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REVIEW

The effectiveness and cost-effectiveness of clinical fracture-risk assessment tools in reducing future osteoporotic fractures among older adults: a structured scoping review

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Abstract

Summary This scoping review described the use, effectiveness, and cost-effectiveness of clinical fracture-risk assessment tools to prevent future osteoporotic fractures among older adults. Results show that the screening was not superior in preventing all osteoporosis-related fractures to usual care. However, it positively influenced participants' perspectives on osteoporosis, may have reduced hip fractures, and seemed cost-effective.

Purpose We aim to provide a synopsis of the evidence about the use of clinical fracture-risk assessment tools to influence health outcomes, including reducing future osteoporotic fractures and their cost-effectiveness.

Methods We followed the guidelines of Arksey and O'Malley and their modifications. A comprehensive search strategy was created to search CINAHL, Medline, and Embase databases until June 29, 2021, with no restrictions. We critically appraised the quality of all included studies.

Results Fourteen studies were included in the review after screening 2484 titles and 68 full-text articles. Four randomized controlled trials investigated the effectiveness of clinical fracture-risk assessment tools in reducing all fractures among older women. Using those assessment tools did not show a statistically significant reduction in osteoporotic fracture risk compared to usual care; however, additional analyses of two of these trials showed a trend toward reducing hip fractures, and the results might be clinically significant. Four studies tested the impact of screening programs on other health outcomes, and participants reported positive results. Eight simulation studies estimated the cost-effectiveness of using these tools to screen for fractures, with the majority showing significant potential savings.

Conclusion According to the available evidence to date, using clinical fracture-risk assessment screening tools was not more effective than usual care in preventing all osteoporosis-related fractures. However, using those screening tools positively influenced women's perspectives on osteoporosis, may have reduced hip fracture risk, and could potentially be cost-effective. This is a relatively new research area where additional studies are needed.

Keywords Clinical assessment tools · Fractures · Osteoporosis · Risk assessment

Introduction

Osteoporosis is a bone disease identified by a decrease in bone mineral density resulting from an imbalance between bone formation and bone reabsorption [1]. Osteoporosis places significant health and economic burden on society worldwide. Globally, 18.3% (> 200 million) of people have osteoporosis [2, 3]. In Canada alone, an estimated 2 million individuals are affected by osteoporosis, and at least 1 in 3 women and 1 in 5 men will break a bone due to osteoporosis in their lifetime [4]. One of the most serious osteoporotic fractures is those of the hip. Hip fractures lead to the most

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morbidity compared to other fracture sites, with mortality rates reported to be 30% in the first year alone after a hip fracture [5]. The current gold standard for diagnosing osteoporosis is measuring bone mineral density (BMD) via dual-energy X-ray absorptiometry (DXA, previously DEXA). Despite its ability to measure bone density accurately and conveniently, DXA has a low sensitivity for predicting osteoporotic fractures, and it is a costly procedure [6]. This low sensitivity led to the development of several assessment tools that use a wide variety of clinical factors to determine fracture risk. These tools include the Fracture Risk Assessment Tool (FRAX), the Canadian Association of Radiologists and Osteoporosis Canada (CAROC) tool, the Garvan institute bone fracture risk calculator (GARVAN), and the Simple Calculated Osteoporosis Risk Estimation (SCORE). Among these tools, the FRAX appears to be the most cited in the literature and the most widely used tool to predict fracture risk [7]. The FRAX uses clinical risk factors to calculate the absolute 10-year risk of hip fracture or other major osteoporosis-related fractures. Examples of clinical risk factors include body mass index (BMI), alcohol intake, and other secondary conditions, such as rheumatoid arthritis. Although not necessary, BMD can also be included in the FRAX calculation.

The ability of the FRAX to predict osteoporotic fractures has been validated in several places in the world, including North America, through several large-scale studies [8, 9]. After identifying those at risk, healthcare providers could then follow up with more in-depth assessments and implement treatment protocols to increase the health outcomes of those at risk for an osteoporotic fracture. However, despite the predictive value of the FRAX, we do not know whether implementing risk assessment tools can translate into clinically significant outcomes, such as reducing osteoporotic fractures or saving costs, and there is seemingly less research dedicated to determining this. To address this research gap, the primary objective of our study was to review the evidence on the effectiveness of using clinical fracture-risk assessment tools in reducing osteoporotic fractures and/or influencing other health outcomes. A secondary objective was to summarize any evidence of the cost-effectiveness of using these clinical tools during investigations in fracture prevention.

Methods

A scoping review directed by the guidelines of Arksey and O'Malley (2005) and its modifications [10] was carried out to systematically search the peer-reviewed literature. The scoping review methodology was selected to provide an overview of any available evidence on our research question. The updated PRISMA reporting guidelines for scoping reviews were followed [11].

Inclusion and exclusion criteria

We included primary studies relating to fracture risk assessment using a validated screening tool in preventing osteoporosis-related fractures or any other patient health outcomes in all settings and populations. All validated clinical risk assessment tools were included, such as FRAX [12], GARVAN [13], and CAROC [14]. Both qualitative and quantitative studies that contributed relevant information were included. Within our search criteria, we excluded articles older than the year 2000 because the validated clinical risk assessment tools were created after this date, as well as conference proceedings, articles without data, and dissertations. Screening studies not focusing on the value of validated clinical risk assessment tools have been excluded.

Search strategy

With the assistance of a health librarian, a list of combinations of keywords and medical sub-headings was created, and three major databases: Medline, Embase, and CINAHL, were searched until June 29, 2021. In addition, we scanned the references of potential studies to identify any additional relevant articles that did not appear in our initial search. A post hoc search of Medline was done to extend the search until November 06, 2022, to ensure no additional relevant articles were published but no additional articles were included as a result of this additional step. The full search strategy and a list of the keywords used in the Embase search can be found in Appendix 1.

Screening of articles

All abstracts were independently reviewed by two different members of the research team. Any disagreements over inclusion were resolved through consensus and, where necessary, discussion with a third member of the review team. Following the abstract review, this process was replicated to complete the full-article review.

Data extraction and synthesis

Data extraction forms were validated by all members of the research team and were pilot tested in three studies for feasibility and comprehensiveness. Minor adjustments were made until a consensus was reached among all team members. Two reviewers independently reviewed full-text and extracted data into Microsoft Excel. The data included general information such as study design, countries, outcome measures, and details on results, conclusion, limitations, and implications. Narrative data synthesis was undertaken, and a

meta-analysis was not deemed appropriate due to the nature of this review and the data included.

The quality of each study was independently appraised by two different team members using appropriate assessment tools. Specifically, the risk of bias in included randomized controlled trials (RCT)s was assessed using the PEDro scale (Appendix 2). Similarly, the Critical Appraisal Skills Program (CASP) tool was used to evaluate the validity of the qualitative studies (Appendix 3), and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) was used to assess the quality of reporting published health economic evaluations (Appendix 4).

Results

Our literature searches identified 766 articles from Medline, 2220 articles from Embase, and 523 articles from CINAHL, totaling 3509 articles. After removing duplicates, there was a total of 2484 articles. When reviewing the abstracts, 64 articles were selected for a full-text review. Four additional articles were identified from manually searching relevant reference lists and added to the full-text review. Following the full-text review of the 68 articles, 32 were excluded because they focused on the predictive ability of the tools rather than investigating clinical outcomes such as fracture prevention, and 22 were excluded due to lacking primary data, such as review studies and conference proceedings. Thus, a total of 14 articles were included in the review. Figure 1 presents the PRISMA flow chart of article inclusion.

Study attributes and characteristics of sample

Table 1 outlines the general information of the 14 included articles, which all were published between 2005 and 2020. Most of the studies were conducted in the USA, and several were published in the Osteoporosis International journal. Except for three studies that used the SCORE [15] and Osteoporosis Self-assessment Tool (OST) [1] to assess clinical fracture risk, respectively, 11 studies used the FRAX as a clinical fracture-risk assessment tool.

In terms of the primary outcome of interest, three RCT studies examined the effectiveness of implementing FRAX in reducing future osteoporotic fractures [16–18]. One additional trial compared the influence of the SCORE-based screening strategy with other two strategies on osteoporosis

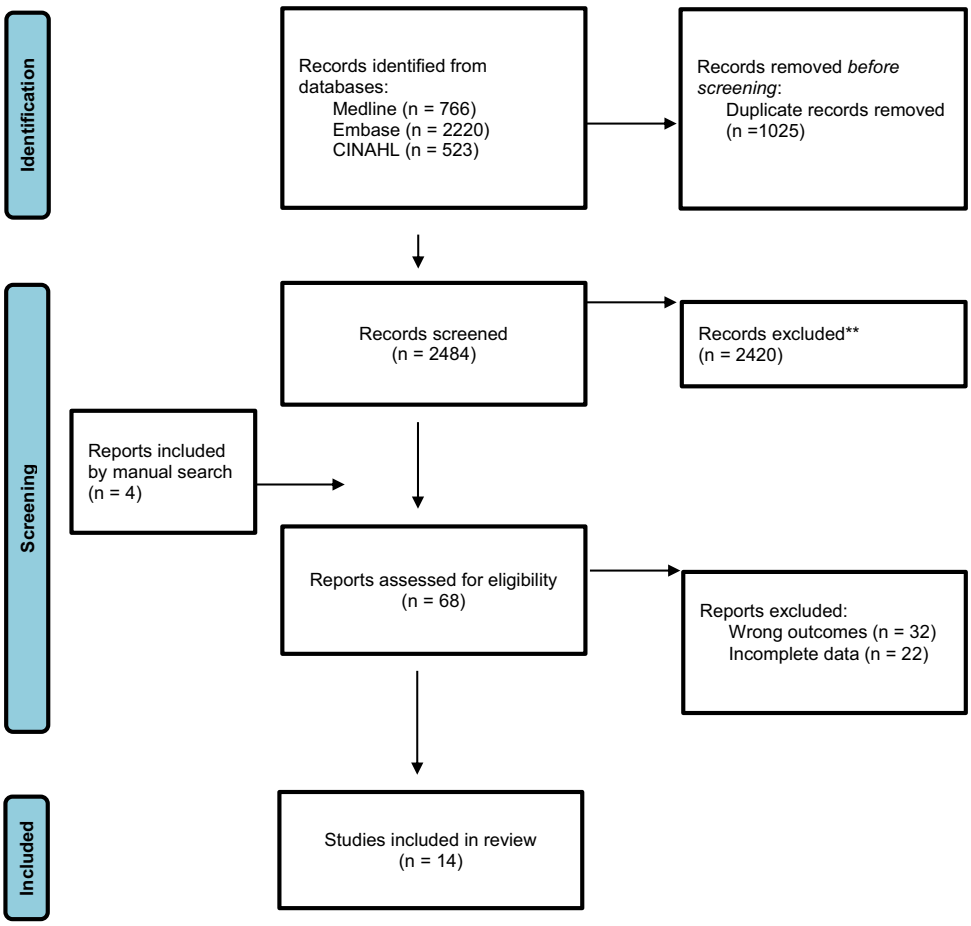

Fig. 1 PRISMA flow diagram

Table 1 Basic study features

Authors, year	Sample size	Country	Journal	Outcomes	Risk assessment Tool	Study design
Studies on osteoporotic fracture-related outcomes and other health outcomes						
LaCroix et al. 2005 [19]	3167	USA	Medical Care	Osteoporosis treatment initiation, risk-related behaviors, osteoporosis knowledge, and the occurrence of fractures	SCORE	RCT
Shepstone et al. 2017 [16]	12,483	UK	The Lancet	**Primary:** incidence of all osteoporosis-related fractures over a 5-year period (excluding the hands, feet, nose, skull, or cervical vertebrae) **Secondary:** hip fracture, any clinical fracture, mortality, anxiety, and quality of life	FRAX	RCT
Rubin et al. 2017 [17]	34,229	Denmark	Osteoporosis International	**Primary:** Incident major osteoporosis-related fractures over a 5-year period **Secondary:** hip fracture and any clinical fracture except fingers and toes	FRAX	RCT
Merlijn et al. 2019 [18]	11,032	Netherlands	Journal of Bone and Mineral Research	**Primary:** the incidence of any type of fractures **Secondary:** osteoporotic fractures, hip fractures, falls, and death	FRAX	RCT
Rothmann et al.2014 [20]	31	Denmark	Archives of Osteoporosis	Perspective, experiences, and acceptance of risk-stratified osteoporosis risk screening	FRAX	Qualitative
Dunniway et al. 2012 [21]	17	USA	Journal of the American Academy of Nurse Practitioners	Modification of bone health risk factors and treatment decision-making	FRAX	Qualitative
Studies on cost-effectiveness-related outcomes						
Nayak et al. 2011 [15]	Unclear	USA	Annals of Internal Medicine	Incremental cost-effectiveness ratios Quality-adjusted life-year	SCORE	Economic evaluation of health intervention
Kingkaew et al. 2011 [1]	Unclear	Thailand	Value in Health	Incremental cost-effectiveness ratios Quality-adjusted life-years	OST	Economic evaluation of health intervention
Ito & Leslie 2015 [22]	Unclear	USA	Osteoporosis International	Incremental cost-effectiveness ratios Quality-adjusted life-years	FRAX	Economic evaluation of health intervention
Walter et al. 2017 [23]	Unclear	Austria	Bone	Incremental cost-effectiveness ratios Quality-adjusted life-years	FRAX	Economic evaluation of health intervention
Soini et al. 2018 [26]	Unclear	Finland	Clinico Economics and Outcomes Research	Incremental cost-effectiveness ratios Quality-adjusted life-years	FRAX	Economic evaluation of health intervention
Su et al. 2018 [27]	Unclear	Hong Kong	Osteoporosis International	Incremental cost-effectiveness ratios Quality-adjusted life-years	FRAX	Economic evaluation of health intervention
Martin-Sanchez et al. 2019 [25]	5,146	Spain	Calcified Tissue International	Incremental cost-effectiveness ratios	FRAX	Economic evaluation of health intervention
Chandran et al. 2020 [24]	1,000,000	Singapore	Osteoporosis International	The cost per quality-adjusted life years	FRAX	Economic evaluation of health intervention

FRAX Fracture Risk Assessment Tool, *SCORE* Simple Calculated Osteoporosis Risk Estimation, *OST* Osteoporosis Self-assessment Tool

treatment initiation, risk-related behaviors, knowledge, and incidence of osteoporosis fractures[19]. Additionally, one of the trials also investigated the impact of using FRAX on anxiety and quality of life [16].

Two qualitative studies were included; one study evaluated women's experiences and perspectives on screening for osteoporosis [20]. The other qualitative study examined whether osteoporosis screening by FRAX would affect women's decision-making on modifying bone health risk factors and treatment of osteoporosis [21].

The remaining eight studies provided health economic analyses to investigate the value for money of using different fracture risk screening strategies [1, 15, 22–27].

Primary outcomes

Fracture prevention

Four trials used clinical fracture-risk assessment tools (FRAX and SCORE) to screen and prevent osteoporosis-related fractures among older women. They determined that including these tools in the osteoporosis screening process may not yield significant health outcomes, such as reducing fractures, but is an important step in the comprehensive screening process [16–19] (Table 2).

Specifically, three studies utilized the FRAX to determine the 10-year probability of sustaining an osteoporotic fracture and measured the proportion of participants who had at least one osteoporosis-related fracture during follow-up. All three studies found that using FRAX in osteoporosis risk selection or in treatment thresholds did not reduce the incidence of all osteoporosis-related fractures compared to usual care. The FRAX-based screening program did, however, significantly reduce the incidence of hip fractures ($p = 0.002$) in the Shepstone study, which was a secondary outcome [16]. Rubin et al., based on the per-protocol analyses, found that the screening group with FRAX followed by DXA had a significant reduction of all fractures as compared to the control group when only FRAX > 15% [17].

The findings of these pragmatic RCTs might have been compromised by potential selection bias, medication non-adherence in the screening groups, as well as higher than expected uptake of screening and medication in the control groups. For instance, in Merlijin et al., the participants in the screening sub-group were younger and healthier than the control participants since those who were of higher age, cigarette and alcohol consumers, and with more comorbidities were either not interested in DXA (12%) or dropped out (17%) in the screening sub-group. They also reported that 31% of the participants with a treatment indication in the screening group did not start taking the prescribed medication by the end of first year.

In terms of the increased uptake in the control group, Shepstone et al. reported that 24% of the screening group received at least one prescription for osteoporosis medication versus 16% of participants in the control group. In Merjilin et al., overall, 20.7% of participants in the screening group reported having antiosteoporosis medication versus 5.3% of the usual care group. Rubin et al. reported that 25% of women in the control group had a DXA scan, compared to 48% in the screening group, and 18% of women in the control group received osteoporosis medication versus 23% in the screening group.

The screening processes were slightly different among the three studies. In Shepstone et al.'s study, the 10-year age-specific hip fracture probability calculated by the FRAX risk algorithm was used to decide whether to recommend a BMD assessment through a dual-energy DXA scan [16]. The 10-year hip fracture probability was then recalculated based on the FRAX-BMD scores. Participants were categorized into age-specific low or high-risk fracture groups using the FRAX-BMD scores. Finally, all participants and their general practitioners (GPs) were informed of the screening results by letters. The participants with a high fracture risk were advised to make an appointment with G.P.s to discuss treatment options. In Rubin et al.'s study, participants with a 10-year probability of major osteoporotic fractures over or equal to 15% were offered a DXA scan. Then participants and their G.P.s received a letter with the results after the DXA and treatment recommendations. Still, the final decision was with the G.P. In Merlijn et al.'s study, the screening included FRAX, DXA, vertebral fracture assessment (VFA), falls, and blood tests. Based on screening results, the participants with a high risk of major osteoporotic fracture were indicated for a personalized anti-osteoporosis medication treatment [18].

Additionally, one trial compared fracture occurrence and other outcomes among women in three screening groups, namely, universal BMD testing, SCORE-based screening, and osteoporotic fracture risk factors-based screening group (no comparison with usual care) [19]. They found that women in the SCORE-based screening group had a significantly higher fracture rate in follow-up compared with the universal BMD testing group.

Overall, all studies concluded that using FRAX or SCORE might not significantly reduce the rate of fractures. Nonetheless, screening tools identify women with a high risk of fracture as well as women who will benefit from additional fracture risk screening.

Additional clinical and health outcomes

The impact of the clinical osteoporosis screening programs on other outcomes such as health perspectives, anxiety, and quality of life, was explored in four studies included in our review [16, 19–21]. Supplementary to investigating fracture

Table 2 Characteristics of RCTs or experimental studies investigating the effectiveness of clinical fracture risk assessment tools to prevent future osteoporosis-related fractures

	Participants	Intervention group	Control group	Main findings	Follow-up length
LaCroix et al. 2005 [19]	Women aged 60–80 years	Three intervention groups: 1. Universal testing group (BMD testing) 2. SCORE testing group (SCORE ≥ 7 leads to BMD testing) 3. SOF-based testing (≥ 5 risk factors leads to BMD testing)	N/A	The fracture rates were significantly lowest in the universal group and highest in the SCORE group. The number of women who had osteoporosis discussed with healthcare providers was significantly higher in the universal testing group than those in the SOF-based testing group followed by the SCORE group. Knowledge about osteoporosis risk factors was highest in the universal group and lowest in the SOF-based group. The osteoporosis treatment initiation did not differ among the three groups	24 to 33 months
Shepstone et al., 2017 [16]	Women aged 70–85, not currently prescribed an anti-osteoporotic drug (excluding calcium or vitamin D)	The intervention included 2 steps: 1. FRAX screening 2. DXA (if classified as high risk) FRAX was then recalculated using the DXA score The G.P. of patients at a high risk of fracture received a communication with standard care, and treatment was recommended	Women were not informed of the result of the FRAX calculation and received the usual care	Though the FRAX-based screening on fracture risk did not reduce the incidence of all osteoporosis-related fractures, the screening led to a statistically significant decrease in hip fractures (secondary objective)	5 years
Rubin et al., 2017 [17]	Women aged 65–80 years and living in the Region of Southern Denmark	FRAX with DXA and recommendations for treatment sent to the G.P. if the risk of osteoporotic fracture is over or equal to 15%	Usual care	There were no overall significant differences in the 5-year incidence of major osteoporotic and risk of fractures between intervention and control. However, per-protocol analysis showed significant results for both major osteoporosis fractures, hip fractures, and all fractures	5 years
Merlijn et al., 2019 [18]	Women aged 65 to 90 years	Screening by DXA, VFA, FRAX, falls, and blood tests with a personalized treatment if indicated	Usual care with DXA and VFA screening (were informed of risk assessment)	The screening with subsequent treatment did not have a significant effect on any type of fractures	36 months

FRAX Fracture Risk Assessment Tool, *DXA* X-ray absorptiometry, *VFA* vertebral fracture assessment, *GP* general practitioner, *SOF* Study of Osteoporotic Fracture

prevention, the RCT completed by Shepstone et al. also studied the impact of the screening process on the anxiety and quality of life of the women screened [16]. Shepstone et al. (2017) did not find that the screening program improved participants' quality of life as measured by the EuroQol-5D and the Short Form 12 Health Survey measure and did not reduce anxiety levels measured by the State-Trait-Anxiety Index [16]. LaCroix et al. found that women in the universal BMD testing group were more likely to discuss osteoporosis with healthcare providers and had better knowledge about osteoporosis risk factors than women in the SCORE-based screening and the osteoporotic fracture risk factors-based screening groups [19].

The remaining two studies were qualitative studies that sought to investigate the perspectives and experiences of the women who underwent fracture risk screening programs [20, 21]. The results of the two qualitative studies indicated that fracture risk screening was a positive experience for older women with no reported adverse effects. Rothman et al. found that screening could be used to reassure individuals about their health status and help them acquire information they would not have known otherwise [20]. Similarly, Dunniway et al. found that undergoing a risk assessment for osteoporosis can help motivate women to change their health behaviors and improve health habits [21]. After receiving an abnormal result (either being diagnosed with osteoporosis or receiving a FRAX score that met the threshold for treatment), women demonstrated a 59% increase in calcium intake and a 94% increase in vitamin D intake over a 3-month period.

Secondary outcome: cost-effectiveness and economic evaluation

Eight simulation studies in our review sought to determine the cost-effectiveness of various osteoporotic screening strategies. Except for one study that focused on both men and women, seven focused solely on women in the simulated analysis. With respect to data analysis, three studies used only a Markov model, two studies used both Markov and decision tree model, one study used a decision tree model alone, one study used a discrete-event simulation model, and one used an individual-level state-transition model. In terms of study perspective, five studies reported using a payer's perspective, one used a national health system perspective, and two adopted a societal perspective with respect to costs. Overall, almost all studies found that different osteoporotic screening strategies using a clinical fracture risk assessment tool were cost-effective in comparison to the no-screening alternative (see Table 3 for features and main findings of the economic evaluation studies).

Nayak et al. examined the cost-effectiveness of three screen strategies compared to a control group of women aged 55 years old and older. The screening strategies include (1) DXA alone, (2) the calcaneal quantitative ultrasonography (QUS) before DXA, and (3) the SCORE tool before DXA [15]. They found that all screening strategies improved quality-adjusted life-years (QALYs) in American women and were cheaper than no screening (screening initiated at age of 65 years and older). They also found that comparing screening initiation ages from 55 to 80, screening at the age of 55 with DXA − 2.5 and rescreening every 5 years was the most cost-effective with an Incremental Cost-Effectiveness Ratio under $ 50,000 per QALY.

Ito and Leslie's study evaluated the health and economic impact of various fracture prevention strategies for women in rural areas in Manitoba, Canada, with limited access to DXA. The fracture prevention strategies were (1) watchful waiting strategy (no DXA screening and pharmacotherapy after a fracture), (2) FRAX-BMD-based strategy (DXA screening, FRAX-BMD screening and pharmacotherapy), and (3) FRAX-based strategy (FRAX screening and pharmacotherapy) [22]. The results indicated that the watchful waiting strategy was the most costly and less effective than other strategies. Furthermore, for women traveling fewer than 25 miles, the FRAX-BMD-based strategy was preferred as the travel cost was moderate, whereas for individuals who had to travel more than 25 miles to receive a DXA scan, FRAX without DXA followed by a pharmacotherapy proved to be the superior screening strategy in terms of cost.

Walter et al.'s study evaluated the cost-effectiveness of implementing the (1) micro RNAs-based osteoporotic fracture risk assessment (osteomiR^{tm} test), (2) the FRAX, (3) DXA, and (4) no screening strategies in a cohort of Austrian women aged 50 and over [23]. The osteomiR^{tm} is a novel tool for assessing fracture risks based on serum microRNA profiles. Their findings revealed that assessment and monitoring using the osteomiR^{tm} test reduced the incidence of fracture compared with the other comparison groups using FRAX, DXA, or no screening and is more cost-effective than both the FRAX and no screening.

In Soini et al.'s study, (1) the two Proposed Osteoporosis Management (POMs) screening models (FRAX followed by point-of-care pulse-echo ultrasound [PEUS] and DXA and fracture prevention treatment [FPT] as needed) and (2) the Conventional Osteoporosis Management (COM) screening model (FRAX followed by DXA and FPT if needed) were economically evaluated among older women in Finland [26]. They found that POMs resulted in considerable savings as well as similar QALY gain when compared with COM.

Su et al. compared the utility and cost-effectiveness of three osteoporotic fracture screening strategies, including (1) DXA, (2) FRAX with DXA, and (3) QUS with DXA for hip fracture prevention with no screening in a cohort

Table 3 General features and main findings of the eight economic evaluation studies

Authors, year	Population	Comparators	Model	Perspective	Time horizon	Main findings
Nayak et al., 2011 [15]	U.S. women ≥ 55 years	1. DXA alone 2. QUS-DXA 3. SCORE-DXA 4. No screen	An individual-level state-transition model	Payer	Lifetime	At all initiation ages, the best strategy was DXA screening with a T-score threshold of − 2.5 or less for treatment and with follow-up screening every 5 years
Kingkaew et al., 2011 [1]	Thailand's postmenopausal women between 45 and 80 years	1. DXA 2. OST-DXA 3. No screen	A decision tree and Markov model	Societal	Lifetime	Both DXA and OST with sequential DXA screening and treatment strategies were not cost-effective compared to no screening. The OST and sequential DXA provided better value for money for osteoporosis screening among young age groups (< 60 years)
Ito et al., 2015 [22]	Canada rural women ≥ 65 years	1. FRAX-DXA 2. FRAX 3. No screen	Markov model	Societal	Lifetime	In areas where DXA is readily available, DXA screening followed by pharmacotherapy guided by BMD would be preferred. In areas with more limited access to DXA, pharmacotherapy for women at high clinical risk for fractures based on FRAX, could both improve health and save money
Walter et al., 2017 [23]	Austrian women ≥ 50 years	1. DXA 2. FRAX 3. osteomiR™ 4. No screen	Markov model	Payer	Lifetime	The osteomiR™ test reduces fracture incidence compared with no monitoring, DXA alone, or FRAX alone
Soini et al., 2018 [26]	Finnish women ≥ 65 years	1. FRAX-PEUS-DXA-FPT 2. FRAX-DXA-FPT	A decision tree and Markov model	Payer	10 years	POMs were cost-effective in all patient subgroups with noteworthy mean per-patient cost savings of €121/76 (ranges €107–132/52–96) depending on the scope of PEUS result interpretation (test and diagnose/test only, respectively) and negligible differences in QALYs gained in comparison with current osteoporosis management
Su et al., 2018 [27]	Hong Kong men and women ≥ 65 years	1. DXA 2. FRAX-DXA 3. QUS-DXA 4. No screen	A decision tree	Payer	10 years	All the screening strategies, including the universal screening with DXA and the pre-screening with FRAX or QUS before DXA, were consistently more cost-effective than no screening for people aged 65 years or over
Martin-Sanchez et al. 2019 [25]	Spanish women aged 70 to 89 years	1. FRAX without BMD 2. FRAX with BMD	A discrete-event simulation model	Spanish national health system perspective	20 years	The ICER exceeded the acceptability threshold of 25,000€ in both FRAX with and without BMD screening, followed by alendronate treatment for high-risk women
Chandran et al., 2020 [24]	Singaporean women ≥ 50 years	1. FRAX IT-No treatment 2. FRAX IT-Alendronate treatment	Markov model	Payer	5 years	Generic alendronate was cost-effective at MOF ITs from 65 years, while H.F. ITs were cost-effective from the ages of 60 and 65 years, assuming full and real-world adherence, respectively. A 14%MOF and a 3.5% H.F. ITs were required for alendronate to be cost-effective above 50 years

DXA dual-energy X-ray absorptiometry, *SCORE* Simple Calculated Osteoporosis Risk Estimation tool, *OST* Osteoporosis Self-assessment Tool, *FRAX* Fracture Risk Assessment Tool, *BMD* Bone Mineral Density, *osteomiR*™ MicroRNAs based fracture risk assessment tool, *PEUS* Pulse-Echo Ultrasound, *FPT* Fracture Prevention Treatment, *QALYs* quality adjusted life-years, *POMs* osteoporosis management pathways including *PEUS* pulse-echo ultrasound, *QUS* quantitative ultrasonography, *FRAX IT* Fracture Risk Assessment Tool Intervention Thresholds, *MOF IT* Major Osteoporotic Fracture Intervention Thresholds, *H.F.* hip fracture, *ICER* Intervention thresholds Incremental Cost-Effectiveness Ratio, *IT* intervention thresholds

of older Chinese men and women (aged 65 or over) in Hong Kong [27]. They found that all three strategies led to more QALYs than no screening. No screening was more expensive than any other strategy in men at any age and in women aged 70 years or over. Additionally, they found that pre-screening with FRAX followed by DXA for women aged between 65 and 75 years old was the most cost-effective in the high-risk group.

Chandran et al. sought to determine the FRAX-based intervention thresholds (ITs) at which the therapeutic intervention with generic alendronate becomes cost-effective among Singaporean women over 50 years of age [24]. The use of generic alendronate was shown to reduce healthcare costs at the major osteoporotic fracture (MOF) intervention thresholds for women over 65 years. In comparison, hip fracture intervention thresholds were cost-effective between 60 and 65 years, assuming full adherence. Furthermore, they found that administering alendronate was only cost-effective for women above 50 years if the MOF and hip fracture intervention thresholds were 14% and 3.5%, respectively.

Finally, contradicting findings were presented in Kingkaew et al.'s study [1]. They analyzed the cost-effectiveness of three strategies in screening and treating osteoporosis among postmenopausal women in Thailand, namely (1) no screening, (2) DXA screening, and (3) Osteoporosis Self-assessment Tool (OST) with sequential DXA screening. Findings showed that both DXA and OST with sequential DXA screening and treatment strategies were not cost-effective compared to no screening. However, they pointed out that using OST in conjunction with DXA was less expensive than using DXA alone for the younger age group (< 60 years old).

Critical appraisal (divided by design)

The quality assessment of the four included RCTs revealed that trials are of good or fair internal validity as they scored 5/10 in LaCroix et al. [19], 7/10 in Merlijin et al.'s study [18], 6/10 in Shepstone et al. [16], and 5/10 in Rubin et al. [17] on the PEDro scale. Although these studies demonstrated significant strengths, all studies did not conceal allocation, and there was no evidence of study therapists being blinded, as seen in Appendix 2.

The quality of the two qualitative articles was assessed using the CASP tool, and both were determined to be high-quality articles by the assessors, as seen in Appendix 3.

The quality appraisal of the cost analysis studies was overall high. The CHEERS checklist reporting compliance score (a higher score is better) was: 24/28 in three studies, 25/28 in three studies, 26/28 in one study, and 22/28 in one study. The least reported CHEERS checklist items were item #4 (health economic analysis plan), which was reported in two studies, item #21 (approach to engagement with patients and others affected by the study) reported in two studies, and item #25 (effect of engagement with patients and others affected by the study), which was reported in no study (Appendix 4).

Discussion

This scoping review examined whether the clinical fracture risk assessment tools are effective in improving patient outcomes, reducing future fractures and producing other clinically significant outcomes. Among the 14 included studies, four trial studies looked at incident fracture prevention as the primary outcome, and overall, there was insufficient evidence about their value. However, some evidence indicated that questionnaire-based screening is promising in reducing hip fractures in older women, as shown in Rubin et al.'s and Shepstone et al.'s studies when followed with a DXA scan. Additionally, four articles explored other health outcomes, and two of them suggested that FRAX screening can positively change women's perspectives and health behaviors on osteoporosis treatments and fracture risk modifications without causing an increase in anxiety levels. Finally, eight simulated studies investigated whether using osteoporotic fracture risk screenings and subsequent treatments is cost-effective. Except for one study, all studies suggested that different osteoporotic fracture risk screening strategies were cost-effective and led to increased QALYs in comparison to no screening.

Although the results of our study did not find statistically significant evidence to indicate that using the FRAX is effective at preventing osteoporosis-related fractures at all fracture sites, several factors perhaps diluted the intervention effect. First, given the nature of these pragmatic trials, we cannot rule out the contamination effect in the control group. Simply screening with FRAX might increase awareness of osteoporotic fracture risks. Rubin et al. found that 25% of women in the control group had a DXA scan, compared to 48% in the screening group, and 18% of women in the control group received osteoporosis medication versus 23% in the screening group [17]. Second, compliance with the treatment in the intervention group might limit the intervention effects in these trials. It was reported in the Merlijin et al. study that 31% of the participants with a treatment indication in the intervention group did not even start taking the prescribed medication, and medication adherence reduced over time [18].

Therefore, both increased chances of treatment uptake in the control group and decreased treatment compliance over time could have reduced the intervention's effectiveness. Vertebral fractures also were not investigated independently in the included studies, which might have contributed to the nonsignificant results.

In Shepstone et al.' study, the 10-year risk of hip fracture rather than the risk of all osteoporotic fractures was used [16]. Using the hip fracture risk as the screening approach would be more sensitive to predicting and, therefore, better at preventing hip fractures, rather than fractures at other sites. The per-protocol analysis in Rubin et al.' study yielded a significant hip fracture reduction in the screening sub-group who had DXA scan compared to participants in the control group with FRAX ≥ 15% [17]. However, this finding might have potential selection bias. The participants in the screening sub-group were younger and healthier than the control participants since those of higher age, cigarette and alcohol consumers, and with more comorbidities were either not interested in DXA (12%) or dropped out (17%) in the screening group. Despite the bias, the positive findings from these studies might be clinically relevant. As compared to all osteoporosis-related fractures, those of the hip are the most severe. In addition, to the high mortality rates, research demonstrates that older adults who survive a hip fracture have high rates of disability, are more likely to be admitted to a nursing home and have a poor quality of life [5, 28, 29]. Therefore, steps taken to prevent hip fractures can positively impact those at risk and the healthcare system overall. The research also suggests that using FRAX scores to identify women at risk and subsequently completing a DXA scan may lead to greater fracture prevention compared to using FRAX alone. However, only women who met a certain FRAX score threshold received a DXA scan. Therefore, due to these implications of the 2-step study design, it is challenging to discern whether the greater fracture prevention was due to the utilization of DXA screening or the greater susceptibility of the women.

Four articles explored other health outcomes. The results suggest that screening tools may positively influence women's health behaviors by encouraging them to obtain information about osteoporosis [20]. Similarly, for individuals who may be at risk of or who have been diagnosed with osteoporosis, abnormal test results can also increase their awareness of the disease [30]. Based on these results, it can be inferred that when women know their personal risk level paired with an understanding of the associated implications and treatment options, they will be more adept at avoiding the negative consequences of the disease. In the article investigating the quality of life, the positive effects of screening were not reflected, however, the study only utilized simple objective measures [16]. Thus, it is possible that the women did notice positive changes in their lives that were not captured by the tools used. The same article also demonstrated that screening does not increase anxiety, which suggests no negative impact of screening. Overall, there is minimal research investigating the impacts of screening on health outcomes, but the research suggests that screening can positively influence health with minimal to no adverse effects.

Various simulation studies have explored the cost-effectiveness of using risk assessment tools compared to more costly methods, such as DXA or X-ray, to assess fracture risk. Although there is insufficient or weak evidence on the use of clinical fracture risk assessment tools such as FRAX, reviewed evidence suggests that using these tools as part of screening strategies is cost-effective compared to no screening. In our included studies, reviewed evidence indicated that in conjunction with osteoporosis medications, different screening strategies with or without a questionnaire-based pre-screening significantly reduced fracture risk-related costs compared with no screening at all. However, the cost-effectiveness of different strategies varied widely under different circumstances. An Incremental Cost-Effectiveness Ratio threshold and age can impact the cost-effectiveness of screening strategies. Nayak et al. found that pre-screened by SCORE followed a DXA − 2.5 cost less than DXA screening alone at ages between 55 to 65, assuming Incremental Cost-Effectiveness Ratios less than $20,000 per QALY, while DXA − 2.5 alone with rescreening every 5 years were most cost-effective at ages 60 and over assuming a willingness-to-pay $ 100,000 per QALY [15]. Furthermore, the geographic proximity of DXA might be another factor that influences the cost-effectiveness of screening strategies. Due to the travel burden, Ito et al.'s study showed that the FRAX without DXA could be more cost-effective than DXA alone for women with a travel distance ≥ 25 miles, while it was the opposite for women with a travel distance < 25 miles [22]. Of importance to note is that these cost studies used fracture reduction rates data from drug studies and not pragmatic trials of screening tools, and this might have contributed to the high savings estimated in these studies.

The use of FRAX and DXA is the gold standard for fracture risk assessment and is most frequently investigated in the literature for osteoporosis management [7, 31]. One limitation of using DXA is that it is rarely

available in many primary care facilities due to cost. Some novel osteoporosis diagnosis tools, such as PEUS and serum microRNA (osteomiR™), seem promising alternatives. Soini and colleagues found that by incorporating PEUS in a conventional screening strategy (FRAX followed DXA), osteoporosis management costs were reduced significantly [26]. This might be because accessing the DXA is expensive, especially in remote areas considering the traveling costs. The cost-utility of osteomiR™ in Walter's study revealed that compared with using DXA alone or with FRAX alone, osteomiR™ led to increased QALYs and reduced incidence of fractures [23]. They noted that due to the insufficient accuracy of DXA for identifying high fracture risks, osteomiR™ should be included in the standard care to increase the diagnostic performance of osteoporotic fracture risks.

Implications on the healthcare system

This research will serve as foundational knowledge as the global population continues to age, and the number of fractures is projected to increase significantly [32]. A 2015–2016 report from Osteoporosis Canada states that it costs the Canadian Healthcare system approximately 2.3 billion dollars a year to treat osteoporosis and the resulting fractures [33]. Older women are at a higher risk than men for hip fractures; thus, it is appropriate that research to date focused on older women. Each hip fracture alone costs about $21,000 within the first year after hospitalization, and those costs more than double per year if the patient needs to be institutionalized [33]. Therefore, if more fractures could be prevented and at a lower overall cost to the healthcare system by using these tools, there is a significant benefit to increasing the utilization and research surrounding these tools.

Future research directions

Overall, more high-quality pragmatic experimental studies, such as RCTs, are needed to investigate the effectiveness of using clinical risk assessment tools to produce clinically significant outcomes. Specifically, additional research should compare the effectiveness of utilizing the FRAX compared to DXA screening for women with the same fracture risk level and follow participants for longer periods. In addition, much of the current research is focused on FRAX. Therefore, there is also a need for additional research to explore the effectiveness of using the different types of assessment tools (e.g. CAROC, GARVAN). Exploring various tools will allow researchers to determine if they are as effective as the FRAX at preventing fractures or which tool has the most significant impact on fracture prevention. Vertebral fractures should be included as an independent outcome in future studies. Once more trials are available on this topic, a meta-analysis can help pool results from several studies to provide a better conclusion. Finally, future trials should include a cost-analysis component, or simulated cost-analysis studies should use rates from pragmatic trials to improve the cost-saving estimation.

Strengths and limitations

This review has many strengths. First, to the best of our knowledge, this is the first review to summarize evidence on the effectiveness of clinical fracture-risk assessment tools in preventing fractures and producing other clinical outcomes. Second, a comprehensive search strategy was created with the help of an information specialist to ensure a valid strategy was employed. Third, at least two independent reviewers were included throughout the process to bolster the rigor of the results. Finally, we have critically appraised all included studies and found that the majority of included studies have a high level of internal validity (less sources of bias). A limitation of this review is that only studies completed in English were included, so relevant studies in other languages may have been excluded. Lastly, like all literature reviews, our results are limited by the published research available. With more data available, the results might change.

Conclusion

While previous research has been focused on validating clinical risk assessment tools, there has been significantly less research investigating whether utilizing these tools produces tangible clinical outcomes, including fracture prevention. Although based on limited studies, this scoping review suggested that screening with osteoporosis clinical risk assessment tools was not more effective than usual care in preventing the incidence of all osteoporotic fractures. This finding might have resulted from suboptimal participation and adherence in the intervention groups and higher than expected screening and osteoporosis medication uptake in the control groups. However, screening tools could play a role in osteoporotic hip fracture prevention. Also, we found that using these tools positively influenced women's perspectives on osteoporosis and subsequent lifestyle choices. Our review also suggests that including these tools in the screening has the potential to be a cost-effective approach to preventing osteoporosis-related fractures, especially hip fractures.

Appendix 1. Search Strategies for three databases

Medline	
Search terms	Results
1 frax.mp	1484
2 garvan.mp	65
3 qfracture.mp	42
4 caroc.mp	22
5 (fracture* adj5 risk assessment*).mp	1639
6 risk assessment*.mp	327,007
7 Risk Assessment/	283,558
8 1 or 2 or 3 or 4 or 5 or 6 or 7	327,557
9 osteoporosis/ or osteopSearchorosis, postmenopausal/	57,951
10 osteoporosis.mp	91,742
11 osteoporotic fracture*.mp	11,997
12 fragility fracture*.mp	4084
13 hip fractures/ or femoral neck fractures/	25,509
14 hip fracture*.mp	24,547
15 or/9–14	120,913
16 8 and 15	5482
17 limit 16 to humans	5070
18 limit 17 to yr = "2000–current"	4864
19 limit 18 to dt = 20,180,701–20,210,629	762
20 fracture risk scale*.mp	6
21 19 or 20	766

Embase	
Search terms	Results
1 frax.mp	4017
2 garvan.mp	154
3 qfracture.mp	110
4 caroc.mp	46
5 (fracture* adj5 risk assessment*).mp	3185
6 risk assessment*.mp	651,218
7 risk assessment/	619,253
8 1 or 2 or 3 or 4 or 5 or 6 or 7	653,210
9 exp osteoporosis/	143,291
10 osteoporosis.mp	170,261
11 osteoporotic fracture*.mp	13,188
12 fragility fracture*.mp	22,012
13 exp hip fracture/	42,826
14 hip fracture*.mp	37,422
15 or/9–14	208,790
16 8 and 15	16,518
17 limit 16 to human	15,890
18 limit 17 to yr = "2000–current"	15,084
19 limit 18 to dc = 20,180,701–20,210,629	4114
20 fracture risk scale*.mp	8
21 19 or 20	4118
22 limit 21 to (books or chapter or conference abstract or conference paper or "conference review" or editorial)	1898
23 21 not 22	2220

CINAHL			
Search ID#	Search terms	Search options	Results
S16	S14 OR S15	Expanders—Apply related words; Apply equivalent subjects Search modes—Boolean/Phrase	497
S15	"fracture risk scale*"	Limiters—Published Date: 20,180,701–20,210,731; Human Expanders—Apply related words; Apply equivalent subjects Search modes—Boolean/Phrase	1
S14	S8 AND S13	Limiters—Published Date: 20,180,701–20,210,731; Human Expanders—Apply related words; Apply equivalent subjects Search modes—Boolean/Phrase	497
S13	S9 OR S10 OR S11 OR S12	Expanders—Apply related words; Apply equivalent subjects Search modes—Boolean/Phrase	33,588
S12	(MH "Hip Fractures")	Expanders—Apply related words; Apply equivalent subjects Search modes—Boolean/Phrase	10,843
S11	"fragility fracture*"	Expanders—Apply related words; Apply equivalent subjects Search modes—Boolean/Phrase	1,400
S10	(MH "Osteoporotic Fractures")	Expanders—Apply related words; Apply equivalent subjects Search modes—Boolean/Phrase	629
S9	(MH "Osteoporosis+")	Expanders—Apply related words; Apply equivalent subjects Search modes—Boolean/Phrase	23,589
S8	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7	Expanders—Apply related words; Apply equivalent subjects Search modes—Boolean/Phrase	124,629
S7	"risk assessment"	Expanders—Apply related words; Apply equivalent subjects Search modes—Boolean/Phrase	124,231
S6	(MH "Risk Assessment")	Expanders—Apply related words; Apply equivalent subjects Search modes—Boolean/Phrase	116,820
S5	"fracture risk assessment*"	Expanders—Apply related words; Apply equivalent subjects Search modes—Boolean/Phrase	376
S4	"caroc"	Expanders—Apply related words; Apply equivalent subjects Search modes—Boolean/Phrase	6
S3	"qfracture"	Expanders—Apply related words; Apply equivalent subjects Search modes—Boolean/Phrase	17
S2	"garvan"	Expanders—Apply related words; Apply equivalent subjects Search modes—Boolean/Phrase	199
S1	"frax"	Expanders—Apply related words; Apply equivalent subjects Search modes—Boolean/Phrase	523

Appendix 2. PEDro Scales completed for the RCT studies

PEDro Criteria	LaCroix, 2005	Shepstone, 2017	Rubin, 2017	Merlijn, 2019
1. Eligibility criteria were specified	✓	✓	✓	✓
2. Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	1	1	1	1
3. Allocation was concealed	0	0	0	0
4. The groups were similar at baseline regarding the most important prognostic indicators	0	1	1	1
5. There was blinding of all subjects	1	0	0	0

PEDro Criteria	LaCroix, 2005	Shepstone, 2017	Rubin, 2017	Merlijn, 2019
6. There was blinding of all therapists who administered the therapy	0	0	0	0
7. There was blinding of all assessors who measured at least one key outcome	0	0	0	1
8. Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	1	1	0	1
9. All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analyzed by "intention to treat"	1	1	1	1
10. The results of between-group statistical comparisons are reported for at least one key outcome	1	1	1	1
11. The study provides both point measures and measures of variability for at least one key outcome	0	1	1	1
Overall PEDro Score	5/10	6/10	5/10	7/10

Appendix 3. CASP tool for qualitative studies

CASP tool	Dunniway,2010	Rothman,2014
Section A: Are the results valid		
1. Was there a clear statement of the aims of the research?	Yes	Yes
2. Is a qualitative methodology appropriate	Yes	Yes
3. Was the research design appropriate to address the aims of the research?	Yes	Yes
4. Was the recruitment strategy appropriate to the aims of the research?	Yes	Yes
5. Was the data collected in a way that addressed the research issue?	Yes	Yes
6. Has the relationship between researcher and participants been adequately considered	No	Unclear
Section B: What are the results?		
7. Have ethical issues been taken into consideration?	Unclear	Yes
8. Was the data analysis sufficiently rigorous?	Yes	Yes
9. Is there a clear statement of findings?	Yes	Yes
Section C: Will the results help locally?		
10. How valuable is the research	Page 7	Page 8

Appendix 4. CHEERS for economical evaluations

CHEERS 2022 Checklist			Studies							
Item #	Items	Guidance for Reposting	Nayak, 2011	Kingkaew, 2011	Ito,2015	Walter, 2017	Soini, 2018	Su, 2018	Martin-Sanchez, 2019	Chandra, 2020
1	Title	Identify the study as an economic evaluation and specify the interventions being compared	Reported	Reported	Reported	Reported	Reported	Reported	Reported	Reported
2	Abstract	Provide a structured summary that highlights context, key methods, results, and alternative analyses	Reported	Reported	Reported	Reported	Reported	Reported	Reported	Reported
3	Background and objectives	Give the context for the study, the study question, and its practical relevance for decision-making in policy or practice	Reported	Reported	Reported	Reported	Reported	Reported	Reported	Reported
4	Health economic analysis plan	Indicate whether a health economic analysis plan was developed and where available	Not Reported	Not Reported	Not Reported	Reported	Reported	Not Reported	Not Reported	Not Reported
5	Study population	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics)	Reported	Reported	Reported	Reported	Reported	Reported	Reported	Reported
6	Setting and location	Provide relevant contextual information that may influence findings	Reported	Reported	Reported	Reported	Reported	Reported	Reported	Reported
7	Comparators	Describe the interventions or strategies being compared and why chosen	Reported	Reported	Reported	Reported	Reported	Reported	Reported	Reported
8	Perspective	State the perspective(s) adopted by the study and why chosen	Reported	Reported	Reported	Reported	Reported	Reported	Reported	Reported
9	Time horizon	State the time horizon for the study and why appropriate	Reported	Reported	Reported	Reported	Reported	Reported	Reported	Reported
10	Discount rate	Report the discount rate(s) and reason chosen	Reported	Reported	Reported	Reported	Reported	Not Reported	Reported	Reported
11	Selection of outcomes	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s)	Reported	Reported	Reported	Reported	Reported	Reported	Reported	Reported
12	Measurement of outcomes	Describe how outcomes used to capture benefit(s) and harm(s) were measured	Reported	Reported	Reported	Reported	Reported	Reported	Reported	Reported
13	Valuation of outcomes	Describe the population and methods used to measure and value outcomes	Reported	Reported	Reported	Reported	Reported	Reported	Reported	Reported
14	Measurement and valuation of resources and costs	Describe how costs were valued	Reported	Reported	Reported	Reported	Reported	Reported	Reported	Reported
15	Currency, price date, and conversion	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion	Reported	Reported	Reported	Reported	Reported	Not Reported	Reported	Reported
16	Rationale and description of model	If modeling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed	Reported	Reported	Reported	Reported	Reported	Reported	Reported	Reported

CHEERS 2022 Checklist			Studies							
Item #	Items	Guidance for Reposting	Nayak, 2011	Kingkaew, 2011	Ito,2015	Walter, 2017	Soini, 2018	Su, 2018	Martin-Sanchez, 2019	Chandra, 2020
17	Analytics and assumptions	Describe any methods for analyzing or statistically transforming data, any extrapolation methods, and approaches for validating any model used	Reported	Reported	Reported	Reported	Reported	Reported	Reported	Reported
18	Characterizing heterogeneity	Describe any methods used for estimating how the results of the study vary for sub-groups	Reported	Not Reported	Not Reported	Not Reported	Not Reported	Reported	Reported	Reported
19	Characterizing distributional effects	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations	Reported	Not Reported	Not Reported	Reported	Not Reported	Reported	Reported	Reported
20	Characterizing uncertainty	Describe methods to characterize any sources of uncertainty in the analysis	Reported	Reported	Reported	Reported	Reported	Reported	Reported	Reported
21	Approach to engagement with patients and others affected by the study	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (e.g., clinicians or payers) in the design of the study	Not Reported	Reported	Not Reported	Not Reported	Not Reported	Not Reported	Reported	Not Reported
22	Study parameters	Report all analytic inputs (e.g., values, ranges, references) including uncertainty or distributional assumptions	Reported	Reported	Reported	Reported	Reported	Reported	Reported	Reported
23	Summary of main results	Report the mean values for the main categories of costs and outcomes of interest and summarize them in the most appropriate overall measure	Reported	Reported	Reported	Reported	Reported	Reported	Reported	Reported
24	Effect of uncertainty	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable	Reported	Reported	Reported	Reported	Reported	Reported	Reported	Reported
25	Effect of engagement with patients and others affected by the study	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	Not Reported	Not Reported	Not Reported	Not Reported	Not Reported	Not Reported	Not Reported	Not Reported
26	Study findings, limitations, generalizability, and current knowledge	Report key findings, limitations, ethical or equity considerations not captured, and how these could impact patients, policy, or practice	Reported	Reported	Reported	Reported	Reported	Reported	Reported	Reported
27	Source of funding	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	Reported	Reported	Not Reported	Reported	Reported	Reported	Reported	Reported
28	Conflicts of interest	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements	Reported	Reported	Reported	Reported	Reported	Reported	Reported	Reported

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Declarations

Ethical approval Not applicable

Conflicts of interest None.

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