The Relationship Between Fragility Fractures and Pain Experience: A Systematic Review

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Purpose: This systematic review is conducted to explore the relationship between fragility fractures and pain experience.

Methods: We searched for relevant studies on Pubmed, Embase, Web of Science, and the Cochrane library without restrictions on language from inception until February 4th, 2021. The risk of bias and methodological quality was evaluated using the Newcastle-Ottawa Scale and ROBINS-I tool.

Results: Twenty-one studies were included in this systematic review. The so-called study reported participants with continuous post-fracture pain. The included studies showed that post-fractured pain can decrease with time, however, the continual pain can last at least 1 year even longer, and some participants would need to self-manage pain. Moreover, the limited range of motion was considered as a factor that might distress the normal development of daily activities.

Conclusions: The current evidence could not fully support that pain continues to influence patients’ lives after a fragility fracture. However, it still showed the pain might come with fracture. The findings also could be useful to help health care providers better recognize and manage this clinical consequence of fractures. Nonetheless, future large-scale longitudinal studies will be required to evaluate the long-term effects of pain in fragility fractures.

Keywords: fragility fracture, pain, systematic review, fracture, discomfort

INTRODUCTION

The World Health Organization located osteoporosis at the primary health care level, reporting that "a fracture caused by injury that would be insufficient to fracture a normal bone...the result of reduced compressive and/or torsional strength of bone" (1). From a clinical perspective, fragility fractures are considered as skeletal complications, leading to substantial morbidity, longer hospitalization period, higher health care costs, poorest quality of life, more severe disabilities, and death (2). Different fracture locations may as well involve diverse symptoms across time. Hip fractures are conceived as the most serious kind; with a 1-year mortality rate of 21% for women and 31% for men (3). Other kind of fragility-related fractures at other anatomical locations has been related with lower quality conditions of life, although most studies tend to focus on the impacts of the hip or the vertebral fractures (4).
While significant improvements have been achieved—both in surgical procedures and treatment tools—in this area, current information on incidences, risk factors, and medical costs of pain appears to be highly restricted. Currently, pain assessment and relief for patients with fragility fractures before and after surgery are placed as crucial topics for research. Besides, as surgical indications tend to be a direct procedure for most patients suffering from this kind of fragility fracture and adequate anesthesia is the basis for these successful so-called surgical procedures, there is still room for improvement in various anesthesia and sedation techniques. A part of the patients with fragility fractures, however, show surgical contraindications or prefer conservative treatment; in this kind of situation it becomes, indeed, highly significant to use methods to help to relieve this related discomfort, reduce the risk of adverse effects and improve the overall quality of life, accurate diagnosis and efficient pain eradication.

The purpose of this study was to assess the relationship between fragility fractures and pain experience. The results from this systematic review could further understand the fragility of fractures related to pain and guide health care to address the issues which matter to such patients.

**MATERIALS AND METHODS**

The methodology was written based on several studies published (5–7).

**Literature Review**

The Pubmed, Embase, Web of Science, and the Cochrane library for relevant studies without language limitations were used from inception until February 04, 2021. These databases included most of the academic research articles on this topic. The searched eligible studies were identified by scanning electronic databases using various combinations of Medical Subject Headings (MeSH) and non-MeSH terms.

**Data Sources and Search Methods**

The search process was extended by (1) perusing the reference section of all relevant studies, and (2) manually searching through the abstracts of key journals and articles published at major annual meetings. The review's population, intervention, comparison, outcome (PICO) items defined the search strategy: Population: all population, Intervention: fracture, Comparison: not applicable; Outcome: Pain. The search terms included all field and the following: (fragility OR fracture OR low traumatic) AND (fracture OR break OR split OR crack) AND (Pain OR Long-term pain OR Painful OR suffer OR discomfort OR hurt OR irritation OR tenderness OR soreness OR Fracture-related limitations OR disability Or disabled). Table 1 shows the search strategy of databases.

**Data Extraction and Quality Assessment**

A data extraction form was used to obtain the following data from the included studies: first author (publication year), country, study duration, study subjects, age of study subjects, sex, assigned

### Table 1 | Search strategy in Pubmed up till February 4th, 2021.

| Pubmed N | Cochrane N |
|----------|------------|
| #1 fragility [all field] 19,914 | #1 fragility [all field] 1,454 |
| #2 fragile [all field] 22,727 | #2 fragile [all field] 376 |
| #3 low traumatic [all field] 12,625 | #3 low traumatic [all field] 2,223 |
| #4 #1 OR #2 OR #3 53,368 | #4 #1 OR #2 OR #3 4,313 |
| #5 fracture [all field] 322,337 | #5 fracture [all field] 18,713 |
| #6 break [all field] 119,498 | #6 break [all field] 4,066 |
| #7 split [all field] 102,207 | #7 split [all field] 10,282 |
| #8 crack [all field] 20,423 | #8 crack [all field] 390 |
| #9 #5 OR #6 OR #7 OR #8 554,762 | #9 #5 OR #6 OR #7 OR #8 32,832 |
| #10 Pain [all field] 869,082 | #10 Pain [all field] 191,678 |
| #11 Long-term pain [all field] 45,413 | #11 Long-term pain [all field] 13,367 |
| #12 Painful [all field] 900,316 | #12 Painful [all field] 12,200 |
| #13 Suffer [all field] 1,307,321 | #13 Suffer [all field] 7,294 |
| #14 discomfort [all field] 48,254 | #14 discomfort [all field] 16,901 |
| #15 hurt [all field] 4,865 | #15 hurt [all field] 779 |
| #16 irritation [all field] 52,785 | #16 irritation [all field] 16,901 |
| #17 tenderness [all field] 24,481 | #17 tenderness [all field] 16,901 |
| #18 soreness [all field] 3,526 | #18 soreness [all field] 3,526 |
| #19 Fracture-related limitations [all field] 85 | #19 Fracture-related limitations [all field] 85 |
| #20 disability [all field] 374,533 | #20 disability [all field] 374,533 |
| #21 disabled [all field] 374,533 | #21 disabled [all field] 374,533 |
| #22 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 1,740,707 | #22 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 1,740,707 |
| #23 #4 AND #9 AND #22 1,479 | #23 #4 AND #9 AND #22 745 |

(Continued)
TABLE 1 | Continued

| Embase                        | N     |
|-------------------------------|-------|
| #1 fragility [all field]      | 41,107|
| #2 fragile [all field]        | 29,990|
| #3 low traumatic [all field]  | 144   |
| #4 #1 OR #2 OR #3             | 69,324|
| #5 fracture [all field]       | 396,777|
| #6 break [all field]          | 72,142|
| #7 split [all field]          | 91,222|
| #8 crack [all field]          | 9,824 |
| #9 #5 OR #6 OR #7 OR #8       | 563,937|
| #10 Pain [all field]          | 1,378,467|
| #11 Long-term pain [all field]| 1,777 |
| #12 Painful [all field]       | 90,626|
| #13 Suffer [all field]        | 98,951|
| #14 discomfort [all field]    | 84,393|
| #15 hurt [all field]          | 6,051 |
| #16 irritation [all field]    | 48,794|
| #17 tenderness [all field]    | 37,726|
| #18 soreness [all field]      | 4,539 |
| #19 Fracture-related limitations [all field] | 1 |
| #20 disability [all field]    | 334,924|
| #21 disabled [all field]      | 60,695|
| #22 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 | 1,916,555|
| #23 #4 AND #9 AND #22         | 4,262 |

| Web of Science                | N     |
|-------------------------------|-------|
| #1 fragility [all field]      | 27,390|
| #2 fragile [all field]        | 40,871|
| #3 low traumatic [all field]  | 24,839|
| #4 #1 OR #2 OR #3             | 91,094|
| #5 fracture [all field]       | 509,008|
| #6 break [all field]          | 407,261|
| #7 split [all field]          | 287,946|
| #8 crack [all field]          | 261,946|
| #9 #5 OR #6 OR #7 OR #8       | 1,351,490|
| #10 Pain [all field]          | 708,471|
| #11 Long-term pain [all field]| 42,587|
| #12 Painful [all field]       | 96,902|
| #13 Suffer [all field]        | 98,951|
| #14 discomfort [all field]    | 84,393|
| #15 hurt [all field]          | 6,051 |
| #16 irritation [all field]    | 48,794|
| #17 tenderness [all field]    | 37,726|
| #18 soreness [all field]      | 4,539 |
| #19 Fracture-related limitations [all field] | 1 |
| #20 disability [all field]    | 334,924|
| #21 disabled [all field]      | 60,695|
| #22 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 | 1,916,555|
| #23 #4 AND #9 AND #22         | 4,262 |

Data Synthesis

The outcomes of the selected studies were assessed focusing on various measurements.

Follow by characteristics of outcome measurement:

1. Von Kroff questionnaire (which points both pain intensity score and disability score): It was developed in order to grade the severity of chronic pain (8).
2. EQ-5D (pain/discomfort): It is a standardized tool used to assess general health problems, which covers 5 main domains such as mobility, self-care, daily activities, pain/discomfort, and anxiety/depression (9). Thoughout this present research, only domains related to pain/discomfort will be discussed.
3. Numeric rating scale (NRS): Which displays results verabally reported by patients. The scale ranges from 0 (no pain) to 10 (worst imaginable pain) (10).
4. Visual Analog Scale (VAS, 0–10): Scale used in order to quantify a trait or attitude that is assumed to extend across a spectrum of values and cannot be directly measured easily. It is also used to measure the severity or frequency of different symptoms through epidemiological and clinical research (10).
5. SF-36 (pain/discomfort), which consists of an eight scaled score, containing weighted sums of questions (0–100). The eight sections are: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health (10).
6. The Quality of Life Questionnaire (QUALEFFO-41; pain domain): To investigate about the improvements in the quality of life associated to day-to-day living, general well-being, and specific well-being of patients who have had any kind of the vertebral fractures named by International Osteoporosis Foundation (IOF) (11).
7. Geriatric Pain Scale (GPS, 0–100): Used to classify pain in patients and to assess physical, mental, cognitive, and behavioral responses to pain (12).
FIGURE 1 | Prisma study flow chart.
8. Pain Regulation Questionnaire (PRQ) which includes competences, intensity, anxiety, depression, avoidance, withdrawal and distraction of pain (13).

9. The amounts of individuals reporting pain.

The ROBIS tool was applied to assess the risk of bias in this systematic review. This tool consists of three phases; and this systematic review more specifically evaluated phase 2 and phase 3. During phase 2 there were four aspects evaluated: study eligibility criteria, identification and selection of studies, data collection and study appraisal, and synthesis and findings. Moreover, phase 3 integrated the overall risk from phase 2 (14).

**Statistical Analysis**

The tool Review Manager 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, 2014) was used in this study. We presented the risk of pain as OR with 95% CI and assessed heterogeneity by using the $I^2$ statistic. The $I^2$ statistic is used to evaluate the degree of variation across studies due to heterogeneity rather than by chance alone (15).

**RESULTS**

**Study Characteristics**

Figure 1 illustrates the results of this systematic review. From all the databases we searched in, with 8,250 records collected and after removing 1,803 duplicate articles, there was a total of 1,162 records which were excluded due to is protocol or other conference abstracts. Five thousand two hundred sixty-four full-text articles were also excluded for reasons such as irrelevancy of the topic, incapability to find the related text, differences on the purposes on the study design, conferences abstracts, or fracture-pain related articles with drugs/treatment. Finally, following a thorough review of all candidate papers, we identified a total of 21 studies that addressed the relationship between fragility fractures and pain experience.

**Fragility Fracture and Pain Experience**

**Assessment of Pain and Disability**

In Chou et al. (16), Jung et al. (17), and Ross et al. (18) fracture group showed a higher frequency on reported pain. However, Zetterberg et al. (19) indicated a different tendency from the other 3 studies. Figure 2 displays that pain was not significantly associated with fracture than the control group. Figure 3 specifies that pain was not related to the fracture group ($p = 0.75$). Among the 21 included studies, there were 8 which investigated the risk for fragility fracture and pain in postmenopausal females and 3 in the elderly, due to its higher vulnerability.

Apart from the above mentioned studies, other studies that were also utilized used different measurements to illustrate pain and disability. Table 2 demonstrated some characteristics of the included studies. Firstly, Jin et al. (27), Hallal (25), and Kapucu and Unver (29) classified similar pain grades as *Slight, Mild, Moderate, Severe, Extreme*. However, we were not able to synthesize the data together, owing to the fact that the data classification was not standardized. Secondly, the duration of the presence of pain was delved in researches of authors as Jin et al. (27), Hallal (25), and Ozdemir et al. (31). Jin et al. (27) research indicated that pain would continue for $<2$, 2–8, $\geq 8$ week, respectively, 183 (51.1%), 116 (32.4%), 59 (16.5%). In Hallal (25), pain could be sever hour: 40 (47.6%), 1 day:11 (13.1%), several days: 11 (13.1%), several weeks: 4 (4.8%), constantly:
## TABLE 2 | Characteristics of included studies.

| References          | Country     | Duration                  | Participants          | Female/male | Age(year) | Outcome (20, 21)                           | NOS score* |
|---------------------|-------------|---------------------------|-----------------------|-------------|-----------|--------------------------------------------|------------|
| Briem et al. (13)   | Germany     | Average follow-up of 5.3 ± 1.7 years after injury Range 3–8 | Thoracolumbar fracture group = 85; control = 584 | Thoracolumbar fracture group- Mean ± SD: 47.8 ± 12.8 Range 25-65 control: N/A | Thoracolumbar fracture vs. control group (Mean ± SD) *SF-36 questionnaire -pain domain 65.78 ± 2.87 vs. 78.90 ± 8.87 (p < 0.05) *Pain Regulation Questionnaire (PRQ) Pain competence: 41.40 ± 1.12 vs. 36.98 ± 8.41 (p < 0.001) Pain intensity: 23.84 ± 1.30 vs. 29.55 ± 8.62 (p < 0.001) Pain anxiety: 26.63 ± 11.59 vs. 31.90 ± 8.58 (p < 0.001) Pain depression: 21.15 ± 1.27 vs. 25.33 ± 9.60 (p < 0.001) Pain avoidance: 25.72 ± 0.94 vs. 25.38 ± 8.10 Pain withdrawal: 24.93 ± 1.23 vs. 28.90 ± 10.90 (p < 0.001) Pain distraction: 33.29 ± 1.03 vs. 32.37 ± 8.21 | S*** C** O*** |
| Chou et al. (16)    | Taiwan      | Oct. 2002–Mar. 2003       | 24,435                | 11,937/12,498 Over 20 years | 1. 2,912 participants with osteoporosis, 1,416 reported low back pain (p < 0.001). 2. Osteoporosis vs. non-osteoporosis, with low back pain OR = 2.55 (95% CI = 2.33–2.78); with frequent low back pain OR = 4.15 (95% CI = 3.66–4.70). 3. Adjusted sociodemographic factors, ORs of associated osteoporosis or not for frequent low back pain in females and males were 3.49 (95% CI = 2.99–4.07) and 5.77 (95% CI = 4.66–7.15), respectively. | S**** C** O*** |
| Ciubean et al. (22) | Romania     | Jun. 2016–Aug. 2017       | 364 postmenopausal women | 364/0 Mean ± SD: Osteoporosis (n = 228): 65.5 ± 7.39 Control (n = 136): 63.45 ± 8.16 Range: 46–85 | *SF-36 questionnaire -pain domain [median (IQR)] 1. Osteoporosis vs. Control: 45 (45; 67.5) vs. 72.5 (55; 77.5) (p < 0.001) 2. Osteoporosis patients with fracture (n = 132) vs. without fracture (n = 96): 45 (45; 67.5) vs. 45 (35; 57.5) (p = 0.035) *QUALIFICO-41 -pain domain [median (IQR)] 1. Osteoporosis patients with fracture (n = 132) vs. without fracture (n = 96): 55 (30; 65) vs. 50 (30; 65) (p = 0.446) | S** C* O*** |
| Fechtenbaum et al. (23) | France   | –                         | 588 have osteoporosis | 588/0 Mean ± SD vertebral fracture (n = 548) vs. control group: 71.61 ± 5.01 vs. 71.90 ± 5.19 (p = 0.43) | QUALFICO scores- pain domain[0-100] patients with no fracture (n = 40): 60 patients with sum of grade of fracture is 1 or 2 (n = 133): 51 patients with sum of grade of fracture is 3 or 4 (n = 189): 58 patients with sum of grade of fracture is 5–9 (n = 146): 58 patients with sum of grade of fracture is ≥10 (n = 80): 55 Patients self-reported pain (Some gave more than one answer and horizontal aggregates of percentages are therefore >100) None (no infirmity): 31 (10.1%); foot (foot/leg/knee pain): 135 (44%); back (back pain): 96 (31.3%); hip (hip pain): 53 (17.3%) | S** C O** |
| Finsen (2-4)        | Norway      | –                         | 307 subjects age of 50 years | 222/85 Over 50 years | Patients reported pain (30 female,4 male). | S*** C* O*** |
| Gheorghita et al. (4) | Canada | At least 1 year           | 67                     | 55/12 Range: 47–89 | 34 participants reported pain (30 female,4 male). | S*** C O*** |
| Halil (25)          | USA         | –                         | 101 women with diagnosed postmenopausal osteoporosis | 101/0 Mean: 62.6 | 1. 84 participants reported the presence of back pain. 2. Frequency of back pain (daily: 33, weekly: 6, monthly: 20, less than once per month: 15) 3. Duration of back pain (sever hour: 40, 1 day: 11, several days:11, several weeks:4, constantly:18) 4. Severity of back pain (very: 14, moderately: 45, mildly: 25) | S** C* O** |

(Continued)
| References          | Country     | Duration            | Participants | Female/male | Age (year) | Outcome (20, 21)                                                                 | NOS score |
|---------------------|-------------|---------------------|--------------|-------------|------------|---------------------------------------------------------------------------------|-----------|
| Chen et al. (26)    | Austria     | Jun 2007–Jun. 2008  | 222          | 173/49      | Mean ± SD: total: 79.3 ± 8.5                                                    | S***      |
|                     |             |                     |              |             | Osteopenic patients: 3.2 ± 2.6                                                   | C**       |
|                     |             |                     |              |             | Osteoporotic patients without fracture history: 3.2 ± 2.5                       | O***      |
|                     |             |                     |              |             | Osteoporotic patients with fracture history: 3.9 ± 2.7 (p > 0.05)                |           |
| Jin et al. (27)     | China       | Nov. 1, 2016–Sep. 30, 2018 | 358          | 284/74      | Mean ± SD: 72.3 ± 9.4                                                            | S***      |
|                     |             |                     |              |             | 1. Pain duration, weeks (< 2: 183, 2–8: 116, 8≥59)                               | C**       |
|                     |             |                     |              |             | 2. Spinal palpation tenderness: 177                                              | O**       |
|                     |             |                     |              |             | 3. Axial spinal percussion pain: 83                                              |           |
|                     |             |                     |              |             | 4. Radiating pain: 76.5. Pain grades (mild: 17, moderate: 121, severe: 229)      |           |
| Jung et al. (17)    | Korea       | At least 6 month    | 196          | 165/31      | Mean ± SD: 72.7 ± 7.9                                                            | S***      |
|                     |             |                     |              |             | *EQ-5D (pain/discomfort domain)                                                  |           |
|                     |             |                     |              |             | 1. No problem-39 (19.9%); 1 some problems: 139 (70.9%); serious problems: 18 (9.2%) |           |
|                     |             |                     |              |             | 2. Age 50–59 (n = 13) vs. reference population 84.6 vs. 30.6% (P < 0.001)       |           |
|                     |             |                     |              |             | 3. Age ≥ 60 (n = 183) vs. Reference population 79.8 vs. 62.7% (P < 0.001)       |           |
| Kapucu and Ünver (29) | Turkey     | –                   | 105          | 105/0       | Mean: 74 ± 7.5                                                                   | S***      |
|                     |             |                     |              |             | 1. No problem-39 (19.9%); 1 some problems: 139 (70.9%); serious problems: 18 (9.2%) |           |
|                     |             |                     |              |             | 2. Age 50–59 (n = 13) vs. reference population 84.6 vs. 30.6% (P < 0.001)       |           |
|                     |             |                     |              |             | 3. Age ≥ 60 (n = 183) vs. Reference population 79.8 vs. 62.7% (P < 0.001)       |           |
| Miyakoshi et al. (30) | Japan      | –                   | 174          | 174/0       | Mean ± SD back pain (n = 159) vs. Non-back pain (n = 15); 67.8 ± 6.5 vs. 65.5 ± 7.0 (p = 0.18) | S**       |
|                     |             |                     |              |             | 1. 159 patients (91.4%) complained of back pain.                                | C*        |
|                     |             |                     |              |             | 2. Age 50–59 (n = 13) vs. reference population 84.6 vs. 30.6% (P < 0.001)       | O**       |
| Qzdemir et al. (31) | Turkey      | –                   | 909          | 909/0       | Mean: 60                                                                        | S***      |
|                     |             |                     |              |             | 1. 695 patients (76.45%) reported experiencing pain                             | C*        |
|                     |             |                     |              |             | 2. The duration of the presence of pain was 8.7 ± 5.27 year [Min:1, Max: 26]     | O**       |
| Ramírez-Pérez et al. (32) | Mexico | 6 month             | 136          | 95/41       | Mean ± SD: 77 ± 10                                                               | S**       |
|                     |             |                     |              |             | EQ-5D (pain/discomfort domain)                                                   | C**       |
|                     |             |                     |              |             | 1. 1st, 3rd, and 6th month patients report pain, respectively, 122 (89.7%), 92 (68%), 72 (52.9%) | O**       |
|                     |             |                     |              |             | 2. patients report pain, respectively, in level 1, 2, 3 1st month: 148.735; 6th month: 646.210 |           |
|                     |             |                     |              |             | level 1: indicating no problem; level 2: indicating some problems; level 3: indicating extreme problems |           |
| Ribom et al. (33)   | Sweden      | –                   | 36           | 36/0        | Mean ± SD: 74.6 ± 8.3                                                            | S**       |
|                     |             |                     |              |             | Numeric rating scale (NRS)                                                       | C*        |
|                     |             |                     |              |             | 1. Maximum pain: Mean ± SD: 5.9 ± 1.8; median: 6; range: 2–8 2. Minimum pain: Mean ± SD: 1.9 ± 2.5; median: 2; range: 0–8 | O***      |
|                     |             |                     |              |             | 3. Average pain: Mean ± SD: 4.8 ± 2.1; median: 5; range: 0–8                    |           |
| Ross et al. (18)    | USA         | Each of ~1.5 years duration | 1,098        | 1,098/0     | Mean: 63.3                                                                      | S***      |
|                     |             |                     |              |             | 1. 200 of these women had responded to questions about back pain, the number who reported increased frequency of back pain after the fracture was 16 (46%) of 35 subjects with new vertebral fractures, 1 (10%) of 10 subjects with prevalent fractures only, and 21 (14%) of 155 subjects without vertebral fractures. | C*        |

(Continued)
TABLE 2 | Continued

| References | Country | Duration       | Participants | Female/male | Age(year) | Outcome (20, 21) | NOS scorea |
|------------|---------|----------------|--------------|-------------|-----------|------------------|-------------|
| Sale et al. (34) | Canada | 6 month | 21 who had sustained fractures | 16/5 | Range: 51–87 | 2. Incidence of increased frequency of back pain vs. without vertebral fractures. Incident fractures: OR = 6.4 (95% CI: 2.6–15.6); p < 0.05. Prevalent fractures OR = 1.7 (95% CI: 0.5–6.8); p > 0.05. *The most examination (n = 203). 1. 28.1% reported some frequency of back pain since their previous visit. 2. Among the subjects with and without incident vertebral fractures (n = 45 and 158), the proportions reporting some frequency of back pain were 53 and 21%, respectively. O** |
| Scaturro et al. (35) | Italy | Jan. 2016–Jan. 2018 | 513 post-menopausal women over 50, having back pain for at least 3 months, not responding to conservative treatment, with NRS between 2 and 4 (mild pain) and SF 36 between 60 and 100. | 513/0 | Mean: 72 | Numeric rating scale (NRS) 1. 77.5% (n = 165) of patients reported an NRS rate between 2 and 3 (first group) and 22.5% (n = 48) a rate of 4 (second group). 2. The correlation between the pain (NRS) and the number of vertebral fragility fractures (P < 0.001). S*** C* O*** |
| Suzuki et al. (36) | Sweden | A year (Dec. 2003–Nov. 2006) | 107 | 72/35 | Mean ± SD: 75.5 ± 11.9 Range: 42–96 | “Von Korff Pain Intensity score(0–100) 70.9 ± 19.3 (3 weeks), 61.5 ± 21.4 (3 months), 60.7 ± 21.6 (6 months), 60.5 ± 23.0 (12 months); “Von Korff Disability score (0–100) disability means scored 68.9 ± 23.6 (3 weeks), 56.4 ± 25.5 (3 months), 51.0 ± 27.5 (6 months), 53.9 ± 27.8 (12 months) (P < 0.001). *EQ-5D 1. Total score: 0.37 ± 0.37 (3 week), 0.52 ± 0.35 (3 months), 0.54 ± 0.36 (6 months), 0.52 ± 0.38 (12 month) (p < 0.001). 2. The number of patients reporting moderate or severe problems in pain/discomfort domain 97% (3 week), 89% (3 months), 87% (6 months), 89%(12 month) (p < 0.001). S** C* O*** |
| Tulay et al. (37) | Turkey | Jan.-Dec. 2016 | 172 with rib fracture | 66/106 | Median: 47 Range: 18–85 | Numeric rating scale (NRS) (0–10) 1. At 15th days, 3rd month, 6th month, the pain level of <65 yr participants were significant lower than ≥65 yrs group. 2. At 15th days, 3rd month, 6th month, the pain level of < female were significant higher than ≥ male. 3. Patients have 2 rib fractures with significant higher pain level than who has only one fracture. S** C* O*** |

(Continued)
TABLE 2 | Continued

| References          | Country       | Duration | Participants | Female/male | Age (year) | Outcome | NOS score |
|---------------------|---------------|----------|--------------|-------------|------------|---------|-----------|
| Zetterberg et al.   | Sweden        | 1 year   | Hip fracture patients: 868 (final was 840 patients) | Control group: 2,251 | Hip fracture patients mean | Back pain during last 10 years | NOS score: Hip fracture patients: 623/245  |
|                     |               |          | Female: 79.0 | Male: 73.9  | 1. Female (P < 0.001) Hip fracture patients: 23% (n = 143) vs. Control group: 45% (n = 600) | 2. Male (P < 0.001) Hip fracture patients: 20% (n = 49) vs. Control group: 48% (n = 441) | 2 |
|                     |               |          |              |             |            |         | Scale domains: S selection of study groups, C comparability, O outcome assessment. Each "*" counts one point in different domain. |

Self-Reported Pain

In 10 studies have patients self-reported pain (4, 16, 18, 23–25, 27, 30, 31, 34). Chou et al. (16) study had 2,912 participants from which 1,416 reported some kind of low back pain (48.6%, p < 0.001). Fichtenbaum et al. (23) 548 of 588 reported pain problems. Finsen (24) could report 276 cases of pain out of 307 subjects who had any kind of fracture, among the 307 participants who reported pain, the different body parts affected would be seen as followed, foot (foot/leg/knee pain): 135 (44%); back (back pain): 96 (31.3%); hip (hip pain): 53 (17.3%).

Risk of Bias Assessments

Twenty-one of the included studies were rated on the NOS scale, where the higher the score rated the better quality it would proof (see Table 2), a total of 7 were rated as “high quality,” and none of the included studies was rated as “low quality.” Also, ROBINS-I was used to evaluate the risk of bias throughout the
| References                        | Type of research | Pre-intervention | At intervention bias in classification of intervention | Post-intervention | Total bias |
|----------------------------------|------------------|------------------|-------------------------------------------------------|-------------------|------------|
| Briem et al. (13)                | Retrospective    | Low              | Low                                                   | Low               | Low        |
| Chou et al. (16)                 | Cross-sectional  | Low              | Low                                                   | Low               | Low        |
| Ciubean et al. (22)              | Cross-sectional  | Low              | Low                                                   | Low               | Low        |
| Fechtenbaum et al. (23)          | Prospective      | Low              | Low                                                   | Low               | Low        |
| Finsen (24)                      | Quantitative cohort | Low            | Low                                                   | Low               | Low        |
| Gheorghita et al. (4)            | Qualitative cohort | Low            | Low                                                   | Low               | Low        |
| Hallal (25)                      | Prospective      | Low              | Low                                                   | Low               | Low        |
| Jahelka et al. (26)              | Prospective      | Low              | Low                                                   | Low               | Low        |
| Jin et al. (27)                  | Prospective      | Low              | Low                                                   | Low               | Low        |
| Jung et al. (17)                 | Ambispective     | Low              | Low                                                   | Low               | Low        |
| Kapucu and Ünver (29)            | Descriptive      | Low              | Low                                                   | Low               | Low        |
| Miyakoshi et al. (30)            | Observational    | Low              | Low                                                   | Low               | Low        |
| Qzdemir et al. (31)              | Retrospective    | Low              | Low                                                   | Low               | Low        |
| Ramirez-Pérez et al. (32)        | Prospective      | Low              | Low                                                   | Low               | Low        |
| Ribom et al. (33)                | Prospective      | Low              | Low                                                   | Low               | Low        |
| Ross et al. (19)                 | Cross-sectional  | Low              | Low                                                   | Low               | Low        |
| Sale et al. (34)                 | Qualitative cohort | Low            | Low                                                   | Low               | Low        |
| Scaturro et al. (35)             | Observational    | Low              | Low                                                   | Low               | Low        |
| Suzuki et al. (36)               | Prospective cohort | Low            | Low                                                   | Low               | Low        |
| Tulay et al. (37)                | Prospective      | Low              | Low                                                   | Low               | Low        |
| Zetterberg et al. (19)           | Prospective      | Low              | Low                                                   | Low               | Low        |
study (Table 3). Six articles were evaluated as “moderate risk” and 1 as “high risk” to have bias. Due to the small number of papers and the degree of heterogeneity in study designs, interventions, and outcome indices, the meta-analysis was not considered fully appropriate.

The Result Summary of ROBIS
A summary of the findings and the ROBIS assessment for each domain can be seen in Table 4. In phase 2, study eligibility criteria, identification and selection of studies, data collection, and study appraisal were rated as “low risk.” Due to the fact that the used studies included different assessments, synthesis, and findings, the domain was rated as “high risk.” Throughout phase 3, the overall risk of bias was rated “low risk.”

**DISCUSSION**

**Clinical Implications**
To the best of our knowledge, we comprehend this study to be the first systematic review and meta-analysis to examine the impacts of pain among the fragility fracture population. Our study results support the hypothesis that frail patients with fractures were suffering from a continuous risk of pain, and as this further exceeded the typical length of time assumed essential for curing and resolution of pain. Also, our results also provide more clear evidence related to patients undergoing fragility fracture may experience significant long-term pain effects.

The trajectories of frailty degrees in the elder population could vary substantially, particularly when estimating the short- or long-term treatment effect, personal lifestyle change, related comorbidity development, and severe disease progression (38). Exploring the frailty transition chronologically would help clinicians to obtain a further knowledge related to the effects modifications of frailty and a better estimate on future fracture risk. Previous studies indicated that due to changes in the spine shape and height loss, patients may experience uninterrupted back pain even after the acutely painful episode subsides after a vertebral fracture (4, 39). Wrist fractures also have been projected to be able to recover after 6 weeks’ post-fracture (40). However, another study showed one physiological cycle of bone which would remodel in healthy adults, lasting from 4 to 6 months (41). Risk fracture is a most frequent feature on the Complex regional pain syndrome(CRPS) (42). Patients with hip fractures often presented comorbidities and cognitive impairment that frequently prevented their recovery (43).

To examine the relationship between fragility fracture and pain, our study included only observational studies. Ordinary meta-analyses on the efficacy of interventions merely obtained high-quality evidence from randomized controlled trials (6). However, randomized controlled trials are often not the best source of evidence for harm due to the study duration is often too short to detect long-term or rare adverse events (44, 45). In addition, it is not possible to randomize patients into the categories “with fragility fracture” or “without fragility fracture.” Including observational studies in this systematic review was a strong point, as these studies could indicate the effect of short-term and long-term pain in the fragility fracture population.

**Clinical Practice**
This systematic review found that there is an influence of pain following fragility fracture. Based on the results, medical teams should develop the treatment and rehabilitation protocol to prevent or reduce the pain of post-fracture, and the protocol should include meditation, exercises, and integrated physical treatment. Some consideration about the role of painkillers as well as anti-osteoporosis drugs for pain relief in fragility fracture patients should be provided (46–48). For better pain improvement, the program should be continuous, progressive, and combined alternative strategies.

**Methodological Considerations**
From the methodological viewpoint, our study included several limitations. Firstly, based on the current information, we could not assess the fluctuating frailty status concerning the risk of fragility fracture. Secondly, due to the number of selected studies that could be quantified, it was not sufficient. Due to the various measurements, it was difficult to conduct a meta-analysis with enough sample sizes. Finally, when we used the ROBIS approach to assess the quality of the evidence for the systematic review, the evidence from all the included observational studies was initially rated as relatively low quality because of imprecision. The addition of more studies in the future may increase the quality of evidence.

**Conclusions**
The current evidence could not fully support that pain continues to influence patients’ lives after a fragility fracture. However, it still exposed the pain might come with fracture. The findings also could be useful to help health care providers to better recognize and manage this clinical consequence of fractures. We
recommend research on a wider range of populations to provide more comprehensive and accurate findings.

**DATA AVAILABILITY STATEMENT**

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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