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# The global prevalence and potential determinants of resistant hypertension A meta-analysis

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2026, 43(Συμπλ 1):16–30

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OBJECTIVE **To determine the global prevalence and potential contributing factors of resistant hypertension.** METHOD **The study employed a meta-analysis design to consolidate existing research on resistant hypertension. Scopus, Embase, and PubMed were the selected databases for the search strategy, covering the period from January 5th to February 20th, 2025. Data collection encompassed author information, study designs, sample sizes, locations, endpoints, prevalence rates of resistant hypertension, and associated factors. Statistical analysis involved a single-arm meta-analysis to establish the frequency of resistant hypertension across studies. Furthermore, the Mantel-Haenszel test or inverse variance method was utilized to determine potential contributing factors associated with resistant hypertension.** RESULTS **In our study, a total of 42 articles were included, comprising data from 1,641,846 patients. Our investigation unveiled that the prevalence of resistant hypertension among hypertensive patients was 28.0%. Additionally, we identified several factors associated with an increased risk of resistant hypertension, including age, duration of hypertension, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure, diabetes mellitus (DM), dyslipidemia, coronary heart disease (CHD), chronic kidney disease (CKD), microalbuminuria, left ventricular hypertrophy (LVH), and estimated glomerular filtration rate (eGFR). However, we did not find any association between male gender, smoking, and the risk of resistant hypertension.** CONCLUSIONS **Our study has identified the global prevalence of resistant hypertension and potential associated factors. These findings can serve as a reference for developing strategies to manage resistant hypertension.**

Η παγκόσμια επικράτηση και οι πιθανοί παράγοντες που συμβάλλουν στην ανθεκτική υπέρταση: Μια μετα-ανάλυση

*Περίληψη στο τέλος του άρθρου*

**Key words**

Meta-analysis
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Hypertension is a chronic disease that remains a serious global issue. Data on its prevalence vary across studies. In 2019, the worldwide incidence of hypertension in individuals aged 30–79 years stood at 32% for women and 34% for men.[1] The global mortality rate due to hypertension is approximately 7.6 million deaths per year worldwide, accounting for 13.5% of total deaths.[2] Managing hypertension poses its own challenges, as the selection of antihypertensive medications needs to be tailored to the type of comorbidities, such as uncomplicated hypertension, chronic kidney disease (CKD), heart failure, coronary artery disease (CAD), and atrial fibrillation (AF).[3–6] The difficulty in managing hypertension in these populations necessitates a personalized approach to achieve blood pressure targets. Unfortunately, attaining these targets in each hypertensive population is not always straightforward and frequently results in resistant hypertension.[7]

Resistant hypertension, characterized by elevated blood pressure unresponsive to intensive medical treatment, presents a significant global health challenge.[8] The prevalence of resistant hypertension shows considerable variability in different investigations, with rates spanning from 10% to 23% across studies.[9,10] Individuals afflicted with resistant hypertension exhibit a 47% heightened susceptibility to cardiovascular disease mortality relative to their counterparts lacking this condition.[11] Complications stemming from resistant hypertension encompass a heightened susceptibility to cardiovascular incidents like stroke, myocardial

infarction, and heart failure, alongside the onset of CKD and organ impairments.[12,13] The severe implications associated with resistant hypertension emphasize the critical need for specialized attention in its management. However, despite established guidelines for treating resistant hypertension, their effectiveness in reducing its prevalence remains insufficient.[14] Furthermore, the global prevalence of resistant hypertension remains uncertain, impeding the assessment of therapeutic effectiveness and the quantification of reduction in prevalence over time with guideline implementation. Additionally, precise information concerning the determinants of resistant hypertension in hypertensive individuals is lacking, presenting challenges in personalized management approaches. Hence, meta-analysis study was warranted to ascertain the global prevalence of resistant hypertension among hypertensive patients and to identify contributing risk factors.

## MATERIAL AND METHOD

### Study design

We performed a meta-analysis from January 5th to February 20th, 2025, to assess the prevalence and risk factors of resistant hypertension among hypertensive patients. The methodologies in our meta-analysis were in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[15] The PRISMA checklist for our present study is outlined in the supplementary file.[16] We conducted searches and collected papers from PubMed, Embase, and Scopus to determine event rates, odds ratios (OR), or mean differences with 95% confidence intervals (95% CI) using either fixed or random effects models. This review has been registered in PROSPERO with the registration number 548851.

### Search strategy

Documents available in PubMed, Embase, and Scopus were searched and collected up to January 25, 2025. To obtain sufficient papers, our search strategy involved the following keywords: ["risk factors" OR "predictors"] AND ["resistant hypertension"]. These keywords were aligned with medical subject headings (MeSH) terms. Language restrictions were not applied during the search. For papers not written in English or Indonesian, consultation with the Language Center of Universitas Brawijaya was conducted. Additionally, if two papers utilized identical datasets, only the paper with the larger sample size or more recent data was incorporated. Furthermore, we manually searched through the reference lists of relevant articles to find additional papers.

### Eligibility criteria

The criteria for including studies in our analysis were as follows: (a) All studies with the following designs: randomized controlled trials (RCTs), cross-sectional, prospective, and retrospective; (b) assessment of the prevalence and risk factors of resistant hypertension among hypertensive patients; and (c) provision of adequate data for calculating OR or mean difference (MD) with 95% CI. Documents were disregarded if they fulfilled any of the subsequent criteria: Irrelevant title and or abstract, review or commentary articles, incomplete and or non-standardized data presentation, and poor quality.

### Data extraction

To acquire sufficient data for the calculation of OR or MD with 95% CI, the subsequent essential information was collected from each study: (a) First author name; (b) year of publication; (c) the nation from which the study population was drawn; (d) the number of participants in both the case and control groups; and (e) frequency of risk factors in case and control groups. To ensure data validity, the investigators (JKF, FT, NS) were appointed to extract data. Data extraction was conducted using a piloted data extraction form. In cases where discrepancies arose between the two authors, consensus was reached through discussion.

### Evaluation of the quality of the methodology

The evaluation of each paper's quality included in our analysis was independently assessed by investigators (JKF, FT, NS) using the Newcastle-Ottawa Scale (NOS). The scale evaluates three basic points reflecting the quality of each article: Patient selection (up to 4 points), the similarity between the groups (up to 2 points), and establishing the exposure (up to 3 points). Each paper was categorized based on its total score: Good (score ≥7), moderate (score ≥5 to <7), and poor (score ≤4). In cases of discrepancy between the two investigators, a consensus was reached through discussion to resolve the discrepancy.

### Measure outcome

The primary outcome evaluated was the incidence of resistant hypertension among hypertensive patients. The predictor covariates included age, gender (male), smoking, body mass index (BMI), duration of hypertension, pulse pressure, diastolic blood pressure (DBP), systolic blood pressure (SBP), diabetes mellitus (DM), dyslipidemia, coronary heart disease (CHD), left ventricular hypertrophy (LVH), microalbuminuria, CKD, and estimated glomerular filtration rate (eGFR). The identification of these predictor covariates was based on the preliminary examination of the accessible data presented in the studies that were included.

### Statistical analysis

A Z-test was employed to determine the frequency and notable risk factors of resistant hypertension among individuals with hypertension (A statistical significance level of $p<0.05$ was deemed significant). For effect estimation, OR or MD with CI were

calculated using either a fixed or random effects model. Prior to identifying significant risk factors, we assessed data heterogeneity and potential publication bias. Heterogeneity was assessed through the Q-test calculation. If the p-value was less than 0.10, a random effects model was used; otherwise, a fixed effects model was employed.[17] Additionally, we conducted Egger's test to examine publication bias, with a p-value below 0.05 suggested the existence of bias.[18] To ensure high-quality analysis, the comprehensive analyses were conducted using two distinct software applications (Review Manager [Revman Cochrane, London, UK], version 5.3 and Comprehensive Meta-Analysis [CMA, New Jersey, USA], version 2.1) by two independent authors (JKF, FT).

## RESULTS

### Eligible studies

A total of 75,536 documents were identified in Embase, PubMed, and Scopus. Of these, 36 papers were removed because they were duplicates, and 75,390 papers were omitted because their titles and or abstracts were irrelevant. We included 110 papers for further evaluation in full text. During this evaluation, 56 papers were excluded due to being review articles, and 12 papers were excluded due to insufficient data. Ultimately, we included 42 papers in our analysis.[11,19–59] The flowchart illustrating the inclusion pathway in our study is provided in figure 1. Additionally, we have summarized the baseline characteristics of the studies included in our study in table 1.

### The prevalence and risk factors of resistant hypertension among hypertensive patients

In our analysis, we included a total of 42 papers, which encompassed 345,267 cases and 1,296,579 controls.[11,19–59] Our analysis determined that the prevalence of resistant hypertension among patients with hypertension was 28.0% (event rate: 0.28; 95% CI: 0.22, 0.35; p<0.0001; p heterogeneity <0.0001; p Egger: 0.5090). Moreover, our initial evaluation identified 15 potential risk factors: Age, gender (male), smoking, duration of hypertension, BMI, SBP, DBP, pulse pressure, DM, dyslipidemia, CHD, LVH, microalbuminuria, CKD, and eGFR, suitable for meta-analysis. Among these covariates, we found that age, duration of hypertension, BMI, SBP, DBP, pulse pressure, DM, dyslipidemia, CHD, LVH, microalbuminuria, CKD, and eGFR were associated with the likelihood of developing resistant hypertension, while gender (male) and smoking were not. A total of 32 studies assessed age as a factor contributing to the risk of resistant hypertension. Of those, 27 studies were identified providing association,[19,21,23–25,29–33,35,36,38,40,41,44,45,48–54,56–58] while five other studies[26,39,43,46,59] failed to clarify the association. Our

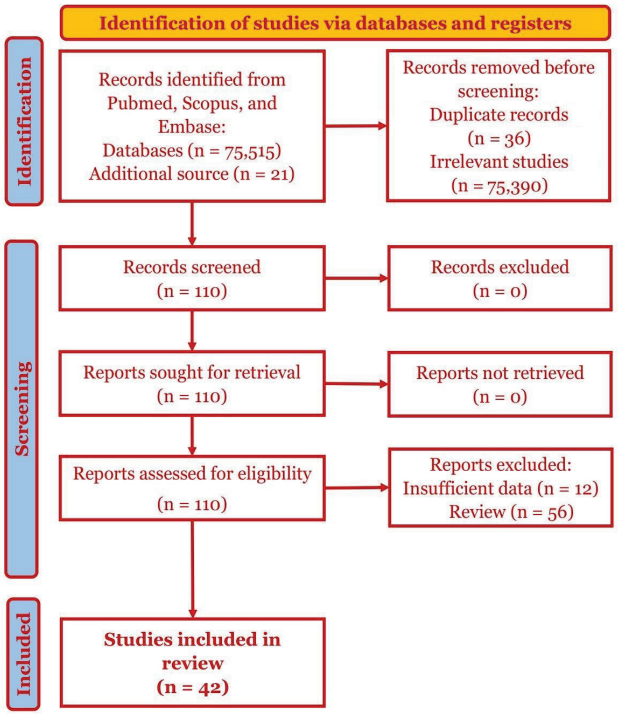


**Figure 1.** Eligibility pathway of papers included in our meta-analysis.

combined data revealed that increased age was linked to a heightened risk of resistant hypertension (MD: 2.67; 95% CI: 1.99, 3.35; p<0.0001; p heterogeneity <0.0001; p Egger: 0.2242). For the duration of hypertension, we collected five papers available for our analysis. Of those, three of them found the association,[25,36,57] and two other studies showed no association.[43,54] Our cumulative calculation found that a longer duration of hypertension was correlated with a heightened risk of resistant hypertension (MD: 2.76; 95% CI: 0.67, 4.85; p: 0.0100; p heterogeneity <0.0001; p Egger: 0.6898). For BMI, of 31 papers, the correlation was observed in 21 studies[11,19,21–25,27–29,31–33,38,40,44–46,52,53,58] and 10 other studies showed no association.[26,30,35,39,41,43,47,51,54,59] Our pooled data found that higher BMI was linked to an elevated risk of resistant hypertension (MD: 1.73; 95% CI: 1.07, 2.38; p<0.0001; p heterogeneity <0.0001; p Egger: 0.3574). For SBP, we included 25 papers in our analysis, and all of them showed correlation.[11,19,23,24,27,28,31,33,35,36,38–40,43,46–51,53,55–58] Our analysis found that higher SBP was connected with heightened risk of resistant hypertension (MD: 18.69; 95% CI: 15.08, 22.31; p<0.0001; p heterogeneity <0.0001; p Egger: 0.5362). For DBP, from 25 papers, the association was observed in 23 papers,[11,19,23,24,27,28,31,33,35,36,38,40,46–51,53,55–58] and two other studies found no association.[39,43] Our analysis confirmed that higher DBP was correlated with increased risk of resistant hypertension (MD: 5.44; 95% CI: 3.52, 7.36; p<0.0001; p heterogeneity <0.0001; p Egger: 0.8046). For pulse pressure, we included

**Table 1.** Baseline characteristics of studies included in pur meta-analysis.

| Author and year | RHT (n) | CHT (n) | Total sample (n) | Study design | Country | End-point | NOS |
|---|---|---|---|---|---|---|---|
| Bangalore et al, 2014[19] | 724 | 8,889 | 9,613 | Cohort | US | CHD | 7 |
| Carey et al, 2019[20] | 88 | 3,226 | 3,314 | Cross-sectional | US | Mixed | 6 |
| Chew et al, 2012[21] | 43,161 | 13,253 | 56,414 | Cross-sectional | Malaysia | DM | 7 |
| Culjak et al, 2018[22] | 104 | 85 | 189 | Cross-sectional | Croatia | Renal transplant | 6 |
| Daugherty et al, 2012[23] | 3,960 | 19,952 | 23,912 | Case-control | US | Mixed | 6 |
| de Beus et al, 2015[24] | 363 | 156 | 519 | Cohort | Netherlands | CKD | 7 |
| de la Sierra et al, 2012[25] | 14,461 | 13,436 | 27,897 | Case-control | Spain | Mixed | 6 |
| De Nicola et al, 2013[26] | 100 | 118 | 218 | Cohort | Italy | CKD | 6 |
| Egan et al, 2011[27] | 8,918 | 4,457 | 13,375 | Cross-sectional | US | Mixed | 7 |
| Egan et al, 2013[28] | 147,635 | 321,242 | 468,877 | Case-control | US | Mixed | 6 |
| Gandelman et al, 2019[29] | 106 | 938 | 1,044 | Cohort | US | SLE | 5 |
| García et al, 2019[30] | 69 | 43 | 112 | Cohort | Spain | Mixed | 6 |
| Gijón-Conde et al, 2014[31] | 6,292 | 42,452 | 48,744 | Cross-sectional | Spain | Mixed | 6 |
| Haddadin et al, 2019[32] | 50 | 711 | 761 | Cross-sectional | US | Obesity | 6 |
| Hanus et al, 2017[33] | 3,060 | 5,857 | 8,917 | Cross-sectional | Poland | Mixed | 6 |
| Hein et al, 2019[34] | 272 | 401 | 673 | Case-control | Belgium | Mixed | 7 |
| Holmqvist et al, 2016[35] | 7,436 | 1,742 | 9,178 | Case-control | Sweden | Mixed | 5 |
| Irvin et al, 2014[36] | 1,320 | 723 | 2,043 | Case-control | US | Mixed | 7 |
| Kaczmarski et al, 2019[11] | 1,185 | 469 | 1,654 | Cross-sectional | US | Mixed | 7 |
| Kumara et al, 2013[37] | 53 | 224 | 277 | Cross-sectional | Sri Lanka | Mixed | 5 |
| Lotufo et al, 2015[38] | 453 | 3,663 | 4,116 | Cross-sectional | Brazil | Mixed | 5 |
| Mazza et al, 2017[39] | 33 | 547 | 580 | Cross-sectional | Italy | Mixed | 6 |
| Muntner et al, 2014[40] | 1,870 | 12,814 | 14,684 | Cohort | US | ESRD | 6 |
| Muxfeldt et al, 2005[41] | 313 | 184 | 497 | Cross-sectional | Brazil | Mixed | 6 |
| Naseem et al, 2017[42] | 62 | 453 | 515 | Cross-sectional | Pakistan | Mixed | 5 |
| Oliveras et al, 2010[43] | 103 | 40 | 143 | Cross-sectional | Spain | Mixed | 6 |
| Patel et al, 2019[44] | 772 | 2,212 | 2,984 | Cross-sectional | US | Mixed | 7 |
| Persell, 2011[45] | 539 | 2,035 | 2,574 | Cross-sectional | US | Mixed | 5 |
| Pierdomenico et al, 2005[46] | 130 | 340 | 470 | Cross-sectional | Italy | Mixed | 6 |
| Ríos et al, 2013[47] | 522 | 260 | 782 | Cross-sectional | Spain | Mixed | 7 |
| Sim et al, 2015[48] | 37,223 | 410,059 | 447,282 | Cohort | US | Mixed | 6 |
| Sim et al, 2013[49] | 60,327 | 410,059 | 470,386 | Cross-sectional | US | Mixed | 5 |
| Smith et al, 2014[50] | 83 | 390 | 473 | Cohort | US | CHD | 6 |
| Tanaka et al, 2019[51] | 539 | 2460 | 2,999 | Cohort | Japan | CKD | 5 |
| Thomas et al, 2016[52] | 1,359 | 2,008 | 3,367 | Cohort | US | CKD | 6 |
| Van der Sande et al, 2018[53] | 441 | 2,564 | 3,005 | Cohort | Netherlands | Mixed | 6 |
| Veglio et al, 2001[54] | 30 | 19 | 49 | Cross-sectional | Italy | Mixed | 5 |
| Vemulapalli et al, 2017[55] | 468 | 3,935 | 4,403 | Cohort | US | Mixed | 6 |
| Verdalles et al, 2016[56] | 82 | 536 | 618 | Case-control | Spain | CKD | 5 |
| Wu et al, 2018[57] | 169 | 2,664 | 2,833 | Cross-sectional | China | Mixed | 6 |
| Yokoyama et al, 2015[58] | 295 | 585 | 880 | Cross-sectional | Japan | DM | 7 |
| Zheutlin et al, 2018[59] | 97 | 378 | 475 | Cohort | US | Mixed | 7 |

RHT: Resistant hypertension, CHT: Controlled hypertension, CHD: Coronary heart disease, DM: Diabetes mellitus, CKD: Chronic kidney disease, NOS: Newcastle-Ottawa Scale, US: United States, ESRD: End-stage renal disease

three studies,[24,33,47] and the association was only found in two studies.[24,33] Our combination data found that elevated pulse pressure was related to increased risk of resistant hypertension (MD: 9.95; 95% CI: 1.04, 18.86; p<0.0290; p heterogeneity <0.0001; p Egger: 0.8417). For DM, a total of 34 papers were included in our analysis. Of them, 28 papers showed association,[11,19–21,23,25–28,31,35–38,40,43–46,48–53,55–57] and six other papers showed no association.[24,39,41,42,47,54] Our pooled data revealed that patients with DM was 1.82-fold associated with increased risk of resistant hypertension (OR: 1.82; 95% CI: 1.56, 2.13; p<0.0001; p heterogeneity <0.0001; p Egger: 0.9143). For dyslipidemia, we included 11 studies. Of them, the association was observed in five studies,[25,31,32,34,50] and six others showed no association.[30,37,41–43,57] Our analysis revealed that subjects with dyslipidemia were associated with increased risk of resistant hypertension (OR: 1.36;

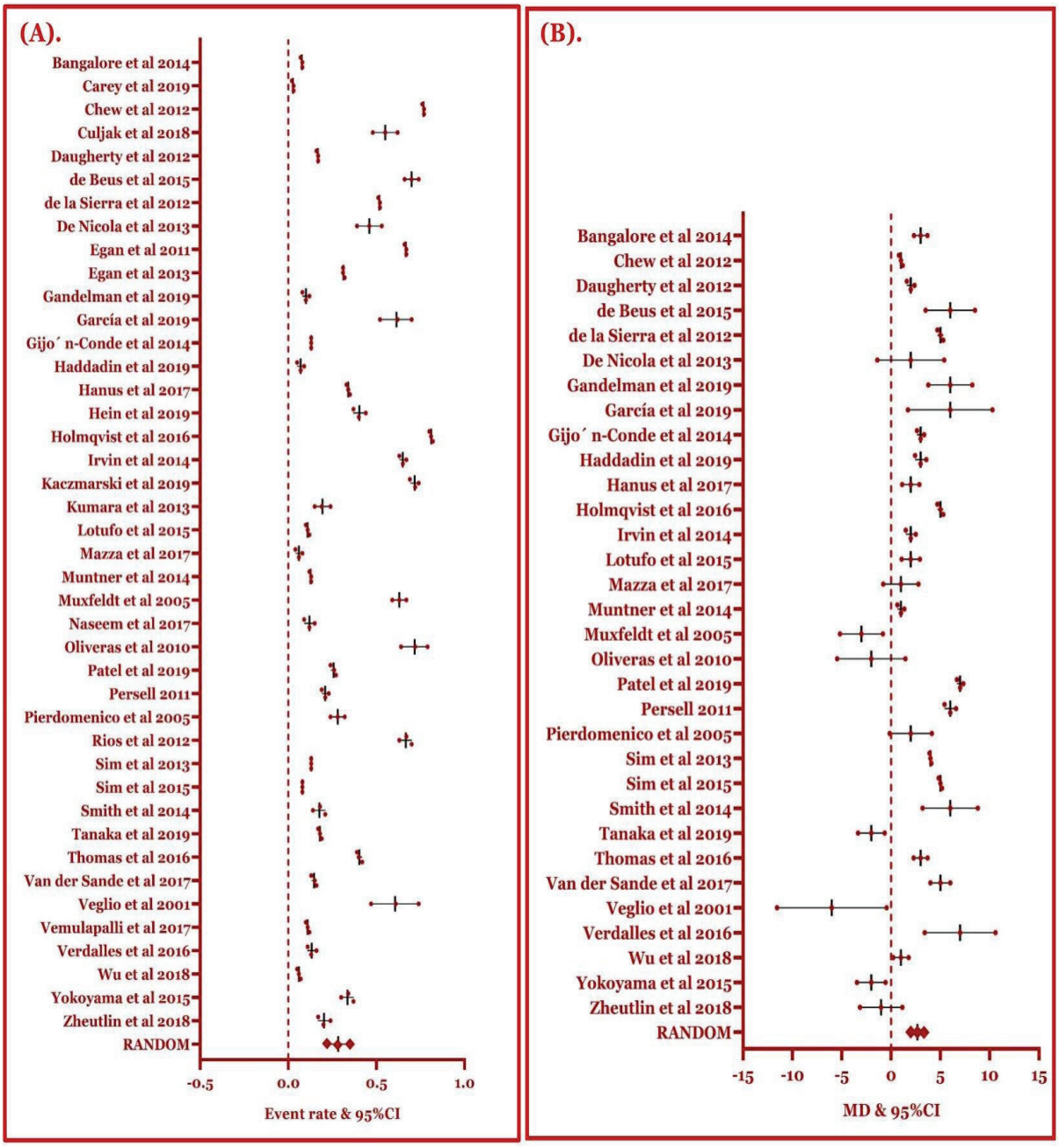


**Figure 2.** Forest plot of the prevalence of resistant hypertension [Event rate: 0.28; 95% confidence interval [CI]: 0.22, 0.35; p<0.0001; p heterogeneity <0.0001; p Egger: 0.5090] (A) and the association between increased age as the risk factors of resistant hypertension [mean difference [MD]: 2.67; 95% CI: 1.99, 3.35; p<0.0001; p heterogeneity <0.0001; p Egger: 0.2242] (B).

95% CI: 1.17, 1.58; p<0.0001; p heterogeneity <0.0001; p Egger: 0.6020). For CHD, a total of 22 papers were included in our analysis. Of those, the correlation was found in 18 papers,[19,23,26,31,33,35–38,40,44,45,48,49,52,53,55,56] and four other papers found no association.[32,41,50,58] Our data indicated that patients with CHD had 1.67-fold increased risk of resistant hypertension (OR: 1.67; 95% CI: 1.47, 1.90; p<0.0001; p heterogeneity <0.0001; p Egger: 0.0586). For LVH, we included 10 studies. We found the association in eight studies,[25,26,30,38,40,41,46,53] while two studies showed no association.[39,43] Our pooled data revealed that increased risk of resistant hypertension was observed higher in patients with LVH (OR: 2.75; 95% CI: 2.07, 3.66; p<0.0001; p heterogeneity <0.0001; p Egger: 0.3046). For microalbuminuria, of six papers,[23,30,38,39,53,58] the association was found in four papers.[23,30,38,53] Our pooled calculation found that patients with microalbuminuria were observed to have increased risk of resistant hypertension (OR: 2.70; 95% CI: 1.55, 4.70; p<0.0001; p heterogeneity <0.0001; p Egger: 0.7215). For CKD, we involved 13 studies. Of those, 10 studies showed association,[19,20,23,28,30–32,47–49] and three studies showed no correlation.[27,37,42] Our combination data indicated that patients with CKD was 1.77-fold associated with increased risk of resistant hypertension (OR: 1.77; 95% CI: 1.11, 2.83; p: 0.0170; p heterogeneity <0.0001; p Egger: 0.9336). Moreover, for eGFR, a total of 16 papers were analyzed. Of them, the correlation was observed in 11 papers,[26,29,31,33,40,45,48,52,53,56,58] and no association was found in five papers.[11,24,39,43,47] Our analysis indicated that patients with resistant hypertension showed a correlation with lower eGFR (MD: -6.52; 95% CI: -8.83, -4.21; p<0.0001; p heterogeneity <0.0001; Egger's p=0.1592). The summary of potential risk factors for resistant hypertension is provided in table 2.

## The cause of heterogeneity and potential bias in publication

We detected evidence of heterogeneity (pH <0.10) across all covariates (age, male, smoking, duration of hypertension, BMI, SBP, DBP, pulse pressure, DM, dyslipidemia, CHD, LVH, microalbuminuria, CKD, and eGFR). Therefore, data interpretation for all covariates was conducted using a random-effects model. Furthermore, to assess publication bias, we conducted an Egger test. The Egger test calculation revealed that all covariates showed no potential publication bias (pE >0.05). Table 2 provides an overview of potential publication bias and heterogeneity.

**Table 2.** Summary of factors associated with the risk of resistant hypertension.

| Parameters | NS | Model | RHT | | Controlled-HT | | OR*/ MD** | 95% CI | pH | pE | p |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Value | n | Value | n | | | | | |
| Age *(years)* | 32 | Random | 63.8±6.2 | 184,189 | 61.3±6.6 | 1,012,304 | 2.67** | 1.99–3.35 | <0.0001 | 0.2242 | <0.0001 |
| Male | 39 | Random | 185,449 [53.8] | 344,983 | 667,238 [51.5] | 1,295,726 | 0.99* | 0.93–1.06 | <0.0001 | 0.3129 | 0.8640 |
| Smoking | 24 | Random | 4,971 [12.0] | 41,289 | 20,706 [12.9] | 160,228 | 0.92* | 0.85–1.01 | <0.0001 | 0.0621 | 0.0800 |
| Duration of HT *(years)* | 5 | Random | 13.0±5.5 | 16,083 | 10.8±4.1 | 28,638 | 2.76** | 0.67–4.85 | <0.0001 | 0.6898 | 0.0100 |
| BMI (mmHg) | 31 | Random | 30.5±4.9 | 238,503 | 28.7±2.5 | 518,416 | 1.73** | 1.07–2.38 | <0.0001 | 0.3574 | <0.0001 |
| SBP (mmHg) | 25 | Random | 151.6±7.7 | 172,035 | 133.0±11.6 | 1,269,353 | 18.69** | 15.08–22.31 | <0.0001 | 0.5362 | <0.0001 |
| DBP (mmHg) | 25 | Random | 81.8±5.8 | 172,035 | 76.4±5.4 | 1,269,353 | 5.44** | 3.52–7.36 | <0.0001 | 0.8046 | <0.0001 |
| Pulse pressure (mmHg) | 3 | Random | 66.0±5.3 | 2,018 | 56.0±14.0 | 2,797 | 9.95** | 1.04–18.86 | <0.0001 | 0.8417 | 0.0290 |
| Diabetes mellitus | 34 | Random | 107,617 [46.3] | 232,361 | 320,764 [30.2] | 1,061,358 | 1.82* | 1.56–2.13 | <0.0001 | 0.9143 | <0.0001 |
| Dyslipidemia | 11 | Random | 10,820 [48.5] | 22,238 | 23,166 [37.8] | 61,270 | 1.36* | 1.17–1.58 | <0.0001 | 0.6020 | <0.0001 |
| Coronary heart disease | 22 | Random | 45,276 [36.0] | 125,781 | 213,891 [21.8] | 982,162 | 1.67* | 1.47–1.90 | <0.0001 | 0.0586 | <0.0001 |
| LVH (ECG) | 10 | Random | 3,381 [18.8] | 17,973 | 3,605 [10.7] | 33,749 | 2.75* | 2.07–3.66 | <0.0001 | 0.3046 | <0.0001 |
| Microalbuminuria | 6 | Random | 326 [6.2] | 5,251 | 600 [2.2] | 27,354 | 2.70* | 1.55–4.70 | <0.0001 | 0.7215 | <0.0001 |
| ESRD | 13 | Random | 45,467 [21.1] | 215,460 | 179,298 [15.2] | 1,179,709 | 1.77* | 1.11–2.83 | <0.0001 | 0.9336 | 0.0170 |
| eGFR | 16 | Random | 62.0±16.0 | 51,646 | 68.4±15.4 | 477,962 | -6.52** | [-8.83]–[-4.21] | <0.0001 | 0.1592 | <0.0001 |

Data were presented in mean±SD or n[%]

NS: Number of studies, SD: Standard deviation, HT: Hypertension, RHT: Resistant hypertension, OR: Odd ratio, MD: Mean difference, pH: p heterogeneity, pE: p Egger, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, LVH: Left ventricular hypertrophy, ECG: Electrocardiography, CKD: Chronic kidney disease, eGFR: Estimated glomerular filtration rate

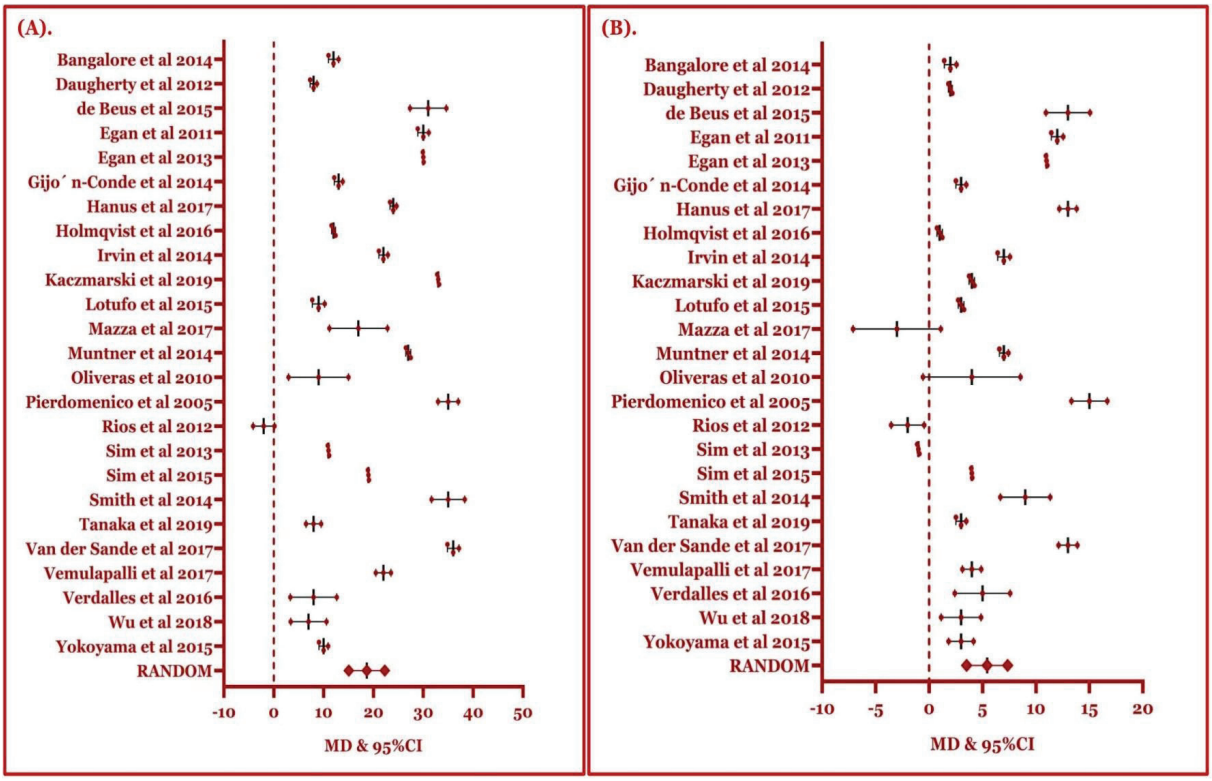


**Figure 3.** Forest plot of increased systolic blood pressure (SBP) [mean difference [MD]: 18.69; 95% confidence interval [CI]: 15.08, 22.31; p<0.0001; p heterogeneity <0.0001; p Egger: 0.5362] (A) and diastolic blood pressure (DBP) [MD: 5.44; 95% CI: 3.52, 7.36; p<0.0001; p heterogeneity <0.0001; p Egger: 0.8046] (B) as the risk factors of resistant hypertension.

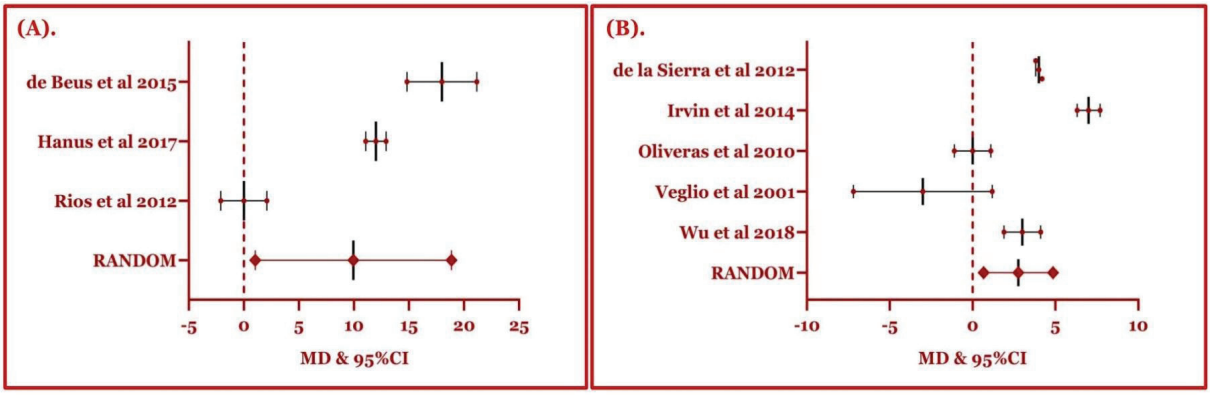


**Figure 4.** Forest plot describing pulse pressure (PP) [mean difference [MD]: 9.95; 95% confidence interval [CI]: 1.04, 18.86; p<0.0290; p heterogeneity <0.0001; p Egger: 0.8417] (A) and duration of hypertension [MD: 2.76; 95% CI: 0.67, 4.85; p: 0.0100; p heterogeneity <0.0001; p Egger: 0.6898] (B) as the risk factors of resistant hypertension.

## DISCUSSION

In our study, the general prevalence of resistant hypertension among patients with hypertension was 28%. A previous meta-analysis on this topic conducted in 2015 determined the overall occurrence of resistant hypertension among hypertensive patients to be 14%.[60] The total prevalence in our study was higher than that reported in the previous meta-analysis, prompting a need for clarification regarding the techniques and methods used in data calculation. We identified several differences in data calculation between our study and the previous one. Firstly, there was a variance in sample size between our study and the previous one. While our study involved 42

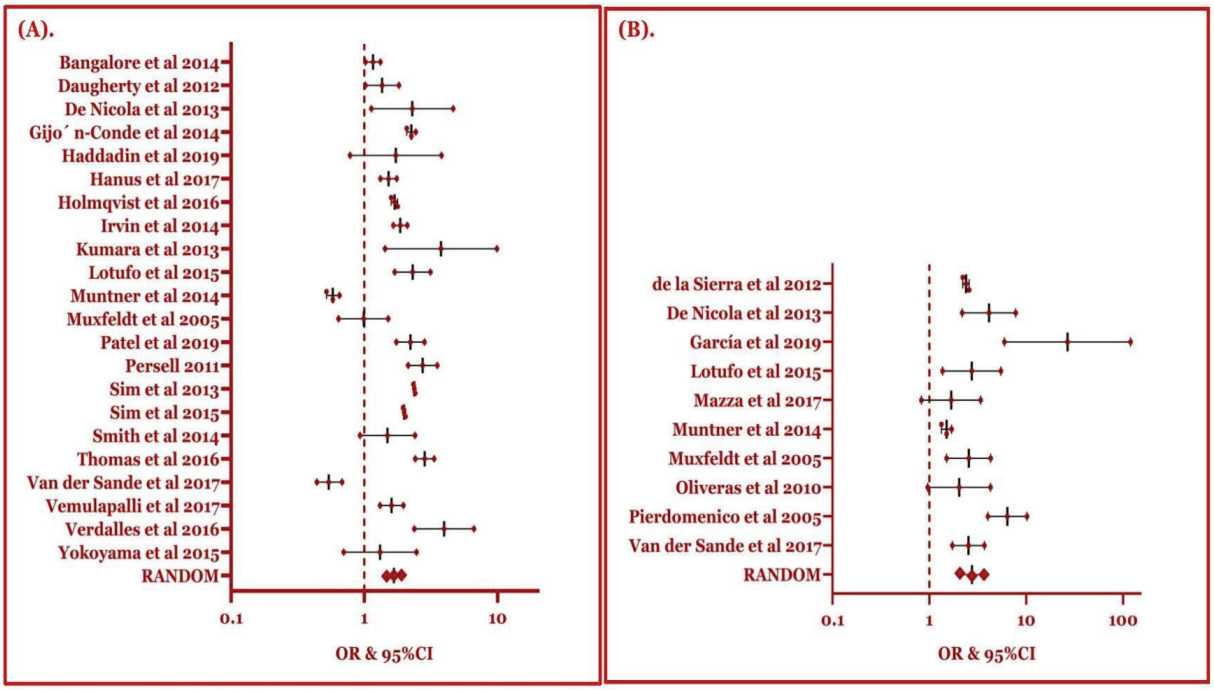


**Figure 5.** Forest plot describing coronary heart disease (CHD) [odds ratio [OR]: 1.67; 95% confidence interval [CI]: 1.47, 1.90; p<0.0001; p heterogeneity <0.0001; p Egger: 0.0586] (A) and left ventricular hypertrophy (LVH) [OR: 2.75; 95% CI: 2.07, 3.66; p<0.0001; p heterogeneity <0.0001; p Egger: 0.3046] (B) as the risk factors of resistant hypertension.

articles, the previous study included only 24 articles. This suggests that our study's calculations were more robust in determining the total prevalence of resistant hypertension among hypertensive patients. Secondly, the previous study did not address potential publication bias in data calculation, whereas our study reported on potential publication bias. Publication bias is a critical factor in determining the cumulative effect estimate in meta-analysis. Differences in publication bias values in meta-analysis imply variations in the model for determining effect estimates. Thirdly, the previous study solely reported on the total prevalence of resistant hypertension, without mentioning factors that may have contributed to its development. In addition to reporting the total prevalence of resistant hypertension, our study also identified potential factors that may have contributed to increasing the risk of resistant hypertension. Thus, our study provided more accurate and comprehensive information compared to the previous meta-analysis.

The findings of this investigation revealed an association between advanced age, prolonged duration of hypertension, elevated SBP, DBP, pulse pressure (PP), history of CHD, and LVH with an increased susceptibility to resistant hypertension. Theoretical explication of these findings presents challenges, yet several hypotheses may elucidate the mechanisms underlying this association. Aging is postulated to heighten the risk of resistant hypertension through alterations in the renin-angiotensin-aldosterone pathway, which is integral to blood pressure regulation and becomes dysregulated with advancing age.[61] Additionally, age-related cumulative damage to the cardiovascular system, such as increased plaque formation and arterial stiffness, may exacerbate resistant hypertension.[62,63] Furthermore, comorbidities prevalent in the elderly population, such as DM, sleep apnea, and chronic renal disease, may exacerbate susceptibility to resistant hypertension.[64,65] On the other hand, we also found that a prolonged duration of hypertension emerged as a significant risk factor for resistant hypertension. Individuals with this condition are at an elevated risk of developing cardiovascular diseases, stroke, coronary artery disease, renal disease, and dementia, conditions often associated with resistant hypertension.[66] Moreover, cardiac pathologies, particularly a history of heart disease, were identified as a major predisposing factor for resistant hypertension. The association between heart disease and resistant hypertension is multifaceted, encompassing structural and functional alterations in blood vessels and impaired renal function, which collectively contribute to the refractory nature of hypertension in these individuals.[67,68] LVH, resulting from longstanding, uncontrolled hypertension, emerged as another significant contributor to resistant

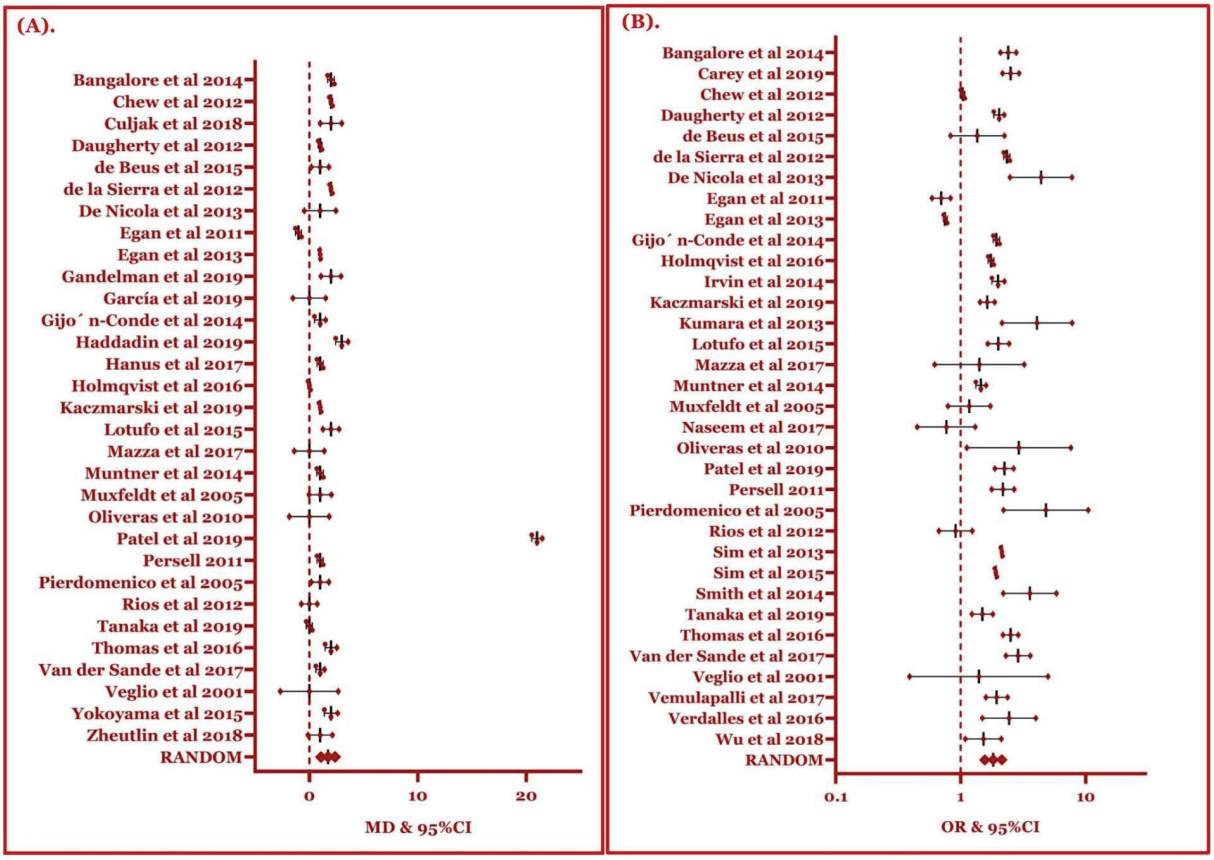


**Figure 6.** Forest plot of body mass index (BMI) [mean difference [MD]: 1.73; 95% confidence interval [CI]: 1.07, 2.38; p<0.0001; p heterogeneity <0.0001; p Egger: 0.3574] (A) and diabetes mellitus (DM) [odds ratio [OR]: 1.82; 95% CI: 1.56, 2.13; p<0.0001; p heterogeneity <0.0001; p Egger: 0.9143] (B) as the risk factors of resistant hypertension.

hypertension. Pathophysiological mechanisms underlying this relationship include increased vascular resistance, impaired arterial compliance, salt retention, activation of the renin-angiotensin-aldosterone system, and endothelial dysfunction, collectively perpetuating the refractory nature of hypertension in individuals with LVH.[69]

Our investigation revealed an association between elevated BMI, DM, and dyslipidemia with an increased likelihood for resistant hypertension. Various mechanisms could elucidate these observations. The mechanism underpinning the association of high BMI with resistant hypertension involves several key factors. First, obesity triggers heightened secretion of certain hormones and inflammatory markers such as insulin, leptin, and adiponectin, disrupting normal blood pressure regulation and fostering the development of hypertension.[70] Second, excess adiposity may increase sympathetic nervous system activity, which regulates blood pressure.[71] Third, obesity frequently coexists with insulin resistance and metabolic syndrome, both of which exacerbate hypertension development.[72] Additionally, excessive weight gain can induce structural and functional changes in blood vessels, such as endothelial dysfunction and arterial stiffness, further promoting resistant hypertension.[73] Moreover, high BMI often accompanies unhealthy lifestyle behaviors such as poor diet and physical inactivity, which independently contribute to the development of hypertension and exacerbate its effects.[74,75] On the other hand, DM and dyslipidemia are chronic conditions implicated in the development of resistant hypertension. Both conditions affect blood pressure regulation and promote the occurrence of resistant hypertension. DM may elevate blood pressure due to impaired glucose metabolism and dysregulation of the renin-angiotensin-aldosterone system.[76] Furthermore, dyslipidemia can induce a hyperinflammatory state and endothelial dysfunction, contributing to the development of resistant hypertension.[77] Additionally, dyslipidemia may lead to arterial plaque accumulation, narrowing arteries, and increasing blood flow resistance. These factors, combined with the underlying pathophysiological mechanisms of DM and dyslipidemia, may synergistically contribute to the development of resistant hypertension.[78]

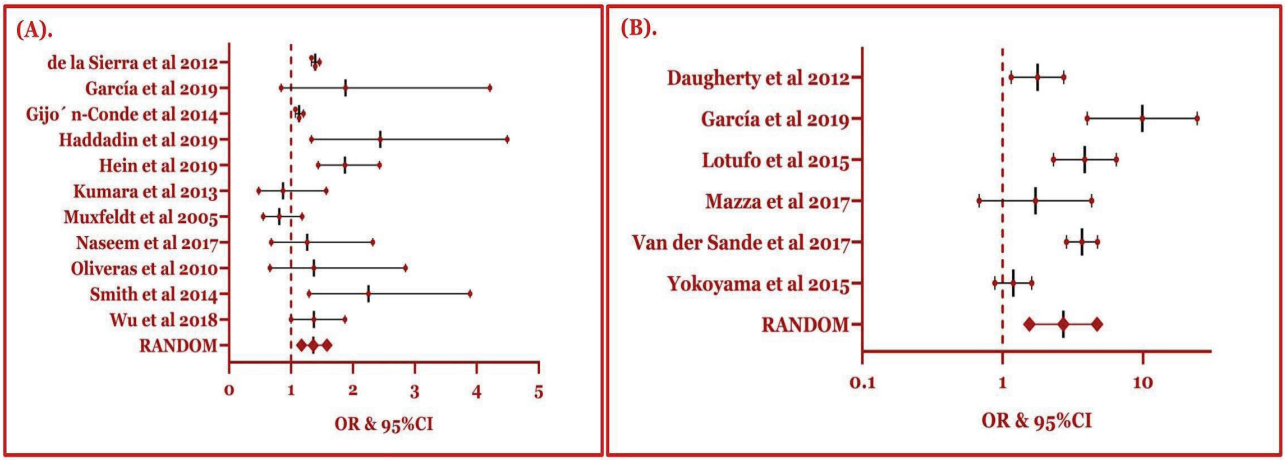


**Figure 7.** Forest plot describing dyslipidemia [odds ratio [OR]: 1.36; 95% confidence interval [CI]: 1.17, 1.58; p<0.0001; p heterogeneity <0.0001; p Egger: 0.6020] (A) and microalbuminuria [OR: 2.70; 95% CI: 1.55, 4.70; p<0.0001; p heterogeneity <0.0001; p Egger: 0.7215] (B) as the risk factors of resistant hypertension.

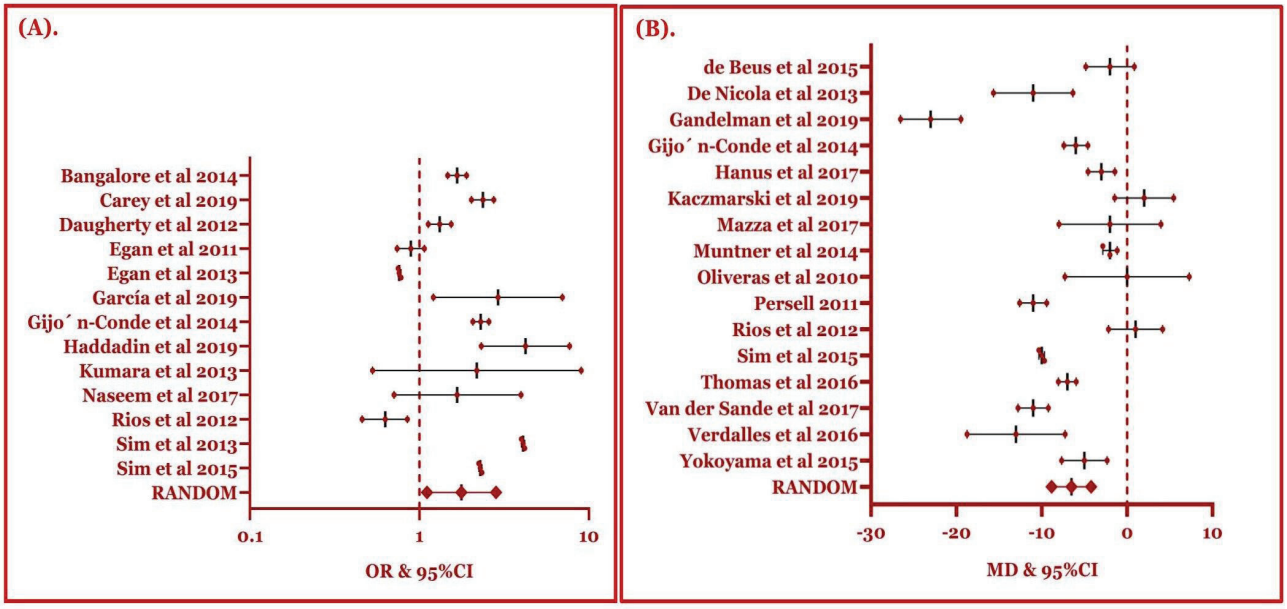


**Figure 8.** Forest plot describing end-stage renal disease (ESRD) [odds ratio (OR): 1.77; 95% confidence interval (CI): 1.11, 2.83; p: 0.0170; p heterogeneity <0.0001; p Egger: 0.9336] (A) and estimated glomerular filtration rate (eGFR) [mean difference [MD]: (-6.52); 95% CI: (-8.83), (-4.21); p<0.0001; p heterogeneity <0.0001; p Egger: 0.1592] (B) as the risk factors of resistant hypertension.

Our investigation identified microalbuminuria, decreased eGFR, and CKD as pivotal predictive factors for the onset of resistant hypertension. This discovery is intriguing and likely occurs through various mechanisms. CKD denotes irreversible kidney damage, resulting in impaired waste filtration and regulation of fluid-electrolyte balance.[79] Conversely, microalbuminuria entails the excretion of small amounts of albumin in urine, serving as a marker for the progression of chronic renal failure. Patients with microalbuminuria face an elevated risk of transitioning to macroalbuminuria and eventual CKD.[80] Moreover, individuals with CKD exhibit a heightened susceptibility to resistant hypertension.[81] This interconnectedness stems from multiple factors. First, CKD-related kidney damage disrupts blood pressure regulation, potentially leading to treatment-resistant hypertension. Second, microalbuminuria indicates renal blood vessel damage, further impeding blood pressure regulation. Additionally, both CKD and microalbuminuria foster inflammation and oxidative stress, recognized contributors to resistant hypertension.[82]

Identifying the total prevalence and risk factors for resistant hypertension holds significant clinical implications across various domains. Data on the total prevalence of resistant hypertension serve as initial epidemiological insights and references in policy-making for managing the condition. Furthermore, insights into the risk factors of resistant hypertension can inform personalized interventions to prevent or manage the condition more effectively. By identifying these risk factors, healthcare providers can tailor treatment strategies to individual patients, prioritizing interventions such as weight loss, blood sugar control, and cardio-protective medications for those with specific risk factors like obesity, DM, or a history of cardiovascular disease.[83] Moreover, early identification of risk factors can facilitate the detection and intervention of underlying conditions contributing to the development of resistant hypertension, such as kidney disease, thereby prompting timely management to mitigate its impact. Additionally, recognizing risk factors empowers healthcare providers to educate patients on lifestyle modifications like reducing sodium intake and increasing physical activity, thereby reducing the risk of developing resistant hypertension. This comprehensive approach to identifying risk factors not only enhances clinical decision-making and treatment optimization but also fosters early intervention and lifestyle changes to mitigate risk.[83] Future investigations should aim to deepen our understanding of the multifaceted mechanisms underlying resistant hypertension, encompassing genetic, lifestyle, and socio-economic determinants. Additionally, focusing on developing targeted interventions and personalized treatment strategies based on identified risk factors is crucial for improving blood pressure control in high-risk hypertensive patients. This approach has the potential to revolutionize the management landscape of resistant hypertension.

This meta-analysis study faced several limitations that warranted attention. First, several factors potentially influencing the development of resistant hypertension, such as xanthine oxidase activity, mitochondrial DNA damage-associated molecular patterns, circulating ACE2 levels, brain natriuretic peptide, and troponin, were not evaluated in this study.[37] Second, disparities in sample size proportions across individual studies required special consideration when generalizing or interpreting the overall study findings. Third, the majority of articles included in this study were based on observational study designs; therefore, further research applying interventions to risk factors might have been needed to enhance the quality of evidence generated. Fourth, the variability in endpoints among the included studies in this meta-analysis may have led to diverse outcomes, adding complexity to the analysis and interpretation of the data. Therefore, it was crucial to interpret the results of this study with caution, considering all these limitations.

In conclusion, our study identified that the prevalence of resistant hypertension among hypertensive patients was 28%. Additionally, we found associations between various factors and the risk of resistant hypertension, including age, duration of hypertension, BMI, SBP, DBP, pulse pressure, DM, dyslipidemia, CHD, LVH, microalbuminuria, CKD, and eGFR. These findings may serve as initial reference points for formulating policies regarding the management of resistant hypertension.

## ΠΕΡΙΛΗΨΗ

**Η παγκόσμια επικράτηση και οι πιθανοί παράγοντες που συμβάλλουν στην ανθεκτική υπέρταση: Μια μετα-ανάλυση**

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**ΣΚΟΠΟΣ** Καθορισμός της παγκόσμιας επικράτησης και των πιθανών παραγόντων που συμβάλλουν στην ανθεκτική υπέρταση. **ΥΛΙΚΟ-ΜΕΘΟΔΟΣ** Η μελέτη χρησιμοποίησε σχεδιασμό μετα-ανάλυσης για να ενοποιήσει την υπάρχουσα έρευνα σχετικά με την ανθεκτική υπέρταση. Τα Scopus, Embase και PubMed ήταν οι επιλεγμένες βάσεις δεδομένων για τη στρατηγική αναζήτησης, καλύπτοντας την περίοδο από 5 Ιανουαρίου έως 20 Φεβρουαρίου 2025. Η συλλογή δεδομένων περιλάμβανε πληροφορίες συγγραφέων, σχεδιασμούς μελετών, μεγέθη δειγμάτων, τοποθεσίες, τελικά

σημεία, ποσοστά επικράτησης ανθεκτικής υπέρτασης και σχετικούς παράγοντες. Η στατιστική ανάλυση περιέλαβε ανάλυση μίας μόνο ομάδας (single-arm meta-analysis) για τον καθορισμό της συχνότητας της ανθεκτικής υπέρτασης σε διάφορες μελέτες. Επί πλέον, η δοκιμή Mantel-Haenszel ή η μέθοδος αντίστροφης διασποράς χρησιμοποιήθηκε για τον προσδιορισμό των πιθανών παραγόντων που σχετίζονται με την ανθεκτική υπέρταση. **ΑΠΟΤΕΛΕΣΜΑΤΑ** Περιλήφθηκαν συνολικά 42 άρθρα, που περιλάμβαναν δεδομένα από 1.641.846 ασθενείς. Αποκαλύφθηκε ότι η επικράτηση της ανθεκτικής υπέρτασης μεταξύ των υπερτασικών ασθενών ήταν 28%. Επί πλέον, εντοπίστηκαν αρκετοί παράγοντες που σχετίζονται με αυξημένο κίνδυνο ανθεκτικής υπέρτασης, όπως η ηλικία, η διάρκεια της υπέρτασης, η συστολική αρτηριακή πίεση, η διαστολική αρτηριακή πίεση, η διαφορά των πιέσεων, ο σακχαρώδης διαβήτης, η δυσλιπιδαιμία, η στεφανιαία νόσος, η χρόνια νεφρική νόσος, η μικρολευκωματινουρία, η υπερτροφία της αριστερής κοιλίας και ο εκτιμώμενος ρυθμός σπειραματικής διήθησης. Ωστόσο, δεν βρέθηκε κάποια συσχέτιση μεταξύ του ανδρικού φύλου, του καπνίσματος και του κινδύνου ανθεκτικής υπέρτασης. **ΣΥΜΠΕΡΑΣΜΑΤΑ** Η μελέτη μας εντόπισε την παγκόσμια επικράτηση της ανθεκτικής υπέρτασης και τους πιθανούς σχετικούς παράγοντες. Αυτά τα ευρήματα μπορεί να χρησιμεύσουν ως αναφορά για την ανάπτυξη στρατηγικών διαχείρισης της ανθεκτικής υπέρτασης.

**Λέξεις ευρετηρίου:** Ανθεκτική υπέρταση, Επικράτηση, Μετα-ανάλυση, Προγνωστικοί παράγοντες

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