REVIEW



Risk factors for benign paroxysmal positional vertigo recurrence: a systematic review and meta-analysis

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Abstract

Background and purpose Benign paroxysmal positional vertigo is one of the most common vestibular diseases, especially in the elderly. Although the treatment of BPPV is relatively successful, many patients suffer recurrence after treatment. Therefore, identifying potential risk factors for BPPV recurrence may help improve treatment outcome and patient prognosis. However, some related risk factors for BPPV recurrence are relatively controversial and poorly studied. This meta-analysis aims to identify potential risk factors associated with BPPV recurrence, thereby reducing the recurrence rate of BPPV and improving the prognosis of patients.

Methods This meta-analysis was conducted through systematically searching PubMed, Embase, and the Cochrane Library for eligible English original studies published up to June 2020. All search results were reviewed based on our inclusion and exclusion criteria. We calculated the pooled odds ratios (ORs) or the mean differences (MDs) with their corresponding 95% confidence intervals (CIs) to evaluate the effects of included risk factors on BPPV recurrence.

Results A total of 14 studies involving 3060 BPPV patients published between 2010 and 2019 were finally included, including six prospective studies and eight retrospective studies, with a NOS score ranged from 6 to 9. Our pooled results of this meta-analysis suggested that the recurrence of BPPV was closely related to female gender (OR = 1.42; 95% CI 1.17–1.74; P = 0.0004), hypertension (OR = 2.61; 95% CI 1.22–5.59; P = 0.01), diabetes mellitus (OR = 2.62; 95% CI 1.25–5.48; P = 0.01), hyperlipidemia (OR = 1.60; 95% CI 1.23–2.09; P = 0.0006), osteoporosis (OR = 1.72; 95% CI 1.03–2.88; P = 0.04) and vitamin D deficiency (MD = -3.29; 95% CI -5.32 to -1.26; P = 0.001).

Conclusion This meta-analysis indicated that female gender, hypertension, diabetes mellitus, hyperlipidemia, osteoporosis, and vitamin D deficiency were risk factors for BPPV recurrence. However, the effects of other potential risk factors including advanced age, migraine, head trauma, and Menière's disease on BPPV recurrence need further investigations. Furthermore, most studies included in this meta-analysis were performed in Asia, so our results cannot easily be extended to the whole world population. Therefore, more large-scale prospective studies in different countries are required to further investigate these risk factors.

Keywords Benign paroxysmal positional vertigo · Recurrence · Risk factors · Systematic review · Meta-analysis

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Introduction

Benign paroxysmal positional vertigo (BPPV) is one of the most common peripheral vestibular dysfunctions encountered in clinical practice, with a reported 1-year prevalence of 1.6% and a lifetime prevalence of 2.4% [1, 2]. BPPV is characterized by recurrent episodes of vertigo with corresponding nystagmus, generally provoked by changes in head position [3]. A 9-year follow-up nationwide study indicated that BPPV patients were more susceptible to future ischemic stroke [4]. Some studies also found that patients with BPPV were at increased risk of falls, fractures, hypertension and

dementia [4–6]. In addition, BPPV may cause physical and psychological distress during episodes of vertigo. Therefore, BPPV severely decreases patients' quality of life and impairs the performance of daily activities.

Currently, although canalith repositioning procedures (CRPs) are a relatively successful treatment for BPPV, many patients suffer recurrence after successful treatment, with a reported recurrence rate of approximately 50% during the 10-year follow-up [7]. The frequent recurrence of BPPV may cause great inconvenience in the daily life of BPPV patients. Therefore, identifying the underlying risk factors for BPPV recurrence is imperative for improving treatment outcome and preventing relapse. In addition, a recent metaanalysis suggested that many risk factors related to the recurrence of BPPV may also be risk factors for BPPV occurrence [8], such as hypertension and osteoporosis, which may help reduce the high incidence of BPPV [9, 10]. Recently, studies have shown that the recurrence rate of BPPV was affected by many risk factors, such as advanced age, head trauma, Menière's disease, vascular diseases, vitamin D deficiency, and osteoporosis [10-23]. However, some risk factors associated with the recurrence of BPPV in these studies are relatively controversial and poorly studied, which may be explained by the fact that risk factors for BPPV recurrence may depend on genetic variables which differ between different parts of the world.

Therefore, this meta-analysis was conducted to identify potential risk factors associated with BPPV recurrence, thereby improving the prognosis and treatment outcome of patients at high risk of recurrence.

Methods

This meta-analysis was performed in accordance with MOOSE guidelines for meta-analysis of observational studies and PRISMA guidelines [24].

Literature search strategy

Two reviewers (SL Zhang and K Cui) systematically and independently searched the literature published before June 2020 in PubMed, EMBASE, and the Cochrane Library for relevant original English literature studying risk factors for BPPV recurrence. We combined the MeSH terms 'Benign Paroxysmal Positional Vertigo', 'Recurrence' and all related free search terms to search potential articles. The detailed search strategy and process can be found in the supplemental file. In addition, reference list of each study included in this meta-analysis was also manually examined in detail to further identify other potentially eligible literature. Any differences in the literature search process were resolved through a full discussion with a third reviewer (JB Chen).

Inclusion and exclusion criteria

Titles and abstracts of all search results were screened first, and then the full text of eligible literature was further examined independently by two reviewers (CX Liu and SL Zhang). Any disagreements in the study selection process were resolved through a full consultation with a third reviewer (JB Chen). Studies included in this meta-analysis must meet the following criteria: (1) all involving patients with BPPV are divided into recurrent group and non-recurrent group according to the recurrence after treatment; (2) the diagnosis of BPPV patients included in studies was based on a definitive medical history of recurrent positional vertigo or a typical nystagmus during Dix-Hallpike tests or Roll tests; (3) the outcome was BPPV recurrence, defined as recurrent vertigo symptoms along with positive diagnostic tests after successful treatment during follow-up; (4) sufficient data on risk factors for BPPV recurrence studied in this meta-analysis were reported; (5) retrospective or prospective English original studies. The following studies were excluded: (1) sufficient data studied in this meta-analysis were not available; (2) the definition of recurrence or the diagnosis of BPPV was unclear; (3) follow-up after treatment was less than 6 months, which may limit the observation of treatment outcome; and (4) reviews, letters, meeting abstracts, supplements, and case reports.

Data extraction and quality assessment

We used a standard pre-extraction form to initially extract data needed for this meta-analysis, and further revised this form based on the preliminary extraction results. Two reviewers (K Cui and CX Liu) independently extracted the following information, using the revised extraction form from June 2020 to July 2020: (1) Study characteristics: first author, publication year, geographic region, study design, sample size, sample overall age and follow-up time and (2) Baseline characteristics of recurrence group and non-recurrence group: age $(mean \pm SD)$, female gender, hypertension, diabetes mellitus, hyperlipidemia, migraine, head trauma, Menière's disease, osteoporosis, and serum vitamin D level (ng/ml) (mean \pm SD). The same two reviewers independently used the Newcastle Ottawa Scale [25] to evaluate the quality of each included study, with a NOS score \geq 7 indicating high quality. The NOS scores of each included study were, respectively, presented in Table 1. Any disagreements about data extraction or quality assessment were resolved through a full discussion with a third reviewer (JB Chen).

Statistical analysis

The pooled odds ratios (ORs) or mean differences (MDs) with their corresponding 95% confidence intervals (CIs)

| Literature | Publi- cation (Year) | Geographic region | Study design | Sample size (Recurrence/ Non-recur- rence) | Sample overall age (Mean±SD) | Follow up | Risk factors reported | NOS scores |
|------------------|----------------------------|----------------------|------------------------|---|------------------------------------|------------------------|---------------------------|------------|
| Kim [10] | 2017 | Korea | Retrospective study | 67/131 | NA | more than 12 months | F1, F2, F3, F4, F9 | 9 |
| Zhu [11] | 2019 | China | Retrospective study | 255/757 | NA | 12 months | F2, F3, F4, F5, F6, F8 | 9 |
| Yamanaka [12] | 2013 | Japan | Retrospective study | 22/39 | 63.7 ± 7.40 | more than 12 months | F1, F9 | 8 |
| Su [13] | 2016 | Taiwan | Retrospective study | 46/197 | 57.5 ± 13.9 | more than 24 months | F2, F7 | 8 |
| Sreenivas [14] | 2019 | India | Retrospective study | 16/55 | 49 ± 14 | 6–12 months | F3, F4, F5 | 8 |
| Rhim [15] | 2019 | Korea | Retrospective study | 53/279 | 50/24 (Median/ IQR) | 12–24 months | F2, F3, F4, F5 | 8 |
| Rhim [16] | 2016 | Korea | Retrospective study | 41/191 | 50.35/13–88 (Mean/ Range) | 10.2 ± 3.64 months | F1, F2, F10 | 7 |
| Kansu [17] | 2010 | Turkey | Retrospective study | 39/79 | 51.8 ± 14.7 | 64 ± 7.7 months | F2, F6, F7, F8 | 7 |
| Wang [18] | 2018 | China | Prospective study | 25/42 | 63.99 ± 12.15 | 24 months | F1, F2, F3, F4, F5 | 9 |
| Do [19] | 2011 | Korea | Prospective study | 46/92 | 51.56 ± 16.39 | 8–14 months | F1, F2, F7 | 8 |
| Talaat [20] | 2015 | Kuwait | Prospective study | 36/44 | 47.6±9.1 | more than 12 months | F1, F2, F10 | 8 |
| Webster [21] | 2015 | Brazil | Prospective study | 26/46 | NA | 41 months | F4 | 7 |
| Lee [22] | 2013 | Korea | Prospective study | 16/20 | NA | more than 12 months | F1, F2 | 6 |
| Babac [23] | 2014 | Serbia | Prospective study | 62/338 | 58.75 ± 12.0 | 12 months | F2, F6, F7, F9 | 8 |

Table 1 Baseline characteristics of all included studies in our meta-analysis

Risk Factors: F1, advanced age; F2, female gender; F3, hypertension; F4, diabetes mellitus; F5, hyperlipidemia; F6, migraine; F7, head trauma; F8, Menière's disease; F9, osteoporosis; F10, vitamin D deficiency. *NA* not available

were calculated to estimate the effect of each included risk factor on the recurrence of Benign Paroxysmal Positional Vertigo. The heterogeneity across all included studies was assessed and quantified using the Cochrane Q statistics and I^2 statistics, respectively [26]. $I^2 > 50\%$ indicated heterogeneity across included studies was significant, so a random-effect model was subsequently used to pool these results. A fixed-effect model was used when heterogeneity was not significant ($I^2 < 50\%$). Publication bias of studies included in female gender analysis was assessed using a visual funnel plot. All statistical analyses involved in this meta-analysis were conducted using the statistical software" Review Manager 5.3".

Results

Study selection and study characteristics

After the literature search process, a total of 799 potentially eligible articles were initially identified. Additional two studies were identified through reviewing the reference lists of all included studies. After the elimination of 258 duplicates, 497 studies were further excluded through screening the titles/abstracts, since these articles were not associated with risk factors for BPPV recurrence. And then the remaining 46 studies were eligible for full-text

| A Advanced age | | | | | | | | | |
|---|------------|------------------------------|------------------|-------------------------|----------|------------------|--------------------|----------------------|--|
| 11 Havaneea age | Rec | urrenc | e | No-Re | curren | e | | Mean Difference | Mean Difference |
| Study or Subgroup | Mean | SD | Tota | Mean | SD ' | Total \ | Weight | IV. Fixed, 95% C | I IV. Fixed, 95% CI |
| Do,Y.K. 2011 | 50.11 | 16.81 | 46 | 54.46 | 15.31 | 92 | 8.4% | -4.35 [-10.13, 1.43] | - |
| Kim, S. Y. 2017 | 60.7 | 11.5 | 67 | 63.1 | 12.3 | 131 | 23.4% | -2.40 [-5.87, 1.07] | 1 |
| Lee, J. D. 2013 | 50.3 | 9.5 | 16 | 6 47.1 | 10.5 | 20 | 6.6% | 3.20 [-3.35, 9.75] | 1- |
| Rhim, G. I. 2016 | 48.37 | 13.93 | 41 | 50.77 | 17 | 1 9 1 | 11.7% | -2.40 [-7.30, 2.50] | 7 |
| Talaat, H. S. 2015 | 48.3 | 9.4 | 36 | 6 47 | 8.9 | 44 | 17.2% | 1.30 [-2.74, 5.34] | Ť |
| Wang,Y 2018 | 63.52 | 12.3 | 25 | | 12.21 | 42 | 7.6% | • • • | Ť |
| Yamanaka, T. 2013 | 65.3 | 4.7 | 22 | 2 63.8 | 8.6 | 39 | 25.2% | 1.50 [-1.84, 4.84] | Ī |
| Total (95% Cl) | | | 253 | 5 | | 559 1 | 100.0% | -0.45 [-2.13, 1.22] | • |
| Heterogeneity: Chi ² = 6 | 6.81, df = | = 6 (P = | 0.34) | ; l² = 12% | 1 | | | | |
| Test for overall effect: 2 | Z = 0.53 | (P = 0. | 60) [′] | | | | | | -100 -50 0 50 10 Favours experimental Favours control |
| B Female | | | | | | | | | |
| DICHIMIC | Rec | urrenc | е | No-Recu | Irrence | | | Odds Ratio | Odds Ratio |
| Study or Subaroup | Ever | nts T | otal | Events | Tot | al Wei | iaht | M-H. Fixed. 95% C | M-H. Fixed. 95% Cl |
| Babac, S 2014 | | 48 | 62 | 233 | 33 | | .5% | 1.55 [0.82, 2.93] | + |
| Do,Y.K. 2011 | | 25 | 46 | 67 | | | .9% | 0.44 [0.21, 0.93] | |
| Kansu, L 2010 | | 25 | 39 | 49 | | | .8% | 1.09 [0.49, 2.42] | _ _ |
| Kim, S. Y. 2017 | | 49 | 67 | 90 | 13 | | .5% | 1.24 [0.64, 2.39] | |
| Lee, J. D. 2013 | | 14 | 16 | 16 | | | .0% | 1.75 [0.28, 11.05] | |
| Rhim, G. I. 2016 | | 31 | 41 | 138 | 19 | | .9% | 1.19 [0.55, 2.60] | |
| Rhim, G. I. 2019 | | 43 | 53 | 189 | 27 | | 6% | 2.05 [0.98, 4.26] | |
| Su, P 2016 | | 43 42 | 46 | 154 | 19 | | .0% | 2.93 [1.00, 8.63] | |
| • | | 42 27 | 40 36 | 25 | | | .0 <i>%</i> .3% | | |
| Talaat, H. S. 2015 | | 27 17 | 30 25 | 25 20 | | | .3% .8% | 2.28 [0.87, 5.97] | |
| Wang,Y 2018 | | | | | | | | 2.34 [0.83, 6.59] | - |
| Zhu, C. T. 2019 | 1 | 87 | 255 | 493 | 75 | 07 30 | .6% | 1.47 [1.07, 2.02] | - |
| Total (95% CI) | | | 686 | | 217 | 0 100 | .0% | 1.42 [1.17, 1.74] | ◆ |
| Total events | 5 | 08 | | 1474 | | | | | |
| Heterogeneity: Chi ² = | 14.93, | df = 10 | (P = | 0.13); l ² : | = 33% | | | | |
| Test for overall effect: | | | - | - | | | | E. | 0.01 0.1 1 10 100 |
| C Hypertension | | • | | | | | | Fi | avours experimental Favours control |
| C Hypertension | Recu | irrence | • • | lo-Recur | rence | | | Odds Ratio | Odds Ratio |
| Study or Subgroup | Even | | | Events | | Weia | uht M | I-H. Random, 95% (| CI M-H. Random. 95% CI |
| Kim, S. Y. 2017 | 2 | 27 | 67 | 5 | 131 | 18.0 | 0% | 17.01 [6.14, 47.10 | |
| Rhim, G. I. 2019 | 1 | 6 | 53 | 72 | 279 | 22.3 | 3% | 1.24 [0.65, 2.37 | j |
| Sreenivas, V 2019 | | 8 | 16 | 13 | 55 | 16.4 | 1% | 3.23 [1.01, 10.31 | j - |
| Wang,Y 2018 | 1 | 6 | 25 | 22 | 42 | 18.0 |)% | 1.62 [0.58, 4.47 | i ∔ ∎— |
| Zhu, C. T. 2019 | 8 | 39 2 | 255 | 187 | 757 | 25.4 | 1% | 1.63 [1.20, 2.22 | |
| Total (95% CI) | | | 16 | | 1264 | 100.0 | 10/ | 2.61 [1.22, 5.59] | |
| | 42 | | NV. | 299 | 1204 | 100.0 | . 10 | 7.01 [1.22, 0.33] | |
| Total events Heterogeneity: Tau ² = | | 56 • hi2 – 2 [,] | 1 4 4 | | - 0 000 |), 12 – C | 040/ | | |
| Test for overall effect: | • | | | ui – 4 (P | - 0.0003 | y, ⊨ – c | 5170 | | 0.01 0.1 1 10 10 |
| reactor overall effect: | 2 - 2.4 | 0 (17 = 1 | 5.01) | | | | | F | Favours experimental Favours control |
| | | | | | | | | | |

Fig. 1 Forest plot of advanced age (a), female gender (b), and hypertension (c)

review, of which 14 studies met the inclusion and exclusion criteria and were finally included in our meta-analysis [10-23]. A flow chart of the literature selection process was shown in supplemental Fig. 1. Among these studies, there were six prospective studies [18-23] and eight retrospective studies [10-17], published between 2010 and 2019, most of which were retrospectively performed in Asia. Our meta-analysis involved 3060 BPPV patients, including 750 patients in the BPPV recurrence group and

2310 patients in the non-recurrence group. The baseline characteristics of the 14 included studies are presented in Table 1. The pooled effects of each risk factor are summarized in Table 2. The visual funnel plot indicated that no significant publication bias was found among included studies (Supplemental Fig. 2). In addition, the NOS scores indicated a moderate and high quality of all included studies (Supplemental Table 1), with a NOS score ranged from 6 to 9. We finally analyzed ten risk factors for BPPV

| Risk factors | Number of | Recurrence/ | Pooled eff | fects | | Heterogeneity | | Analysis model | |
|-----------------------|-----------------------|----------------|------------|-----------------|---------|---------------------|---------|---------------------|--|
| | included stud- ies | Non-recurrence | OR/MD | 95% CI | P value | $\overline{I^2,\%}$ | P value | | |
| Advanced age* | 7 | 253/559 | - 0.45 | - 2.13, 1.22 | 0.60 | 12 | 0.34 | Fixed-effect model | |
| Female gender | 11 | 686/2170 | 1.42 | 1.17, 1.74 | 0.0004 | 33 | 0.13 | Fixed-effect model | |
| Hypertension | 5 | 416/1264 | 2.61 | 1.22, 5.59 | 0.01 | 81 | 0.0003 | Random-effect model | |
| Diabetes mellitus | 6 | 442/1310 | 2.62 | 1.25, 5.48 | 0.01 | 69 | 0.007 | Random-effect model | |
| Hyperlipidemia | 4 | 349/1133 | 1.60 | 1.23, 2.09 | 0.0006 | 0 | 0.80 | Fixed-effect model | |
| Migraine | 3 | 356/1174 | 1.23 | 0.45, 3.36 | 0.69 | 73 | 0.03 | Random-effect model | |
| Head trauma | 4 | 193/706 | 1.70 | 0.95, 3.06 | 0.08 | 0 | 0.82 | Fixed-effect model | |
| Menière's disease | 2 | 294/836 | 3.13 | 0.64, 15.15 | 0.16 | 71 | 0.06 | Random-effect model | |
| Osteoporosis | 3 | 151/508 | 1.72 | 1.03, 2.88 | 0.04 | 0 | 0.41 | Fixed-effect model | |
| Vitamin D deficiency* | 2 | 77/235 | - 3.29* | - 5.32 , - 1.26 | 0.001 | 0 | 0.63 | Fixed-effect model | |

Table 2 Pooled analysis of each included risk factor for BPPV recurrence in this meta-analysis

OR odds ratio; MD mean difference

*, continuous variable

recurrence with scientific and clinical value, including advanced age, female gender, hypertension, diabetes mellitus, hyperlipidemia, migraine, head trauma, Menière's disease, osteoporosis and vitamin D deficiency.

Advanced age

The association between advanced age and BPPV recurrence was investigated in seven studies involving 812 BPPV patients. The pooled effects of seven studies indicated that there was no significant difference in age between the recurrence group and non-recurrence group (MD = -0.45; 95% CI -2.13-1.22; P=0.60) (Fig. 1). No statistical heterogeneity was detected among these studies, so a fixed-effect model was used to pool the results ($I^2 = 12\%$; P=0.34).

Female

The association between female gender and BPPV recurrence was analyzed in eleven studies including 2856 BPPV patients. The pooled results of eleven studies suggested that female patients with BPPV had a slightly higher risk of recurrence than male (OR = 1.42; 95% CI 1.17–1.74; P=0.0004) (Fig. 1). A fixed-effect model was used to pool the results, since no significant heterogeneity was detected across these studies ($I^2=33\%$; P=0.13). The visual funnel plot indicated that there was no significant publication bias among these studies included in the female gender analysis (Supplemental Fig. 2).

Hypertension

The effect of hypertension on BPPV recurrence was analyzed in five studies involving 1680 BPPV patients. The

pooled results of these studies indicated that BPPV patients with hypertension had a higher risk of recurrence than BPPV patients without hypertension (OR = 2.61; 95% CI 1.22–5.59; P = 0.01) (Fig. 1). A random-effect model was used to pool the results, due to the significant statistical heterogeneity across these studies ($I^2 = 81\%$; P = 0.0003). The reliability of our results was limited due to the significant heterogeneity across included studies.

Diabetes mellitus

The association between diabetes mellitus (DM) and BPPV recurrence was evaluated in six studies including 1752 BPPV patients. Our analysis results of included studies showed that BPPV patients with DM were more susceptible to relapse (OR = 2.62; 95% CI 1.25–5.48; P = 0.01) (Fig. 2). A random-effect model was used, since substantial heterogeneity was detected among included studies (I^2 = 69%; P = 0.007).

Hyperlipidemia

The impact of hyperlipidemia on BPPV recurrence was reported in four studies involving 1482 BPPV patients. The pooled evidence indicated that BPPV patients with hyperlipidemia were more susceptible to relapse (OR = 1.60; 95% CI 1.23–2.09; P=0.0006) (Fig. 2). A fixed-effect model was used to pool these results, since no heterogeneity was found across included studies (I^2 =0%; P=0.80).

Migraine

Three studies including 1530 BPPV patients reported the impact of migraine on BPPV recurrence. Our pooled

A Diabetes Mellitus

| | Recurre | ence | No-Recur | rence | | Odds Ratio | | Odds | s Ratio | |
|-----------------------------------|------------------------|----------|---------------|-----------|---------|--------------------|---------|--------------|--------------------|-----|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% (| | M-H, Rand | <u>lom, 95% Cl</u> | |
| Kim, S. Y. 2017 | 14 | 67 | 3 | 131 | 14.5% | 11.27 [3.11, 40.84 |] | | — | |
| Rhim, G. I. 2019 | 5 | 53 | 23 | 279 | 17.4% | 1.16 [0.42, 3.20 |] | | - | |
| Sreenivas, V 2019 | 5 | 16 | 3 | 55 | 11.9% | 7.88 [1.64, 37.95 |] | | | |
| Wang,Y 2018 | 12 | 25 | 11 | 42 | 17.1% | 2.60 [0.92, 7.39 |] | | | |
| Webster, G. 2015 | 8 | 26 | 7 | 46 | 15.8% | 2.48 [0.78, 7.88 |] | - | | |
| Zhu, C. T. 2019 | 24 | 255 | 63 | 757 | 23.2% | 1.14 [0.70, 1.87 |] | - | - | |
| Total (95% CI) | | 442 | | 1310 | 100.0% | 2.62 [1.25, 5.48] | 1 | | • | |
| Total events | 68 | | 110 | | | | | | | |
| Heterogeneity: Tau ² = | 0.55; Chi ² | = 15.97 | , df = 5 (P = | = 0.007); | ² = 69% | | 0.01 | 0.1 | + + 1 10 | 100 |
| Test for overall effect: | Z = 2.55 (F | P = 0.01 |) | | | F | +·· · · | experimental | Favours cor | |

B Hyperlipidemia

| 51 1 | Recurre | ence | No-Recurr | ence | | Odds Ratio | | C | dds Rati | 0 | |
|-------------------------------------|--------------|----------|---------------------------|-------|--------|-------------------|----------------|-----------------|----------------|-----------------|-------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% C | | М-Н, | Fixed, 9 | 5% CI | |
| Rhim, G. I. 2019 | 12 | 53 | 37 | 279 | 11.3% | 1.91 [0.92, 3.97] | | | _ - ■- | _ | |
| Sreenivas, V 2019 | 10 | 16 | 23 | 55 | 4.8% | 2.32 [0.74, 7.29] | | | - | | |
| Wang,Y 2018 | 8 | 25 | 12 | 42 | 7.6% | 1.18 [0.40, 3.44] | | | <u>+</u> | - | |
| Zhu, C. T. 2019 | 84 | 255 | 182 | 757 | 76.3% | 1.55 [1.14, 2.12] | | | | | |
| Total (95% CI) | | 349 | | 1133 | 100.0% | 1.60 [1.23, 2.09] | | | • | | |
| Total events | 114 | | 254 | | | | | | | | |
| Heterogeneity: Chi ² = (| 0.99, df = 3 | 3 (P = 0 | .80); I ² = 0% | | | | | | | | |
| Test for overall effect: | | | | | | Fa | 0.01 avours | 0.1 experime | ntal Fav | 10 ours cont | 100 trol |

C Migraine Recurrence No-Recurrence **Odds Ratio Odds Ratio** Study or Subaroup M-H. Random. 95% C . Random. 95% Cl Events Total Events Total Weight Babac, S 2014 6 62 49 338 33.9% 0.63 [0.26, 1.55] Kansu, L 2010 5 39 11 79 29.1% 0.91 [0.29, 2.83] Zhu, C, T, 2019 14 255 15 757 37.0% 2.87 [1.37, 6.04] Total (95% CI) 1.23 [0.45, 3.36] 356 1174 100.0% 75 **Total events** 25 Heterogeneity: Tau² = 0.57; Chi² = 7.29, df = 2 (P = 0.03); l² = 73% . 0.01 100 0.1 10 Test for overall effect: Z = 0.40 (P = 0.69) Favours experimental Favours control

Fig. 2 Forest plot of diabetes mellitus (a), hyperlipidemia (b), and migraine (c)

evidence suggested that there was no significant difference in recurrence rate between patients with migraine and patients without migraine (OR = 1.23; 95% CI 0.45–3.36; P=0.69) (Fig. 2). Significant heterogeneity was detected among these studies (I^2 = 73%; P=0.03), so a random-effect model was used.

Head trauma

The correlation between head trauma and the recurrence of BPPV was investigated in four studies involving 899 BPPV patients. Our pooled results of four studies indicated that there was no significant relationship between head trauma and the recurrence of BPPV (OR = 1.70; 95% CI 0.95–3.06; P = 0.08) (Fig. 3), with no heterogeneity among included studies ($I^2 = 0\%$; P = 0.82). The small number of included studies may limit the reliability of our results.

Menière's disease

Two studies including 1130 BPPV patients reported the association between Menière's disease and BPPV recurrence. The pooled evidence of two studies showed that there was no significant difference in recurrence rate between patients with Menière's disease and patients without Menière's disease (OR = 3.13; 95% CI 0.64–15.15; P=0.16) (Fig. 3). A random-effect model was used, since significant heterogeneity among these studies was detected ($I^2 = 71\%$; P = 0.06). Significant heterogeneity and the small number of included studies may limit the reliability of our results.

Osteoporosis

Three studies involving 659 BPPV patients analyzed the influence of osteoporosis on BPPV recurrence. The pooled

| A Head trauma | | | | | | | | |
|---|--|---|--|--|--|--|---|------------|
| | Recurre | | No-Recu | | | Odds Ratio | Odds Ratio | |
| Study or Subgroup | Events | Total | Events | | Weight | <u>M-H, Fixed, 95% Cl</u> | M-H, Fixed, 95% Cl | |
| Babac, S 2014 | 4 | 62 | 14 | 338 | 25.8% | 1.60 [0.51, 5.02] | | |
| Do,Y.K. 2011 | 3 | 46 | 4 | 92 | | 1.53 [0.33, 7.16] | | |
| Kansu, L 2010 | 12 | 39 | 13 | 79 | 37.7% | 2.26 [0.91, 5.57] | | |
| Su, P 2016 | 2 | 46 | 9 | 197 | 20.7% | 0.95 [0.20, 4.55] | | |
| Total (95% CI) | | 193 | | 706 | 100.0% | 1.70 [0.95, 3.06] | ◆ | |
| Total events | 21 | | 40 | | | | | |
| Heterogeneity: Chi ² = | 0.94, df = 3 | 3 (P = 0. | 82); l ² = 0 | % | | | 0.01 0.1 1 10 10 | - I |
| Test for overall effect: | Z = 1.78 (I | ⁻ = 0.08 |) | | | Fa | vours experimental Favours control | 0 |
| B Meniere disease | <u>,</u> | | | | | 10 | | |
| | Recurre | nce | No-Recur | rence | | Odds Ratio | Odds Ratio | |
| Study or Subgroup | Events | Total | Events | Total | Weight | <u>M-H, Random, 95% C</u> | I M-H. Random. 95% Cl | |
| Kansu, L 2010 | 3 | 39 | 5 | 79 | 42.8% | 1.23 [0.28, 5.45] | | |
| Zhu, C. T. 2019 | 16 | 255 | 8 | 757 | 57.2% | 6.27 [2.65, 14.83] | | |
| | | | | | | | | |
| Total (95% CI) | | 294 | | 836 | 100.0% | 3.13 [0.64, 15.15] | | |
| Total events | 19 | | 13 | | | | | _ |
| Heterogeneity: Tau ² = | • | • | • | 0.06); l² = | • 71% | | 0.01 0.1 1 10 10 | <u></u> |
| | | | | | | | | <i>i</i> 0 |
| Test for overall effect: | Z = 1.41 (P | · = 0.16) | | | | F | avours experimental Favours control | |
| C Osteoporosis | | , | | | | | | .0 |
| C Osteoporosis | Recurre | nce | No-Recu | | | Odds Ratio | Odds Ratio | 10 |
| C Osteoporosis | Recurre Events | nce Total | No-Recu Events | Total | Weight | Odds Ratio M-H, Fixed, 95% Cl | | |
| C Osteoporosis <u>Study or Subgroup</u> Babac, S 2014 | Recurre Events 12 | nce <u>Total</u> 62 | No-Recu Events 53 | Total 338 | 64.7% | Odds Ratio <u>M-H. Fixed. 95% Cl</u> 1.29 [0.64, 2.59] | Odds Ratio | |
| C Osteoporosis <u>Study or Subgroup</u> Babac, S 2014 Kim, S. Y. 2017 | Recurre Events 12 7 | nce Total 62 67 | No-Recu Events 53 7 | <u>Total</u> 338 131 | 64.7% 20.7% | Odds Ratio <u>M-H. Fixed, 95% Cl</u> 1.29 [0.64, 2.59] 2.07 [0.69, 6.16] | Odds Ratio | |
| C Osteoporosis <u>Study or Subgroup</u> Babac, S 2014 | Recurre Events 12 | nce <u>Total</u> 62 | No-Recu Events 53 | Total 338 | 64.7% | Odds Ratio <u>M-H. Fixed. 95% Cl</u> 1.29 [0.64, 2.59] | Odds Ratio | |
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| C Osteoporosis <u>Study or Subgroup</u> Babac, S 2014 Kim, S. Y. 2017 Yamanaka, T. 2013 | Recurre Events 12 7 | ence Total 62 67 22 | No-Recu Events 53 7 | <u>Total</u> 338 131 39 | 64.7% 20.7% 14.6% | Odds Ratio <u>M-H. Fixed, 95% Cl</u> 1.29 [0.64, 2.59] 2.07 [0.69, 6.16] 3.16 [0.97, 10.29] | Odds Ratio | |
| C Osteoporosis <u>Study or Subgroup</u> Babac, S 2014 Kim, S. Y. 2017 Yamanaka, T. 2013 Total (95% CI) Total events | Recurre Events 12 7 9 28 | ence <u>Total</u> 62 67 22 151 | No-Recu Events 53 7 7 67 | Total 338 131 39 508 | 64.7% 20.7% 14.6% | Odds Ratio <u>M-H. Fixed, 95% Cl</u> 1.29 [0.64, 2.59] 2.07 [0.69, 6.16] 3.16 [0.97, 10.29] | Odds Ratio M-H. Fixed. 95% Cl | |
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Fig. 3 Forest plot of head trauma (a), Menière's disease (b), osteoporosis (c), and vitamin D deficiency (d)

evidence suggested that BPPV patients with osteoporosis were more susceptible to relapse (OR = 1.72; 95% CI 1.03–2.88; P = 0.04) (Fig. 3). No statistical heterogeneity was found across included studies, so a fixed-effect model was used to pool the results ($l^2 = 0\%$; P = 0.41).

Vitamin D deficiency

Two studies involving 312 BPPV patients measured serum vitamin D level (ng/ml) to evaluate the effect of vitamin D deficiency on the recurrence of BPPV. Our analysis results suggested that the serum vitamin D level was lower in recurrence

BPPV group than in non-recurrence group (MD = -3.29; 95% CI -5.32 to -1.26; P=0.001) (Fig. 3). In our analysis, BPPV patients with vitamin D deficiency have a higher risk of recurrence. There was no heterogeneity across included studies ($I^2=0\%$; P=0.63), so a fixed-effect model was used to pool these results.

Discussion

Previously, some studies reported that the recurrence rate of BPPV was affected by many risk factors, such as advanced age, head trauma, Menière's disease, vascular diseases, vitamin D deficiency, and osteoporosis [10-23]. However, some related risk factors were relatively controversial. Risk factors for BPPV recurrence may depend on genetic variables which differ between different parts of the world. This may explain why many previous studies obtained controversial results. This meta-analysis suggested that female gender, hypertension, diabetes mellitus, hyperlipidemia, osteoporosis, vitamin D deficiency were risk factors for BPPV recurrence. However, the effects of other potential risk factors including advanced age, migraine, head trauma, and Menière's disease on BPPV recurrence still need further investigations. In addition, most studies included in this meta-analysis were performed in Asia, so our results cannot easily be extended to the whole world population. Identifying risk factors for BPPV recurrence can help improve prognosis and treatment outcome of patients. Further large-scale studies are necessary to confirm our results due to the small number of included studies for some risk factors.

A nationally epidemiological survey showed that age was independently associated with BPPV and the 1-year prevalence of BPPV increased significantly with age [2]. A recent study on the long-term follow-up of horizontal canal BPPV confirmed that the risk of recurrence increased with age [27]. So advanced age may be a potential risk factor for BPPV recurrence, which can be explained by the fact that the otoconial detachment increased with age [23]. And furthermore, elderly patients usually suffer from more chronic diseases, such as hypertension, vitamin D deficiency and osteoporosis, which may also increase the risk of BPPV recurrence. However, our meta-analysis indicated that advanced age had no impact on the recurrence of BPPV and there was no heterogeneity among included studies. In most of the included studies, the age of patients was relatively concentrated. This may explain why the age of patients was comparable between the recurrence and non-recurrence groups. In addition, the age of BPPV onset was most commonly between 50 and 70 years old [3], but the mean age of patients in some included studies was relatively young, ranging from 48 to 50 years. The small number of patients in included studies may also limit the reliability of our results. Further large-scale investigations are necessary to establish the effect of advanced age on BPPV recurrence.

Previous studies have found that female BPPV patients were more likely to relapse than male [11, 28]. This metaanalysis analyzed the effect of female gender on BPPV recurrence. Our pooled results indicated that female gender increased the risk of BPPV recurrence, which may be related to otoconial demineralization, which may be explained by the fact that older women were more susceptible to osteoporosis due to estrogen deficiency [29]. In addition, patients with osteoporosis were more likely to relapse [30]. Therefore, treatment of osteoporosis may have a preventive effect on the recurrence of BPPV in elderly women, thereby reducing the potential recurrence rate.

Previous studies demonstrated that vascular comorbidities including hypertension, diabetes mellitus and hyperlipidemia may have adverse effects on the occurrence [2] or recurrence [10, 11, 31] of BPPV. Vascular damage, ischemia, or atherosclerosis induced by vascular comorbidities may cause displacement or degenerative changes of otoconia [32, 33], which may explain why vascular comorbidities have adverse effects on BPPV. Our pooled results showed that hypertension, diabetes mellitus and hyperlipidemia may increase the risk of BPPV recurrence. Therefore, vascular comorbidities should be actively treated to eliminate potentially vascular risk factors for BPPV recurrence, which may help reduce the recurrence rate and improve the prognosis of BPPV patients.

Previously, Ishiyama et al. reported that BPPV patients with migraine had a higher recurrence rate than patients without migraine [34]. In a nationally epidemiological survey, the authors found that BPPV had a strong association with migraine [2]. Similarly, a recent retrospective study also reported that the recurrence rate of BPPV patients with migraine was higher than BPPV patients without migraine, although there was no statistically significant difference [35]. The relationship between migraine and BPPV may be explained by the fact that BPPV patients with migraine suffer from recurrent vestibular cell damage due to repeated vasospasm of the labyrinthine arteries, which may predispose them to recurrent BPPV [34, 36]. However, our analysis found no significant association between migraine and the recurrence of BPPV. The controversial results may be explained by the fact that two of the three included studies did not report definitive diagnostic criteria for migraine. In addition, the reliability of our results may be limited due to significant heterogeneity and the small number of included studies.

Previously, Prokopakis et al. reported that 23% of patients with BPPV had a history of head trauma [37]. Similarly, Kansu et al. also found that BPPV patients with a history of head trauma were more susceptible to recurrence than patients with other etiology [17]. Compared with idiopathic patients, post-traumatic BPPV patients usually require more repeated treatments to be fully recover. This may be explained by the fact that head trauma and related hemorrhage can lead to otoconia detachment [23], which may increase the risk of BPPV recurrence. However, the pooled

results in this meta-analysis suggested that head trauma did not increase the recurrence rate of BPPV. The reliability of our results may be limited due to the small number of studies included. In addition, two studies only included patients with posterior canal BPPV, which may have some influence on our pooled results.

Previous studies reported that the incidence of Menière's disease (MD) among BPPV patients ranged from 0.5 to 30% [38–40]. Subsequent studies also showed that BPPV patients with Menière's disease exhibited a higher risk of recurrence than patients without MD [11, 17]. The association between BPPV and MD can be explained by the fact that loose otoconia caused by BPPV can reduce the absorption of endolymph, resulting in MD, while endolymphatic hydrops caused by MD can also impair inner ear function and lead to otoconia detachment, resulting in BPPV [41]. In most cases, BPPV was secondary to Menière's disease [40]. Therefore, we hypothesized that Menière's disease was a risk factor for BPPV recurrence. A recent meta-analysis indicated that BPPV patients with Menière's disease (MD) were more susceptible to relapse and required more canalith repositioning procedures than BPPV patients without MD [42]. However, our pooled results showed that patients with MD were not associated with an increased risk of BPPV recurrence. Horizontal canal was more common in BPPV patients with MD [42], but Kansu et al. only studied patients with posterior canal BPPV [17]. This may explain why our results are different from other studies. In addition, only two studies met our inclusion criteria and significant heterogeneity was detected, which may also limit the reliability of our results.

A previous systematic review provided evidence that osteoporosis was possibly associated with BPPV [43]. Our meta-analysis confirmed the conclusion of this review. This association may be explained by the fact that osteoporosis change has a negative impact on the synthesis/absorption of otoliths [10]. Our pooled results indicated that BPPV patients with osteoporosis were more susceptible to recurrence. So the treatment of osteoporosis may reduce the recurrence rate of BPPV, thereby improving the prognosis of patients after treatment [44]. However, the reliability of our results may be limited due to the small number of studies included. The effects of osteoporosis treatment on the prevention of BPPV recurrence in BPPV patients with osteoporosis need further larger-scale research.

A previous meta-analysis demonstrated that vitamin D deficiency was an independent risk factor for BPPV occurrence and recurrence [45]. Our results were consistent with this meta-analysis. This correlation may be explained by the fact that vitamin D deficiency may disrupt calcium metabolism in the inner lymphatic fluid and bone metabolism, leading to osteoporosis and increasing the risk of BPPV [46]. Our analysis results showed that

BPPV patients with vitamin D deficiency were more likely to recur. Therefore, vitamin D supplements may have a preventive effect on BPPV recurrence, thereby effectively improving symptoms and prognosis of patients after treatment [47, 48]. Further large-scale studies are necessary to establish the role of vitamin D supplements in the prevention of BPPV recurrence.

However, considering the limited literature available, some potentially relevant risk factors were not included in this meta-analysis, such as some inner ear diseases, physical inactivity, frequent falls, sleep disorder and depression. A questionnaire survey suggested that physical inactivity was a contributing factor for the onset of BPPV and furthermore mild to moderate physical activity may prevent BPPV occurrence [49]. In addition, some studies also reported that intense physical activity such as swimming or mountain biking can trigger BPPV [50, 51], but BPPV caused by intense physical activity was a relatively rare condition. A traumatic mechanism may explain this relationship. However, a recent meta-analysis indicated that regular exercise had no protective effect on the occurrence of BPPV [8]. In addition, some studies cannot find that daily exercise had any effect on the recurrence of BPPV [52]. Further studies are needed to investigate the association between the degree of physical activity and BPPV. Furthermore, frequent falls may be a potential risk factor for BPPV. On the other hand, a large number of studies have found that BPPV was associated with an increased risk of falls and fracture [5, 53]. Fracture increases mortality and impacts quality of life. Therefore, it is necessary to determine the effect of frequent falls on the recurrence of BPPV to improve the quality of life of patients. Further studies are required to explore the relationship between falls and BPPV.

Limitations

There are some inevitable limitations in our meta-analysis. First, the small number of included studies and sample size may limit the reliability of our results for some risk factors. Second, considering the limited literature available, some potentially relevant risk factors were not included in this meta-analysis, such as physical inactivity, frequent falls, duration of symptoms, otologic diseases, sleep disorder and depression. In addition, we did not perform a subgroup analysis based on the number of recurrence due to the limited data available. Further studies should be performed to investigate the effects of other potential risk factors and the treatment of certain risk factors on BPPV recurrence, such as vitamin D supplements or corresponding medicine.

Conclusions

In summary, our pooled results of this meta-analysis identified the following risk factors as being significantly associated with the recurrence of BPPV: female gender, hypertension, diabetes mellitus, hyperlipidemia, osteoporosis or vitamin D deficiency, but not advanced age, migraine, head trauma, or Menière's disease. Therefore, treatment of these comorbidities may reduce the risk of BPPV recurrence, thereby improving the prognosis of patients. Further largescale studies are needed to confirm our results due to the inevitable limitations of this meta-analysis.

Author contributions JC, SZ, KC, and CL: literature search, data extraction, statistical analysis, drafting and revision of the manuscript. JC, and SZ: critical revision of the manuscript.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

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