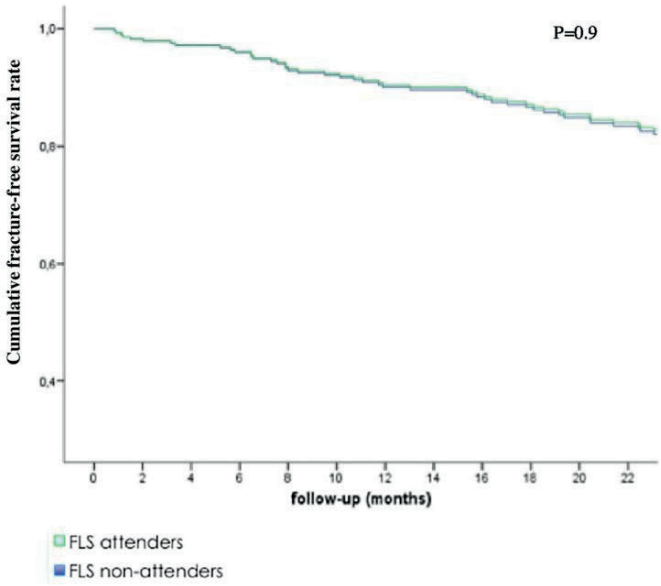
The included patients were relatively representative of their mean age. In the analysis of fall risk assessment, 36% had severe immobility problems, while 40% of the patients had balance difficulty during the Four Test Balance Scale [15]. Handgrip strength was 21.7 kg (SD 2) for women and 34.3 kg (SD 6) for men. When we compare these results with the reference values for the age of 85 years of Dodds et al., our patients match the 75th percentile [16]. In our study population 14% of our patients had visual impairment, while 18.9% of our patients had some form of cognitive problems. In the FLS attenders population 59% of the patients had a T-score ≤2.5 and 45% had a previous fracture (before the current fracture) in the history compared to 30% in the FLS non- attenders group. In the FLS attenders population 51 patients were treated for osteoporosis, 38 patients with a combination of calcium, vitamin D and bisphosphonates and 13 patients with strontium. 21 patients who were diagnosed with osteoporosis did not receive medical treatment. 11 patients had reluctancy to take any kind of treatment and 10 patients had side-effects of osteoporotic treatment.The subsequent fracture incidence for the first 2-year was 19% in both the FLS attenders and non-attenders group (p=1.0). Subsequent fracture location was predominantly at the hip region accounting for 40% of subsequent fractures in the FLS attenders group and 60% in the non-attenders group (Table 2).

Table 2 Characteristics FLS attenders and non-attenders.

	FLS attenders ($N=122$)	FLS non-attenders ($N=160$)
Median age (range, years)	87 (85–95)	89 (85–101)
Men	19 (16%)	31 (19%)
Women	103 (84%)	129 (81%)
Previous fractures (N patients)	$N=55$ (45%)	$N=48$ (30%)
Major fractures	27 (49%)	34 (71%)
Minor fractures	28 (51%)	14 (29%)
Subsequent fractures (N patients)	$N=23$ (19%)	$N=30$ (19%)
Major fractures	18 (78.3%)	23 (77%)
Hip	9	18
Vertebral	6	2
Proximal humerus	2	3
Multiple rib	1	0
Minor fractures	5 (21.7%)	7 (23%)

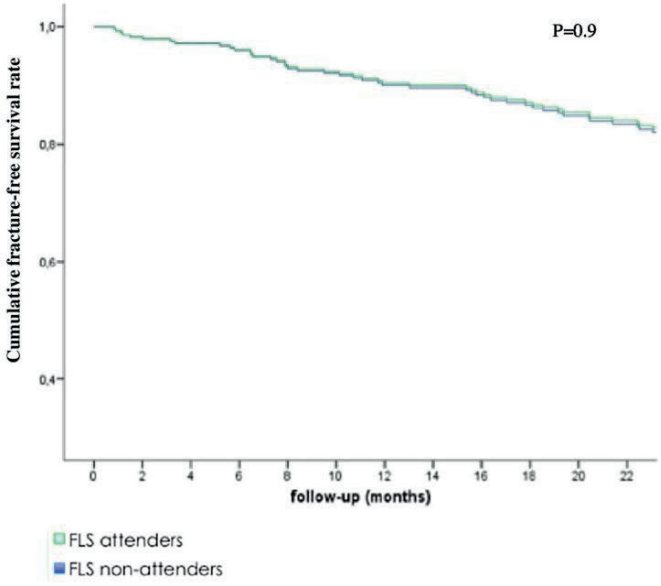
Absolute 2-year cumulative mortality was high in both groups: 27% in the FLS attenders versus 36% in the non-attenders (p=0.1). Cox-regression with adjustments for age, gender and fracture type did not demonstrate a different subsequent fracture risk in the follow-up period between the FLS attenders and non-attenders aged 85 years and older (Fig. 2).

Fig. 2 Cumulative fracture-free survival in 2 years: FLS attenders and non-attenders.



In contrast on Cox-regression analysis, there was a significant higher cumulative mortality in the FLS non-attenders group (Fig. 3).

Fig.3 Cumulative mortality in 2 years: FLS attenders and non-attenders.



Discussion

Although osteoporotic fractures and aging are a significant public health challenge worldwide, there's a paucity of evidence-based literature for the screening and management of osteoporosis in the extreme elderly. In the EU approximately 3.5 million new fragility fractures occur annually. The number of deaths causally related to fractures in 2010 was estimated at 43,000. Only in the year 2010 fragility fractures resulted in costs of €37 billion. Total costs are expected to increase to €76.7 billion in the year 2050 based on the expected changes in the demography of Europe [17, 18]. Many studies have demonstrated that advancing age is a significant predictor of increased fracture risk in the elderly [19, 20]. The human costs associated with osteoporotic fractures are numerous. Increased mortality and decreased quality of life have been well documented after hip and vertebral fractures [21–30]. The risk of sustaining a hip fracture increases with age and is highest in the oldest patient category [31]. These findings suggest that in the elderly patient>85 years a pro-active approach in the diagnosis and treatment of osteoporosis and in the prevention of fall-related subsequent fractures may have significant impact. In this study we demonstrate that an outpatient screening and treatment program for osteoporosis and fall-related risk factors for elderly patients above 85 years of age, is not associated with a lower subsequent fracture risk. Although screened patients at the extreme of ages have an associated lower mortality risk compared to patients who do not undergo this screening and treatment protocol. Our study follow-up period of 2 years is shorter than other comparable studies, which can be a limitation. However, past studies of van Helden et al. and Center et al. already showed that the highest incidence of subsequent fracture rate is within 2 years of the initial fracture [13, 14]. Therefore, we chose to maintain our follow-up period. Our study also shows that in daily practice there are problems in implementing the guidelines in patients at the extremes of age, with a significant lower compliance rate in this age category compared to the younger patients. In practice other factors, besides the sustained fracture and subsequent fracture risk influence the decision to initiate osteoporosis screening in the elderly. In a large proportion of the patients reduced physical and mental capability was the reason for not attending this screening program. Indeed, mortality rate in the non-screened population corrected for age, gender and fracture type was higher than the screened population, probably indicating the severity of the co-morbidities. This may be a confounding factor. FLS may not have had an impact on mortality, rather the population with co-morbidities and higher mortality risk may not have attended. Apparently, implementation of these guidelines in the elderly is also dependent on factors, such as the inability or unwillingness to come to the outpatient department. In addition, there is lack of persistence to the prescribed treatment after the screening has indicated the presence of osteoporosis. There is evidence to suggest that non-persistence is more critical than

non-compliance, with more than 90% of the clinical burden of poor adherence resulting from non-persistence [32]. In our study, for the 51 patients in which osteoporosis treatment was prescribed, we found that only 27 patients (63%) were persistent to their prescribed therapy at 1 year, and only 22 patients (51%) were persistent at 2 years. In eight patients (15.7%) we could not find any information about medication persistence, because of changed conditions. Improving adherence with osteoporosis screening program and medication is needed to improve the cost–effectiveness of osteoporosis screening strategy, as demonstrated by Hiligsman [33]. Solomon et al. found a compliance rate of 25% after 5 years for prescribed osteoporosis medication in patients 85 years and older, which was significantly lower compared to younger patients [34]. A large survey on adherence for osteoporosis medication was performed by Netelenbos et al. 12-month compliance was analyzed for ten oral osteoporosis medication in The Netherlands. This survey indicated a high compliance, expressed as the medication possession ratio (91%), calculated by dividing the supply of drugs in treatment days by the interval time between first and last date of dispensing, with a low persistence (43%) and no restart in 78% of the patients who discontinued their medication after 18 months [35]. Management of osteoporosis in the elderly should be tailored to the individual patient. Although there is good evidence for the benefits of bisphosphonates, Denosumab, Teriparatide, and Strontium ranelate in vertebral fracture reduction, there are few reports on the efficacy of osteoporosis treatments in non-vertebral fractures in the elderly above 85 years [36–41]. Based on recommendations of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO), patients with serum 25-hydroxyvitamin D (25[OH]D) levels of 50 nmol/L. Similar relationships have been reported for frailty, non-vertebral and hip fracture, and all-cause mortality, with poorer outcomes among those with 25[OH]D levels at <50 nmol/L. In this perspective the ESCEO recommends fragile elderly patients to have a minimum serum 25(OH)D concentration of 75 nmol/L (ie, 30 ng/mL) for the greatest impact on fracture risk reduction [42, 43]. Strontium ranelate is the only anti-osteoporotic drug that has shown a sustained reduction in the risk of vertebral and non-vertebral fracture in the elderly population aged≥80 years. There is, however, caution to treat patients with significant cardiovascular risk factors. Strontium ranelate should only be used after careful consideration [44].There is sufficient evidence to promote the treatment of osteoporosis in the elderly; however, there is still a low prevalence of osteoporosis treatment and low persistence in this population, particularly among those aged over 80 years. In the extreme elderly population we have to focus on treatment for osteoporosis and long-term follow-up to ensure adherence for minimizing subsequent fracture risk.

Conclusions

The results of our study show that the elderly population (>85 years) can be assigned as high-risk population with a high subsequent fracture risk and high mortality rate. However, in practice a FLS seems to have limited value in reducing subsequent fracture risk in this high-risk population. Different strategies may need to be employed in diagnosing and managing older patients with osteoporosis as their fracture risks and treatment strategies may be quite different from younger populations.

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3

CHAPTER III

Percutaneous cement augmentation in the treatment of osteoporotic vertebral fractures (OVFs) in the elderly: a systematic review.

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Eur Spine J. 2020;29(7):1553-1572. doi: 10.1007/s00586-020-06391-x.

Abstract

Purpose: A systematic review, to study treatment effects for osteoporotic vertebral fractures (OVFs) in the elderly including all available evidence from controlled trials on percutaneous cement augmentation.

Methods: Primary studies, published up to December, 2019, were searched in PubMed and the Cochrane Library. Selected were all prospective controlled studies including patients>65 years of age and reporting on at least one main outcome. Main outcomes were pain, disability and quality of life (QOL) 1 day post-intervention and at 6 months postoperatively. Excluded were meta-analyses or reviews, retrospective or non-controlled studies, case studies, patients' groups with neoplastic and/ or traumatic fractures and/or neurologically compromised patients.

Results: Eighteen studies comprising 2165 patients (n=1117 percutaneous cement augmentation, n=800 conservative treatment (CT), n=248 placebo) with a mean follow-up of up to 12 months were included. Pooled results showed signifcant pain relief in favor of percutaneous cement augmentation compared to CT, direct postoperative and at 6 months follow-up. At 6 months, a significant difference was observed for functional disability scores in favor of percutaneous cement augmentation. When comparing percutaneous cement augmentation to placebo, no significant differences were observed.

Conclusion: This review incorporates all current available evidence (RCTs and non-RCTs) on the efficacy of percutaneous cement augmentation in the treatment of OVFs in the elderly. Despite methodological heterogeneity of the included studies, this review shows overall significant sustained pain relief and superior functional effect in the short- and long term for percutaneous cement augmentation compared to conservative treatment.

Introduction

Worldwide osteoporosis causes more than 8.9 million fractures annually [1]. The combined lifetime risk for wrist, hip and spine fractures coming to clinical attention is on average 40% and equals the risk of cardiovascular disease [2]. Three-quarters of these fractures affect patients of 65 years and older [3]. Mortality rates of osteoporotic vertebral fractures (OVFs) are high and exceed those of hip fractures [4]. In the elderly, a high risk of falling is not uncommon. In addition, aging is accompanied by a loss of bone stock leading to osteoporosis with a higher risk of fractures. In the elderly population, osteoporosis is one of the most important factors that affect quality of life. Management of OVFs focuses on pain relief and independence in activities of daily living. When despite conservative treatment OVF patients suffer from immobility caused by pain, dependency and/or additional complications due to being bedridden, surgical interventions should be considered. However, due to the osteoporosis and other comorbidities in the elderly patient, major invasive surgery should be avoided. It remains unclear whether an effective and safe minimally invasive surgical treatment is available for elderly patients with symptomatic OVFs. A recent meta-analysis of RCTs concluded that percutaneous vertebroplasty (PV) and percutaneous kyphoplasty (PKP) significantly decrease pain when compared to conservative treatment [5]. However, not in all countries PV/PKP acknowledged efective treatments for OVFs and recommended as such in national guidelines. A recent Cochrane review concluded that there is a lack of high-quality evidence to support the benefit of any minimal invasive surgical technique and noticed a potential for harm in the treatment of OVF [6]. This manuscript aims to provide an updated comprehensive review on the use of percutaneous cement augmentation, with a special focus on the frail elderly with symptomatic OVFs, using data from RCTs and prospective non-RCTs comparing PV or PKP with conservative treatment or sham procedures.

Materials and methods

This systematic review and meta-analysis are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. Search strategy and selection criteria PubMed and Cochrane databases were searched up to December 1, 2019, for primary research articles, focusing on minimally invasive surgical procedures for the treatment of OVF in elderly patients. Search terms were: ((((((medical treatment) OR optimal medical treatment) OR conservative treatment) OR non-surgical treatment) OR placebo) AND full text AND Humans[MESH] AND aged[MESH])) AND (aged [MESH] OR elderly)) AND (comparative effectiveness research [MESH]) OR patient safety [MESH]) OR pain Measurement

[MESH]) OR effectivity) OR effectiveness) OR success rate) OR success) OR safety) OR patient safety) OR pain relief assessment) OR visual analog scale)))) AND (((((((((((kyphoplasty [MESH]) OR vertebroplasty [MESH]) OR kyphoplasty) OR balloon kyphoplasty) OR vertebroplasty) OR percutaneous screw fxation) OR less invasive treatment) OR minimal invasive treatment) OR minimal invasive surgical procedure) OR minimal invasive surgery) OR less invasive surgical procedure) OR less invasive surgery)))) AND ((((((((((osteoporotic compression fracture) OR osteoporotic vertebral fracture) OR spinal fractures [MESH]) OR osteoporosis) OR osteoporosis [MESH]))). We selected all controlled studies in which patients in the age group> 65 years were treated. Abstracts were reviewed by two reviewers (P.W and I.S). For studies meeting the eligibility criteria, full-text articles were obtained. Two authors independently reviewed the text of each study and came to a mutual decision on which studies to include. We examined reference lists of included studies for any additional relevant studies. For studies with the same study protocol and/or study sample, only the most recent or most comprehensive paper with longest follow-up data was included. In case of disagreement, a third reviewer (R.d.B) was consulted for consensus. When necessary, authors were contacted for provision of additional data. Studies were excluded that did not report outcomes that met the inclusion criteria, being meta-analyses, retrospective analyses, review articles, non-controlled studies, studies which included neoplastic and/or traumatic fractures and/or neurologic compromises patients, as well as case reports. Two reviewers (P.W and I.S) independently evaluated the risk of bias of included studies using the risk of bias assessment from the Cochrane Handbook, version 5.1.0 [7]. Bias risk assessment included seven aspects: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other potential sources of bias. Three levels were used to evaluate the trials: low risk of bias (all the items were in low risk of bias), high risk of bias (at least one item was in high risk of bias) and unclear risk of bias (at least one item was in unclear risk of bias).

Data analysis

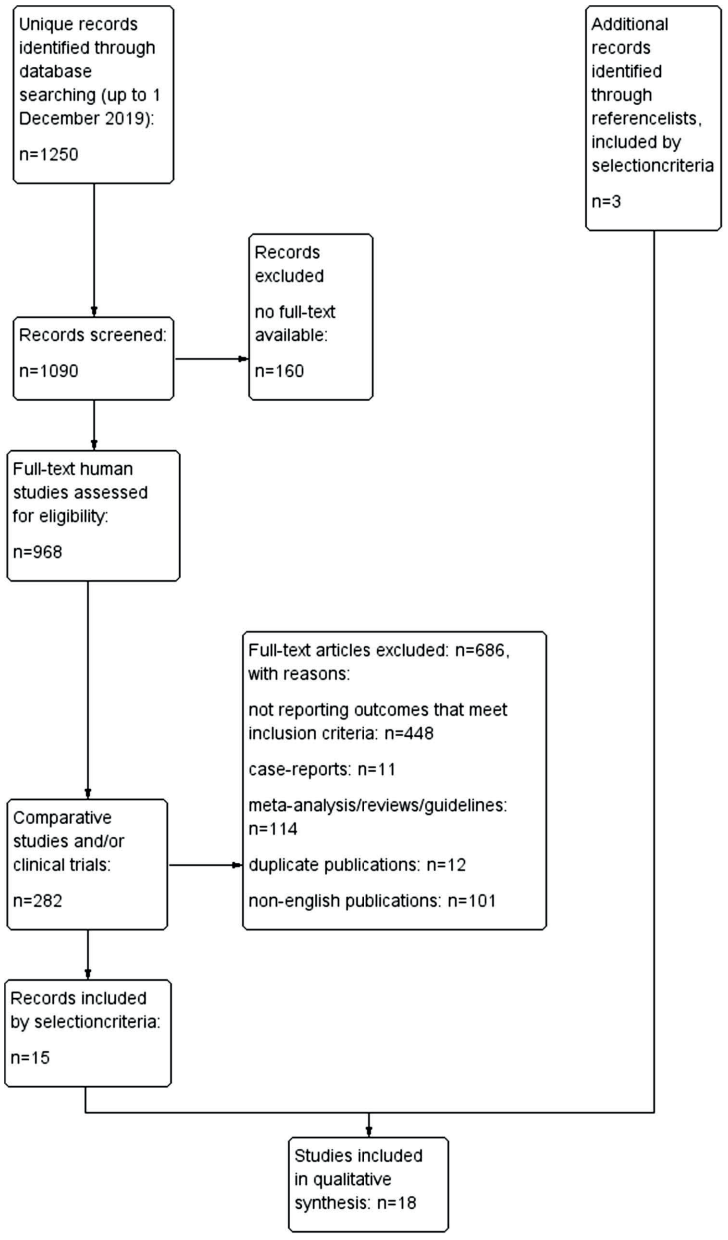
The main outcome measures were: pain relief (assessed on a 0–100 mm VAS or 0–10 point NRS) at 1 day postoperatively and at 6 months, functional disability (RMDQ and ODI) and QOL (QUALEFFO-41) at 6 months [8–10]. The secondary outcome measure was: safety (expressed as morbidity and/ or mortality). Data of intention-to-treat analyses were used, if applicable, wherein data from all patients were analyzed on the basis of their initial group allocations. Mean diferences (MDs) and 95% con-

fidence intervals (CI) were calculated, and used as measure of effect. For continuous outcomes with no SDs, we calculated SD from 95% CIs. If no measures of variance were reported, we used the pooled SD of other trials included in the same analysis. Testing for between-study homogeneity was done using I^2. An I^2>50% was considered to indicate significant heterogeneity, and in those cases, we used the random efects model to pool results. In all other cases, we used a fixed effects model. Results are presented as forest plots. Analyses were performed using R version 3.5.1 and the meta-package. A two-sided $p<0.05$ was considered statistically signifcant.

Results

The primary search identifed 1250 references. After filtering for full-text human studies, 968 records remained and were screened. References of retrieved papers were searched manually. Eighteen studies were eligible for inclusion (eleven RCTs and seven prospective non-RCTs comparing percutaneous cement augmentation with conservative treatment or placebo). A PRISMA flow diagram of the study selection process is shown in Fig. 1.

Fig. 1 PRISMA flowchart.



All included studies were either prospective RCTs or non-RCTs (see Table 1) [11–28]. Baseline characteristics of all included study population are shown in Table 2.

Tabl;e 1 study characteristics.

RCTs	Comparators	*N* total	Age mean (years)	*N* female (%)	Fracture age	VAS mean baseline (cm)	Inclusion	Exclusion
RCTs P V versus Placebo/sham								
1. Firanescu et al. [28]	PV versus Placebo/sham	180	75.65	75.5	<6 weeks	PV 7.7 versus Placebo/sham 7.9	Patient > 50 years, 1–3 vertebral compression fractures, T5–L5 focal back pain at the level of fracture for up to 6–9 weeks, score of 5 or higher on a VAS, diminished bone density (T-score −1 or less) on a dual energy X-ray absorptiometry (DEXA) scan, 15% or more loss of vertebral height and bone edema on magnetic resonance imaging	Severe cardiopulmonary morbidity, untreatable coagulopathy, systemic or local spine infection, suspected malignancy, neurological symptoms or inability to undergo magnetic resonance imaging
2. Clark et al. [12]	PV versus placebo/sham	120	80	68	<6 weeks	PV 8.1 versus placebo 8.2	Patients > 60 years, a NRS score of 7 or more (out of 10), and an MRI confirming 1 or 2 recent fractures	Inability to provide informed consent, chronic back pain requiring opiate use, substantial fracture retropulsion, acute infection, spinal malignancy, neurological complications and greater than 2 VFs
3. Kroon et al. [13]	PV versus placebo/sham	78	76.7	79	<12 months	PV 7.4 versus placebo 7.1	Presence of acute onset back pain of no more than 12 months duration with 1 or 2 recent VFs, defined as vertebral collapse greater than or equal to grade 1 according to the grading system of Genant and colleagues and edema, a fracture line, or both within the vertebral body on MRI	No VF ($n=114$), fracture > 12 months or failed MRI criteria ($n=67$), no significant pain ($n=24$), MRI contraindication to vertebroplasty ($n=10$), > 2 new fractures ($n=10$), significant other health problems ($n=8$), active malignancy ($n=6$), dementia ($n=4$), not correctable coagulation disorder ($n=1$), neurological complications ($n=1$), significant trauma ($n=2$), previous vertebroplasty ($n=1$), refused to participate ($n=141$), died ($n=1$)

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RCTs	Comparators	*N* total	Age mean (years)	*N* female (%)	Fracture age	VAS mean baseline (cm)	Inclusion	Exclusion
4. Comstock et al. [15]	PV versus control intervention	131	73.4	75.6	< 12 months	PV 6.88 versus control intervention 7.16	Patients 50 years or older, with a diagnosis of 1–3 painful OVF between vertebral levels T4 and L5, who had inadequate pain relief with standard medical therapy, and rated their pain intensity with a score of at least three on a scale from 0 to 10. Fractures were required to be less than 1 year old, as indicated by patient-reported duration of pain	Evidence or suspicion for neoplasm in the target vertebral body, substantial retropulsion of bony fragments, concomitant hip fracture, active infection, uncorrectable bleeding diathesis, surgery within the previous 60 days, lack of access to a telephone, inability to communicate in English and dementia
RCTs PV/PKP versus CT								
1. Yang et al. [11]	PV versus CT	135	76.2	64.7	< 1 week	PV 7.5 versus CT 7.7	VF after minor of mild trauma, with 5 scores of more of VAS of back pain, low signal on T1 weighted and high signal on T2 weighted in MRI, level of fracture of T5 or lower, independent living sans use of wheelchair prior to trauma, decreased bone mineral density (BMD) T-score ≤ − 1	Chronic back pain prior to trauma, suspicion of underlying malignant disease, spine infection, retropulsion of bony fragments, spinal cord compression syndrome, concomitant hip fracture, severe cardiopulmonary comorbidity, major coagulopathy
2. Chen et al. [14]	PV versus CT	96	64.6	69.8	> 3 months	PV 6.5 versus CT 6.4	Patients with chronic osteoporotic compression fractures on MRI and persistent back pain for at least 3 months	Not clearly described
3. Blasco et al. [16]	PV versus CT	125	71.3	73	< 12 months	PV 7.21 versus CT 6.31	Painful OVFs from T4–L5, confirmed by spine radiograph and by the presence of edema on MRI or activity on bone scan, and with a minimal VAS score of 4 for pain	Untreatable coagulopathy, active local or systemic infection, current malignancy, vertebral canal occupation by a fragment of the vertebral body or non-osteoporotic VF, active associated disorders (i.e., fibromyalgia or spondyloarthropathies) or other disorders (i.e., dementia) that may interfere with correct assessment of QOL and pain

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RCTs	Comparators	*N* total	Age mean (years)	*N* female (%)	Fracture age	VAS mean baseline (cm)	Inclusion	Exclusion
4. Boonen et al. [17]	PKP versus CT	300	72.2	77.2	<3 months	PKP 3.65 versus CT 5.92	Thoracic or lumbar (T5–L5) VF with bone marrow signal changes on MRI and at least one with 15% decreased height compared with adjacent vertebrae. Up to 3 vertebrae could be treated if they had also signal changes, rapidly progressive height loss or pseudoarthrosis and were considered painful. Pain score of at least 4 on a self-assessed back pain scale	Primary bone tumors, osteoblastic metastases, fractures due to high-energy trauma
5. Farrokhi et al. [18]	PV versus CT	82	72	71	<12 months	PV 8.4 versus CT 7.2	VFs with 10–70% loss of vertebral body height on X-ray, severe back pain related to VF that was refractory to analgesic medication for at least 4 weeks and no longer than 1 year, focal tenderness on physical examination related to the level of VF, bone attenuation (T-score less than −2.5) on bone densitometry, vacuum phenomenon or bone marrow edema of the VF on MRI and unresponsiveness to the medical therapy before entering the trial	Uncorrected coagulopathy, local or systemic infection, secondary osteoporosis, inability to give informed consent, impaired cardiopulmonary function, dementia, posterior wall defect of the vertebral body on computed tomography, painless VF, spinal cancer, traumatic fracture and neurological complications
6. Klazen et al. [19]	PV versus CT	202	75.2	69	<6 weeks	PV 7.8 versus CT 7.5	Patients aged 50 years or older, VF on X-ray (minimum 15% height loss), level of fracture at T5 or lower, back pain for 6 weeks or less, VAS score of 5 or more; bone edema of VF on MRI, focal tenderness at fracture level, as assessed on physical examination and decreased bone density (T-scores ≤ −1)	Severe cardiopulmonary comorbidity, untreatable coagulopathy, systemic or local spine infection, suspected underlying malignant disease, radicular syndrome, spinal-cord compression syndrome and contraindication for MRI

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RCTs	Comparators	*N* total	Age mean (years)	*N* female (%)	Fracture age	VAS mean baseline (cm)	Inclusion	Exclusion
7. Rousing et al. [20]	PV versus CT	50	80	76	<8 weeks	PV 7.5 versus CT 8.8	Intractable pain because of acute (fracture age 2 weeks) or subacute (fracture age between 2 and 8 weeks) OVFs	Age less than 65 years, senile dementia or other cerebral disease, uncorrected therapeutic anticoagulation, infection, malignant disease, bone metabolic disease, fracture of tubular bone or allergy to radiopaque agents
Non-RCTs								
1. Andrei et al. [21]	PV versus CT	66	66.3	77	<2 months	PV 5.9 versus CT 6.28	Painful OVFs (<2 months) after minor trauma matched with imagistic findings. In the assessment of these patients, the level of OVFs was diagnosed by X-ray, the approximate time from the injury to admission was determined correlating anamnestic data with MRI and the vertebral body volume was measured on computed tomography	VF older than 2 months, a newly developed fracture during follow-up, pathologic fractures due to tumors that involves vertebral body, neurological deficit related to fracture and no understanding of the pain scale due to cognitive dysfunction
2. Marcías-Hernández et al. [22]	PV versus CT	31	72	100	Acute/subacute, not specified	PV 7.31 versus CT 6.86	Women aged 60 years or older, with pain of acute or subacute onset, with vertebral collapse of 15–50% without affections of the posterior segment and without neurological compromise, an identifiable fracture line or a geographical pattern with low signal on T1 or with a high-intensity signal on T2 on MRI. T-score of −2.5 SD in at least one segment of the lumbar spine in a DEXA test	Patients with persistent pain > 50 mm were evaluated if they met the criteria to undergo PV. Those who did not fulfill the criteria for PV were excluded

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RCTs	Comparators	*N* total	Age mean (years)	*N* female (%)	Fracture age	VAS mean baseline (cm)	Inclusion	Exclusion
3. Lee et al. [23]	PKP versus CT	259	66.2	59	Acute after minor trauma, not specified	PKP 7.5 versus CT 7.2	Patients aged 50 years or older and were admitted via the emergency room because of acute severe back pain after minor trauma. One or 2 VFs were confirmed by low-intensity signal changes on T1-weighted image, high-intensity changes on T2-weighted image and bone edema on short-tau inversion recovery sequence images of MRI. Other inclusion criteria were level of fracture at T8 or lower, focal tenderness on the back after minor trauma and anterior wedge compression fractures	Severe cardiopulmonary comorbidity, major coagulopathy, spine infection, suspected neoplasm in the target vertebral body, retropulsion of bony fragments, spinal cord compression syndrome, dementia and fractures related to major trauma
4. Wang et al. [24]	PV versus CT	55	72.2	84	<6 weeks	PV 7.5 versus 7.1 CT	Acute pain (lasting less than 6 weeks), low signal intensity on T1-weighted and high signal intensity on T2-weighted MRI images of the fractured vertebrae, VFs with more than 20% loss of height, age over 50 years, focal tenderness at the fractured level and decreased bone density T-score − 1	Pathological fracture due to malignancy/myeloma, osteomyelitis, major retropulsion of bony segments into the spinal canal and coagulopathy

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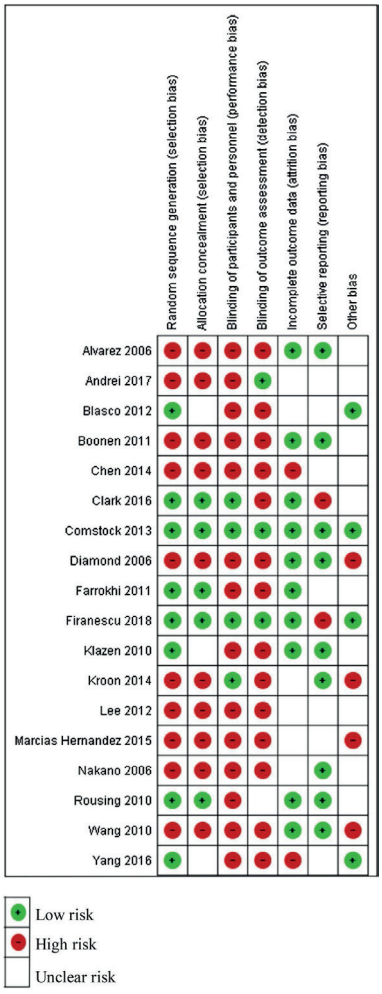
RCTs	Comparators	*N* total	Age mean (years)	*N* female (%)	Fracture age	VAS mean baseline (cm)	Inclusion	Exclusion
5. Nakano et al. [25]	PV versus CT	60	77	73	<4 weeks	PV 7.93 versus CT 7.47	An isolated OVF within the thoracic, thoracolumbar or lumbar region as demonstrated by X-ray, bone mineral density and MRI or bone scintigraphy; computed tomography evidence of posterior wall fracture of the vertebral body with displacement and bulging of less than two mm; presentation fewer than 4 weeks after the time of the injury; and a minimum age of 60 years	Pathological fracture due to myeloma/metastasis and osteomyelitis, and coagulopathy; a neurological deficit related to the fracture, an osteoporotic vertebral, fracture occurring within 1 year before the present injury, a continuously followed regimen of analgesic medication or steroid agent before injury, an inability to understand the pain scale because of severe dementia and cognitive dysfunction, and a traffic- or labor-related accident that resulted in monetary compensation
6. Alvarez et al. [26]	PV versus CT	128	69.7	80	<12 months	PV 8.72 versus CT 7.37	OVF (<12 months) with a less than satisfactory response to conventional therapy over at least a 6-week period. All fractures were confirmed by MRI findings of marrow signal changes, such as a hypointense signal on T1-weighted images, hyperintense signal on T2-weighted images and short-tau inversion recovery sequences	Pathologic fractures due to metastasis or myeloma, infection, uncorrectable coagulopathy or major retropulsion of bony fragments into the spinal canal. In the cases (22.6%) of suspected malignancy, an intraprocedural biopsy was performed. Excluded were also patients whose fractured vertebrae had a loss of height greater than 7.0% and a fracture age dated more than 12 months
7. Diamond et al. [27]	PV versus CT	126	76.1	69	<6 weeks	PV 2 versus CT 2	Acute VF pain occurring within 1–6 weeks of the event and not relieved by analgesia. Imaging criteria of acute fracture activity	Pathologic fracture caused by myeloma/metastasis, osteomyelitis, major retropulsion of bony fragments into the spinal canal, coagulopathy

Table 2 Baseline characteristics study-population.

Age mean (range years)	74 (65–80)
Female patients (%)	60
Fracture-age (n = studies)	
< 6–9 weeks	9
< 3 months	1
> 3 months	1
< 12 months	5
Non-specified/acute/subacute fractures	2
Comparators (n = studies)	
PV versus CT	12
PV versus sham/placebo	4
PKP versus CT	2

Risk of bias of individual studies was assessed. Eight RCTs were considered as having low risk of selection bias, seven RCTs showed low risk attrition bias and fve RCTs low risk reporting bias. The placebo/sham-controlled studies were overall of better methodological quality with lower risk of bias comparing to the other included RCTs (see Table 3).

Table 3 Risk of bias.



The pooled results of the included studies indicate that percutaneous cement augmentation is a safe procedure (see Table 4 and Fig. 2).

Table 4 morbidity and mortality during mean follow-up of the studies

Study	Comparators	*N* total	Total new VFs	Procedure/fracture-related mortality	Morbidity	Morbidity definition	Cement extravasation
RCTs PV versus placebo/sham							
1. Firanescu et al. [28]	PV versus placebo	180	31 versus 28	NR	2 ($n=2$) versus 0	1 respiratory insufficiency the day after the procedure, related to underlying pulmonary disease, 1 vasovagal reaction during the procedure that spontaneously resolved	105 (91%)
2. Clark et al. [12][a]	PV versus Placebo	120	3 versus 7	–	2 ($n=2$) versus 2 ($n=2$)	1 respiratory arrest post-sedation, 1 supracondylar humerus fracture in a paretic arm during transfer versus 2 spinal cord compressions due to interval collapse and retropulsion of the fracture	Asymptomatic 21 (34%)
3. Kroon et al. [13]	PV versus Placebo	78	12 versus 11	NR	NR	NR	Asymptomatic 13 (39.3%)
4. Comstock et al. [15]	PV versus control	131	NR	NR	NR	NR	NR
RCTs PV/PKP versus CT							
1. Yang et al. [11]	PV versus CT	135	5 versus 4 $p=0.992$	–	10 ($n=9$) versus 24 ($n=18$) $p<0.0001$	2 urinary tract infections, 2 deep vein thrombosis, 2 depressions, 4 sleep disorders versus 2 pneumonia, 5 urinary tract infections, 4 deep vein thrombosis, 5 depressions, 8 sleep disorders	Asymptomatic 22 (33.8%)
2. Chen et al. [14]	PV versus CT	96	3 versus 7 $p=0.277$	NR	NR	NR	Asymptomatic 36 (52%)
3. Blasco et al. [16]	PV versus CT	125	29 versus 8	–	NR	NR	Asymptomatic 23 (49%)
4. Boonen et al. [17][b]	PKP versus CT	300	56 versus 45 $p=0.68$	–	$n=134$, SAE 74 versus $n=134$, SAE 73	2 SAE related to kyphoplasty; one recollapse of a treated vertebrae with anterior migration of cement, another patients with spondylodiscitis	NR
5. Farrokhi et al. [18][b]	PV versus CT	82	1 versus 6 $p<0.01$	–	$n=1$ versus 0	No significant complications except one complication related to cement extravasation in the vertebroplasty group	14 (14%), in 1 patient epidural cement leak caused severe right lower extremity pain and weakness

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Table 4

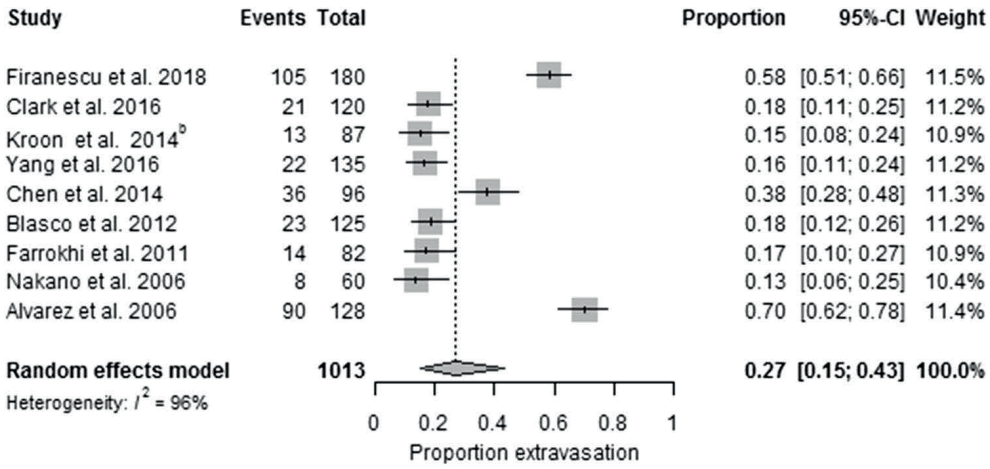
Study	Comparators	*N* total	Total new VFs	Procedure/fracture-related mortality	Morbidity	Morbidity definition	Cement extravasation
6. Klazen et al. [19]	PV versus CT	202	18 versus 30 $p=0.44$	–	$n=2$ versus 0	1 urinary tract infection, 1 asymptomatic cement deposition in a segmental pulmonary artery in the vertebroplasty group	Asymptomatic cement leakage frequency NR
7. Rousing et al. [20]	PV versus CT	50	4 versus 3	–	$n=0$	No significant complications	Asymptomatic cement leakage frequency NR
Non-RCTs							
1. Andrei et al. [21]	PV versus CT	66	4 versus 5	–	$n=0$	No significant complications	NR
2. Marcías-Hernández et al. [22]	PV versus CT	31	1 versus 0	NR	$n=1$	1 radiculopathy in the vertebroplasty group	NR
3. Lee et al. [23]	PKP versus CT	259	5 versus 8 $p>0.05$	NR	$n=0$	No significant complications	Asymptomatic cement leakage frequency NR
4. Wang et al. [24]	PVP versus CT	55	8 versus 1		$n=1$	No significant complications except one complication related to asymptomatic cement migration toward the lungs	1 asymptomatic pulmonary PMMA emboli, cement leakage frequency NR
5. Nakano et al. [25]	PV versus CT	60	NR	NR	$n=1$	1 temporary respiratory insufficiency during CPC injection in the vertebroplasty group	Asymptomatic 8 (26.7%)
6. Alvarez et al. [26]	PV versus CT	128	36 versus 3 $p<0.01$	NR	$n=8$	1 transitory paraparesis from a massive PMMA leakage into the canal, 5 transitory radicular neuritis, 2 rib fractures related to positioning in the vertebroplasty group	90 (59.6%), 7% symptomatic
7. Diamond et al. [27]	PV versus CT	126	29 versus 11 $p=0.76$	5 fracture-related deaths, 4 occuring in the CT group	$n=3$	2 fractured transverse processes, 1 psoas muscle hematoma in the vertebroplasty group	NR

NR not reported, *SAE* serious adverse event

[a]Results only available and reported for the 6-month follow-up period

[b]Results only available and reported for the 24-month follow-up period

Fig. 2 Random effects model plot of cement extravasation.

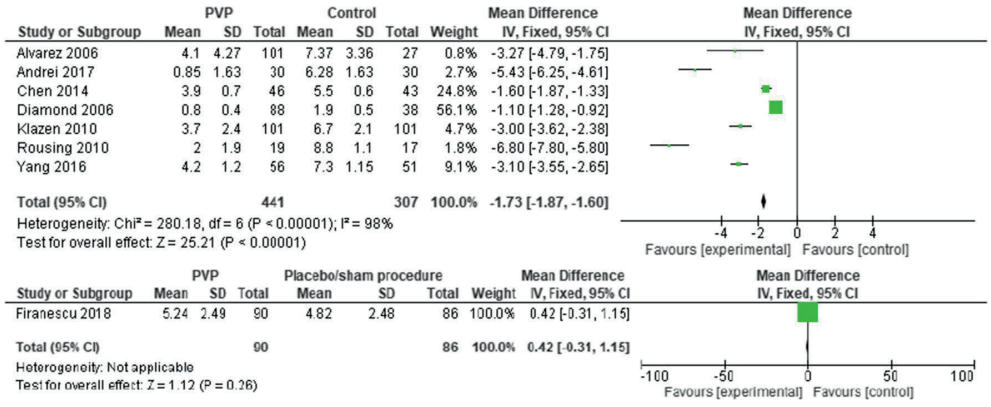


Pain

The included 12 PVs versus conservative treatment studies were heterogeneous ($p < 0.00001$, $I^2 = 93\%$). Pooled results indicated no signifcant differences in pain at baseline between the PV and conservative treatment group, the PKP versus conservative treatment group and PV versus placebo.

Seven PVs versus conservative treatment studies reported direct postoperative outcomes at day one. The pooled results showed heterogeneity and signifcant pain relief in favor of PV. MDs were, respectively, −1.73 (−1.87, −1.60); $p<0.00001$, $I^2=98\%$. None of the two studies reported direct postoperative outcomes for PKP versus conservative treatment. One RCT comparing PV versus placebo presented direct postoperative results at day one, with no significant difference (see Fig. 3).

Fig. 3 Forest plot of patient-reported pain scores at day one postoperative.



Ten PVs versus conservative treatment studies, and two studies comparing PKP with conservative treatment, reported 6 months outcomes. Although clinically comparable, the studies were statistically heterogeneous, and therefore not pooled. All showed signifcant pain relief in favor of PV. MDs were −1.08 (−1.16, −1.00) for PV versus conservative treatment. MDs were −0.39 (−0.57, −0.20) for PKP (two studies) versus conservative treatment. The PV versus placebo groups (four studies) showed no signifcant pain relief in favor of one of the two groups. The MD was −0.58 (−1.09, −0.08); p=0.63, I^2=0% (see Fig. 4). Results were sustained at 12-month follow-up (see Figs. 5, 6).

Fig. 4 Forest plots of pain at follow-up of 6 months.

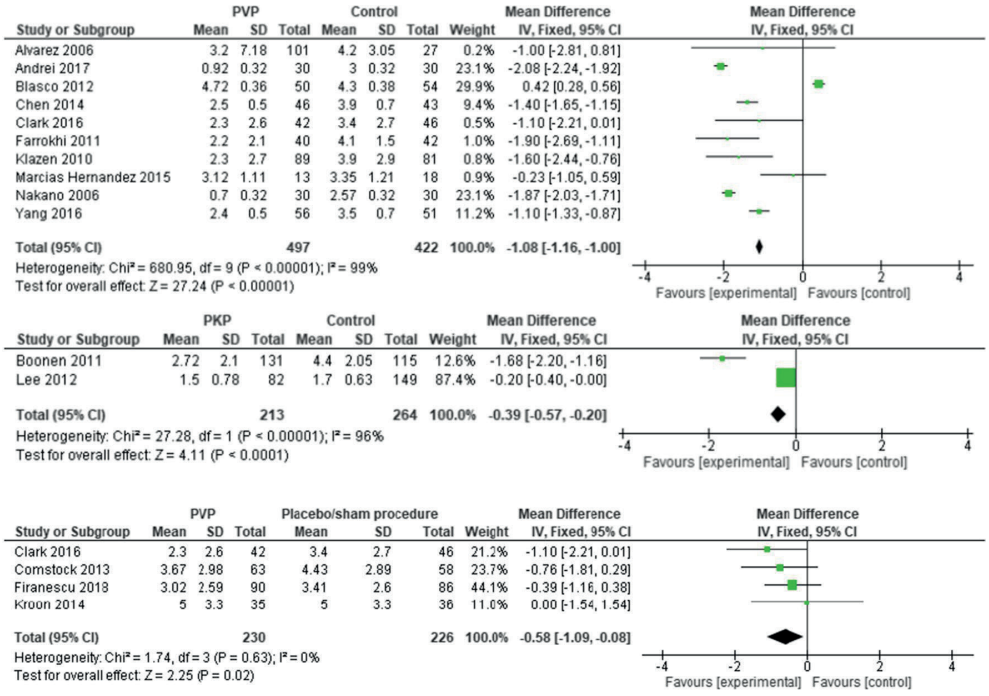


Fig. 5 Random effects model plot pains scores PVP versus conservative treatment up to 12 months.

Study	PVP Total	PVP Mean	PVP SD	Control Total	Control Mean	Control SD	MD	95%-CI	Weight
Follow-up = Post-op									
Alvarez et al. 2006	101	4.10	4.27	27	7.37	3.36	-3.27	[-4.79; -1.75]	2.5%
Andrei et al. 2017	30	0.85	1.63	30	6.28	1.63	-5.43	[-6.25; -4.61]	3.3%
Chen et al. 2014	46	3.90	0.70	43	5.50	0.60	-1.60	[-1.87; -1.33]	3.8%
Diamond et al. 2006	88	0.80	0.40	38	1.90	0.50	-1.10	[-1.28; -0.92]	3.8%
Klazen et al. 2010	101	3.70	2.40	101	6.70	2.10	-3.00	[-3.62; -2.38]	3.5%
Rousing et al. 2010	19	2.00	1.90	17	8.80	1.10	-6.80	[-7.80; -5.80]	3.1%
Yang et al. 2016	56	4.20	1.20	51	7.30	1.15	-3.10	[-3.55; -2.65]	3.6%
Random effects model	**441**			**307**			**-3.41**	**[-4.52; -2.29]**	**23.6%**
Heterogeneity: I^2 = 98%									
Follow-up = 6 months									
Alvarez et al. 2006	101	3.20	7.18	27	4.20	3.05	-1.00	[-2.81; 0.81]	2.2%
Andrei et al. 2017	30	0.92	0.32	30	3.00	0.32	-2.08	[-2.24; -1.92]	3.8%
Blasco et al. 2012	50	4.72	0.36	54	4.30	0.38	0.42	[0.28; 0.56]	3.8%
Chen et al. 2014	46	2.50	0.50	43	3.90	0.70	-1.40	[-1.65; -1.15]	3.8%
Clark et al. 2016	42	2.30	2.60	46	3.40	2.70	-1.10	[-2.21; 0.01]	3.0%
Farrokhi et al. 2011	40	2.20	2.10	42	4.10	1.50	-1.90	[-2.69; -1.11]	3.3%
Klazen et al. 2010	89	2.30	2.70	81	3.90	2.90	-1.60	[-2.44; -0.76]	3.3%
Marcias Hernandez et al. 2015	13	3.12	1.11	18	3.35	1.21	-0.23	[-1.05; 0.59]	3.3%
Nakano et al. 2006	30	0.70	0.32	30	2.57	0.32	-1.87	[-2.03; -1.71]	3.8%
Yang et al. 2016	56	2.40	0.50	51	3.50	0.70	-1.10	[-1.33; -0.87]	3.8%
Random effects model	**497**			**422**			**-1.19**	**[-1.95; -0.44]**	**34.0%**
Heterogeneity: I^2 = 99%									
Follow-up = 12 months									
Alvarez et al. 2006	101	2.84	0.63	27	3.30	0.63	-0.46	[-0.73; -0.19]	3.8%
Andrei et al. 2017	30	0.92	1.39	30	2.36	1.23	-1.44	[-2.11; -0.77]	3.5%
Blasco et al. 2012	47	4.49	0.39	48	4.32	0.40	0.17	[0.01; 0.33]	3.8%
Chen et al. 2014	46	2.50	0.50	43	4.10	0.80	-1.60	[-1.88; -1.32]	3.7%
Diamond et al. 2006	88	0.30	0.40	38	0.40	0.50	-0.10	[-0.28; 0.08]	3.8%
Farrokhi et al. 2011	38	2.20	2.10	39	4.10	1.80	-1.90	[-2.77; -1.03]	3.2%
Klazen et al. 2010	86	2.20	2.70	77	3.90	2.90	-1.70	[-2.56; -0.84]	3.3%
Marcias Hernandez et al. 2015	13	3.23	1.12	18	3.61	1.24	-0.38	[-1.22; 0.46]	3.3%
Nakano et al. 2006	30	0.67	1.39	30	1.97	1.23	-1.30	[-1.97; -0.63]	3.5%
Rousing et al. 2010	22	2.00	0.48	22	2.90	0.63	-0.90	[-1.23; -0.57]	3.7%
Wang et al. 2010	32	2.30	1.40	23	3.20	1.90	-0.90	[-1.82; 0.02]	3.2%
Yang et al. 2016	56	1.80	0.50	51	3.10	0.70	-1.30	[-1.53; -1.07]	3.8%
Random effects model	**589**			**446**			**-0.95**	**[-1.38; -0.51]**	**42.5%**
Heterogeneity: I^2 = 95%									
Random effects model	**1527**			**1175**			**-1.61**	**[-2.01; -1.20]**	**100.0%**
Heterogeneity: I^2 = 98%									
Test for overall effect: z = -7.76 (p < 0.01)									

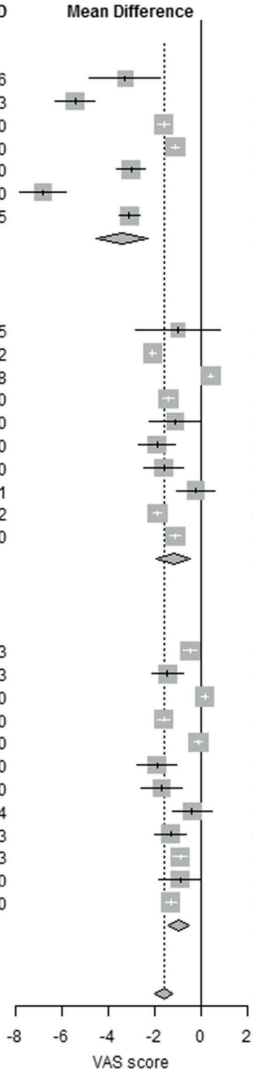
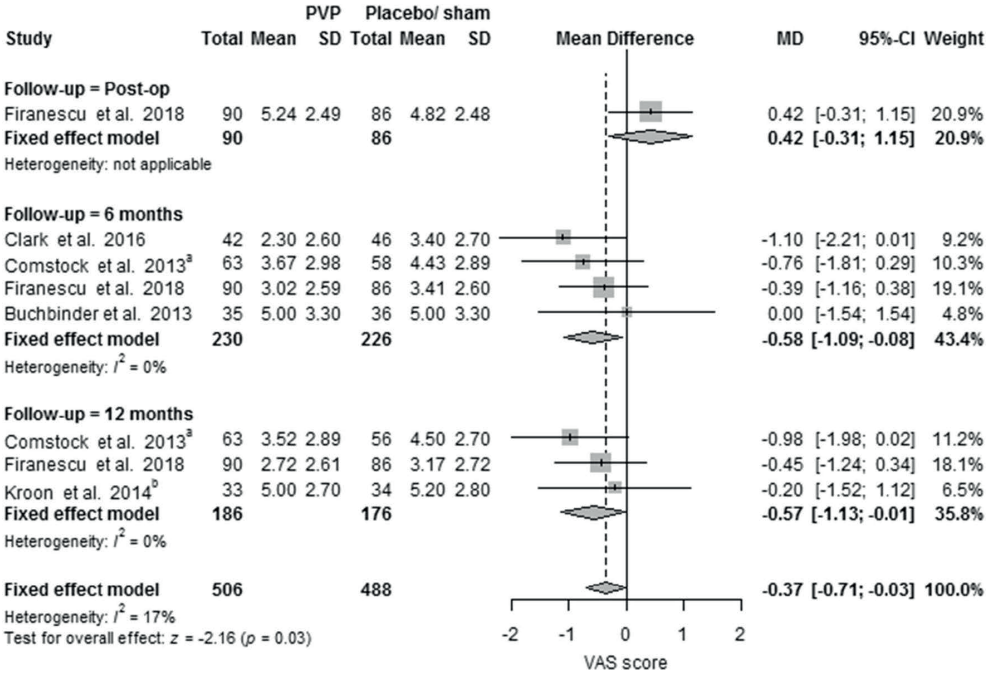


Fig. 6 Fixed effect model plot pain scores PVP versus sham treatment up to 12 months.

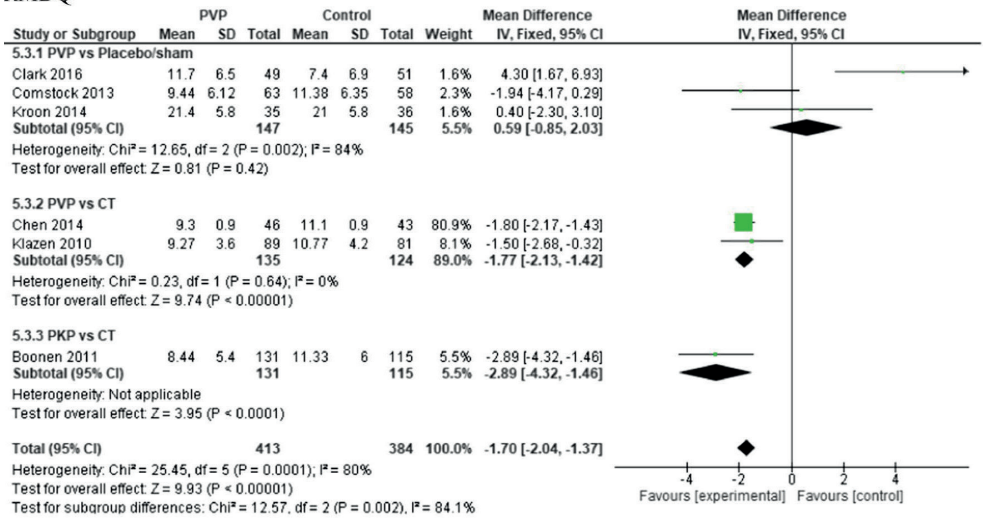


Functional outcomes

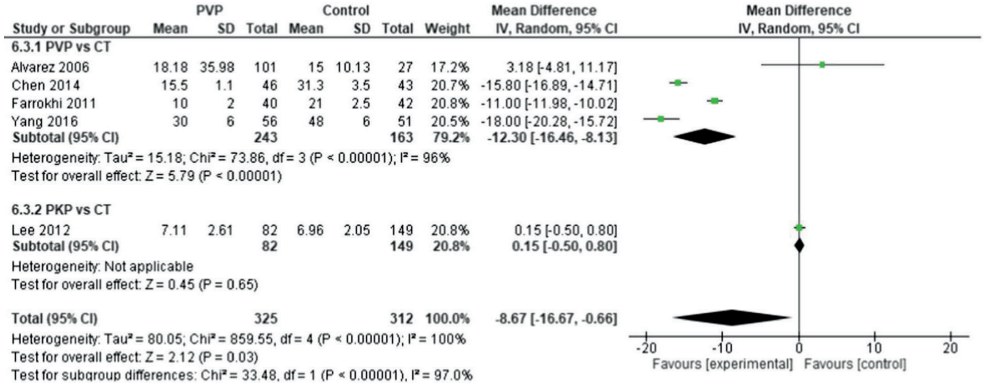
At 6-month follow-up, there was significant diference in RMDQ scores in favor of the PV group compared to conservative treatment (two studies) with a total MD of −1.77 (CI −2.13, −1.42); p<0.0001 and for PKP versus conservative treatment (one study) with a total MD of −2.89 (CI −4.32, −1.46); p<0.00001. For ODI scores at 6-month follow-up, the pooled results were in favor of PV versus conservative treatment (four studies) with a total MD of −12.30 (CI −16.46, −8.13); p<0.00001, I^2=96%. In the PV versus placebo groups, no significant difference in functional outcome results was found (see Fig. 7).

Fig. 7 Forest plots of functional outcome scores at follow-up of 6 months.

RMDQ



ODI

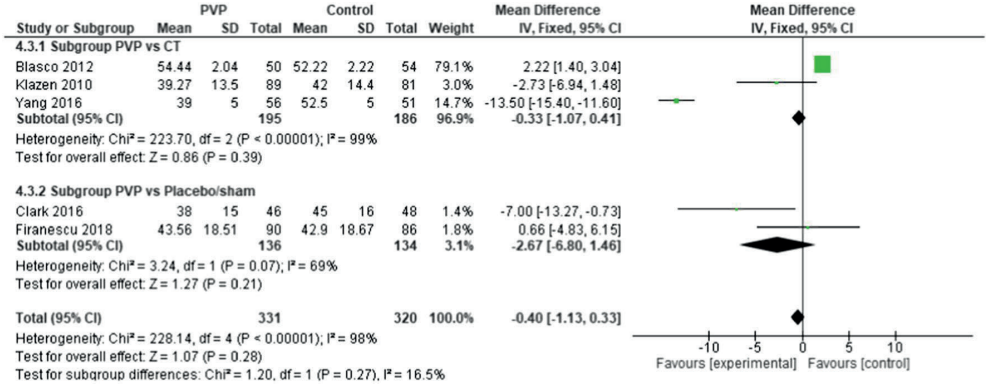


QOL

QOL (QUALEFFO-41) was recorded in three of the 12 included PVs versus conservative treatment studies, and two of the PVs versus placebo studies. There was no significant difference in scores at 6-month follow-up (see Fig. 8).

Fig. 8 Forest plots of QUALEFFO-41 outcome at follow-up of 6 months.

QOL



Discussion

In this systematic review, we included all retrievable prospective controlled trials that compared percutaneous cement augmentation to conservative treatment or placebo in the management of OVFs in the elderly. Pooled results indicate signifcant pain relief and functional improvement up to 12 months of follow-up for percutaneous cement augmentation compared to conservative treatment. Consensus guidelines about the role of percutaneous cement augmentation in OVFs are lacking, and divergent opinions exist. In the European Guidance for the diagnosis and management of osteoporosis in postmenopausal women, a role for percutaneous cement augmentation has been suggested in patients with recent OVF in whom pain persists for 2–3 weeks despite a well-conducted analgesic program [29]. In accordance with the European guidance, the UK NICE guidelines recommend percutaneous cement augmentation only in patients who have severe ongoing pain after a recent, unhealed fracture despite optimal pain management [30]. The American Academy of Orthopaedic Surgeons strongly recommends against vertebroplasty based on evidence regarding two Level I studies that compared vertebroplasty to a sham procedure and showed no significant difference between the two procedures in pain relief and function [31]. However, these two studies have been criticized thoroughly [32, 33]: Both studies included patients with symptoms of up to 1-year duration, which is a time period in which fractures can heal naturally. Moreover, patients with an NRS score of three points out of ten were eligible for inclusion. Ryu and Park reported that there is a strong correlation between severity of pre-intervention pain score and the post-intervention outcome; more severe pain resulted in more significant improvement following PV [34]. The low participation rates of eligible patients and high crossover rates in both studies have also been questioned. In the study of Kallmes et al., at 3-month follow-up, many patients in the control group (43%) crossed over to the PV group due to persisting pain, as compared to the number of patients in the PV group who crossed over to the control group (12%), a difference that reached statistical signifcance ($p<0.001$). Finally, patients assigned to the sham procedures received injection of Bupivacaine into the periosteum next to the facet joints. However, in a study of Tischer et al., degenerative facet joint lesions were found on gross histologic analysis in 80% of the elderly, with most found at the L4–L5 level [35]. In the Framingham Heart Study, moderate or severe lumbar facet joint osteoarthritis on CT-imaging was present in 89% of those above 65 years of age [36]. Pain improvement rates after facet blocks or an medial branch block in patients with back pain has been reported in the range of 29–60% in the literature [37]. Park et al. reported a satisfaction level of "excellent" or "good" 12 months after the first injection in 78.9% of the patients with osteoporotic spinal compression complaining of persistent low back pain [38]. In the series of Heui Seung Lee and the study of Kim et al., 69.6% and 70% of the patients have benefitted

from a medial branch block for their back pain, respectively [39, 40]. In our systematic review, a tertiary analysis with a random effects model showed a substantial within-group reduction in VAS score of 3.6 (95% CI: 1.2; 3.0, $p<0.001$, $I^2=93.0\%$) in a 6-month follow-up period for the sham groups. A blinded RCT studying the outcome of facet blocks against percutaneous cement augmentation in the elderly would be of great value. Because of the results of the two sham trials of 2009, in some countries PV/PKP were not reimbursed anymore [41]. Ong et al. showed us that the mortality risk for VFC is high. In this study, more than two million patients were analyzed and the mortality in the overall VFC cohort was 85.1 (95% CI 84.7–85.5) at 10 years. The conservative treated group showed a 24% and 8% larger mortality risk than the PKP and PV, respectively. The mortality of patients was also signifcantly greater in the period 2010–2014 compared to 2005–2009 [42]. A more recently published blinded Australian trial comparing PV to placebo treating patients with a less than 6 weeks old fracture showed a larger mean reduction in pain in the PV group than in the placebo control group at all follow-up moments [12]. The patients in this trial were older, had higher pain scores and increased disability at enrollment than those patients in previous placebo-controlled trials. In contrast to previous trials in which the posterior vertebral cortex was anesthetized, this trial used local anesthesia subcutaneously. Also, this trial used odorless PMMA kits with a closed mixing and delivery system that was not opened during placebo procedures. Additionally, in this trial there was the absence of a crossover option and 57% of patients were in-hospital patients, in contrast to the other placebo-controlled trials which excluded or did not report on these patients. A median reduction in 5.5 hospital days was achieved in the PV group of the VAPOUR trial. This trial has been criticized for its lack of generalizability and methodological faws. On average, 84% of the patients were recruited from one institute, while the study was performed as a multicentre trial. Besides, comorbidities in the studied cohorts were not recorded and most subgroup analyses had a limited number of patients achieving outcome. The differences in results for primary outcomes of the placebo-controlled studies could be explained by inclusion criteria and study methodology. The Cochrane vertebroplasty review of April 2018 was updated in November 2018 to address complaints to the Chief Editor of Cochrane about errors in the report [6]. There is ongoing debate that the review does not accurately report the evidence for vertebroplasty in patients with severe symptoms and early fractures.The importance of early interventions positively affecting final outcome has already been studied in hip fractures, which have been traditionally regarded to represent frailty. A Canadian cohort of 42.230 patients with a mean age of 80 years found significant benefits of early surgery. Significantly lower 30-day mortality (5.8% vs. 6.5%), less postoperative complications and significantly less adverse outcomes at 30 days (10% vs. 12%) were found with early surgery (<24 h) [43]. Appropriate attention and early management are also needed for frail patients with OVFs because of

reciprocal interaction. Frailty deficits worsen by fracture, and accelerated risk of OVFs arises by frailty [44]. Delaying surgical intervention in the fragile elderly can sometimes lead to suboptimal care. The results of recent RCTs suggest a shift to an earlier and more aggressive approach in the form of percutaneous cement augmentation instead of conservative treatment for acute and subacute thoracolumbar fractures in the elderly [11, 12]. Moreover, delayed diagnosis and lack of proactive management may result in a vicious circle with recurrent or prolonged hospitalization, acute and chronic back pain, polypharmacy with painkillers (often poorly tolerated by the elderly population), reduced pulmonary function, failure in overall sagittal compensation and progressive spinal kyphosis with consequent loss of function and independency and potential premature death. Furthermore, severe osteoporosis and aging are risk factors for failure of conservative treatment [23, 45]. In the study of Lee et al., a cutoff value of 76.5 years old was a risk factor for failure. The failure rate for early (3 weeks) conservative treatment was 35% in this study. Zhang et al. showed that a modifed frailty index (mFI) of >3 and severe osteoporosis were important risk factors for conservative treatment failure. The failure rate was 41% for early (3 weeks) conservative treatment. In summary, many authors suggest to choose for conservative treatment in the early weeks after OVFs. Minimal invasive treatments like PV and PKP are indicated if conservative treatment fails. Elderly patients with osteoporotic fractures should be considered as frail elderly. In the frail elderly, prolonged non-effective conservative management can lead to a patient becoming bedridden with a range of complications and even premature death as a consequence. Besides, the increasing danger of opioid abuse should be recognized. This systematic review is limited by the signifcant heterogeneity and moderate quality evidence of included studies. Potential bias cannot be excluded due to inadequate blinding of patients and personnel. In some studies, the control groups were formed by the population that rejected percutaneous cement augmentation, which introduces selection bias. Besides, conservative treatment characteristics varied considerably: offering bed rest, analgesia, a variation of rehabilitation program or brace treatment, and in one study, even intrathecal infusion was offered. In addition, outcome measures varied between studies. Adverse events of the procedures were not described in detail since most studies mainly focused on pain or function. In this review, we conclude that in the frail elderly with (sub) acute OVF, severe pain despite early conservative measures, focal tenderness and edema on MRI scans concordant with the level of the fracture, when no absolute contra-indications are present, percutaneous cement augmentation is safe and effective and can be ofered to hasten return to normal function and bypass the consequences of prolonged immobilization. Given the limited methodological quality of included studies, the present findings should be confirmed with more high-quality and well-designed studies.

Acknowledgements We would like to thank Dr. J. Blasco, who provided additional data to complete this review.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. The corresponding author has full access to all the data in the study and bears full responsibility for submission.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest

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4

CHAPTER IV

Less Invasive Surgery is Feasible in the Management of Traumatic Thoracolumbar Fractures in Isolated and Polytrauma Injury.

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Int J Spine Surg. 2019;13(6):561-567. doi: 10.14444/6078.

Abstract

Background: Less invasive stabilization systems (LISSs) have gained popularity. However, limited quality of life (QOL) and clinical outcome data exist for trauma patients treated with LISSs. The objective of this study is to describe QOL and outcome for posterior percutaneous pedicle screw fixation in the management of traumatic thoracolumbar fractures.

Methods: Between January 2006 and December 2011, data from all patients treated with a posterior percutaneous pedicle screw fixation technique for thoracolumbar fractures were collected and analyzed. Sixty-nine patients met the inclusion criteria. Additional vertebral reduction and cement augmentation was used in 25 patients, when there was more than 50% of vertebral body comminution.

Results: Mean follow up of 19 months (range= 6–49 months). Fifty-one percent of the study population consisted of polytrauma patients, with 22% having injury severity score ≥15. In 6 cases (8.7%) there were perioperative complications. Response rate for the follow-up health survey was 78%, with a satisfactory overall median EuroQuol score of 0.811 (Q1–Q3 95% confidence interval= 0.709–0.897).

Conclusions: Posterior percutaneous pedicle screw fixation proves to be effective in the management of traumatic thoracolumbar fractures, with a good overall functional outcome. Percutaneous techniques that reduce perioperative morbidity are an alternative approach well suited for damage control orthopaedics, as long as there are no neurological deficits. Especially in polytrauma patients with spine fractures, the spinal column can be stabilized in an emergency setting, while limiting the risks of "a second hit" at the patients' already frail condition.

Introduction

The management of traumatic thoracolumbar fractures remains challenging. The levels of evidence for treatment practices can alter the decision-making process. In the new era, percutaneous pedicle screw fixation has become a popular method as a less invasive approach in the management of thoracolumbar fractures. Several studies have described the multiple advantages of posterior pedicle screw fixation techniques in thoracolumbar fractures [1-9]. Open surgical techniques are associated with significant morbidity due to high blood loss and infection rates. Blood loss rates of 1000 mL for open posterior, anterior, or anterior-posterior procedures can be reduced to 50 mL in less invasive spine surgery. The high infection rate of 10% in open surgery is reduced to 0–1% [4-9]. In contrast to open techniques, percutaneous fixation induces minimal paraspinal muscle injury and shows a positive correlation with postoperative back muscle performance [10]. With the knowledge that, on average, 36% of polytrauma patients have associated spine injuries, less invasive approaches would be favorable in limiting the risks for the already vulnerable patient [11]. However, it is not yet established whether less invasive approaches lead to comparable clinical outcome in the isolated and/or the multi-injured patient. To our knowledge, little is known about health-related quality of life (QOL) outcomes. The low-grade evidence and unclear long-term outcomes further limit the evidence available for this technique. There is a need for more evidence to inform clinical decisions using percutaneous pedicle screw fixation in the treatment of traumatic thoracolumbar fractures. The aim of this study is to describe the QOL and radiological outcome of posterior percutaneous pedicle screw fixation in the treatment of traumatic thoracolumbar fractures from a single trauma center.

Material and Methods

Our center started using the posterior percutaneous pedicle screw fixation technique for traumatic thoracolumbar spine fractures in January 2006. All trauma patients in our center are included in a prospective registry. The primary outcome of our study was to analyze the functional and radiological outcome of patients from this database. For this purpose, all patients with traumatic thoracolumbar fractures treated with a percutaneous spinal fixation technique between January 2006 and December 2011 were included. Follow-up data were extracted from electronic medical records. Excluded were all patients with a follow up less than 6 months after surgery, pathological vertebral body fractures, or accompanying neurological symptoms necessitating open decompression. Classification type C was excluded from EuroQuol (EQ-5D) analysis because only a single observation was available. Seventeen patients were lost to follow

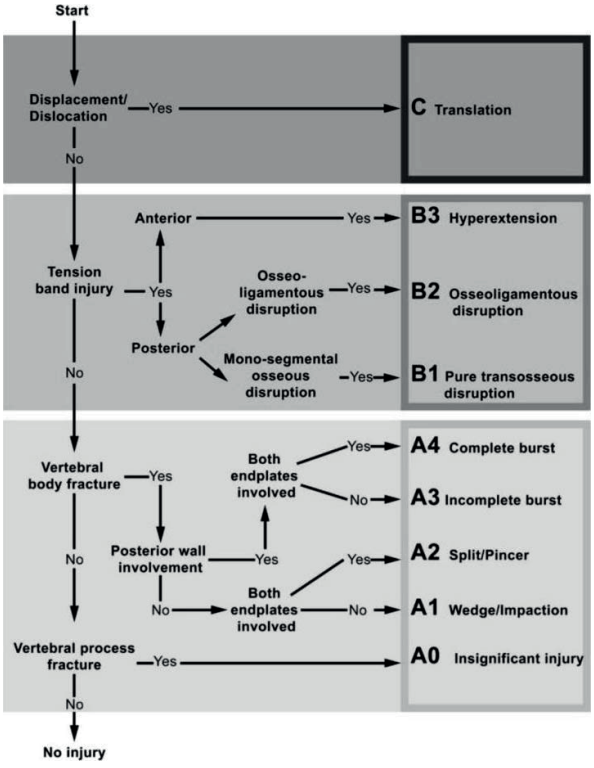
up (relocation, no-show) during this period; a total of 69 patients remained for analysis. Spine stabilization was performed by use of the percutaneous multilevel implant fixation system CD Horizont Longitude (Medtronic, Memphis, TN, USA). In 3 patients, the SpiRIT® system (Synthes GmbH, Oberdorf, Switzerland) was used. In 46 patients, short-segment pedicle screw instrumentation with bilateral pedicle screws (1 level above and 1 below the fracture) was performed. In 23 patients, a long-segment fixation (2 or more levels above and below fracture) was performed, with 7 patients having fractures at 2 or more levels. Additional vertebral balloon assisted endplate reduction (BAER) and cement augmentation techniques were used when substantial vertebral body comminution (more than 50%) was seen on the preoperative computed tomography (CT) scans. In 25 patients with substantial comminution of the vertebral body, this combined technique with percutaneous anterior column augmentation was performed. During the initial phase of inclusion, some of the surgeons in our group decided to use bracing following operative spinal stabilization (Table 1). All fractures were classified according to the AOSpine classification (Figure 1) [12].

Table 1 Baseline patient characteristics.

Baseline Characteristics	Value, N = 69
Gender, No. (%)	
Male	48 (70)
Female	21 (30)
Age (y), mean (SD)	45.58 (±16.59)
Underlying osseous pathology, No. (%)	
Osteoporosis	5 (7)
Ankylosing spondylitis	2 (3)
Polytrauma patients, No. (%)	35 (51)
ISS ≥ 15	15 (22)
ISS < 15	20 (29)
AOSpine classification, No. fractures (%)	
Type A (0,1,2,3,4)	41 (55)
Type A 0–2	4 (5)
Type A 3–4	37 (50)
Type B (1,2,3)	33 (44)
Type C	1 (1)
Fracture location, No. (%)	
Thoracic	17 (25)
Thoracolumbar	37 (54)
Lumbar	15 (22)
Segment fixation, No. (%)	
Short segment	46 (67)
Long segment	23 (33)

Abbreviations: ISS, injury severity score; SD, standard deviation.

Figure 1 AOSpine classification.



QOL was determined by use of EQ-5D. A survey was sent to all patients after the last follow-up visit. The EQ-5D is an instrument designed to measure generic health status across 5 dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with 3 response levels (no problems, some problems, extreme problems) [13]. A unique EQ-5D health state is defined by combining 1 level from each of the 5 dimensions, and scores range from -0.109 to 1.0, with score 1 indicating the best overall health. For validation of our EQ-5D results, we used the time trade-off for the Dutch population [14]. The radiological outcome was assessed (and its reliability tested) by 2 reviewers (I.S. and A.S.), measuring the local kyphosis and segmental wedge angles on supine preoperative and standing postoperative and follow-up x-rays. Kyphosis angle was defined as the measured angle between the superior and inferior endplates of the fractured vertebra and segmental angle as the angle of the stabilized segments measured between the superior endplate of the upper instrumented vertebra and the inferior endplate of the lower instrumented vertebra.

Statistical Methods

Analyses were done using the R statistical package version 15.2, the car and irr packages [15-16]. Baseline variables are given as absolute number and percentages when describing categorical data. For continuous variables, the mean with standard deviation (SD) is given. If the observations were nonnormally distributed, the median (Q2) and first and third quartiles (Q1–Q3) are given. The average agreement between reviewers determining the kyphosis and segmental outcomes was evaluated using the intraclass correlation coefficient (ICC) at follow up. Q-Q plots were used to determine if the outcome residuals were normally distributed. To evaluate surgery effectiveness, the kyphotic or segmental angles, postsurgery and during follow-up, were subtracted from the presurgery angles. Changes over time were analyzed using a mixed model with a random intercept for patient, time of measurement, and adjustment for baseline (presurgery) angle. As a sensitivity analysis, we corrected for differences in follow-up time, showing no improved fit. Approximate 95% confidence intervals (CIs) were calculated based on the pooled standard error and a t distribution with 68 degrees of freedom. Finally, given that the residuals of the EQ-5D were not normally distributed, which could not be ameliorated by customary transformation, Wilcoxon tests, with a continuity correction, were used.

Results

Clinical Outcome and EQ-5D

Within the cohort of 86 patients, 69 patients fulfilled the inclusion criteria for the study. The baseline characteristics of the study are described in Table 1. The mean follow up was 19 months (range=6–49 months). The study population consisted of a high percentage of men, with a high overall percentage of polytrauma patients in an average young study population, with a mean age of 46 years. The median blood loss for subjects with short-segment fixation was 50 mL (range=10–100 mL) and for long-segment fixation 108 mL (range=50–500 mL; P= 0.05). The response rate for the follow-up health survey was 78%, with an overall median EQ-5D score of 0.811 (Q1–Q3 95% CI= 0.709–0.897; $P < 0.01$). EQ-5D scores were non-significantly different, for subjects younger than 50 years of age (Q2=0.843) and older (Q2= 0.811; P=0.57). Stratifying EQ-5D for males and females again did not show significant difference in distributions (P=0.72). EQ-5D did not differ significantly for subjects with polytrauma (Q2= 0.811) versus no polytrauma (Q2=0.843; P= 0.46). The median EQ-5D scores for AOSpine classification type A and B were 0.827 and 0.811. The Spearman correlation of AOSpine classification type A and B to EQ-5D was -0.13, suggesting that the EQ-5D decreases with classification type B; however, these associations were not significant. Patients who underwent a long-segment fixation

showed no significant difference in EQ-5D (Q2=0.827 versus 0.811 in short-segment fixation; P= 0.84).

Complications

In 8.7% (6 cases), we found perioperative complications. In 4 patients, possible cerebrospinal fluid leakage was observed during insertion of the Jamshidi needles in the pedicles. After repositioning, there were no further consequences. In 1 patient, ventral K-wire migration was observed fluoroscopically during surgery without any consequences. In another patient, a loosening of the balloon was seen in a noninflated stent during a stenting procedure, without clinical consequences. In the postoperative period, cardiopulmonal, urogenital, and gastrointestinal complications predominated with a total postoperative risk of 30%. The mortality rate of the whole group was 2.9%, not procedure related. Polytrauma patients had an increased risk of perioperative complications as shown by the risk difference (RD) of 0.03 (95% CI=-0.09–0.15) and postoperative complications (0.25, 95% CI= 0.04– 0.46). The RD for perioperative complications due to long-segment fixation was 0.09 (95% CI= -0.06– 0.24), and for postoperative complications, the RD was 0.13 (95% CI=-11–0.37). There was a deep infection rate of 3% (2 cases). In both patients, the material was extracted 3 months postoperatively. There was a 6% material failure rate with 2 patients experiencing dislocations of material (Table 2).

Table 2 Complications of spinal fixation.

Type of Complication	Number
Preoperative	
Suspected dural lesion	4
K-wire migration	1
BAER balloon dislocation	1
Postoperative	
Hematoma	1
Rod dislocation	1
Bend rod	1
Dislocation of set screw	1
Screw breakage	1
Lumbosacral plexopathy	2
Wound infection	2
Wound leakage	1
Subsidence in kyphosis	1
Pneumonia	5
Urinary tract infection	2
Atrial fibrillation	1
Ileus	1
Bladder retention	1
Respiratory insufficiency	1
Pneumothorax	1

Abbrevation: BAER, balloon assisted endplate reduction.

Radiological Outcome

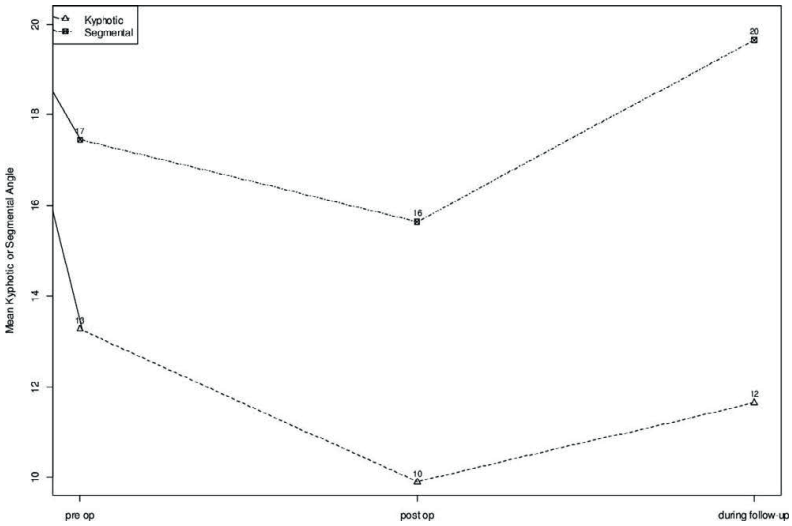
ICC at follow up between the 2 raters was 0.93 (95% CI= 0.89–0.96) for kyphosis and 0.98 (95% CI= 0.97–0.99) for the segmental angles. Assuming no difference over time, this indicates that agreement between observers is overall very high and even higher for the segmental angles. Our study showed a kyphosis correction with a kyphotic angle mean of 3.268 and segmental angle mean of 1.818 (P< 0.01). Loss of correction was calculated by subtracting follow up from postoperative measurement. The mean kyphotic subsidence was -1.99, -1.45, and -1.798 for thoracic, thoracolumbar, and lumbar locations, respectively (P=0.85). The mean segmental subsidence was -5.11, -4.19, and -2.308 for thoracic, thoracolumbar, and lumbar locations, respectively (P=0.32). The mean subsidence, based on the segmental angle was -4.668 for younger subjects (<50 years of age) and -3.068 for older subjects (P=0.23). For the kyphotic angle, the mean was -1.648 for younger subjects and -1.698 for older subjects (P=0.95). When we correlated an additional intervention (anterior column augmentation) to percutaneous pedicle screw fixation, the mean subsidence was -4.438 for the segmental angle in patients receiving kyphoplasty/vertebroplasty/vertebral body stenting (VBS) and -3.778 in subjects receiving percutaneous pedicle screw fixation as a standalone procedure (P=0.65). For the kyphotic angle, the means were -2.298 in patients receiving BAER with augmentation interventions and -1.308 in subjects receiving no additional intervention (P=0.32; Table 3, Figure 2).

Table 3 Primary outcome results.

Outcomes	Point Estimates	Mean Difference (95% CI) *P* Value
Wedge mean (SD)		Reference overall
Pre-operation	13.35 (6.74)	$P < 0.01$*
Postoperation	10.09 (5.54)	3.26 (2.06–4.45)
Last follow up	11.75 (6.21)	1.60 (0.40–2.79)
Segmental mean (SD)		Reference overall
Pre-operation	17.45 (11.34)	$P < 0.01$*
Postoperation	15.64 (11.83)	1.81 (0.05–3.56)
Last follow up	19.65 (11.37)	−2.20 (−3.96 to −0.45)
EQ-5D median (Q1–Q3)†	0.811 (0.709–0.897)	$P < 0.01$‡

Abbreviations: CI, confidence interval; EQ-5D, EuroQuol; SD, standard deviation.
*The overall *P* values for the wedge and segmental outcomes are based on a mixed model with random intercept for patient and adjusted for baseline angle.
†First and third quartiles (Q1–Q3) are given.
‡Mann-Whitney test; null-hypothesis population EQ-5D is 0.450.

Figure 2 Mean wedge and segmental angles at presurgery, postsurgery, and at last follow up.



Discussion

At present, the evolution of less invasive stabilization systems (LISSs) is adding major goals to spine surgery. Besides improving pain and neurologic deficit with a reduction of approach-related morbidity, spine surgery is focused on improving QOL. To date, several studies have described the multiple advantages of posterior pedicle screw fixation techniques in thoracolumbar fractures [1-9]. However, QOL outcome data are limited for spine trauma patients. Besides that, the role of LISSs remains unclear in treating spine fractures in polytrauma patients. Cimatti et al. evaluated Short-Form 36 questionnaire (SF-36) outcomes in a 2 year prospective study of percutaneous pedicle screw fixation in 32 patients with unstable single-level thoracolumbar fractures. Concerning the SF-36 physical scale, patients achieved 46.43 points for male, 46.19 for female patients, representing a better outcome than the back pain population (44.79) but worse compared with the scores achieved with the normal population (50.21). The average score achieved in the SF-36 psychological score was 56.22, which exceeds the scores from the back pain population (48.25) and the normal population (51.54) [17]. In the study of Schmidt et al., of the 76 patients with type A fractures who were treated with minimally invasive instrumentation, 32 patients (42.1%) had no substantial discomfort and pain as compared before surgery. Six months following surgery, 58 patients (76.3%) met their expectations or were highly pleased by their individual postoperative results [18]. In our study, we used EQ-5D for evaluation of QOL and observed a significant high overall median EQ-5D score of 0.811 (Q1–Q3 95% CI= 0.709–0.897). The EQ-5D results of the nonspecific low back pain

population is 0.731 (SD=0.172) [19]. We found no statistical significant difference in EQ-5D outcome when EQ-5D was stratified for gender, age, polytrauma, AOSpine classification, or long-segment fixation. Despite results in improvement of sagittal alignment and kyphosis correction, numerous studies report loss of correction during follow up for pedicle screw fixation [5-6, 8]. However, there is no clear correlation between the loss of correction and clinical results. Wild et al. describe a retrospective analysis of a fixation alone technique for type A fractures using a percutaneous internal fixator in 10 cases and an open procedure in 11 cases [5]. Five years after implant removal, the loss of correction of the bisegmental wedge angle averages 7.62° (median 7°; range=0° –20°; SD=4.5°) in both groups; however, neither in the Hannover-Spine-Score nor in the SF-36 Health Questionnaire did these groups show any difference. In our study, we found a mean subsidence of 1.60° for the kyphotic angle and 2.20° for the segmental wedge angle at the end of the follow-up period with a high QOL. Our use of augmentation techniques for substantial comminution has probably limited complications and loss of correction. In our study, significant comminution of the vertebral body resulted in the same radiological outcome as less comminuted fractures. In the trauma population, which is prone for infection and blood loss, lower infection rates and minimal blood loss are described for percutaneous pedicle screw fixation compared to the open techniques. Infection rates of 3.1–10% for the open surgical technique described by Verlaan et al. can be reduced to 0–1% by use of the percutaneous pedicle screw [4]. Minimal blood loss rates of 50 mL are described in percutaneous pedicle screw techniques [5-9]. In our study, the infection rate and blood loss was comparable to other studies. Posterior percutaneous pedicle screw fixation can be performed fast and less invasively in the trauma patient. The technique allows immediate stable fixation because the screws transverse all 3 columns. Anatomic or best possible alignment of the spinal column is obtained. Operation time is reduced to an average of 78 minutes. Especially in polytrauma patients with spinal fractures, the spinal column can be stabilized in an emergency setting, while limiting the risks of the patients' condition. In chest trauma, patients can be mobilized early, preventing respiratory complications [19]. The features of percutaneous pedicle screw fixation make the approach suitable for a damage control protocol. The circumstances of the critical polytrauma patient make it complex to supply level 1 evidence. However, many observational studies show a significant difference between patients who were treated with a spinal damage control regimen compared to a delayed surgery group by means of mean length of operative time, length of hospital stay, number of ventilator dependent days, and several early complications, such as wound and pulmonary complications and pressure sores [11, 20-22]. In our study, 31 patients with a type B fracture (ASIA grade E) and 1 patient with a type C fracture (ASIA grade A), with traumatic complete paraplegia who was hemodynamically unstable to perform open surgery, could be successfully stabilized by use of a percutaneous approach. In our

opinion, posterior percutaneous pedicle screw fixation technique can be used for all spinal fractures when there are no neurologic problems. Limitations of this study are the retrospective analysis of data, limited number of patients, and the heterogeneity of our population, with a large group of type A fractures. This case series represents also the learning curve of the technique. The overall young study population can confound the QOL outcomes because of general favorable results due to age. It should be noticed that our study comprises a high population (51%) of polytrauma patients, with 22% who sustained more severe injury (injury severity score [ISS] ≥15). In our opinion, the high overall postoperative complication rate of 30% as shown in our study can be clarified with this high percentage of polytrauma patients. Another limitation of this study is the use of a standard time period for measurement for QOL outcome at the end of the follow-up period. To date, a disease-specific QOL score does not exist for spinal trauma patients, and there is no valid tool to obtain preinjury QOL data. Another shortcoming of the study is the sparse use of CT scans postoperatively for fusion assessment. We only used CT scans postoperatively when patients presented with complaints. In our opinion, use of routine standard x-rays in combination with clinical results are adequate and satisfactory to assess alignment, material failure, and fracture healing. The relatively long follow-up period with a mean of 19 months (range= 6–49 months) comprising all spinal fracture locations including AO type B fractures and standardized outcome assessment (EQ-5D) represent the strength of this article.

Conclusions

Percutaneous pedicle screw fixation can be recommended in the management of traumatic thoracolumbar fractures, as well as in polytrauma cases when decompressive surgery is not necessary. Development of percutaneous spine approaches that reduce perioperative morbidity can be a good alternative approach following the damage control principles. The technique has a good overall functional outcome. Given the heterogeneity and the lack of robust evidence, these findings warrant verification in larger prospective registries and randomized controlled trials.

Disclosures and COI: No funds or grants were received for this manuscript. The authors declare no conflict of interest.

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5

CHAPTER V

Prognostication of Patients with Spinal Bone Metastases (SBM): External Validation Study Comparing the Utility of Two Current Prediction Models.

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Clinical Oncology and Research 2020;3(7): 2 - 7. doi:10.31487/j.cor.2020.02.05

Abstract

Purpose: A majority of developed prediction models for SBM are not used in clinical practice, where there is lack of external validation studies describing their performance on independent patient data.

Methods: Primary aim was to externally validate two prediction models and to demonstrate whether these can be generalized for patients treated in different centers. Secondary aim was to identify additional prognostic factors predicting survival in patients with SBM.

Results: Our results show modest predictive capacity for patients with symptomatic SBM in daily clinical practice by use of the existing two prediction models Van der Linden and Bollen. A slightly better performance in discrimination and calibration is found for the Bollen model with a C-statistic of 0.67 (95% CI: 0.63 –0.71) based on the validation dataset (95% CI: 0.65 –0.73) in contrast to Van der Linden with a C-statistic of 0.65 (95% CI: 0.60–0.71). Impact of brain or visceral metastases was significantly associated with survival, with a Hazard Ratio (HR) of 3.8 and 1.34 respectively. For breast cancer patients with SBM, hormone receptor status was of importance for prognostication (C-statistic of 0.67).

Conclusion: With this first external validation study, we found modest predictive capacity for the prediction models by van der Linden and Bollen, with a slightly better performance for the Bollen model. Predictive impact of overall visceral and brainmetastases should not be underestimated. Breast tumor subtypes based on immunohistochemistry markers, seem to be of importance for the prognostication of breast cancer patients with SBM.

Introduction

Due to improvements in systemic treatment of primary tumors, the overall survival for patients suffering from metastatic cancer is rising, resulting in a prolonged palliative phase [1, 2]. During the course of cancer, the incidence of spinal metastases varies up to 70% [3]. In more than 50%, the primary tumor for spinal metastases origins from breast, prostate, or lung cancer [3]. Spinal bone metastases (SBM) are often accompanied by a significant morbidity, causing pain due to actual or impending pathologic fractures or due to neurological complications, such as nerve root or spinal cord compression. Prediction of survival is not only crucial in counseling patients or appropriate allocation of resources, but also in selecting the most adequate treatment. Patients with a short expected survival (< 3-6 months) are likely to benefit most from a short radiotherapy course or supportive care, whereas patients with a relatively long expected survival may benefit from high-dose radiotherapy including stereotactic ablative radiotherapy, minimal invasive surgery or even more extensive surgical interventions. Over- or undertreatment due to inadequate prognostication may have a large impact on activity of daily living, dependency and quality of remaining lifespan.

Several prediction models have been developed, all with their own pitfalls, but widely used in clinical practice [4-11]. Because the performance of a prediction model is generally overestimated in the sample in which it was developed, external validation of a model in an independent sample is crucial to broadly evaluate the performance and thus the potential utility of the model in different populations and settings [12]. The Dutch Guideline Database Oncoline recommends the use of, amongst others, one of two prediction models developed in the Netherlands, the models by van der Linden and by Bollen [9, 11, 13]. Both prediction models incorporate the variables Karnofsky performance status (KPS), primary tumor, and visceral involvement in their scoring systems. The first model by Van der Linden, based on the Dutch Bone Metastasis Study (DBMS) database, is a prospective database which included only irradiated patients and stratified patients into 3 prognostic groups. No patients in the DBMS database had spinal cord compression (only patients with Harrington Class I and II lesions were included) or pathologic fracture at randomization. Patients with renal carcinoma, melanoma and cervical SBM were also excluded from randomization. The other model by Bollen stratified patients into 4 prognostic categories from a retrospective database, including surgical patients. The current study focuses on a consecutive cohort of SBM patients in a university hospital, listed for solely palliative radiotherapy or a combination of surgery and postoperative radiotherapy, also with palliative intent. The primary aim was to externally validate the two abovementioned prediction models and to demonstrate whether these prediction models could be

generalized to patients treated in different centers. Our secondary aim was to identify additional prognostic factors predicting survival in patients with SBM.

Methods

I Eligibility

The electronic medical records of consecutive patients, diagnosed with symptomatic SBM and receiving palliative radiotherapy for the first time between the January 1, 2014 – April 1, 2016, were included in this retrospective cohort study. Follow-up data were extracted from electronic medical records until November 6, 2018. Two validation cohorts were generated because of the differences in patient selection between the two models by Van der Linden and Bollen. The eligibility criteria for the Van der Linden model were similar to the original study, containing solely radiotherapy patients, and we excluded SBM which had already been irradiated for the spine, patients with renal carcinoma, melanoma, cervical SBM, spinal cord compression and pathologic fractures. The eligibility criteria for the Bollen validation cohort were similar to the original study. Prognostic factors that were analyzed were: pathologic fracture, spinal cord compression, VAS pre-treatment, lymphogenic metastases, visceral metastases, brain metastases, ER/PR/Her2Neu expression in breast cancer, and EGFR/ALK/KRAS mutation in lung cancer. Patients with direct ingrowth of the primary tumor in the vertebra, patients irradiated for bone metastases solely in the sacral or sacroiliac region, leptomeningeal or intradural metastases, metastases deriving from primary tumors of hematologic or unknown origin, metastases deriving from rare primary tumors, were excluded. The primary tumors were categorized based on the Tomita classification modified by Bollen et al. [6, 11]. The original Tomita classification used growth speed alone to assign a primary tumor into 1 of 3 groups. However, as growth speed was not the only factor determining survival, the classification was renamed "clinical profile" by Bollen to encompass other contributing factors such as availability of effective systemic treatment options for the primary tumor. The clinical profile of a primary tumor was considered to be favorable, moderate, or unfavorable. The survival status of the patient or date of death was obtained from medical records and/or Municipal Personal Records Database. The Internal Review Board (IRB) approved the study.

II Statistical Analysis

On the total cohort, we selected patients separately for the external validation of both prediction models to match the source population of the two development studies. External validation cohorts were described in terms of patient characteristics using means and standard deviations, and frequencies and percentages. For both external

validations separately, the median follow-up time was computed using the reversed-censoring method, to yield the median follow-up time for survivors. Overall survival measures were computed and visualised using Kaplan Meier estimates.

III External Validation

Individual patient risk scores were calculated for external validation. For the model by Bollen a risk score was computed based on the estimated regression coefficients of the Cox Proportional Hazards regression. In order to accomplish this, we computed the natural logarithm of the Hazard Ratios (HRs) that were reported in the study and computed each individual's linear sum of regression coefficients multiplied by their respective predictor value. This step was performed as predictors are only additive on the log HR scale. The formula which was derived for the model by Bollen was: Bollen score = log(1.6)*Moderate clinical profile (yes = 1) + log(3.5)*Unfavourable clinical profile (yes = 1) + log(1.9)*Impaired Karnofsky performance status (yes = 1) + log(1.5)*Visceral/brain metastases present (yes = 1).

The manuscript by Van der Linden Hazard Ratios did not report regression coefficients or HRs. Therefore, we were only able to validate the simplified risk score in our data. The formula which was derived for the model by Van der Linden was: Van der Linden score = Karnofsky performance status (50-70 = 1, 80-100 = 2) + primary tumor (lung = 1, prostate = 2, breast = 3) + visceral metastases (no = 1). Karnofsky performance scores were not readily available for the study population and were derived from the WHO performance status of the patients. Based on expert opinion (group of 10 radiation oncologists of the MAASTRO clinic), the following conversion table was used: WHO 0- 1: KPS 80-100%, WHO 2-3: KPS 50-70%, WHO 4: 10-40%.

The performance of the prediction models was evaluated by assessing discrimination and calibration [14, 15]. Discrimination describes the ability of a prediction model to distinguish individuals who experience the outcome sooner versus those who remain event free or experience the outcome later. Predictive performance was expressed as the concordance-statistic, or Harrell's C-statistic, a generalization of the area under the Receiver Operating Characteristic curve. A C-statistic of 0.5 indicates the model performs no better than chance; a C-statistic of 0.7 to 0.8 indicates modest or acceptable discriminative ability, and a threshold of greater than 0.8 indicates good discriminative ability [16].

A calibration plot was plotted comparing predicted versus actual probabilities to those provided for subgroups in the original manuscripts. A 45 degree line would indicate perfect agreement between the predicted probabilities by the model, and the actual, or observed, probabilities in our cohort. Both prediction models presented clinical

profiles based on total scores (e.g. A, B, C and where applicable D groups), which were replicated in our data. Both Kaplan Meier curves were subsequently stratified by clinical profile. We used the log rank test to test for differences in survival between strata.

Results

A total cohort of 250 patients was included in the study, of which 128 patients were eligible for external validation of the prediction model by Van der Linden, and all 250 were eligible for external validation of the model by Bollen. Detailed patient and treatment characteristics of the total study cohort are shown in (Table 1). Figure 1 shows the Kaplan-Meier curve for the cohort.

Table 1 Baseline characteristics total study population (n=250).

Gender	**N (%)**
Male	143 (57.2%)
Female	107 (42.8%)
Age at time of RT (mean +SD y)	69 ±10.9
Radiation field	
Cervical	16 (6.4%)
Cervicothoracic	11 (4.4%)
Thoracic	91 (36.4%)
Thoracolumbal	30 (12%)
Lumbal	84 (33.6%)
Multiple locations	18 (7.2%)
Radiation dose	
1x8 Gy	166 (66.4%)
5x4 Gy	76 (30.4%)
10x3 Gy	6 (2.4%)
13x3Gy	2 (0.8%)
Treatment	
RT only	242 (96.8%)
RT and surgery	8 (3.2%)
VAS pretreatment (mean SD cm)	6.5±2.4
valid	176 (70.4%)
missing	74 (29.6%)
Number spinal metastases	
1 or 2	107 (42.8%)
multiple	143 (57.2%)
Visceral metastases	
present	96 (38.4%)
not present	154 (61.6%)
Brain metastases	
present	11 (4.4%)
not present	239 (95.6%)

Table 1

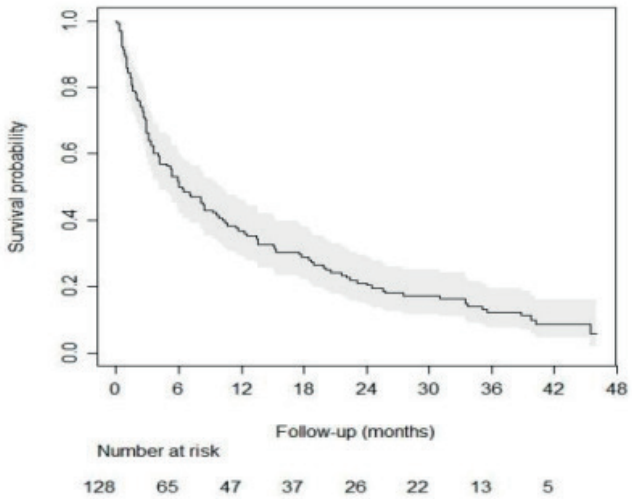
Lymphogenic metastases	
present	114(45.6%)
not present	136(54.4%)
Clinical profile	
Favorable	50 (20%)
Moderate	71 (28.4%)
Unfavorable	129 (51.6%)
Breast cancer (total N=49)	
Hormone receptorstatus	4 (1.6%)
ER/PR positive, Her2 positive	28 (11.2%)
ER/PR positive, Her2 negative	2 (0.8%)
ER/PR negative, Her2 positive	3 (1.2%)
ER/PR negative, Her2 negative	9 (3.6%)
ER+/PR-, Her2 negative	1 (0.4%)
ER+/PR-, Her2 postive	1 (0.4%)
ER+/PR+, Her2 unknown	1 (0.4%)
ER negative, Pr+, Her2 negative	
Lung cancer type (total N=76)	
NSCLC	62 (81.6%)
SCLC	12 (15.8%)
not defined	2 (2.6%)
EGFR/ALK mutation NSCLC	
present	6 (9.6%)
not present	24 (38.7%)
unknown	32 (51.6%)
KRAS mutation NSCLC	
present	18 (29%)
not present	8 (13%)
unknown	36 (58%)
KPS	
80-100	105 (42%)
10-70	145 (58%)

I External Validation of the Prediction Model by Bollen

The median follow-up time of survivors was 42.3 months. The median survival time for the 250 patients in this external validation cohort was 5.9 months (95% CI: 4.2 –8). Figure 1 shows the survival curve for the external validation cohort we used for the model by Bollen. When using the suggested simplified risk score (groups A through D), the C-statistic was 0.67 (95% CI: 0.63 –0.71). The Kaplan Meier curves stratified by this simplified score is shown in (Figure 2). The four groups do not overlap and make a clear distinction between low- and high risk of survival. The 1-year survival for the four groups are 92.9% (95% CI: 59.1 – 99.0), 63.6% (95% CI: 49.5 – 74.8), 28.9% (95% CI: 20.5 – 37.7), and 10.4% (95% CI: 4.9 – 18.4) for risk group A, B, C, and D, respectively. The calibration plot comparing predicted survival according to the Bollen model versus the actual survival probability observed in the

external validation cohort is shown in (Figure 3). It shows good agreement between survival probabilities according to the manuscript by Bollen and those in the external validation cohort.

Figure 1 Kaplan Meier curve of the overall survival in the external validation cohort for the Van der Linden prediction model.



*The grey area denotes the 95% confidence band.

Figure 2 Kaplan Meier curve stratified by clinical profile for the van der Linden prediction model.

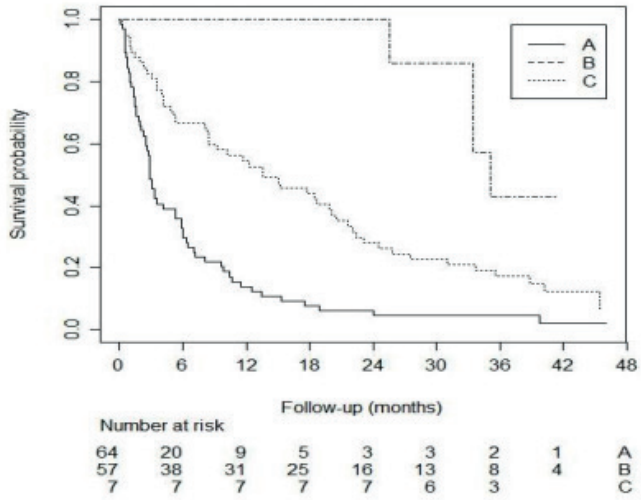
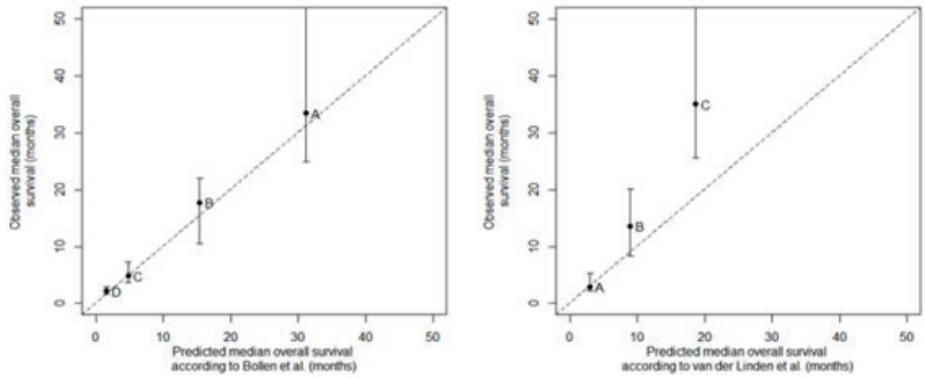


Figure 3 Calibration plots with predicted versus actual probabilities.



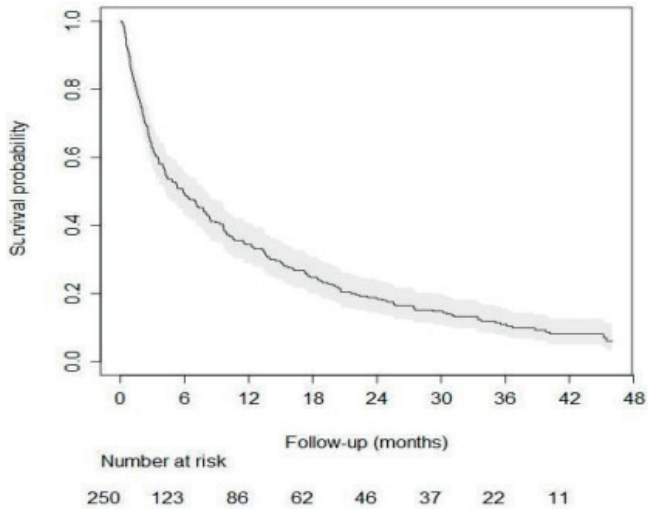
N=14(A), N=55(B), N=104(C), N=77(D)

N=64(A), N=57 (B), N=7 (C)

II External Validation of the Prediction Model by van der Linden

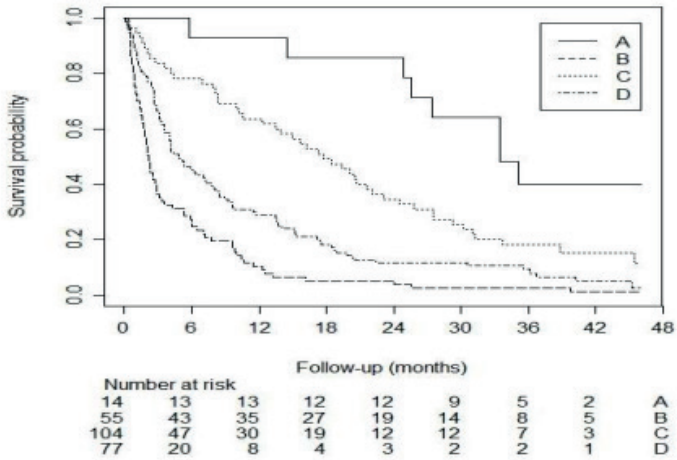
The patients who survived during the course of follow-up had a median follow-up time of 41.4 months. The median survival time for the 128 patients was 6.2 months (95% confidence interval [CI]: 4.2 – 9.6). Figure 4 shows the survival curve for the external validation cohort we used for the model by van der Linden. A simplified risk score was published by creating three risk groups: A, B, and C. The C-statistic for this simplified risk score was: 0.65 (95% CI: 0.60–0.71). A Kaplan Meier curve stratified by the simplified risk score is shown in (Figure 5). It shows that the three risk groups do not overlap and that there is a substantial difference in survival between the three groups. The 1-year survival probability for risk group A, B, and C are 14.1% (95% CI: 6.9 – 23.7), 54.4% (95% CI: 40.7 – 66.2), and 100% (95% CI: 100 – 100). The calibration plot is shown in (Figure 3). It shows the survival probability for each group according to the original publication on the x-axis, and the actual survival probability in our cohort on the y-axis. The simplified risk score by van der Linden yields underestimated risks compared to patients in the external validation cohort.

Figure 4 Kaplan Meier curve of the overall survival in the external validation cohort for the Bollen prediction model.



*The grey area denotes the 95% confidence band.

Figure 5 Kaplan Meier curve stratified by clinical profile for the Bollen prediction model.

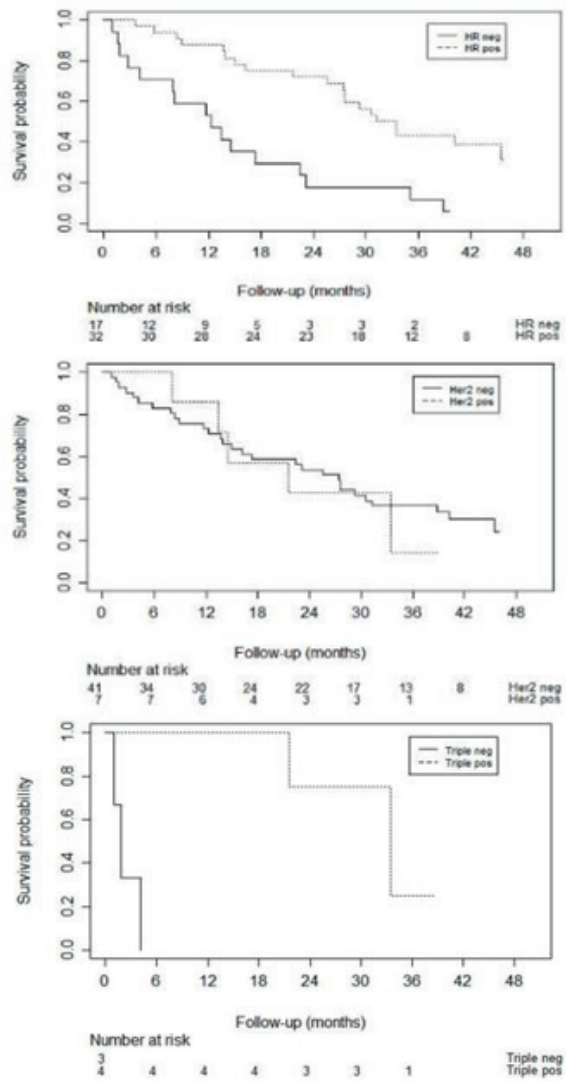


III Prognostic Factors

Impact of brain or visceral metastases was significantly associated with survival, the presence of brain metastases showed an HR of 3.8 (95% CI: 2.0 – 7.1, $p < 0.001$) and HR of 1.34 for visceral metastases (95% CI: 1.0 – 1.8, $p = 0.030$). VAS score of pain at baseline, which was scored as a continuous variable, was not significantly associated with survival (HR 1.1, 95% CI: 0.94 – 1.07, $p = 0.971$). We found no evidence of an effect on survival for the presence of a pathologic fracture (HR = 0.99,

95% CI: 0.72 – 1.34, p = 0.926), spinal cord compression (HR = 1.03, 95% CI: 0.76 – 1.30, p = 0.866), or the presence of lymphogenic metastases (HR = 1.06, 95% CI: 0.82 – 1.38, p = 0.651). In breast cancer patients different tumor expressions were associated with survival (C-statistic: 0.67), as shown in (Figure 6). In lung cancer patients, we did not find an association between different tumor types (non-small cell versus small cell, HR = 0.95, 95% CI: 0.50-1.82). Because of few events, we did not reach significant power to perform a survival analysis for the epidermal growth factor (EGFR)/anaplastic lymphoma kinase (ALK)/Kras (KRAS) mutations.

Figure 6 Kaplan meier curves for the survival of breast cancer patients with different tumor expressions.



Discussion

Although the analyzed models are relatively simple to use in clinical practice and impose no additional burden on both patient and physician, the existing models fall short in performance. We hypothesize that the incorporation of histological and molecular subtypes of the primary tumor would yield more discriminative ability. Especially for the most common primary malignancies of SBM patients, like breast- and lung cancer. We think that there is substantial heterogeneity between these subgroups with different effects on treatment and variation of median survival within the same primary cancer, with a significant part of patients who may benefit from more aggresive treatment. In our study we showed that the C-statistic for the variable tumor expression in breast cancer was 0.67, indicating moderate discriminative ability. A study of Tan et al. showed that the breast tumor histological subtype was of crucial importance for the prognostication of breast cancer patients with spinal metastases[17]. The revised Tokuhashi score 2014 suggested that hormone receptor negative and triple-negative breast cancer patients should be given a modified Tokuhashi histological score of 3 rather than a score of 5. Besides these interesting findings for breast cancer, Kumar et al. found differences in prognosis in spinal metastases patients with small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) [18]. While the median survival time of SCLC patients was 2.4 months (95% CI 2.13-2.68) with a 6-month survival of 16.7%, the median survival of NSCLC patients was 5.1 months (3.78-6.41) with a 6-month survival of 47.5%. In addition, patients with an EGFR mutation and patients on a combinationtherapy of EGFR tyrosine kinase inhibitors and platinum doublet chemotherapy reached a median survival of 13.3 months and a 6-month survival of 72.7%, which was significantly better than the overall survival of all types of lung cancer (6-month survival up to 44.4%). In our study sample, only 6 patients (9.6%) had a confirmed epidermal growth factor (EGFR)/anaplastic lymphoma kinas (ALK) mutation. Because of the small number of patients in our cohort, we did not have significant statistical power to perform a survival analysis for these prognostic factors. A recent systematic review suggested that prognostication for patients with spinal metastases should be based on an accurate primary tumor classification, combined with a performance score, in which the added benefit of visceral metastases and other possible predictive factors should be studied further [19]. In our study brain and visceral metastases were significantly associated with survival, with an HR of 3.8 for brain metastases and HR of 1.34 for visceral metastases.

A review of Gotay et al. showed that in 36 of the 39 cancer studies (metastatic and non-metastatic disease) at least one patient-reported outcome was significantly associated with survival in the multivariate analysis [20]. In 7 of these 36 studies pain was a significant patient reported outcome related to survival. Also, in the study of

Westhoff et al. a higher patient reported pain score was associated with a higher risk of death. This study used follow-up questionnaires consisting, amongst others, of a pain scale. Pain was measured using an 10-point numeric rating scale, ranging from 0 (no pain) to 10 (the worst pain imaginable) [21]. However, in our multivariable analysis, patient-reported pain score did not contribute to the prediction of survival. We used reported VAS scores in the electronic medical records of our study patients. Moreover, tumor biology information could add more value. Features derived from radiomic analysis can provide tumor biology in vivo information that is complementary to other relevant clinical information in prediction of survival and can augment current available clinical decision support systems. With this method, it is possible to extract diverse quantitative features from digital images from CT or MRI and make a correlation with pathologic substrates, which can be used as imaging biomarkers. Various studies have shown the potential of radiomics features in prediction of survival [22-24].

The main strength of the current study is that this is the first study to externally validate and compare two prediction models recommended by the Dutch Guideline Database Oncoline. The retrospective design is a limitation of our study. Additionally, the relatively small patient cohort restricted the power and hampered analysis of specific prognostic variables like EGFR mutation, which may be relevant. Only 48.4% of our lung cancer patients underwent EGFR testing, and although this testing rate is in line with the worldwide literature, the testing rate is still low [25].

In conclusion we have externally validated two existing prediction models. Although the models successfully grouped patients into lower-and higher-risk strata, accurate individualized prediction remains suboptimal. A slightly better performance in discrimination and calibration is found for the Bollen model. Caution is warranted, when making individual clinical decisions based on the analyzed prediction models. In our study we found an essential predictive impact of overall visceral and brainmetastases. Besides, breast tumor subtypes based on immunohistochemistry markers, seem to be of importance for the prognostication of breast cancer patients with SBM.

Conflicts of Interest None

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6

CHAPTER VI

Radiomics biopsy signature for predicting survival in patients with spinal bone metastases (SBMs).

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Clin Transl Radiat Oncol. 2022 Jan 5;33:57-65. doi: 10.1016/j.ctro.2021.12.011.

Abstract

Study design: Retrospective analysis of a registered cohort of patients treated and irradiated for metastases in the spinal column in a single institute.

Objective: This is the first study to develop and internally validate radiomics features for predicting six-month survival probability for patients with spinal bone metastases (SBM).

Background data: Extracted radiomics features from routine clinical CT images can be used to identify textural and intensity-based features unperceivable to human observers and associate them with a patient survival probability or disease progression.

Methods: A study was conducted on 250 patients treated for metastases in the spinal column irradiated for the first time between 2014 and 2016, at the MAASTRO clinic in Maastricht, the Netherlands. The first 150 available patients were used to develop the model and the subsequent 100 patient were considered as a test set for the model. A bootstrap (B = 400) stepwise model selection, which combines both the forward and backward variable elimination procedure, was used to select the most useful predictive features from the training data based on the Akaike information criterion (AIC). The stepwise selection procedure was applied to the 400 bootstrap samples, and the results were plotted as a histogram to visualize how often each variable was selected. Only variables selected more than 90 % of the time over the bootstrap runs were used to build the final model. A prognostic index (PI) called radiomics score (radscore) and clinical score (clinscore) was calculated for each patient. The prognostic index was not scaled, the original values were used which can be extracted from the model directly or calculated as a linear combination of the variables in the model multiplied by the respective beta value for each patient.

Results: The clinical model had a good discrimination power. The radiomics model, on the other hand, had an inferior performance with no added predictive power to the clinical model. The internal imaging characteristics do not seem to have a value in the prediction of survival. However, the Shape features were excluded from further analyses in our study since all biopsies had a standard shape hence no variability.

Introduction

Spinal bone metastases (SBMs) are often accompanied by a significant burden of morbidity, causing cancer-induced bone pain, pathologic fractures, or neurological complications as a consequence of nerve root and spinal cord compression, leading to a reduced quality of life and impaired survival [1]. An accurate estimation of survival is required to prevent invasive surgery in patients with only a short-term survival expectancy and to prevent the omission of treatment in patients with a more prolonged survival. Two systematic reviews showed that physicians' assessment of life expectancy based solely on their clinical experience is inaccurate [2–4]. Controversies often exist between the best clinical practices determined by scientific evidence and the actual care provided to patients; about 30–40 % of patients do not receive care based on the current scientific evidence, and about 20–25 % of the care provided is unnecessary or even potentially harmful to patients [5]. Hence, prediction of prognosis is crucial for counselling patients and for selecting the most adequate treatment for a patient, thus ensuring appropriate allocation of health care resources. Several studies have been published to assess the prognostic value of single variables, and multiple variables combined into predictive models. However, existing predictive models lack discriminative ability, particularly predicting which patients will survive for more than 3 to 6 months and become potential candidates for surgical treatment [5–15]. Therefore, there's a significant need for new prognostic biomarkers. Tissue markers derived from tumor biopsies usually represent only a small tumor subregion at a single time point. Therefore, they are often not representative of the tumors' biology or the biological alterations during and after treatment. Radiomics has the potential to give complete three-dimensional tumor information. Radiomics, which extracts and analyses vast amounts of advanced quantitative imaging features with high throughput from medical images like Computed Tomography (CT), is gaining interest in health care and becoming increasingly important [16].

The analyses of Big Data (Omics) allows us to define biomarker signatures, which may significantly improve the prediction of outcomes [17]. Extracted radiomics features from routine clinical CT images can be used to train a machine-learning prediction model to identify textural and intensity-based features unperceivable to human observers and associate them with a patient survival probability or disease progression. Furthermore, these predicted probabilities can be used to classify patients into risk categories for more precise and timely therapeutic interventions. These non-invasive techniques for guiding treatment decisions could complement the present conventional methods. And with our increasing knowledge of cancer biology, these techniques could play an essential role in the future of cancer treatment.

The aim of this study was to develop and internally validate radiomics features in a predictive model. Can the use of (current) radiomics help improve the prediction of survival as based on clinical features in SBM patients?

Materials & methods

Patients A retrospective study was conducted on 250 patients treated for metastases in the spinal column irradiated for the first time between January 1, 2014, and December 31, 2016, at the MAASTRO clinic in Maastricht, the Netherlands. The first 150 available patients were used to develop the model and the subsequent 100 patient were considered as a test set for the model. Of the 100 patients included in the test data, 13 (13 %) had no images reducing the test data set to 87 patients. The following patient characteristics were considered for their prognostic value for predicting survival: age, gender, primary tumor type metastasis, location treated spinal metastases causing symptoms, radiation field, radiotherapy fractionation schedule, pathological fracture, spinal compression, lymphatic metastases, pain score, visceral metastases, brain metastases, World Health Organization (WHO) performance score. The primary tumors were categorized based on the classification used by Bollen et al. [11]. In the original Tomita classification, growth speed alone was used to assign a primary tumor into 1 of 3 groups [6]. Bollen renamed the classification "clinical profile" to encompass other contributing factors such as the availability of effective systemic treatment options for the primary tumor. The clinical profile of a primary tumor was considered to be favorable, moderate, or unfavourable [11]. These variables were complemented with SBM tumor characteristics by the use of Radiomics analysis.

Feature extraction and processing

One physician (IS) and a physician assistant (KtH) independently segmented the regions of interest by taking multiple (5 to 10) "virtual" biopsies (A small portion of the ROI that is large enough to capture the heterogeneity of the tumor) of 1 cm in diameter from the obtained CT scans. Seven feature classes were extracted using the Ontology-guided Radiomics Analysis Workflow (O-RAW) version 2.0 software (https://gitlab.com/UM-CDS/o-raw).

- Shape
- First-order
- Texture:

o Gray Level Dependence Matrix (GLDM)

o Gray Level Size Zone Matrix (GLSZM)

o Gray Level Co-occurrence Matrix (GLCM)

o Gray Level Run Length Matrix (GLRLM)

o Neighboring Gray Tone Difference Matrix (NGTDM)

The Shape features were excluded from further analyses since all biopsies had a standard shape hence no variability. To ensure reproducibility, the intra-class correlation coefficient (ICC), which evaluates the degree of agreement and correlation between measurements, was used to assess the stability and robustness of the extracted radiomics feature values between the two physicians (ICC < 0.50, low agreement; 0.50 ≤ ICC < 0.80, median agreement; ICC ≥ 0.80, high agreement). The maximum value of ICC is 1, which indicates perfect agreement. The lower the ICC, the lower the similarity among the features extracted values between the two physicians. Only features with an ICC > 0.8 were considered for subsequent analyses.

Feature selection and signature building

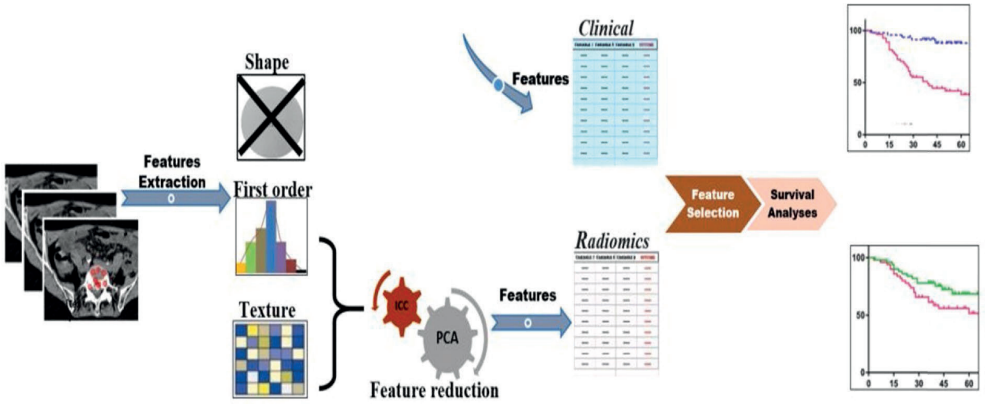
A bootstrap (B = 400) stepwise model selection, which combines both the forward and backward variable elimination procedure, was used to select the most useful predictive features from the training data based on the Akaike information criterion (AIC). Only variables selected more than 90 % of the time over the bootstrap runs were used to build the final model. A prognostic index (PI) called radiomics score (rad-score) and clinical score (clinscore) was calculated for each patient via a linear combination of the selected features and weighted by their respective regression coefficients for a practical application. Higher values for these scores indicate a poorer prognosis for the patients'survival outcomes.

Statistical analysis

Exploratory data analysis (EDA) and principal component analysis (PCA) were performed to detect abnormal patterns and possible outliers within the data. Survival time was defined as the difference between the start of treatment for the spinal metastasis and the date of death or last follow-up record. Those patients alive at the end of their follow-up were censored. Cox proportional hazard regression models were fitted to evaluate the performance of the selected clinical and radiomic predictors. Harrell's C statistic, which estimates the probability of concordance between predicted and observed responses, was used to validate the models' predictive value. Survival curves

were estimated using the Kaplan-Meier method, and log-rank tests were used to compare the differences in survival curves. A p-value <0.05 was considered statistically significant. The Z-score transformation was applied to have the radiomics features on the same scale. Fig. 1 shows the analysis schema for this study.

Fig. 1 Analyses scheme for building the spinal metastases models to predict siX months' survival using radiomics biopsy and clinical information.



Software packages

Statistical analysis, model training, validation, and visualization were performed in R version 3.6.1.

Results

The majority of the patients in the study were males 135 (57 %), and the median age (range) of all patients was 68 years (24–92 years) (Table 1). There was no statistically significant difference between patients who were alive and those who died for almost all the variables for both the train and test data, except for the variables clinical profile and visceral metastases. The pain score variable was excluded from the analyses because of the high percentage of missing values. The interobserver agreement of the extracted features was good (Table 2). Hence, the median biopsy radiomics value for each patient was considered in this study. The first radiomic feature reduction process, which considered only features with an ICC value above 0.8 and the exclusion of shape features, reduced the radiomics feature from 105 to 19. Two patients, one with a missing WHO performance score (Table 1) and another with extreme outlying value (Fig. 1, supplementary material) due to artifacts on the image, were excluded reducing

the total training sample size to 148. The stepwise selection procedure selected three radiomics features (glszm Small Area Emphasis, gldm Small Dependence Emphasis, gldm Dependence Non-Uniformity Normalized) and two clinical features (Clinical profile and WHO performance score) as shown in Fig. 2. The median follow-up time was 22.37 (95 % CI: 10.22–36.14) and 15.21 (95 % CI: 9.79–20.60) months for the training and testing data, respectively.

Table 1 Detailed characteristic of the studied cohorst

Characteristic	Train on 150			Validate on 87		
	Dead	Alive	p-value	Dead	Alive	p-value
Age at RT in years [mean (Min-Max)]	67 (24–92)	68 (46–88)	0.524	72 (50–88)	67 (39–86)	0.041
Sex						
Male	39 (48.8 %)	41 (51.2 %)	0.844	31 (56.4 %)	24 (43.6 %)	0.392
Female	33 (47.1 %)	37 (52.9 %)		15 (46.9 %)	17 (53.1 %)	
WHO performance score						
Restricted	28 (40.0 %)	42 (60.0 %)	0.174	13 (46.4 %)	15 (53.6 %)	0.215
Self-care	29 (50.0 %)	29 (50.0 %)		17 (47.2 %)	19 (52.8 %)	
Limited Self-care	14 (66.7 %)	7 (33.3 %)		16 (72.7 %)	6 (27.3 %)	
Missing	1 (100 %)	0(0.0 %)		0 (0.0 %)	1 (100 %)	
Clinical profile						
Favorable	3 (8.8 %)	31 (91.2 %)	<0.005	4 (28.6 %)	10 (71.4 %)	0.021
Moderate	15 (37.5 %)	25 (62.5 %)		11 (42.3 %)	15 (57.7 %)	
Unfavorable	54 (71.1 %)	22 (28.9 %)		31 (66.0 %)	16 (34.0 %)	
Location treated spinal metastases						
Diffuse	22 (66.7 %)	11 (33.3 %)	0.212	6 (46.2 %)	7 (53.8 %)	0.692
Cervical	4 (40.0 %)	6 (60.0 %)		2 (33.3 %)	4 (66.7 %)	
Lumbar	23 (40.4 %)	34 (59.6 %)		15 (57.7 %)	11 (42.3 %)	
Thoracic	23 (46.0 %)	27 (54.0 %)		23 (54.8 %)	19 (45.2 %)	
Number of spinal metastases						
1	15 (45.5 %)	18 (54.5 %)	0.486	10 (66.7 %)	5 (33.3 %)	0.308
2	17 (41.5 %)	24 (58.5 %)		07 (63.6 %)	04 (36.4 %)	
3 or more	40 (52.6 %)	36 (47.4 %)		29 (47.5 %)	32 (52.5 %)	
# of extra spinal bone metastases						
None	23 (46.9 %)	26 (53.1 %)	0.376	6 (60.0 %)	4 (40.0 %)	0.883
1 or 2	13 (61.9 %)	8 (38.1 %)		5 (50.0 %)	5 (50.0 %)	
3 or more	36 (45.0 %)	44 (55.0 %)		35 (52.2 %)	32 (47.8 %)	
Visceral metastases						
Present	32 (59.3 %)	22 (40.7 %)	0.038	26 (66.7 %)	13 (33.3 %)	0.020

Table 1

Characteristic	Train on 150			Validate on 87		
	Dead	Alive	p-value	Dead	Alive	p-value
Not present	40 (41.7 %)	56 (58.3 %)		20 (41.7 %)	28 (58.3 %)	
Brain metastases						
Present	9 (100 %)	0 (0.0 %)	0.001	2 (100 %)	0 (0.0 %)	0.176
Not present	63 (44.7 %)	78 (55.3 %)		44 (51.8 %)	41 (48.2 %)	
Pain score						
No pain	1 (33.3 %)	2 (66.7 %)	0.251	1 (33.3 %)	2 (66.7 %)	0.784
Mild	2 (28.6 %)	5 (71.4 %)		2 (66.7 %)	1 (33.3 %)	
Moderate	16 (64.0 %)	9 (36.0 %)		6 (60.0 %)	4 (40.0 %)	
Severe	11 (45.8 %)	13 (54.2 %)		10 (66.7 %)	5 (33.3 %)	
Very severe	19 (48.7 %)	20 (51.3 %)		10 (43.5 %)	13 (56.5 %)	
Worst possible	6 (75.0 %)	2 (25.0 %)		2 (40.0 %)	3 (60.0 %)	
Missing	17 (38.6 %)	27 (61.4 %)		15 (53.6 %)	13 (46.4 %)	
Pathological fracture						
Yes	15 (50.0 %)	15 (50.0 %)	0.806	14 (53.8 %)	12 (46.2 %)	0.906
No	57 (47.5 %)	63 (52.5 %)		32 (52.5 %)	29 (47.5 %)	
Spinal compression						
Yes	8 (28.6 %)	20 (71.4 %)	0.022	12 (54.5 %)	10 (45.5 %)	0.856
No	64 (52.5 %)	58 (47.5 %)		34 (52.3 %)	31 (47.7 %)	
lymphatic metastases						
Present	32 (53.3 %)	28 (46.7 %)	0.286	24 (53.3 %)	21 (46.7 %)	0.929
Not present	40 (44.4 %)	50 (55.6 %)		22 (52.4 %)	20 (47.6 %)	

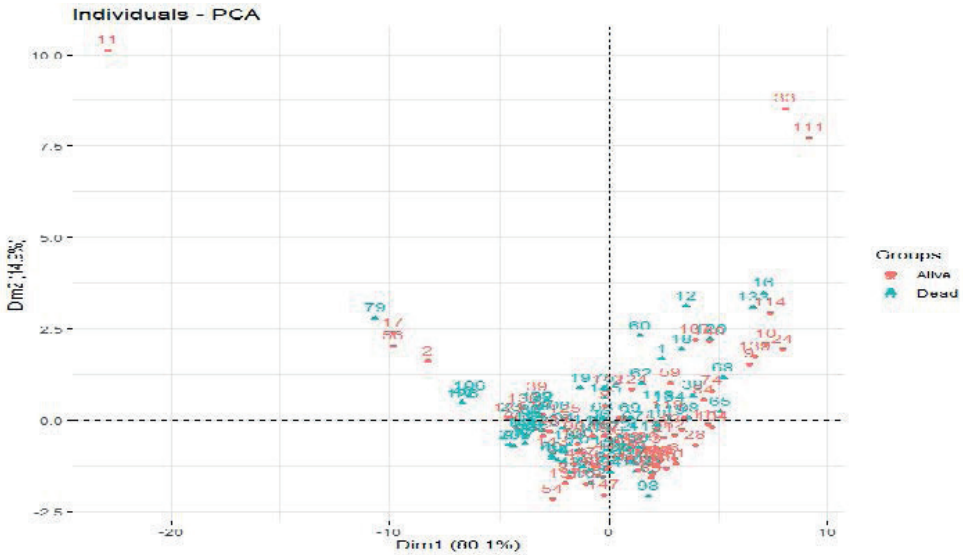
RT: Radiotherapy, #: Number.

Table 2

N-⁰	Stability class	N	ICC	ICC (95 % CI)
1	First order statistics			
	High stability	8	0.810	0.795–0.823
	Medium stability	8	0.510	0.478–0.540
	Low stability	1	0.330	0.292–0.366
2	Gray Level Co-occurrence Matrix (GLCM)			
	High stability	3	0.820	0.805–0.833
	Medium stability	13	0.500	0.468–0.530
	Low stability	6	0.240	0.200–0.278
3	Gray Level Run Length Matrix (GLRLM)			
	High stability	1	0.810	0.795–0.823
	Medium stability	7	0.52	0.488–0.549
	Low stability	8	0.240	0.200–0.278
4	Gray Level Size Zone Matrix (GLSZM)			
	High stability	5	0.810	0.795–0.823
	Medium stability	7	0.54	0.509–0.568
	Low stability	4	0.24	0.200–0.278
5	Gray Level Dependence Matrix (GLDM)			
	High stability	2	0.820	0.805–0.833
	Medium stability	6	0.680	0.656–0.701
	Low stability	6	0.240	0.200–0.278
6	Neighbouring Gray Tone Difference Matrix (NGTDM)			
	High stability	1	0.800	0.784–0.814
	Medium stability	4	0.500	0.468–0.530
	Low stability	–	–	–

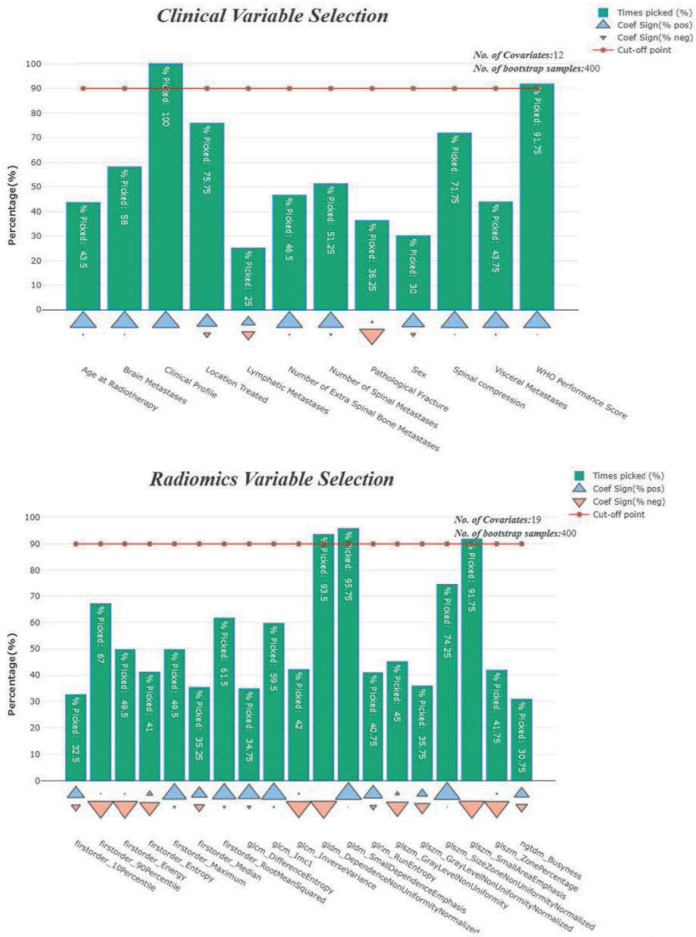
Inter-observer analysis, showing the ICC values and the number of stable features per feature group, defined as high (ICC>0.8), median (0.8>ICC<0.5), and low (ICC<0.5) stability.

Fig. 1, supplementary material.



PCA biplot showing individuals' contributions to the first and second principal components by their survival status. Patients 33 and 111 are somewhat different from the others and patient 11 is clearly different. A reexamination of the images of these patients reviled some artifacts for patient 11 and was excluded from further analysis.

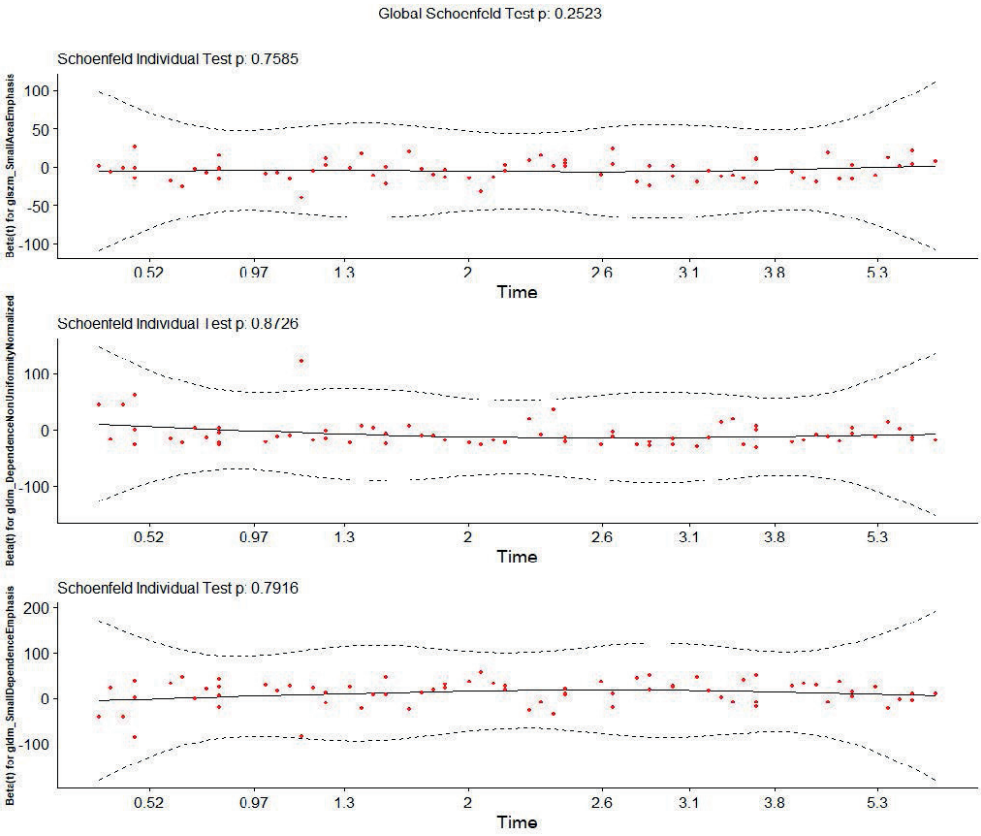
Fig. 2



Bootstrap (B = 400) stepwise variable selection procedure for the clinical and radiomics data. The green bars show the percentage of time a variable was selected. The blue and red triangles (Coef Sign) show a represented rate of times the variable's coefficient was positive or negative in each bootstrap run, respectively. The horizontal line shows the cut-off point for selected variables. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The three radiomic features and two clinical features selected by the stepwise procedure in the training dataset were used to compute the radscores- and clinscores. The proportional hazards assumption was supported since there was a non-significant relationship between scaled Schoenfeld residuals and time. The plot of the scaled Schoenfeld residuals against the transformed time also had no pattern (Fig. 2, supplementary material).

Fig. 2, supplementary material.



The scaled Schoenfeld residuals for each radiomics feature against the transformed time. The solid line is a smoothing spline fit to the plot, with the dashed lines representing a +/- 2-standard-error band around the fit.

Table 3 shows the univariable and multivariable performance of the scores in the training and testing data. As observed from the table, both scores are significant independent prognostic factors for six months survival in the train data with a p-value <0.05. However, the discriminating power of the radscore model was lower than the clinscore model with a C-index of 0.623 (95 % CI: 0.553–0.693). The clinscore models, on the contrary, had a relatively better discriminating power with a C-index of 0.731 (0.682–0.801). Based on the results of multivariable analysis, both scores were still significantly associated with the outcome (p-value < 0.05), but with a C-index of 0.740 (0.686–0.794), which is an indication that the radiomics model adds little or no information to the clinical model.

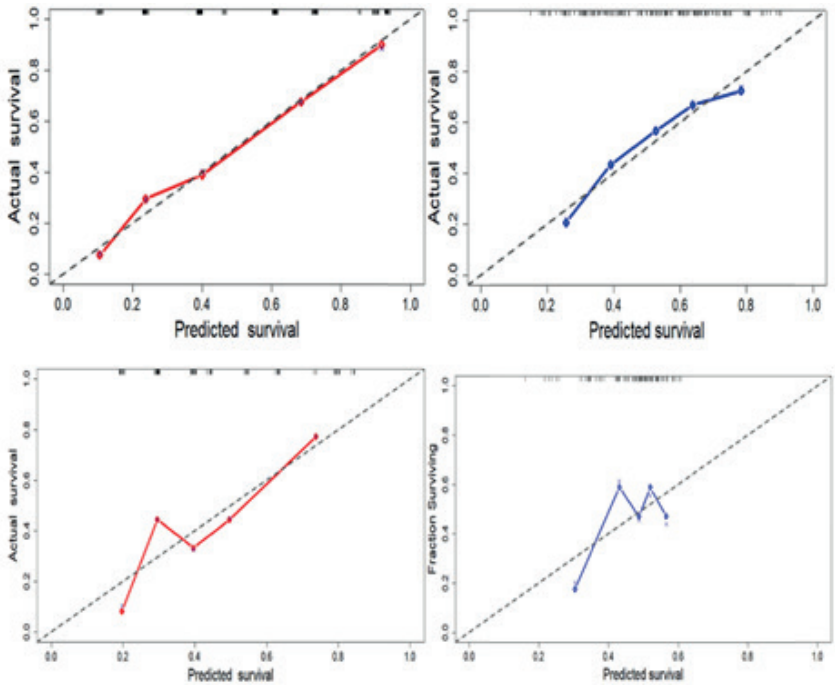
Table 3 Univariate an multivriate predictive performance of the scores.

Variables	Training Data		Testing data
	C-index (95 % CI)	p-value	C-index (95 % CI)
Univariate scores			
RadScore	0.623 (0.553–0.693)	<0.05	0.570 (0.497–0.642)
ClinScore	0.731 (0.682–0.801)	<0.05	0.686 (0.602–0.770)
Multivariate scores			
RadScore	0.740 (0.686–0.794)	0.01	0.669 (0.598–0.740)
ClinScore		<0.05	

The clinscore still had a decent discriminating power in the test data, but with a slightly low C-index of 0.686 (0.602–0.770) compared to the train data. The radscore, on the other hand, had a poor performance with a C-index of 0.570 (0.497–0.642), which is only slightly better than a random guess. The multivariable model with both scores shows that the addition of the radscore negatively affected the model's discriminating power with a reduced C-index value of 0.669 (0.598–0.740), which might indicate overfitting.

The calibration plot, which measures the similarities between the observed and predicted probabilities, was used to evaluate further the performance of the score models in the training and testing data. The closer the points are to the diagonal dotted line, the more accurate the model predicts the outcome. Fig. 3 show that the model is well calibrated on the train data, especially for clinscore. However, the model looks less well-calibrated on the test data, especially the radscore with its point falling far from the diagonal line.

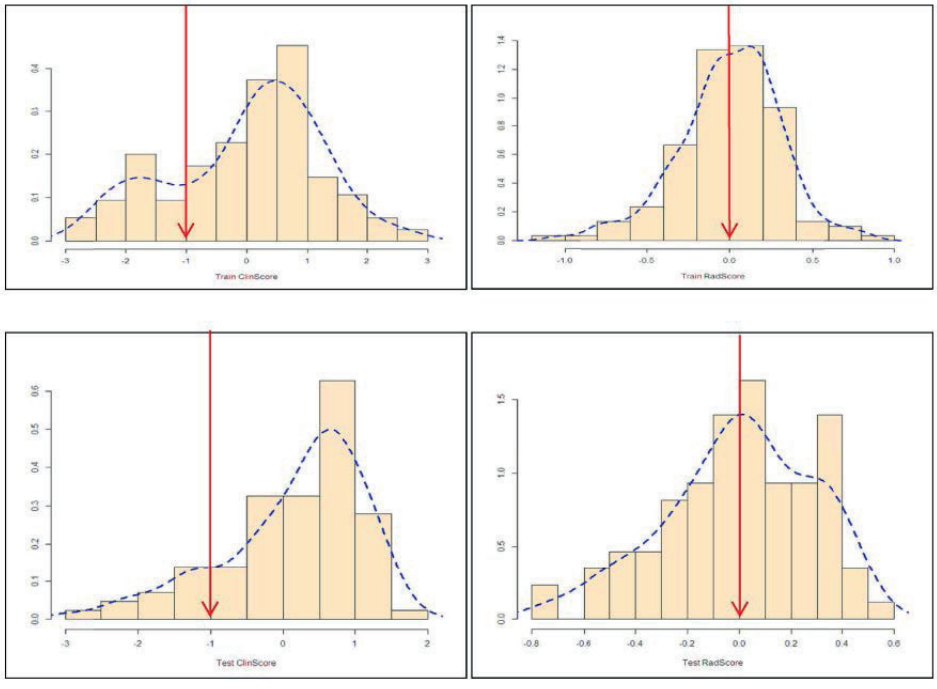
Fig. 3



Calibration plots for clinscore and radscore, respectively, for the train(top) and test(bottom) data. The predicted survival is plotted on the x-axis, and the actual survival is plotted on the y-axis. The dotted gray line represents an ideal fit where the predicted probabilities perfectly match the observed probabilities. The diamonds show the estimated model performance, and the crosses indicate bias-corrected estimates.

The scores values were categorized to separate the patient into two risk groups based on some cut-off values determined from the frequency distribution of the scores as shown on the histogram plot (Fig. 4). The chosen cut-off scores used for separating the patients into high (>cut-off) and low (≤cut-off) risk groups from the train data were translated to the test data. The clinscore had a bimodal distribution; hence a cut-off value of − 1, which separates the two distributions, was chosen. For the radscore, which had anormal distribution, the median value of 0.044 was chosen.

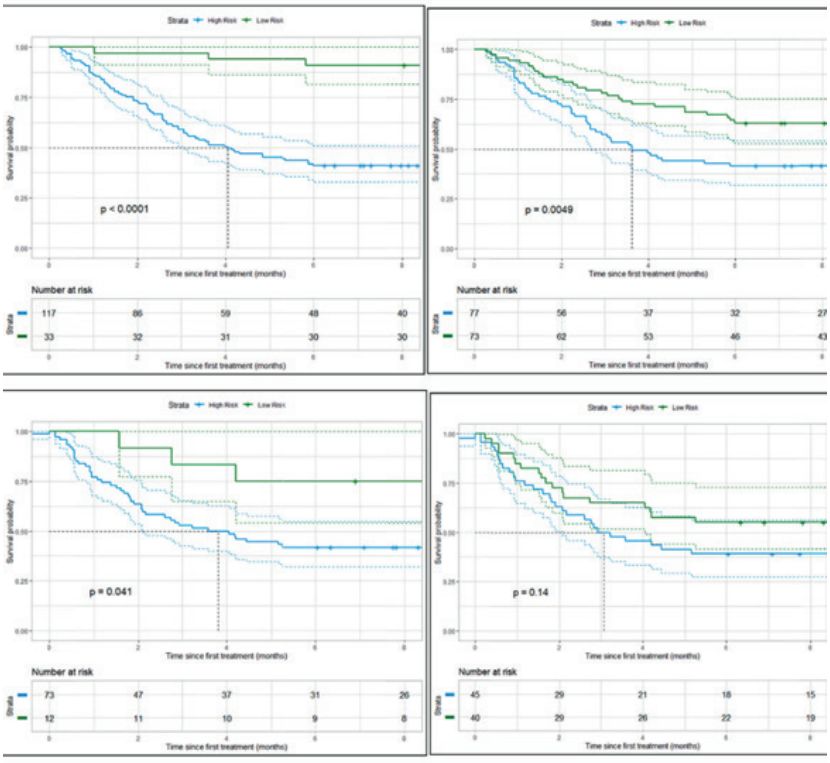
Fig. 4



Histogram of the clinscore and radscore in the train and test datasets respectively. The red arrows indicates the optimal cut-off point used to categorize the patients into a low and high risk groups in each dataset. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.

Furthermore, stratification analyses based on the risk groups showed that both scores were still independent predictors in discriminating the survival of SBM patients with a p-value <0.05 in the train data. In the test data, no statistical significance survival difference was observed between the two radscore groups with a p-value of 0.14, suggesting that the radscore might be slightly over-fitted to the train data. However, there was a borderline significance difference (p-value 0.04) between the two clinscore risk groups (Fig. 5).

Fig. 5



Kaplan-Meier curves for six months' survival in the low and high-risk groups based on the cut-off points in the clinscore and radscore for the train (top) and test (below) datasets, respectively.

Discussion

The number of people in society diagnosed with cancer is increasing. Additionally, survival of patients with cancer is extended because of improved treatment options, thus allowing for the emergence of more metastases.2 The spinal column is a common site of metastatic disease. In autopsy studies, up to 90 % of patients with cancer, metastatic deposits are observed, of which approximately 30 % of patients will be symptomatic. Adult patients with cancer of the lung, breast, and prostate are most likely to be affected [18]. For patients with SBMs, the primary goals of treatment should be focused on quality of life. Prediction of survival is crucial for guiding the appropriate choice of treatment (patient-tailored treatment). Numerous tools have been established to predict individual patient's survival and propose an appropriate corresponding therapeutic strategy. External validation studies, however, demonstrated confusing inconsistency between predicted and actual survival [19–21].

In the retrospective study of Bollen et al. in which 1043 patients were treated for symptomatic SBMs, only clinical profile of the primary tumour, performance status, and in the subgroup of favourable clinical profile, the presence of visceral and brain metastases was associated with survival. Van der Linden et al. showed in their prospective randomized radiotherapy trial that primary tumor, Karnofsky performance score, and absence of visceral metastases were significant predictors in the survival of patients with painful SBMs. In our study, only two prognostic factors showed significant association with survival, that is clinical profile, and the WHO performance status. The presence of visceral metastasis and clinical profile of the patient were the only predictors with a statistically significant difference between SBM survivors and no-survivors in both the training and testing data, although visceral metastasis was not selected. However, the predictive value of visceral metastasis for survival in patients with spinal metastases is controversial in current literature [22–23]. A recent meta-analysis suggested that the occurrence of visceral metastases has a strong negative impact on survival and should be considered when choosing a precision treatment [24]. Interestingly, the presence of visceral metastases exhibited various impacts on survival in different primary tumors. However, visceral metastasis in thyroid, breast and renal cancer could not yet be confirmed as a significant prognostic factor for survival. Large prospective trials are required to define better the prognostic value of visceral metastasis in a patient with different tumors. In our study, the clinscore models showed a good discrimination power with a C-index of 0.73. There seems to be a role for specific clinical factors in survival prediction. However, the number of patients in our training and test set was low. Ideally, with higher numbers, we might have better performance with a smaller chance of overfitting.

In clinical practice, invasive biopsy and molecular assays are needed to specify tumors. However, spatial and temporal pathologic heterogeneity limits the ability of one-moment invasive biopsies to capture their biological diversity or disease evolution. Furthermore, repeated invasive tumor sampling can be troublesome, expensive, and limited by the practical number of tissue sampling that can be undertaken to monitor disease progression or treatment response. By contrast, the non-invasive imaging phenotype potentially contains a treasure of information that can inform on the expression of the genotype, the tumor microenvironment, and the susceptibility of the tumor to treatment.

Radiomics can be described as the next era of possibilities in precision medicine. An emerging research field aiming to find associations between qualitative and quantitative information extracted from clinical images and clinical data, to support evidence-based clinical decision-making. Different kinds of features can be derived from clinical images. Quantitative features are usually categorized into the following subgroups [25]. Shape features describing the shape of the traced region of interest (ROI) and its geometric properties. First-order statistics features describe the distribution of individual voxel values without concern for spatial relationships. Second-order statistics features are obtained, calculating the statistical interrelationships between neighboring voxels. They provide a measure of the spatial arrangement of the voxel intensities and hence of intra-lesion heterogeneity. Higher-order statistics features are obtained by statistical methods after applying filters or mathematical transforms to the images.

In this paper, we studied the predictive value of first-order and texture radiomics signatures. We found no added discriminative effect of the studied radiomics signatures. So the internal imaging characteristics do not seem to have a value in the prediction of survival. However, the Shape features were excluded from further analyses in our study since all biopsies had a standard shape hence no variability. Especially volume seems to predict well in many Radiomics analyses. A study by Roy et al. found that of all radiomic features tested in their study, 16 were found to be volume-dependent [26]. Their evidence indicates that tumor volume significantly impacts radiomic features in co-clinical imaging, in which they propose a volume-dependency correction scheme and identify a set of robust radiomic features for co-clinical imaging studies.

A major strength of a radiomics approach for cancer is that digital radiologic images are obtained for almost every patient with cancer, and all of these images are potential sources for radiomics databases. It is conceivable that the lack of quantitative information leads to increased follow-ups or invasive biopsies that would be deemed unnecessary given the unused information in medical images. Besides features encode

morphological information beyond the limits of the human eye. When the feature extraction is performed expertly, artificial intelligence trained on handcrafted radiomics features can perform as deep learning, especially in smaller data sets.

However there are some other critical comments which can be made. Algorithms contain human bias and delineation of hand crafted radiomics features is time consuming. Besides routine clinical imaging techniques show a wide variation in acquisition parameters, such as image spatial resolution; administration of contrast agents; kVp and mAs (among others) for CT; type of sequence, echo time, repetition time, number of excitations, and many other sequence parameters for MRI. Furthermore, different vendors offer different reconstruction algorithms, and reconstruction parameters are customized at each institution, with possible variations in individual patients. All these variables affect image noise and texture, and consequently, radiomic features. Standard CT phantoms, allow the evaluation of imaging performance and the assessment of how far image quality depends on the adopted technique. Despite not being intended for this, they may provide useful information on the parameters potentially affecting image texture. Segmentation is another critical step of the radiomics process because data are extracted from the segmented volumes. This is challenging because many tumors show unclear borders, and the reproducibility of the segmentation is questionable. Hence radiomic features are susceptible to image acquisition and segmentation variability. Ideally, only features robust to these variations would be incorporated into predictive models for good generalizability or a reproducible, automated algorithm for segmentation should be used. Other factors such as the presence of artifacts due to metallic prostheses, may affect image quality and impair quantitative analysis. Furthermore, electronic density quantification expressed as Hounsfield Units may vary with the reconstruction algorithm or scanner calibration.

Radiomics is a growing field based on the analysis of hand-crafted features, which depend on an arbitrary decision to apply a statistical analysis to an image as a form of feature engineering. Deep learning can extract learned features from images which may be more helpful in determining the required outcome. Combining the learned features extracted via deep learning and the current hand-crafted radiomic features may possibly improve outcome prediction. Deep learning combined with machine learning has the potential to advance the Radiomics field, provided the raw data is available for the results to be determined robustly across all patient and tumor types [27].

Conclusions

We have developed and validated a clinical and Radiomics model for predicting six-month survival probability for patients with SBM. The clinical model had a good discrimination power. The radiomics model, on the other hand, had an inferior performance with no added predictive power to the clinical model, which might be due to the excluded shape feature. Therefore using a more sophisticated approach like deep learning that uses features from the entire image maybe a better method to show the predictive benefit of medical images.

Declaration of Competing Interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements No funds or grants were received for this manuscript.
Appendix A. Supplementary data Supplementary data to this article can be found online at https://doi. org/10.1016/j.ctro.2021.12.011.

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7

CHAPTER VII

Overall survival nomogram for patients with spinal bone metastases (SBM).

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Clin Transl Radiat Oncol. 2021 Mar 11;28:48-53. doi: 10.1016/j.ctro.2021.02.010.

Abstract

Background: Nomograms can estimate patient-specific probability of an outcome and can be used as decision support system for clinicians. Until now, no prognostic nomogram has been established for spinal bone metastases (SBM).

Aim: This study aims to develop a nomogram with a user-friendly digital interface that can estimate the 1, 3, and 6-months overall probabilities of survival for patients with SBM and guide individualized patient management decisions.

Methods: Between January 2014 and April 2016, we retrospectively collected a series of 250 SBM patients treated with radiotherapy from the electronic medical record (EMR) system at Maastro Clinic, Maastricht, The Netherlands. We extracted the following variables: age, sex, WHO performance status, pathological fracture, spinal cord compression, number of spinal metastases, extra-spinal metastases, visceral metastases, brain metastases, lymphatic metastases, pain score, and primary tumor for this analysis. We only included patients with a primary tumor of the breast, prostate, colon, rectum, or lung in this study. Overall survival (OS) at 1, 3, and 6 months was defined as the primary outcome of interest.

Results: The median follow-up time for this study was 46.78 (37.03–56.34) months with a 1, 3, and 6-months overall survival probability of 88%, 67%, and 53%, respectively. The proposed nomogram has a relatively good C-index of 0.72 (95% CI, 0.683 – 0.757) and performs well in calibration. A digital version of the nomogram is also provided for easy insertion into the treatment workflow for better decision-making in managing SBM and offering practical guidance to caregivers.

Conclusion: The present nomogram might be a suitable tool for clinical assistance; however, external validation is needed to ascertain its clinical reliability.

Introduction

Tumor metastasis is the leading cause of morbidity and mortality in cancer patients [1,2]. The spine is the third most common site for cancer cells to metastasize after lung and liver, and 30–70% of patients with a tumor have metastatic spinal disease at autopsy [1,3–5]. Primary tumors of the breast, prostate, thyroid, lung, gastrointestinal (GI), and kidney are the most common to metastasize to the spine [1,3–5]. Within the spinal column, metastases are more commonly found in the thoracic spine, followed by the lumbar spine, while the cervical spine is the least likely location to find metastasis. Spinal bone metastases (SBM) account for over 70% of all osseous metastases and are slightly more common in men than in women. Adults between the ages of 40 and 65 are affected more than any other age group [4–6]. The prognosis of SBM is abysmal and heavily depends on the primary tumor [7]. Only 10 to 20 percent of the diagnosed patients have survival of more than two years, which implies that caregivers should tailor treatment based on an individual patient profile for an optimal outcome.

Graphical tools such as nomograms that can be used to estimate an event's probability by assigning scores to each important risk factor known to impact the events of interest combined with a prediction model can be used in such a situation. Since nomograms can estimate patient-specific probability of an outcome, they are an excellent decision support system for clinicians and caregivers. Numerous nomograms have been developed for different cancer-specific outcomes [8–13] and thanks to the technological advancements in the oncological field in the last decade, some of these nomograms have been digitalized [14]. However, until now, no prognostic nomogram has been established for SBM. Therefore, this study aims to develop a nomogram with a user-friendly digital interface that can estimate the 1, 3, and 6-months overall probabilities of survival for patients with SBM and guide individualized patient management decisions.

Materials and methods

Between January 2014 and April 2016, we retrospectively collected a series of 250 cancer patients treated for SBM from the electronic medical record (EMR) system at Maastro Clinic, Maastricht, The Netherlands, after acquiring approval from the internal review board. All the patients received radiotherapy for their metastatic tumor. We extracted the following patient demographics and clinical information age, sex, WHO performance status, pathological fracture, spinal cord compression, number of spinal metastases, extra spinal metastases, visceral metastases, brain metastases, lymphatic

metastases, pain score, and primary tumor for this analysis. We only included patients with a primary tumor of the breast, prostate, colon, rectum, or lung in this study. Overall survival (OS) at 1, 3, and 6 months was defined as the primary outcome of interest. The OS was calculated as the time difference between the date of diagnosis and the date of death or last follow-up.

Statistics

Descriptive statistics and data visualization were applied to understand and detect the data sets underlying patterns such as missing information and possible outlying values. A 5-fold cross-validation Cox proportional hazard regression model with the least absolute shrinkage and selection operator (LASSO) penalty [35] was used to select features that can predict survival for patients with SBM. The optimal λ values which compromises model complexity and performance, were determine using the cv.glmnet function. Variables with a non-zero coefficient under the λmin value were used to fit a multi-variate Cox proportional hazard regression model. The fitted multivariate Cox proportional hazard regression model was translated to a nomogram for visualization using the nomogram function from the rms package [15]. The accuracy of the nomogram on a repeated (R = 10) 5-fold cross validation was measured based on the concordance index (C-index) value with a C-index of 1 indicating a perfect nomogram and a C-index of 0.5 implying the nomogram is as reliable as tossing a coin. An internal bootstrap (B = 500) correction plot of observed against nomogram-predicted survival probability was used to calibrate the nomogram at the different time points of interest.

The linear predictors (LP) which are the linear combination of the coefficients of the variables in the nomogram were discretized to create the survival risk groups. Survival difference was visualized and tested using Kaplan-Meier plots and log-rank test, respectively. To evaluate the models ability to classify future patients into the different risk groups, we compared the predicted mean survival curves for each of the risk groups with the true Kaplan-Meier survival curves of each risk group by overlaying the two plots. All statistical analyses were performed using R software [16] and the glmnet package [17] was used for variable selection and model fitting process.

Results

A total of 250 patients with SBM were identified at Maastro Clinic. Of these patients, 195 had a primary tumor of the breast, prostate, colon, rectum, or lung (see table 1). One patient with missing WHO performance status was excluded from this analysis. The variable 'pain score' was excluded from the study due to its high percentage (45%)

of missing information. The median age of patients in this study was 69 (39–92) years. There was no statistical survival difference between surviving and non-surviving patients for all considered variables but visceral metastasis and the primary tumor. The median follow-up time for this study was 46.78 (37.03–56.34) months with a 1, 3, and 6-months overall survival probability of 88%, 67%, and 53%, respectively. Table 1 shows the general patient characteristics for this study.

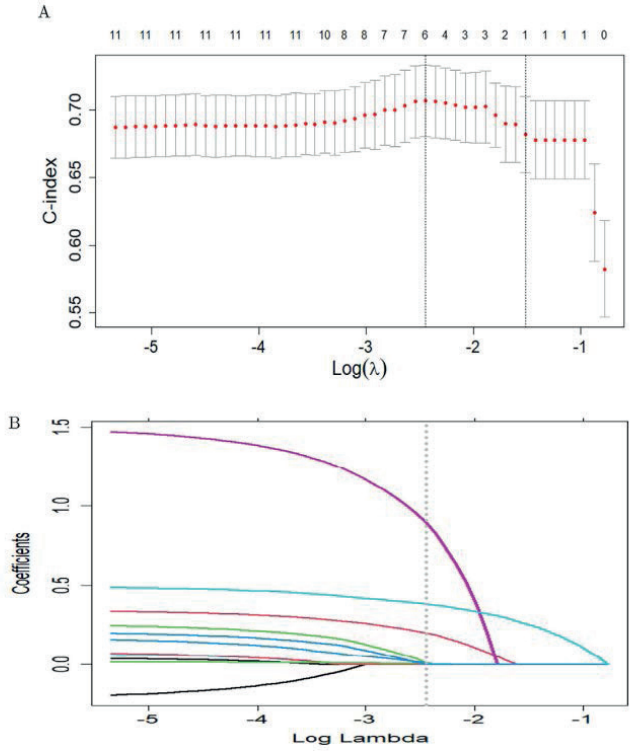
Table 1 General characteristics for surviving and non-surviving patients.

Variable	Levels	Survivors		Non-Survivors		p-value
Age at RT in years	Mean (sd)	67.8 (8.8)		68.9 (10.4)		0.651
Sex	Female	10	(66.67%)	80	(44.40%)	0.097
	Male	05	(33.33%)	100	(55.60%)	
WHO performance score	Active	01	(6.67%)	05	(2.78%)	0.854
	Restricted	07	(46.67%)	69	(38.33%)	
	Self-care	05	(33.33%)	74	(41.11%)	
	Bed-bound	02	(13.33%)	31	(17.22%)	
	Missing	00	(0.00%)	01	(0.56%)	
Pathological fracture	Yes	11	(73.33%)	141	(78.33%)	0.654
	No	04	(26.67%)	39	(21.67%)	
Spinal compression	No	14	(93.33%)	142	(78.89%)	0.179
	Yes	01	(6.67%)	38	(21.11%)	
Number spinal metastases	One	03	(20.00%)	33	(18.33%)	0.981
	Two	03	(20.00%)	39	(21.67%)	
	Three +	09	(60.00%)	108	(60.00%)	
Extra spinal bone metastases	No	04	(26.67%)	41	(22.78%)	0.731
	Yes	11	(73.33%)	139	(77.22%)	
Visceral metastases	Absent	13	(86.67%)	109	(60.56%)	0.045
	Present	02	(13.33%)	71	(39.44%)	
Brain metastases	Absent	00	(0.00%)	10	(5.56%)	0.348
	Present	15	(100%)	170	(94.44%)	
Lymphatic metastases	Absent	09	(60.00%)	102	(56.67%)	0.802
	Present	06	(40.00%)	78	(43.33%)	
Pain score	No pain	00	(0.00%)	05	(2.78%)	0.431
	Mild	01	(6.67%)	06	(3.33%)	
	Moderate	05	(33.33%)	35	(19.44%)	
	Severe	07	(46.67%)	76	(42.22%)	
	Missing	02	(13.33%)	58	(32.22%)	
Primary tumor	Breast	10	(66.67%)	35	(19.44%)	<0.05
	Prostate	05	(33.33%)	50	(27.78%)	
	Lung	00	(0.00%)	70	(38.89%)	
	Colon	00	(0.00%)	14	(07.78%)	
	Rectum	00	(0.00%)	11	(06.11%)	

WHO = World Health Organization, sd = standard deviation.

Fig. 1A shows a plot of the model performance (C-index) against the log values of the different λ used in the cross-validation process for variable selection. The values at the top of the plot indicate the number of non-zero variables in the model for a particular λ value and the performance of the said model can be read on the y-axis. Based on the selected λmin value from the repeated 5-fold cross-validation of the LASSO Cox proportional hazard regression model, the 11 considered variables were reduced to 6 potential predictors (age, spinal cord compression, brain metastasis, visceral metastasis, WHO performance status, and primary tumor) with a non-zero coefficient. Fig. 1B shows the coefficients of the 11 variables represented by different colors against the log(λ) values. The vertical dotted gray line was drawn at the selected λmin value which resulted in the 6 variables with nonzero coefficients.

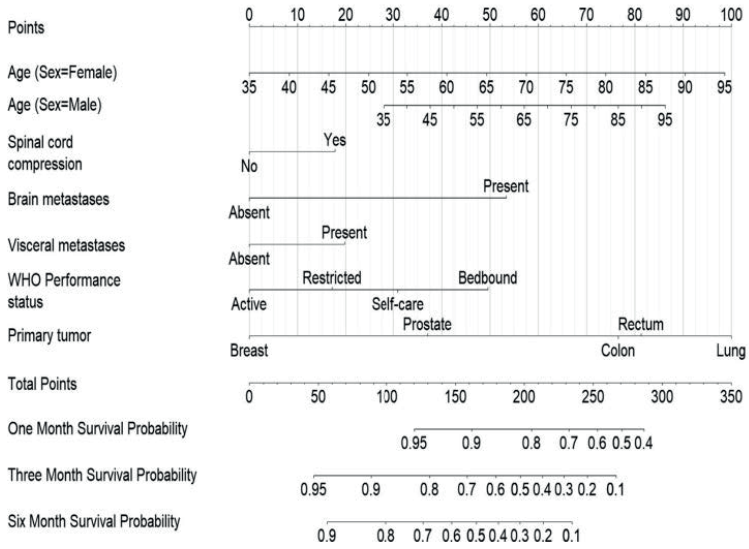
Fig. 1



Variable selection using the LASSO cox proportional hazard regression model. **[A]** Selection plot of the tuning parameter (λ) for the LASSO model on the repeated 5-fold cross-validation. The C-index values were plotted against the log(λ) values. Dotted vertical lines are drawn at the optimal λ values λmin and $\lambda_{1\text{-SE}}$ respectively. **[B]** Profile plot of the LASSO coefficient against the log(λ) sequence for the 11 considered variables. The dotted gray line represents the selected λmin value (0.0895) which gives a log (λmin) of -2.413.

The fitted multivariate Cox proportional hazard regression model with the selected variables was translated to the prognostic nomogram shown in Fig. 2.

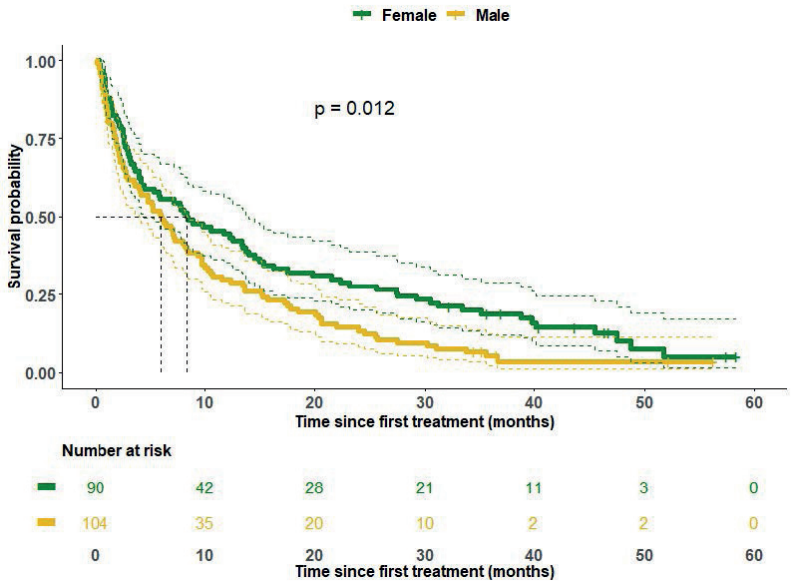
Fig. 2



Developed nomogram to predict 1, 3, and 6-months overall survival for metastatic spinal bone patients using seven clinical characteristics. To use the nomogram, locate the patient's variable on the corresponding axis, draw a vertical line to the points axis, sum the points, and draw a vertical line from the total points axis to the 1, 3, or 6 -months overall survival probability axis.

The variable sex was included in the model though not selected based on the chosen λ value because it is known to be an important factor based on literature. Also, The Kaplan-Meier plot for sex (Supplementary Fig. 8) showed a significant survival difference. The mean C-index and the 95% confidence interval (CI) of the nomogram was 0.720 (0.683– 0.757).

Fig. 8, supplementary.

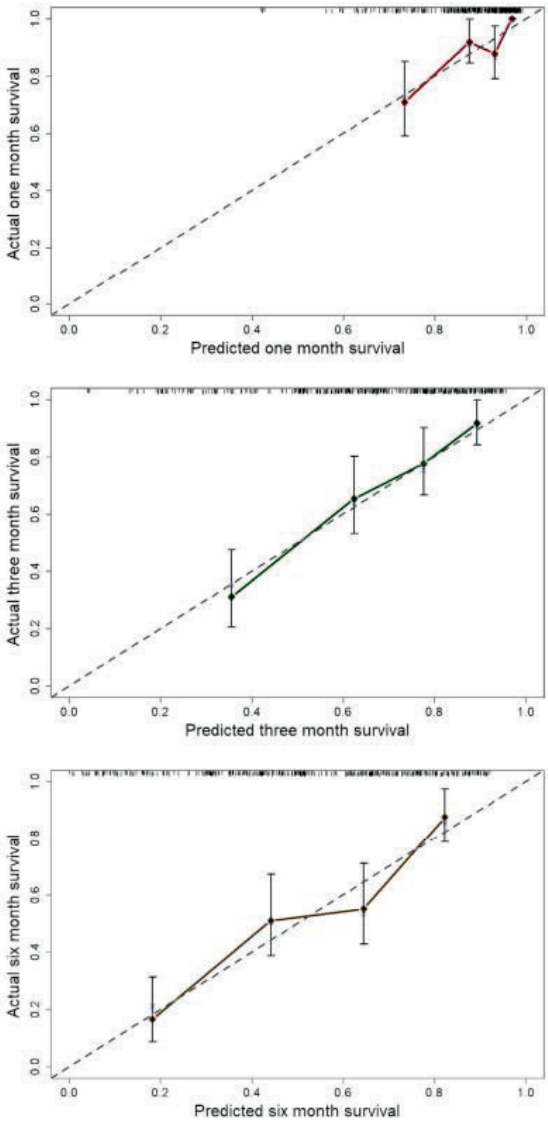


The Kaplan-Meier survival curve for sex.

We have also provided a user-friendly online version of this nomogram to facilitate its widespread use by physicians and researchers (https://bich.shinyapps.io/SpinalMets/). The Web application allows predicted survival probabilities and curves for each input information to be stacked making comparison easier

To evaluate the developed nomogram, we presented its performance in predicting 1, 3, and 6-months overall in terms of discrimination by plotting the actual survival probabilities against the nomogram predicted probabilities. This plot shows the similarity between the predicted probabilities and the observed probabilities, with all points falling precisely on the perfect model's diagonal line. The calibration curve in Fig. 3 reveals good agreement between the predictions of the nomogram and observation.

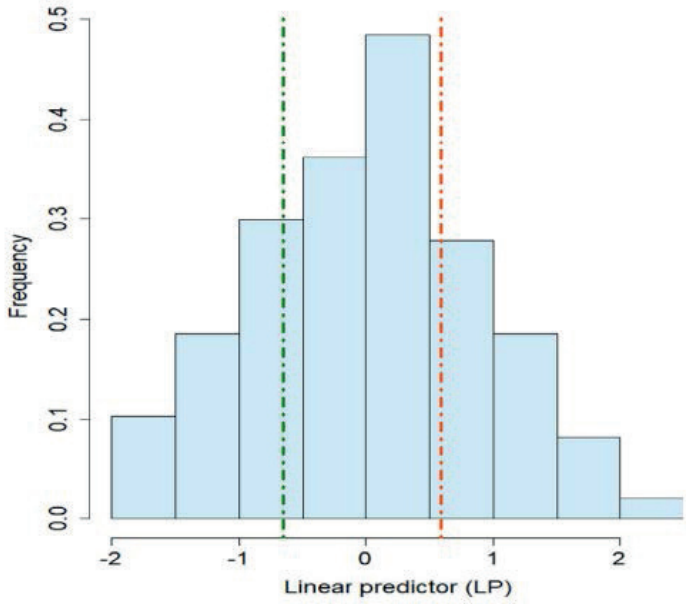
Fig. 3



SBM overall survival nomogram calibration plots for 1, 3, and 6-months, respectively. The nomogram-predicted overall survival is plotted on the x-axis, and the actual overall survival is plotted on the y-axis. The dashed line represents the ideal fit where the nomogram-predicted probability matches the observed probability. The vertical solid lines represent the 95% confidence interval.

The nomograms' ability to discriminate between patients based on their survival probability was evaluated by first making a histogram of the linear predictors, as shown in Fig. 4 with higher values indicating poor prognosis. The linear predictors were then discretized into three risk groups with cutoff values at the 25th and 75th percentile, as shown on the plot. We considered patients between the cutoff values to have a moderate risk of death. Patients below and above the 25th and 75th percentile values were considered to have a lower and higher risk of death, respectively.

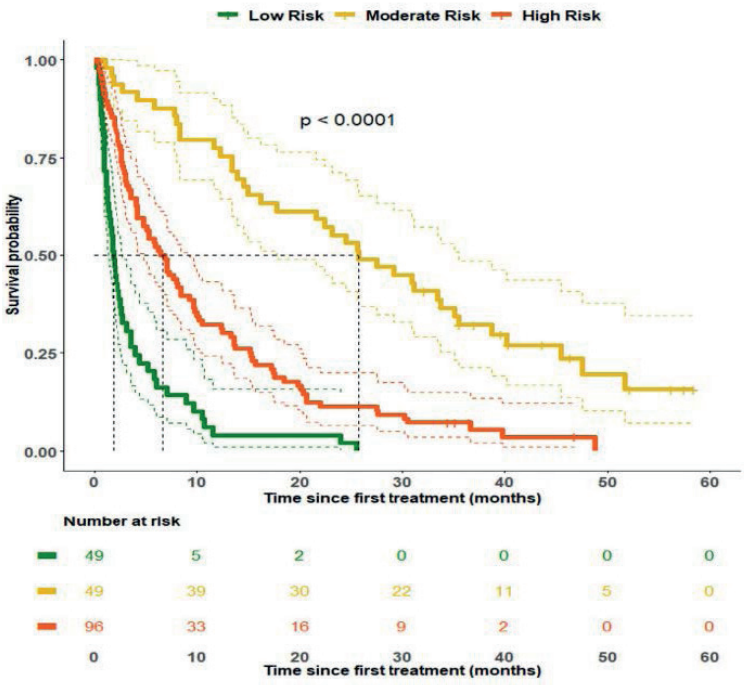
Fig. 4



Histogram of the linear predictor extracted from the nomogram. The vertical lines indicates the 25th (green), and 75th (red) percentile respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The percentages of patients in the three risk groups are 25.3%, 49.4%, and 25.3%, respectively. The Kaplan-Meier curves for overall survival stratified by the risk groups, as shown in Fig. 5, agree with the c-index value and calibration plots, indicating that the nomogram has some discriminating power as the three curves are significantly separated with a p-value < 0.005. Patients in the high-risk group had a median survival time of 1.77 (0.92– 3.98) months and the moderate group had 6.90 (2.66–15.21) while the low-risk group had 25.72 (13.40–45.47) months as shown in Fig. 5.

Fig. 5

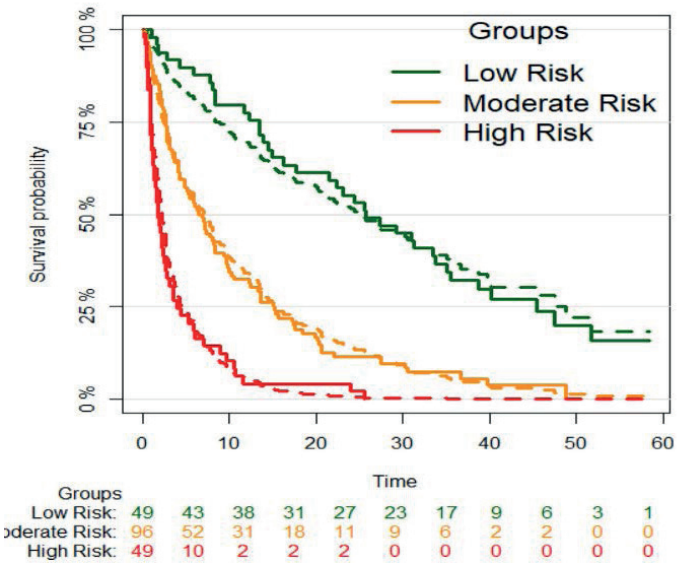


The Kaplan-Meier survival curve for the low, moderate, and high-risk groups based on the percentile cutoff values.

To further evaluate the nomogram's performance, we compared the predicted mean survival curves for each of the risk strata with the Kaplan-Meier survival curves, as shown in Fig. 6.

Fig. 6 indicates that the nomogram is well-calibrated given the close similarity between the predicted (dotted lines) and actual (solid lines) survival curve for all except the low-risk group, where the model slightly under predicts at the beginning and over-predict over time.

Fig. 6



Comparison of predicted mean survival curves (dotted lines) and stratified Kaplan-Meier (solid lines) for the different risk groups.

Discussion

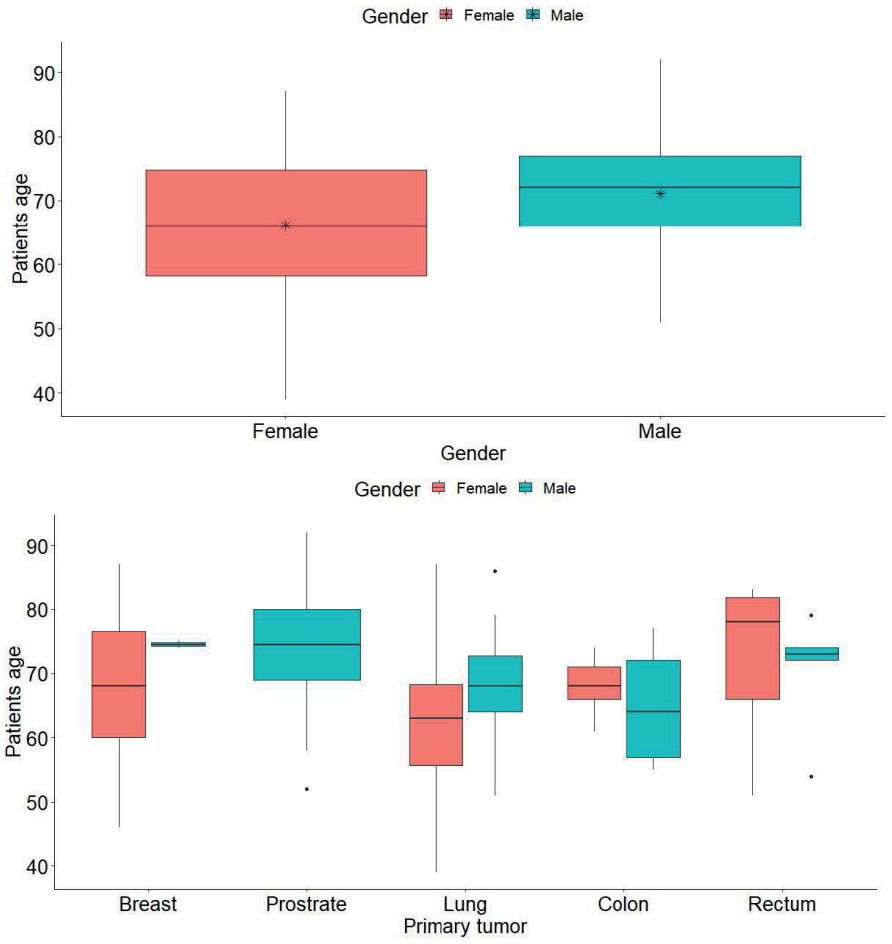
The disease burden and mortality rate of SBM have opened up intriguing research possibilities in the field, focusing on improving patients' quality of life via a personalized treatment procedure for an optimal outcome. Despite the significant progress in understanding tumor metastasis and the underlying mechanisms, the precise process remains complicated with multiple sequential and interrelated biochemical events, which still needs elucidation.

The treatment choice for spinal metastases depends on correctly localizing the affected vertebra(e), the patient's priorities for treatment, and other individual patient characteristics. However, no therapy has proven to increase the life expectancy of these patients [5]. Hence, treatment aims to improve quality of life, spinal cord compression, relieve pain, or prevent a vertebral collapse [18].Therefore, assessing a patient's prognosis before treatment is very pivotal for an optimal treatment selection. That is, caregivers should tailor treatment based on each patient's desires and their overall prognosis.

Renowned prognostic scoring systems (Bauer, Tokuhashi, Tomita, van der Linden, Sioutos, Katagiri, and NESMS) have been developed to assist clinicians and care providers in determining the survival prognosis of metastatic spine tumor patients for an optimal therapeutic choice [19–27]. In contrast to this study, none of these scoring systems include demographic features such as age and sex. Logically, these variables should be included in any scoring system given that men are more susceptible to developing a primary tumor than women [29,30].

Yang, Xu, Liu, et al. [31], Liu, Yang, Li, et al. [32] and Pereira, Janssen, Dijk, et al. [33] have previously developed nomograms to support the personalized predictions of survival probability for patients with spinal metastasis disease from non-small cell lung cancer (NSCLC), colorectal cancer, and operable patients respectively. These nomograms did consider age, sex, performance status, primary tumor, visceral, and brain metastasis as significant prognostic factors associated with spine metastasis survival, which are in concordance with this study. However, none of these studies have considered including both age and sex in the same nomogram. This assumes all patients have an equal risk of dying from the disease irrespective of their age, sex, or both variables despite the sea of literature supporting these difference [4–6,28,30,34,35] especially when more than one primary tumor is considered (Supplementary Fig. 7).

Fig. 7, supplementary.



Box-plots showing the age distribution for sex and primary tumor respectively.

This variable omission implies the predicted survival probabilities from such nomograms are less personalized.

We developed a nomogram with seven variables, including an interaction between age and sex, to improve previously developed scoring systems. The developed nomogram captures the age effect within the sex variable as there is over 15 points survival difference between males and females of the same age. From the nomogram, women have relatively better survival than men before 75 years. However, after 75 years, the reverse is seen with men having a somewhat better survival than women. The proposed nomograms have a relatively good c-indexes of 0.72 (95% CI, 0.683 – 0.757) and

perform well in calibration. A digital version of the nomogram is also provided for easy insertion into the treatment workflow for better decision-making in managing spinal metastases and offering practical guidance to caregivers.

All the existing scoring systems for SBM known to us are between 1 and 24 months. The digital version of the present nomogram can make predictions at any given time point as low as half a month. Besides the survival probability, it also provides the confidence interval of the predicted survival probability and a personalized survival curve, which gives the caregiver more insights to determine the optimal therapeutic strategy for a patient, such as, e.g., stereo-tactic body radiation therapy (SBRT). The personalized survival curve could serve as a good starting point for shared decision making between patients and caregivers. The present nomogram might be a suitable tool for clinical assistance; however, the performance is still not optimal due to some limitations. The nomogram's clinical-reliability could not be evaluated at the moment, given the study's single-center nature. However, we performed a thorough internal validation (bootstrap) and planned to do a proper external validation to ascertain the nomogram's clinical usefulness. A direct comparison between our developed nomogram and the other nomograms was not possible due to population difference. However, Liu, Yang, Li, et al. [32] and Pereira, Janssen, Dijk, et al. [33] did consider hematological parameters such as carcinoembryonic antigen (CEA), hemoglobin levels, and white-bloodcell count (WBC) for their nomogram. Given the pivotal role of blood and lymph in tumor metastasis, we believe these variables could be essential prognostic features but were, however, absent in the current study because of its retrospective nature. Yang, Xu, Liu, et al. [31] on the other hand, used a renowned scoring system called the Frankel score in their nomogram, which was also not included in the present study. However, this feature might not be predictive of spinal metastasis survival since it was only designed to categorize spinal cord injuries [36].

Access to population-based registries and adding other variables to the nomogram, such as (radi)omics, pathology, and hematological parameters, might further improve the nomograms' performance. Also, accessing these databases will make the nomogram more generalizable by including more primary tumors and increase number of patients in each primary tumor.

At present, the nomogram is limited to five primary tumors, which implies that patients with other primary tumors like cervix, kidney, bladder, etc., cannot benefit from this nomogram.

Conclusions

We have established a user-friendly and easy to use prognostic nomogram for patients with SBM using seven known clinical parameters. It has a digital version that can be integrated into the current treatment workflow to aid treatment decision-making in managing cancer patients with SBM. However, proper external validation is needed to ascertain its clinical reliability.

Declaration of Competing Interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
Appendix A. Supplementary data Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2021.02.010.

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8

CHAPTER VIII

Discussion

General Discussion

Osteoporosis is a highly prevalent condition worldwide and a major cause of long-term morbidity. Osteoporosis affects 200 million women worldwide, involving 22.5% of the women and 6.8% of the men over 50 years of age [1-2]. Every year, 2.7 million fractures occur in the six nations France, Germany, Italy, Spain, Sweden, and the UK with an associated healthcare cost of €37 billion, which is predicted to increase by 23% (to €47 billion) by 2030 [3]. The clinical relevance of osteoporosis lies in associated fragility fractures as these are a cause of pain and disability and are a major risk factor for subsequent fractures. E.g., after a vertebral fracture, the risk of any other fracture increases 200% and that of a subsequent hip fracture increases 300% [4]. Fracture liaison services (FLS) have been designed for secondary prevention and evaluate all patients > 50 years of age presenting to a medical care system with a new fracture ,initiating preventive treatment when appropriate [5]. In an FLS bone mineral density is assessed as well as an evaluation of the risk of falling, and relevant laboratory and imaging investigations to identify any underlying secondary causes of osteoporosis and help inform drug treatment decisions. Appropriate therapy is implemented to prevent subsequent fractures as well as the associated morbidity and mortality. FLS services are increasingly regarded as the gold standard in secondary fracture prevention and have been found to achieve a nearly 40 % reduction in the 3-year risk of major bone fractures, and a nearly 30 % reduction of any bone fracture [6-7]. The number needed to treat to prevent a subsequent fracture is 20 [8]. To date 739 FLS (registered in the 'Capture the Fracture' campaign of the International Osteoporosis Foundation) have been implemented in 50 countries worldwide [9].

Research has shown that anti-osteoporotic medication can achieve a significant reduction in vertebral and non-vertebral fracture risk in women aged 70–100 years [5-8]. However, the number of patients who take this medications is still low and adherence to treatment in this population is poor, particularly among those aged over 80 years. Some studies document that less than 20% of patients receive therapies to reduce the risk of a new fracture in the year following the index fracture event, with treatment rates particularly poor for the elderly and for people who reside in long-term care facilities [10]. Strategies to implement systematic identification of individuals at high fracture risk in primary care, and to personalise management by targeting the most effective interventions to those at the highest fracture risk, should be essential components in the optimisation of osteoporosis care.

The age at which a Fracture Liaison Service (FLS) no longer offers significant benefit is unknown. In Chapter II, the advantage of an FLS was assessed in reducing subsequent fracture risk, specifically in patients > 85 years. Should we screen these patients

for osteoporosis or treat them directly because of a high risk for frailty fractures? In daily practice a large proportion of these patients is not screened. We demonstrated that an outpatient screening and treatment program for osteoporosis and fall-related risk factors for elderly patients above 85 years of age, is not associated with a lower subsequent fracture risk [11]. However, screened patients at the extreme of ages (> 85 years) had an associated lower mortality risk compared to patients who did not undergo this screening and treatment protocol. Other studies have also reported a reduction of mortality associated with the use of a fracture liaison service [12-13]. The exact reasons behind this beneficial impact on mortality are not clear, However, the multidisciplinary approach followed in the FLS may aid in the identification of health hazards and comorbidities, and therefore improve the health care of these complex patients. Moreover a recent model based cost-effectiveness analysis of an FLS in China found that for the elderly patients (80 years and older), the FLS was not cost-effective, which could be explained by the shorter life expectancy which might render fewer opportunities for benefitting from the FLS [9]. The elderly with osteoporosis-related fractures should perhaps not be thought of as 'average elderly' but rather as frail elderly for whom a holistic management, is the best choice of treatment.

The elderly are particularly susceptible for vertebral fractures, as the risk of this condition increases with advancing age [14]. Osteoporotic vertebral fractures (OVFs) are among the most common type osteoporotic fractures and are clinically significant as they can lead to severe disability. Moreover, patients are at high risk of secondary vertebral compression fracture. Nearly 30% of patients who are symptomatic may suffer from chronic pain and advancing kyphosis. This causes a serious decrease in quality of life which is more severe than in patients affected by geriatric hip, forearm, or humeral fractures [15]. Besides, in the elderly population, OVFs cause other sequelae such as limited mobilization and disability due to pain with enhanced risk of major cardiovascular events (myocardial infarction, stroke, cardiac death) [16]. Therefore, it is crucial to treat pain and regain mobilization capacity as soon as possible in these patients. The role of operative treatment of OVFs in elderly patients is controversial as surgical procedures may constitute major risks of complications. Safety of spine surgery in general has previously been evaluated for elderly cohorts. Studies in the very elderly, have shown complication rates of 20% [17-18]. Patients aged ≥90 years are at an even higher risk for complications after spine surgery, with a rate 5.2 times higher than that for patients of all ages [19].

As in other osteoporotic fractures in the elderly, the key for a good outcome may be a combination of interdisciplinary treatment approaches and adapted surgical procedures. Percutaneous cement augmentation procedures aim to stabilise an affected vertebra by the introduction of an approved bone void filler, usually PMMA, usually

via a transpedicular or extrapedicular approach under continuous fluoroscopic control. The literature covering both procedures has been reviewed in Chapter III of this thesis. Previous RCTs and the latest Cochrane review provoked an academic debate on the efficacy of vertebral augmentation, not supporting percutaneous vertebroplasty as standard pain treatment in patients with acute OVFs [20-23]. This in contrast to findings of the VAPOUR trial, a multicentre randomised double-blind placebo-controlled trial, showing benefit of vertebroplasty over placebo, particularly when the intervention occurred within 3 weeks of fracture. Trials of fractures <6-week duration support the positive findings of the VAPOUR trial [24-27]. We reinforce these results and conclude that percutaneous cement augmentation techniques are effective in pain reduction in patients with an OVF as compared to conservative care, but in placebo controlled trials not proven to be more effective than injection of local anaesthetic at the pedicle entry site, a so-called facet-or medial branch block.

We propose that in patients who suffer < 6 weeks from an acute OVF not responding to conservative treatment, percutanenous cement augmentation procedures to achieve better pain control and quality of life could be considered. Percutaneous cement augmentation procedures should also be considered in elderly patients with severely disabling vertebral fractures with a risk of bed rest immobilization. We recommend that this minimally invasive treatment option should be discussed with patients in informed decision in order to make treatment more personalized.

Primarly minimally invasive percutaneous pedicle screw fixation (PPSF) was initially intended for treating degenerative diseases of spine, but later on PPSF has been used for thoracolumbar spine fractures. With very encouraging overall outcomes, and because of the advantages of a minimal invasive technique with significantly less perioperative complications including blood loss, infections, and shorter hospital stays, as shown in Chapter IV of the current thesis, PPSF has become a preferred method for treating thoracolumbar fractures by many spine surgeons 28].

It is still a challenge for spine surgeons to manage the severe osteoporotic thoracolumbar fractures in older patients. As conservative treatment may fail, and open posterior fusion could represent overtreatment, PPSF could be a usefull strategy for treating osteoporotic thoracolumbar fractures in the elderly. Recent studies have shown that PPSF combined with vertebroplasty provides a safe and effective option for treatment of severe thoracolumbar OVFs [29-30]. However, the long-term outcomes have not been well established yet.

In this respect, another novel minimally-invasive augmentation technique, Stent-Screw Assisted Internal Fixation (SAIF), has been proposed recently for the treatment

of severe osteoporotic and neoplastic fractures [31-32]. The spectrum of severity ranges in osteoporotic vertebral fractures from mild and stable compression fractures affecting the disc-endplate region to unstable fractures with high-degree osseous fragmentation, middle column involvement, and kyphotic deformity. The stent screw–assisted internal fixation (SAIF) technique includes percutaneous insertion and balloon-expansion of 2 vertebral body stents (Vertebral Body Stenting System [VBS]) followed by placement of cannulated and fenestrated pedicular screws in the lumen of the stents and cement augmentation through the screws. While pain relief has been similarly reported by standard augmentation techniques, the SAIF approach could achieve greater improvement in kyphosis, potentially improving biomechanics and ambulation [31-32]. Further research is warranted for effective and cost-saving minimal invasive techniques for treating patients with OVF not responding to conservative measures.

The aging population, with increased incidence of cancer, combined with the longer survival of patients with cancer, has resulted in more people being confronted with metastatic disease, in which the skeleton is often affected. Bone metastases most frequently occur in the spinal column [33]. The main purpose of treating bone metastases is to improve symptoms and prevent the development of skeletal-related events. Surgical and/or medical treatment may be determined according to the prognosis of patients with cancer. Patients with a poor prognosis may be treated with less invasive palliative treatment. Patients with a life expectancy of 3–12 months should be preferably treated with less invasive surgical reconstruction that does not require long-term rehabilitation. Scoring systems for the prognosis of patients with metastatic spinal tumors have been prepared by frontline orthopedists and radiologists from clinical points of view [34-36]. These studies were important efforts to better understand what factors should be taken into consideration when estimating survival. However, these prediction models do not inform on the survival probability at fixed time points, thus making it difficult to understand how long a patient is estimated to survive. It would be favorable for the physician to be informed on the probability (in %) of a patient to survive certain time points, so that this information can be used for patient counseling an to decide further treatment. Until now, no prognostic nomogram has been established for spinal bone metastases (SBM). In Chapter VII of the current thesis, we developed a nomogram with seven variables, including an interaction between age and sex, to improve previously developed scoring systems [37]. However, external validation is needed to ascertain its clinical reliability.

Since the field of treatment options has changed for metastatic spine disease, some existing scoring systems may have become outdated for the actual situation. Recent advances include: the development of stereotactic spine radiosurgery (SRS), introduc-

tion of minimally invasive surgical techniques, and the evolution of various target therapies for individual primary cancers [38]. In Chapter V, we externally validated the existing Dutch prediction models and found modest predictive capability. Future challenges include the development of personalized scoring systems that correspond to the histology of the primary tumor, the specific genetic and anatomical prerequisites of particular tumors and also incorporate the individual patient's needs [39].

Personalized medicine requires the integration and analysis of vast amounts of patient data to realize individualized care. The term Radiomics was introduced by Gillies et al. in 2010 and adopted by Lambin et al. in 2012 [40-41]. The hypothesis is that quantitative analysis of medical image data can provide complementary information to help physicians in the treatment decision-making process, aided by automatic or semiautomatic software, in a fast and reproducible way. Radiomics is the result of several decades of computer-aided diagnosis, prognosis, and therapeutics research. Nowadays, radiomics has made great progress in tumor diagnosis, classification of malignant tumors, tumor prognosis, and the monitoring of curative effects [42-47]. Radiomics publications show significant annual growth of about 178% [48]. Altough radiomics was mostly employed in oncology up to now, in the last years it has shown its potential for other clinical applications as well. A field in which radiomics may provide a relevant contribution is bone disease studies. Radiomics methods have been reported for the early identification of osteoporosis and for classification of osteoporotic patients compared to normal subjects or those suffering from osteopenia [49-50]. There is a need for more accurate individualized prediction of survival in spinal bone metastases which remains suboptimal. Radiomics could aid in prognostication. To test this hypothesis, we published the first study assessing radiomics features for prediction of survival in patients with SBM [51]. In Chapter VI of this thesis, we studied the predictive value of first-order and texture radiomics signatures and found no added discriminative effect of the studied radiomics signatures. So, the internal imaging characteristics have no added value in the prediction of survival. The question remains if there is a signal in the data and what should be done to find the signal, in other words quantify images differently or quantify different features. Radiomics should not be regarded as the magic bullet that solves all our decision-making conundrums. However, incorporation of non-radiomic features (e.g., data from clinical records, or biological or genetic sources) into more holistic models could facilitate the identification of biological correlates. Radiomics is a complex multi-step post-processing technique facing reproducibility issues which hinders actual translation of radiomics models into clinical practice. Future large-scale multi-center studies should be performed to address the generalizability and to validate the results. Second, most studies are retrospective, and may be limited by inherent confounding variables such as a heterogeneous study cohort, multiple different imaging protocols and scanners,

and various imaging reconstruction methods. Findings indicate that methodological quality has not been rising along with quantity, with many studies presenting methodological shortcomings in their radiomic pipelines [52-53]. Big and standardized clinical data are expected to make radiomics clinically applicable. However, to achieve that data sharing is essential, which is challenging because of logistical, political and ethical barriers.

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CHAPTER IX

Summary

Summary

Part 1: Impaired spinal stability due to (osteoporotic) vertebral fractures (OVF)

In the first part of this thesis we evaluate the impact on outcome of alternative diagnostic and therapeutic strategies in (osteoporotic) vertebral fractures with a special focus on the elderly.

In chapter II we analyse the role of the fracture liaison service (FLS) in reducing subsequent fracture risk in the elderly patients (>85 years of age). We show that the subsequent fracture incidence for the first 2-years of follow-up is comparable and 19% ($p = 1.0$) in both the FLS attenders and non-attenders group. Of the patients aged 50–85 years, compliance with the screening and treatment program is 72% ($p < 0.05$), with only 51% persistent in the prescribed therapy at 2 years. Therefore the advantage of a FLS in reducing subsequent fracture risk in patients > 85 years seems to be limited. And in practice a large proportion of these patients are not screened. The elderly with osteoporosis-related fractures should perhaps not be thought of as 'average elderly' but rather as 'frail' for a holistic managment of these elderly population, indicating that additional/personalized strategies are needed for this group.

In chapter III we systematically review the use of minimal invasive percutaneous cement augmentation in symptomatic osteoporotic vertebral fractures (OVFs), with special focus on the elderly. Using data from RCTs and prospective non-RCTs comparing percutaneous vertebroplasty (PV) or percutaneous kyphoplasty (PKP) with conservative treatment or sham procedures. We show that in contrast to current guidelines based on results of two RCT's published in 2009, pooled results indicate significant painrelief and functional improvement up to 12 months of follow-up for percutaneous cement augmentation compared to conservative treatment. We conclude that in the frail elderly with (sub-)acute OVF, with severe pain despite early conservative measures, focal tenderness and edema on MRI-scans concordant with the level of the fracture, when no absolute contraindications are present, percutaneous cement augmentation is safe and effective and can be offered to hasten return to normal function and bypass the consequences of prolonged immobilization.

In chapter IV we investigate treatment outcomes of traumatic thoracolumbar spine fractures managed with another minimal invasive technique: posterior percutaneous pedicle screw fixation technique (PPSF). We show that minimal invasive treatment strategies are faesible with good overall functional outcome, while minimizing pain, blood loss and morbidity PPSF may represent a useful strategy for treating osteoporotic thoracolumbar fractures in the older patient. Recent studies show that percutaneous

pedicle screw fixation combined with vertebroplasty provides a safe and effective option for the treatment of severe osteoporotic thoracolumbar compression fractures.

Part 2: Impaired spinal stability due to spinal bone metastases (SBM)

The aim of this part of the thesis is focused on analysing the predictive power of existing prediction models in the new era of treatment for spinal bone metastases (SBM). We try to guide personalized medicine by development of a digital user-friendly nomogram. Moreover, attempt to provide additional prognostic information, by use of radiomics features.

In chapter V we aim to externally validate two prediction models and to demonstrate whether these can be generalized for patients treated in different centers. Secondary we try to identify additional prognostic factors predicting survival in patients with SBM. With this first external validation study, we show modest predictive capacity for the validated two prediction models by van der Linden and Bollen, with a slightly better performance for the Bollen model. Since the field of treatment options has changed for metastatic spine disease, the existing scoring systems have become outdated for the actual situation and there is room for improvement for achievement of patient tailored care.

In chapter VI we focus on development of radiomics features for predicting 6 month survival probability for SBM patients. We find no added discriminative effect of radiomics signatures in the prediction of survival in patients with SBM. We state that here is still significant room for improvement necessary regarding the reproducibility of radiomics results, the assessment of clinical utility and open science.

In chapter VII we aim to guide patient tailored treatment by development of a prediction tool with a user-friendly digital interface that could be used to reliably estimate the 1, 3, and 6-months survival for patients with SBM. The digital version of the present nomogram can make predictions at any given time point as low as half a month. Besides the survival probability, it also provides the confidence interval of the predicted survival probability and a personalized survival curve, which gives the health care provider more insights to determine the optimal therapeutic strategy for a patient. The personalized survival curve could serve as a good starting point for shared decision making between patients and provider.

I

CHAPTER X

Impact Paragraph

Impact Paragraph

This paragraph briefly outlines the potential impact of the findings of the present dissertation on a societal and academic level, in which therapeutic and prognostic aspects for decision making and management of osteoporotic fractures and metastases of the thoracolumbar spine are elaborated.

Osteoporosis and its associated fragility fractures have a major impact on health and quality of life. Fragility fractures can be life-changing events and can bring pain, social isolation and dependence. The decline in quality of life following a fragility fracture does not only impact the person who has experienced the fracture, but also their family and other (informal) caretakers. As such, fragility fractures present major medical and socioeconomic challenges, to individuals, but also to society, exemplified above all by a substantial incidence of approximately 76,000 new fragility fractures in the Netherlands per year, consisting roughly of about 13,000 hip fractures, 12,000 vertebral fractures, 12,000 forearm fractures, and 38,000 other fractures [1]. By 2025, when accounting for the demographic projections, the number of incident fractures is estimated at 107,000, representing an increase of 31,000 fractures and the associated economic burden in the Netherlands is estimated to increase by 30% to € 1069 million [2]. Osteoporosis treatment can reduce the incidence of fractures by up to a half. Nevertheless, about 50% of women and 90% of men with minimum trauma fractures are not treated with any anti-fracture medication [3-4]. A Fracture liaison service (FLS) has been recognized as the most successful approach to achieve secondary prevention and is highly supported by the International Osteoporosis Foundation (IOF), other international and national scientific organizations and authorities. FLSs are well established in the Netherlands, however, the low FLS attendance rate of patients with a recent fracture and low compliance rates for prescribed anti-osteoporosis medication considered a huge problem needing further exploration [5-6]. In this thesis we posed the question if FLS is effective in the elderly >85 years [7]. This is the first study to show, that there is no risk benefit of an FLS programme in the extreme elderly patient population. The low FLS attendance rate was also considered a substantial problem in our study. 282 patients sustained a fracture at an age > 85 years in which only 122 patients (43%) underwent post-fracture assessment by the FLS. In 160 patients (57%) aged 85 years and older no screening was performed because of dementia (32%), at the request of patients or relatives (37%), for age-related reasons ('too old') (9%), immobility (1%), other reasons (4%) and 17% did not attend their scheduled appointment without explanation. When we look at the risk factors in the elderly population of extreme ages, the risk factors for osteoporosis fractures are the highest. In our study we showed that the risk factors were multifactorial, with a high percentage (92%) of osteoporosis or osteopenia in which 45% of the patients

had a previous fracture (before the current fracture). Hence there is tremendous need for treatment to reduce subsequent risk. Besides there's need for more adherence of anti-osteoporosis medication. For the patients in which osteoporosis treatment was prescribed, we found that 63% after 1 year and 51% after 2 years were persistent to their prescribed therapy. However, screening patients at an extreme of ages (> 85 years) was associated with lower mortality risk compared to patients who did not undergo this screening and treatment protocol. The multidisciplinary approach followed in the FLS can potentially aid in the identification of health hazards and comorbidities, and therefore improve health-care for these complex patients. We conclude that more emphasis should be laid on guidance of this elderly population instead of screening.

Vertebral fractures are the hallmark of osteoporosis as they are the most common fragility fractures [8]. Besides secondary prevention of new osteoporotic fractures, it is crucial to treat pain and disability after an osteoporotic vertebral fracture (OVF) in order to regain ambulation and functional capacity as soon as possible in elderly patients. In a systematic review of the literature, we conclude that minimally invasive percutaneous cement augmentation techniques are effective in pain reduction in patients with an OVF as compared to conservative care [9]. The results of our systematic review are in contrast to the latest Cochrane guideline [10]. Minimally invasive percutaneous cement augmentation procedures can be considered in elderly patients with severely disabling vertebral fractures in the acute phase (<6 weeks). We recommend that this minimally invasive treatment option should be discussed with patients in informed decision in order to make treatment more personalized.

In many patients with bone metastases, bone mineral density (BMD) is decreased, leading to osteopenia or osteoporosis as a consequence of hormone and/or chemotherapy or osteolysis, thus increasing the risk of vertebral fractures [11]. Spine metastases affect more than 70% of terminal cancer patients [12]. Advances in medical treatment for systemic disease have improved survival rates among patients with cancer, which has contributed to an increased incidence of spinal bone metastases. Quality of life in these patients is affected considerably because of pain, loss of functional abilities and possible spinal cord injury. Bone metastases can cause skeletal- related events (SREs), defined as a pathologic fracture, spinal cord compression, necessity for radiation (for pain or impending fracture) or surgery. The occurrence of SREs contributes significantly to the cost of care [13]. Data from a large study across four major European countries showed that all types of SREs are associated with considerable health resource utilization (HRU) and costs of up to €12,082 per SRE [14]. About 30–40% of patients do not receive care based on the current scientific evidence, and about 20–25% of the care provided is unnecessary or even potentially harmful to patients [15]. In order to provide a treatment that is optimally tailored to a patient's individual

situation, it is important to estimate the remaining life expectancy as accurately as possible. This could be achieved by implementing an accurate prediction model. However, most existing prediction models have been based on cohorts treated several decades ago and lag behind the evolution in oncology, which profoundly impact care for these patients. Ours is the first study to externally validate and compare two prediction models recommended by the Dutch Guideline Database Oncoline and we found that accurate individualized prediction remains suboptimal when using those existing prediction models. Besides, we found an essential predictive impact of overall visceral and brainmetastases. Finally, we showed that breast tumor subtypes based on immunohistochemistry markers seem to be important for the prognostication of breast cancer patients with spinal bone metastases (SBM). Since cancer biology plays a dominant role in patient survival, our findings regarding tumor type-specific prognostic parameters could contribute to prognostic models' accuracy.

There is lack of an easy-to-use prediction support system essential in the clinical scenario of SBM. With the development of a digital nomogram for SBM we tried to reliably estimate the 1, 3, and 6-months overall probabilities of survival for these patients and guide personalized medicine. This nomogram is the first to include both age and sex as prognostic factors, which can make predictions at any given time point as low as half a month. Besides the survival probability, it also provides the confidence interval of the predicted survival probability and a personalized survival curve. This could serve as a good starting point for shared decision making between patients and physicians.

Furthermore in this thesis, we aimed to identify radiomics based prognostic markers for survival prediction of SBMs. As yet, we didn't find added discriminative performance of radiomics signatures. Therefore, radiomics may not be the magic bullet that solves all our decision-making dilemmas in clinical practice for our domain. Integration of all health data, will accelerate the revolution of personalised medicine in oncology as well as expand and further study the role of radiomics.

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A

CHAPTER XI

Appendices

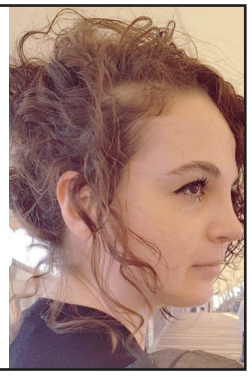
Dankwoord

Dit proefschrift zou niet tot stand zijn gekomen, zonder de directe en indirecte bijdrage van velen. Ik wil iedereen hiervoor van harte bedanken en een aantal mensen in het bijzonder, met een persoonlijk dankwoord bijgevoegd aan hun exemplaar van het proefschrift.

I am grateful I got the opportunity to work together with beautiful people. Thank you so much for your support and guidance.

Curriculum Vitae

Details



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