#### Bone 111 (2018) 92-100

Contents lists available at ScienceDirect

# Bone

journal homepage: www.elsevier.com/locate/bone

# Full Length Article

# Fracture liaison services improve outcomes of patients with osteoporosis-related fractures: A systematic literature review and meta-analysis

Chih-Hsing Wu<sup>a,b,\*</sup>, Shih-Te Tu<sup>c</sup>, Yin-Fan Chang<sup>a</sup>, Ding-Cheng Chan<sup>d,e,f</sup>, Jui-Teng Chien<sup>g</sup>, Chih-Hsueh Lin<sup>h</sup>, Sonal Singh<sup>i</sup>, Manikanta Dasari<sup>j</sup>, Jung-Fu Chen<sup>k</sup>, Keh-Sung Tsai<sup>1,\*\*</sup>

<sup>a</sup> Department of Family Medicine, National Cheng Kung University College of Medicine and Hospital, 138 Sheng-Li Road, Tainan 70428, Taiwan

<sup>b</sup> Institute of Gerontology, National Cheng Kung University College of Medicine, 138 Sheng-Li Road, Tainan 70428, Taiwan

<sup>c</sup> Changhua Christian Hospital, LuKang Branch, 135 Nanhsiao Street, Changhua City 500, Taiwan

<sup>d</sup> National Taiwan University Hospital Chu-Tung Branch, No. 52 Jshan Rd, Hsinchu County 31064, Taiwan

<sup>e</sup> Department of Geriatrics and Gerontology, National Taiwan University Hospital, No. 7 Chung Shan S Road, Taipei City 10002, Taiwan

<sup>f</sup> Department of Internal Medicine, National Taiwan University Hospital, No. 1 Changde St, Zongzheng District, Taipei City 10048, Taiwan

<sup>g</sup> Buddhist Dalin Tzuchi Hospital, 2, Min-Sheng Rd., Dalin, Chiayi, Taiwan

<sup>h</sup> Department of Family Medicine, China Medical University Hospital, No. 2 Yuh Der Road, Taichung, Taiwan

<sup>1</sup> Department of Family Medicine and Community Health, Meyers Primary Care Institute, University of Massachusetts Medical School, 55 Lake Ave North, Worcester, MA 01655-0002, USA <sup>j</sup> Complete HEOR Solutions, LLC.1046 Knapp Road, North Wales, PA 19454, USA

<sup>k</sup> Division of Endocrinology and Metabolism, Department of Internal Medicine, Chang Gung Memorial Hospital, 123 Ta-Pei Road, Niao-Sung District, Kaohsiung City, Taiwan

<sup>1</sup> Department of Internal Medicine, National Taiwan University Hospital, 7 Zhong Shan South Road, Taipei 10048, Taiwan

# ARTICLE INFO

Article history: Received 1 November 2017 Revised 14 March 2018 Accepted 15 March 2018 Available online 16 March 2018

Keywords: Osteoporosis Fracture liaison services (FLS) Meta-analysis Re-fracture Outcomes

# ABSTRACT

*Objectives:* This systematic review and meta-analysis evaluated the outcomes of patients with osteoporosis-related fractures managed through fracture liaison services (FLS) programs.

Methods: Medline, PubMed, EMBASE, and the Cochrane Library were searched (January 2000–February 2017 inclusive) using the keywords 'osteoporosis', 'fractures', 'liaison', and 'service' to identify randomised controlled trials and observational studies of patients aged ≥50 years with osteoporosis-related fractures in hospital, clinic, community, or home-based settings who were managed using FLS. Risk of bias was assessed at outcome level. Meta-analysis followed a random-effects and fixed-effects model. Outcomes of interest were incidence of bone mineral density (BMD) testing, treatment initiation, adherence, re-fractures, and mortality due to osteoporosis treatment.

*Results:* A total of 159 publications were identified for the systematic literature review; 74 controlled studies (16 RCTs; 58 observational studies) were included in the meta-analysis. Overall, 41 of 58 observational studies and 12 of 16 RCTs were considered of high quality. Compared with patients receiving usual care (or those in the control arm), patients receiving care from an FLS program had higher rates of BMD testing (48.0% vs 23.5%) and treatment initiation (38.0% vs 17.2%) and greater adherence (57.0% vs 34.1%). Unweighted average rates of re-fracture were 13.4% among patients in the control arm and 6.4% in the FLS arm. Unweighted average rates of mortality were 15.8% in the control arm and 10.4% in the FLS arm. Meta-analysis revealed significant FLS-associated improvements in all outcomes versus non-FLS controls, with BMD testing increased by 24 percentage points (95% confidence interval [CI] 0.18–0.29), 20 percentage points for treatment rates (95% CI 0.16–0.25), and 22 percentage points (95% CI –0.08 to –0.03) and mortality reduced by three percentage points (95% CI –0.05 to –0.01). *Conclusion:* FLS programs improved outcomes of osteoporosis-related fractures, with significant increases in

BMD testing, treatment initiation, and adherence to treatment and reductions in re-fracture incidence and mortality.

© 2018 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (http:// creativecommons.org/licenses/by/4.0/).

\* Correspondence may also be addressed to: C.-H. Wu, Department of Family Medicine, National Cheng Kung University Hospital, No. 138, Sheng Li Road, Tainan 70428, Taiwan. \*\* Corresponding author.

*E-mail addresses*: paulo@mail.ncku.edu.tw (C.-H. Wu), 10836@cch.org.tw (S.-T. Tu), yinfan@mail.ncku.edu.tw (Y.-F. Chang), 5496@mail.cmuh.org.tw (C.-H. Lin), Sonal.Singh@umassmemorial.org (S. Singh), Manikanta.dasari@cheors.com (M. Dasari), 0722cjf@cgmh.org.tw (J.-F. Chen), paulo@mail.ncku.edu.tw (K.-S. Tsai).

### https://doi.org/10.1016/j.bone.2018.03.018

8756-3282/© 2018 The Authors. Published by Elsevier Inc, This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).







# 1. Introduction

Osteoporosis is characterised by a reduction in bone mass and strength, predisposing patients to an increased risk of fragility fractures [1]. The condition is asymptomatic and therefore its first clinical manifestation is often a low-trauma (fragility) fracture. Fragility fractures cause significant morbidity and mortality, and therefore are a considerable public health burden [2]. The National Osteoporosis Foundation estimated that 10.2 million Americans had osteoporosis in 2010, and that 1 in 2 women and 1 in 5 men will experience an osteoporotic-related fracture during their lifetime [3]. Furthermore, a previous low-trauma fracture, at any site, increases the risk of a subsequent fracture by approximately two fold in women and men [4,5].

Fracture liaison services (FLS) are coordinator-based models of secondary fracture prevention services with a broad remit. They are designed to identify patients who are at increased risk of secondary fractures and, following a comprehensive assessment, ensure that patients initiate appropriate treatment via improved care coordination and communication [6-8]. Indeed, 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) [9] and European League Against Rheumatism (EULAR)/European Federation of National Associations of Orthopaedics and Traumatology (EFFORT) [10]. FLS have made significant contributions towards improving bone mineral density (BMD) testing rates and treatment initiation rates after MTF when FLS have adopted a fully coordinated intensive approach to patient care, as shown in a systematic literature review (SLR) and meta-analysis performed in 2012 covering publications in 1996-2011 [11]. However, it is acknowledged that treatment gaps remain [11], and pharmacological prevention remains suboptimal. In 2013, the International Osteoporosis Foundation (IOF) initiated the promotion of FLS programs, continually being implemented worldwide, but their outcomes show wide variability in the literature.

The present SLR and meta-analysis aimed to update, critically reevaluate, and quantify the available evidence on the incidence of BMD testing, treatment initiation, adherence, re-fractures, and rates of mortality associated with FLS in patients with osteoporosis.

#### 2. Methods

#### 2.1. Study identification

A systematic search of the literature using Medline, PubMed, and EMBASE databases and the Cochrane Library was conducted for publications (January 2000–February 2017 inclusive) using the key words: 'osteoporosis' AND 'fractures' AND 'liaison' AND 'service'. The detailed search strategy is presented in **Supplementary Table 1**. Other local databases, websites, and grey literature sources were also searched for relevant articles. The SLR adheres to the methodology of the Cochrane Collaboration.

#### 2.2. Study selection and data abstraction

Inclusion criteria for studies were: conducted in patients aged ≥50 years, with all types of osteoporosis-related fractures; randomised or non-randomised phase 1–4 trials, retrospective or prospective observational studies. Excluded were studies related to primary fracture prevention or other bone-associated disease (e.g. osteoarthritis); publication types of narrative reviews, systematic reviews, meta-analyses, opinion articles, editorials, case reports, letters, and publications in languages other than English. Two independent reviewers selected studies by screening first the title and abstract followed by full-text articles. Discrepancy between the two reviewers was resolved by consensus or by a third independent reviewer, when required. Data extraction used the Population, Intervention, Comparison, Outcomes, Setting

(PICOS) criteria and included general information about the article (e.g. authors, publication year), study characteristics (e.g. design, sample size), patient characteristics (e.g. fracture type, osteoporosis duration), and outcomes (BMD testing, treatment initiation, adherence, persistence, rates of re-fracture, and mortality).

Data synthesis and findings were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. Quality assessments of the eligible study methodologies were performed using the Newcastle–Ottawa scale for nonrandomised studies and the Cochrane Collaboration's Risk of Bias Tool for randomised controlled trials (RCTs).

### 2.3. Meta-analysis

All studies included in the SLR were reviewed for inclusion in the meta-analysis. The inclusion criteria were based on PICOS elements: population (aged ≥50 years with osteoporosis-related fractures); interventions (FLS); comparison (FLS vs non-FLS care), outcomes (measurement of BMD at any site, treatment initiation, adherence to treatment, incidence of re-fractures, and rates of all-cause mortality); and study design (RCTs, observational studies). Studies with no control groups or denominator data, or with pre-post intervention design were excluded, except for adherence outcomes.

Data were extracted for each outcome, including study design, study duration, and number of participants with reported outcome/total number of participants in the respective arms. Adjusted and unadjusted estimates of relative risk, odds ratio, hazard ratio, and confounders were extracted. A hierarchical meta-analysis was performed on the intention-to-treat population for each outcome, first on all studies, then separately for RCTs and controlled observational studies. Meta-analyses were conducted when  $\geq 2$  studies could be pooled, with consideration of clinical and statistical heterogeneity. Random-effect meta-analysis was used as the primary model. Sensitivity analyses were performed for influence of study design and fixed-effect model on outcomes. Statistical heterogeneity was measured by the Eggers test when  $\geq 10$  studies were included and analysed using funnel plots.

Summary statistics of population characteristics for continuous variables included number and percentage of discrete variables, mean, and standard deviation. Statistical significance was considered at  $\alpha = 0.05$ and confidence intervals (CI) were set at 95%.

All meta-analysis were carried out in StatsDirect [12].

# 3. Results

A total of 6608 records from databases and 628 from other sources were retrieved; 1573 were duplicates. Of 5663 unique citations identified, 5108 did not meet the selection criteria, leaving 555 relevant publications, which were evaluated as full-text articles. A total of 396 publications were excluded from the SLR for reasons including duplicates, language, publication type, population not of interest, and irrelevant outcome. The remaining 159 publications were included in the qualitative analysis. This consisted of 141 full-text articles, 16 conference abstracts, and 2 reports. The 159 studies contributed 316 osteoporosis outcomes.

The meta-analysis included studies with control groups or denominator data, with the exception of adherence outcomes. This provided a total of 74 publications, which included 16 RCTs and 58 observational studies (Fig. 1). These 74 studies contributed a total of 141 osteoporosis outcomes. Due to the low number of studies reporting on persistence, this outcome was excluded from quantitative analysis resulting in a total of 73 papers contributing 134 osteoporosis outcomes. A total of 37 RCTs and controlled observational studies reported on BMD testing, 46 studies on treatment rates, and 25 studies including RCTs, controlled, and uncontrolled observational studies reported on adherence to treatment. A total of 11 RCTs and controlled observational studies reported on re-fracture rates, and 15 on mortality. Outcomes quantified in the meta-analysis are reported in Table 1. For each outcome, largely similar results were obtained in the fixed-effects model (**Supplementary Table 2**).

# 3.1. BMD testing

BMD testing, along with the identification of at-risk patients, is a major part of any primary or secondary fracture prevention program. The meta-analysis included 37 studies reporting on BMD testing (13 RCTs and 24 controlled observational studies; **Supplementary Table 3**). Unweighted average rates of BMD testing were 23.5% of patients in the control arm and 48.0% in the FLS arm, with a follow-up period ranging from 3 to 26 months. Furthermore, the meta-analysis showed a significant increase in BMD testing rates with FLS interventions by 24 percentage points compared with controls (absolute risk increase [ARI] 0.24, 95% CI 0.18 to 0.29;  $I^2 = 96.1\%$ ; NNT = 4) (Fig. 2; Table 1). A similar increase was also shown in separate analyses of RCTs and of controlled observational studies (Table 1).

### 3.2. Treatment initiation rates

Most of the studies indicated that, across the globe, FLS have led to dramatic increases in the rates of clinical management among patients who have experienced fragility fractures (**Supplementary Table 4**). The meta-analysis included 46 studies reporting treatment rates (14 RCTs and 32 controlled observational studies). Unweighted average rates of treatment initiation were 17.2% of patients in the control arm and 38.0% in the FLS arm, with a follow-up range of 3–72 months across the studies. The meta-analysis confirmed that FLS interventions were associated with significant higher treatment rates by 20 percentage points compared with controls (ARI 0.20, 95% CI 0.16 to 0.25;  $I^2 = 96\%$ ; NNT = 5) (Fig. 3; Table 1). Results were similar in separate analyses of RCTs alone and controlled observational studies alone (Table 1).

#### 3.3. Adherence to treatment

Adherence to osteoporosis medication was reported in 25 studies that were included in the meta-analysis (two RCTs, seven controlled, and 16 uncontrolled observational studies) (Supplementary Table 5). In the nine controlled studies, unweighted average rates of adherence were 34.1% in the control arm and 57.0% in the FLS arm, with a follow-up range 3-48 months across the studies. The meta-analysis for pooled RCTs and controlled observational studies showed FLS interventions significantly increase adherence by 22 percentage points compared with controls (ARI 0.22; 95% CI 0.13 to 0.31;  $I^2 = 75.8\%$ ; NNT = 5) (Fig. 4; Table 1). Similarly, analysis of only RCTs indicated an increase (ARI 0.14; 95% CI –0.06 to 0.35;  $I^2 = 69.6\%$ ) as did analysis of only controlled observational studies (ARI 0.24, 95% CI 0.13 to 0.35;  $I^2 = 79.8\%$ ; NNT = 4) (Table 1). Meta-analysis of the uncontrolled studies reported a 75% proportion for adherence in patients enrolled in FLS programs (ARI 0.75; 95% CI 0.69 to 0.80;  $I^2 = 90.7\%$ ).

# 3.4. Re-fracture

Eleven studies provided data on re-fracture rates (two RCTs and nine controlled observational studies) and were included in the meta-analysis (**Supplementary Table 6**), providing data on 19,519 patients with osteoporosis who experienced a fragility fracture. Unweighted average rates of re-fracture were 13.4% of patients in the control arm and 6.4% in the FLS arm, with a follow-up range of 6–72 months. Meta-analysis indicated that FLS interventions significantly reduced the risk of re-fracture by five percentage points compared with controls (absolute risk reduction [ARR] –0.05, 95% CI –0.08 to -0.03;  $I^2 = 91\%$ ; numbers needed to treat [NNT] = 20) (Fig. 5; Table 1). Results were similar in separate analyses of RCTs only and controlled observational studies only (Table 1).



Fig. 1. PRISMA flow diagram. MA, meta-analysis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; SLR, systematic literature review.

#### Table 1

Summary results from meta-analysis of RCTs and controlled observational studies.<sup>a</sup>

Outcome	Study design	Number of studies	Study/follow-up duration (months)	Absolute risk difference, 95% Cl (intervention vs control)	Unwei averag (interv vs cont	ghted es rention trol)	Statistical heterogeneity $(I^2)$ , %	NNT
BMD testing	RCTs	13	3-13	0.23 (0.16 to 0.29)*	-	-	90	4
-	Controlled observational	24	1–26	0.24 (0.15 to 0.33)	-	-	96.9	4
	Total	37	3–26	0.24 (0.18 to 0.29)	23.5%	48.0%	96.1	4
Treatment	RCTs	14	3-12	$0.14 (0.09 \text{ to } 0.18)^*$	-	-	85.6	7
initiation	Controlled observational	32	3–72	0.22 (0.16 to 0.28)	-	-	96.4	5
	Total	46	3–72	0.20 (0.16 to 0.25) <sup>*</sup>	17.2%	38.0%	95.8	5
Adherence	RCTs	2	6-24	0.14 (-0.06 to 0.35)	-	-	69.6	-
	Controlled observational	7	3-48	0.24 (0.13 to 0.35)	-	-	79.8	4
	Total	9	6-48	$0.22 (0.13 \text{ to } 0.31)^*$	34.1%	57.0%	75.8	5
Re-fracture	RCTs	2	6	-0.004 ( $-0.04$ to 0.03)	-	-	0	-
	Controlled observational	9	6-72	-0.06 (-0.09 to -0.03)	-	-	92.8	-
	Total	11	6-72	$-0.05 (-0.08 \text{ to } -0.03)^*$	13.4%	6.4%	91.1	20
Mortality	RCTs	4	6-12	-0.02 (-0.06 to 0.03)	-	-	75.8	-
	Controlled observational	11	12–72	-0.04 (-0.07 to -0.01)	-	-	83	25
	Total	15	6–72	$-0.03 (-0.05 \text{ to } -0.01)^*$	15.8%	10.4%	81.2	33

BMD, bone mineral density; CI, confidence interval; n/a, not applicable; NNT, number needed to treat; RCT, randomised controlled trial.

<sup>a</sup> Random-effects model.

\* p ≤ 0.05.

#### 3.5. Mortality

Fifteen studies provided data on mortality (four RCTs and 11 controlled observational studies) and were included in the meta-analysis (**Supplementary Table 7**). Unweighted average rates of mortality were 15.8% of patients with fragility fractures in the control arm and 10.4% in the FLS arm, with a follow-up range of 6–72 months. Meta-analysis revealed that FLS interventions significantly reduced the risk of mortality by three percentage points compared with controls (ARR –0.03, 95% CI –0.05 to -0.01;  $I^2 = 81\%$ ; NNT = 33) (Fig. 6; Table 1). Separate analyses by RCTs or by controlled observational studies showed the same trends (Table 1). The quality rating for the controlled observational studies and RCTs is shown in **Supplementary Tables 8 and 9**.

# 4. Discussion

The present SLR and meta-analysis were conducted to identify and quantify contemporary data from the literature on the impact of FLS on patient outcomes following an osteoporosis-related fracture. Most studies indicated that FLS across the globe have led to a tremendous increase in the rates of clinical management and treatment among patients who experienced fragility fractures, and in turn a reduction of re-fracture and mortality rates. On the other hand, despite the marked improvements to services made available to osteoporosis patients experiencing fragility fractures through FLS, there is still room for improvement: the present study found that adherence to treatment remains rather poor and just under half of the patients in the FLS arm undergo BMD testing.

Specifically, the findings here show FLS to have been successful in reducing the rates of clinical re-fractures due to bone fragility and of mortality with absolute reductions of five and three percentage points, respectively, representing about 30% and 20% reduction and translating into number needed to treat of 20 and 33 patients who would need to be enrolled in an FLS program to avoid one re-fracture or death, respectively. This significant improvement in patients' outcomes seen with FLS is a result of the coordinated efforts of different healthcare professionals, the patient, and the appropriate patient evaluation. This interdisciplinary approach comprises identification and risk assessment of clinical factors among fragility fracture patients. Analysis of the evidence supporting the cost-effectiveness of FLS services is currently ongoing and will be reported separately.

For the present meta-analysis, both random- and fixed-effects models were considered. The rather conservative random-effects model was chosen for the primary analysis because it provides more reliable estimates in most cases due to the presence of substantial statistical heterogeneity. An exception was in the case of re-fracture rate in RCTs, where fixed effects were deemed appropriate due to the low number of RCTs available for analysis. Overall results from fixed-effects analyses were consistent with the outcomes of the random-effects models.

The findings of the systematic review and meta-analysis presented here are consistent with and extend those reported in the opinion piece by Briot et al. [14] and the meta-analysis by Ganda et al. [11] for BMD testing and treatment initiation. The present meta-analysis assessed 74 publications based on searches from 2000 to 2017, expanding on the 42 publications obtained over the period 1996-2011 that were evaluated by Ganda and colleagues. Briot et al. provided a narrative review of the evidence without any quantitative synthesis, in contrast to our analysis. Apart from a quantitative synthesis of the evidence of BMD testing and treatment initiation that has accumulated since Ganda et al. published their meta-analysis in 2012, we also conducted additional meta-analysis on re-fracture, mortality, and adherence rates. We have also conducted sensitivity analyses to examine the robustness of our results based on study design. We provide ratings on the quality of the studies to allow readers better to judge the evidence. Therefore, to date, the present publication is the first to have provided quantitative analyses and outcomes for publications after 2012. In addition, it is important to note that the present analysis is the first publication, to our knowledge, that quantitatively reports on re-fracture, mortality, and adherence rates in these populations.

Another differentiating aspect of the present analysis compared with that of Ganda et al. lies in the inclusion of study types. Ganda et al. included controlled cross-sectional studies in addition to RCTs and controlled observational studies, whereas this analysis only included RCTs and controlled observational studies for all outcomes, but with uncontrolled and pre-post studies when assessing adherence. Despite these differences and the significant heterogeneity associated with



Fig. 2. Forest plot of risk difference in BMD testing from RCTs and controlled observational studies.\*\*Random-effects model. BMD, bone mineral density; RCT, randomised controlled trial. The follow-up range across studies was 3–26 months.

observational studies, the consistency between the findings of both analyses validates our findings.

FLS is associated with greater adherence to treatment in patients with osteoporosis with a history of fragility fracture. However, studies reporting adherence and persistence to treatment remain scarce. Ganda et al. reported a similar statistically significant absolute increase of 29% in the rates of treatment, which approximates to the ARI of 20%

reported in the analysis. Additional long-term follow-up studies are required to support the value of FLS in improving adherence rates.

There are a number of inherent limitations in this analysis. Differences in the baseline characteristics of patients, such as sex, age, and baseline fracture location, may impact analysis and the generalisability of the results. Furthermore, there was a significant statistical heterogeneity of outcome measures due to variability in study design, follow-



Fig. 3. Forest plot of risk difference in treatment initiation rates from RCTs and controlled observational studies.\* \*Random-effects model. RCT, randomised controlled trial. The follow-up range across studies was 3–72 months.

up duration, patient characteristics, and other qualitative attributes. Although we did not find evidence of publication bias for several of the analyses, reporting biases cannot be ruled out. To assuage this limitation and any possible impact on the data and its interpretation, we separately analysed only RCTs that were descriptively balanced at baseline. The findings for these separate RCT analyses were aligned with the overall findings and conclusions that were based on all studies. The majority of observational studies were non-randomised, which may result in a considerable selection bias while identifying eligible populations i.e. may have been susceptible to biases such as the healthy user effect and measured or unmeasured confounding, such as patients able and willing to participate at the FLS are "healthier" than those who are not able/willing to attend the FLS. This could influence the data on survival and re-fracture risk. Furthermore, some studies made some adjustments, and others not. Better-designed RCTs and controlled observational studies with longer duration of follow-up and refined methodology may aid the quantification of the effectiveness of FLS programs. In future analyses, if individual patient data were available, potentially refined methodology could include propensity scores or instrumental variables. Ideally, an RCT should include a double-blind, randomised design with an adequate control group such as usual care, and be of sufficient power and duration to detect long-term differences in outcomes of interest, such as mortality risk. An ideal setting for such RCTs might be real-world practice, so as to ensure generalisability of findings. Another potential confounder was the wide variation of length of follow-up in included studies. This is especially problematic because it is known that the risk of re-fracture is not constant over time [13,15]. However, since this was a summary meta-analysis we did not have individual participant data to conduct time-to-event analyses. Future studies should prospectively analyse individual participant data. In addition, there was no way to control for a consistent implementation of FLS programs between hospitals and clinics. There is a reliance on hospital-based data, which may lead to an underestimation of re-fracture rates and mortality outcomes, if some patients present to other hospitals; however, this would apply equally to FLS and non-FLS settings. The cost of implementing FLS services and the practical implementation and cost-effectiveness of care in different settings is an important consideration for any healthcare system but was not considered in this analysis. In addition, most of the studies identified in our SLR are from the USA, Europe, and Australia. Because FLS programs have proven very effective to improve treatment outcomes and reduce medical costs, it is important that further studies are conducted to address the evidence gap in other geographic regions, particularly in Asia-Pacific, where more than half of all hip fractures are expected to occur by 2050 [16]. It is also important to note that within this study the terms low-trauma fragility fractures and osteoporosis-related fractures are



Fig. 4. Forest plot of risk difference in adherence rates from RCTs and controlled observational studies.\* \*Random-effects model. RCT, randomised controlled trial. The follow-up range across studies was 6–48 months.

used interchangeably. This was accounted for by ensuring that all lowtrauma fragility fractures included for analysis here were osteoporosis-related. However other FLS studies may differentiate the two terms and therefore other comparisons to the current study must be made with caution. Also of note, as mentioned earlier, despite the noticeable improvements to FLS services that have been made available to



Fig. 5. Forest plot of risk difference in re-fracture rates from RCTs and controlled observational studies.\*\* Random-effects model. RCT, randomised controlled trial. The follow-up range across studies was 6–72 months.



Fig. 6. Forest plot of risk difference in mortality rates from RCTs and controlled observational studies.\*\*Random-effects model. RCT, randomised controlled trial. The follow-up range across studies was 6–72 months.

osteoporosis patients experiencing fragility fractures, it is clear that the situation may be further improved e.g., as shown in the current analysis, adherence to treatment remains poor and just under half of the patients included in the FLS arm underwent BMD testing.

Importantly, under the 'Capture the Fracture' campaign of the IOF, many hospitals and clinics all over the world joined the Best Practice Programme of secondary fracture prevention. The program was guided by specific practice guidelines. Thus far, only 54 of over 150 participating institutions worldwide have received a gold star award from the IOF, with the majority receiving silver stars and a smaller proportion bronze stars [17]. FLS, in conjunction with such guidelines, would likely show greater improved outcomes of all the parameters included in the present review. The results of this study, therefore, are potentially an underestimation of the total benefits of FLS services.

### 5. Conclusion

This SLR and meta-analysis suggests that FLS programs have improved the management of osteoporosis-related fractures, resulting in higher rates of BMD testing, treatment initiation, and adherence, and significant reductions in re-fracture and mortality rates. The evidence here suggests that, as more FLS programs are developed and improved, outcomes such as those assessed herein will also improve correspondingly. FLS are clinically effective across a range of important outcomes in patients with fractures of osteoporosis, indicating that they play a significant role in minimising the burden of disease.

### Data statement

All data sources used in our systematic literature review and metaanalysis can be publicly accessed via Medline, PubMed, EMBASE, and/ or the Cochrane Library.

# **Conflicts of interest**

Chih-Hsing Wu, Shih-Te Tu, Yin-Fan Chang, Jui-Teng Chien, Chih-Hsueh Lin, Manikanta Dasari, Jung-Fu Chen, and Keh-Sung Tsai declare no conflicts of interest.

Ding-Cheng Chan receives consulting fees or other remuneration (payment) from Amgen, Inc.

Sonal Singh served as an advisor on meta-analysis for Complete HEOR solutions, LLC.

Elements of this article have been reported at the 5th scientific meeting of Asian Federation of Osteoporosis Societies (AFOS), Kuala Lumpur, Malaysia, 2017. CH Wu, ST Tu, YF Chang, DC Chan, JT Chien, CH Lin, S Singh, M Dasari, JF Chen, KS Tsai. Fracture Liaison Services Improve Outcomes of Patients with Osteoporosis-related Fractures: A Systematic Literature Review and Meta-Analysis. Osteoporosis and Sarcopenia 2017; 3: S51–S52.

#### Acknowledgements

The authors would like to thank Dr. Zhongyun Zhao for facilitating this research and author collaborations.

#### Funding

This work was supported by Amgen Inc. Systematic literature review was conducted by Complete HEOR Solutions LLC and funded by Amgen Inc. Writing and editorial assistance was provided by ApotheCom and funded by Amgen Inc. and Grant from NCKUH (NCKUH-10609007, 10605021).

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi. org/10.1016/j.bone.2018.03.018.

#### References

- L.G. Raisz, Pathogenesis of osteoporosis: concepts, conflicts, and prospects, J. Clin. Invest. 13 (2) (2005) 1089–1094.
- [2] J.R. Curtis, Q. Cai, S.W. Wade, B.S. Stolshek, J.L. Adams, A. Balasubramanian, H.N. Viswanathan, J.D. Kallich, Osteoporosis medication adherence: physician perceptions vs. patients' utilization, Bone 55 (1) (2013) 1–6.
- [3] N.C. Wright, A.C. Looker, K.G. Saag, J.R. Curtis, E.S. Delzell, S. Randall, B. Dawson-Hughes, The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine, J. Bone Miner. Res. 29 (11) (2014) 2520–2526.
- [4] D. Bliuc, D. Alarkawi, T.V. Nguyen, J.A. Eisman, J.R. Center, Risk of subsequent fractures and mortality in elderly women and men with fragility fractures with and without osteoporotic bone density: the Dubbo Osteoporosis Epidemiology Study, J. Bone Miner. Res. 30 (4) (2015) 637–646.
- [5] J.A. Kanis, O. Johnell, C. De Laet, H. Johansson, A. Oden, P. Delmas, J. Eisman, S. Fujiwara, P. Garnero, H. Kroger, E.V. McCloskey, D. Mellstrom, LJ. Melton, H. Pols, J. Reeve, A. Silman, A. Tenenhouse, A meta-analysis of previous fracture and subsequent fracture risk, Bone 35 (2) (2004) 375–382.
- [6] K. Akesson, D. Marsh, P.J. Mitchell, A.R. McLellan, J. Stenmark, D.D. Pierroz, C. Kyer, C. Cooper, I.O.F.F.W. Group, Capture the fracture: a best practice framework and global campaign to break the fragility fracture cycle, Osteoporos. Int. 24 (8) (2013) 2135–2152.
- [7] A.N. Miller, A.F. Lake, C.L. Emory, Establishing a fracture liaison service: an orthopaedic approach, J. Bone Joint Surg. Am. 97 (8) (2015) 675–681.
- [8] S. Walters, T. Khan, T. Ong, O. Sahota, Fracture liaison services: improving outcomes for patients with osteoporosis, Clin. Interv. Aging 12 (2017) 117–127.
- [9] J.A. Eisman, E.R. Bogoch, R. Dell, J.T. Harrington, R.E. McKinney Jr., A. McLellan, P.J. Mitchell, S. Silverman, R. Singleton, E. Siris, For the ASBMR task force on secondary fracture prevention, making the first fracture the last fracture: ASBMR task force

report on secondary fracture prevention, J. Bone Miner. Res. 27 (10) (2012) 2039–2046.

- [10] W.F. Lems, K.E. Dreinhöfer, H. Bischoff-Ferrari, M. Blauth, E. Czerwinski, J.A.P. da Silva, A. Herrera, P. Hoffmeyer, T. Kvien, G. Maalouf, D. Marsh, J. Puget, W. Puhl, G. Poor, L. Rasch, C. Roux, S. Schüler, B. Seriolo, U. Tarantino, T. van Geel, A. Woolf, C. Wyers, P. Geusens, EULAR/EFFORT recommendations for management of patients older than 50 years with a fragility fracture and prevention of subsequent fractures, Ann. Rheum. Dis. 76 (2017) 802–810.
- [11] K. Ganda, M. Puech, J.S. Chen, R. Speerin, J. Bleasel, J.R. Center, J.A. Eisman, L. March, M.J. Seibel, Models of care for the secondary prevention of osteoporotic fractures: a systematic review and meta-analysis, Osteoporos. Int. 24 (2) (2013) 393–406 [12] StatsDirect Ltd. StatsDirect statistical software. http://www.statsdirect.com. England: StatsDirect Ltd. 2013.
- [12] StatsDirect Ltd, StatsDirect statistical software. http://www.statsdirect.com StatsDirect Ltd, England, 2013.
- [13] Y.K. Soong, K.S. Tsai, H.Y. Huang, R.S. Yang, J.F. Chen, P.C. Wu, K.E. Huang, Risk of refracture associated with compliance and persistence with bisphosphonate therapy in Taiwan, Osteoporos. Int. 24 (2) (2013) 511–521.
- [14] K. Briot, Fracture liaison services, Curr. Opin. Rheumatol. 29 (2017) 416-421.
- [15] P.C. Hsiao, T.J. Chen, C.Y. Li, C.M. Chu, T.P. Su, S.H. Wang, H.H. Pan, K.Y. Wang, Risk factors and incidence of repeat osteoporotic fractures among the elderly in Taiwan: a population-based cohort study, Medicine 94 (7) (2015), e532.
- [16] J.A. Kanis, Assessment of osteoporosis at the primary health care level, WHO Scientific Group Technical Report, University of Sheffield, UK, 2007.
- [17] International Osteoporosis Foundation, Capture the fracture Available at: http:// www.capturethefracture.org/map-of-best-practice?field\_rating\_tid=2&country= All%20Information%20from%20capture%20thefracture%20site%20to%20be%20added 2017, Accessed date: January 2018.