Subclinical myocardial injury, coagulopathy, and inflammation in COVID-19: A meta-analysis of 41,013 hospitalized patients

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ABSTRACT

Background: Infection with the SARS-CoV-2 virus can lead to myocardial injury, evidenced by increases in specific biomarkers and imaging.
Objective: To quantify the association between biomarkers of myocardial injury, coagulation, and severe COVID-19 and death in hospitalized patients.
Methods: Studies were identified through a systematic search of indexed articles in PubMed, Embase, CINAHL, Cochrane, Web of Science, and Scopus, published between December 2019 to August 2021. Effect estimates from individual studies for association between markers of myocardial injury (Troponin), myocardial stretch (N-terminal-pro hormone BNP, NT-proBNP), and coagulopathy (D-Dimer) and death or severe/critical COVID-19 were pooled using inverse variance weighted random-effects model. Odds Ratios (OR), Hazard Ratios (HR), and 95% Confidence Intervals (CI) were pooled separately and reported by outcomes of critical/severe COVID-19 and death. A *meta*-analysis of proportions was also performed to summarize the pooled prevalence of co-morbidities in patients hospitalized with COVID-19.
Results: We included 62 articles, with a total of 41,013 patients. The pooled proportion of patients with history of hypertension was 39% (95% CI: 34–44%); diabetes, 21% (95% CI: 18%–24%); coronary artery disease, 13% (95% CI: 10–16%); chronic obstructive pulmonary disease, 7% (95% CI: 5–8%); and history of cancer, 5% (95% CI: 4–7%). Elevated troponin was associated with higher pooled odds of critical/severe COVID-19 and death [Odds Ratio (OR: 1.76, 95% CI: 1.42–2.16)]; and also separately for death (OR: 1.72, 95% CI: 1.32–2.25), and critical/severe COVID-1919 (OR: 1.93, 95% CI: 1.45–2.40). Elevations in NT-proBNP were also associated with higher severe COVID-19 and death (OR: 3.00, 95% CI: 1.58–5.70). Increases in D-dimer levels was also significantly associated with critical/severe COVID-19 and death (pooled OR: 1.38, 95% CI: 1.07–1.79).
Conclusions: This meta-analysis synthesizes existing evidence showing that myocardial injury, and coagulopathy are complications of COVID-19. The durability of these complications and their contributions to long-term cardiac implications of the disease is still being investigated. Patients who have recovered from COVID-19 may benefit from minimally invasive assessment for markers of myocardial injury, stretch and coagulopathy for early risk stratification purposes.

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1. Background

While COVID-19 may begin as a respiratory disease, sometimes causing pneumonitis and severe acute respiratory distress syndrome (ARDS), other major organs may also be affected, particularly the cardiovascular system, kidneys, and brain [1]. COVID-19 is associated with a wide range of symptoms, and a spectrum of clinical illnesses characteristic of multisystem disease with cardiovascular consequences [2,3]. The characteristic of immune system activation may result in cytokine storm with the release of massive amounts of cytokines, causing both local and systemic inflammatory response, which contributes to disarray in immune, cardiac and inflammatory biomarkers [4,5].

Infection with SARS-CoV-2 virus can lead to elevations in cardiac biomarkers and electrocardiographic changes that are associated with poorer clinical outcomes, including ICU admission, mechanical ventilation and death [6-8]. These cardiac biomarkers include troponin (cTnI), n-terminal pro-b-type natriuretic peptide (NT-proBNP), galectin-3, d-dimer, interleukin-6 (IL-6), and c-reactive protein (CRP) [9-11]. In one study of 2,736 patients hospitalized for COVID-19 in New York City, small elevations in cTnI laboratory values were associated with increased mortality. NT-proBNP, a hormone that is predominantly produced by ventricular myocytes in response to increased ventricular wall stress, is an established biomarker for diagnosis and prognosis of heart failure [12]. Elevated NT-proBNP is associated with increased risk of cardiogenic shock [13], acute heart failure [14,15], myocardial infarction [14], right ventricular dysfunctions, left ventricular dysfunction [16,17], stress cardiomyopathy [16,17], arrhythmias [13-15], and venous and arterial thrombosis [18,19] among hospitalized COVID-19 patients [20]. According to the American College of Cardiology (ACC), based on case reports from China, US, and Europe, about 40% of hospitalized COVID-19 patients have cardiovascular or cerebrovascular disease, 16.7% of them developed arrhythmias, and 7.2% developed acute cardiac injury [21-23].

Understanding accumulating evidence on the cardiac consequences of infection with SARS-CoV-2 virus is critical to better understanding biomarkers that may indicate poorer clinical outcomes. Thus, we conducted a systematic review and meta-analysis to quantify the association between biomarkers of myocardial injury (troponin), myocardial stretch (NT-proBNP, Gal-3), coagulation (D-Dimer), inflammation (CRP, IL-6) and severe COVID-19 or death in hospitalized patients. We also calculated pooled proportions of underlying co-morbidities (hypertension, CAD, diabetes, COPD, and cancer) from the articles reviewed.

2. Methods

2.1. Search strategy

This systematic review and meta-analysis followed recommendations from Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (**eTable 1 in the Supplement**). A detailed literature search was conducted in relevant scientific databases, including MEDLINE (PubMed), Embase, CINAHL, Cochrane, Web of Science, and Scopus. Search terms and strategy were developed with the help of an informationist to search for studies conducted between December 2019 and January 2021. An updated search was conducted for articles between January and August 2021. The complete search strategy for each database is available in **eTable 2 in the Supplement**. This review was registered in the PROSPERO database with registration number CRD42021229341.

2.2. Study selection and eligibility criteria

All studies identified via databases searches were imported into Covidence [24]. Three reviewers (O.O., B.K., O.A.F.) independently screened identified studies for title and abstract eligibility. Discrepancies and divergencies were discussed and adjudicated with the help of two independent reviewers (L.T. and A.F.A.). The following criteria full-text review inclusion were: 1) study type: retrospective, prospective, observational, or case-control studies, reporting on cardiac biomarkers (specifically Troponin I or T, NT-proBNP, CRP, IL-6, and Gal-3); 2) population: adult patients diagnosed with COVID-19; 3) exposure/ intervention: confirmed COVID 19 infection; 4) outcome indicators: myocardial injury, severe or critical clinical status, and death. Studies excluded include case reports, editorials, letters to the editor and correspondence, and conference abstracts that did not contain primary data. Preprints and non-peer reviewed articles, other review articles, and articles not published in English were also excluded.

2.3. Data extraction

Following title/abstract screening, three reviewers (O.O., B.K., O.A. F.) worked in pairs to independently assess the studies for full-text eligibility. A third and fourth reviewer performed conflict resolution, one adjudicator per article, to reach a consensus (L.T., and A.F.A.). After full-text eligibility screening, data were extracted independently by a total of five reviewers (O.O., B.K., O.A.F., L.T., and D.M.); for each article, there were two primary independent reviewers and one adjudicator. Discrepancies for extracted data were resolved by consensus, results adjudicated where applicable and confirmation checks were done. A predesigned and piloted data template in Covidence was used for data extraction. Data extracted included author, publication year, study design, sample size, participant characteristics, proportion of comorbidities in the sampled population, median or mean levels of cardiac biomarkers and their cut-off points, outcomes of interest (COVID-19 severity, death, ICU admission, etc.), and reported measures of association.

2.4. Definitions

For this review, data on severe COVID-19 was abstracted based on the definition and categories as reported in the reviewed articles. Studies conducted in China defined severity of COVID-19 according to the Chinese guideline for COVID-19 management; [25] severe cases were defined as the presence of at least one of the following: (i) respiratory rate > 30 breaths per minute; (ii) oxygen saturation (SpO2) ≤ 93%; and (iii) PaO2/FiO2 ratio ≤ 300 mmHg. Critical cases were defined as those including at least one of the following: (i) respiratory failure requiring mechanical ventilation; (ii) shock; (iii) presence of other organ damage apart from respiratory; and (iv) admission to intensive care unit. Other studies used the World Health Organization definitions of severe pneumonia (Adolescent or adult: fever or suspected respiratory infection, plus one of respiratory rate > 30 breaths/min, severe respiratory distress, or SpO2 < 90% on room air) or ARDS (Onset: new or worsening respiratory symptoms within one week of known clinical insult; Chest imaging (radiograph, CT scan, or lung ultrasound): bilateral opacities, not fully explained by effusions, lobar or lung collapse, or nodules; Origin of edema: respiratory failure not fully explained by cardiac failure or fluid overload; o exclude hydrostatic cause of edema if no risk factor present; Oxygenation (adults): PaO2/FiO2 ≤ 100 mmHg with PEEP ≥ 5 cmH2O, or non-ventilated) [26]. Majority of the articles defined myocardial injury as hs-Troponin I (hs-TnI) ≥ 99th percentile of the upper reference limit, regardless of new abnormalities in electrocardiography and echocardiography [27].

2.5. Quality assessment

Quality Assessment was conducted using the Newcastle Ottawa Quality Assessment Scale (NOS) [28] which assesses design quality of non-randomized, cohort and case-control studies. A maximum score of 9 was aggregated across three domains of the NOS scale: selection of study groups (4 possible points), comparability of groups (2 possible points), and ascertainment of outcomes (3 possible points). The overall risk of

bias was classified as either "high", "some concern", or "low" based on the cumulative NOS scores. The risk-of-bias assessment summary table and plots were created using the *robvis* application [29].

2.6. Data synthesis and statistical analysis

Analysis was conducted using the *meta* commands in Stata/IC 16.1 [30]. All reported medians or mean values for biomarkers: Troponin I or T, NT-proBNP, Gal-3, IL-6, D-Dimer, and CRP were summarized in the original unit measured in the studies. When studies did not report mean and standard deviations, reported sample sizes, median and interquartile ranges were abstracted. Measures of associations reported in relevant studies (odds or hazard ratios) and the primary outcomes were summarized. For the meta-analysis, unadjusted hazard ratios (HR) and odds ratios (OR) and their 95% confidence intervals (CI), reported from each study were natural log-transformed [31]. OR, HRs and 95% CIs were pooled separately and reported by outcomes of death or critical/severe COVID-19. Random effect models with the inverse variance method were used to derive pooled measures of association, and the 95% CI and p-values to quantify the associations between elevated biomarkers and cardiovascular complications, and COVID-19 severity and death.

The pooled effect sizes were represented as forest plots. Heterogeneity of study estimates was assessed by Hedge's I^2 statistic, which was interpreted as $I^2 < 25\%$, 25–50%, 50–75%, and $> 75\%$, which indicates no, low, moderate, and high between-study heterogeneity [32]. The risk of publication bias was assessed using funnel plots. Egger's meta-regression was performed to assess for small-study effects. We visually inspected the distribution of relevant studies for asymmetry or by p-value < 0.1, indicating possible publication bias [33].

To calculate pooled proportions from the reported underlying comorbidities (hypertension, CAD, diabetes, COPD, and cancer) from each article, we performed a meta-analysis of proportions of this binomial data, using the *metaprop* package in Stata [34]. Using a random-effects model, we calculated 95% exact confidence intervals for each study and the overall pooled estimate for each comorbidity. We reported the measure of heterogeneity (I^2) and displayed the outputs using forest plots.

3. Results

Fig. 1 shows the PRISMA flow chart for study selection. A total of 3,106 records were identified through the databases on initial search, and 2,032 records from the updated search; 2,454 duplicates were removed, and 2,684 titles and abstracts were screened for inclusion. Following title and abstract screening, 2,274 articles were excluded leaving 410 articles for full-text retrieval, 58 of which full-text versions were unretrievable or conference abstracts. Upon screening, a total of 290 articles were further excluded, leaving 62 articles that met the inclusion criteria and were included in the review and meta-analysis for this study. The PRISMA flowchart was completed according to the updated 2020 guideline [35], and generated using an available online Shiny App [36].

4. Study characteristics

The characteristics of the 62 studies included are presented in Table 1. Most studies were conducted in China (50%), Italy (14%), the United States (12%), Turkey (3%), Spain (3%), the United Kingdom (2%), France (2%), Iran (2%), Korea (2%), Mexico (2%), Morocco (2%),

Identification of new studies via databases and registers

Identification

Records identified from:
Databases (n = 5,138) → Records removed before screening:
Duplicate records (n = 2,454)

Screening

Records screened
(n = 2,684) → Records excluded
(n = 2,274)

Reports sought for retrieval
(n = 410) → Reports not retrieved
(n = 58)

Reports assessed for eligibility
(n = 352) → Reports excluded:
No/insufficient relevant results (n = 61)
Myocardial injury not assessed (n = 54)
Case reports/series/editorials (n = 40)
RCT protocol papers (n = 34)
Pediatric/other populations (n = 32)
No cardiovascular outcomes (n = 28)
Review/meta-analysis (n = 24)
Non-English (n = 17)

Included

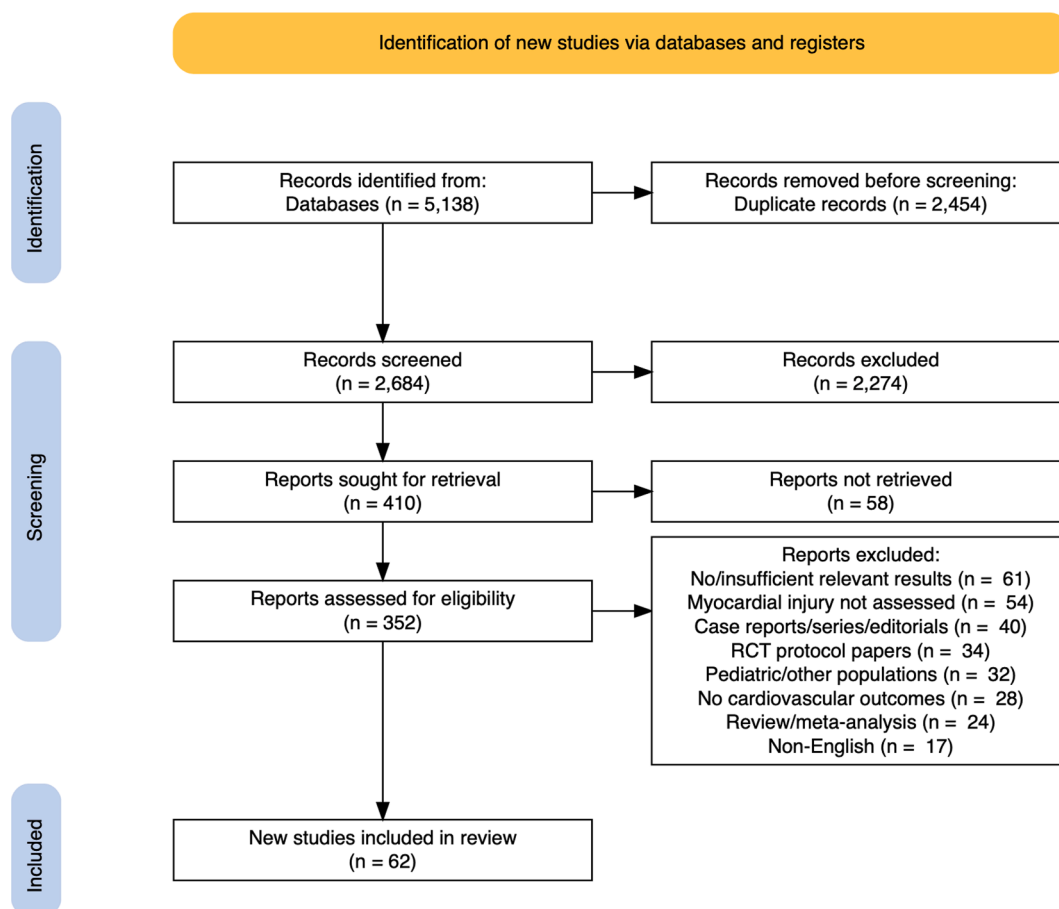New studies included in review
(n = 62)

Fig. 1. PRISMA flowchart showing study search and selection.

Table 1

Characteristics of studies examining cardiac biomarkers and COVID-19 outcomes, N = 62.

First Author, Year	Country	Sample size	Sex		Study Design	Mean Age, (±SD); Median Age (IQR)	Population	Main Cardiovascular Outcome/biomarker assessed	Primary Outcome assessed
			Female, n (%)	Male, n (%)					
Abdeladim 2020 [51]	Morocco	73	45 (61.6)	28 (38.4)	Retrospective	54.6 (±17.6)	Hospitalized COVID-19 patients with Mild, Severe and Critical cases	Myocardial Injury (cTnI)	Death, severe COVID-19
Cao I 2020 [52]	China	244	111 (45.5)	–	Retrospective	62.6 (±13.4)	Hospitalized COVID-19 patients with no preexisting cardiovascular disease or renal dysfunction	Myocardial Injury (hs-cTnI)	Death (Non-survivors)
Cao II 2020 [53]	China	100	55 (55)	45 (45)	Retrospective	71.1 (±14.5)	Critically ill COVID-19 patients on ICU admission	Myocardial Injury (MYO, CK-MB and hs-cTnI)	Death
Bardaji 2020 [54]	Spain	433	174 (40.3)	259 (59.7)	Retrospective	67.5 (52.5–77.5)	Consecutive hospitalized patients treated for suspected SARS-CoV-2 infection	Myocardial Injury (cTnI)	30-day mortality
Deng I 2020 [55]	China	264	–	130 (49.2)	Retrospective	64.5 (53.3–74.0)	Inpatients who had a COVID-19 diagnosis.	Cardiac biomarkers (cTnI-ultra, CKMB, MYO, NT-proBNP)	In-hospital death
Deng II 2020 [56]	China	112	55 (49.1)	57 (50.9)	Retrospective	65 (49–70.8)	Diagnosed hospitalized COVID-19 Patients	Myocardial injury, myocarditis[a] and cardiac dysfunction	Composite endpoint of ICU admission, MV, ECMO, or death
Chen I 2020 [57]	US	143	–	89 (62)	Retrospective	67 (±16)	Laboratory confirmed hospitalized COVID-19 patients	Cardiac function (cTnI & Echocardiograms)	In-hospital death
Chen II 2020 [58]	China	54	18 (33.3)	36 (66.7)	Retrospective	57.6 (44.9–70.3)	Hospitalized COVID-19 patients	Myocardial Injury (TnI)	Severe COVID-19 (ARDS, Pneumonia)
Doyen 2020 [59]	France	43	7 (16)	36 (84)	Prospective	60 (±13)	COVID-19 patients on ICU admission	Cardiac functioning (ECG, hs-TnI, TTE)	ICU discharge or death
Fan I 2020 [60]	China	73	24 (32.9)	49 (67.1)	Retrospective	58.4 (±14.3)	ICU admitted COVID-19 patients	Myocardial Injury (cTnI)	Death
Fan II 2020 [61]	China	353	–	186 (52.7)	Retrospective	60.5 (±10.1)	Hospitalized patients with confirmed COVID-19 diagnosis,	Myocardial Injury (cTnI)	Severity of myocardial injury
Ferrante 2020 [62]	Italy	332	95 (28.6)	(71.4)	Retrospective	66.9 (55.4–75.5)	Patients on ICU admission with COVID-19	Myocardial Injury (hs-cTnI)	Death, duration of Hospital and admission into ICU
Gao 2020 [20]	China	54	30 (55.6)	24 (44.4)	Retrospective	60.4 (±16.1)	Patients with severe COVID-19	In-hospital death	Death
Ghio 2020 [63]	Italy	340	107 (31.4)	233 (68.6)	Retrospective	69.8 (58.6–78.3)	Adult patients admitted with the suspected diagnosis of COVID-19	Myocardial injury (hs-TnI)	Death and/or ICU admission, MV
Giustino 2020 [64]	US and Italy	305	100 (32.8)	205 (67.2)	Retrospective	63 (53–73)	Hospitalized patients with COVID-19	Myocardial Injury (hs-TnI), TTE abnormalities	Death
Guo I 2020 [65]	China	74	25 (33.8)	49 (66.2)	Retrospective	67.2 (±14.6)	Patients on ICU admission with severe or critical COVID-19	Myocardial Injury (cTnI, NT-proBNP, CK-MB, MYO)	Death, MV time
Guo II 2020 [66]	China	187	–	91 (48.7)	Retrospective	58.5 (±14.7)	Hospitalized patients with confirmed COVID-19	Myocardial Injury (TnT)	Death
Lala 2020 [67]	US	2736	1,106 (40.4)	1630 (59.6)	Retrospective	66.4	Patients admitted with a laboratory-confirmed SARS-CoV-2 infection	Myocardial Injury (TnI)	Death, intubation, or hospital discharge
Han 2020 [68]	China	273	176 (64.5)	97 (35.53)	Retrospective	58.9 (±10.8)	Hospitalized patients diagnosed with SARS-CoV-2 infection	Cardiac biomarkers (ultra-TnI, NT-proBNP, CK-MB, MYO)	COVID-19 severity
He I 2020 [69]	China	1031	493 (47.8)	538 (52.2)	Retrospective	63 (52–70)	Inpatients with laboratory-confirmed COVID-19	Acute cardiac Injury (hs-TnI)	Severe COVID-19 (ARDS, Pneumonia)
Heberto 2020 [70]	Mexico	254	87 (34.3)	167 (65.7)	Prospective	53.8 (±12.7)	Hospitalized patients, with and without myocardial injury, and a confirmed test result of COVID-19	Cardiac markers (hs-TnI, NT-proBNP)	COVID-19 complications: MV, Death
	China	93			Retrospective				–

Table 1 (*continued*)

First Author, Year	Country	Sample size	Sex		Study Design	Mean Age, (±SD); Median Age (IQR)	Population	Main Cardiovascular Outcome/biomarker assessed	Primary Outcome assessed
			Female, n (%)	Male, n (%)					
Jin 2020 [71]			52 (55.9)	41 (44.1)		48.0 (35.5–62.5)	COVID-19 patients on hospital admission	Myocardial Injury (hs-TnI, CK-MB, CMR)	
Almeida Junior 2020 [72]	Brazil	183	63 (34.4)	120 (65.59)	Retrospective	66.8 (±17)	Patients admitted for COVID-19	Myocardial Injury (TnT-ultra, BNP)	ICU admission, MV, all-cause death
Maeda I 2020 [73]	US	224	–	125 (55.8)	Retrospective	64.0 (±16.6)	Patients admitted with COVID-19	Myocardial Injury (cTnI), ECG abnormality	In-hospital death
Majure 2020 [74]	US	11,159	4464 (40)	6695 (60)	Retrospective	66 (56–77)	Hospitalized patients diagnosed with COVID 19	Myocardial Injury (cTnI, TnT), ECG abnormality	In-hospital death
Kim 2020 [75]	Korea	38	16 (40.9)	22 (59.1)	Retrospective	69.6 (±14.9)	In-patients with confirmed COVID-19	Myocardial Injury (cTnI, CK-MB)	–
Li I 2020 [76]	China	2,068	–	1,005 (48.6)	Retrospective	63 (51–70)	Critical and non-critical hospitalized COVID-19 patients	Myocardial Injury (hs-cTnI)	Death
Li II 2020 [77]	China	100	56 (56)	44 (44)	Retrospective	62.0 (51.0–70.8)	Patients admitted with COVID-19	Myocardial Injury (hs-cTnI, CK-MB, MYO)	Discharge, death
Lombardi 2020 [78]	Italy	614	179 (29.2)	435 (70.8)	Retrospective	67 (±13)	Hospitalized patients with laboratory-confirmed SARS-CoV-2 infection	Myocardial Injury (hs-TnI, TnT)	Discharge, death
Metkus 2020 [79]	US	243	95 (39.1)	148 (60.9)	Retrospective	62.8 (±14.9)	Intubated confirmed COVID-19 patients who underwent troponin assessment 24hrs post intubation	Myocardial Injury (hs-TnI, TnT)	ARDS unrelated to COVID
Mu 2020 [80]	China	113	51 (45.1)	62 (54.9)	Retrospective	63.00 (49.5–70.0)	Hospitalized patients with confirmed COVID-19 diagnosis	Myocardial Injury (cTnI)	Severe COVID-19 (ARDS, Pneumonia)
Karbalai Saleh 2020 [81]	Iran	386	58 (38.9)	–	Retrospective	59.5 (±15.8)	Hospitalized patients withCOVID-19	Myocardial Injury (hs-TnI), ECG abnormalities	Death, ICU admission
Salvatici, 2020 [82]	Italy	1,055	339 (32.1)	355 (67.9)	Retrospective	64.4 ± 14.2	Hospitalized patients with confirmed SARS-CoV-2	Myocardial Injury (cTnI)	Death
Schiavone 2020 [83]	Italy	674	268 (39.8)	406 (60.2)	Retrospective	60.8 (±15.9)	Hospitalized COVID-19 patients, with or without chronic coronary syndromes	Myocardial Injury (cTnI)	Death
Qian 2020 [84]	China	77	24 (31.2)	53 (68.8)	Retrospective	65.5 (±12.2)	Newly admitted ICU patients with COVID-19	Myocardial Injury (cTnI)	ICU admission, Death
Qin 2020 [85]	China	6,033	3174 (52.61)	2859 (47.39)	Retrospective	57 (45–66)	Hospitalized COVID-19 patients	Myocardial Injury (hs-TnI, CK-MB)	28-day mortality, ICU admission, MV
Raad 2020 [86]	US	1,020	511 (50)	509 (50)	Retrospective	63 (52–73)	Hospitalized adult patients diagnosed with SARS-CoV-2	Myocardial Injury (hs-TnI)	Death and LOS
van den Heuvel 2020 [87]	Netherlands	51	10 (20)	41 (80)	Prospective	63 (51–68)	Hospitalized patients with COVID-19	Myocardial Injury (hs-TnI), ventricular dysfunction (TTE)	ICU admission
Wang I 2020 [88]	China	222	109 (49.1)	113 (50.9)	Retrospective	63.0 (50.0–69.0)	Hospitalized patients with laboratory-confirmed COVID-19 infection	Myocardial Injury (hs-TnI)	Death, recovery
Wei 2020 [89]	China	101	–	54 (53.5)	Prospective	49 (34–62)	Hospitalized patients with laboratory confirmed SARS- CoV-2 infection	Myocardial Injury (hs-TnT)	ICU admission, MV, death
Shi I 2020 [90]	China	671	349 (52)	322 (48)	Retrospective	63 (50–72)	Hospitalized patients with laboratory-confirmed COVID-19	Myocardial Injury (cTnI)	Death
Shi II 2020 [91]	China	416	211 (50.7)	–	Retrospective	64 (21–95)	Hospitalized patients with laboratory-confirmed COVID-19	Myocardial Injury (hs-TnI, CK-MB, MYO)	Death
Yan 2020 [92]	China	119	66 (55.5)	52 (44.5)	Retrospective	69 (66–76)	Hospitalized patients over 60 years diagnosed with COVID-19	Cardiac markers (hs-TnI, CK-MB, MYO)	–
Yang I 2021 [93]	China	357	–	185 (51.8)	Prospective	56.0 (43.0–68.0)	Hospitalized patients with COVID-19	Cardiac markers (hs-TnT, CK-MB, MYO)	Death

Table 1 (*continued*)

First Author, Year	Country	Sample size	Sex		Study Design	Mean Age, (±SD); Median Age (IQR)	Population	Main Cardiovascular Outcome/biomarker assessed	Primary Outcome assessed
			Female, n (%)	Male, n (%)					
Yang II 2020 [94]	China	203	88(43.3)	115 (56.7)	Retrospective	62.0 (49.0–69.0)	Hospitalized patients with COVID-19	Myocardial Injury (TnI)	Death
Zaninotto 2020 [95]	Italy	113	33 (29)	80 (71)	Retrospective	65 (53–75)	Hospitalized patients with confirmed COVID-19	Myocardial Injury (hs-TnI)	–
Fan III 2020 [96]	China	89	–	49 (55.1)	Retrospective	61.8 (±16.1)	Hospitalized patients diagnosed with COVID-19	Myocardial Injury (TnI)	–
Zhou 2020 [97]	China	68	34 (50)	34 (50)	Retrospective	67 (30–86)	Hospitalized patients diagnosed with COVID-19	Myocardial Injury (hs-TnI)	Death
Barman 2020 [98]	Turkey	607	–	334 (55)	Retrospective	62.5 (±14.3)	Patients hospitalized for COVID-19	Myocardial Injury (hs-TnI)	Death
Chen III, 2021 [99]	China	726	–	392 (54.1)	Retrospective	68 (58–77)[§]	Patients hospitalized for COVID-19	Myocardial Injury (hs-TnI)	Death, severe COVID-19
De Marzo 2021 [100]	Italy	343	–	119 (34.7)	Retrospective	75 (68–83)	Patients ≥ 60 years hospitalized with COVID-19	Myocardial Injury (cTnI)	Death
Demir 2021 [101]	UK	277	–	197 (71)	Retrospective	55.1 (±13.9)	Hospitalized patients with confirmed COVID-19	Myocardial Injury (hs-TnT)	Death
Guadiana-Romualdo 2021 [102]	Spain	2873	–	1699 (59.1)	Retrospective	66 (54–76)	Hospitalized patients with confirmed COVID-19	–	All-cause mortality
He II 2021 [103]	China	304	–	160 (52.6)	Retrospective	65 (54–74)	Hospitalized patients diagnosed with COVID-19	Myocardial Injury (hs-TnI)	Death
Liaqat 2021 [104]	Pakistan	201	82 (40.8)	119 (59.2)	Retrospective	44.6 (±15.2)	Hospitalized patients diagnosed with COVID-19	Myocardial Injury (TnI, CK-MB), Ventricular dysfunction (TTE), ECG abnormalities	COVID-19 severity, death
Lu 2021 [105]	China	77	–	50 (65)	Retrospective	59 (54–63)	Hospitalized patients diagnosed with COVID-19	Myocardial Injury (hs-TnI)	Death, COVID-19 severity
Maeda II 2021 [106]	US	181	–	100 (55.8)	Retrospective	64.0 (±16.6)	Patients admitted with COVID-19	Myocardial Injury (hs-TnI), ECG abnormalities	In-hospital death
Mengozzi 2021 [107]	Italy	266	–	180 (67.7)	Prospective	63 (±15)	Patients hospitalized for COVID-19	Myocardial Injury (hs-TnT)	ARD, MV, ICU admissionIn-hospital, all-cause death
Omar 2021 [108]	Turkey	355	–	172 (48.5)	Retrospective	58 (35.5–71)	Patients hospitalized for COVID-19	Myocardial Injury (hs-TnT), ECG abnormalities	Death
Selçuk 2021 [109]	Turkey	137	–	72 (52.5)	Retrospective	55 (±14)	Patients hospitalized for COVID-19	Cardiac markers (cTnI, NT-proBNP)	In-hospital death
Wang II 2021 [110]	China	242	–	151 (62.4)	Retrospective	68 (61–75)	Patients hospitalized for COVID-19	Myocardial Injury (cTnI)	ARDS, Death
Zhu 2021 [111]	China	499	–	253 (50)	Retrospective	59 (±15)	Hospitalized severe/critically ill patients with COVID-19	Myocardial Injury (cTnI, MYO)	Death

ICU: Intensive Care Unit; MV: Mechanical Ventilation; ECMO: extracorporeal membrane oxygenation; LOS: Length of Stay; hs-cTnI: high-sensitivity cardiac troponin I; TnT; Troponin T; NT-proBNP: N-terminal pro-B-type natriuretic peptide; cTnI-ultra: cardiac troponin I-ultra; CK-MB: creatinine kinase-myocardial band; MYO: Myoglobin; CKMB: Creatinine kinase–myocardial band; ECG: Electrocardiogram; TTE: Transtheoracic Echocardiography; CMR: cardiac magnetic resonance.
[a] Myocarditis related abnormalities defined as: triple elevation in hypersensitive cardiac Troponin I (over 0.12 ng/mL) plus abnormalities on echocardiography and/or electrocardiogram; [§]Critical patients; [†]With cardiac injury.

Brazil (2%), Pakistan (2%), and the Netherlands (2%). Total sample size from the studies was 41,013, ranging from 38 to 11,159 patients, and median age of participants ranged from 44.6 to 75 years. The pooled proportion of participants who had severe COVID-19 or died during hospitalization was 16.8% (1,978/11,764).

4.1. Study quality

For the papers included in the meta-analysis, 24 were rated to have a low risk of bias, while 16 were rated to have a high risk of bias. Four were rated as unclear (**eFig. 1 in the Supplement**). Those studies assessed to have a high risk of bias were primarily due to incomplete outcome reporting.

4.2. Underlying cardiovascular diseases and comorbidities

A majority of the studies reported history of comorbidities among patients included in the study. The pooled proportion of patients with hypertension was 39% (95% CI: 35–43%), ranging from 15 to 73% (Fig. 2). For history of diabetes, the pooled proportion was 21% (18%–
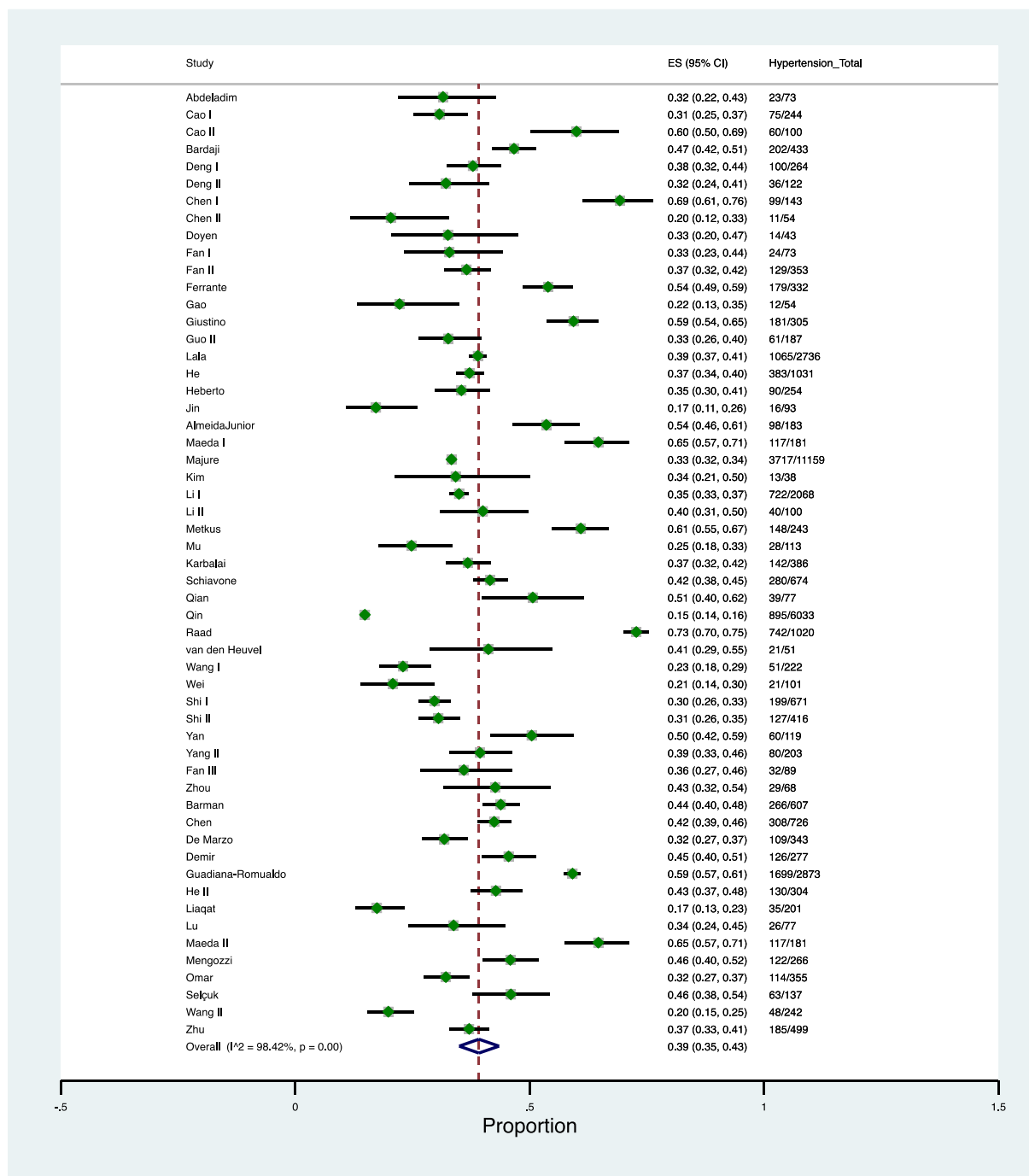
Study	ES (95% CI)	Hypertension_Total
Abdeladim	0.32 (0.22, 0.43)	23/73
Cao I	0.31 (0.25, 0.37)	75/244
Cao II	0.60 (0.50, 0.69)	60/100
Bardaji	0.47 (0.42, 0.51)	202/433
Deng I	0.38 (0.32, 0.44)	100/264
Deng II	0.32 (0.24, 0.41)	36/122
Chen I	0.69 (0.61, 0.76)	99/143
Chen II	0.20 (0.12, 0.33)	11/54
Doyen	0.33 (0.20, 0.47)	14/43
Fan I	0.33 (0.23, 0.44)	24/73
Fan II	0.37 (0.32, 0.42)	129/353
Ferrante	0.54 (0.49, 0.59)	179/332
Gao	0.22 (0.13, 0.35)	12/54
Giustino	0.59 (0.54, 0.65)	181/305
Guo II	0.33 (0.26, 0.40)	61/187
Lala	0.39 (0.37, 0.41)	1065/2736
He	0.37 (0.34, 0.40)	383/1031
Heberto	0.35 (0.30, 0.41)	90/254
Jin	0.17 (0.11, 0.26)	16/93
AlmeidaJunior	0.54 (0.46, 0.61)	98/183
Maeda I	0.65 (0.57, 0.71)	117/181
Majure	0.33 (0.32, 0.34)	3717/11159
Kim	0.34 (0.21, 0.50)	13/38
Li I	0.35 (0.33, 0.37)	722/2068
Li II	0.40 (0.31, 0.50)	40/100
Metkus	0.61 (0.55, 0.67)	148/243
Mu	0.25 (0.18, 0.33)	28/113
Karbalai	0.37 (0.32, 0.42)	142/386
Schiavone	0.42 (0.38, 0.45)	280/674
Qian	0.51 (0.40, 0.62)	39/77
Qin	0.15 (0.14, 0.16)	895/6033
Raad	0.73 (0.70, 0.75)	742/1020
van den Heuvel	0.41 (0.29, 0.55)	21/51
Wang I	0.23 (0.18, 0.29)	51/222
Wei	0.21 (0.14, 0.30)	21/101
Shi I	0.30 (0.26, 0.33)	199/671
Shi II	0.31 (0.26, 0.35)	127/416
Yan	0.50 (0.42, 0.59)	60/119
Yang II	0.39 (0.33, 0.46)	80/203
Fan III	0.36 (0.27, 0.46)	32/89
Zhou	0.43 (0.32, 0.54)	29/68
Barman	0.44 (0.40, 0.48)	266/607
Chen	0.42 (0.39, 0.46)	308/726
De Marzo	0.32 (0.27, 0.37)	109/343
Demir	0.45 (0.40, 0.51)	126/277
Guadiana-Romualdo	0.59 (0.57, 0.61)	1699/2873
He II	0.43 (0.37, 0.48)	130/304
Liaqat	0.17 (0.13, 0.23)	35/201
Lu	0.34 (0.24, 0.45)	26/77
Maeda II	0.65 (0.57, 0.71)	117/181
Mengozzi	0.46 (0.40, 0.52)	122/266
Omar	0.32 (0.27, 0.37)	114/355
Selçuk	0.46 (0.38, 0.54)	63/137
Wang II	0.20 (0.15, 0.25)	48/242
Zhu	0.37 (0.33, 0.41)	185/499
Overall (I^2 = 98.42%, p = 0.00)	0.39 (0.35, 0.43)	

Fig. 2. Pooled proportion for history of hypertension.

23%), this ranged from 8% to 44%. The pooled proportion for history of CAD was 13% (95% CI: 11–16%), and this ranged from 1 to 49%. In the total sample, the pooled proportion of patients who had COPD was 7% (95% CI: 6–9%), which ranged from 2 to 23%, for history of cancer, the pooled proportion was 6% (95% CI: 5–7%) which also ranged from 2 to 16% (**eFigs. 4–7 in the Supplement**).

4.3. Biomarkers of myocardial injury, stretch, and coagulation

For studies that reported myocardial injury, the proportion of patients who developed myocardial injury was 18.5% (3,943/ 21,367) (**eTable 3 in the Supplement**). The overall pooled odds ratio for the association between elevated troponin levels and death and critical/

severe disease was 1.76 (95% CI: 1.42, 2.16); for the outcome of death, the pooled odds was OR: 1.72 (95% CI: 1.32, 2.25); and for the outcome of critical/severe COVID-19, the pooled odds ratio was 1.93 (95% CI: 1.45, 2.40) (Fig. 3). Similarly, the overall hazards ratio for elevated troponin and death and critical/severe disease was 1.55 (95% CI: 1.36, 1.77). The hazards for elevated troponin and death was 1.51 (95% CI 1.31, 1.75), and for critical or severe COVID-19 was 1.75 (95 %CI 1.48, 2.10).

Elevations in NT-proBNP were also associated with severe COVID-19 and death: OR: 3.00 (95% CI: 1.58–5.70). The hazards ratio associated with elevated NT-proBNP and death, or critical/severe COVID-19 was 1.65 (pooled HR: 1.65, 95 %CI: 0.88–3.10) (Fig. 3). Increased D-dimer levels were also significantly associated with death and severe disease,
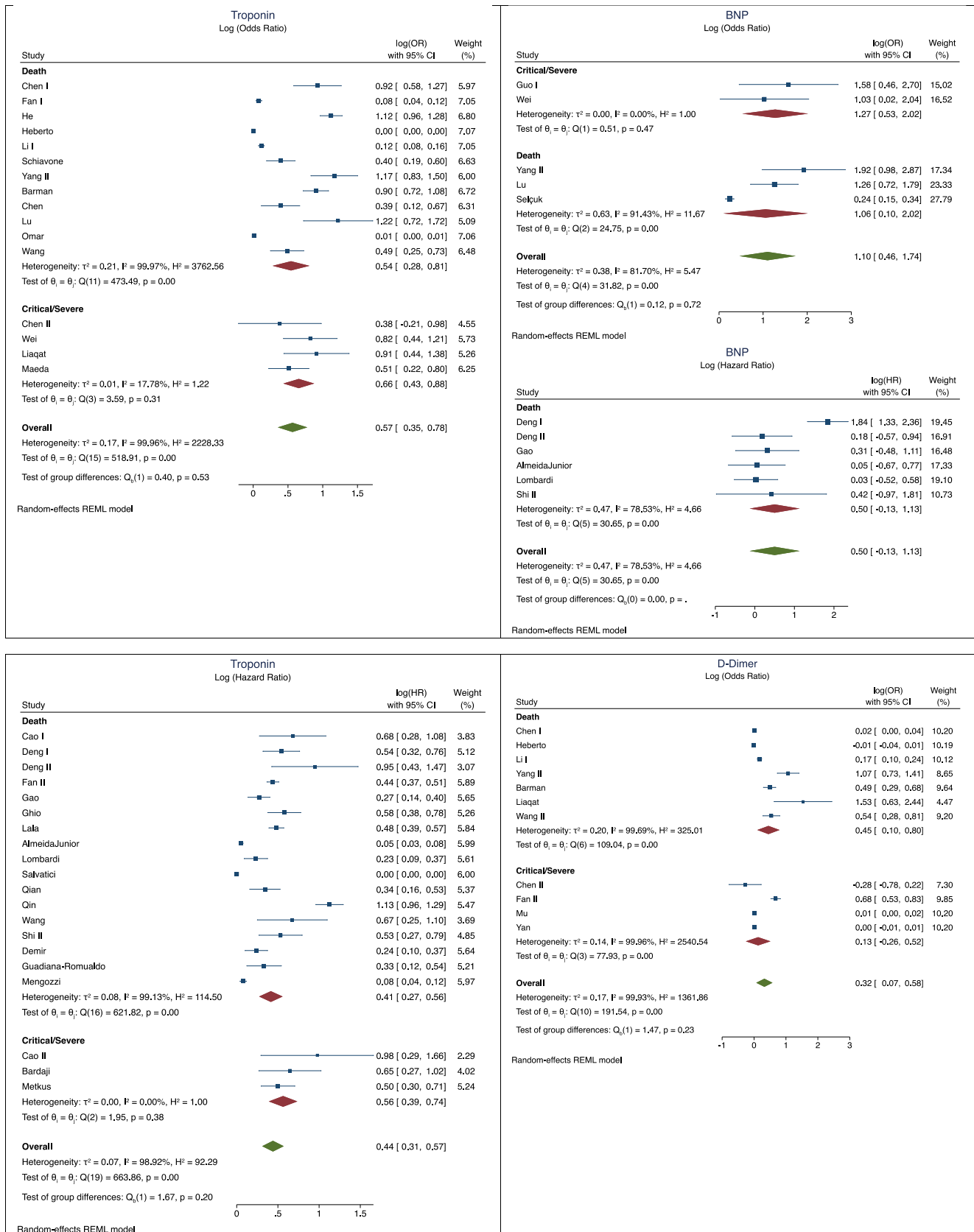
Fig. 3. Association between biomarkers of myocardial injury, stretch and coagulation with severe COVID-19 and death: meta-analysis results.
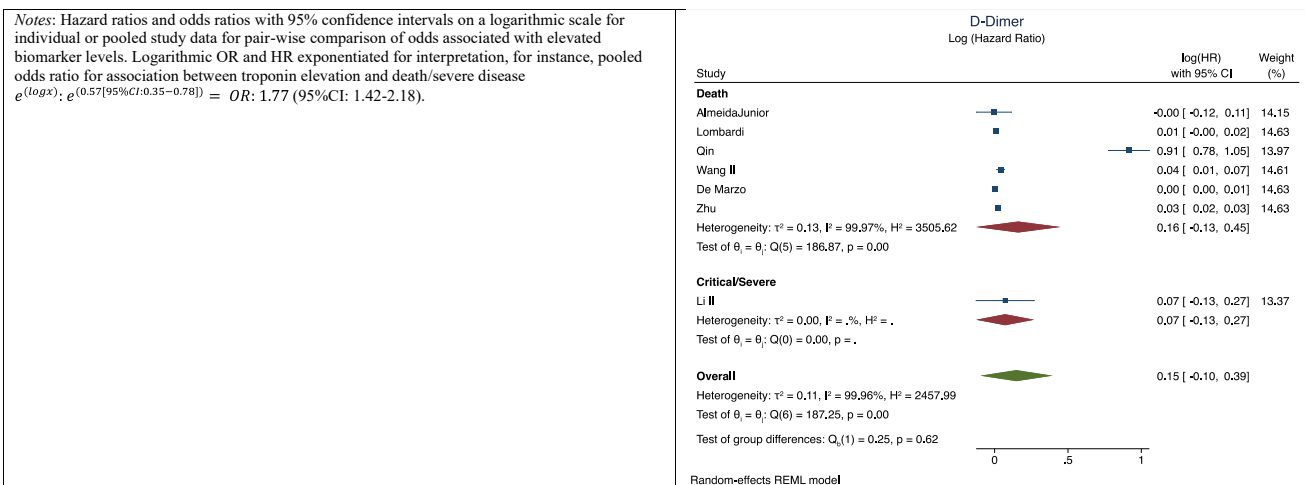
Notes: Hazard ratios and odds ratios with 95% confidence intervals on a logarithmic scale for individual or pooled study data for pair-wise comparison of odds associated with elevated biomarker levels. Logarithmic OR and HR exponentiated for interpretation, for instance, pooled odds ratio for association between troponin elevation and death/severe disease $e^{(logx)}: e^{(0.57[95\%CI:0.35-0.78])} = OR: 1.77\ (95\%CI: 1.42\text{-}2.18)$.

Fig. 3. (*continued*).

pooled OR: 1.38 (95 %CI: 1.07–1.79). While the pooled hazards ratio associated with either death, critical/severe disease, and elevated D-dimer levels was HR: 1.16 (95% CI: 0.9, 1.48) (Fig. 3).

Abnormal increases in CRP were also associated with higher severe COVID-19 and death: OR: 1.60 (95% CI: 1.13–2.25). The hazards ratio associated with increased CRP and death or critical/severe COVID-19 was 1.15 (pooled HR: 1.15, 95% CI: 0.94–1.42) (e**Fig. 2 in Supplement**). Elevated IL-6 levels were also significantly associated with death and severe disease, pooled OR: 1.55 (95% CI: 1.14–2.14) (e**Fig. 3 in the Supplement**).

5. Discussion

In this meta-analysis, we aimed to assess the association between biomarkers of myocardial injury and stretch, coagulation, and severe COVID-19 and death. From 62 articles reviewed, hospitalized COVID-19 patients had a high prevalence of underlying comorbidities such as hypertension, diabetes, COPD, CAD, and malignancy. Furthermore, the pooled data demonstrated that elevated biomarkers of inflammation, subclinical myocardial injury, coagulation, were significantly associated with severe COVID-19 and death.

Our findings are consistent with previous findings, which have reported early in the COVID-19 pandemic that individuals who have an underlying or preexisting cardiovascular disease such as heart failure, coronary heart disease and risk factors such as being of older age, hypertension, diabetes are over-represented in COVID-19 hospitalization [37]. In similar meta-analyses examining the association between COVID-19 and poor COVID-19 outcomes, there is a strong association between biomarker evidence of cardiac injury and worse COVID-19 outcomes; they include elevation of cTn, NT-proBNP, d-dimer, which predict poor clinical outcomes [38,39].

Cardiac involvement in COVID-19 is determined by the extent of the viral inoculum, and magnitude of host immune response, and the presence of underlying comorbidities [10]. Some of the mechanisms through which direct and indirect cardiac injury may occur in the context of COVID-19 are through inflammation, endothelial activation, and microvascular thrombosis (e**Fig. 8 in the Supplement**) [10,40]. In direct viral myocardial invasion, the outer membrane spike of the SARS-CoV-2 virus has a high affinity for the ACE2 receptors and the protease transmembrane protease serine 2 (TMPRSS2), which are highly expressed in cardiac tissues [41]. Hence, direct viral myocardial invasion is highly plausible, and evidence of SARS-CoV-2 positivity in cardiac tissues has been documented in autopsy reports [42]. The activation of macrophages (major sources of cytokines and the inflammatory cytokine tumor necrosis factor (TNF)-α) is promulgated by

metalloproteinase domain 17 (ADAM-17), which is also responsible for shedding of ACE2. Loss of ACE2 receptor density due to binding from the SARS-CoV-2 spike protein leads to accumulation of Angiotensin II (Ang II), and continued triggering of ADAM-17 [43]. This creates vicious positive feedback of activated ADA-19, more ACE2 shedding, and increased Ang II-mediated inflammatory responses, which is partially responsible for the cytokine storm characteristic of the SARS-CoV-2 immune response [10,44].

In the context of COVID-19, plaque destabilization and eruption can be facilitated by viral products from the systemic circulation, which could activate immune receptors on cells in already existing plaques in coronary vasculature [45]. The ongoing infection and inflammation could also lead to dysregulation of coronary vascular endothelial function leading to vasoconstriction and thrombosis [46]. Endothelial dysfunction is expressed through alteration in the vessel barrier, promotion of a coagulative state, induction of endothelial inflammation, and mediation of leukocyte infiltration [47]. Importantly, myocardial oxygen supply and demand may result from the following: endothelial dysfunction in coronary microcirculation; fixed coronary atherosclerosis limiting myocardial perfusion, high levels of circulating Ang II and arteriolar vasoconstriction resulting in systemic hypertension, and hypoxemia from ARDS or pulmonary thrombosis [10]. The immense physiologic demands that result from the SARS-CoV-2 infection response and the systemic inflammatory cascade, may be sufficient to trigger this supply–demand mismatch, even in the absence of an atherothrombotic plaque [10]. Another possible contributory mechanism associated with high fatality in COVID-19 and complications is disseminated intravascular coagulation (DIC), with the cross-talk between inflammation and coagulation mediated through protease-activated receptors (PARS); there have been recommendations for clinical use of direct oral anti-coagulants to inhibit PARS in acute care of COVID-19 and in patients experiencing persisting symptoms of COVID-19 [48].

Evidence is emerging on the long-term cardiac sequela of COVID-19-related myocardial injury, with evidence of myocardial fibrosis or myocarditis in 9–78% of patients who have had COVID-19 [37]. Ongoing inflammation has been reported in 60%, and cardiac involvement in 78% of patients recovered from acute COVID-19 [49]. Based on the results of our meta-analysis and other similar studies, and in light of post-acute sequelae of COVID-19, it is important to consider measurements of sustained expression of biomarkers signaling inflammation and myocardial damage in persons who have previously tested positive for COVID-19. Such sustained expression of certain inflammatory biomarkers are yet to be characterized in COVID-19; however, these may indicate long-term hyperinflammatory state with cardiac involvement from damage mediated by the virus during the acute phase, or even

possibilities of host viral reservoir, which is not uncommon in other viruses, but yet to be established in COVID-19 [50]. Considerations of the prognostic value of these biomarkers in persons previously hospitalized for COVID-19, and identification of subclinical myocardial injury can help with risk stratification, and downstream decisions about care.

6. Strengths and limitations

This study has some limitations. First, we could not find a sound and acceptable method for pooling reported medians and interquartile ranges in the literature. This was challenging considering that biomarker values are not typically normally distributed, hence cannot be confidently pooled without introducing bias, particularly when using meta-analysis methods that are reliant on means and standard deviation as measures of central tendency and dispersion. Second, several of the biomarkers were reported in different units, some of which could not be confidently converted to a single unit for use in statistical analyses. This severely limited our inclusion of the biomarker values reported in the articles in the meta-analyses. Third, this review was limited to articles published in English; excluding non-English articles during screening may have introduced some bias.

Nevertheless, this study has major strengths. The meta-analytic approach combined both observational and comparative methods. This included a meta-analysis of proportions for estimating the pooled prevalence of underlying comorbidities, and a comparative meta-analysis of odds and hazards of the associations between elevated biomarker levels and severe COVID-19 and/or death. In addition, our study comprehensively examined biomarkers that are representative of the different pathways of immune response and cardiac injury associated with the COVID-19. This study also offers an updated summary of existing evidence on the relationship between biomarkers of inflammations, myocardial injury in COVID-19, and their value in prognosis. Our meta-analysis included 41,013 patients from diverse global regions and contexts. Findings from our study also corroborate with findings from other studies showing an over-representation of persons with pre-existing comorbidities in persons with poor COVID-19 outcomes.

7. Conclusions

Our systematic review and meta-analysis showed significant associations between markers of myocardial injury and stretch, and coagulopathy with poor COVID-19 outcomes. There is also evidence in the literature of persisting symptoms suggestive of complications in patients recovered from COVID-19. The durability of these complications and their contributions to long-term cardiac implications of the disease is still being investigated. Recovered patients, may benefit from minimally invasive assessment for markers of myocardial injury and stretch and coagulopathy for early risk stratification purposes.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2021.100950.

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