ORIGINAL ARTICLE

A network meta-analysis of association between cardiometabolic risk factors and COVID-19 outcome severity

Alina Binbin Li[1] | Bo Yang[1] 🔵 | Yufei Li[1] | Rachel Huynh[1] |
Samuel Shim[1] | Kenneth Lo[2,3] | Jie Li[1,4,5] | Andrew Zullo[1] |
Wen-Chih Wu[1,6] 🔵 | Simin Liu[1,2,4,5]

[1]Department of Epidemiology, School of Public Health, Brown University, Providence, Rhode Island, USA

[2]Centre for Global Cardiometabolic Health, Departments of Epidemiology, Medicine, and Surgery, Brown University, Providence, Rhode Island, USA

[3]Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Kowloon, Hong Kong, China

[4]Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China

[5]Global Health Research Center, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China

[6]Division of Cardiology, Veterans Affairs Medical Center and The Miriam Hospital, Department of Medicine, Alpert Medical School, Providence, Rhode Island, USA

Correspondence
Simin Liu, Center for Global Cardiometabolic Health, and Departments of Epidemiology, Medicine, and Surgery, Brown University, Providence, RI 02912, USA.
Email: simin_liu@brown.edu

Abstract

Background: Cardiometabolic comorbidities have been associated with a higher risk of COVID-19 severity and mortality, but more investigations are needed to determine which comorbidity is more detrimental.

Methods: Embase, Emcare, and MEDLINE were searched systematically for prospective and retrospective studies assessing the associations of cardiometabolic risk factors and COVID-19 outcomes of hospitalization, severity, and mortality among COVID-19-diagnosed patients. Literature search was performed from first publication to May 19, 2021. Study quality was assessed by the Newcastle-Ottawa Scale.

Results: From the literature search, 301 studies suggested that all included cardiometabolic risk factors were associated with a higher risk of COVID-19 hospitalization, severity, and mortality, except that overweight was associated with a decreased risk of mortality (relative risk [RR] 0.88; 95% CI, 0.80–0.98). Patients with diabetes (RR 1.46; 95% CI, 1.45–1.47) were most likely to be hospitalized; patients with heart failure had the highest risk for severe COVID-19 outcomes (RR 1.89; 95% CI, 1.71–2.09); while patients with stroke were most susceptible to overall mortality (RR 1.99; 95% CI, 1.90–2.08). In the network meta-analysis, cerebrovascular disease had the highest impact (RR 1.69; 95% CI, 1.65–1.73) on COVID-19 outcomes compared to other cardiometabolic risk factors. For different combinations of risk factors, cardiovascular disease and diabetes combined (RR 6.98; 95% CI, 5.28–9.22) was more detrimental than others.

Conclusions: Considering the high prevalence of cardiometabolic comorbidities and risk of all severe outcomes, patients with cardiometabolic comorbidities should be prioritized in vaccination and treatment development of COVID-19.

Alina Binbin Li, Bo Yang, and Yufei Li contributed equally.

Highlights

- Among 301 studies, diabetes mellitus was the most studied cardiometabolic risk factor.
- In the network meta-analysis, cerebrovascular disease had the highest impact (relative risk [RR] 1.69; 95% CI, 1.65–1.73) on COVID-19 outcomes compared to other cardiometabolic risk factors.
- For different combinations of risk factors, cardiovascular disease and diabetes mellitus combined (RR 6.98; 95% CI, 5.28–9.22) was more detrimental than others.

1 | INTRODUCTION

COVID-19 caused by SARS-CoV-2 was first reported in December 2019[1] and spread rapidly worldwide, leading to an ongoing pandemic. It can infect people of all age groups, although severe symptoms are more common in older adults.[2] Infected patients present a wide range of clinical manifestations and outcomes, including subclinical infections, hospitalization, organ dysfunction, and death.[3]

Nearly half of the patients with COVID-19[2–4] have comorbidities, including obesity, hypertension (HTN), diabetes mellitus (DM), and cardiovascular diseases (CVD).[5,6] Patients with underlying cardiometabolic comorbidities are more likely to have severe symptoms and get admitted to the intensive care unit (ICU).[4] Moreover, the percentages of patients with cardiometabolic comorbidities are much higher among the fatality cases than survival cases.[7] Much of the prior research conducted has revealed associations between single underlying comorbidities and COVID-19 outcomes.[7–16] Studies have also been done to analyze the effects of combinations of comorbidities toward the adverse outcomes of COVID-19.[17–21] Inconsistencies in the associations were observed among the publications, and definitive conclusions have yet to be made. A rapid increase in systematic reviews and meta-analyses has provided a great summary of the published papers[22–26]; however, due to the methodological restrictions of meta-analyses,[27] different cardiometabolic risk factors of COVID-19 cannot be compared with one another because of the heterogeneity among the studies.

To compare and systematically evaluate the associations of cardiometabolic risk factors with COVID-19 incidence and adverse outcomes, we conducted a quantitative network meta-analysis treating multiple risk factors simultaneously as if they were from a network of studies connected by both direct and indirect evidence.[28,29] The impact of individual and combined cardiometabolic risk factors toward COVID-19 outcomes was subsequently assessed to rank the relative importance of these influential risk factors.

2 | METHODS

2.1 | Search strategy

This systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement and Agency for Healthcare Research and Quality (AHRQ) guidelines. The search terms consisted of subject headings and keywords for cardiometabolic risk factors and study population. Risk factors of interest included atrial fibrillation (AF), coronary artery disease (CAD), cerebrovascular disease (CBD), CVD, DM, heart failure (HF), HTN, myocardial infarction (MI), obesity, overweight, and stroke. Outcomes of interest included hospitalization and length of stay; disease severity as measured by days in emergency room, days in ICU, days on ventilator, and complications—blood clots (e.g., stroke, heart attack, pulmonary embolism, deep vein thrombosis), kidney failure/dialysis, and mortality. The study population was restricted to patients diagnosed with COVID-19.

The literature search was performed by two researchers (K. Lo and S. Liu) in three databases with a language restriction of English and Chinese: (1) Embase 1910 to May 19, 2021; (2) Ovid Emcare 1995 to 2021 Week 21; and (3) Ovid MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations 1946 to May 19, 2021. Studies that were (a) literature reviews, letters, and abstracts from

First publication to May 19, 2021
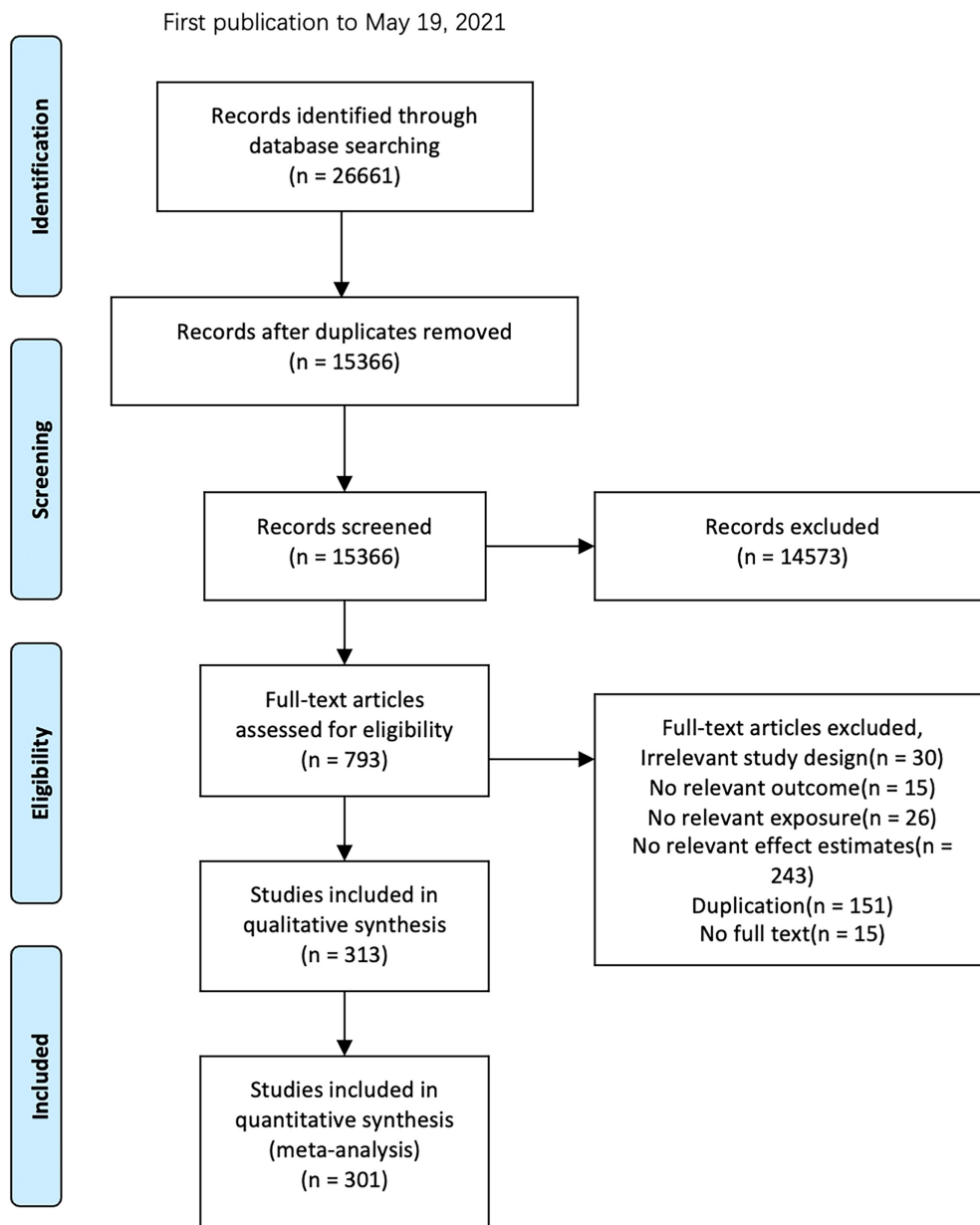
F I G U R E   1   Search and selection process by timeframe according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.

conference proceedings; (b) providing insufficient data information; or (c) duplicate publications were excluded. The full search strategy is presented in Table S1.

2.2 | Study selection

All study information retrieved from the literature search was downloaded into Microsoft Excel. After duplication removal, three researchers performed abstract screening and full-text screening (B. Yang, Y. Li, and A. Li). Disagreements were resolved by a third investigator (K. Lo) or by consensus. Only primary studies that provided the required association information between cardiometabolic risk factors and COVID-19-related outcomes were

included in our study. A total number of 301 studies were included in the meta-analyses (Figure 1).

2.3 | Data extraction and quality assessment

The three investigators performing the literature selection extracted the data from the included studies. A data extraction form was developed for this project and extracted the following information: author, date, country, number of males, age, sample size, comorbidities, basis of disease severity, and the effect size estimates. The assessment of literature quality was performed by four investigators (B. Yang, Y. Li, S. Shim, and R. Huynh)

following the Newcastle-Ottawa Scale (NOS). Disagreements were resolved by a third investigator or by consensus. The NOS evaluate the quality of a study according to three aspects: selection, outcome, and comparability. Higher NOS scores represent higher literature quality, where a maximum of nine can be given. NOS scores of all included studies can be found in Table S3.

2.4 | Data synthesis and analysis

A conventional meta-analysis and a network meta-analysis were performed using R version 3.6.2. The relative risk (RR) and relevant 95% CI calculated from the fixed effect models were used to estimate the pooled results from included studies. Statistical heterogeneity across included studies was investigated using the inconsistency index (I^2), with I^2 of at least 50% indicating moderate heterogeneity and $I^2 \geq 75\%$ indicating high heterogeneity. We further conducted a sensitivity analysis by restricting the meta-analysis to studies with a sample size larger than 1000. This is to reduce the heterogeneity between studies and identify potential exaggerated effects of the small studies on the pooled estimates.

The ranking of combined and independent effects of cardiometabolic risk factors toward COVID-19 outcomes was assessed through the network meta-analysis approach. The risk factor ranking was computed by means of the P-scores, which measure the certainty that one risk factor is more influential than another. The evidence network was illustrated to visualize the network geometry and node connectivity in network plots. The comparative effects of the risk factors were calculated using a multivariate fixed effect meta-analysis model. Q statistics both within designs and between designs in the model were used to evaluate the heterogeneity across studies.

3 | RESULTS

A total of 26 661 studies were identified through the literature search, and 301 of them were included in the qualitative synthesis and meta-analyses after the abstract and full-text screening (Figure 1). Most studies reported COVID-19 outcomes of disease severity ($n = 402$) and mortality ($n = 605$), but fewer reported hospitalizations ($n = 120$) (Table S2). DM was the most studied cardiometabolic risk factors for COVID-19 ($n = 334$), followed by HTN ($n = 254$), while AF was the least studied condition ($n = 13$) (Table S2). The study qualities were rated in the NOS. Of the 301 studies, 241 studies were of high, 59 of moderate, and 1 of low quality (Table S3).

3.1 | Conventional meta-analysis on cardiometabolic risk factors

As shown in Table 1, all cardiometabolic risk factors were associated with an increased risk of hospitalization. These associations were all statistically significant except for CAD (RR 1.07; 95% CI, 0.99–1.15). Patients with DM had the highest risk of hospitalization due to COVID-19 compared to all other risk factors (RR 1.46; 95% CI, 1.45–1.47). Patients with HF or AF also had more than 40% higher risk of hospitalization compared to those without (1.43 [95% CI, 1.41–1.44] and 1.40 [95% CI, 1.22–1.61], respectively). MI and overweight were not synthesized since there were not enough studies.

As for COVID-19 disease severity, patients with HF had the highest risk (RR 1.89; 95% CI, 1.71–2.09), followed by stroke (RR 1.61; 95% CI, 1.27–2.05) and CAD (RR 1.50; 95% CI, 1.38–1.64). Compared to hospitalization, the pooled estimates of the associations between each cardiometabolic risk factor and disease severity were all increased, except for DM which had a 4% lower risk and a wider CI. AF and MI were not analyzed due to the limited number of studies.

Over half of the publications were on overall mortality, and we were able to identify enough studies of each cardiometabolic risk factor for meta-analysis. Among all the included cardiometabolic conditions, stroke and CBD were the most significant risk factors for COVID-19-related mortality. Patients with stroke had almost two-fold the risk of mortality compared to those without stroke (RR 1.99; 95% CI, 1.90–2.08). CBD was found to increase the risk of mortality by over 70% (RR 1.72; 95% CI, 1.67–1.77). All other cardiometabolic risk factors were associated with an increased risk of mortality except overweight. It was shown that overweight was associated with a 12% decrease of mortality risk (RR 0.88; 95% CI, 0.80–0.98).

Comparing the associations between each cardiometabolic risk factor and the three outcomes, it was found that DM (RR 1.46, 1.42, and 1.50), HTN (RR 1.25, 1.26, and 1.25), and obesity (RR 1.35, 1.48, and 1.41) had consistent effects on hospitalization, disease severity, and mortality (Table 1). It was surprising that the effects of obesity and DM on the outcomes were almost comparable. Other cardiometabolic risk factors had more varied effects on the outcomes, with stroke showing the most drastic differences in its effects on outcomes (RR: hospitalization 1.13, disease severity 1.61, and mortality 1.99).

3.2 | Network analyses

Hospitalizations, severe outcomes, or mortality due to COVID-19 were combined as one composite outcome

TABLE 1 Effect estimates of associations between cardiometabolic risk factors and hospitalization, disease severity, and overall mortality in COVID-19 patients.

	Hospitalization RR (95% CI)	Disease severity RR (95% CI)	Overall mortality RR (95% CI)
Atrial fibrillation	1.40 (1.22–1.61)	NA	1.22 (1.07–1.40)
Coronary artery disease	1.07 (0.99–1.15)	1.50 (1.38–1.64)	1.23 (1.20–1.25)
Cerebrovascular disease	1.17 (1.03–1.34)	1.24 (1.07–1.43)	1.72 (1.67–1.77)
Cardiovascular disease	1.23 (1.22–1.25)	1.33 (1.31–1.36)	1.20 (1.17–1.23)
Diabetes mellitus	1.46 (1.45–1.47)	1.42 (1.39–1.45)	1.50 (1.49–1.51)
Heart failure	1.43 (1.41–1.44)	1.89 (1.71–2.09)	1.65 (1.62–1.69)
Hypertension	1.25 (1.23–1.26)	1.26 (1.22–1.31)	1.25 (1.23–1.26)
Myocardial infarction	NA	NA	1.21 (1.16–1.26)
Obesity	1.35 (1.34–1.37)	1.48 (1.45–1.52)	1.41 (1.39–1.42)
Overweight	NA	1.33 (1.22–1.44)	0.88 (0.80–0.98)
Stroke	1.13 (1.11–1.15)	1.61 (1.27–2.05)	1.99 (1.90–2.08)

Note: Estimates based on fewer than three studies were not included.

Estimates were computed based on pooled analysis of fixed effects model.

Disease severity was measured by days in emergency room, days in intensive care unit, days on ventilator, and complications—blood clots (e.g., stroke, heart attacks, pulmonary embolism, deep vein thrombosis), and kidney failure/dialysis.

Abbreviations: NA, not applicable; RR, relative risk.
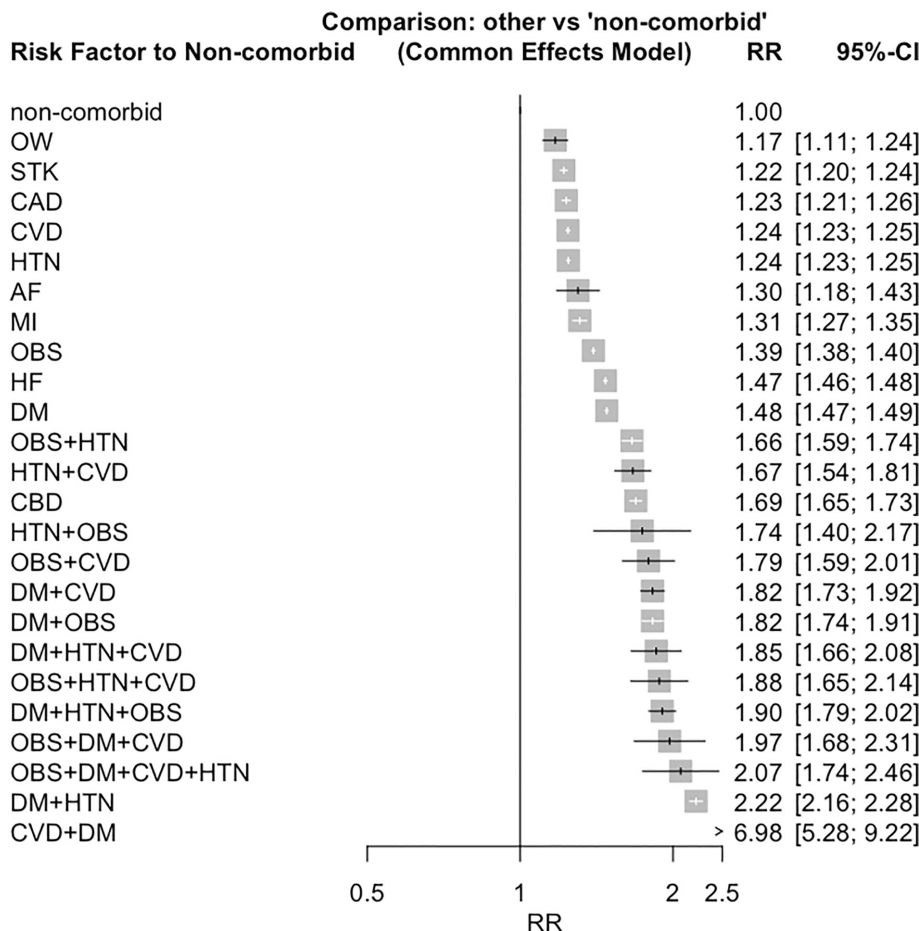
FIGURE 2 Network Meta-Analysis on Associations of Cardiometabolic Risk Factors and COVID-19 Outcomes. AF, atrial fibrillation; CAD, coronary artery disease; CBD, cerebrovascular disease; CVD, cardiovascular disease; DM, diabetes mellitus; HF, heart failure; HTN, hypertension; MI, myocardial infarction; non-comorbid, absence of any cardiometabolic comorbidity; OBS, obesity; OW, overweight; STK, stroke.

TABLE 2 Effect estimates of associations between cardiometabolic risk factors and hospitalization, disease severity, and overall mortality in COVID-19 patients in studies with a sample size larger than 1000.

	Hospitalization RR (95% CI)	Disease severity RR (95% CI)	Overall mortality RR (95% CI)
Atrial fibrillation	1.40 (1.22–1.61)	NA	1.24 (1.08–1.43)[a]
Coronary artery disease	1.07 (0.99–1.15)	1.50 (1.37–1.64)[a]	1.24 (1.22–1.27)[a]
Cerebrovascular disease	1.17 (1.03–1.34)	1.24 (1.07–1.43)	1.72 (1.67–1.77)
Cardiovascular disease	1.23 (1.22–1.25)	1.33 (1.31–1.36)	1.19 (1.16–1.22)[a]
Diabetes mellitus	1.46 (1.45–1.47)	1.41 (1.37–1.44)[a]	1.50 (1.49–1.51)
Heart failure	1.43 (1.41–1.44)	1.91 (1.73–2.11)[a]	1.65 (1.62–1.69)
Hypertension	1.25 (1.23–1.26)	1.25 (1.21–1.30)[a]	1.27 (1.25–1.28)[a]
Myocardial infarction	NA	NA	1.21 (1.16–1.26)
Obesity	1.35 (1.34–1.37)	1.48 (1.45–1.51)[a]	1.41 (1.39–1.42)
Overweight	NA	1.33 (1.22–1.45)[a]	0.87 (0.79–0.97)[a]
Stroke	1.13 (1.11–1.15)	1.64 (1.25–2.15)[a]	2.11 (2.01–2.21)[a]

Note: Estimates based on fewer than three studies were not included.

Estimates were computed based on pooled analysis of fixed effects model.

Disease severity was measured by days in emergency room, days in intensive care unit, days on ventilator, complications—blood clots (e.g., stroke, heart attacks, pulmonary embolism, deep vein thrombosis), and kidney failure/dialysis.

Abbreviations: NA, not applicable; RR, relative risk.

[a]Effect estimates in sensitivity analysis are different from those in main analysis.

and studied in a network analysis of all data accrued ($n = 301$). Diabetes, HTN, and obesity had the greatest number of studies on risk of COVID-19 outcomes (Figure S1). The ranking of any cardiometabolic risk factor affecting hospitalization, severe outcomes, or mortality was led by CBD (RR 1.69; 95% CI, 1.65–1.73). DM, HF, and obesity each had at least a 35% greater risk of the composite COVID-19 outcome (Figure 2). Combined risk factors, such as DM + HTN, all had higher impacts toward the outcome than individual risk factors with a minimum of 1.66 times the risk. CVD together with DM had the greatest RR estimates of 6.98 (95% CI, 5.28–9.22). Possible publication bias was indicated by the funnel plot (Figure S2; $p = 0.0113$), and a moderate amount of heterogeneity was suggested across studies likely due to the varied methodology and exposures studied ($I^2 \geq 50\%$).

When analyzing the outcomes one at a time, the rankings of cardiometabolic factors were different from each other. For hospitalization (Figure S3), combined risk factors were the most influential ones, with DM + HTN having the highest risk (RR 2.60; 95% CI, 2.04–3.31). When comparing single risk factors, DM had the highest ranking in hospitalization risk, while CAD had the lowest. The most detrimental combination of cardiometabolic risk factors for COVID-19 severity was HTN + CVD (RR 4.52; 95% CI, 2.59–7.89; Figure S4). The ranking of single cardiometabolic risk factors was

led by HF (RR 1.89; 95% CI, 1.71–2.08), stroke, and CAD. More reports were on mortality, where CVD + DM was the most significant risk factor (RR 6.89; 95% CI, 5.28–9.22; Figure S5). Stroke had the highest ranking among all cardiometabolic risk factors and was more detrimental than a large proportion of the cardiometabolic risk factor combinations (RR 1.99; 95% CI, 1.90–2.08). For all three outcomes, the heterogeneity among studies in the network meta-analysis was substantial ($I^2 \geq 75\%$).

3.3 | Sensitivity analyses

The included studies were restricted to those with a sample size larger than 1000 in the sensitivity analyses. Although some of the pooled estimates changed, the differences were very small (Table 2). The effect estimates in the sensitivity and main analysis were comparable. Studies with small sample size did not significantly affect the pooled estimates in the meta-analyses.

4 | DISCUSSION

In this systematic review and quantitative assessment of all published literature concerning cardiometabolic risk
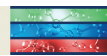
factors and COVID-19 outcomes, we observed strong positive associations between them, except for the combination of obesity and mortality. The significant associations of CBD, DM, obesity, HTN, stroke, and HF with hospitalization, severity, and mortality were consistent with prior reports.

This network meta-analysis is a comprehensive evaluation of 747 prospective and retrospective studies, 73 928 213 COVID-19 patients, and multiple cardiometabolic comorbidities. This analysis uniquely compares combinations of 12 cardiometabolic risk factors individually or in combination through network meta-analysis. Since cardiometabolic diseases are frequently clustered, the network meta-analysis accounts for comorbidities, study heterogeneity, and indirect associations. Previously, a meta-analysis including 24 studies on DM, HTN, chronic pulmonary diseases, and CVD found similar association patterns with COVID-19 adverse outcomes.[30] There were also two studies that attempted to rank cardiometabolic risk factors with models and reported a different relative ranking of cardiometabolic risk factors than our network analysis.[31,32] Although heterogeneities existed across studies, CHD, CAD, and CVD appeared to have the largest impact on COVID-19 mortality and severity, followed by HTN and DM.[30,33,34] Cardiac injury, stress, and other complications indicated by biomarkers are particularly prevalent among individuals with cardiometabolic disorders, possibly leading to an increased risk of mortality.[35] Like the strong associations for obesity found in our network analysis, one genome-wide association study (GWAS) reported body mass index to be strongly associated with COVID-19 hospitalization.[34] Underlying genotypic and phenotypic factors related to angiotensin I-converting enzyme 2 (ACE2) are associated with obesity and DM and may be involved in the mechanisms of COVID-19 pathogenesis.[36] Obesity and DM were found to be consistently associated with COVID-19-related hospitalization, severity, and mortality in our study. This aligns with prior reports that worse COVID-19 outcomes were associated with the presence of impaired glucose metabolism.[37]

As the COVID-19 pandemic continues to rage on, additional or unanticipated factors may affect the associations between cardiometabolic comorbidities and COVID-19 outcomes, including the recognition of the Omicron and Delta SARS-CoV-2 variants and vaccinations that affect COVID-19 severity.[38–40] It should also be noted that the risk factors for the included cardiometabolic comorbidities can also attribute to the risk of COVID-19 outcomes. For instance, visceral obesity and characteristics of impaired metabolic health such as hyperglycemia, HTN, and subclinical inflammation are associated with a high risk of severe COVID-19.[41] Moreover, recent data further indicate that these factors might also promote vaccine breakthrough COVID-19 infections in fully vaccinated individuals.[42]

This can be due to the downregulating of the immune responses in patients with cardiometabolic comorbidities. For instance, hyperglycemia and insulin resistance have been found to modulate the body's immune response, potentially driving immunosenescence and contributing to an increased risk of severe COVID-19.[42] Future research should explore the differences of risk among populations with different cardiometabolic comorbidities and variants of COVID-19.

Although we tried to conduct a comprehensive meta-analysis and included 11 different comorbidities, certain cardiometabolic conditions have still been overlooked, for example, chronic kidney disease (CKD) and liver disease. Emerging evidence suggests that individuals with CKD and liver disease are at a higher risk of severe outcomes when infected with COVID-19. Several studies have reported a significant association between CKD and adverse clinical outcomes, including higher rates of hospitalization, ICU admission, and mortality in COVID-19 patients with preexisting kidney disease.[43,44] CKD has been identified as an independent risk factor for COVID-19 severity, with decreased kidney function correlating with worse outcomes.[45] Moreover, CKD patients on maintenance dialysis have been reported to be particularly vulnerable, with an increased risk of complications and mortality compared to the general population.[43] Similarly, individuals with liver disease, such as cirrhosis or chronic liver disease, have also been shown to have an increased risk of severe COVID-19 outcomes.[46] Liver dysfunction, immune dysregulation, and impaired coagulation profiles in liver disease patients may contribute to the higher susceptibility and worse prognosis in this population.[47,48] These findings underscore the importance of recognizing CKD and liver disease as significant comorbidities in the context of COVID-19 research and management.

Another limitation of this study is the heterogeneity among included studies. In the sensitivity analysis, the pooled estimates were calculated from studies with sample sizes larger than 1000. We were expecting that the exclusion of small studies may reduce the heterogeneity, but the contrary was observed. There were no large changes in either effect estimates or heterogeneity. In the network meta-analysis, the heterogeneity was substantial when analyzed either by each outcome or the three outcomes combined. These differences between the included studies can be due to the heterogeneity of the methods, sample population, and model adjustments used by the individual studies identified. Differences in treatments,[49–51] genetics, ethnicity,[52] and location[13,52] may impact consistency of results. While heterogeneity was high in the conventional meta-analysis, the network meta-analysis can account for this, and our findings remain meaningful. The risk factor rankings of this network analysis allow for a more comprehensive comparison between cardiometabolic

comorbidities. These findings provide a basis for clinical understanding of which conditions should be treated as greater risks.

This meta-analysis and network analysis strengthened existing evidence on increased risk of COVID-19 hospitalization, severity, and mortality among those with cardiometabolic comorbidities. The high prevalence and risk of cardiometabolic comorbidities should be accounted for when predicting prospects of the COVID-19 pandemic.

ACKNOWLEDGEMENTS

CONFLICT OF INTEREST STATEMENT

S.L. reports consulting payments and honoraria or promises of the same for scientific presentations or reviews at numerous venues, including but not limited to Barilla, Johns Hopkins University, Fred Hutchinson Cancer Center, Harvard University, University of Buffalo, Guangdong Provincial Hospital, Fuwai Hospital, the Chinese Academy of Medical Sciences, and the NIH. S.L. is also a member of the Data Safety and Monitoring Board for several trials, including the SELECT Trial-Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity sponsored by Novo Nordisk and a trial of pulmonary HTN in diabetes patients sponsored by Massachusetts General Hospital. S.L. receives royalties from UpToDate and receives an honorarium from the American Society for Nutrition for his duties as Associate Editor. Other authors report no competing interests.

ORCID

Bo Yang 🄳 https://orcid.org/0000-0002-9809-4599
Wen-Chih Wu 🄳 https://orcid.org/0000-0002-2834-2024

REFERENCES

1. Report of clustering pneumonia of unknown etiology in Wuhan City. Wuhan Municipal Health Commission. 2019.
2. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020; 395(10223):507-513. doi:10.1016/S0140-6736(20)30211-7
3. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506. doi:10.1016/S0140-6736(20)30183-5
4. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061-1069. doi:10.1001/jama.2020.1585
5. Li B, Yang J, Zhao F, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol*. 2020;109(5):531-538. doi:10.1007/s00392-020-01626-9
6. Wang B, Li R, Lu Z. Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis. *Aging*. 2020;2020:12-6057.
7. Yang X, Yu Y, Xu J. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study [published correction appears in Lancet Respir Med]. *Lancet Respir Med*. 2020;8(5):475-481.
8. Hernández-Garduño E. Obesity is the comorbidity more strongly associated for Covid-19 in Mexico. A case-control study. *Obes Res Clin Pract*. 2020;14(4):375-379.
9. Guan WJ, Liang WH, Zhao Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J*. 2020;55(5):2000547. doi:10.1183/13993003.00547-2020
10. Grasselli G, Greco M, Zanella A. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy [published correction appears in JAMA Intern Med]. *JAMA Intern Med*. 2021;180(10):1345-1355.
11. Price-Haywood EG, Burton J, Fort D. Hospitalization and mortality among black patients and white patients with Covid-19. *N Engl J Med*. 2020;382(26):2534-2543.
12. Docherty AB, Harrison EM, Green CA. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO clinical characterisation protocol: prospective observational cohort study. *BMJ*. 2020;2020(369):m1985.
13. Barron E, Bakhai C, Kar P, et al. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. *Lancet Diabetes Endocrinol*. 2020; 8(10):813-822. doi:10.1016/S2213-8587(20)30272-2
14. Iaccarino G, Grassi G, Borghi C. Age and multimorbidity predict death among COVID-19 patients: results of the SARS-RAS study of the Italian Society of Hypertension. *Hypertension*. 2020;76(2):366-372.
15. Berenguer J, Ryan P, Rodríguez-Baño J. Characteristics and predictors of death among 4035 consecutively hospitalized patients with COVID-19 in Spain. *Clin Microbiol Infect*. 2020; 26(11):1525-1536.
16. Xu PP, Tian RH, Luo S, et al. Risk factors for adverse clinical outcomes with COVID-19 in China: a multicenter, retrospective, observational study. *Theranostics*. 2020;10(14):6372-6383. doi:10.7150/thno.46833
17. Bezzio C, Saibeni S, Variola A, et al. Outcomes of COVID-19 in 79 patients with IBD in Italy: an IG-IBD study. *Gut*. 2020;69(7): 1213-1217. doi:10.1136/gutjnl-2020-321411
18. Williamson EJ, Walker AJ, Bhaskaran K. Factors associated with COVID-19-related death using OpenSAFELY. *Nature*. 2020;584(7821):430-436.
19. Ebinger JE, Achamallah N, Ji H, et al. Pre-existing traits associated with Covid-19 illness severity. *PloS One*. 2020;15(7): e0236240. doi:10.1371/journal.pone.0236240
20. Owen RK, Conroy SP, Taub N. Comparing associations between frailty and mortality in hospitalised older adults with or without COVID-19 infection: a retrospective observational study using electronic health records. *Age Ageing*. 2021;50(2):307-316.
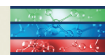
21. Du H, Pan X, Liu N, et al. The effect of vascular risk factor burden on the severity of COVID-19 illness, a retrospective cohort study. *Respir Res*. 2020;21(1):241. doi:10.1186/s12931-020-01510-0

22. Zheng Z, Peng F, Xu B, et al. Risk factors of critical & mortal COVID-19 cases: a systematic literature review and meta-analysis. *J Infect*. 2020;81(2):e16-e25. doi:10.1016/j.jinf.2020.04.021

23. Fang X, Li S, Yu H, et al. Epidemiological, comorbidity factors with severity and prognosis of COVID-19: a systematic review and meta-analysis. *Aging (Albany NY)*. 2020;12(13):12493-12503. doi:10.18632/aging.103579

24. Li J, Huang DQ, Zou B, et al. Epidemiology of COVID-19: a systematic review and meta-analysis of clinical characteristics, risk factors, and outcomes. *J Med Virol*. 2021;93(3):1449-1458. doi:10.1002/jmv.26424

25. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. *Int J Infect Dis*. 2020;94:91-95. doi:10.1016/j.ijid.2020.03.017

26. Allotey J, Stallings E, Bonet M, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. *BMJ*. 2020;370:m3320. doi:10.1136/bmj.m3320

27. Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. *BMJ*. 1997;315(7121):1533-1537. doi:10.1136/bmj.315.7121.1533

28. Rouse B, Chaimani A, Li T. Network meta-analysis: an introduction for clinicians. *Intern Emerg Med*. 2017;12(1):103-111. doi:10.1007/s11739-016-1583-7

29. Xu Y, Amiche MA, Tadrous M. Network meta-analysis: an introduction for pharmacists. *Int J Clin Pharmacol*. 2018;40(5):942-947. doi:10.1007/s11096-018-0656-2

30. Liu H, Chen S, Liu M, Nie H, Lu H. Comorbid chronic diseases are strongly correlated with disease severity among COVID-19 patients: a systematic review and meta-analysis. *Aging Dis*. 2020;11(3):668-678. doi:10.14336/AD.2020.0502

31. Ioannou GN, Green P, Fan VS, et al. Development of COVID-Vax model to estimate the risk of SARS-CoV-2-related death among 7.6 million US veterans for use in vaccination prioritization. *JAMA Netw Open*. 2021;4(4):e214347. doi:10.1001/jamanetworkopen.2021.4347

32. Gude-Sampedro F, Fernandez-Merino C, Ferreiro L, et al. Development and validation of a prognostic model based on comorbidities to predict COVID-19 severity: a population-based study. *Int J Epidemiol*. 2021;50(1):64-74. doi:10.1093/ije/dyaa209

33. Tian W, Jiang W, Yao J, et al. Predictors of mortality in hospitalized COVID-19 patients: a systematic review and meta-analysis. *J Med Virol*. 2020;92(10):1875-1883. doi:10.1002/jmv.26050

34. Leong A, Cole JB, Brenner LN, Meigs JB, Florez JC, Mercader JM. Cardiometabolic risk factors for COVID-19 susceptibility and severity: a Mendelian randomization analysis. *PLoS Med*. 2021;18(3):e1003553. doi:10.1371/journal.pmed.1003553

35. Pellicori P, Doolub G, Wong CM, et al. COVID-19 and its cardiovascular effects: a systematic review of prevalence studies. *Cochrane Database Syst Rev*. 2021;3:CD013879. doi:10.1002/14651858.CD013879

36. El-Sayed Moustafa JS, Jackson AU, Brotman SM, et al. ACE2 expression in adipose tissue is associated with cardio-metabolic risk factors and cell type composition-implications for COVID-19.

Int J Obes (Lond). 2022;46(8):1478-1486. doi:10.1038/s41366-022-01136-w

37. Smith SM, Boppana A, Traupman JA, et al. Impaired glucose metabolism in patients with diabetes, prediabetes, and obesity is associated with severe COVID-19. *J Med Virol*. 2021;93(1):409-415. doi:10.1002/jmv.26227

38. Yang W, Shaman J. COVID-19 pandemic dynamics in India, the SARS-CoV-2 Delta variant and implications for vaccination. *J R Soc Interface*. 2022;19(191):20210900. doi:10.1098/rsif.2021.0900

39. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Covid-19 vaccines against the B.1.617.2 (Delta) variant. *N Engl J Med*. 2021;385(7):585-594. doi:10.1056/NEJMoa2108891

40. European Centre for Disease Prevention and Control. Implications of the emergence and spread of the SARS-CoV-2 B.1.1.

41. Stefan N, Birkenfeld AL, Schulze MB. Global pandemics interconnected – obesity, impaired metabolic health and COVID-19. *Nat Rev Endocrinol*. 2021;17(3):135-149. doi:10.1038/s41574-020-00462-1

42. Stefan N. Metabolic disorders, COVID-19 and vaccine-breakthrough infections. *Nat Rev Endocrinol*. 2022;18(2):75-76. doi:10.1038/s41574-021-00608-9

43. Chung EYM, Palmer SC, Natale P, et al. Incidence and outcomes of COVID-19 in people with CKD: a systematic review and meta-analysis. *Am J Kidney Dis*. 2021;78(6):804-815. doi:10.1053/j.ajkd.2021.07.003

44. Yang L, Li J, Wei W, et al. Kidney health in the COVID-19 pandemic: an umbrella review of meta-analyses and systematic reviews. *Front Public Health*. 2022;10:963667. doi:10.3389/fpubh.2022.963667

45. Jdiaa SS, Mansour R, El Alayli A, Gautam A, Thomas P, Mustafa RA. COVID-19 and chronic kidney disease: an updated overview of reviews. *J Nephrol*. 2022;35(1):69-85. doi:10.1007/s40620-021-01206-8

46. Marjot T, Webb GJ, ASt B, et al. COVID-19 and liver disease: mechanistic and clinical perspectives. *Nat Rev Gastroenterol Hepatol*. 2021;18(5):348-364. doi:10.1038/s41575-021-00426-4

47. Dufour JF, Marjot T, Becchetti C, Tilg H. COVID-19 and liver disease. *Gut*. 2022;71(11):2350-2362. doi:10.1136/gutjnl-2021-326792

48. Jothimani D, Venugopal R, Abedin MF, Kaliamoorthy I, Rela M. COVID-19 and the liver. *J Hepatol*. 2020;73(5):1231-1240. doi:10.1016/j.jhep.2020.06.006

49. Awortwe C, Cascorbi I. Meta-analysis on outcome-worsening comorbidities of COVID-19 and related potential drug-drug interactions. *Pharmacol Res*. 2020;161(105250):105250. doi:10.1016/j.phrs.2020.105250

50. Chen C. Relations of treatments for Cardiometabolic Co-morbidities with critical outcomes and mortality in hospitalized patients with coronavirus disease 2019 (COVID-19): A retrospective cohort study. Available at SSRN. 2020;2020:3696829.

51. Kaur U, Chakrabarti SS, Patel TK. Renin-angiotensin-aldosterone system blockers and region-specific variations in COVID-19 outcomes: findings from a systematic review and meta-analysis. *Ther Adv Drug Saf*. 2021;12:20420986211011345. doi:10.1177/20420986211011345

52. Manohar J, Abedian S, Martini R, et al. Social and clinical determinants of COVID-19 outcomes: modeling real-world data from a

pandemic epicenter. *medRxiv*. 2021:2021.04.06.21254728. doi:10.1101/2021.04.06.21254728

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.