Rates and Outcomes of Vertebral Augmentation for the Treatment of Osteoporotic Vertebral Fractures Among the Commercially Insured

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Abstract

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Introduction: Approximately 750,000 people per year in the U.S. sustain osteoporotic vertebral fractures (OVF). Vertebroplasty and kyphoplasty, collectively termed vertebral augmentation are commonly used to treat OVF yet the strength of evidence supporting the use of vertebroplasty is weak. Kyphoplasty lacks a robust evidence base to support or reject its use. Prior studies of vertebral augmentation have focused primarily on patients >65 years old. Our aims were twofold; to determine the temporal changes in vertebral augmentation rates over the past decade in a commercially insured, working-age (under 65) American population, and to compare the rates of major medical complications, resource utilization and medication use among a cohort of patients with OVF treated with vertebral augmentation as compared to propensity matched patients not treated with vertebral augmentation .

Materials and Methods: Analysis of patients with OVF in the IBM MarketScan® Commercial Claims and Encounters Databases of Americans with employer-provided health insurance for the 2008-2017 period. To determine changes in OVF and vertebral augmentation rates over time we used ICD-CM 9/10 codes among a total of 149 million individual patients with an age range of 18-65 while excluding those with alternative fracture etiologies such as cancer, infection or transport accidents. We also 1:1 matched augmented patients to controls using propensity scores based on age, gender, region, fracture year, comorbidities, hospital admission at index fracture, and prior pain medication use, with further exact matching on use of opioids and advanced imaging in the time period until augmentation. We assessed rates of major medical complications, opioid use and all cause gross covered payments after augmentation and the analogous number of days from OVF in the control group (baseline day).

Conditional logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (95% CI) for categorical variables, with median regression used for the continuous variables.

Results: We identified 19,944 patients with OVF with an average incidence of 5.44 OVF per 100,000 MarketScan enrollees per year from 2008 - 2017. A total of 3424 patients (17.2%) with OVF underwent vertebral augmentation. Specifically, 708 (3.5%) were treated with vertebroplasty, 2571 (12.9%) received kyphoplasty and 145 (0.7%) had both. There was a trend of decreased utilisation of vertebroplasty, with a concomitant increase in kyphoplasty procedures performed over the time period. The percentage of patients with OVF treated with vertebral augmentation remained relatively stable.

In our outcome analysis, which required 1 year post fracture enrollment we identified 14,995 patients with OVF of whom 2363 (16%) were augmented and 2304 (98%) were matched 1:1 to non-augmented controls, giving a total matched analysis subset of 4608 patients. We combined vertebroplasty and kyphoplasty subjects into a single augmented group for our primary analysis. Approximately 75% of the matched subset were female with a median age of 58 in each group. We did not observe meaningful differences in the odds of major medical complications within 30 days (adjusted OR= 0.89; 95%CI= 0.55, 1.43) comparing augmented to non-augmented patients, or all cause median costs between groups from 3 days post baseline to 1 year post OVF (adjusted difference between medians = $1285; 95%CI= -312, 2703). However, augmented patients were more likely to have filled opioid medications in the 7 to 30 days after the procedure with 33.9% filling a prescription compared to 28.4% among non-augmented subjects (adjusted OR= 1.40; 95%CI= 1.19, 1.64). We noted significant differences in the rates of major spine surgeries, with the augmented group much less likely to receive surgery than the non-augmented control group in the year after OVF with annual rates of 4.86% vs 8.55% (adjusted OR= 0.43; 95%CI= 0.31, 0.60).

Conclusions: In our analysis of a large administrative claims database cohort of those under the age of 65 from 2008-2017 we found that 17% of patients with OVF were observed to have undergone vertebral augmentation. The ratio of those treated with kyphoplasty increased overtime and represented 87% of all augmentations performed in 2017.

Contrary to previously published findings (in older adults), this analysis found that patients less than 65 years old who underwent vertebral augmentation did not have decreased major medical complications, opioid fills, or all cause payments in the year following their OVF. We found that all cause costs (with cost of augmentation excluded) to be similar in the year following OVF. Augmented patients were significantly less likely to undergo major spine surgery in the year following OVF, suggesting augmentation may diminish the ultimate need for surgery in this younger patient cohort.

Clinical Relevance Statement:

Vertebral augmentation used to treat osteoporotic fractures in those <65 was not meaningfully associated with decreased major medical complications or opioid use compared to controls.

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Abbreviations

CI	Confidence Interval
CMS	Centers for Medicare & Medicaid Services
CPT	Current Procedural Terminology
CT	Computed Tomography
DVT	Deep Venous Thrombosis
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
MRI	Magnetic Resonance Imaging
NSAID	Non-Steroidal Anti-inflammatory Drug
OR	Odds Ratio
OVF	Osteoporotic vertebral fracture

Introduction

Osteoporosis is characterized by a critical decrease in bone mineral density, defined by the World Health Organization as less than 2.5 standard deviations below that of normal peak bone mass in a healthy adult. It results in a deterioration of microarchitecture of bone tissue with an increase in bone fragility and consequently susceptibility to fracture. Most cases of osteoporosis are associated with the aging process and is termed primary osteoporosis. When there is a specific cause of the disease, such as steroid use, endocrine disorders, or prolonged immobilization it is referred to as secondary osteoporosis. Osteoporotic vertebral fractures (OVF) have an overall incidence that is higher than other fragility fractures of the hip and wrist. [1] With our aging society, the already high costs associated with OVF, estimated in 2005 as $11 billion per year in the U.S. alone, have already and will assuredly continue to rise in the future. [1]

These fractures are often associated with pain, disability, and decreased quality of life. Oral opioid analgesics remain a common approach for OVF management, despite a lack of evidence in support of this. [2] Long term opioid therapy has been associated with increased health care utilization as well as the risk of complications ranging from constipation to dependence, abuse, and overdose. [3] The U.S. is in the grips of a long term “Opioid Epidemic”.[4] Starting in the mid 1990’s until 2010 there was a 9-fold increase in opioid prescriptions in older adults. [5] In 2015 it was reported that 35% of patients aged older than 50 years with chronic pain admitted misusing their opioid prescriptions in the prior 30 days. [6] More recently the COVID-19 pandemic does not appear to have altered the observed prescriptions for opioids in the US, apart from a dip in March to May 2020 in new opioid prescriptions. However, there is early evidence emerging that the COVID-19 pandemic has been associated with a new wave of opioid related complications including death. [7, 8] The ongoing use of opioids for the management of pain associated with OVF, must be considered within this context of the current opioid crisis.

The treatment of OVF remains controversial and vertebral augmentation, specifically vertebroplasty and/or kyphoplasty, have been proposed for symptomatic relief. Vertebroplasty, first described in 1987 [9], involves injection of an acrylic polymer or “bone cement”, such as polymethylmethacrylate

(PMMA) into a vertebral body fracture to relieve pain and provide stability. Kyphoplasty (also known as balloon-assisted vertebroplasty) is a subsequent modification of vertebroplasty in use since 2001. [10] The procedure involves imaging guided insertion of a balloon into the partially collapsed vertebral body. Theoretically, kyphoplasty reduces some of the bony deformity and abnormal spinal angulation, with potential improvement in the patient's pain. Although minimally-invasive, vertebral augmentation is not without risk. There are known procedural complications, including infection, subsequent additional fractures, and respiratory distress related to anesthesia, as well as complications associated with cement leakage; including inadvertent embolization to the lungs. [11]

Since 2009 robust evidence has been published challenging the purported efficacy of vertebroplasty. [12-15] It is no longer endorsed by some professional societies. [16] Similar to early studies of vertebroplasty, observational studies of kyphoplasty have reported high rates of pain relief and open-label randomized controlled trials (RCT) demonstrated improvements in pain, disability, and quality of life with these procedures compared to conservative therapy. [17-19] A 2018 Cochrane review meta-analysis has suggested no significant difference in outcomes comparing vertebroplasty to kyphoplasty. [14] In 2019 the "Efficacy and Safety of Vertebral Augmentation: A Second ASBMR Task Force Report" was published by The American Society for Bone and Mineral Research with their findings and recommendations. They give a strong recommendation that vertebroplasty provides no demonstrable clinically significant benefit over placebo or sham procedure, however they give a weak recommendation that kyphoplasty provides a small clinical benefit over nonsurgical management. They note there has been no high quality, randomized placebo/sham controlled trials investigating kyphoplasty. [20]

Similar to 2008, when societies advocated for the use of vertebroplasty with limited evidence [21], some medical societies are now advocating for kyphoplasty, suggesting it may be more useful in younger patients. [22] Kyphoplasty is also more expensive; 2.5x the cost of vertebroplasty per level instrumented due in part to additional equipment, aesthesia, and hospital costs. [23] More recent observational cohort studies, have claimed there is a survival advantage associated with vertebral augmentation compared to non-surgical management. [24, 25] However there is concern that these studies have not corrected for immortal time bias; by using a time fixed analysis in cohort studies where death can only occur in one group – the non-augmented group. Anyone who dies before they can be augmented will only be included in the non-augmented group for analysis. This is a well known

bias due to the inappropriate accounting of follow-up time and treatment status in the design and analysis of such studies. [26, 27]

The IBM/Watson MarketScan® Commercial Claims and Encounters Databases, is a convenience sample research data set of insurance claims information from people with employer-sponsored insurance and their dependents in the United States. It represents a large sample, with over 40 million covered lives in 2016. It cannot be considered representative of all working age Americans, but the data contained is a likely approximation of what would be found in the population of those privately insured.[28] These patients are younger than those studied previously (typically using Medicare CMS data [29]). This work will address two fundamental issues:

TRENDS: Determine the annual rate and temporal change in volume of vertebral augmentation procedures (vertebroplasty and/or, kyphoplasty) performed for the treatment of OVF in the MarketScan cohort.

OUTCOMES: Compare the rates of major medical complications, resource utilization and medication use using propensity matched cohorts of patients with OVF treated with vertebral augmentation vs. those not treated with vertebral augmentation

This analysis of the MarketScan population will provide a unique patient cohort compared to prior analyses of OVF. We hypothesize in this younger cohort vertebral augmentation will be associated with reduced opioid usage compared to those not augmented, due to its efficacy in treating OVF associated pain. As secondary hypotheses we will see this benefit translated into reduced major medical complications ,reduced usage of other pain associated medications and lower resource utilization in the longer term.

Figure 1 demonstrates the conceptual model for the study.

Materials and Methods

Data Source:

IBM/Watson MarketScan® Commercial Claims and Encounters Databases from 2007-2018. These databases contain inpatient, outpatient, and pharmacy claims for patients covered by employer-sponsored commercial insurance across the U.S. The inpatient and outpatient claims databases include procedure and visit level details from medical claims such as International Classification of Diseases, 9th and 10th Revisions, Clinical Modification (ICD-9-CM and ICD-10-CM) diagnosis and Current Procedural Terminology (CPT) medical procedure codes, dates of service, and variables describing the financial expenditures of both the patients and their insurance plans. The outpatient pharmacy claims database provides prescription dispensing details that include National Drug Code (NDC) and generic identifiers of the drugs dispensed, dates dispensed, quantities, days' supply, and payments made for each claim. A separate eligibility and demographics file provides additional information about each subject such as age, gender, insurance plan type, geographic location, and enrolment status by month. Survival data cannot be ascertained using the MarketScan database, as mortality is not accurately coded, and withdrawal from the database may be for multiple reasons other than death ie loss of employer provide health insurance.

ICD 9 and 10 Codes:

ICD-CM provides codes to classify diseases and a wide variety of signs, symptoms, abnormal findings, complaints, social circumstances and external causes of injury or disease. The replacement of ICD-9-CM to ICD-10-CM codes occurred on 1 October 2015; this was a federally mandated change affecting all payers and providers. While ICD-9-CM and ICD-10-CM have similar structures, ICD-10 is more detailed and complex, with more than 141,000 codes, a 700% increase when compared to ICD-9. [30] There are instances where a single ICD-9-CM code can map to more than 50 distinct ICD-10-CM codes. [31] In studies of vertebral augmentation that used ICD-9-CM, three codes have been used to identify an osteoporotic vertebral fracture when appropriate exclusion criteria were utilized (733.13, 805.2, 805.4). [29, 32, 33]. These codes are not specific for osteoporotic fractures. I found an additional 9 ICD-9-CM codes that could be used to identify thoracic or lumbar OVF (Appendix 1). We

required all patients identified with ICD-9-CM codes to have a diagnosis code for osteoporosis in the year prior or up to 6 months after the initial fracture was coded.

There is no simple way to convert ICD-9-CM to ICD-10-CM codes and so in-depth examination of parent code trees is required to map existing code databases to the newer definitions. There are no currently published studies that have performed this conversion process. I performed this on all inclusion and exclusion criteria, and the outcome codes for major medical complications.

I found 134 codes in ICD-10-CM that could be used with appropriate inclusion and exclusion criteria to code for OVF. Of these, 13 ICD-10-CM codes were specific for osteoporotic fractures of the spine, and an additional 121 codes were similar to ICD-9 CM codes, that when present with a diagnosis of osteoporosis could be used to code for an OVF of the thoracic or lumbar vertebra.

The similarities and differences in inclusion, exclusion and treatment group criteria for the Trends and Outcomes analyses are summarized in Table 1 and detailed below.

TRENDS: Determine the annual rate and temporal change in volume of vertebral augmentation procedures (vertebroplasty and/or, kyphoplasty) performed for the treatment of osteoporotic vertebral compression fractures from 2008-2017 in the working age MarketScan population (18- 65 years old).

Inclusion Criteria:

Patients in the database from 2008-2016 were included for the temporal trends analysis. We used ICD-9-CM and ICD-10-CM to extract those with codes indicating OVF with 1 year enrolment prior to fracture and 6 months after in order to capture as many fractures and vertebral augmentation procedures as possible.

Exclusion Criteria:

In order to identify patients with thoracic and lumbar osteoporotic vertebral fractures, we excluded patients who had any of the following diagnoses that could explain or be a cause of fracture in the 365 days prior to their current fractures: neoplasm, intraspinal abscess, inflammatory

spondylarthropathies, discitis/osteomyelitis, spinal cord injuries and transportation accidents. To ensure that each OVF was an index event, we excluded patients who in the previous year had either been hospitalized with a primary diagnosis of an OVF or had a vertebral augmentation procedure.

Groups:

Treatment groups were defined based on the presence (augmented group) or absence (control group) of Current Procedural Terminology (CPT) and ICD-9, ICD-10 procedural codes for vertebroplasty or kyphoplasty in the 6 months following the index fracture. Vertebral Augmentation has typically been studied in acute to subacute vertebral fractures. The further out we get from the index fracture the less certain we become that the augmentation performed was for this event.. Patients were also excluded with procedural codes that were ambiguous for vertebral augmentation including CPT 22899 “Other procedures of the spine”, ICD-9 procedure code 7849 “Unlisted procedure, spine” or ICD-10 procedure codes for “Repair of Thoracic or Lumbar Vertebra”.

OUTCOMES: Compare the rates of major medical complications, resource utilization and medication use using propensity matched cohorts of patients with OVF treated with vertebral augmentation vs. those not treated with vertebral augmentation

Inclusion Criteria:

Patients in the database from 2008-2016 were included for the outcomes analysis with 1 year of enrolment prior to fracture and 1 year after to assess for pre-fracture comorbid status, allow for adequate follow-up and outcomes comparison, and to ensure this was the index diagnosis of OVF.

Exclusion Criteria:

In order to extract patients with thoracic and lumbar osteoporotic vertebral fractures, if patients had any of the following diagnoses that could explain/be a cause of fracture in the 365 days prior to their current fractures they were excluded; neoplasm, intraspinal abscess, inflammatory spondylarthropathies, discitis/osteomyelitis, spinal cord injuries and transportation accidents. In addition, those who had vertebral augmentation 180 days after OVF, or had ambiguous procedural codes (which could have meant that those in the non-augmented group had a vertebral augmentation

procedure) were excluded. To ensure that each OVF was an index event, the patient could not have been hospitalized in the previous year with a primary diagnosis of an OVF or have had a vertebral augmentation procedure during the previous year.

Demographics and Measures of Comorbidity:

We collected all available demographic information including age, sex, insurance type, employment status, geographic region, admission at diagnosis, all available codes for comorbidities, fracture level and year, the use of advanced imaging and time between diagnosis and treatment, if performed. Race and ethnicity data are not available in MarketScan. Baseline patient comorbid conditions were accounted for using the modified Quan/Charlson comorbidity index and I used the total health gross covered payments and total spine-related gross covered payments in the year prior to fracture as an additional measure of overall health status; with those who had higher expenditures in the year prior likely to have co-morbid conditions, and/or spine related conditions .[34] We defined spine-related procedures using a validated algorithm that incorporated ICD diagnosis codes and CPT codes. [35, 36]

Propensity Score Matching:

Propensity score matching methods were used to better account for selection bias inherent in observational/claims database studies in which patients are selected for a given treatment in a non-random manner and compared with untreated patients.-This score is based on the probability of receiving a particular treatment, conditioned on a set of covariate values. A caliper width of 0.2 was used. The propensity score was evaluated using: age, gender, health plan type, region of residence, year of fracture, Charlson co-morbidity score, whether the patient was admitted for the index fracture, filling medications (opioids, NSAIDs, muscle relaxers, gabapentin, benzodiazepines, pregabalin) in the 90 days through 1 day prior to fracture, total health gross covered payments in year prior to fracture, total spine-related gross covered payments in year prior to fracture and the level of the index fracture (lumbar, thoracic, or other).

The augmented cohort was then matched with control patients 1-to-1 with four separate matches performed. As I did not have data on pain severity the matches were based on filled opioid medication

prescriptions from fracture to augmentation day and the use of advanced imaging in the perifracture/peritreatment period. The perifracture/peritreatment period was defined as 6 weeks prior to coded OVF, and then up to the day of augmentation and the same period of time in the non-augmented matched control. The use of advanced imaging – such as CT or MRI was much more common in the augmented group than non-augmented group. This additional matching criteria was used as a marker of fracture severity, as many OVF are diagnosed and followed up with x-ray alone. In addition the augmented and non-augmented controls could not have had spine surgery, a new cancer diagnosis, or major medical complications prior to or on their match's augmentation dates.

The baseline treatment date, from now on referred to as "<u>baseline</u>" in the matched control group will be the corresponding number of days from OVF, referred to as "<u>index</u>", until augmentation.

Match 1: Any opioid medication prescription between fracture and baseline; received advanced imaging from 6 weeks prior to fracture to day prior to baseline
Match 2: No opioid medication prescription between fracture and baseline; received advanced imaging from 6 weeks prior to fracture to day prior to baseline
Match 3: No opioid medication prescription between fracture and baseline; did not receive advanced imaging from 6 weeks prior to fracture to day prior to baseline
Match 4: Any opioid medication prescription between fracture and baseline; did not receive advanced imaging from 6 weeks prior to fracture to day prior to baseline

Figure 2 provides an overall schema for Match 1, in an attempt to better explain the matching process.

Overall this matching process on specific events in the treatment cycle of these patients allows for improved matching of controls with similar pretreatment/peritreatment care patterns, and hopefully stronger control of potential confounders.

Primary outcomes:

I identified one primary outcomes and two secondary outcomes a priori:

- **Any major medical complication within 30 days after baseline**

- Any fill of an opioid prescription from 7 days after baseline to 30 days later (to exclude periprocedural prescriptions)
- Costs from the 3 days after baseline through 365 days after OVF (to exclude the cost of the augmentation procedure)

Complications:

Using the patients and treatment groups identified above, we assessed the occurrence of major medical complications within 30 days of baseline and also 1 year from the time of the index OVF. These time periods were chosen to examine the periprocedural period, and then a longer time frame to assess for later or persistent differences. Major medical complications included diagnosis codes for cardiorespiratory arrest, acute myocardial infarction, respiratory failure, pulmonary embolism, DVT, pneumonia, and stroke as well as the relevant procedural codes (Appendix 1) [37] These complications are recognized as severe and potentially catastrophic outcomes, and are also more likely to be consistently coded than minor complications. I also included DVT as this has been used in previous analysis of vertebral augmentation in Medicare claims analysis. [32]

Medication Usage:

I assessed whether patients filled any pain medication prescriptions from the 6 drug classes of interest (opioids, NSAIDs, muscle relaxers, gabapentin, benzodiazepines, pregabalin) from 7-30 days after the baseline, the subacute post matching period and also 7 days after the baseline through 365 days after the index fracture, the later post matching period. These dates were chosen to control for medications prescribed for the treatment of any acute post treatment pain of vertebral augmentation as a potential confounder.

Health Care Utilization and Cost:

I recorded general hospital admissions during the year following OVF. Using previously reported analyses with ICD-9 codes I created a database for lumbar spine surgeries, and hip/wrist fracture and

updated it with ICD-10 codes in a similar process as described above. I also recorded hip/wrist fracture rates during the year following the index vertebral fracture as a surrogate marker for severity of osteoporosis. [29]

To assess healthcare utilization associated with OVF I evaluated overall and spine-related gross covered payments from the index vertebral fracture date through 30 days post baseline, which included the cost of the vertebral augmentation, and from 3 days post-baseline through 365 days after the incident OVF, in order to examine costs without procedural costs included.

Statistical Analysis:

After propensity score matching I calculated descriptive statistics of the matching variables comparing the groups to check that these were similar. For binary outcome variables, I used conditional logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs). Median regression was used for the continuous variables, calculating difference between medians and 95% CIs. All models were performed unadjusted and then adjusted for age, gender, year of OVF, Charlson co-morbidities, admission for the index OVF, filling of prescription pain medications prior to OVF, overall and spine-related costs in the year prior to the OVF, and the anatomic level of the OVF. We did not adjust for race or ethnicity as this data is not available in MarketScan. These are additional potential interaction variables. Statistical analyses were performed with R (version 3.6.2; R Foundation; Vienna, Austria.) P-values <0.05 were considered statistically significant.

Results

TRENDS:

There was no observed change in the number of patients with osteoporotic fractures identified using the new ICD-10-CM codes in 2015, when their use became mandatory, suggesting the new codes continued to capture those previously identified with published code databases. (figure 3) The new ICD-9/10-CM code database for the inclusion, exclusion criteria, and medical complications can be seen in Appendix 1.

The temporal analysis of OVF and augmentation rates are detailed in table 2 and 3. There was a decline over the course of the study in the number of patients enrolled in the MarketScan Database. I identified 36,033 patients with OVF who met our inclusion criteria and 19,944 patients after exclusion criteria had been applied. We found an average incidence rate 9.64 OVF per 100,000 MarketScan enrollees per year without exclusion criteria applied and 5.44 OVF per 100,000 MarketScan enrollees per year with exclusion criteria applied (figure 3). 3424 (17.2%) underwent vertebral augmentation from Jan 2008 to June 2017. By category of procedure 708 (3.5%) were treated with vertebroplasty, 2571 (12.9%) received kyphoplasty and 145 (0.7%) had both. Table 3 details the rate and volume of procedures performed in 6 month intervals. There is a trend of decreased utilisation of vertebroplasty, with a concomitant increase in kyphoplasty procedures performed over the observed time period (figure 4). As a percentage of augmentations performed, vertebroplasty decreased from a high of 30.9% in July – December 2009 to a low of 10.1% in January to June 2015 whereas kyphoplasty increased from 65.4% to 84.9% across the same time period. The overall percentage of OVF treated with vertebral augmentation remained relatively stable over the time period ranging from a low of 13.6% in July - Dec 2011 to a high if 19.1% in Jan - June 2017 (figure 5).

OUTCOMES:

14,995 US adults aged 18 to 64 years with OVF met our inclusion and exclusion criteria. 2556 (17%) received vertebral augmentation and 12,439 (83%) did not. (figure 6) After further post OVF exclusions there were 2363 patients assigned to the Augmentation Match Group, and 12,328 in the No Augmentation Match Group. (figure 7) After propensity score matching was performed 2304 (98%)

were matched 1:1 to non-augmented controls, giving a total matched analysis population of 4608 patients. Table 4 details the characteristics of the matched cohorts, with approximately ¾ being female and a median age of 58 years old in each group. Approximately 1/3 were admitted for their index fracture, and over 90% had advanced imaging performed before their baseline day. 50% had been prescribed an opioid medication from fracture to baseline. In summary, the measured characteristics between the two cohorts were very similar. The median time to procedure in the augmentation group was 18 days (IQR: 5, 44). Comparisons of outcomes are shown in Table 5, with the unadjusted and adjusted results broadly similar, and differences are detailed below.

Major Medical Complications:

There was no difference in the odds of major medical complications in the augmented cohort compared to the non-augmented controls during the 30 days following baseline, which was my primary outcome (adjusted OR= 0.89; 95%CI= 0.55, 1.43). There was also no difference at 1 year post OVF (adjusted OR= 1.17; 95%CI= 0.96, 1.42) Figure 8 displays a 1-year Kaplan-Meier curve for time to major medical complication. Owing to the small number of complications, when we assessed them on an individual basis, many of the logistic regression models would not run. I did not observe any significant difference between the groups where a result was computable. The most common complications in the augmented group at 1 year post OVF were pneumonia (7.99%), respiratory failure (4.90%) and stroke (4.38%). 5.34% had suffered a venous thromboembolic event either a pulmonary embolism and/or DVT at 1 year., The most common complication in the non- augmented group at 1 year post OVF was pneumonia (7.29%), stroke (4.69%) and respiratory failure (3.90%). 4.43% had suffered a venous thromboembolic event at 1 year

Medication Related Outcomes:

Despite matching on opioid prescriptions prior to baseline the augmented cohort was more likely to have a filled a prescription for opioid medication in the 7 to 30 days after their procedure compared to the same post baseline period in the non-augmented controls; 33.9% compared to 28.4% (adjusted OR= 1.40; 95%CI= 1.19, 1.64). This was a secondary outcome. When we assessed over a longer follow-up period (7 days post baseline up to 1 year post OVF) the observed difference in prescription fills persisted; 58.3% compared to 54.4%, and was significantly different before adjustment (OR=

1.21; 95%CI= 1.06, 1.38,) but the adjusted odds of filling an opioid prescription was no longer significantly different between the two groups (adjusted OR= 1.07; 95%CI= 0.91, 1.25). This same pattern was also observed in fills of muscle relaxant medication, the augmented cohort were more likely to have a filled a prescription for muscle relaxants in the 7 to 30 days after baseline (adjusted OR= 1.28; 95%CI= 1.03, 1.60), but were not more likely than the non-augmented controls to fill a muscle relaxant prescription over the longer adjusted follow-up period (adjusted OR= 1.10; 95%CI= 0.94, 1.28). I did not observe any other significant difference in prescription fills in other measured medications.

Additional Outcomes:

There was no difference in the likelihood of suffering a wrist or hip fractures during the year following the index vertebral fracture between the groups, suggesting roughly similar severity of osteoporosis. There was also no difference observed either in the likelihood of patients requiring hospitalisation after baseline day, or in cancer diagnoses to one year after OVF. I did observe a significant difference in the rates of major spine surgeries, with the augmented group less likely to receive surgery than the non-augmented control group, (adjusted OR= 0.43; 95%CI= 0.31, 0.60). In both groups the majority of surgeries related to spinal fusion or decompression either of intervertebral discs or spinal lamina. In the augmentation group 54.8% of coded procedures related to spinal fusion compared to 64.8% in the non-augmented group.

Cost Related Outcomes:

All cause median costs between groups from 3 days post baseline to 1 year post OVF (to exclude procedure costs) were similar at $24,617 in the augmented group, and $22,074 in the non-augmented group, (adjusted difference between medians = $1285; 95%CI= -312, 2703). All cause costs from OVF to 30 days post baseline (that likely included the billing for the procedure) were significantly higher in the augmented group, (adjusted difference between medians = $23,082; 95%CI= 21,438, 24,905). The spine related component of this difference was higher in the augmented group but only accounted for a third of the observed difference in all cause costs over that same time period, (adjusted difference between medians = 7109; 95%CI= 6727, 7438).

Discussion

TRENDS:

This analysis of a large database of administrative claims data in the under 65's is the first to demonstrate that vertebral augmentation is used to treated approximately one fifth of patients with OVF. As expected in a younger population, the incidence of OVF is very low [38, 39], but the percentage treated with augmentation is similar or higher than that observed in other analyses of CMS claims data [29, 32]. Interestingly kyphoplasty was already the dominant treatment option, even before publication of the first negative trials of vertebroplasty in 2009. This differs from CMS data, where vertebroplasty was the preferred augmentation procedure at this time. [40] Vertebroplasty demonstrated a relatively consistent decline in utilization from 2009, and I observed an increase in utilization of kyphoplasty from 2011 onwards. It does appears that kyphoplasty is being substituted for vertebroplasty in the treatment of some OVF, despite a lack of evidence for its use [14, 20]. The overall rate of vertebral augmentation in the cohort was relatively consistent over time, again in contrast to the CMS data where vertebral augmentation rates declined precipitously in the early 2010's before a more recent kyphoplasty led recovery. [40]

OUTCOMES:

The results from this study suggest that treatment of OVF with vertebral augmentation In adults under 65 years old is not associated with improved outcomes in relation to medication usage, specifically opioid medication, major medical complications or reduced health care costs in the year following fracture when compared to those not augmented in a large convenience sample of working age commercially insured Americans. The size of the database allowed us to maintain an analytically sufficient population despite assessing a relatively rare disease in the age group covered.

I observed higher rates of opioid and muscle relaxant medication use in the early postprocedural follow up amongst those augmented. The time period from 7 – 30 days after baseline was specifically designated a priori to reduce the chance of capturing medications that may have been prescribed as a regular post procedure medication. Interestingly the augmented group had 1.4 times higher odds (95% CI 1.19, 1.64) of an opioid fill, which is a very similar finding in a study of pooled individual

patient level data in a meta-analysis of the two randomized placebo controlled trials of verterboplasty published in 2009, (25% more likely to be taking opioids at one month than patients randomised to placebo). [41] This was the opposite of what we had expected, as the control group had not had a pain limiting procedure performed, however, the clinical significance of a relatively small difference in actual opioid fills is uncertain, but likely negligible. Although there remained an observed difference in the opioid fills at 1 year post OVF, it was no longer significant. However the observed rate of filling of any pain and musculoskeletal medications remains high in both groups suggesting neither group's symptoms are well under control.

The rationale for vertebral augmentation, in addition to the purported pain-relieving effect, is a reduced risk of medical complications from immobility such as venous thromboembolic events or pneumonia, and reduced risk of subsequent hospitalization for medical or pain management, and early return to rehabilitation. I did not observe any significant difference in major medical complications in the early postprocedural timeframe or over a year of follow up, and there was no significant difference in observed rates of rehospitalization in the year following fracture. We did not observe improved outcomes in younger patients. Indeed, when using registry or patient databases, now commonly referred to as "real world evidence", it has been suggested that for any observed differences to be considered clinically significant, the magnitude of observed difference needs to be large given the increased risk of observing a significant difference due to chance alone, when assessing multiple outcomes.[42] Our observed rate of 30 day complications of about 3% is slightly lower than a study utilizing the 2012-2014 American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database assessing vertebral augmentation. Choo et al observed a 30 day complication rate of 5.8% in their cohort that contained 2433 patients who had vertebral augmentation for any reason, of whom 20% were under the age of 65. However, they included urinary tract infections in their definition of complication which accounted for 2.1%, so our rates appear similar, and we could anticipate a lower complication rate in this younger population. [43]

As expected, when we assessed cost from the fracture to 30 days post baseline, they were considerably higher in the augmented group compared to the non-augmented group. When we looked at purely spine related costs - which would include the cost of the augmentation procedure, these only

accounted for 1/3 of the increased all cause costs observed in the augmentation group. This suggests that overall health care utilization is higher in the augmented group for reasons other than just the procedure. This could reflect other specialist input or investigations needed prior to treatment, anesthesia, or operating room time. An analysis of kyphoplasty costs from 2010 to 2018 of Medicare Part B has shown an increase in the average per patient procedure cost from $3,844 to $5,073 driven in a large part by a shift toward more office-based kyphoplasty. [40] In this setting the procedure attracts a higher “nonfacility” rate which incorporates overhead, staff, and equipment. It may be that our codes aren’t capturing some of these associated procedure costs. I did not assess a change in median costs over time or delve in more detail into the breakdown of costs per patient. This may be an interesting further analysis.

At one year post OVF our observed all cause median costs were similar, despite the higher odds the non-augmented group had of undergoing major spinal surgery in the longer follow-up period. Spinal surgeries are associated with high health utilization costs with the median inpatient cost for a single level lumbar fusion from 2008-12 was estimated at $21,781. In the Medicare population from 2002-07 adjusted mean hospital charges for complex spinal fusion procedures were $80,888 and for decompression alone were $23,724 [44, 45] This raises an interesting question, Is vertebral augmentation protective against the need for subsequent back surgery in these younger patients? It may be that vertebral augmentation is being substituted for operative spinal fusion in some of these younger patients with worsening or severe kyphotic deformities, given that some traumatic and osteoporotic vertebral fractures are managed with spinal fusion. [46]

Overall, our results are in contradistinction to other published observational analyses of older/ elderly adults undergoing augmentation; that usually found improved medical outcomes in those treated with vertebral augmentation compared to non-augmented controls. [32, 47, 48] An analysis of CMS data revealed fewer medical complications in the pre procedure time, when compared to the matched controls in keeping with an unmeasured selection bias, and this raised concerns regarding unmeasured selection bias in these observational studies. [29] In addition to a robust sample size in an age population in which these fractures are relatively rare events, we attempted to account for selection biases and unmeasured confounders with propensity scoring and a rigorous matching algorithm designed to reduce the risk of biased comparisons between groups.

Our use of propensity score matching is a well described method to attempt to control for treatment selection bias in observational studies. The propensity score is an estimate of the likelihood of receiving treatment based on observed baseline covariates. By assembling a study population in which we have tried to balance known confounding factors between treatment groups, it is an attempt to replicate a randomized trial; the probability of being assigned to a particular treatment between each case or control being comparable. [49, 50]. Because we did not have data on pain severity, we matched on specific perifractural events; fills of opioids, receipt of cross-sectional imaging and admission for index fracture, obtaining matched controls with similar acute care patterns and thus stronger control for potential confounders. If we had instead stratified the results on these variables, it would have led to a significant reduction in statistical power. .We measured outcomes from the same starting point post OVF in each matched pair. We found close matches for 98% of our augmentation cases and Table 4 illustrates how similar these two groups were. The 59 augmentation cases we could not match had such differences in baseline covariates that we could not find not a patient similar to them from a pool of over 12,000 controls. As this is not an RCT we cannot ascertain the probability of receiving treatment based on unobserved covariates, and so the potential for some selection bias remains. Additionally we ended up with a highly selected group of cases and controls, that may limit generalizability.

Limitations:

This study has some important limitations. Although the majority of ICD-10-CM fracture codes include site – thoracic or lumbar, not all do. Site is not mentioned in any ICD-9-CM code. It is possible some cervical fractures are included in this cohort, particularly those selected using ICD-9 CM codes, but their prevalence is rare compared to thoracic and lumbar fractures [51], and the majority of cervical fractures are the result of trauma, cancer or inflammatory conditions which we address in our exclusion criteria [52, 53]. There is also no established consensus on how to define osteoporotic vertebral fractures using billing data, and no previously published study that used ICD-10-CM codes, so these codes have not been externally validated or used in the analysis of another administrative database. Previous validation studies of ICD-10 codes have required the use of extensive chart reviews of patients with known conditions; such as hyponatremia or sepsis, across multiple sites and health care systems in order to perform sensitivity analyses on how these known medical conditions

have been coded. They have found ICD-10 codes to be specific but not overly sensitive for identifying cases of interest from billing databases or patient registries. [54, 55] It may be that we are underestimating the prevalence of OVF in this population.
Additionally as these fractures can be the event that leads to the diagnosis of osteoporosis, it possible we missed some OVF that were only diagnosed or coded 6 months post OVF, or were miscoded. Also our use of very stringent exclusion criteria to ensure we were as much as possible only assessing OVF limited the size of our final cohort, as seen in Table 2.

I did not perform a subgroup analysis looking at vertebroplasty and kyphoplasty separately, so it is possible there are significant differences between the two in terms of measured outcomes. A recent randomized non blinded trial comparing kyphoplasty and vertebroplasty for OVF from Italy found no difference in visual assessed pain score at 12 months, although somewhat unusually the published study does not list the actual pain scores, p value or confidence intervals in their results. [56] A relatively large systematic review and meta-analysis comparing vertebroplasty and kyphoplasty across 29 randomized, prospective nonrandomized, and retrospective studies found no differences in pain or disability scores. [57].

We are limited by our reliance on billing data, and diagnosis and procedure codes may have been miscoded. As we do not have any access to clinical data, we relied on surrogate markers (medications and coded major complications) for patient reported outcomes such as pain and disability. Our analysis of costs is limited by calculating medical expenditure data for employees of self-insured firms alone, again limiting generalizability. The pharmacy claims for medications reflect that the patient filled their prescription; whether the patient takes it cannot be assessed on administrative data. Mortality cannot be measured or assessed in MarketScan as patients can enter or leave the database for reasons other than death, such as loss of insurance. We required two years of full enrollment to be eligible, essentially excluding anyone that died in that time period. Patients may therefore have been healthier than the general MarketScan population, however death can occur because of a major medical complication, thus the rate of major medical complications may be higher than we observed. MarketScan does also not include some other important demographic data that

have well-established associations with the prevalence of comorbidities such as body mass index or race/ethnicity.

Conclusions

In this analysis of a large database of administrative claims data in the under 65's from 2008-2017 17% of patients with OVF were observed to have undergone vertebral augmentation. The ratio of those treated with kyphoplasty increased overtime and represented 87% of all augmentations performed in 2017. It appears that kyphoplasty has been substituted for vertebroplasty in the treatment of some of these OVF over the study period.

Contrary to previously published findings (in older adults), this analysis found that patients less than 65 years who underwent vertebral augmentation did not have decreased major medical complications, opioid fills, or all cause payments in the year following their OVF. We found that all cause costs are significantly increased in those augmented. Augmented patients were however significantly less likely to undergo major spine surgery in the year following OVF, suggesting augmentation may diminish the ultimate need for surgery in this younger patient cohort.

The updated ICD-10-CM code and matching methodology will form the basis for a complementary analysis of CMS data over the same time period, which has the potential to assess mortality outcomes, missing from the MarketScan database. Together these analyses will provide a comprehensive picture of vertebral augmentation practices and outcomes in the U.S.

Our results and the presence of immortal time bias in other observational cohort studies implies the need for rigorous studies assessing the efficacy of kyphoplasty, similar to the high quality, randomized placebo/sham controlled trials performed to assess vertebroplasty. It is incumbent that we include younger adults with osteoporosis in any further randomised, controlled trials assessing vertebral augmentation.

Figures and Tables:

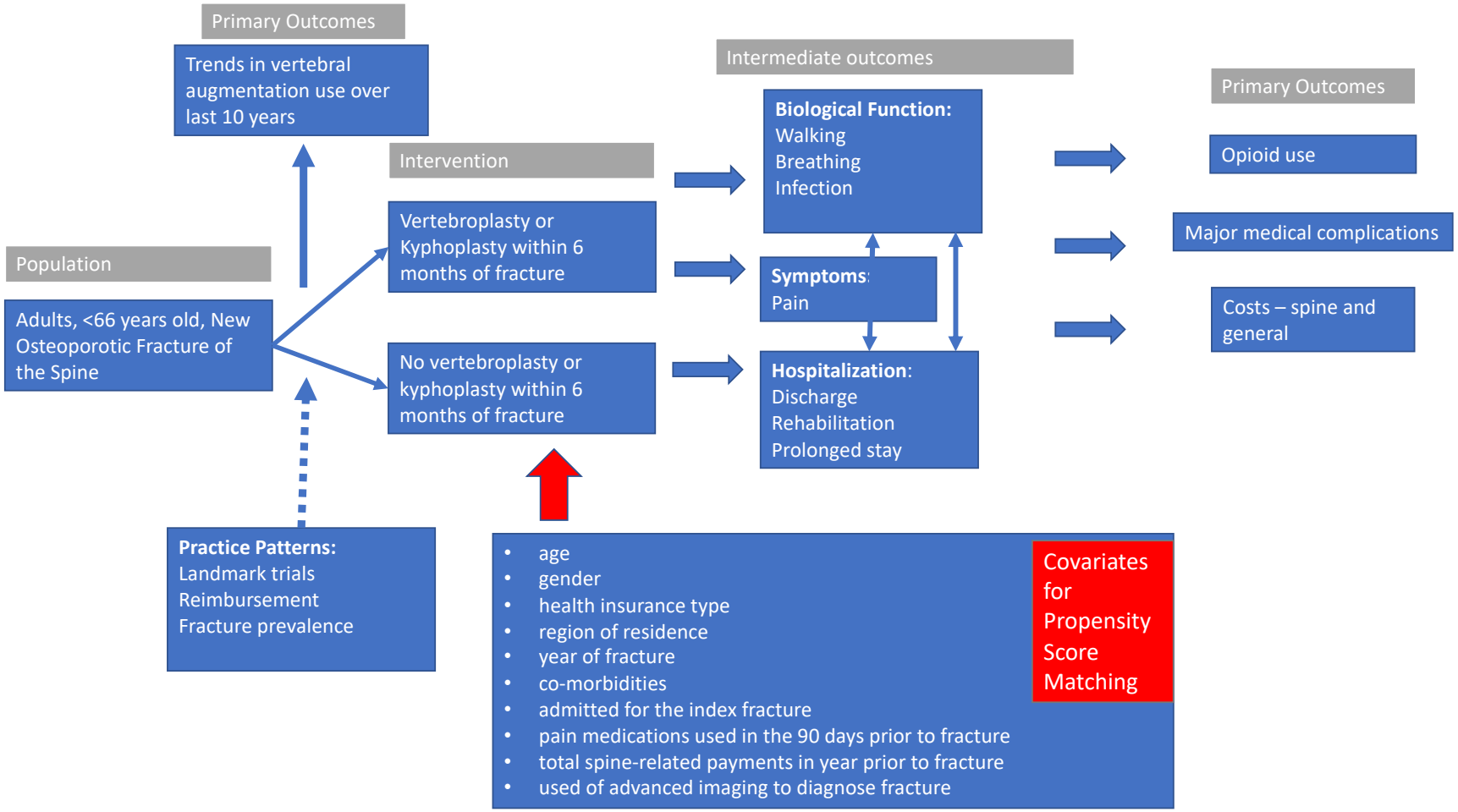
Primary Outcomes
Trends in vertebral augmentation use over last 10 years
Intermediate outcomes
Primary Outcomes
Biological Function:
Walking
Breathing
Infection
Intervention
Opioid use
Vertebroplasty or Kyphoplasty within 6 months of fracture
Major medical complications
Population
Symptoms:
Pain
Adults, <66 years old, New Osteoporotic Fracture of the Spine
Costs – spine and general
No vertebroplasty or kyphoplasty within 6 months of fracture
Hospitalization:
Discharge
Rehabilitation
Prolonged stay
Practice Patterns:
Landmark trials
Reimbursement
Fracture prevalence
age
gender
health insurance type
region of residence
year of fracture
co-morbidities
admitted for the index fracture
pain medications used in the 90 days prior to fracture
total spine-related payments in year prior to fracture
used of advanced imaging to diagnose fracture
Covariates for Propensity Score Matching

Figure 1

MarketScan Analysis	Time Period	Inclusion Criteria	Exclusion Criteria	Enrolment criteria	Augmentation Group	Non-Augmentation Group
Trends	2007-2017	ICD-9-CM or ICD-10-CM codes indicating OVF	Any ICD-9-CM and ICD-10-CM code that could explain/cause a vertebral fracture in preceding 12 months: neoplasm, intraspinal abscess, inflammatory spondyloarthropathies, discitis/osteomyelitis, spinal cord injuries and transportation accidents Any CPT, ICD-9-CM and ICD-10-CM codes indicating OVF or vertebral augmentation in prior 12 months	1 year pre OVF, 6 months post OVF*	CPT, ICD-9 or ICD-10 procedural codes for vertebroplasty or kyphoplasty within 6mos	No ambiguous procedural codes ie CPT 22899 “Other procedures of the spine”,
Outcomes				1 year pre and post OVF*	Same as above No CPT, ICD-9-CM and ICD-10-CM codes for spine surgery, neoplasm, or major medical complication from Index to Augmentation	Same as above # No CPT, ICD-9-CM and ICD-10-CM codes for spine surgery, neoplasm, or major medical complication

Table 1 Inclusion and Exclusion criteria for inclusion into the Trends and Outcomes Analysis in MarketScan population

*Requiring a year of pre-OVF enrolment for inclusion in both groups the earliest index OVF was January 2008. The latest a patient could be included was June 2017 in Trends, and Jan 2017 for Outcomes with different post enrolment follow-up periods. # These criteria were only applied once the baseline date from the matched augmentation pair was known.

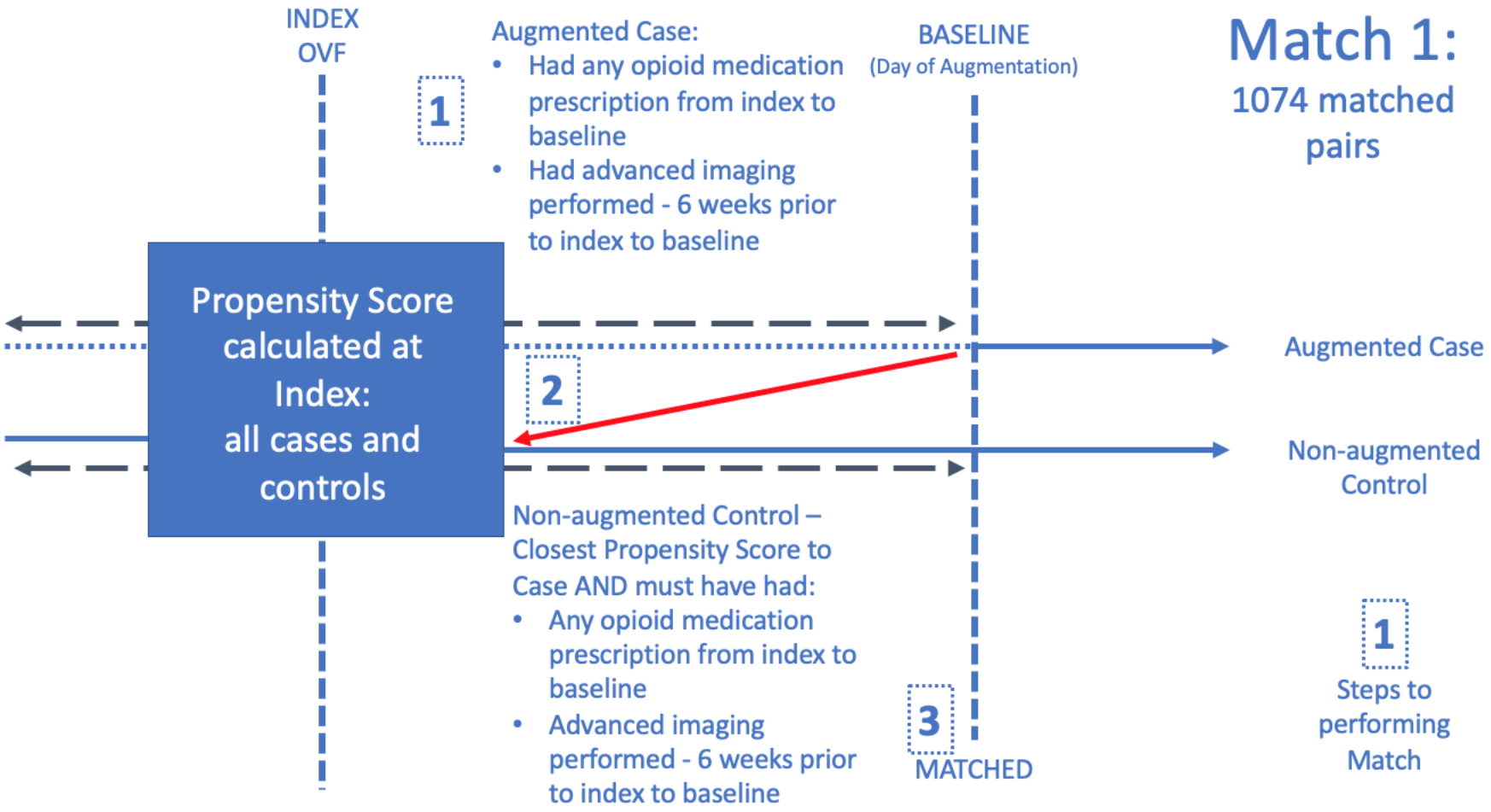
INDEX
OVF
1
Augmented Case:
• Had any opioid medication prescription from index to baseline
• Had advanced imaging performed - 6 weeks prior to index to baseline
BASELINE
(Day of Augmentation)
Match 1:
1074 matched pairs
Propensity Score calculated at Index: all cases and controls
2
Augmented Case
Non-augmented Control
Non-augmented Control – Closest Propensity Score to Case AND must have had:
• Any opioid medication prescription from index to baseline
• Advanced imaging performed - 6 weeks prior to index to baseline
3
MATCHED
1
Steps to performing Match

Figure 2

Table 2: Annual rate and temporal trends for OVF and vertebral augmentation procedures in MarketScan population

Semi-year of OVF	MarketScan Enrollees	OVF (no enrolment exclusions applied)	Fracture rate per 100000 lives	OVF (with enrolment exclusions applied)	Fracture rate per 100000 lives	Enrollees with OVF undergoing VA	Percentage of OVF undergoing VA
Jan-June 2008	44916177	2324	5.17	1271	2.83	224	17.6%
July-Dec 2008	45143222	1933	4.28	905	2.00	157	17.3%
Jan-June 2009	45357881	2571	5.67	1725	3.80	327	19.0%
July-Dec 2009	45303991	2304	5.09	1261	2.78	230	18.2%
Jan-June 2010	41388491	2088	5.04	1270	3.07	245	19.3%
July-Dec 2010	41710106	1863	4.47	1030	2.47	159	15.4%
Jan-June 2011	47898290	2489	5.20	1249	2.61	205	16.4%
July-Dec 2011	47655199	2133	4.48	1019	2.14	139	13.6%
Jan-June 2012	48502432	2270	4.68	1362	2.81	236	17.3%
July-Dec 2012	48409700	2003	4.14	869	1.80	147	16.9%
Jan-June 2013	39648843	1929	4.87	1041	2.63	172	16.5%
July-Dec 2013	40284002	1688	4.19	913	2.27	152	16.6%
Jan-June 2014	43177775	2192	5.08	1165	2.70	197	16.9%
July-Dec 2014	43006889	1871	4.35	784	1.82	120	15.3%
Jan-June 2015	26174060	1244	4.75	825	3.15	139	16.8%
July-Dec 2015	25903737	1259	4.86	831	3.21	135	16.2%
Jan-June 2016	25901756	1308	5.05	877	3.39	162	18.5%
July-Dec 2016	25714132	1287	5.01	760	2.96	128	16.8%
Jan-June 2017	24344645	1277	5.25	787	3.23	150	19.1%
Total/Incidence per year	149036139	36033	9.64	19944	5.44	3424	17.2%

Table 3: Vertebral augmentation procedures in MarketScan population by type

Semi-year of OVF	Enrollees with OVF undergoing vertebroplasty	Percentage of OVF undergoing vertebroplasty	Enrollees with OVF undergoing kyphoplasty	Percentage of OVF undergoing kyphoplasty	Enrollees with OVF undergoing vertebroplasty and kyphoplasty	Percentage of OVF undergoing vertebroplasty and kyphoplasty
Jan-June 2008	56	4.4%	160	12.6%	8	0.6%
July-Dec 2008	45	5.0%	106	11.7%	6	0.7%
Jan-June 2009	101	5.9%	214	12.4%	12	0.7%
July-Dec 2009	61	4.8%	165	13.1%	4	0.3%
Jan-June 2010	61	4.8%	174	13.7%	10	0.8%
July-Dec 2010	36	3.5%	113	11.0%	10	1.0%
Jan-June 2011	47	3.8%	153	12.2%	5	0.4%
July-Dec 2011	34	3.3%	99	9.7%	6	0.6%
Jan-June 2012	50	3.7%	176	12.9%	10	0.7%
July-Dec 2012	26	3.0%	120	13.8%	1	0.1%
Jan-June 2013	27	2.6%	140	13.4%	5	0.5%
July-Dec 2013	25	2.7%	123	13.5%	4	0.4%
Jan-June 2014	27	2.3%	157	13.5%	13	1.1%
July-Dec 2014	21	2.7%	97	12.4%	2	0.3%
Jan-June 2015	14	1.7%	118	14.3%	7	0.8%
July-Dec 2015	16	1.9%	109	13.1%	10	1.2%
Jan-June 2016	21	2.4%	125	14.3%	16	1.8%
July-Dec 2016	21	2.8%	98	12.9%	9	1.2%
Jan-June 2017	19	2.4%	124	15.8%	7	0.9%
Total/Average	708	3.5%	2571	12.9%	145	0.7%

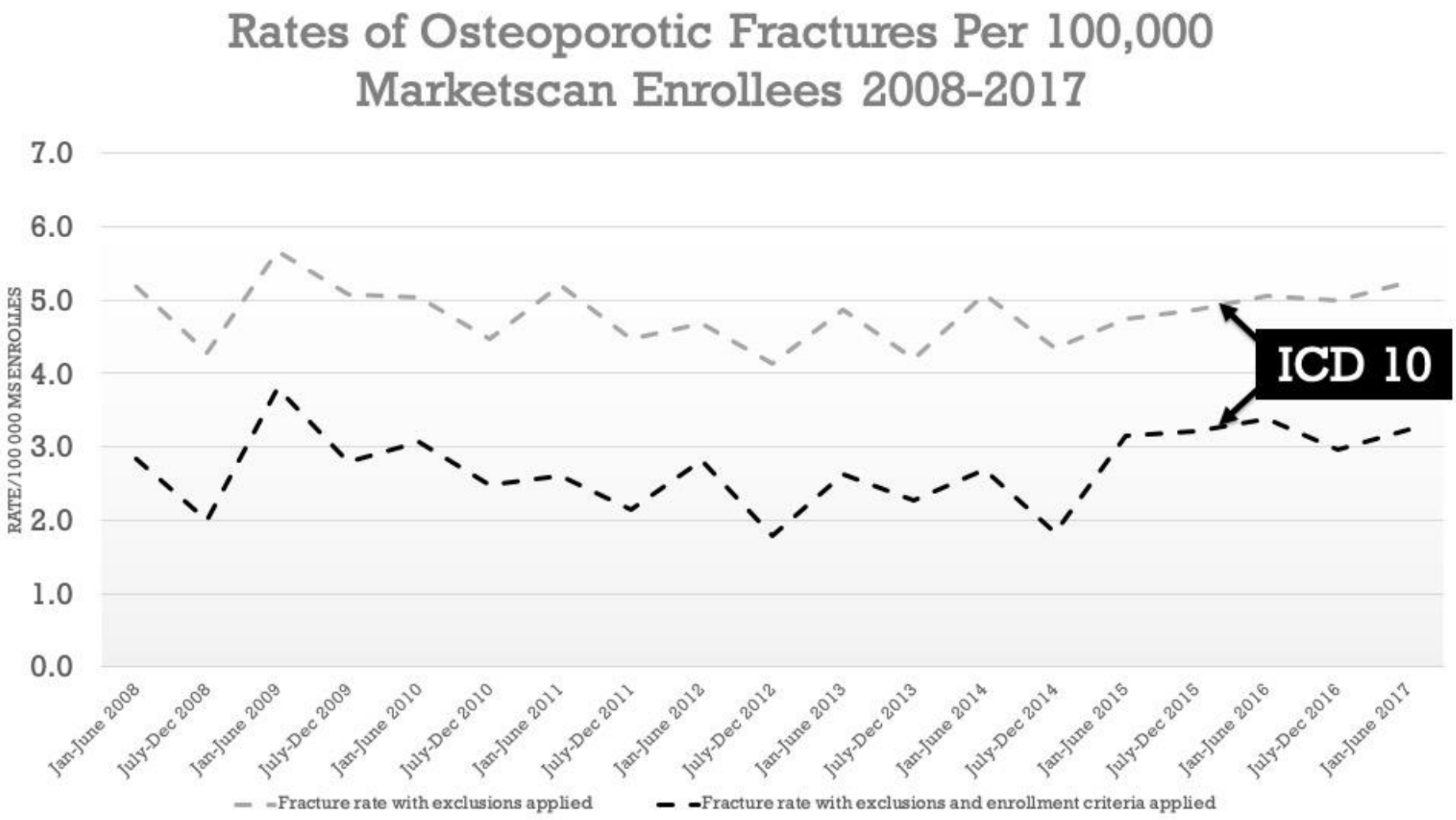
Rates of Osteoporotic Fractures Per 100,000
Marketscan Enrollees 2008-2017
RATE/100 000 MS ENROLLES
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ICD 10
Jan-June 2008
July-Dec 2008
Jan-June 2009
July-Dec 2009
Jan-June 2010
July-Dec 2010
Jan-June 2011
July-Dec 2011
Jan-June 2012
July-Dec 2012
Jan-June 2013
July-Dec 2013
Jan-June 2014
July-Dec 2014
Jan-June 2015
July-Dec 2015
Jan-June 2016
July-Dec 2016
Jan-June 2017
Fracture rate with exclusions applied
Fracture rate with exclusions and enrollment criteria applied

Figure 3

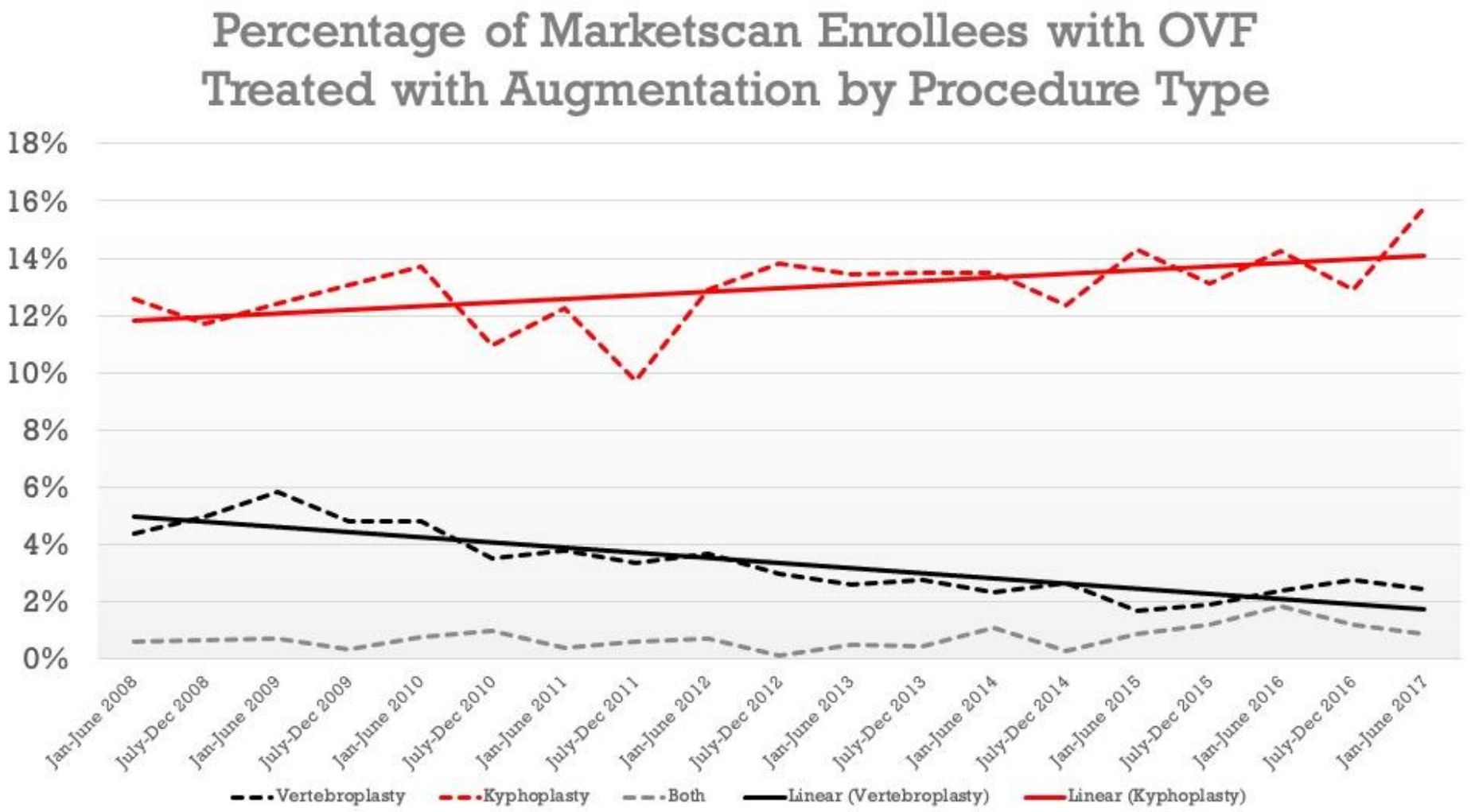
Percentage of Marketscan Enrollees with OVF Treated with Augmentation by Procedure Type
18%
16%
14%
12%
10%
8%
6%
4%
2%
0%
Jan-June 2008
July-Dec 2008
Jan-June 2009
July-Dec 2009
Jan-June 2010
July-Dec 2010
Jan-June 2011
July-Dec 2011
Jan-June 2012
July-Dec 2012
Jan-June 2013
July-Dec 2013
Jan-June 2014
July-Dec 2014
Jan-June 2015
July-Dec 2015
Jan-June 2016
July-Dec 2016
Jan-June 2017
Vertebroplasty
Kyphoplasty
Both
Linear (Vertebroplasty)
Linear (Kyphoplasty)

Figure 4

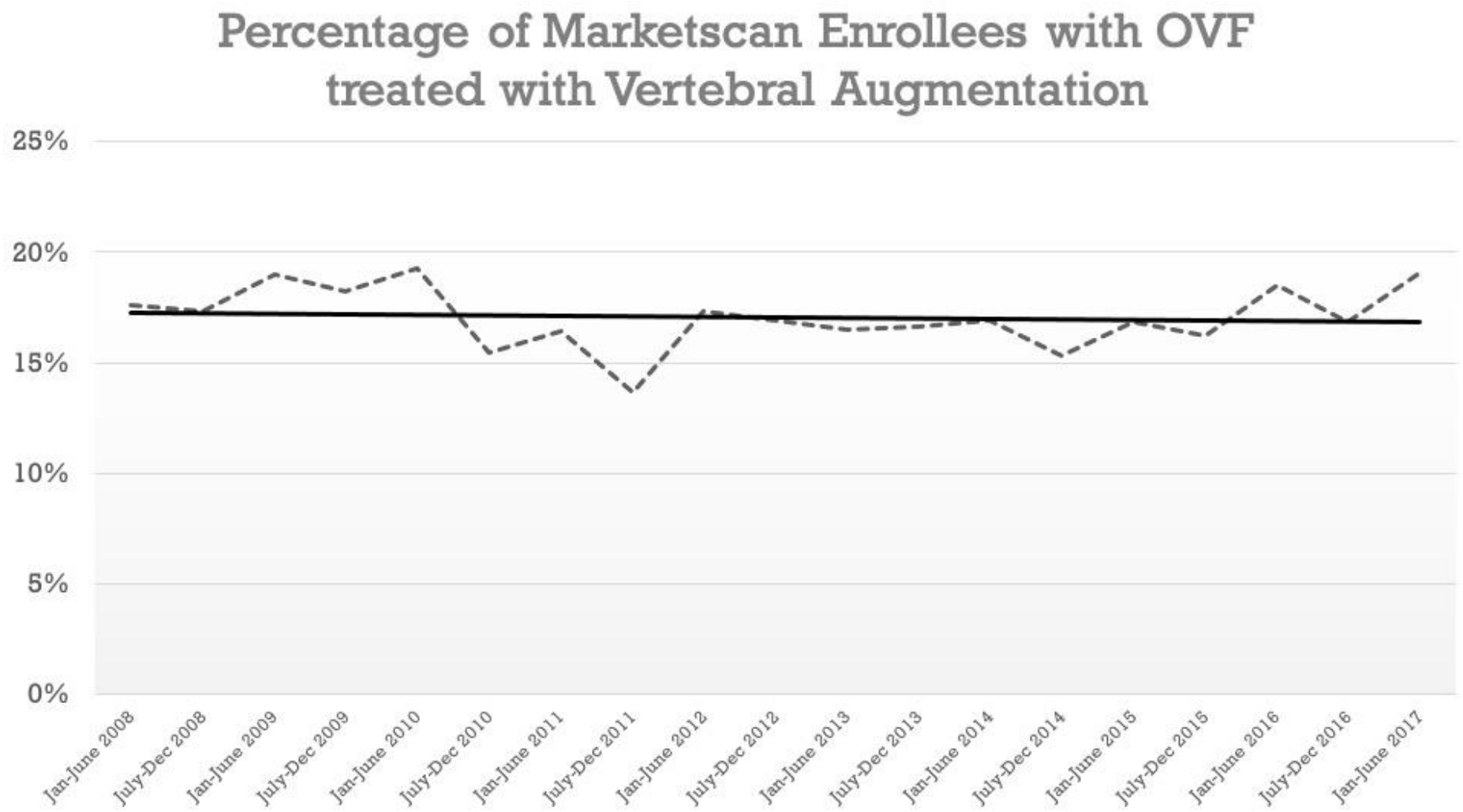
Percentage of Marketscan Enrollees with OVF treated with Vertebral Augmentation
25%
20%
15%
10%
5%
0%
Jan-June 2008
July-Dec 2008
Jan-June 2009
July-Dec 2009
Jan-June 2010
July-Dec 2010
Jan-June 2011
July-Dec 2011
Jan-June 2012
July-Dec 2012
Jan-June 2013
July-Dec 2013
Jan-June 2014
July-Dec 2014
Jan-June 2015
July-Dec 2015
Jan-June 2016
July-Dec 2016
Jan-June 2017

Figure 5

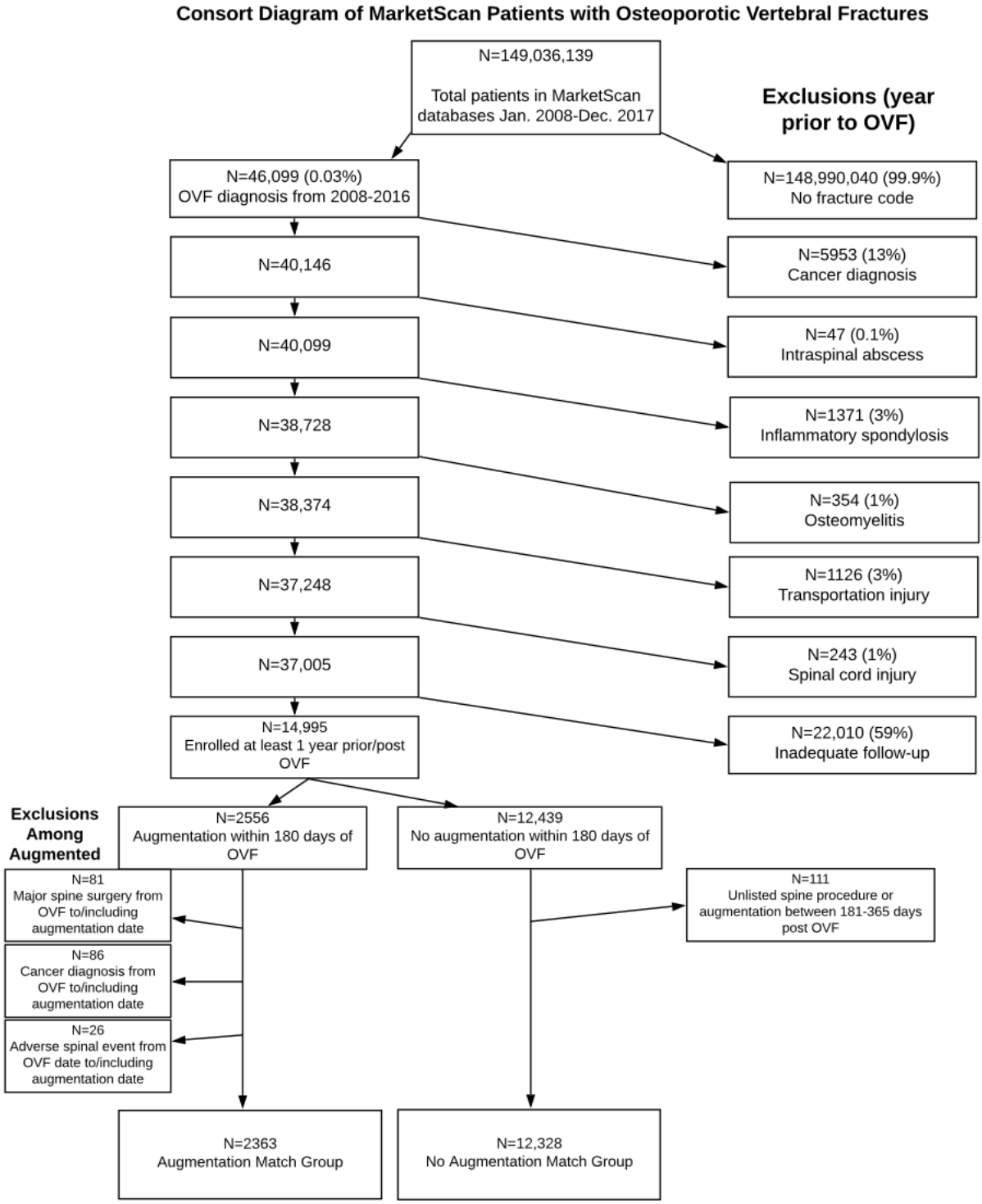
Consort Diagram of MarketScan Patients with Osteoporotic Vertebral Fractures
N=149,036,139
Total patients in MarketScan databases Jan. 2008-Dec. 2017
Exclusions (year prior to OVF)
N=46,099 (0.03%)
OVF diagnosis from 2008-2016
N=148,990,040 (99.9%)
No fracture code
N=40,146
N=5953 (13%)
Cancer diagnosis
N=40,099
N=47 (0.1%)
Intraspinal abscess
N=38,728
N=1371 (3%)
Inflammatory spondylosis
N=38,374
N=354 (1%)
Osteomyelitis
N=37,248
N=1126 (3%)
Transportation injury
N=37,005
N=243 (1%)
Spinal cord injury
N=14,995
Enrolled at least 1 year prior/post OVF
N=22,010 (59%)
Inadequate follow-up
Exclusions Among Augmented
N=2556
Augmentation within 180 days of OVF
N=12,439
No augmentation within 180 days of OVF
N=81
Major spine surgery from OVF to/including augmentation date
N=111
Unlisted spine procedure or augmentation between 181-365 days post OVF
N=86
Cancer diagnosis from OVF to/including augmentation date
N=26
Adverse spinal event from OVF date to/including augmentation date
N=2363
Augmentation Match Group
N=12,328
No Augmentation Match Group

Figure 6

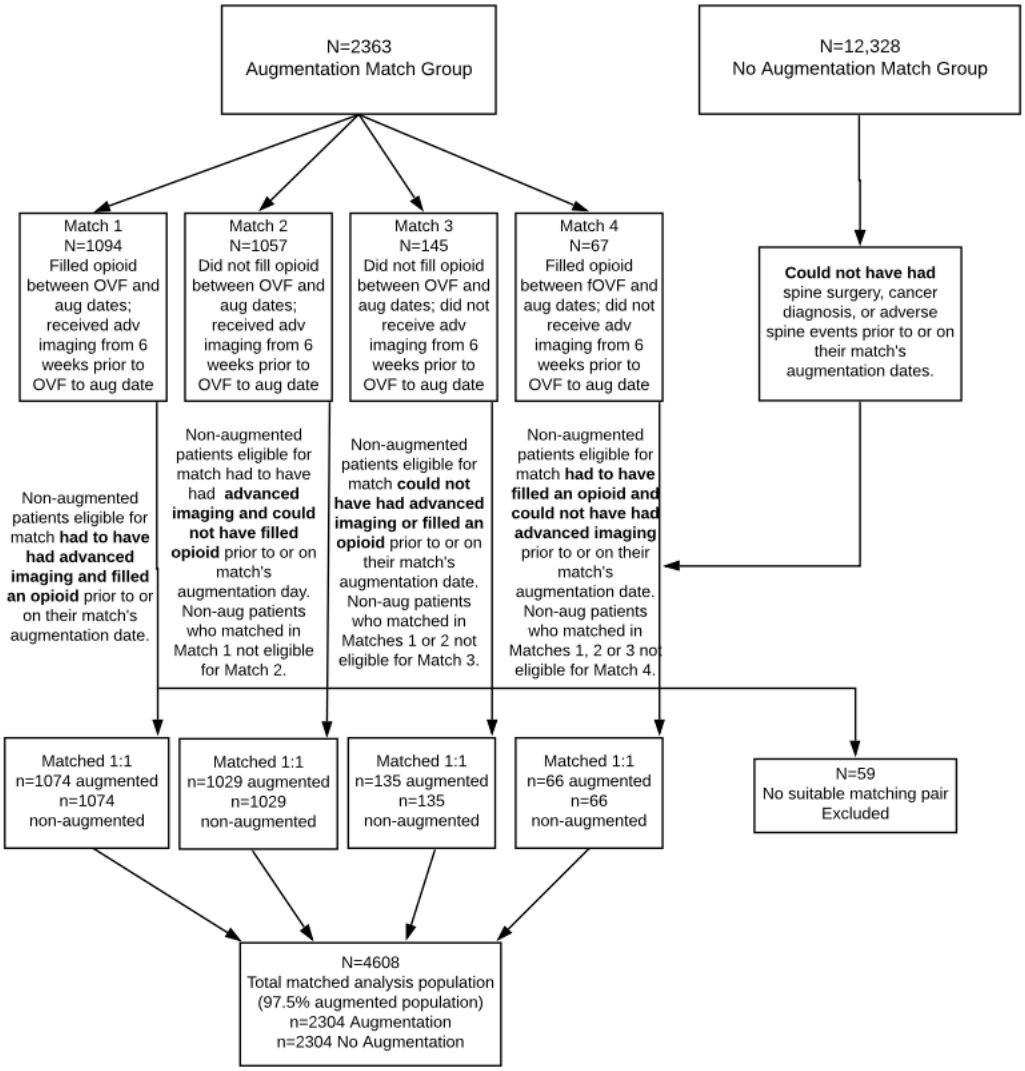
N=2363
Augmentation Match Group
N=12,328
No Augmentation Match Group
Match 1
N=1094
Filled opioid between OVF and aug dates; received adv imaging from 6 weeks prior to OVF to aug date
Match 2
N=1057
Did not fill opioid between OVF and aug dates; received adv imaging from 6 weeks prior to OVF to aug date
Match 3
N=145
Did not fill opioid between OVF and aug dates; did not receive adv imaging from 6 weeks prior to OVF to aug date
Match 4
N=67
Filled opioid between fOVF and aug dates; did not receive adv imaging from 6 weeks prior to OVF to aug date
Could not have had spine surgery, cancer diagnosis, or adverse spine events prior to or on their match's augmentation dates.
Non-augmented patients eligible for match had to have had advanced imaging and could not have filled opioid prior to or on match's augmentation day. Non-aug patients who matched in Match 1 not eligible for Match 2.
Non-augmented patients eligible for match could not have had advanced imaging or filled an opioid prior to or on their match's augmentation date. Non-aug patients who matched in Matches 1 or 2 not eligible for Match 3.
Non-augmented patients eligible for match had to have filled an opioid and could not have had advanced imaging prior to or on their match's augmentation date. Non-aug patients who matched in Matches 1, 2 or 3 not eligible for Match 4.
Non-augmented patients eligible for match had to have had advanced imaging and filled an opioid prior to or on their match's augmentation date.
Matched 1:1
n=1074 augmented
n=1074
non-augmented
Matched 1:1
n=1029 augmented
n=1029
non-augmented
Matched 1:1
n=135 augmented
n=135
non-augmented
Matched 1:1
n=66 augmented
n=66
non-augmented
N=59
No suitable matching pair
Excluded
N=4608
Total matched analysis population
(97.5% augmented population)
n=2304 Augmentation
n=2304 No Augmentation

Figure 7

Table 4
Comparing propensity matched* MarketScan Enrollees with OVF who received vertebral augmentation to those who did not with 1:1 matching.

Variable	Augmented N=2304	% of Augmented	Not Augmented N=2304	% of Not Augmented
Age (Median, IQR)	58.0	(55-61)	58.0	(53-61)
Sex				
Male	572	24.8%	601	26.1%
Female	1732	75.2%	1703	73.9%
Type of health plan				
Comprehensive	176	7.6%	150	6.5%
Exclusive/Preferred provider org.	1481	64.3%	1485	64.5%
Health maintenance org.	222	9.6%	226	9.8%
Point of service	202	8.8%	221	9.6%
Consumer-directed/High-deductible	183	7.9%	181	7.9%
Missing	40	1.7%	41	1.8%
Geographic region				
Northeast	225	9.8%	243	10.5%
North Central	666	28.9%	630	27.3%
South	1057	45.9%	1083	47.0%
West	316	13.7%	309	13.4%
Missing	40	1.7%	39	1.7%
Year of index fracture				
2008	288	12.5%	300	13.0%
2009	379	16.4%	351	15.2%
2010	289	12.5%	288	12.5%
2011	253	11.0%	277	12.0%
2012	244	10.6%	233	10.1%
2013	233	10.1%	251	10.9%
2014	202	8.8%	212	9.2%
2015	204	8.9%	209	9.1%
2016	212	9.2%	183	7.9%
Charlson Co-morbidity Score				
0	1064	46.2%	1115	48.4%
1-2	890	38.6%	839	36.4%
3-4	256	11.1%	242	10.5%
5+	94	4.1%	108	4.7%
Admitted for index fracture	674	29.3%	693	30.1%
≥1 Med Fill from 90 days prior to fx date				
Opioid	1255	54.5%	1200	52.1%
Muscle relaxer	785	34.1%	777	33.7%
Gabapentin	285	12.4%	273	11.9%
Pregabalin	131	5.7%	160	6.9%
NSAID	518	22.5%	500	21.7%
Benzodiazepine	483	21.0%	461	20.0%
All-cause costs year prior to index fracture (Median, IQR)	15,934	(4610, 54,640)	16,136	(4568, 57,776)
Spine-related costs year prior to index fracture (Median, IQR)	400	(0, 1734)	338	(0, 1578)
Fracture Level				
Thoracic	670	29.1%	688	29.9%
Lumbar	847	36.8%	796	34.5%
Unspecified	787	34.2%	820	35.6%
Advanced imaging before baseline day	2103	91.3%	2103	91.3%
Use of Opiate from fracture to baseline	1140	49.5%	1140	49.5%

*Propensity matched on age, gender, health plan type, region of residence, year of fracture, Charlson co-morbidity score, whether the patient was admitted for the index fracture, filling medications (opioids, NSAIDs, muscle relaxers, gabapentin, benzodiazepines, pregabalin) in the 90 days through 1 day prior to fracture, total health gross covered payments in year prior to fracture, total spine-related gross covered payments in year prior to fracture.

Table 5
1:1 Propensity Matched Outcomes in MarketScan Enrollees with OVF comparing those who received vertebral augmentation to those who did not

Variable	Aug. N=2304	% of Aug.	Not Aug N=2304	% of Not Aug	Unadjusted OR/Difference b/w medians (95% CI)	Adjusted* OR/Difference b/w medians (95% CI)
Major Medical Complications						
30 days post baseline	75	3.26%	76	3.30%	0.99 (0.71, 1.37)	0.89 (0.55, 1.43)
1 year post OVF	383	16.62%	350	15.19%	1.12 (0.95,1.32)	1.17 (0.96,1.42)
Cardiac Arrest 30 days post baseline	0	0%	0	0%	NA	NA
Cardiac Arrest 1 year post OVF	8	0.35%	6	0.26%	1.33 (0.46, 3.84)	NA
Acute MI 30 days post baseline	4	0.17%	5	0.22%	0.8 (0.21, 2.98)	NA
Acute MI Arrest 1 year post OVF	25	1.09%	26	1.13%	0.96 (0.56, 1.66)	NA
Stroke 30 days post baseline	9	0.39%	10	0.43%	0.90 (0.37, 2.21)	NA
Stroke 1 year post OVF	101	4.38%	108	4.69%	0.93 (0.71, 1.23))	0.96 (0.64, 1.44)
PE 30 days post baseline	12	0.52%	9	0.39%	1.33 (0.56, 3.16)	NA
PE 1 year post OVF	55	2.39%	38	1.65%	1.45 (0.96, 2.19)	2.57 (0.98, 6.75)
DVT 30 days post baseline	10	0.43%	13	0.56%	0.77 (0.33, 1.75)	NA
DVT 1 year post OVF	68	2.95%	64	2.78%	1.06 (0.75, 1.51)	0.75 (0.40, 1.43)
Resp Failure 30 days post baseline	19	0.82%	26	1.13%	0.73 (0.40, 1.32)	NA
Resp Failure 1 year post OVF	113	4.90%	90	3.90%	1.28 (0.96, 1.70)	1.43 (0.91, 2.25)
Pneumonia 30 days post baseline	31	1.35%	35	1.52%	0.88 (0.53, 1.44)	NA
Pneumonia 1 year post OVF	184	7.99%	168	7.29%	1.11 (0.89, 1.38)	1.16 (0.87, 1.53)
Ventilation 30 days post baseline	0	0%	1	0.04%	NA	NA
Ventilation 1 year post OVF	17	0.74%	18	0.78%	1.00 (0.51, 1.96)	NA
Medication Related Outcomes						
Any opioid fill from 7 days after baseline to 30 days later	781	33.90%	655	28.43%	**1.37 (1.17, 1.53)**	**1.40 (1.19, 1.64)**
Any opioid fill from 7 days after baseline to 365 days post OVF	1342	58.25%	1254	54.43%	**1.21 (1.06, 1.38)**	1.07 (0.91,1.25)
Any opioid fill from 31 days after baseline to 365 days post OVF	1235	53.60%	1168	50.70%	**1.14 (1.01,1.30)**	1.07 (0.92,1.25)
Muscle Relaxant fill from 7 days after baseline to 30 days later	326	14.15%	269	11.67%	**1.25 (1.05, 1.49)**	**1.28 (1.03, 1.60)**
Muscle Relaxant fill from 7 days after baseline to 365 days post OVF	788	34.20%	715	31.03%	**1.16 (1.02, 1.32)**	1.10 (0.94, 1.28)
Gabapentin fill from 7 days after baseline to 30 days later	173	7.51%	159	6.90%	1.10 (0.88, 1.38)	1.12 (0.71, 1.76)
Gabapentin fill from 7 days after baseline to 365 days post OVF	498	21.61%	488	21.18%	1.03 (0.89, 1.18)	1.01 (0.81, 1.25)
Pregabalin fill from 7 days after baseline to 30 days later	68	2.95%	79	3.53%	0.85 (0.61, 1.19)	NA
Pregabalin fill from 7 days after baseline to 365 days post OVF	219	9.51%	227	9.85%	0.96 (0.79, 1.17)	1.08 (0.76, 1.53)
Any benzodiazepine fill from 7 days after baseline to 30 days later	244	10.59%	230	9.98%	1.07 (0.88, 1.30)	1.15 (0.85, 1.57)
Any benzodiazepine fill from 7 days after baseline to 365 days post OVF	627	27.21%	585	25.39%	1.11 (0.97, 1.27)	1.05 (0.87, 1.27)
Any NSAID fill from 7 days after baseline to 30 days later	162	7.03%	141	6.12%	1.16 (0.92, 1.46)	1.05 (0.74, 1.49)
Any NSAID fill from 7 days after baseline to 365 days post OVF	629	27.03%	584	25.35%	1.10 (0.97, 1.26)	1.14 (0.98, 1.34)
Additional Outcomes:						
Hip/Wrist fracture within 30 days baseline	20	0.87%	20	0.87%	1.00 (0.54, 1.86)	NA
Hip/Wrist fracture 1 day post baseline to 365 post OVF	80	3.47%	102	4.43%	0.78 (0.58, 1.05)	0.81 (0.54, 1.19)
Cancer diagnosis from 1 day post baseline to 365 post OVF	108	4.69%	90	3.91%	1.20 (0.91, 1.60)	1.07 (0.73,1.56)

Major Spine Surgery from 1 day post baseline to 365 post OVF	112	4.86%	197	8.55%	**0.54 (0.42, 0.68)**	**0.43 (0.31,0.60)**
No further hospital admissions - 1 day post baseline to 365 post OVF	1723	74.3%	1699	73.7%	1.04 (0.90, 1.19)	0.99 (0.84, 1.17)
Days from OVF to Augmentation (median, IQR)	18	(5,44)				
Cost Related Outcomes						
All Cause costs related costs - 3 days post baseline to 365 post OVF (Median, IQR)	24617	(7718, 91,259)	22074	(6887, 81,678)	3451 (-1478, 7869)	1285 (-312, 2703)
All Cause costs related costs - from OVF to 30 days post baseline (Median, IQR)	48387	(22367, 92,501)	10540	(3781, 38,452)	**32,253 (24,084, 27,737)**	**23,082 (21,438, 24,950)**
Spine-related costs - 3 days post baseline to 365 post OVF (Median, IQR)	1347	(225, 4982)	868	(106, 3357)	**443 (55, 780)**	**273 (108, 348)**
Spine-related costs related costs from OVF to 30 days post baseline (Median, IQR)	10384	(4925, 19,657)	1942	(687, 5092)	**8049 (7391, 8953)**	**7109 (6727, 7438)**

*Adjusted for age, gender, health plan type, region of residence, year of fracture, Charlson co-morbidity score, whether the patient was admitted for the index OVF, filling medications (opioids, NSAIDs, muscle relaxers, gabapentin, benzodiazepines, pregabalin) in the 90 days through 1 day prior to fracture, total health gross covered payments in year prior to OVF, total spine-related gross covered payments in year prior to OVF and anatomic location of OVF.
Bolded are statistically significant

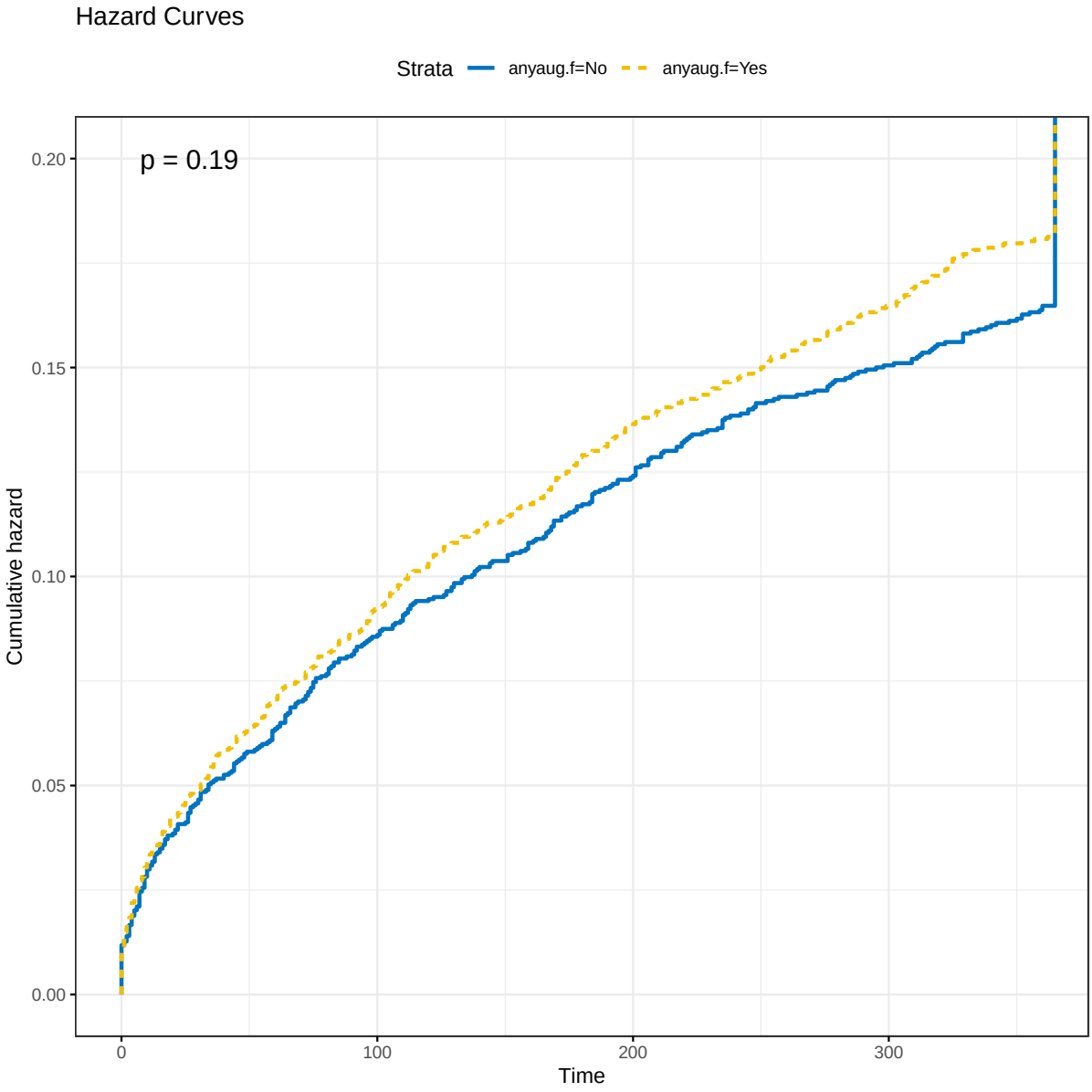

Figure 8 Cumulative Hazard of Any Major Medical Complication up to 1 year post OVF

Appendix 1:

Excel File

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