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Prevalence of cardiovascular symptoms in post-acute COVID-19 syndrome: a meta-analysis

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Abstract

Background Since its emergence in 2019, COVID-19 has continued to pose significant threats to both the physical and mental health of the global population, as well as to healthcare systems worldwide (Raman et al., Eur Heart J 43:1157–1172, 2022). Emerging evidence indicates that COVID-19 may lead to post-acute COVID-19 syndrome (PACS) with cardiovascular implications, potentially driven by factors such as ACE2 interaction with viruses, systemic inflammation, and endothelial dysfunction. However, there remains a limited amount of research on the cardiovascular manifestations of PACS, which may delay the development of optimal treatment strategies for affected patients. Therefore, it is crucial to investigate the prevalence of cardiovascular sequelae in COVID-19 patients and to determine whether COVID-19 infection acts as an independent risk factor for these outcomes.

Methods This meta-analysis adhered to PRISMA guidelines and was registered in PROSPERO (CRD42024524290). A systematic search of PubMed, Embase, and the Cochrane Library was conducted up to March 17, 2024. The primary outcomes included hypertension, palpitations, and chest pain, with pooled effect estimate reported as proportions and odds ratios (ORs) with 95% confidence intervals (CIs). Sensitivity and subgroup analysis were performed to assess the robustness of the results and to identify sources of heterogeneity.

Results A total of 37 studies, encompassing 2,965,467 patients, were included in the analysis. Pooled results from case–control studies revealed that, compared to the control group, the ORs of chest pain in the COVID-19 group was 4.0 (95% CI: 1.6, 10.0). The ORs for palpitation and hypertension were 3.4 (95% CI: 1.1, 10.2) and 1.7 (95% CI: 1.6, 1.8), respectively. The proportions of PACS patients experiencing chest pain, palpitation, and hypertension as sequelae were 22% (95% CI: 14%, 33%), 18% (95% CI: 13%, 24%), and 19% (95% CI: 12%, 31%), respectively.

Conclusions Our findings indicate that 15% of COVID-19 patients experience cardiovascular sequelae. Furthermore, COVID-19 infection significantly increases the likelihood of developing these sequelae compared to uninfected individuals. Future research should prioritize investigating the underlying pathological mechanisms and developing targeted preventive and management strategies.

Trial registration CRD42024524290.

Keywords COVID-19, Post acute COVID-19 syndrome, Cardiovascular symptoms, Meta analysis

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Background

In 2019, the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) triggered a global pandemic, resulting in widespread disease and mortality. During the acute phase, the virus induces immune hyperactivity and multi-organ damage, primarily manifesting as respiratory failure, headache, myalgia, anosmia, ageusia, and vascular inflammation. These symptoms severely affected both the physical and mental health of individuals worldwide, placing immense strain on healthcare systems [1]. Although extensive research has been conducted on the diagnosis, pathogenesis, and acute complications of COVID-19 [2, 3], the long-term sequelae have emerged as an increasingly significant public health concern in the post-pandemic era [4–6].

Reports of post-acute COVID-19 syndrome (PACS) have notably increased, with millions of individuals worldwide affected by its long-term effects [7, 8]. According to the World Health Organization (WHO), PACS is defined as a syndrome that typically manifests in individuals three months following the onset of COVID-19, and cannot be attributed to alternative diagnoses [9]. Common symptoms include fatigue, sleep disturbances, neurological impairments, and more than 200 other manifestations [10]. The mechanisms underlying PACS are associated with viral replication, residual viral components causing immune dysregulation, and interactions between the host microbiome and the virus, which may lead to aberrant immune responses [11].

Cardiovascular disease (CVD) is a leading cause of global mortality, influenced by various environmental, behavioral, and metabolic factors [12, 13]. Research indicates that CVD may be a significant component of PACS [14–16], although the mechanisms underlying long-term cardiac damage after COVID-19 remain poorly understood. Two main hypotheses have been proposed [17] : (1) A persistent viral reservoir in cardiac tissue may trigger a chronic inflammatory response following acute infection. The virus binds to its key receptor, angiotensin-converting enzyme 2 (ACE2), leading to ACE2 downregulation, which in turn causes the accumulation of angiotensin II (Ang II), promoting endothelial inflammation, oxidative stress, and apoptosis, thus exacerbating endothelial dysfunction [18, 19]; (2) In later stages of infection, an autoimmune response against cardiac antigens may develop. Studies have shown an increased frequency of cardiac-specific antibodies in COVID-19 patients [20, 21].

Although several studies have examined the association between PACS and cardiovascular involvement, they have several limitations [14, 22–24]: (1) The majority of studies are retrospective, lacking prospective designs, which restricts causal inferences; (2) The follow-up periods are generally short, typically around 4 weeks, hindering the assessment of long-term cardiovascular outcomes; (3) High heterogeneity across studies diminishes the reliability of the findings. As a result, the relationship between PACS and CVD remains poorly understood, complicating the timely diagnosis and management of affected patients.

To address these limitations, our study aims to provide a comprehensive evaluation of the long-term cardiovascular effects of COVID-19. Specifically, our objectives are: (1) To incorporate more prospective studies and combine both retrospective and prospective data to improve the reliability of the findings; (2) To include studies with longer follow-up periods ($\geq$12 weeks) to more accurately estimate the prevalence and long-term risk trends of cardiovascular sequelae, as defined by the WHO; (3) To reduce heterogeneity and explore its sources through sensitivity and subgroup analyses; (4) While the investigation of mechanisms is beyond the scope of this study, we will quantify the risks associated with COVID-19 cardiovascular symptoms and provide potential directions for future mechanistic research.

Methods

Registration

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, the PRISMA checklist is presented in Additional file 1. The study protocol was registered in PROSPERO, the international prospective register of systematic reviews (CRD42024524290).

Search strategy and selection criteria

Two authors (HML and LWH) systematically searched PubMed, Embase, and the Cochrane Library for relevant articles published in English up to March 17, 2024. The search keywords across all databases included "Post-Acute COVID-19 Syndrome," "long-haul COVID-19," "cardiovascular symptoms," and "adverse cardiac event." The detailed search strategy is provided in Additional file 2: Table S1. Titles, abstracts, and full texts of the selected studies were independently screened by two researchers (HML and BH) using EndNote X9 software, with any discrepancies resolved by consensus or, if necessary, through third-party adjudication (LWH).

Studies were included if they met the following criteria: (1) original research or follow-up studies; (2) reported at least one cardiovascular symptom related to PACS, along with relevant laboratory findings or patient-reported outcomes (e.g., hypertension levels); (3) provided original data suitable for calculation and analysis. Exclusion criteria were as follows: (1) review articles or case report;

(2) studies that did not report a cardiovascular symptom related to PACS; (3) studies with a median or mean follow-up time of less than three months after SARS-CoV-2 infection or COVID-19 diagnosis.

Data extraction and quality assessment

Data extraction

The search results were imported for abstract screening, and duplicates as well as irrelevant studies were excluded based on predefined inclusion and exclusion criteria. To enhance the robustness of our analysis, we established specific diagnostic criteria for cardiovascular symptoms studies included in this study. Data were included for analysis only if they met the following diagnostic requirements: (1) cardiovascular symptoms were defined according to disease classifications in 'The International Statistical Classification of Diseases and Related Health Problems 10th Revision' (ICD-10) or based on guidelines from authoritative organizations such as the American College of Cardiology (ACC) and the European Society of Cardiology (ESC). Meanwhile, these symptoms were according with WHO's standardized definition of PACS; (2) diagnoses were confirmed by qualified clinicians and substantiated with detailed clinical records; (3) patients provided self-reports using internationally validated assessment tools, such as the Post COVID-19 Functional Status (PCFS) scale and the Symptom Burden Questionnaire for Long COVID (SBQ-LC). Two researchers independently extracted data from each eligible study. Data were collected using a predesigned form, which was agreed upon by all authors, to capture study characteristics (e.g., study type, follow-up duration, registration, year of publication, author, and country of enrollment), patient demographics (e.g., age, sex), and outcomes of interest, including the prevalence of PACS-related cardiovascular symptoms such as hypertension, palpitations, and chest pain.

Quality assessment

In this study, the quality of the included observational studies was assessed using the Newcastle–Ottawa Scale (NOS), and the result is presented in Additional file 3: Table S2. The NOS evaluates studies across three key domains: selection (representativeness and definition of the study population), comparability (control of confounding factors), and outcome assessment (reliability of outcome measurements). Each domain comprises specific criteria, yielding a cumulative score ranging from 0 to 9 points. Based on the total score, studies were categorized as follows: high quality (7–9 points), moderate quality (5–6 points), and low quality (below 5 points). Utilizing this systematic approach enables us to better assess and mitigate potential sources of heterogeneity in study quality, thereby enhancing the robustness and reliability of our meta-analysis findings.

Statistical analysis

The study was conducted using R software (version 4.3.1) with the meta package (version 6.5.0). This meta-analysis reports odds ratios (ORs) for the primary outcome and the prevalence of cardiovascular symptoms associated with PACS, accompanied by the corresponding 95% confidence intervals (CIs). While some prospective studies were included in our analysis, the inclusion of retrospective studies was unavoidable. In such mixed-design scenarios, using ORs is generally preferred, as ORs facilitate the integration of data from studies with varying designs.

Heterogeneity was assessed using the I^2 statistic. Due to the variability inherent in observational studies, such as case series, heterogeneity is often high, stemming from differences in study design, sample sources, and other factors. Consequently, a higher I^2 threshold, typically ranging from 60 to 75%, is deemed acceptable [25]. In our analysis, an I^2 value greater than 60% was considered indicative of substantial heterogeneity, necessitating the use of a random-effects model. This model better accounts for inter-study variability and provides more robust overall effect estimates compared to the fixed-effects model. Consequently, the final analysis results were derived using the random-effects model.

Sensitivity and subgroup analyses were conducted to evaluate the robustness of the findings and to investigate potential sources of heterogeneity. Sensitivity analysis involved systematically excluding individual studies or those deemed low quality to assess the impact of factors such as study quality, sample size, and methodological variations on the pooled results. Additionally, subgroup analyses were performed based on factors such as geographic region, age, or other relevant characteristics to identify possible sources of variability. These analyses were intended to confirm the stability and reliability of our results, ensuring that no single study or methodological aspect disproportionately influenced the overall conclusions.

Funnel plots, along with Peters' and Egger's regression tests, were utilized to detect potential biases in the published literature.

Results

Overview of included studies

We identified 1,274 records from all databases during the preliminary literature search: 69 from the Cochrane Library, 580 from Embase, and 625 from PubMed. After removing duplicates, 1,054 studies were screened by title and abstract, with 114 deemed eligible. Following full-text screening, 77 studies were excluded, resulting in 37

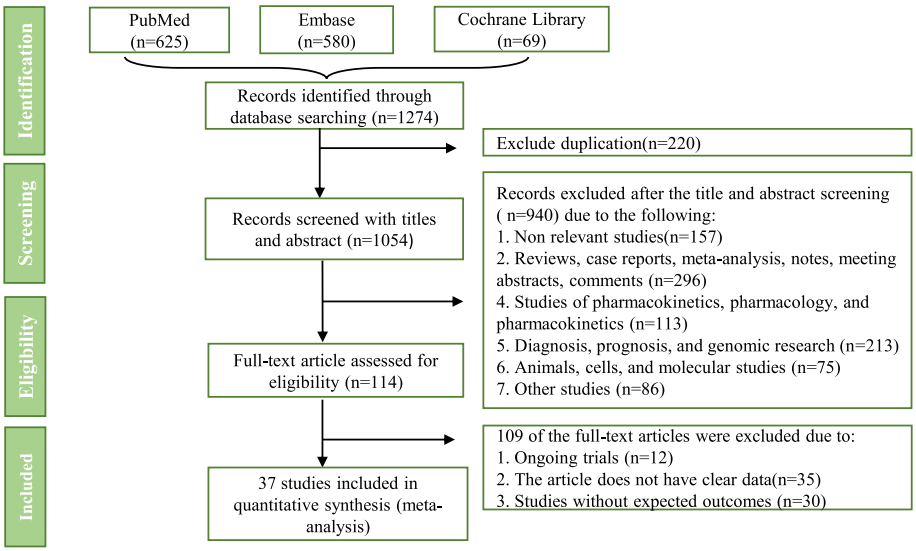

Fig. 1 The process of literature search and selection. The comprehensive searches of PubMed, Embase, and Cochrane Library databases yielded 1274 records. After removing duplicates, 1054 records were screened by title and abstract, and 171 article texts were screened full text. Finally, a total of 37 studies were included in the meta-analysis

articles involving 2,965,467 participants for inclusion in our meta-analysis (Fig. 1).

Five studies analyzed data from the United States, and three each from Poland, Germany, the United Kingdom, and China. Two studies were from Switzerland, Spain, Israel, and India, and one study each from Turkey, Romania, Mexico, Italy, Iran, Greece, Estonia, Croatia, Brunei, Australia, and South Korea. Sample sizes ranged from 60 to 2,386,822, with follow-up periods ranging from 3 to 12 months. Detailed characteristics of the 37 included studies are provided in Table 1.

Results of analysis

We conducted a meta-analysis of studies with both experimental and control groups to assess whether COVID-19 infection significantly increases the risk of developing cardiovascular symptoms compared to uninfected individuals.

Chest pain

Eight case control studies, encompassing a total of 116,778 patients who developed chest pain following COVID-19 infection, were included in this meta-analysis. The pooled analysis indicated that the OR of chest pain in the COVID-19 group compared to the control group was 4.0 (95% CI 1.6, 10.0; Fig. 2).

Palpitation

Five case control studies, including a total of 543,369 patients, were analyzed to assess the risk of palpitation symptom following COVID-19 infection. The pooled analysis revealed that the OR of palpitation in the COVID-19 group compared to the control group was 3.4 (95% CI: 1.1, 10.2; Fig. 3).

Hypertension

A meta-analysis was conducted on nine case control studies involving a total of 17,317 patients with hypertension. The analysis revealed a OR of 1.7 (95% CI: 1.6, 1.8; Fig. 4) for the prevalence of hypertension in the experimental group compared to the control group.

Results of case series studies

The forest plot results indicated that chest pain was the most prevalent cardiovascular symptom in post-acute COVID-19 syndrome (22%, 95% CI: 14%, 33%). Hypertension (19%, 95% CI: 12%, 31%) and palpitations (18%, 95% CI: 13%, 24%) were also commonly observed (Fig. 5).

Clinical interpretation of findings

This meta-analysis indicates that COVID-19 patients face a significantly increased risk of developing sequelae such as hypertension and chest pain. These findings underscore the importance of regular follow-up for convalescing patients to monitor cardiovascular symptoms, enabling early detection of potential long-term complications. Additionally, for clinical patients experiencing persistent symptoms, comprehensive cardiovascular assessments are recommended to rule out chronic conditions. These results could inform future strategies for COVID-19 rehabilitation and long-term patient follow-up.

Table 1 Baseline characteristics of studies included in meta-analysis

Authors	Year	Study design	Country	Sample Size	Age	Male/Female	Follow-up	Quality score
Hyejin Lee et.al	2022	Prospective study	Korea	2386822	NA	1074070/1312052	3 Month	8
Kin Wah Fung et.al	2023	Retrospective study	USA	433869	75	NA	12 Month	8
Claire E Hastie et.al	2022	Retrospective study	England	94443	45	36819/57624	6 Month	8
Anna Tisler et.al	2022	Retrospective study	Estonia	19460	65	8951/10508	12 Month	9
Tanayott Thaweethai et.al	2023	Prospective study	USA	9764	45	2776/6932	6 Month	9
Christin Heidemann et.al	2023	Retrospective study	Germany	4817	NA	2224/2593	12 Month	8
Sudhir Bhandari et.al	2023	Retrospective study	India	3840	NA	2338/1512	5 Month	6
Christian Schmidt-Lauber et.al	2023	Cross-sectional study	USA	2160	56	1006/1154	4 Month	9
Anuradha Thalian Chathoth et.al	2023	Cross-sectional study	India	937	41	NA	3 Month	5
Alejandra Meza Contreras et.al	2023	Retrospective study	USA	843	47	347/496	3 Month	8
Reza Golchin Vafa et.al	2023	Retrospective study	Iran	843	NA	394/449	12 Month	5
Mateusz Babicki et.al	2023	Retrospective study	poland	801	53.5	277/524	12 Month	8
Qiutang Xiong et.al	2020	Prospective study	CHINA	722	NA	341/381	3 Month	7
Xian Chen et.al	2021	Prospective study	CHINA	715	69	367/448	6 Month	6
Salma Charfeddine et.al	2021	Prospective study	Swiss	798	50	315/483	6 Month	9
Lourdes Mateu et.al	2023	Prospective study	Spanish	548	48	217/331	3 Month	6
Adriana Roca-Fernandez et.al	2023	Prospective study	England	534	44	147/387	6 Month	7
Michael Gottlieb et.al	2022	Retrospective study	Poland	488	44	181/307	3 Month	8
Ainur T Tauekelova et.al	2023	Retrospective study	Kazakhstan	322	54	101/211	6 Month	7
Mustafa Erol et.al	2023	Retrospective study	Turkey	289	56	128/161	3 Month	7
Karina Carvalho Marques et.al	2022	Retrospective study	USA	249	42	156/93	3 Month	8
Jun Zhang et.al	2022	Prospective study	CHINA	241	61	112/136	12 Month	9
Isaac Núñez et.al	2023	Prospective study	Mexico	202	53	132/70	3 Month	5
ĐiĐi Delalć et.al	2022	Retrospective study	Croatia	199	57.3	92/107	12 Month	7
Frank Lloyd Dini et.al	2022	Retrospective study	Italy	180	47	69/111	3 Month	5
Giovanna Pelà et.al	2021	Prospective study	Swiss	160	60	96/64	5 Month	6
Julia Hanne Niebauer et.al	2023	Prospective study	Austria	150	53	90/60	6 Month	6
Katarzyna Gryglewska-Wawrzak et.al	2023	Retrospective study	Poland	146	NA	54/92	3 Month	8
Irina Mihaela Abdulan et.al	2023	Retrospective study	Romania	140	60	26/44	3 Month	9
Muhammad Syafiq Abdullah et.al	2023	Retrospective study	Brunei	132	37.1	78/54	12 Month	5
Moritz C Halfmann et.al	2023	Retrospective study	Germany	129	51	64/65	4 Month	6
Yishay Szekely et.al	2021	Prospective study	Israel	106	106	71/35	3 Month	8
Paula Poyatos et.al	2024	Prospective study	Spanish	103	61	NA	3 Month	8
Alon Shechter et.al	2022	Retrospective study	Israel	96	54	44/52	12 Month	5
Mark Philip Cassar et.al	2021	Prospective study	England	88	55	52/36	3 Month	7
Sotiriadou M et.al	2022	Prospective study	Greece	71	55	33/38	3 Month	5
Kirsten Thiele et.al	2022	Retrospective study	Germany	60	62	48/20	6 Month	6

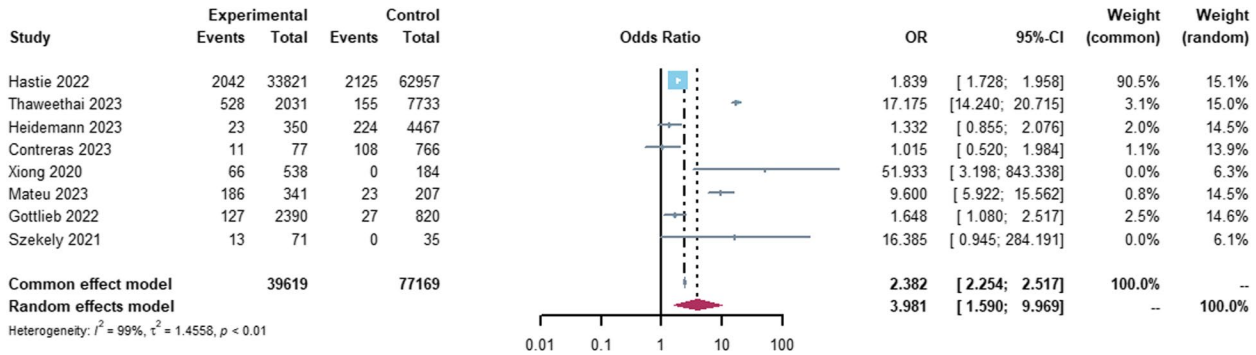

Fig. 2 Forest plot of case control studies for chest pain. Each line represents the 95% confidence interval for the effect size of an individual study. The squares indicating the point estimate of the effect (OR) and the overall effect is represented by the diamond, where a value greater than 1 suggests an increased risk. Heterogeneity across studies was assessed using the I^2 statistic. The results showed that patients with COVID-19 had a higher prevalence of chest pain compared to the uninfected population

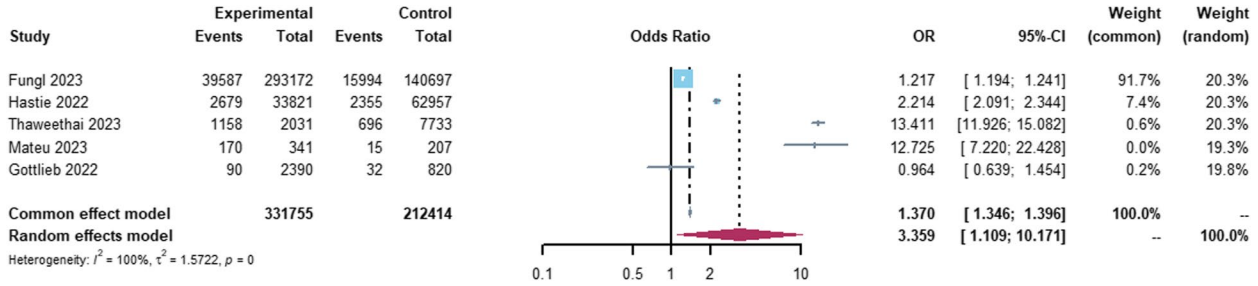

Fig. 3 Forest plot of case control studies for palpitation. Each line represents the 95% confidence interval for the effect size of an individual study. The squares indicating the point estimate of the effect (OR) and the overall effect is represented by the diamond, where a value greater than 1 suggests an increased risk. Heterogeneity across studies was assessed using the I^2 statistic. The results showed that patients with COVID-19 had a higher prevalence of palpitation compared to the uninfected population

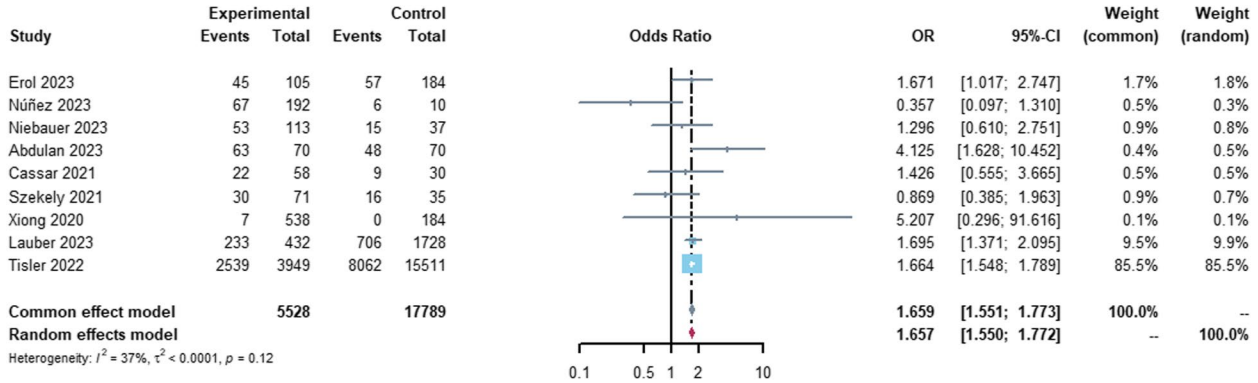

Fig. 4 Forest plot of case control studies for hypertension. Each line represents the 95% confidence interval for the effect size of an individual study. The squares indicating the point estimate of the effect (OR) and the overall effect is represented by the diamond, where a value greater than 1 suggests an increased risk. Heterogeneity across studies was assessed using the I^2 statistic. The results showed that patients with COVID-19 had a higher prevalence of hypertension compared to the uninfected population

Subgroup analysis

To systematically explore the sources of heterogeneity, assess potential differences among specific subpopulations, and confirm the robustness of the overall analysis, we performed subgroup analyses stratified by age (< 60 years vs. ≥ 60 years); geographic region (Europe, America, and Asia) and study type (prospective study, retrospective study).

(1) Subgroup analysis by Study Design for case control study of Hypertension:

In the retrospective case–control study subgroup, the OR was 1.7 (95% CI: 1.6–1.8, $I^2 = 18\%$); In the prospective study subgroup, the OR was 1.0 (95% CI: 0.7–1.6, $I^2 = 16\%$; Additional file 4: Figure S1).

(2) Subgroup analysis by Study Design for case control study of Chest pain:

The OR in retrospective case–control studies was 1.6 (95% CI: 1.3–2.1, $I^2 = 42\%$); The OR in prospective studies was notably higher at 14.2 (95% CI: 8.6–23.4, $I^2 = 46\%$; Additional file 4: Figure S2).

(3) Subgroup analysis by Study Design for case series study of Chest pain:

In the retrospective case-series subgroup, the prevalence was 25% (95% CI: 14%-37%, $I^2 = 99\%$); In the prospective study subgroup, the prevalence was slightly higher at 27% (95% CI: 14%-50%, $I^2 = 99\%$; Additional file 4: Figure S2).

(4) Subgroup analysis by age for case series study of Chest pain:

Individuals under 60 years: Prevalence was 32% (95% CI: 16%-47%, $I^2 = 100\%$); Individuals aged 60 years and above: Prevalence was 18% (95% CI: 12%-25%, $I^2 = 70\%$; Additional file 4: Figure S2).

(5) Subgroup analysis by Study Design for case series study of Palpitations:

In the retrospective case-series subgroup, the prevalence was 20% (95% CI: 12%-27%, $I^2 = 94\%$); In the prospective study subgroup, the prevalence was 17% (95% CI: 6%-27%, $I^2 = 98\%$; Additional file 4: Figure S3).

(6) Subgroup analysis by age for case series study of Palpitations:

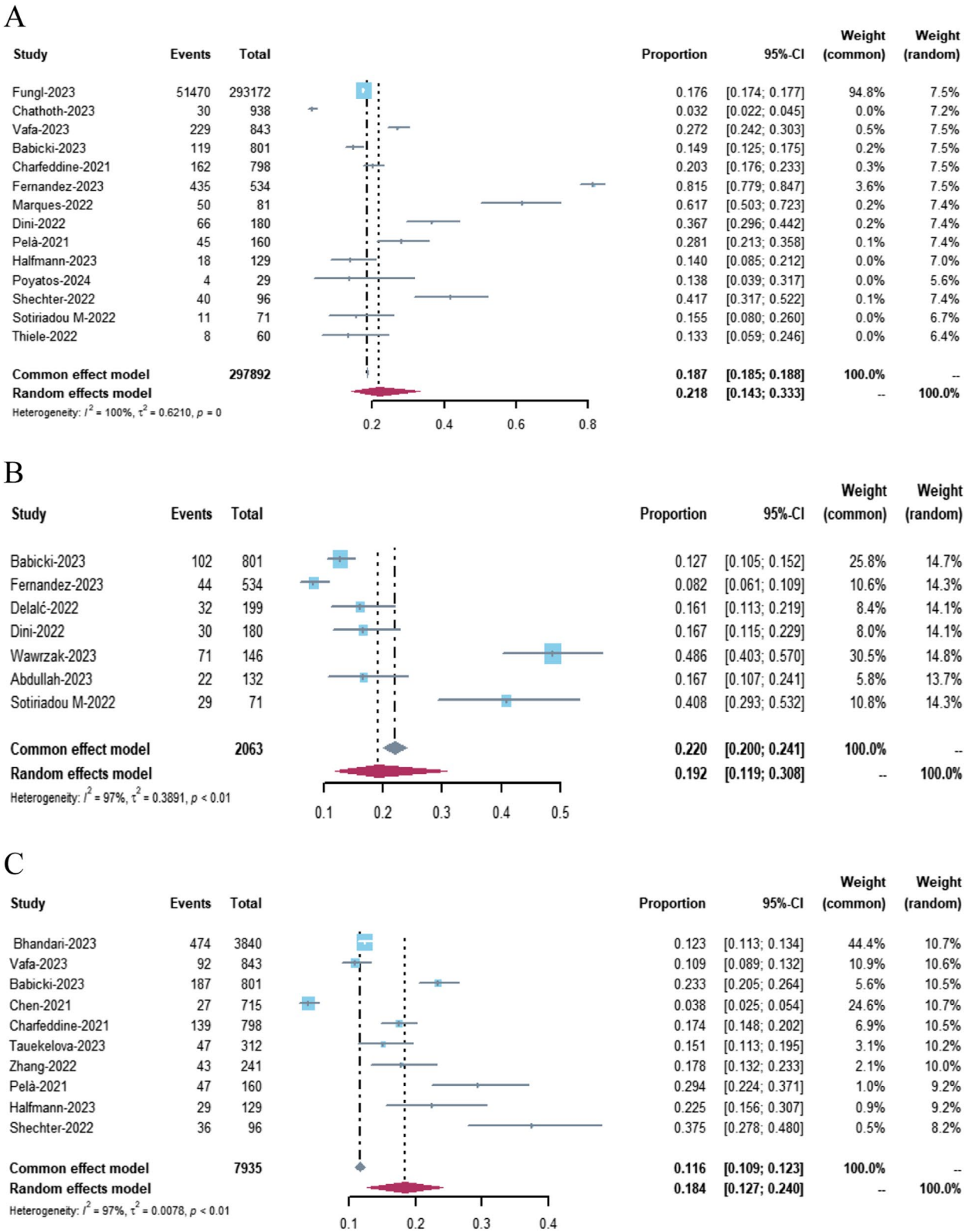

Fig. 5 Results of case series studies. **A** Forest plot of chest pain; (**B**) Forest plot of hypertension; (**C**) Forest plot of palpitation. Each line represents the 95% confidence interval for the effect size of an individual study. The squares indicating the point estimate of the effect (OR) and the overall effect is represented by the diamond, where a value greater than 1 suggests an increased risk. Heterogeneity across studies was assessed using the I^2 statistic. The results showed the prevalence of chest pain、hypertension and palpitation in COVID-19 patients

Individuals under 60 years: Prevalence was 20% (95% CI: 14%-27%, $I^2=93\%$); Individuals aged 60 years and above: Prevalence was 17% (95% CI: 2%-31%, $I^2=97\%$; Additional file 4: Figure S3).

(7) Subgroup analysis by regions for case series study of Palpitations:

In European and America populations, the prevalence was 20% (95% CI: 14%-27%, $I^2=94\%$); In Asian populations, the prevalence was slightly lower at 16% (95% CI: 6%-27%, $I^2=97\%$; Additional file 4: Figure S3).

Sensitivity analysis

To identify sources of heterogeneity in the meta-analysis and to mitigate the impact of excessive heterogeneity from individual studies on the overall results, we performed a sensitivity analysis. This analysis involved sequentially removing each study and re-evaluating the effect estimates and heterogeneity index (I^2) for the remaining studies. We then compared these results with those from the full analysis to determine whether the removal of any single study caused substantial changes in the effect estimates or I^2, thus assessing the robustness of our findings.

Results are as follows:

(1) The sensitivity analysis of the hypertension case series indicated a prevalence rate of 15% (95% CI: 13%-18%; Additional file 5: Figure S4), with low heterogeneity ($I^2=16\%$).

(2) Sensitivity analysis of the case–control studies on chest pain showed an OR of 1.6 (95% CI: 1.3–2.0, $I^2=46\%$). Sensitivity analysis of the case-series studies on chest pain revealed a prevalence of 27% (95% CI: 25%-30%, $I.^2=9\%$; Additional file 5: Figure S5)

(3) Sensitivity analysis of the prospective subgroup in the chest pain case-series study revealed a 20% prevalence of chest pain (95% CI: 15%-26%, $I^2=58\%$; Additional file 5: Figure S5). In contrast, sensitivity analysis of the retrospective subgroup did not substantially reduce heterogeneity, suggesting that study design may be a significant source of heterogeneity.

(4) Sensitivity analysis of the elderly subgroup in the chest pain case-series study revealed a 18% prevalence of chest pain (95% CI: 17%-18%, $I^2=0\%$). The midlife subgroup showed an 18% prevalence of chest pain (95% CI: 13%-22%, $I^2=53\%$; Additional file 5: Figure S5).

(5) Sensitivity analysis of the palpitations case-series study revealed a prevalence of palpitations of 12% (95% CI: 11%-13%, $I^2=43\%$; Additional file 5: Figure S6).

(6) Sensitivity analysis of the prospective subgroup in the palpitations case-series study revealed a prevalence of palpitations of 21% (95% CI: 14%-28%, $I^2=80\%$). In the retrospective subgroup, the prevalence of palpitations was 12% (95% CI: 11%-13%, $I^2=43\%$; Additional file 5: Figure S6).

(7) Sensitivity analysis of the Asian subgroup in the palpitations case-series study revealed a 14% prevalence of palpitations (95% CI: 11%-18%, $I^2=68\%$). In the Europe-America group, the prevalence was 24% (95% CI: 21%-27%, $I^2=23\%$; Additional file 5: Figure S6), suggesting that regional differences may contribute to the observed heterogeneity.

(8) Sensitivity analysis of the palpitation case-series study in the middle-aged subgroup showed a 17% prevalence of palpitations (95% CI: 15%-19%, $I^2=38\%$; Additional file 5: Figure S6).

Risk of bias assessment

In this analysis, we employed Peter's test, Egger's test, and compared effect value between funnel plots and trim-and-fill plots to assess publication bias in the included studies (Additional files 4–5: Figure S1-6). The results of Peter's and Egger's tests (Additional file 6: Table S3) indicated no significant publication bias. Minor variations in effect value were observed between the effect size funnel plots and the funnel plots after applying the trim-and-fill method in both case control studies and case-series studies (Additional files 4–5: Figure S1-6). This suggests that the studies included in the analysis were relatively comprehensive and did not exhibit substantial publication bias. According to the quality assessment criteria,23 studies were classified as high quality, and 14 as medium quality.

Discussion

Interpretation of main findings

The key findings in our analysis include:

(1) Compared to the uninfected control group, the OR for hypertension (1.7, $I^2=37\%$) and cardiovascular symptoms like chest pain (4.0, $I^2=99\%$) and palpitations (3.4, $I^2=100\%$) highlight the significant cardiovascular burden among COVID-19 survivors, consistent with prior research indicating long-term sequelae in this population [26–29].

However, the high heterogeneity observed in the chest pain and palpitations analyses calls attention to the need for further investigation [30]. We performed sensitivity analyses. For chest pain, the OR decreased to 1.6 ($I^2=46\%$), with a reduction in heterogeneity, suggesting that the initial variability was influenced by certain study-specific factors.

(2) The prevalence of cardiovascular sequelae observed in our study was slightly higher than the 14.8% and 11%

reported in previous studies [31, 32]. Specifically, the prevalence of palpitations was 12% ($I^2=43\%$), hypertension was 15% ($I^2=16\%$), and chest pain was 27% ($I^2=9\%$). While the heterogeneity of these analyses was relatively low, the reduction in sample size following sensitivity analyses may limit the external validity of these results. Future studies should include a larger number of high-quality studies to address this limitation.

(3) To further investigate the sources of heterogeneity, subgroup analyses were conducted based on study design and geographic location. Specifically, the prevalence of chest pain was 25% ($I^2=99\%$) in retrospective studies, compared to 27% ($I^2=99\%$) in prospective studies. Following sensitivity analysis, the prevalence in the prospective subgroup was adjusted to 20% ($I^2=58\%$), indicating a reduction in heterogeneity and greater consistency across studies. Similarly, sensitivity analysis revealed that the prevalence of palpitations in the Asian subgroup was reduced from 17% ($I^2=97\%$) to 14% ($I^2=68\%$), while in the European subgroup, it increased from 20% ($I^2=94\%$) to 24% ($I^2=23\%$). These findings suggest that both study design and geographic factors may be key sources of heterogeneity in the analysis [33].

Strengths and limitation

Numerous meta-analyses have explored the sequelae of COVID-19. However, they often exhibit certain limitations: (1) analyses frequently reveal high heterogeneity, which diminishes the reliability of the conclusions; (2) many included studies lack a standardized definition of PACS, often conflating symptom sets from different timeframes (e.g., 4, 8, and 12 weeks post-infection); (3) the sample sizes of the included studies are small, undermining the robustness of the pooled estimates; (4) there is a noticeable geographic bias, with studies concentrated in specific regions, thereby limiting the generalizability of the findings to other populations [34–37].

Our analysis tries to compensate for these limitations: To explore potential sources of heterogeneity, we conducted subgroup analyses, sensitivity analyses, and bias assessments, ensuring that the findings accurately reflected real-world conditions. In our study, we adhered to the WHO's standardized definition of PACS and utilized established cardiovascular symptom definitions from authoritative sources such as ICD-10 and the guidelines of the ACC and ESC. This approach minimizes potential definitional inconsistencies. Additionally, we included studies with a sample size of at least 60 to enhance the robustness of effect size estimates. By incorporating data from diverse populations and rigorously following PRISMA guidelines, we aimed to strengthen the credibility of our findings.

It is essential to acknowledge several limitations of this study. Firstly, the limited number of available studies prevented comprehensive subgroup or sensitivity analyses for key variables, including age, pre- and post-Omicron infection periods, and gender.

Secondly, potential biases and imprecision in our study may stem from population selection bias in the included studies. Specifically, the geographic distribution of study populations is predominantly concentrated in several Western countries. These regions differ from Africa and South America in terms of health systems, socioeconomic and population characteristics, which may influence the presentation and reporting of PACS. For instance, some studies have highlighted a correlation between PACS and lower socioeconomic status [38, 39], with individuals in the most socioeconomically disadvantaged areas of England reporting higher rates of long-term COVID [40]. Ethnic disparities in the burden of PACS have also been observed, with higher prevalence of certain symptoms, such as diabetes, chest pain, and cough, in Black individuals, and olfactory issues in White individuals [41]. Furthermore, a higher prevalence of Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS) has been reported in Black and Asian children [42].

Moreover, inherent biases, such as small sample sizes and publication bias, could further limit the precision and generalizability of our findings.

To address these limitations, future research should aim to include larger sample sizes, standardize study designs, and implement stricter symptom measurement protocols to enhance the reliability and external validity of the results. Future meta-analyses should also take into account factors such as ethnic and geographic variability to explore their potential influence on long-term COVID sequelae.

Future research

The pathological mechanisms underlying cardiovascular damage potentially caused by SARS-CoV-2 infection remain incompletely understood. Several hypotheses have been proposed. First, the SARS-CoV-2 virus may induce significant endothelial injury and promote microthrombus formation [43, 44]. Studies have demonstrated that the lungs of COVID-19 patients exhibit unique vascular characteristics, including significant endothelial injury and widespread thrombosis with microangiopathy [45, 46]. Additionally, biomarkers of endothelial dysfunction in patients with long-term COVID-19 have been shown to persistently elevate [47], possibly as a result of lipid peroxidation [48].Additionally, a marked increase in ACE2-expressing cells was observed in the lungs of

COVID-19 patients compared to those with influenza [45]. Since ACE2 serves as the primary receptor for the virus, its interaction with SARS-CoV-2 [49], particularly within the cardiovascular system, may trigger an overactive inflammatory response, apoptosis, thrombosis, and vasoconstriction, thereby exacerbating cardiovascular complications. Therapeutic strategies involving the use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) or to infuse soluble ACE2 have been proposed to alleviate the severity of cardiovascular manifestations in COVID-19 patients, potentially offering novel approaches for mitigating cardiovascular damage associated with the infection [50, 51]. The clinical validation of the efficacy of these new therapies and the in-depth exploration of the molecular mechanisms will require more studies in the future.

With the increase of acute phase research, many acute phase complications such as dyslipidemia and diabetes have been identified [52–55]. Now, there is increasing attention to the long-term sequelae of COVID-19 [34, 56–58]. Beyond cardiovascular issues, research is expanding into the relationship between COVID-19 sequelae and psychiatric disorders (e.g., depression, cognitive impairment) and respiratory conditions (e.g., pulmonary fibrosis, dyspnea). However, the mechanisms underlying these sequelae are still not fully understood. To address this global challenge, further research is essential to elucidate the pathological mechanisms and establish standardized diagnostic criteria.

Additionally, high heterogeneity can render the pooled effect size unstable, thereby diminishing the robustness and reliability of the results, which limits their generalizability. To improve consistency in future research, adopting standardized and authoritative diagnostic criteria, incorporating a greater number of high-quality prospective studies, and minimizing publication bias are Methods that can be used.

Relevance and implications

Awareness of the long-term effects of COVID-19 is increasing in the post-pandemic era. Long-COVID as a heterogeneous disease with manifestations that differ by sex [59, 60], severity of acute disease [61] and vaccination status [62, 63]. However, there is currently no standardized diagnostic and treatment protocol for PACS especially in CVD disease [64, 65], leading to challenges in patient management [58, 66]. Thus, further research into the pathological mechanisms of PACS-CVD [67] and standardized interventions for COVID-19 patients with cardiovascular sequelae are crucial for improving long-term outcomes and reducing the disease burden [68, 69].

Based on our findings and existing literature, we propose the following clinical recommendations for managing cardiovascular symptoms in PACS: Clinicians should maintain vigilance in monitoring cardiovascular symptoms, even in patients without a prior history of cardiovascular disease, as cardiovascular sequelae can emerge in previously healthy individuals following COVID-19 [70, 71]. More intensive monitoring of individuals with pre-existing cardiovascular risk factors, such as hyperglycemia, using advanced technologies like artificial intelligence, may help detect early signs of cardiovascular dysfunction and improve long-term outcomes [72, 73]. Furthermore, the framework of PACS clinics should be optimized to include more effective screening and management protocols [74], incorporating multidisciplinary expert care models [75]. This integrated approach may have a positive impact on the prognosis of patients with cardiovascular sequelae of COVID-19.

Conclusions

Study conclusions

This meta-analysis, which includes 37 studies, provides an overview of the prevalence of long-term cardiovascular sequelae of COVID-19 and investigates whether COVID-19 infection is a risk factor for cardiovascular symptoms. Our findings indicate that nearly 15% of COVID-19 patients experience cardiovascular sequelae. Compared with uninfected individuals, COVID-19 infection is associated with an increased likelihood of developing cardiovascular sequelae. Future research should focus on the long-term follow-up of COVID-19 patients to explore the enduring impact of sequelae on patient health and inform medical decision-making to optimize patient outcomes.

Abbreviations

PACS	Post-acute COVID-19 syndrome
ORs	Odds ratios
CIs	Confidence intervals
SARS-CoV-2	Severe acute respiratory syndrome coronavirus
WHO	World Health Organization
CVD	Cardiovascular disease
ACE2	Angiotensin-converting enzyme 2
Ang II	Angiotensin II
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ICD-10	The International Statistical Classification of Diseases and Related Health Problems 10th Revision
ACC	American College of Cardiology
ESC	European Society of Cardiology
PCFS	Post COVID-19 Functional
SBQ-LC	Symptom Burden Questionnaire for Long COVID
NOS	Newcastle–Ottawa Scale
PIMS-TS	Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2
ACEIs	Angiotensin-converting enzyme inhibitors
ARBs	Angiotensin receptor blockers

Supplementary Information

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Additional file 1.

Additional file 2.

Additional file 3.

Additional file 4.

Additional file 5.

Additional file 6.

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Authors' contributions
WXP, HML and LWH jointly selected the topic and designed the study. LWH and HML accessed the data, edited it, and implemented the search strategy, which was approved by the other authors. HML and LWH were responsible for article selection, data extraction, and statistical analysis. BH and XBW evaluated the quality of the selected articles. LWH and HML wrote the manuscript, while BH, XBW, QZZ, and WXP reviewed and revised it. All authors reviewed and approved the final manuscript.

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Competing interests
The authors declare no competing interests.

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