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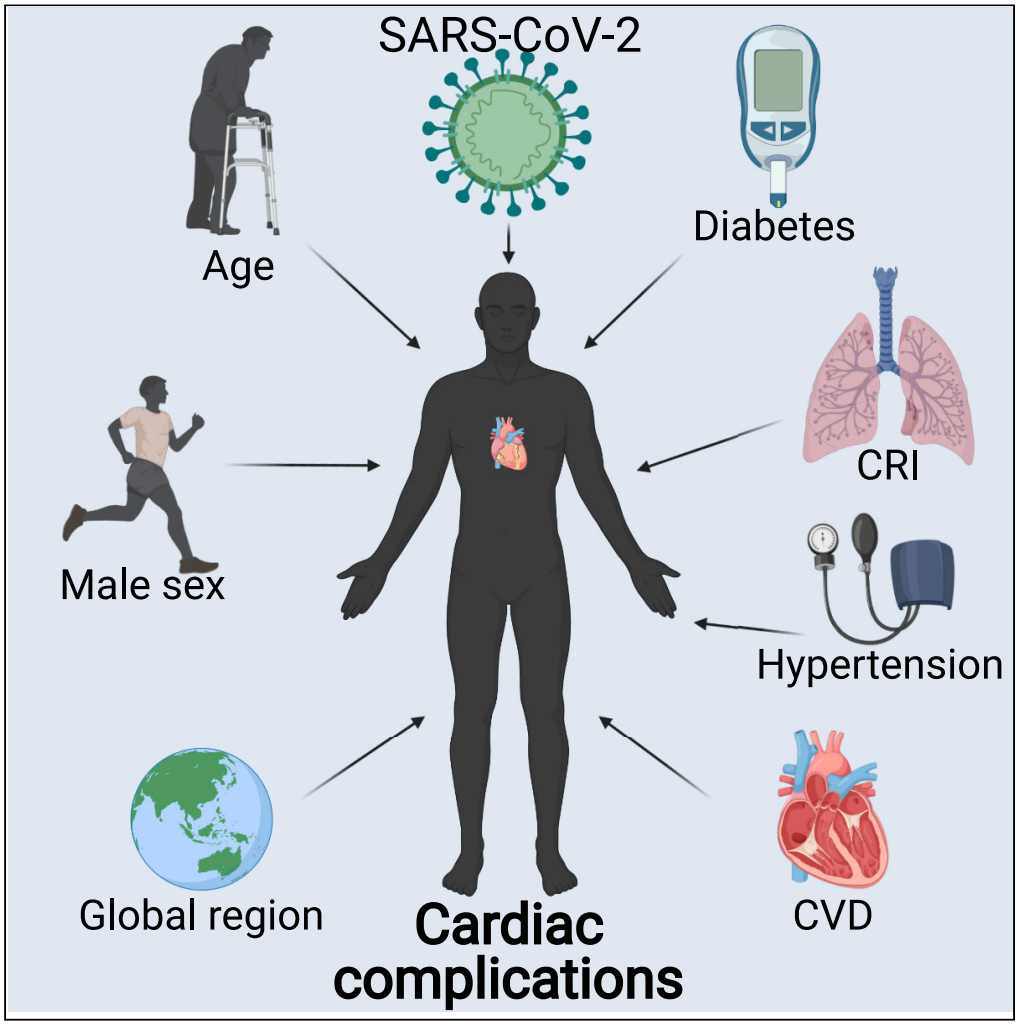

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Highlights

Older age and male sex associated with increased SARS-CoV-2 cardiac complication risk

Chronic illnesses associated with increased SARS-CoV-2 cardiac complication risk

These associations were mostly conserved over differing geographical regions

Multidisciplinary approaches to chronic disease patient management are essential

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A meta-analysis on the role of pre-existing chronic disease in the cardiac complications of SARS-CoV-2 infection

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SUMMARY

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been associated with multiple direct and indirect cardiovascular complications. We sought to analyze the association of host co-morbidities (chronic respiratory illnesses, cardiovascular disease [CVD], hypertension or diabetes mellitus [DM]) with the acute cardiovascular complications associated with SARS-CoV-2 infection. Individual analyses of the majority of studies found median age was higher by ~10 years in patients with cardiovascular complications. Pooled analyses showed development of SARS-CoV-2 cardiovascular complications was significantly increased in patients with chronic respiratory illness (odds ratio (OR): 1.67 [1.48, 1.88]), CVD (OR: 3.37 [2.57, 4.43]), hypertension (OR: 2.68 [2.11, 3.41]), DM (OR: 1.60 [1.31, 1.95]) and male sex (OR: 1.31 [1.21, 1.42]), findings that were mostly conserved during sub-analysis of studies stratified into global geographic regions. Age, chronic respiratory illness, CVD, hypertension, DM, and male sex may represent prognostic factors for the development of cardiovascular complications in COVID-19 disease, highlighting the need for a multidisciplinary approach to chronic disease patient management.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged at the end of 2019 and has since gone on to cause the ongoing coronavirus disease 2019 (COVID-19) pandemic, infecting >95 million people worldwide. SARS-CoV-2 causes a broad range of respiratory symptoms, ranging from subclinical disease to viral pneumonia (Clerkin et al., 2020). However, it is increasingly apparent that SARS-CoV-2 also causes a variety of extra-respiratory complications (Clerkin et al., 2020). Specifically, SARS-CoV-2 infection has been associated with acute myocardial injury, myocarditis, arrhythmias, venous thromboembolism, and other cardiac complications (Inciardi et al., 2020; Guo et al., 2020; Huang et al., 2020a; Sala et al., 2020; Zheng et al., 2020). Although prevalence estimates vary, data from China suggests that approximately 7% of patients infected with SARS-CoV-2 develop cardiac injury (defined as elevated high-sensitivity cardiac troponin I or new echocardiographic or electrocardiographic (ECG) abnormalities) (Wang et al., 2020). This prevalence increases to 25% in those hospitalized with COVID-19 (14), and 22% in patients who required intensive care unit (ICU) admission (Wang et al., 2020). However, at present, the role of pre-existing chronic disease in the cardiac complications of COVID-19 remains to be elucidated.

Pre-existing chronic respiratory disease, cardiovascular disease (CVD), hypertension and diabetes mellitus (DM) have each been associated with increased rates of hospitalization, ICU admission, and death from the respiratory complications of SARS-CoV-2 (Chen et al., 2020a; 2020b; Epidemiology Working Group for NCIP Epidemic ResponseChinese Center for Disease Control and Prevention, 2020; Fang et al., 2020; Giustino et al., 2020; Huang et al., 2020b; Li et al., 2020a; Lippi and Henry, 2020; Ruan et al., 2020; Targher et al., 2020; Wang et al., 2020; Wu et al., 2020; Wu and McGoogan, 2020; Yang et al., 2020a; Yang et al., 2020b; Zhou et al., 2020). It is not yet well defined whether these patient groups are also at an increased risk of SARS-CoV-2 associated cardiac injury. Some small studies have shown that patients with pre-existing CVD are at a higher risk of myocarditis and/or myocardial infarction (MI) from SARS-CoV-2 (Guo et al.,

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2020; Hui et al., 2020; Shi et al., 2020). A retrospective, single-center case series of 187 patients with COVID-19 also found that pre-existing CVD increased the risk of cardiac injury (as defined by troponin elevation) (54.5% vs 13.2%) and mortality compared with patients without CVD (Guo et al., 2020). Similarly, a meta-analysis of 28 observational studies found SARS-CoV-2 associated cardiac injury biomarkers to be related to a history of hypertension but not DM (Li et al., 2020b). In contrast, Zhu et al. found that individuals with type 2 DM had a greater occurrence of acute heart injury (7.3% versus 3.0%) than individuals without DM (Zhu et al., 2020).

There is a clear need to better understand the role of patient host factors in the extra-respiratory complications of SARS-CoV-2 infection. Here, we analyzed the currently available literature on the role of pre-existing chronic respiratory illnesses, CVD, hypertension, and DM in the prevalence of SARS-CoV-2-associated cardiac injury.

RESULTS

Pre-existing chronic illnesses in COVID-19 patients are associated with an increased risk of acute cardiac complications

We identified 1076 articles that described pre-existing chronic disease and cardiac complications of SARS-CoV-2, rejected 996 articles due to a lack of sufficient and/or appropriate data and derived a total of 80 articles (see transparent methods). Twenty-nine of these studies were deemed eligible for inclusion due to containing original research, including both data on patient pre-exiting disease and cardiac complications as an outcome (specifying the cross-over between pre-existing chronic disease and outcome), describing a population generally representative of the wider community within that area (e.g. not specifically pregnant women, transplant recipients, etc.), and involving greater than 10 patients. These studies were subsequently used in a meta-analysis (Figure 1), all of which were deemed to be high quality (Table 1). Baseline characteristics of the patient populations as well as other relevant data are listed in Table 2. The definition of cardiac complications varied between studies, ranging from acute cardiac injury to fulminant myocarditis. Twenty studies measured cardiac outcomes on the day of admission (Abrams et al., 2020; Barman et al., 2020; Bertini et al., 2020; Duerr et al., 2020; Ferrante et al., 2020; Ghio et al., 2020; Guo et al., 2020; Lairez et al., 2020; Lala et al., 2020; Liu et al., 2020; Lombardi et al., 2020; Lorente-Ros et al., 2020; Ma et al., 2020; Pagnesi et al., 2020; Raad et al., 2020; Shahrokh et al., 2020; Shi et al., 2020; Song et al., 2020; Szekely et al., 2020; Xu et al., 2020b), and one at the time of patient death (Arentz et al., 2020), with the remaining eight studies not specifying the time of assessment (Li et al., 2020c; Linschoten and Asselbergs, 2020; Sala et al., 2020; Shah et al., 2020; Toraih et al., 2020; Wei et al., 2020; Xie et al., 2020). The studies were conducted in 10 countries in four geographical locations (U.S.A., the Middle East, Europe, and the People's Republic of China) with a total of 3553 COVID-19 patients developing cardiac complications and 13,225 COVID-19 patients without cardiac complications. Patients who presented with SARS-CoV-2 associated cardiac complications were, on average, 10 years older than in those who did not (Table 2).

In a pooled analysis, chronic respiratory illness (odds ratio (OR): 1.67, 95% confidence interval (CI): [1.48, 1.88]) (Figure 2), CVD (OR: 3.37, 95% CI: [2.57, 4.43]) (Figure 3), hypertension (OR: 2.68, 95% CI: [2.11, 3.41]) (Figure 4), DM (OR: 1.60, 95% CI: [1.31, 1.95]) (Figure 5), and male sex (OR: 1.31, 95% CI: [1.21, 1.42]) (Figure 6), were each associated with a higher risk of SARS-CoV-2 associated cardiac complications. Neither Egger's regression test nor the Rank correlation test was statistically significant for any parameter, finding no evidence of publication bias (see Figures S1–S5).

The association of pre-existing chronic illnesses and the risk of acute cardiac complications from SARS-CoV-2 is mostly conserved during sub-analysis of studies stratified into global geographic regions

As large heterogeneity was detected amongst the total combined study cohort, the cohort was subdivided based on general global region in an attempt to account for this, based on the fact that different countries have different clinical practices and experiences with the pandemic. Cohorts were divided into studies with cohorts primarily situated in the U.S.A (Abrams et al., 2020; Arentz et al., 2020; Lala et al., 2020; Raad et al., 2020; Shah et al., 2020), the Middle East (Barman et al., 2020; Shahrokh et al., 2020; Szekely et al., 2020), Europe (Bertini et al., 2020; Linschoten and Asselbergs, 2020; Duerr et al., 2020; Ferrante et al., 2020; Ghio et al., 2020; Lairez et al., 2020; Lombardi et al., 2020; Lorente-Ros et al., 2020; Pagnesi et al., 2020;

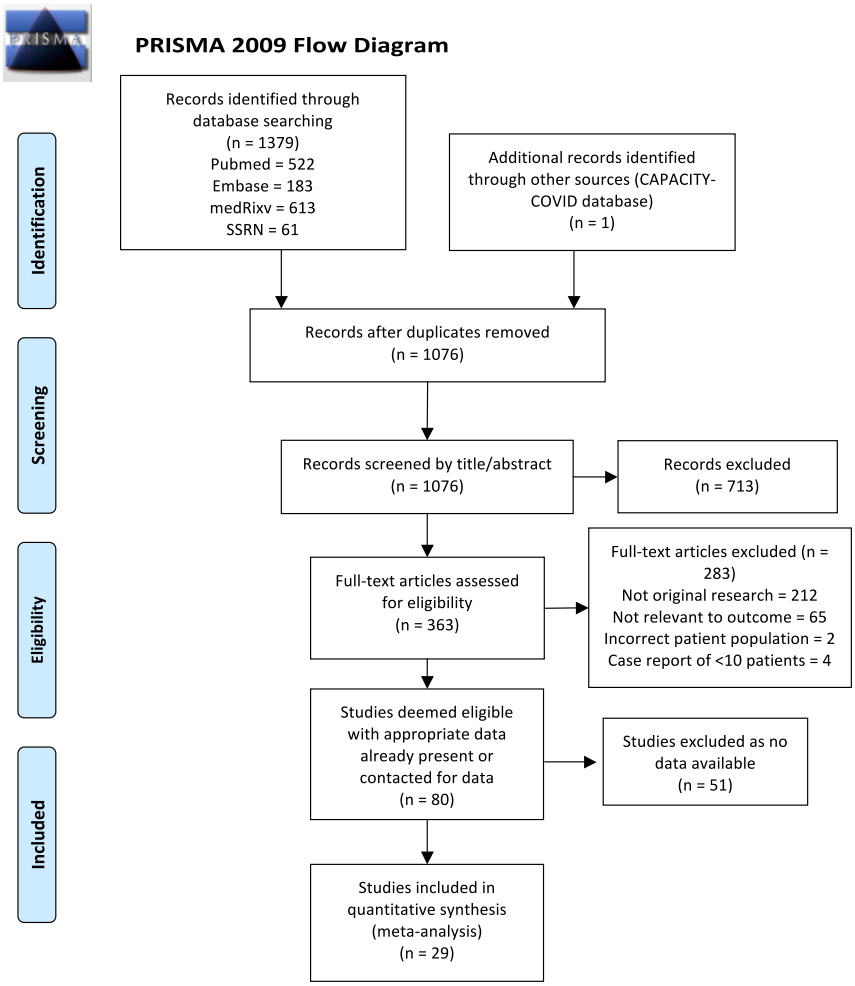

Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flowchart of study selection

Sala et al., 2020), and China (Guo et al., 2020; Shi et al., 2020; Li et al., 2020c; Liu et al., 2020; Ma et al., 2020; Song et al., 2020; Toraih et al., 2020; Wei et al., 2020; Xie et al., 2020; Xu et al., 2020a, 2020b).

Regionally pooled sub-analysis of chronic respiratory illness found it to be associated with a higher incidence of SARS-CoV-2 associated cardiac complications in cohorts from the U.S.A. (OR: 1.64, 95% CI: [1.28, 2.09]) (Figure 7A), Europe (OR: 1.53, 95% CI: [1.28, 1.83]) (Figure 7C) and China (OR: 1.94, 95% CI: [1.49, 2.52]) (Figure 7D) but not the Middle East (Figure 7B). Regional subdivision accounted for the high heterogeneity amongst all but the Middle Eastern cohort.

Regionally pooled sub-analysis of pre-existing CVD found its association with a higher incidence of SARS-CoV-2-associated cardiac complications to be conserved across all cohorts from the U.S.A. (OR: 3.55, 95% CI: [2.51, 5.04]) (Figure 8A), the Middle East (OR: 2.40, 95% CI: [1.25, 4.62]) (Figure 8B), Europe (OR: 2.99, 95% CI: [1.90, 4.69]) (Figure 8C), and China (OR: 5.52, 95% CI: [3.88, 7.85]) (Figure 8D), despite regional subdivision failing to account for high heterogeneity amongst the former three regions.

Regionally pooled sub-analysis of hypertension found its association with a higher incidence of SARS-CoV-2-associated cardiac complications to be similarly conserved across all cohorts from the U.S.A. (OR: 2.23, 95% CI: [1.22, 4.08]) (Figure 9A), the Middle East (OR: 2.24, 95% CI: [1.70, 2.94]) (Figure 9B), Europe (OR: 2.38, 95% CI [1.46, 3.88]) (Figure 9C), and China (OR: 3.94, 95% CI: [3.10, 5.01]) (Figure 9D), although regional subdivision could not account for high heterogeneity amongst the American and European cohorts.

Table 1. Quality assessment of the included studies using the Newcastle Ottawa Scale.

Study	Selection				Comparability	Outcomes		
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the deisng or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up cohorts
Abrams et al. (2020)	Truly or somewhat representative of the average SARS-CoV-2 infection cases in the community *	Drawn from the same community as the exposed cohort *	Secure record (e.g. surgical records) *	Yes *	–	Record linkage *	Yes *	All subjects accounted for or small number lost *
Arentz et al. (2020)	Truly or somewhat representative of the average SARS-CoV-2 infection cases in the community *	Drawn from the same community as the exposed cohort *	Secure record (e.g. surgical records) *	Yes *	–	Record linkage *	Yes *	All subjects accounted for or small number lost *
Barman et al. (2020)	Truly or somewhat representative of the average SARS-CoV-2 infection cases in the community *	Drawn from the same community as the exposed cohort *	Secure record (e.g. surgical records) *	Yes *	–	Record linkage *	Yes *	All subjects accounted for or small number lost *
Bertini et al. (2020)	Truly or somewhat representative of the average SARS-CoV-2 infection cases in the community *	Drawn from the same community as the exposed cohort *	Secure record (e.g. surgical records) *	Yes *	–	Record linkage *	Yes *	All subjects accounted for or small number lost *
Linschoten and Asselbergs (2020)	Truly or somewhat representative of the average SARS-CoV-2 infection cases in the community *	Drawn from the same community as the exposed cohort *	Secure record (e.g. surgical records) *	Yes *	–	Record linkage *	Yes *	All subjects accounted for or small number lost *
Duerr et al. (2020)	Truly or somewhat representative of the average SARS-CoV-2 infection cases in the community *	Drawn from the same community as the exposed cohort *	Secure record (e.g. surgical records) *	Yes *	–	Record linkage *	Yes *	All subjects accounted for or small number lost *

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Table 1. *Continued*

Study	Selection				Comparability	Outcomes		
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the deisng or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up cohorts
Ferrante et al. (2020)	Truly or somewhat representative of the average SARS-CoV-2 infection cases in the community *	Drawn from the same community as the exposed cohort *	Secure record (e.g. surgical records) *	Yes *	–	Record linkage *	Yes *	All subjects accounted for or small number lost *
Ghio et al. (2020)	Truly or somewhat representative of the average SARS-CoV-2 infection cases in the community *	Drawn from the same community as the exposed cohort *	Secure record (e.g. surgical records) *	Yes *	–	Record linkage *	Yes *	All subjects accounted for or small number lost *
Guo et al. (2020)	Truly or somewhat representative of the average SARS-CoV-2 infection cases in the community *	Drawn from the same community as the exposed cohort *	Secure record (e.g. surgical records) *	Yes *	–	Record linkage *	Yes *	All subjects accounted for or small number lost *
Lairez et al. (2020)	Truly or somewhat representative of the average SARS-CoV-2 infection cases in the community *	Drawn from the same community as the exposed cohort *	Secure record (e.g. surgical records) *	Yes *	–	Record linkage *	Yes *	All subjects accounted for or small number lost *
Lala et al. (2020)	Truly or somewhat representative of the average SARS-CoV-2 infection cases in the community *	Drawn from the same community as the exposed cohort *	Secure record (e.g. surgical records) *	Yes *	–	Record linkage *	Yes *	All subjects accounted for or small number lost *
Li et al. (2020a), 2020b, 2020c[42]	Truly or somewhat representative of the average SARS-CoV-2 infection cases in the community *	Drawn from the same community as the exposed cohort *	Secure record (e.g. surgical records) *	Yes *	–	Record linkage *	Yes *	All subjects accounted for or small number lost *

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Table 1. *Continued*

Study	Selection				Comparability	Outcomes		
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the deisng or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up cohorts
Liu et al. (2020)	Truly or somewhat representative of the average SARS-CoV-2 infection cases in the community *	Drawn from the same community as the exposed cohort *	Secure record (e.g. surgical records) *	Yes *	–	Record linkage *	Yes *	All subjects accounted for or small number lost *
Lombardi et al. (2020)	Truly or somewhat representative of the average SARS-CoV-2 infection cases in the community *	Drawn from the same community as the exposed cohort *	Secure record (e.g. surgical records) *	Yes *	–	Record linkage *	Yes *	All subjects accounted for or small number lost *
Lorente-Ros et al. (2020)	Truly or somewhat representative of the average SARS-CoV-2 infection cases in the community *	Drawn from the same community as the exposed cohort *	Secure record (e.g. surgical records) *	Yes *	–	Record linkage *	Yes *	All subjects accounted for or small number lost *
Ma et al. (2020)	Truly or somewhat representative of the average SARS-CoV-2 infection cases in the community *	Drawn from the same community as the exposed cohort *	Secure record (e.g. surgical records) *	Yes *	–	Record linkage *	Yes *	All subjects accounted for or small number lost *
Pagnesi et al. (2020)	Truly or somewhat representative of the average SARS-CoV-2 infection cases in the community *	Drawn from the same community as the exposed cohort *	Secure record (e.g. surgical records) *	Yes *	–	Record linkage *	Yes *	All subjects accounted for or small number lost *
Raad et al. (2020)	Truly or somewhat representative of the average SARS-CoV-2 infection cases in the community *	Drawn from the same community as the exposed cohort *	Secure record (e.g. surgical records) *	Yes *	–	Record linkage *	Yes *	All subjects accounted for or small number lost *

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Table 1. ***Continued***

Study	Selection				Comparability	Outcomes		
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the deisng or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up cohorts
Sala et al. (2020)	Truly or somewhat representative of the average SARS-CoV-2 infection cases in the community *	Drawn from the same community as the exposed cohort *	Secure record (e.g. surgical records) *	Yes *	–	Record linkage *	Yes *	All subjects accounted for or small number lost *
Shah et al. (2020)	Truly or somewhat representative of the average SARS-CoV-2 infection cases in the community *	Drawn from the same community as the exposed cohort *	Secure record (e.g. surgical records) *	Yes *	–	Record linkage *	Yes *	All subjects accounted for or small number lost *
Shahrokh et al. (2020)	Truly or somewhat representative of the average SARS-CoV-2 infection cases in the community *	Drawn from the same community as the exposed cohort *	Secure record (e.g. surgical records) *	Yes *	–	Record linkage *	Yes *	All subjects accounted for or small number lost *
Shi et al. (2020)	Truly or somewhat representative of the average SARS-CoV-2 infection cases in the community *	Drawn from the same community as the exposed cohort *	Secure record (e.g. surgical records) *	Yes *	–	Record linkage *	Yes *	All subjects accounted for or small number lost *
Song et al. (2020)	Truly or somewhat representative of the average SARS-CoV-2 infection cases in the community *	Drawn from the same community as the exposed cohort *	Secure record (e.g. surgical records) *	Yes *	–	Record linkage *	Yes *	All subjects accounted for or small number lost *
Szekely et al. (2020)	Truly or somewhat representative of the average SARS-CoV-2 infection cases in the community *	Drawn from the same community as the exposed cohort *	Secure record (e.g. surgical records) *	Yes *	–	Record linkage *	Yes *	All subjects accounted for or small number lost *

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Table 1. *Continued*

Study	Selection				Comparability	Outcomes		
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the deisng or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up cohorts
Toraih et al. (2020)	Truly or somewhat representative of the average SARS-CoV-2 infection cases in the community *	Drawn from the same community as the exposed cohort *	Secure record (e.g. surgical records) *	Yes *	–	Record linkage *	Yes *	All subjects accounted for or small number lost *
Wei et al. (2020)	Truly or somewhat representative of the average SARS-CoV-2 infection cases in the community *	Drawn from the same community as the exposed cohort *	Secure record (e.g. surgical records) *	Yes *	–	Record linkage *	Yes *	All subjects accounted for or small number lost *
Xie et al. (2020)	Truly or somewhat representative of the average SARS-CoV-2 infection cases in the community *	Drawn from the same community as the exposed cohort *	Secure record (e.g. surgical records) *	Yes *	–	Record linkage *	Yes *	All subjects accounted for or small number lost *
Xu et al. (2020a)	Truly or somewhat representative of the average SARS-CoV-2 infection cases in the community *	Drawn from the same community as the exposed cohort *	Secure record (e.g. surgical records) *	Yes *	–	Record linkage *	Yes *	All subjects accounted for or small number lost *
Xu et al. (2020b)	Truly or somewhat representative of the average SARS-CoV-2 infection cases in the community *	Drawn from the same community as the exposed cohort *	Secure record (e.g. surgical records) *	Yes *	–	Record linkage *	Yes *	All subjects accounted for or small number lost *

Table 2. Summary of baseline characteristics of the included studies.

Study	Population	Sample size (males)		Age (years)		Findings	CC description	Assessment	Time of assessment
		CC	No CC	CC	No CC				
Abrams et al. (2020)	Mortally ill COVID-19 patients hospitalized in 3 New York City hospitals between March 1 and April 3, 2020	11 (9)	122 (74)	64 (58–72)	82 (71.8–89)	p = 0.0009	Arrhythmic death	Last recorded cardiac rhythm	After death
Arentz et al. (2020)	Critically ill COVID-19 patients admitted to Evergreen Hospital ICU, Washington State	15 (8)	6 (3)	74 (61–82)	69.5 (66–73)	p = 0.3699	Cardio-myopathy	Radiologic and laboratory findings	Day of ICU admission and again on day 5
Barman et al. (2020)	Consecutive COVID-19 patients hospitalized in three government hospitals in Istanbul, Turkey	150 (86)	457 (248)	68.5 ± 13.4	56.5 ± 15.2	p < 0.001	Cardiac injury	Laboratory findings only	Day of hospital admission
Bertini et al. (2020)	431 consecutive COVID-19 patients hospitalized in Italy between 10 March and 14 April 2020 who died or were treated with invasive mechanical ventilation.	24 (16)	86 (64)	71 (59–76)	68 (60–78)	p = 0.88	Hs-TnI > 5x the upper reference limit	Laboratory findings only	Day of hospital admission
Linschoten and Asselbergs (2020)	COVID-19 patients registered to the international CAPACITY-COVID collaborative consortium with inclusion current from 13 countries	752 (537)	4811 (3019)	71 (64–77)	66 (55–76)	p < 0.001	Cardiac complication	According to criteria of the European Society of Cardiology	From hospital admission to discharge
Duerr et al. (2020)	COVID-19 patients admitted to the University Hospital Bonn, Germany	9 (4)	10 (5)	NA	NA	NA	Pericardial effusion	Radiologic and laboratory findings	Day of hospital admission
Ferrante et al. (2020)	Consecutive COVID-19 patients undergoing chest CT on admission to Humanitas Research Hospital in Milan, Italy	123 (95)	209 (142)	74.2 (67.8–80.1)	60.7 (51.4–70.5)	p < 0.001	Myocardial injury	Radiologic and laboratory findings	Day of hospital admission

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Table 2. *Continued*

Study	Population	Sample size (males)		Age (years)		Findings	CC description	Assessment	Time of assessment
		CC	No CC	CC	No CC				
Ghio et al. (2020)	Consecutive adult COVID-19 patients admitted to the Emergency Department of Fondazione IRCCS Policlinico San Matteo (Pavia, Italy) from February 21st to March 31st 2020	74 (51)	266 (188)	76.1 (69.7–82.5)	68.6 (56.4–76.4)	$p < 0.001$	Myocardial injury	Laboratory findings only	Day of hospital admission
Guo et al. (2020)	Consecutive COVID-19 patients admitted to the Seventh Hospital of Wuhan City, China	52 (34)	135 (57)	71.4 (SD = 9.43)	53.53 (SD = 13.22)	$p < 0.001$	Myocardial injury	Laboratory findings only	Day of hospital admission
Lairez et al. (2020)	COVID-19 patients admitted to Rangueil Hospital of Toulouse University for dyspnea or chest pain from April 6, 2020, to May 1, 2020.	13 (11)	18 (16)	66 ± 8	52 ± 13	$p = 0.015$	Myocardial injury	Radiologic and laboratory findings	Day of hospital admission
Lala et al. (2020)	COVID-19 patients admitted to five Mount Sinai Health System hospitals in New York City	530 (318)	2206 (1312)	Median = 70-80	Median = 60-70	NA	Myocardial injury	Laboratory findings only	Day of hospital admission
Li et al. (2020a), 2020b, 2020c	Critical type COVID-19 patients randomly selected from Renmin Hospital of Wuhan University, China	34 (23)	48 (29)	70.59% > 70	37.5% > 70	$p = 0.003$	Myocardial damage	Laboratory findings only	NA
Liu et al. (2020)	COVID-19 patients from Shenzhen Third People's Hospital in Shenzhen, China	1 (1)	11 (7)	63	62 (36–65)	NA	Fulminant myocarditis, cardiac failure	Radiologic and laboratory findings	Day of hospital admission
Lombardi et al. (2020)	Consecutive COVID-19 patients hospitalized in 13 Italian cardiology units from March 1 to April 9, 2020.	278 (201)	336 (234)	71.3 (12)	64.0 (13.6)	$p < 0.001$	Myocardial injury	Laboratory findings only	Day of hospital admission
Lorente-Ros et al. (2020)	Consecutive adult COVID-19 patients admitted to a large tertiary hospital in Madrid, Spain	148 (71)	559 (193)	78.7	63.4	Standardized difference = 114%	Myocardial injury	Laboratory findings only	Day of hospital admission

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Table 2. *Continued*

Study	Population	Sample size (males)		Age (years)		Findings	CC description	Assessment	Time of assessment
		CC	No CC	CC	No CC				
Ma et al. (2020)	Adult patients hospitalized with COVID-19 in Yongchuan, Chongqing, China	45 (27)	39 (21)	51 (45.5–63.5)	45 (39–53)	p = 0.026	NA	Radiologic and laboratory findings	Day of hospital admission
Pagnesi et al. (2020)	Hospitalized non-ICU COVID-19 patients from a large tertiary center in Milan, Italy	29 (20)	171 (111)	65 (55–76)	62 (54–74)	p = 0.813	Right ventricular dysfunction	Radiologic and laboratory findings	Day of hospital admission
Raad et al. (2020)	COVID-19 patients admitted to Henry Ford Health System in Southeast Michigan, USA, between March 9 and April 15, 2020.	390 (229)	630 (280)	70 (51–89)	59 (39–79)	NA	Cardiac injury	Laboratory findings only	Day of hospital admission
Sala et al. (2020)	Non-ICU COVID-19 patients admitted to seven COVID-19 units at a third-level hub center in Milan, Italy	12 (NA)	116 (NA)	73 ± 10	64 ± 14	NA	Arrhythmias	Radiologic findings only	NA
Shah et al. (2020)	Covid-19 patients admitted to 3 Phoebe Putney hospitals in Southwest Georgia, USA, between March 2 and June 7, 2020.	116 (62)	193 (70)	68.2 ± 14.1	59.9 ± 14.0	p < 0.001	Cardiac injury	Laboratory findings only	NA
Shahrokh et al. (2020)	COVID-19 patients presenting to the Sina Hospital emergency department in south Tehran, Iran between March and May 2020.	115 (69)	271 (167)	64.98 ± 15.29	57.12 ± 15.48	p < 0.001	Cardiac injury	Radiologic and laboratory findings	Day of hospital admission
Shi et al. (2020)	Consecutive severe COVID-19 inpatients of Renmin Hospital, Wuhan University, China	106 (58)	565 (264)	73 (66–80)	57 (43–70)	p < 0.001	Myocardial injury	Laboratory findings only	Day of hospital admission

(*Continued on next page*)

Table 2. *Continued*

Study	Population	Sample size (males)		Age (years)		Findings	CC description	Assessment	Time of assessment
		CC	No CC	CC	No CC				
Song et al. (2020)	Critically ill COVID-19 patients admitted to the ICU at Tongji Hospital, Wuhan, China	34 (24)	30 (18)	67.8 ± 10.3	61.3 ± 13.3	p = 0.033	Myocardial injury	Laboratory findings only	Day of hospital admission
Szekely et al. (2020)	Consecutive adult COVID-19 patients admitted to Tel Aviv Medical Center, Israel	68 (46)	32 (17)	69.8 ± 16	65.9 ± 20	p = 0.56	Abnormal echocardiogram	Radiologic findings only	Day of admission
Toraih et al. (2020)	COVID-19 patients included in studies exploring pre-existing CVD as COVID-19 risk factors, cardiac injury, ICU admission or mortality	202 (NA)	958 (NA)	NA	NA	NA	Cardiac injury	Laboratory findings only	NA
Wei et al. (2020)	COVID-19 patients admitted to two treatment centers in Sichuan, China	16 (7)	85 (47)	67(61–80.5)	47(33–55)	p < 0.001	Acute myocardial injury	Radiologic and laboratory findings	NA
Xie et al. (2020)	Non-critically ill COVID-19 patients admitted to Tongji Hospital, Wuhanm China	102 (46)	517 (251)	68.9 ± 11.7	56.4 ± 13.6	p < 0.001	Acute cardiac-related injury	Radiologic and laboratory findings	NA
Xu et al. (2020a)	Adult patients with COVID-19 in Guangzhou, China	12 (6)	253 (116)	62.6± 14.5	48.1± 15.5	p = 0.002	Acute cardiac injury	Radiologic and laboratory findings	NA
Xu et al. (2020b)	COVID-19 patients consecutively hospitalized between January 2 and March 17, 2020, in the Public Health Clinical Center of Chengdu, China.	47 (23)	46 (23)	41 (31–51)	54 (40–65)	p < 0.001	Cardiac marker abnormalities	Laboratory findings only	Day of hospital admission

CC, cardiac complications; ICU, intensive care unit; NA, data not available.

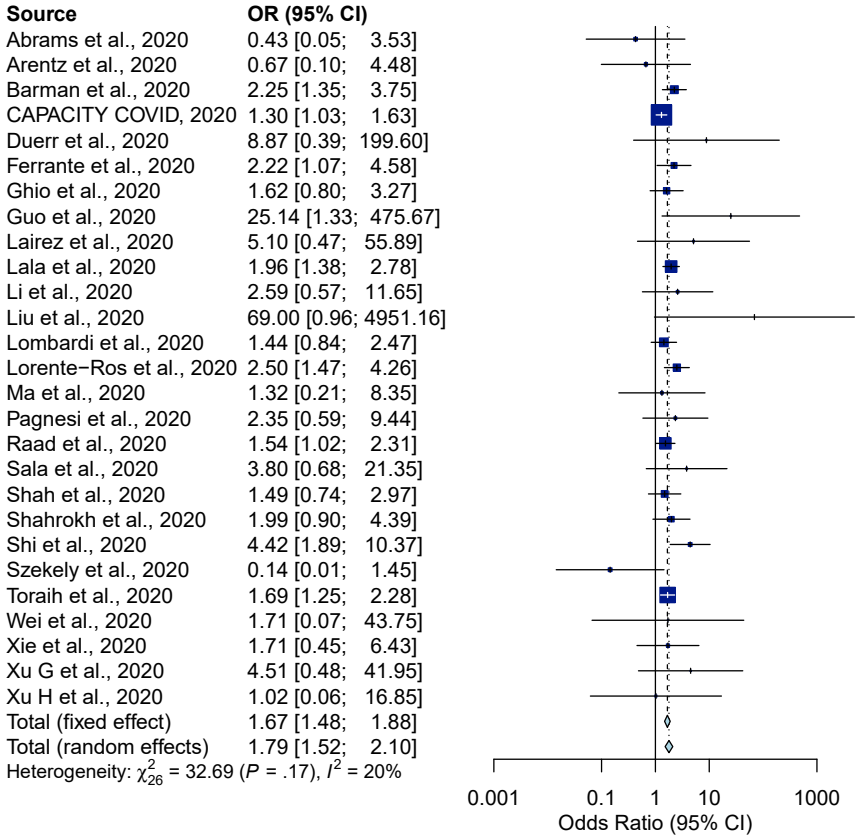

Figure 2. Forest plot of chronic respiratory illness as a risk factor for cardiac complications in COVID-19 patients

Fixed effect models apply when $I^2 < 50\%$.

See also Figure S1.

The association between DM and a higher incidence of SARS-CoV-2-associated cardiac complications was also conserved across all cohorts from the U.S.A. (OR: 1.54, 95% CI: [1.32, 1.78]) (Figure 10A), the Middle East (OR: 1.65, 95% CI: [1.25, 2.19]) (Figure 10B), Europe (OR: 1.50, 95% CI: [1.07, 2.09]) (Figure 10C), and China (OR: 2.04, 95% CI: [1.13, 3.70]) (Figure 10D), despite regional subdivision not accounting for high heterogeneity amongst the European and Chinese cohorts.

Finally, regionally pooled sub-analysis of male sex found it to be associated with a higher incidence of SARS-CoV-2 associated cardiac complications in cohorts from the U.S.A. (OR: 1.55, 95% CI: [1.03, 2.33]) (Figure 11A), and Europe (OR: 1.40, 95% CI: [1.23, 1.59]) (Figure 11C) but not the Middle East (Figure 11B) or China (Figure 11D). Regional subdivision accounted for the high heterogeneity amongst all but the American cohort.

DISCUSSION

Our meta-analysis shows that older age, male sex, and pre-existing chronic respiratory disease, CVD, hypertension, and DM are all associated with the development of cardiac complications associated with SARS-CoV-2 infection, while our regional sub-analysis indicates these associations may depend on geographic region. At present, the reasons for each of these association are unclear; each is a respiratory risk factor and thus might cause an indirect cardiac effect; however it could equally be the case that they exert their own direct catalytic effect on cardiac complications.

Our analysis identified a significant association between pre-existing CVD and the risk of SARS-CoV-2-associated cardiac complications, which was conserved across global geographical regions. This is consistent with previous observations that 30% of patients with SARS-CoV-2 cardiac injury had a history of

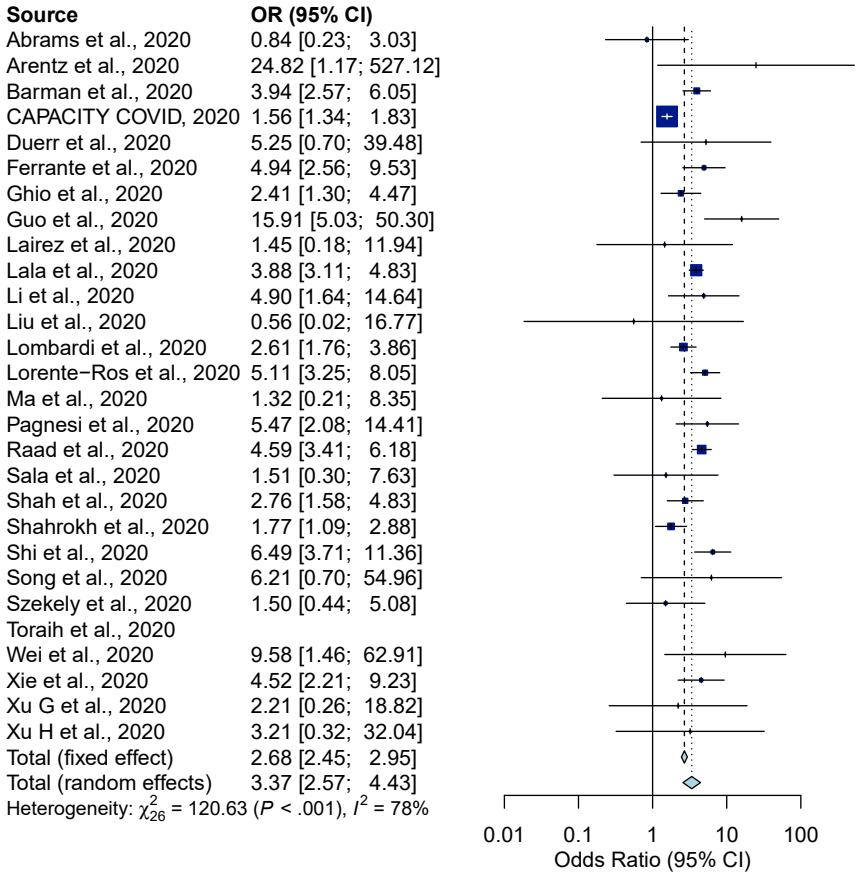

Figure 3. Forest plot of pre-existing cardiovascular disease as a risk factor for cardiac complications in COVID-19 patients

Random effect models apply when I^2 > 50%.

See also Figure S2.

coronary heart disease (Guo et al., 2020; Shi et al., 2020). The reason for this association remains unclear. These data may be the result of pre-existing CVD leading to an altered immune response, excessive cytokine release (Zheng et al., 2020), endothelial dysfunction, increased procoagulant blood activity, rupturing of coronary atherosclerotic plaques (Madjid et al., 2007), and the formation of an occlusive thrombi (Corrales-Medina et al., 2013). However, further investigations are required to validate this hypothesis.

The meta-analysis performed herein also found that chronic respiratory illness was also associated with an increased incidence of SARS-CoV-2 associated cardiac complications. It is possible that these data reflect the established indirect association between severe respiratory disease and subsequent acute cardiovascular event Indeed, COVID-19 patients with pneumonia and acute respiratory distress syndrome (ARDS) display acute right ventricular hypertrophy despite an absence of pulmonary embolism or severe pulmonary hypertension (Martínez-Mateo et al., 2020). However, chronic lung disease has not been consistently associated with SARS-CoV-2 ARDS and hypoxemia (Halpin et al., 2020), and thus this is unlikely to be the sole explanation for the association of cardiac complications in patients with chronic respiratory illness in the present analysis.

The association between underlying DM and cardiac complications from SARS-CoV-2 may be attributable to a multitude of other effects induced by abnormal circulating substrates, including hyperglycaemia, and/or the co-existence and complex interactions with other, even subclinical, conditions in this patient group (Heather and Clarke, 2011). In response to changes in substrate availability, for example, the diabetic heart becomes increasingly dependent on fatty acids as a fuel source, which decreases work efficiency, and dysregulates responses to hypoxia (Iqbal et al., 2014). These metabolic changes may predispose individuals

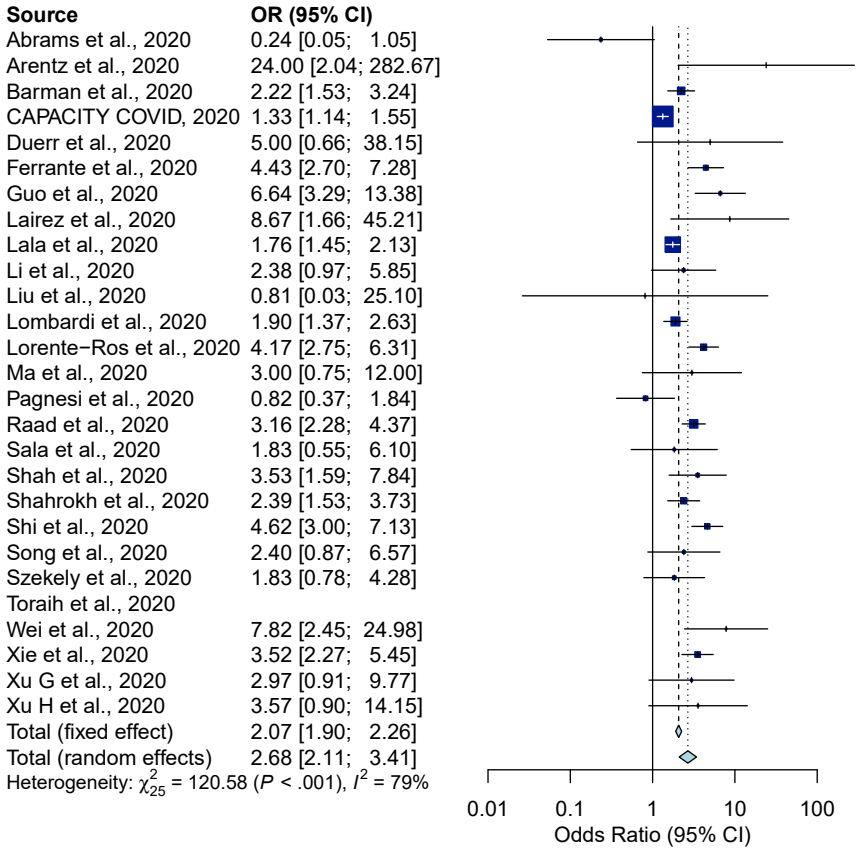

Figure 4. Forest plot of hypertension as a risk factor for cardiac complications in COVID-19 patients

Random effect models apply when I^2 > 50%.

See also Figure S3.

with DM to an increased risk of ischemic cardiac injury upon SARS-CoV-2 infection. The contribution of underlying DM to the risk of SARS-CoV-2-associated cardiac complications, however, depends largely on the duration of pre-existing disease (Rask-Madsen and King, 2013).

Limitations of the study

There are several limitations in our review. Firstly, despite a lack of evidence found for publication bias (see Figures S1–S5) the exclusion of 55 eligible studies due to lack of response from the original authors inserts a critical bias in the meta-analysis. Secondly, the limited number of studies that met the pre-defined selection criteria disallowed correction for other variables that may confound these results. For example, it is possible that our observations were confounded by the strong effect that age has on cardiovascular health. Thus, it is not possible to conclude if people with these pre-existing conditions are just more susceptible to severe COVID-19 and thus the heart complications associated with this increased severity, or if there is indeed a cardiac-specific effect occurring. Similarly, we cannot exclude the possibility that the associations observed herein are due, at least in part, to treatments for severe COVID-19 that may affect the heart, or treatments for underlying conditions. Information regarding which, if any, therapeutics used in these cohorts of patients was not consistently available. We anticipate that as more data on the cardiac complications become available it will be possible for future analyses to correct for these and other confounders; however, it would also be worthwhile testing the effects of each these pre-existing chronic conditions in one of the recently developed murine models of SARS-CoV-2. Another limitation is that in our analysis for the source of heterogeneity, data was not sufficiently available to perform sub-analysis based on other factors such as stage of disease. Global region did not always account for the observed heterogeneity, which may instead be due to clinical and methodological differences between each study. Furthermore, the adjustment of confounding variables may have differed across studies, with studies possibly deploying

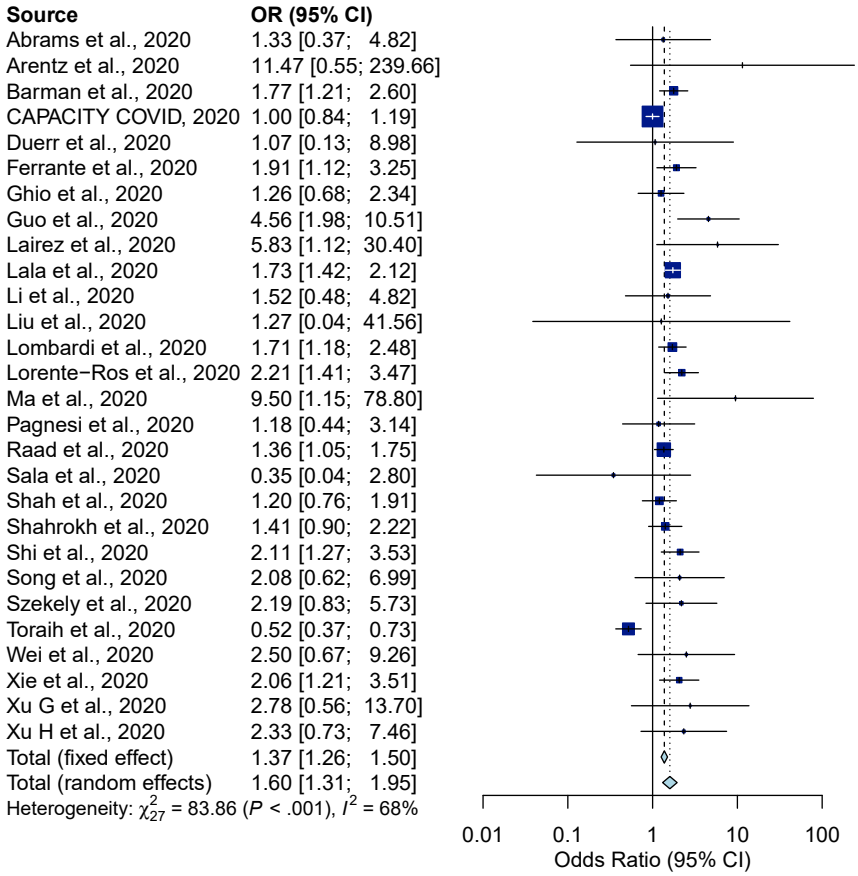

Figure 5. Forest plot of diabetes mellitus as a risk factor for cardiac complications in COVID-19 patients

Random effect models apply when $I^2 > 50\%$.

See also Figure S4.

different multivariate models in the analyses, also contributing to heterogeneity. However, adjusted ORs relevant to our outcome were not readily available from the included studies.

Despite the above limitations, these data have important implications for patient care. Patients with one or more underlying medical conditions should be closely monitored for both severe respiratory and extra-respiratory COVID-19 complications. Furthermore, the exploratory use of medications that are independently associated with cardiac complications should be considered with caution in these patient groups and perhaps bypassed in favor of lower-risk treatment options. There is thus a clear need for a multidisciplinary, collaborative team to manage the complexity of COVID-19 illness observed in patients with one or more underlying chronic disease.

Resource availability

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Dr. Kirsty Short (k.short@uq.edu.au).

Materials availability

This study did not generate new unique reagents.

Data and code availability

All data relevant to this study has been included in the manuscript. Data contributed by Xu et al. (2020a), 2020b, Ma et al. (2020), and Arentz et al. (2020), may be obtained by contacting authors of each respective

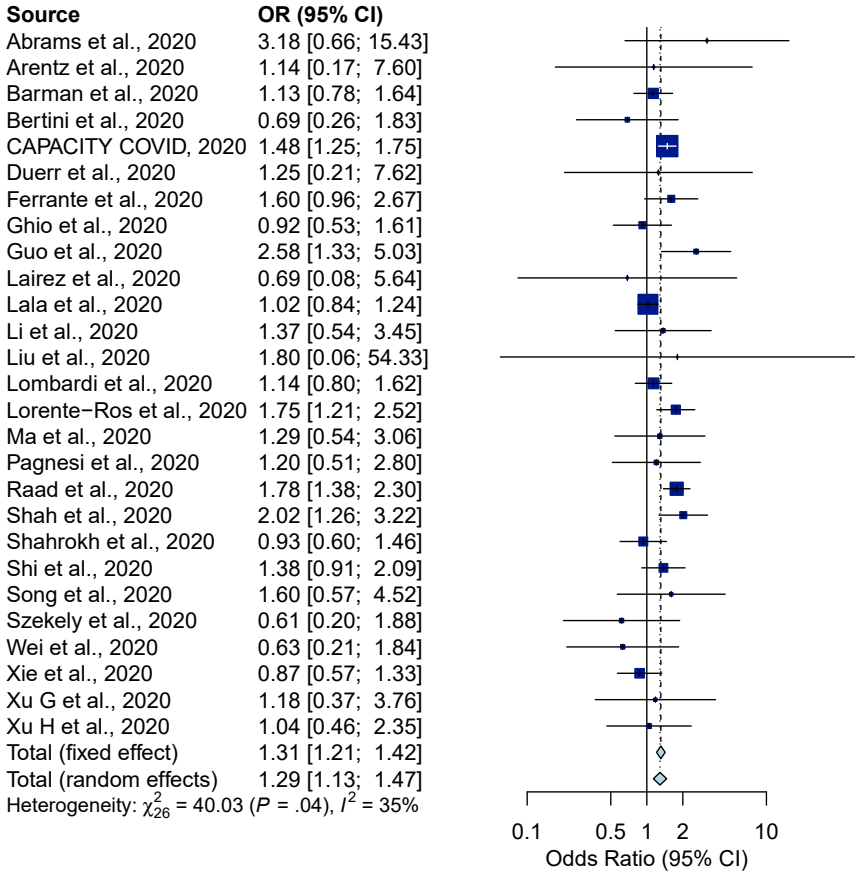

Figure 6. Forest plot of male sex as a risk factor for cardiac complications in COVID-19 patients

Fixed effect models apply when $I^2 < 50\%$.

See also Figure S5.

study. Data retrieved from remaining studies are published and publicly available. R, version 4 0·0 software was used to analyze sex distribution, as well as pre-existing chronic disease and cardiac outcomes through meta-analysis. The data sets/code supporting the current study have not been deposited in a public repository but are available from the corresponding author on request.

METHODS

All methods can be found in the accompanying transparent methods supplemental file.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2021.102264.

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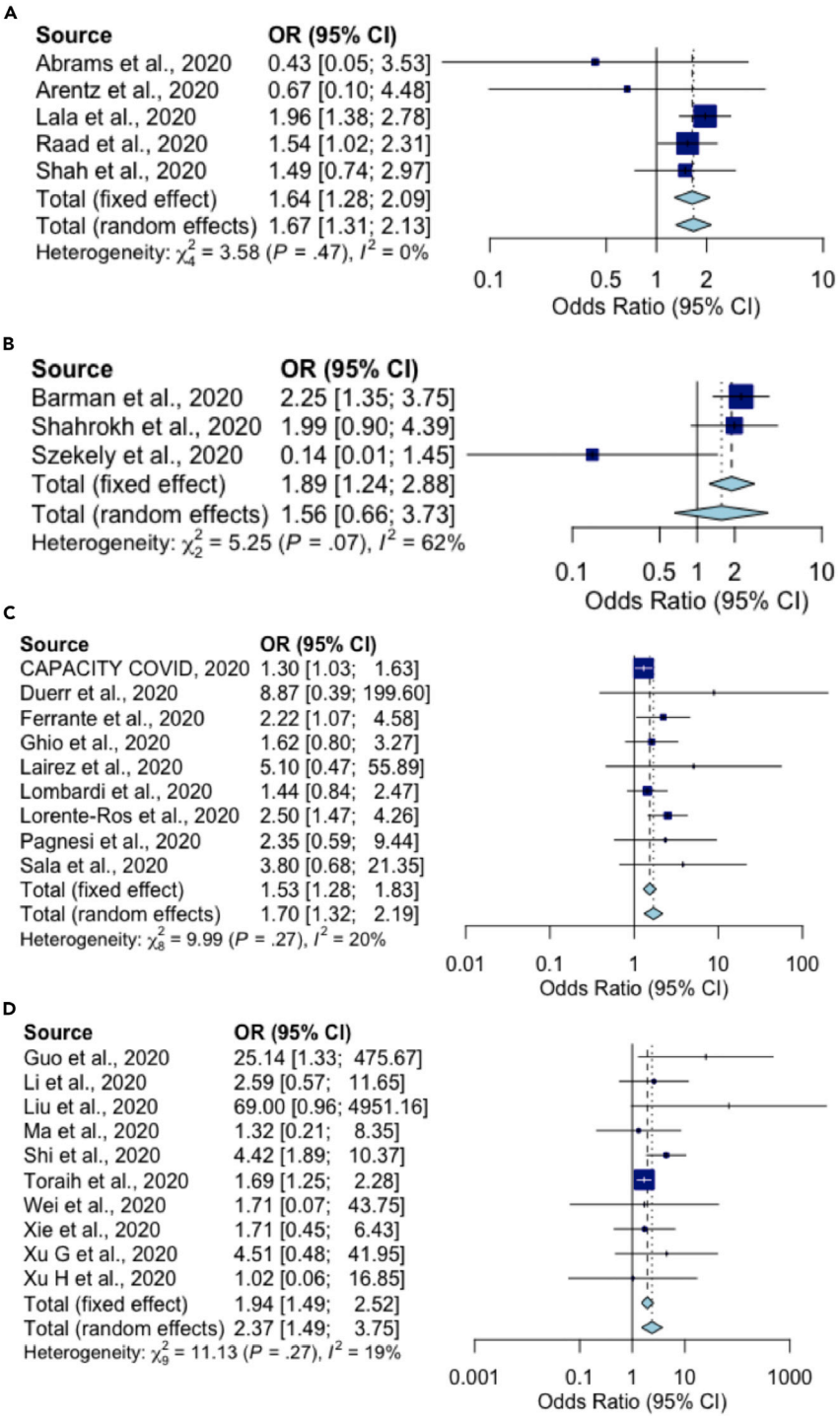

Figure 7. Forest plots of chronic respiratory as a risk factor for cardiac complications in COVID-19 patients divided by geographical region

(A) Studies based primarily in the United States of America.

(B) Studies based primarily around the Middle East.

(C) Studies based primarily in Europe.

(D) Studies based primarily in China.

Fixed effect models apply when $I^2 < 50\%$ and random effects models apply when $I^2 > 50\%$.

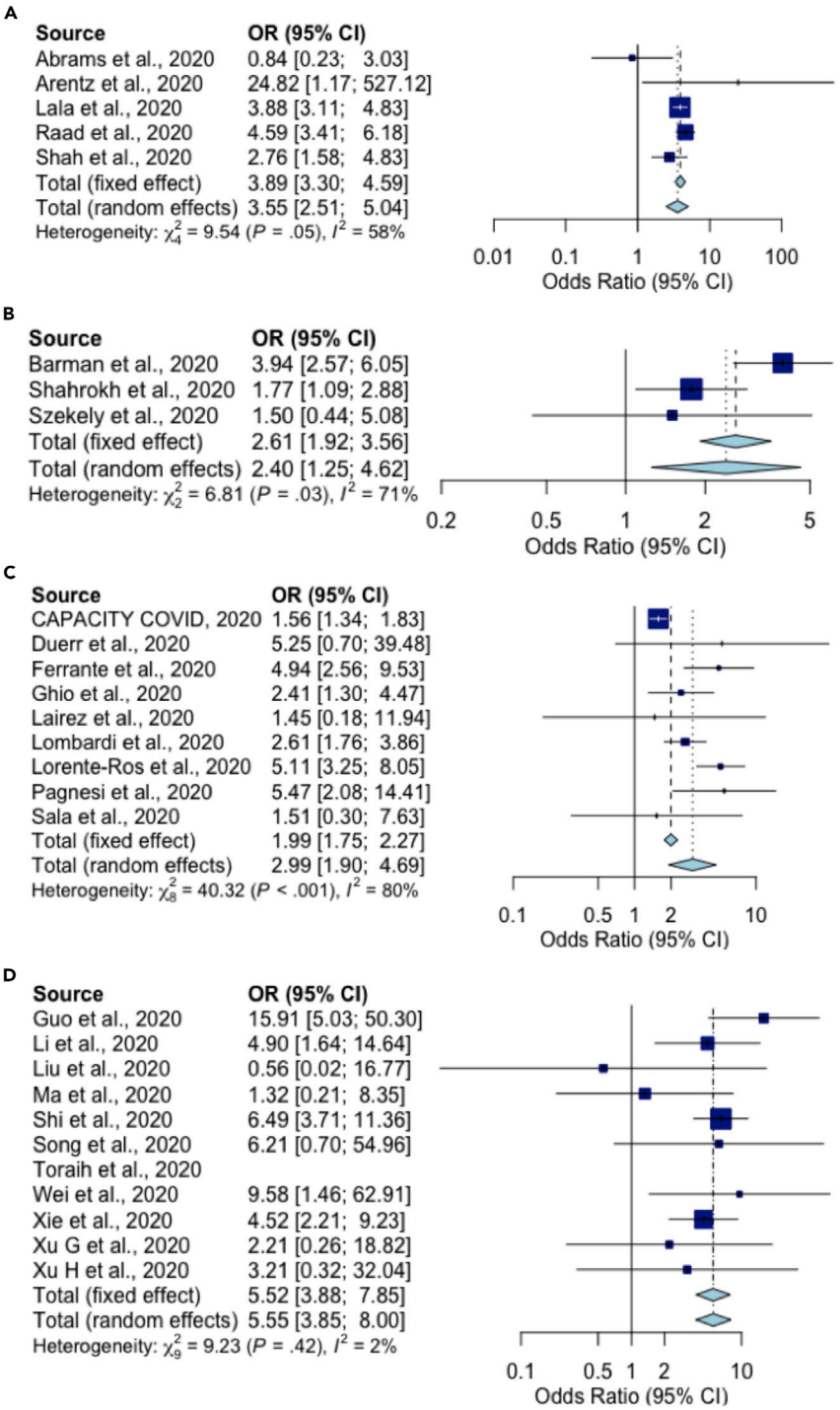

Figure 8. Forest plots of pre-existing cardiovascular disease as a risk factor for cardiac complications in COVID-19 patients divided by geographical region

(A) Studies based primarily in the United States of America.

(B) Studies based primarily around the Middle East.

(C) Studies based primarily in Europe.

(D) Studies based primarily in China.

Fixed effect models apply when $I^2 < 50\%$ and random effects models apply when $I^2 > 50\%$.

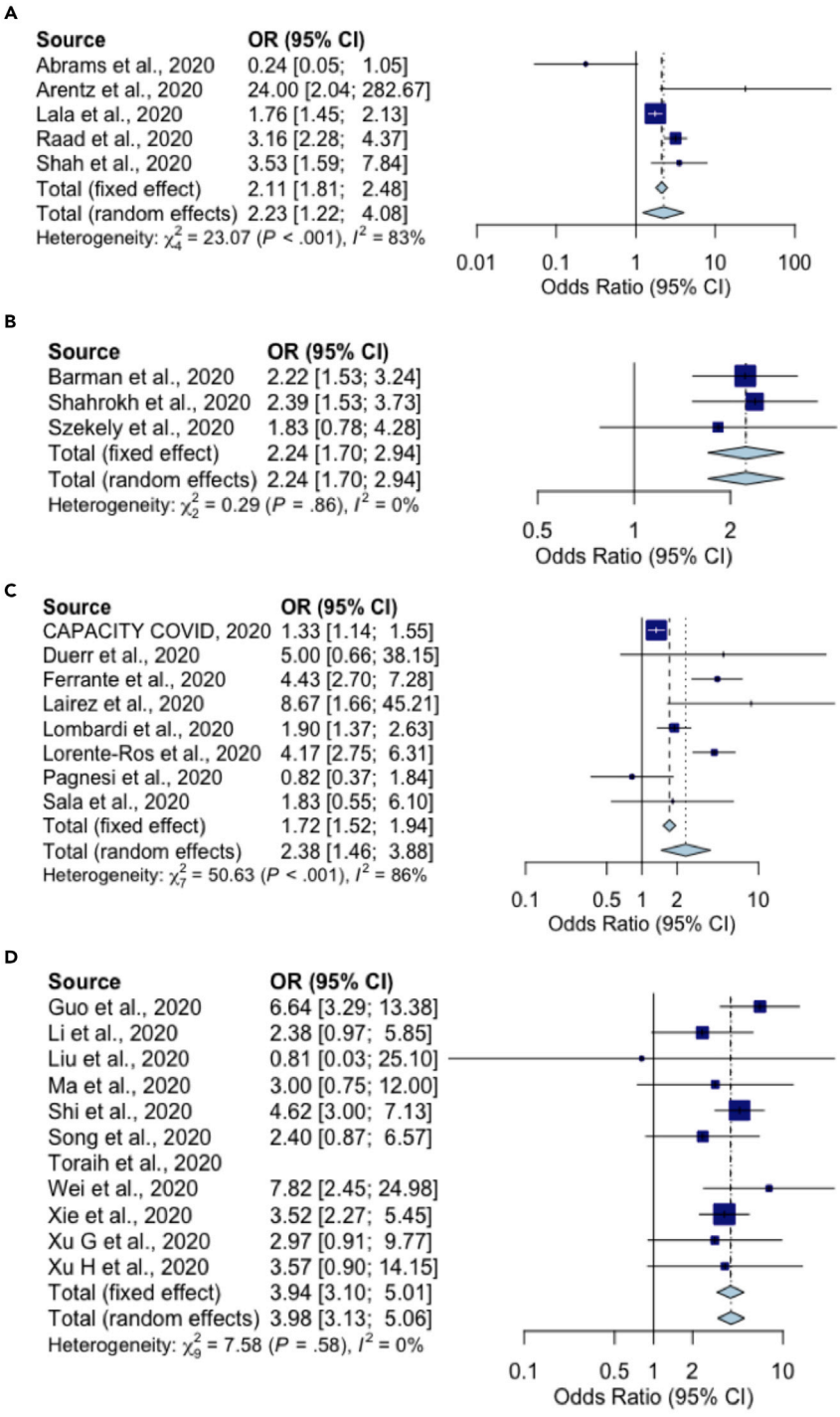

Figure 9. Forest plots of hypertension as a risk factor for cardiac complications in COVID-19 patients divided by geographical region

(A) Studies based primarily in the United States of America.

(B) Studies based primarily around the Middle East.

(C) Studies based primarily in Europe.

(D) Studies based primarily in China.

Fixed effect models apply when I^2 < 50% and random effects models apply when I^2 > 50%.

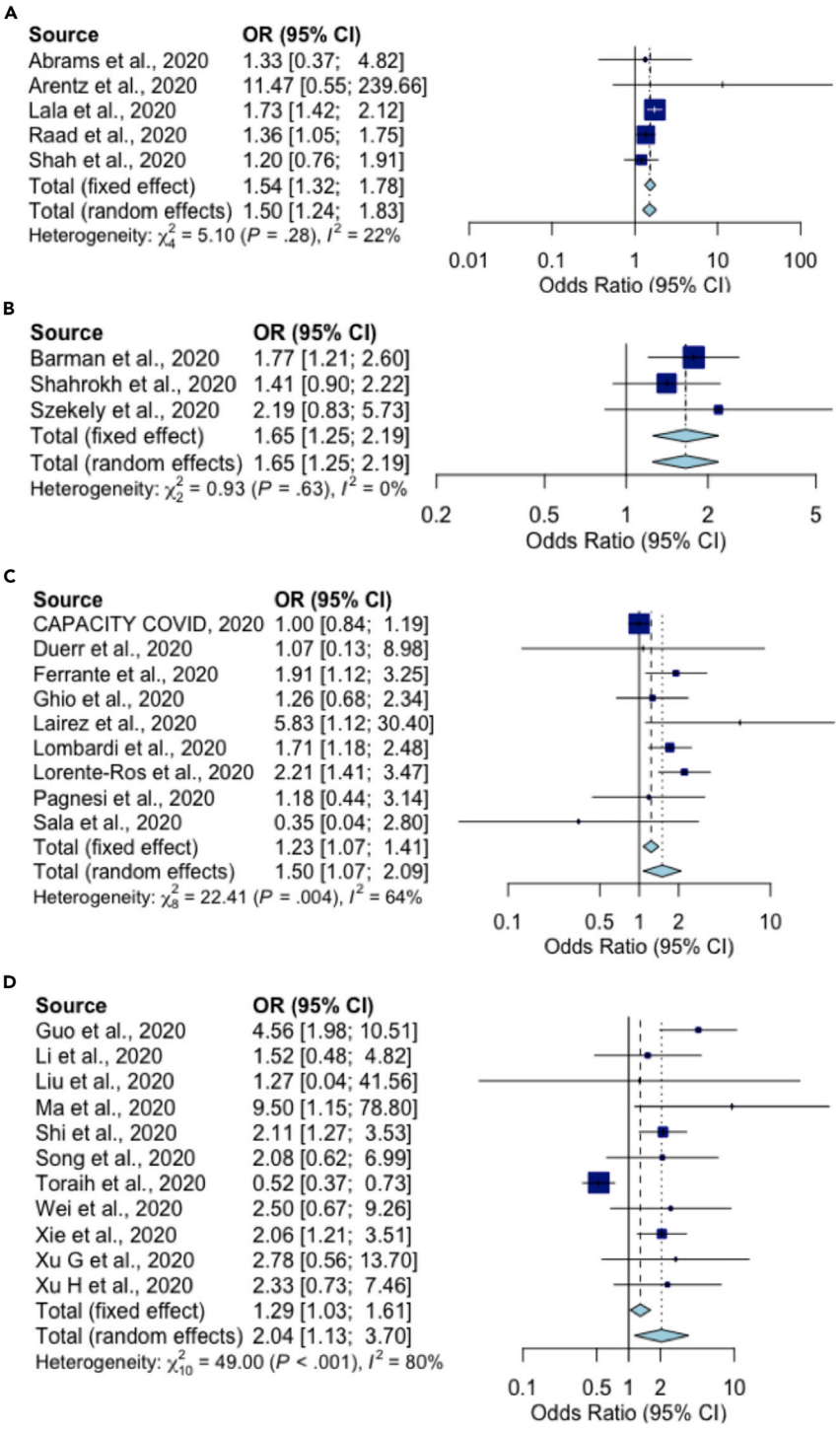

Figure 10. Forest plots of diabetes mellitus as a risk factor for cardiac complications in COVID-19 patients divided by geographical region

(A) Studies based primarily in the United States of America.

(B) Studies based primarily around the Middle East.

(C) Studies based primarily in Europe.

(D) Studies based primarily in China.

Fixed effect models apply when $I^2 < 50\%$ and random effects models apply when $I^2 > 50\%$.

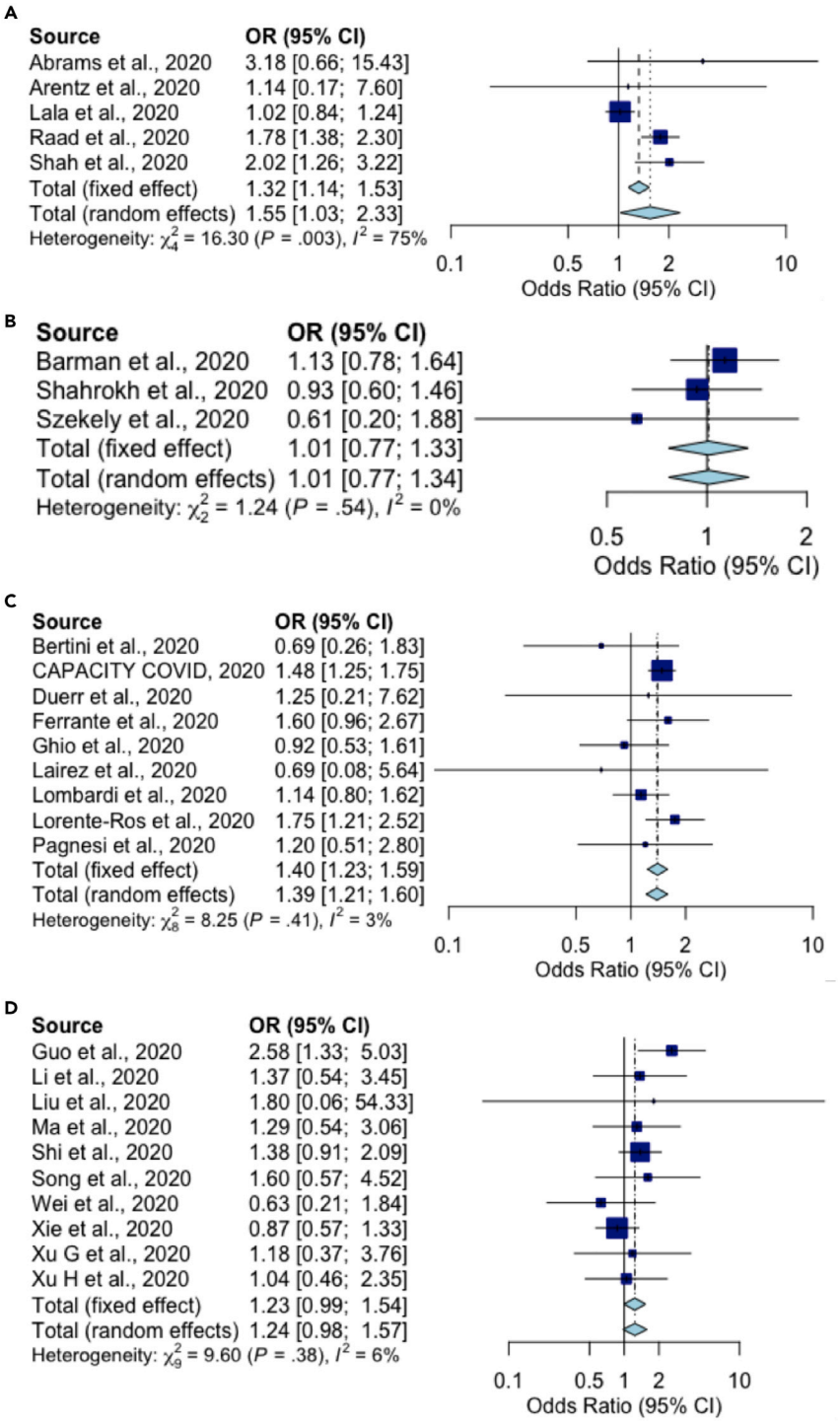

Figure 11. Forest plots of male sex as a risk factor for cardiac complications in COVID-19 patients divided by geographical region

(A) Studies based primarily in the United States of America.

(B) Studies based primarily around the Middle East.

(C) Studies based primarily in Europe.

(D) Studies based primarily in China.

Fixed effect models apply when I^2 < 50% and random effects models apply when I^2 > 50%.

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AUTHORS CONTRIBUTION

Idea and study design: K.R.S., L.A.G.; study selection: J.E.S., Y.Z., K.R.S.; data collection and analysis: J.E.S., Y.Z., G.X., W.M., H.S., K.-L.M., C.-F.C., L.-X.K., K.-Q.W., J.L., M.A., K.R.S.; writing the article: J.E.S., K.R.S.; draft revision: J.E.S., G.X., W.M., H.S., K.-L.M., C.-F.C., L.-X.K., K.-Q.W., J.L., M.A., M.A.R., L.A.G., and K.R.S.; All authors have read the manuscript and have approved this submission.

DECLARATION OF INTERESTS

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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iScience, Volume *24*

Supplemental information

A meta-analysis on the role of pre-existing chronic disease in the cardiac complications of SARS-CoV-2 infection

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Supplemental Information

SUPPLEMENTAL DATA

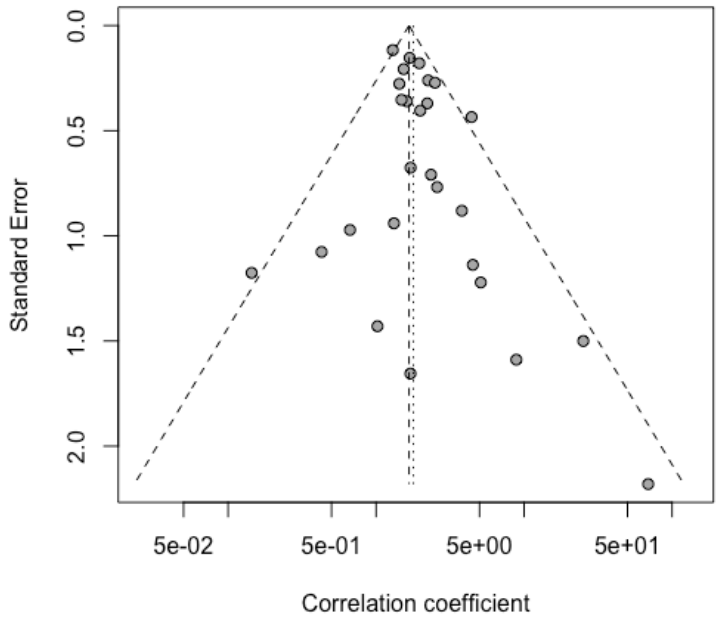

Figure S1. Funnel plot of chronic respiratory illness s a risk factor for cardiac complications in COVID-19 patients, Related to Figure 2. Neither Egger's regression test (p = 0.1104) or the Rank correlation test (p = 0.3004) was statistically significant, finding no evidence of publication bias.

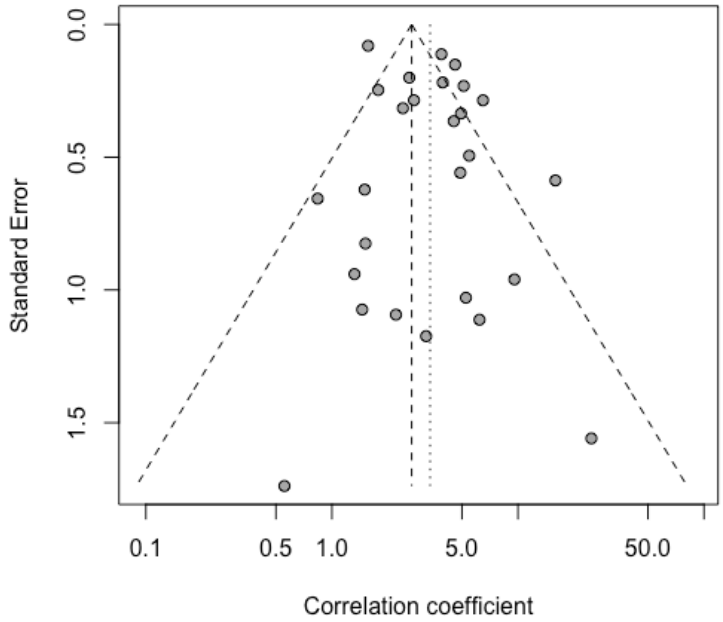

Figure S2. Funnel plot of cardiovascular disease as a risk factor for cardiac complications in COVID-19 patients, Related to Figure 3. Neither Egger's regression test (p = 0.7516) or the Rank correlation test (p = 0.1014) was statistically significant, finding no evidence of publication bias.

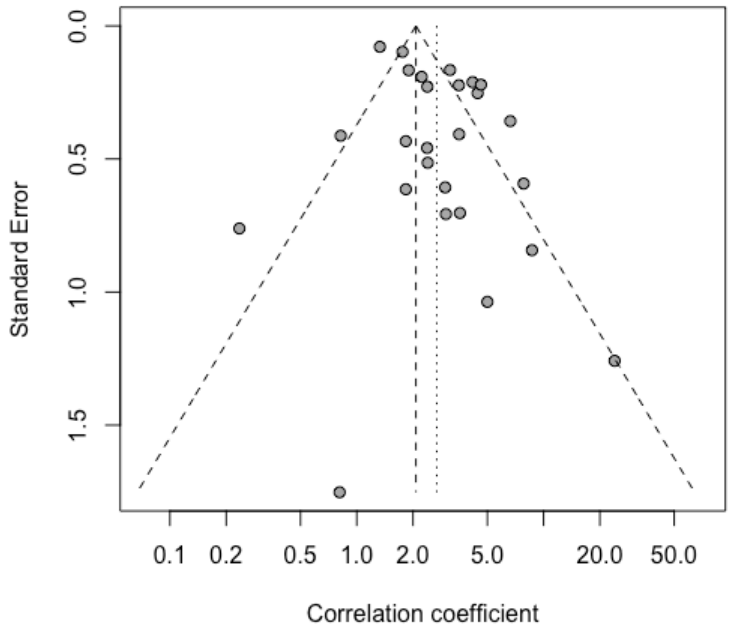

Figure S3. Funnel plot of hypertension as a risk factor for cardiac complications in COVID-19 patients, Related to Figure 4. Neither Egger's regression test (p = 0.8397) or the Rank correlation test (p = 0.5353) was statistically significant, finding no evidence of publication bias.

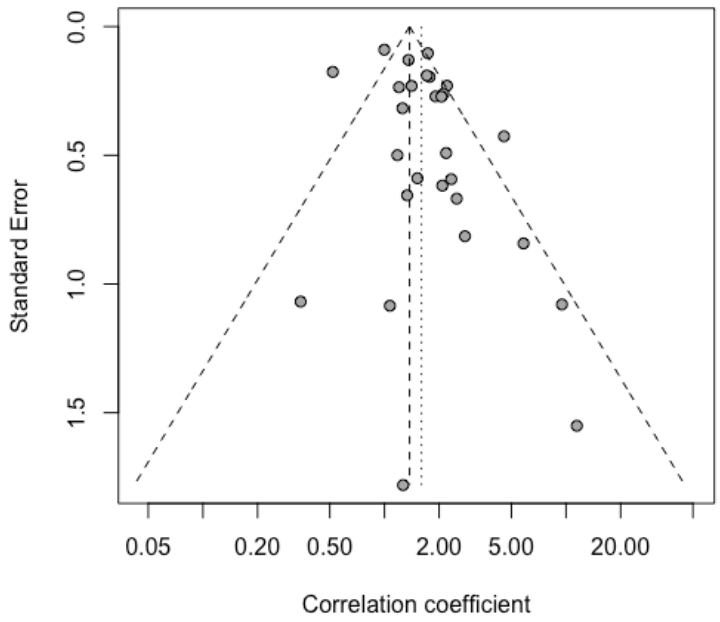

Figure S4. Funnel plot of diabetes mellitus as a risk factor for cardiac complications in COVID-19 patients, Related to Figure 5. Neither Egger's regression test (p = 0.0566) or the Rank correlation test (p = 0.9532) was statistically significant, finding no evidence of publication bias.

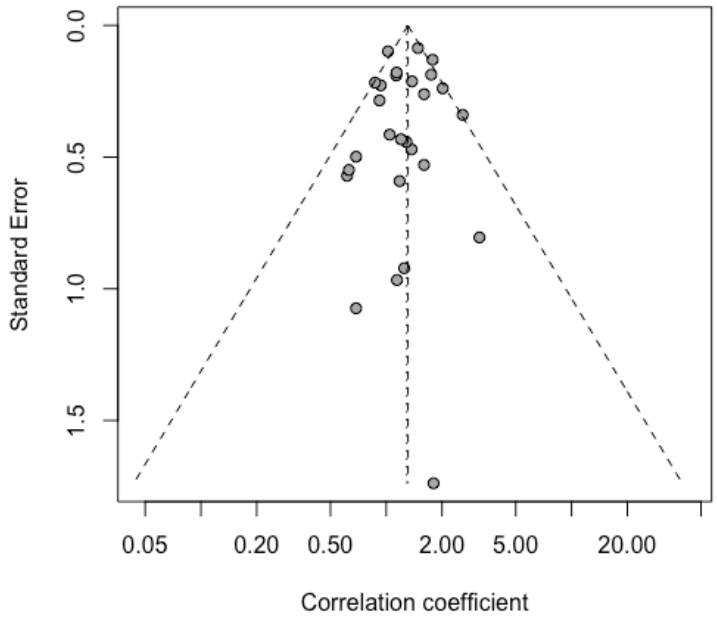

Figure S5. Funnel plot of male sex as a risk factor for cardiac complications in COVID-19 patients, Related to Figure 6. Neither Egger's regression test (p = 0.5352) or the Rank correlation test (p = 0.8688) was statistically significant, finding no evidence of publication bias.

TRANSPARENT METHODS

Study selection

We retrospectively investigated published and pre-printed, publicly released and de-identified data made available between Dec 1, 2019, and October 14, 2020. Information was accessed from four databases (PubMed, Embase, medRxiv and SSRN) using the following search terms: (“covid-19”[All Fields]) OR ("SARS-CoV-2"[All Fields]) AND ("cardiac"[All Fields] AND "comorbid*"[All Fields]). A total of 1076 articles were retrieved after duplicates were removed (available in either English or Chinese), following which 713 records were removed after screening by title and abstract. 363 full-text articles were reviewed. Of these, 283 articles were excluded because i) they did not include original research, ii) they were not relevant to the outcome, iii) they described an inappropriate patient population and/or iv) they described case reports of <10 patients. Study eligibility was assessed by two independent reviewers with disputes resolved by a third independent reviewer. Of the remaining 80 studies that were deemed eligible, due to their containing data on patient pre-existing disease and cardiac complications as an outcome, 25 contained the required data format and these were extracted. The authors of the remaining 55 studies were contacted to request appropriate data (as they presented only aggregate data that did not specify the cross-over between pre-existing chronic disease and outcome), to which four groups responded with data contributions. Thus, a final of 29 studies were included in the meta-analysis. The selection process is shown in Figure 1.

Data extraction and analysis

Extracted variables were aggregate data of median age, sex, underlying chronic disease (chronic respiratory illness, CVD, hypertension and DM) and the occurrence of cardiac complications as an outcome. Patients with co-morbidities were included in all applicable categories. For cases in which the data source reported more than one type of co-morbid CVD separately (such as prevalence of both chronic heart failure and coronary heart disease within their cohort), only the group with the largest number of cases was included to avoid patient double up and overrepresentation of co-morbid CVD. Analyses for each co-morbidity were performed independently, with each assuming one effect (the patient group in question) is considered as the main driver of effects. Median data for age were analysed individually using a Mann-Whitney U test. R version 4·0·0 software was used to analyse sex distribution as well as pre-existing chronic disease and cardiac outcomes through meta-analysis. Heterogeneity among studies was assessed by using the Q statistic with $*P \leq 0.05$ indicating the presence of significant heterogeneity and quantified by using the I^2 statistic. A fixed-effects model was used as when $I^2 < 50\%$ and random-effects model when $I^2 > 50\%$.

Definition of cardiac complications

Cardiac complications were defined as one or more of the following: blood levels of cardiac biomarkers (troponin I or creatine-kinase myocardial band) above the 99th percentile upper reference limit (Wang X. et al., 2017; Thygesen et al., 2018; Yu et al., 2019), and/or abnormalities observed in clinical assessments of the patients’ heart function, including ECG (Estabragh et al., 2013; Gao et al., 2013; Jeyanathan et al., 2013; Wang J. et al., 2017; Ito et al., 2018) or echocardiography (Chacko et al., 2012; Estabragh et al., 2013; Jeyanathan et al., 2013; Wang J. et al., 2017; Ito et al., 2018).

Quality assessment and data synthesis

The included studies were critically appraised using Newcastle Ottawa Quality Assessment Scale (NOS) (Wells et al., 2019). High-quality studies were defined as studies fulfilling NOS score of minimum 7. Data were synthesised from 29 different and high-quality studies. This systematic review was conducted based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) (Moher et al., 2009) statement.

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