Frailty Predicts Poor Prognosis of Patients After Percutaneous Coronary Intervention: A Meta-Analysis of Cohort Studies

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Background: Frailty has been related to a higher risk of cardiovascular events, while the association between frailty and outcomes for patients with coronary artery disease (CAD) after percutaneous coronary intervention (PCI) remains unclear. We performed a meta-analysis of cohort studies to evaluate the above association.

Methods: Cohort studies aiming to determine the potential independent association between frailty and clinical outcomes after PCI were identified by search of PubMed, Embase, and Web of Science databases from inception to February 22, 2021. A random-effects model that incorporates the possible heterogeneity among the included studies was used to combine the results.

Results: Ten cohort studies with 7,449,001 patients were included. Pooled results showed that frailty was independently associated with higher incidence of all-cause mortality [adjusted risk ratio (RR) = 2.94, 95% confidence intervals (CI): 1.90–4.56, \( \hat{\rho} = 56\% \), \( P < 0.001 \) and major adverse cardiovascular events [(MACEs), adjusted RR = 2.11, 95% CI: 1.32–3.66, \( \hat{\rho} = 0\% \), \( P = 0.002 \)]. Sensitivity analyses limited to studies including elderly patients showed consistent results (mortality: RR = 2.27, 95% CI: 1.51–3.41, \( \hat{\rho} = 23\% \), \( P < 0.001 \); MACEs: RR = 2.44, 95% CI: 1.44–4.31, \( \hat{\rho} = 0\% \), \( P = 0.001 \)). Subgroup analyses showed that characteristics of study design, follow-up duration, or type of PCI did not seem to significantly affect the associations (\( P \)-values for subgroup analyses all >0.05).

Conclusions: Frailty may be an independent risk factor of poor prognosis for patients with CAD after PCI.

Keywords: frailty, percutaneous coronary intervention, mortality, major adverse cardiovascular events, meta-analysis

BACKGROUND

Currently, coronary artery disease (CAD) remains one of the most important causes of morbidity and mortality for global population, particularly for the elderly (1). Besides optimized medical treatment, early coronary revascularization has been established as the most effective therapy for alleviating symptoms and improving prognosis in patients with CAD (2). Due to the efficacy and invasiveness of the procedure, percutaneous coronary intervention
(PCI) has become the most widely used method for coronary revascularization (3). For patients with acute CAD, such as ST-segment elevation myocardial infarction (STEMI), primary PCI is recommended as early as possible to avoid the necrosis of myocardium (4). For patients with stable CAD and frequent symptom of angina, elective PCI is also recommended to restore the coronary blood flow for the ischemic myocardium (5). With the development of the devices and techniques, increasing elderly patients with CAD received PCI (6). According to previous studies, more than 20% of patients that received PCI are older than 75 years (3, 6). However, despite of the overall effectiveness of the procedure, adverse cardiovascular events or event deaths remain occur in some patients after PCI, which highlights the importance of risk stratification for CAD patients that received PCI (7).

Frailty is a geriatric syndrome characterized by age-related decrease of reserve capacity of various systems and lack of resilience to stressors (8). Accumulating evidence suggests that frailty is related to poor prognosis of patients with various cardiovascular conditions, such as acute myocardial infarction (AMI) (9), congestive heart failure (10, 11), atrial fibrillation (12), and for patients after transcatheter aortic valve implantation (13). However, the association between frailty and the prognosis of patients after PCI remains unclear (14). Most studies showed that frailty is independently associated with higher risk of mortality and adverse events after PCI (15–22), while some did not (23, 24). Accordingly, a previous meta-analysis included eight cohort studies and showed that frailty was associated with a higher risk of death for patients after PCI (25). However, two of the cohort studies actually included patients who did not receive PCI (26, 27). Besides, this meta-analysis included studies with univariate analysis and a study using continuous gait speed as the indicator of frailty (28), which made the results of the meta-analysis difficult to interpret. Since several relevant cohort studies (17–22, 24) have been published since the previous meta-analysis, we aimed to perform an updated meta-analysis to summarize the current understanding for the association between frailty and prognosis after PCI.

**METHODS**

The Meta-analysis of Observational Studies in Epidemiology (MOOSE) guideline (29) and Cochrane’s Handbook (30) was followed in this study.

**Literature Search**

The electronic databases of PubMed, Embase, and Web of Science databases were searched from inception to February 22, 2021 with a strategy of combined terms including (1) “frailty” OR “frail,” and (2) “percutaneous coronary intervention” OR “stent” OR “angioplasty” OR “revascularization” OR “reperfusion” OR PCI. Only studies reported in English were considered. References of related articles or reviews were also analyzed. The full search term for PubMed database was based on keywords as [“frailty” OR “frail] AND (“coronary artery disease” OR “angina” OR “myocardial infarction” OR “acute coronary syndrome” OR “percutaneous coronary intervention” OR “major adverse cardiovascular events” OR “CAD” OR “STEMI” OR “NSTEMI” OR “ACS” OR “AMI” OR “PCI”).

**Study Identification**

Studies fulfilled these criteria were used: (1) cohort studies published as full-length papers; (2) included adult patients with CAD; (3) frailty was evaluated during the index hospitalization for PCI and considered as exposure; (4) compared the incidence of all-cause mortality and/or major adverse cardiovascular events (MACEs) between patients with and without frailty during follow-up; and (4) reported risk ratios (RRs) for the above associations after adjusting for multiple confounding factors (at least for age and sex). Methods for the assessment of frailty were in accordance with those applied in the original articles. We defined MACEs as a composite outcome of all-cause death, non-fatal myocardial infarction (MI), non-fatal stroke, repeated coronary revascularization, and cardiac readmission. Reviews, preclinical studies, cross-sectional studies, and irrelevant studies were not included.

**Data Extracting and Quality Evaluation**

Two authors implemented database search, data extraction, and study quality assessment separately. If disagreements occurred, they were discussed with the corresponding author. These data were recorded: (1) author, country, and study design characteristics; (2) characteristics of the patients, including the diagnosis, number of participants included, mean age, and sex; (3) methods for the evaluation of frailty and number of patients with frailty at baseline; (4) PCI type and follow-up durations; (5) outcomes reported; and (6) potential confounding factors adjusted in the multivariate analyses for the association. The Newcastle-Ottawa Scale (31) was used for study quality evaluation. This scale is rated from 1 to 9 stars and reflected the quality of the study by aspects of participant selection, comparability between groups, and outcome validation.

**Statistical Analyses**

RRs and the corresponding 95% confidence intervals (CIs) were extracted for every included study. Then, standard errors (SEs) of RRs were estimated from the 95% CIs or P-values. For normalization of their distribution, HRs were logarithmically transformed (30) and combined. Heterogeneity within the included cohort studies was tested via Cochrane’s Q-test, as well as the estimation of $I^2$ statistic (32). An $I^2 > 50\%$ suggests significant level of heterogeneity. A random-effects model was chosen to combine the RRs by incorporating the potential heterogeneity within studies (30). Sensitivity analyses by sequentially excluding either of the included studies were conducted to clarify the influence of a certain study on the overall results (33). Predefined subgroup analyses according to study design, follow-up duration, and type of PCI were also performed. Funnel plots were constructed, and were used for the assessment of publication bias (34). Visually asymmetrical funnel plots implied potential publication bias, which could be further validated by the Egger’s regression asymmetry test. If high risk of publication bias was suggested, a “trim-and-fill” analysis was used for further evaluation, which estimates the influence of possible
studies with negative findings on the meta-analysis outcome (30).

The RevMan (version 5.1; Cochrane Collaboration, Oxford, UK) and STATA software were involved for statistical analyses.

RESULTS

Database Search

Details of the database search are shown in Figure 1. The first-step database search retrieved 1,124 articles after duplicated studies were excluded. Among them, 1,082 studies were further excluded because they were not related to the purpose of the meta-analysis based on titles and abstracts. Then, for the remaining 42 studies evaluated by full text reading, 32 were not included for the reasons presented in Figure 1, which resulted in ten cohort studies finally analyzed in the meta-analysis (15–24).

Study Characteristics

Characteristics of each study of the meta-analysis are shown in Table 1. Overall, ten cohort studies with 7,449,001 patients were considered to be eligible for the meta-analysis (15–24), which were performed in the United States (15, 19), United Kingdom (16, 17, 24), Spain (18), Japan (21, 22), and Indonesia (23), respectively. Five of them were prospective (15–18, 23), and the rest were retrospective (19–22, 24). Three studies included patients with unselected CAD (15, 16, 24), the others included patients with stable CAD (23), non-ST segment elevation acute coronary syndrome (NSTE-ACS) (17), and ST-elevation myocardial infarction (18–22), respectively. The mean ages of the included patients varied between 62 and 85 years, with proportions of males varying from 46 to 75%. Multiple tools were used for the evaluation of frailty among the included studies, including the Fried Frailty Criteria (15, 17), the Canadian Study of Health and Aging Clinical Frailty Scale (16, 22), validated frailty phenotype criteria (23), FRAIL scale (18), Claims-based Frailty Index (19), Safety Management Programme Score (20), Hospital Frailty Risk Score (24), and modified KATZ index (21). A total of 16,183 patients were considered with frailty at baseline. All the patients included in these studies received primary or elective PCI procedures. The follow-up durations varied from within hospitalization to 35 months after PCI. Incidence of all-cause mortality was reported in eight studies (15, 16, 18–22, 24), and incidence of MACEs was reported in five studies (15, 17, 20, 23, 24). Age, sex, body mass index, risk factors for CAD, comorbidities, and coronary lesion features were adjusted.

FIGURE 1 | Scheme of study inclusion.
TABLE 1 | Characteristic of the included studies.

| Study          | Country | Design  | Patient characteristics                        | Sample size | Mean age (years) | Male (%) | Frailty evaluation                                      | No. of patients with frailty | PCI type          | Follow-up duration (months) | Outcomes                  | Variables adjusted                           |
|----------------|---------|---------|-----------------------------------------------|-------------|-----------------|----------|--------------------------------------------------------|----------------------------|-----------------|----------------------------|--------------------------|------------------------------------------------|
| Singh et al. (15) USA | PC     | CAD patients ≥ 65 years who underwent PCI   | 629         | 69.0            | 74.3             |           | Using the Fried Frailty Criteria during index hospitalization | 117                       | Primary or elective | 35                         | All-cause mortality and MACE | Age, sex, Mayo Clinic Risk Score, Charlson Comorbidity Index, and Short-form-36 |
| Mural-Krishnan et al. (16) UK | PC     | CAD patients who underwent PCI               | 746         | 62.2            | 70.1             |           | Using the Canadian Study of Health and Aging Clinical Frailty Scale during hospitalization | 81                        | Primary or elective | 12                         | All-cause mortality | Age, sex, hemodynamically instability, CHF, DM, COPD, renal failure, and TIA/stroke |
| Hamonangan et al. (23) Indonesia | PC     | Stable CAD patients ≥ 60 years who underwent PCI | 100         | 70.0            | 69.0             |           | Using frailty phenotype criteria during hospitalization | 61                        | Elective         | 1                          | MACE                     | Age, sex and comorbidities |
| Calvo et al. (18) Spain | PC     | STEMI patients ≥ 75 years who underwent primary PCI | 259         | 82.6            | 57.9             |           | Using FRAIL scale during hospitalization                | 51                        | Primary           | In-hospitalization | All-cause mortality | Age, sex, LVEF, number of vessels diseased, and Barthel index |
| Batty et al. (17) UK | PC     | NSTEMI patients ≥ 75 years who underwent PCI | 280         | 81.0            | 60.0             |           | Using Fried Frailty Index during hospitalization         | 77                        | Elective          | 12                         | MACE                     | Age, sex, SBP, Killip Class, history of PVD, and BMS use |
| Damluji et al. (19) USA | RC     | STEMI patients ≥ 75 years who underwent primary PCI | 140,089     | 80.9            | 51.0             |           | Using Claims-based Frailty Index during hospitalization | 13,855                    | Primary           | In-hospitalization | All-cause mortality | Age, sex, and comorbidities |
| Hermans et al. (20) The Netherlands | RC     | STEMI patients ≥ 70 years who underwent primary PCI | 206         | 79.0            | 58.0             |           | Using Safety Management Programme Score during hospitalization | 57                        | Primary           | 1                          | All-cause mortality and MACE | Age, sex, CAD risk factors, comorbidities, and treatments |
| Yoshioka et al. (22) Japan | RC     | STEMI patients ≥ 80 years who underwent primary PCI | 273         | 84.6            | 46.2             |           | Using the Canadian Study of Health and Aging Clinical Frailty Scale at admission | 34                        | Primary           | 24                         | All-cause mortality | Age, sex, CAD risk factors, comorbidities, and coronary lesion features |
| Kwok et al. (24) UK | RC     | CAD patients who underwent PCI                | 730,6007    | 66.1            | 65.3             |           | Using a validated Hospital Frailty Risk Score during hospitalization | 1,836                     | Primary or elective | In-hospitalization | All-cause mortality and MACE | Age, sex, Charlson Comorbidity Index, and coronary lesion features |
| Seguchi et al. (21) Japan | RC     | STEMI patients ≥ 80 years who underwent primary PCI | 412         | 84.5            | 60.0             |           | Using the modified Katz index during hospitalization     | 14                        | Primary           | In-hospitalization | All-cause mortality | Age, sex, Killip Class, hemoglobin, comorbidities, and treatments |

PCI, percutaneous coronary intervention; PC, prospective cohort; RC, retrospective cohort; CAD, coronary artery disease; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation acute coronary syndrome; MACE, major adverse cardiovascular events; CHF, congestive heart failure; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; TIA, transient ischemia attack; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; PVD, peripheral vascular disease; BMS, bare-metal stent.
to a varying degree when the associations between frailty and outcomes after PCI were reported. The quality of these studies was good, evidenced by six to nine points of NOS scores (Table 2).

**Association Between Frailty and All-Cause Mortality After PCI**

Eight studies (15, 16, 18–22, 24) reported the outcome of all-cause mortality after PCI. Moderate heterogeneity was detected among the included studies (P for Cochrane’s Q-test = 0.02, I² = 56%). Pooled results with a random-effect model showed that frailty was independently associated with a higher incidence of all-cause mortality (adjusted RR = 2.94, 95% CI: 1.90–4.56, P < 0.001; Figure 2A). Sensitivity analyses by excluding one study at a time showed similar results (RR: 2.33–3.54, P all < 0.05). Sensitivity analysis only including studies with elderly patients (15, 18–22) showed consistent results (adjusted RR = 2.27, 95% CI: 1.51–3.41, P < 0.001), and the heterogeneity was substantially reduced (P for Cochrane’s Q-test = 0.26, I² = 23%). Subgroup analyses showed that the association between frailty and increased risk of all-cause mortality in patients with CAD after PCI was not significantly affected by characteristics of study design (prospective or retrospective), follow-up duration (within or more than 1 month), or type of PCI (primary or elective; P-values for subgroup analyses all >0.05; Figures 2B–D).

**Association Between Frailty and MACEs After PCI**

Five studies (15, 17, 20, 23, 24) reported the outcome of MACEs. No significant heterogeneity was detected (P for Cochrane’s Q-test = 0.80, I² = 0%). Pooled results showed that frailty was independently associated with a higher incidence of MACEs (adjusted RR = 2.11, 95% CI: 1.32–3.66, P = 0.002; Figure 3A). Sensitivity analyses by excluding one study at a time showed similar results (RR: 1.92–2.44, P all < 0.05). Sensitivity analysis limited to studies with elderly patients (15, 17, 20, 23) also showed consistent results (adjusted RR = 2.44, 95% CI: 1.44–4.13, P = 0.001; I² = 0%). Subgroup analyses also showed that characteristics of study design, follow-up duration, or type of PCI did not significantly affect the association (P-values for subgroup analyses all >0.05; Figures 3B–D).

**Publication Bias**

Funnel plots representing the meta-analyses for the associations between frailty and all-cause mortality after PCI were shown in Figure 4A. The plots for the outcome of all-cause mortality were asymmetrical based on visual inspection, raising the possible publication bias (Figure 4A). Egger’s regression test also demonstrated potential risk of publication bias (P = 0.048). We therefore performed a trim-and-fill analysis. As shown in Figure 4A, incorporating a hypothesized study achieved symmetry of the funnel plots, and the results of the meta-analysis remained significant after including the study (adjusted RR = 2.80, 95% CI: 1.83–4.27, P < 0.001; I² = 52%). Funnel plots representing the meta-analyses for the associations between frailty and MACEs after PCI were shown in Figure 4B. These plots were symmetrical judged by visual inspection, reflecting
FIGURE 2 | Forest plots for the meta-analysis concerning the association between frailty and risk of all-cause mortality after PCI: (A) Overall meta-analysis; (B) Subgroup analysis according to study design; (C) Subgroup analysis according to follow-up duration; and (D) Subgroup analysis according to the type of PCI.
### FIGURE 3

Forest plots for the meta-analysis concerning the association between frailty and risk of MACEs after PCI: (A) Overall meta-analysis; (B) Subgroup analysis according to study design; (C) Subgroup analysis according to follow-up duration; and (D) Subgroup analysis according to the type of PCI.

#### Table A

| Study or Subgroup | log(Risk Ratio) | SE | Weight | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI |
|-------------------|----------------|----|--------|-----------------------------|-----------------------------|
| Singh 2011        | 0.896068       | 0.38286219 | 38.8%  | 2.45 [1.16, 5.19]          |                             |
| Hamonanegaran 2016| 0.4054651      | 1.02512267 | 5.4%   | 1.50 [0.20, 11.19]         |                             |
| Batty 2019        | 0.8796267      | 0.54460005 | 19.2%  | 2.41 [0.63, 9.01]          |                             |
| Hermans 2019      | 1.0647107      | 0.61611018 | 15.0%  | 2.90 [0.87, 9.70]          |                             |
| Kwok 2020         | 0.2231436      | 0.51191054 | 21.7%  | 1.25 [0.46, 3.41]          |                             |
| Total (95% CI)    |                |              | 100.0% | 2.11 [1.32, 3.36]          |                             |

Heterogeneity: Tau² = 0.00; CH² = 1.63, df = 4 (P = 0.80); I² = 0%

Test for overall effect: Z = 3.13 (P = 0.002)

#### Table B

| Study or Subgroup | log(Risk Ratio) | SE | Weight | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI |
|-------------------|----------------|----|--------|-----------------------------|-----------------------------|
| Singh 2011        | 0.896068       | 0.38286219 | 38.8%  | 2.45 [1.16, 5.19]          |                             |
| Hamonanegaran 2016| 0.4054651      | 1.02512267 | 5.4%   | 1.50 [0.20, 11.19]         |                             |
| Batty 2019        | 0.8796267      | 0.54460005 | 19.2%  | 2.41 [0.63, 9.01]          |                             |
| Hermans 2019      | 1.0647107      | 0.61611018 | 15.0%  | 2.90 [0.87, 9.70]          |                             |
| Kwok 2020         | 0.2231436      | 0.51191054 | 21.7%  | 1.25 [0.46, 3.41]          |                             |
| Subtotal (95% CI) | 63.3%          |              |        | 2.34 [1.30, 4.31]          |                             |

Heterogeneity: Tau² = 0.00; CH² = 0.21, df = 2 (P = 0.90); I² = 0%

Test for overall effect: Z = 2.83 (P = 0.005)

#### Table C

| Study or Subgroup | log(Risk Ratio) | SE | Weight | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI |
|-------------------|----------------|----|--------|-----------------------------|-----------------------------|
| Singh 2011        | 0.896068       | 0.38286219 | 38.8%  | 2.45 [1.16, 5.19]          |                             |
| Hamonanegaran 2016| 0.4054651      | 1.02512267 | 5.4%   | 1.50 [0.20, 11.19]         |                             |
| Batty 2019        | 0.8796267      | 0.54460005 | 19.2%  | 2.41 [0.63, 9.01]          |                             |
| Hermans 2019      | 1.0647107      | 0.61611018 | 15.0%  | 2.90 [0.87, 9.70]          |                             |
| Kwok 2020         | 0.2231436      | 0.51191054 | 21.7%  | 1.25 [0.46, 3.41]          |                             |
| Subtotal (95% CI) | 36.7%          |              |        | 1.78 [0.79, 4.06]          |                             |

Heterogeneity: Tau² = 0.03; CH² = 1.10, df = 1 (P = 0.29); I² = 9%

Test for overall effect: Z = 1.36 (P = 0.17)

#### Table D

| Study or Subgroup | log(Risk Ratio) | SE | Weight | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI |
|-------------------|----------------|----|--------|-----------------------------|-----------------------------|
| Singh 2011        | 0.896068       | 0.38286219 | 38.8%  | 2.45 [1.16, 5.19]          |                             |
| Batty 2019        | 0.8796267      | 0.54460005 | 19.2%  | 2.41 [0.63, 9.01]          |                             |
| Hermans 2019      | 1.0647107      | 0.61611018 | 15.0%  | 2.90 [0.87, 9.70]          |                             |
| Kwok 2020         | 0.2231436      | 0.51191054 | 21.7%  | 1.25 [0.46, 3.41]          |                             |
| Subtotal (95% CI) | 42.1%          |              |        | 1.73 [0.84, 3.55]          |                             |

Heterogeneity: Tau² = 0.00; CH² = 1.13, df = 2 (P = 0.57); I² = 0%

Test for overall effect: Z = 1.49 (P = 0.14)
low possibility of publication bias. Egger's regression test was not performed because only five datasets were analyzed for this outcome.

**DISCUSSION**

In this meta-analysis of cohort studies, we found that frailty was independently associated with higher incidences of morality and MACEs in patients with CAD after PCI. Sensitivity analyses showed that the significance of the results was not affected by omitting of either of the included studies. Besides, sensitivity analyses limited to studies including elderly patients with CAD showed consistent results. Moreover, results of subgroup analyses showed that the association between frailty and poor prognosis after PCI was not significantly affected by study characteristics such as study design, follow-up duration, and type of PCI. Although risk of publication bias was noticed for the meta-analysis of the association between frailty and all-cause mortality after PCI, results of trim-and-fill analysis by incorporating the imputed study with negative results showed consistent results. Taken together, results of these findings indicated that frailty may be an independent risk factor for poor prognosis in patients with CAD who were treated with PCI.

A previous meta-analysis published in 2017 also showed that frailty may be associated with higher mortality risk for CAD patients after PCI (25). However, several weaknesses regarding the methodology of the meta-analysis have been noticed, which may affect the interpretation of the results. Besides of studies published as full-length articles that underwent peer-review, this meta-analysis has also included studies published in conference abstracts, which may introduce bias to the results. Moreover, this meta-analysis included two studies that not all of the included patients were treated with PCI (26, 27). In addition, one study with frailty measured via gait speed as a continuous variable was also introduced into the meta-analysis, which may confound the results of the meta-analysis (28). Compared to this study, our meta-analysis has several strengths. Firstly, only studies published as full-length articles were included. Secondly, all of the studies included patients with CAD who were treated with PCI. Thirdly, comparisons for the incidence of adverse clinical outcomes were directly made between patients with and without frailty. Moreover, besides all-cause mortality, outcome of MACEs was also evaluated. In addition, only studies with multivariate analyses were considered, which therefore could indicate a potentially independent association between frailty and poor outcomes after PCI. Finally, multiple sensitivity and subgroup analyses were performed, which showed consistent results in elderly patients, in studies with different design, follow-up durations, and types of PCI.

The potential mechanisms underlying the association between frailty and poor outcomes after PCI remain not fully understood. It has been shown that frail patients may have longer recovery time after invasive procedures (16), suggesting these patients may suffer from more post-procedure complications (23). Moreover, frailty has been associated with endothelial dysfunction (35) and activated inflammatory response (36), two key molecular mechanisms underlying the adverse events after PCI, such as in-stent restenosis (37, 38). In addition, in a recent study in elderly Chinese CAD patients after PCI, frailty has been related to high on-aspirin platelet response and high on-clopidogrel platelet response, which may reduce the interpretation of the results. Besides of studies published as full-length articles that underwent peer-review, this meta-analysis has also included studies published in conference abstracts, which may introduce bias to the results. Moreover, this meta-analysis included two studies that not all of the included patients were treated with PCI (26, 27). In addition, one study with frailty measured via gait speed as a continuous variable was also introduced into the meta-analysis, which may confound the results of the meta-analysis (28). Compared to this study, our meta-analysis has several strengths. Firstly, only studies published as full-length articles were included. Secondly, all of the studies included patients with CAD who were treated with PCI. Thirdly, comparisons for the incidence of adverse clinical outcomes were directly made between patients with and without frailty. Moreover, besides all-cause mortality, outcome of MACEs was also evaluated. In addition, only studies with multivariate analyses were considered, which therefore could indicate a potentially independent association between frailty and poor outcomes after PCI. Finally, multiple sensitivity and subgroup analyses were performed, which showed consistent results in elderly patients, in studies with different design, follow-up durations, and types of PCI.

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the predefined protocol during the performance of the study. Secondly, the meta-analysis was not based on data from the study level but not from individual patients, which prevented further analyses on the influence of patient characteristics on the outcome. In addition, significant heterogeneity was detected for the meta-analysis of the association between frailty and mortality after PCI. Although sensitivity analysis limited to studies including elderly patients only significant reduced the heterogeneity ($I^2$ from 56 to 23%), we could not determine whether other factors contribute to the residual heterogeneity. Moreover, multiple scales were used for measurement of frailty, and we could not determine whether difference among these scales may affect the association between frailty and outcomes after PCI. Finally, possible risk of publication bias was raised in the meta-analysis regarding the association between frailty and mortality after PCI. Although sensitivity analysis limited to individual patients, which prevented further analyses on the influence of patient characteristics on the outcome. In addition, significant heterogeneity was detected for the meta-analysis of the association between frailty and mortality after PCI. Although sensitivity analysis limited to studies including elderly patients only significant reduced the heterogeneity ($I^2$ from 56 to 23%), we could not determine whether other factors contribute to the residual heterogeneity. Moreover, multiple scales were used for measurement of frailty, and we could not determine whether difference among these scales may affect the association between frailty and outcomes after PCI. Finally, possible risk of publication bias was raised in the meta-analysis regarding the association between frailty and poor prognosis after PCI. However, further trim-and-fill analysis suggested that the potential publication bias was not likely to affect the finding.

In conclusion, this updated meta-analysis of cohort studies suggested that frailty may be an independent risk factor of poor prognosis for patients with CAD after PCI. Future studies are needed to determine the optimal measurement tool for frailty for patients undergoing PCI, and to evaluate whether strategies to attenuate frailty could provide additional clinical benefits in these patients.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

**AUTHOR CONTRIBUTIONS**

PW and JT designed the study. PW and SZ performed literature search, study quality evaluation, and data extraction. PW and KZ performed statistical analyses. PW, SZ, and KZ interpreted the results. PW drafted the manuscript. All authors contributed to the article and approved the submitted version.

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