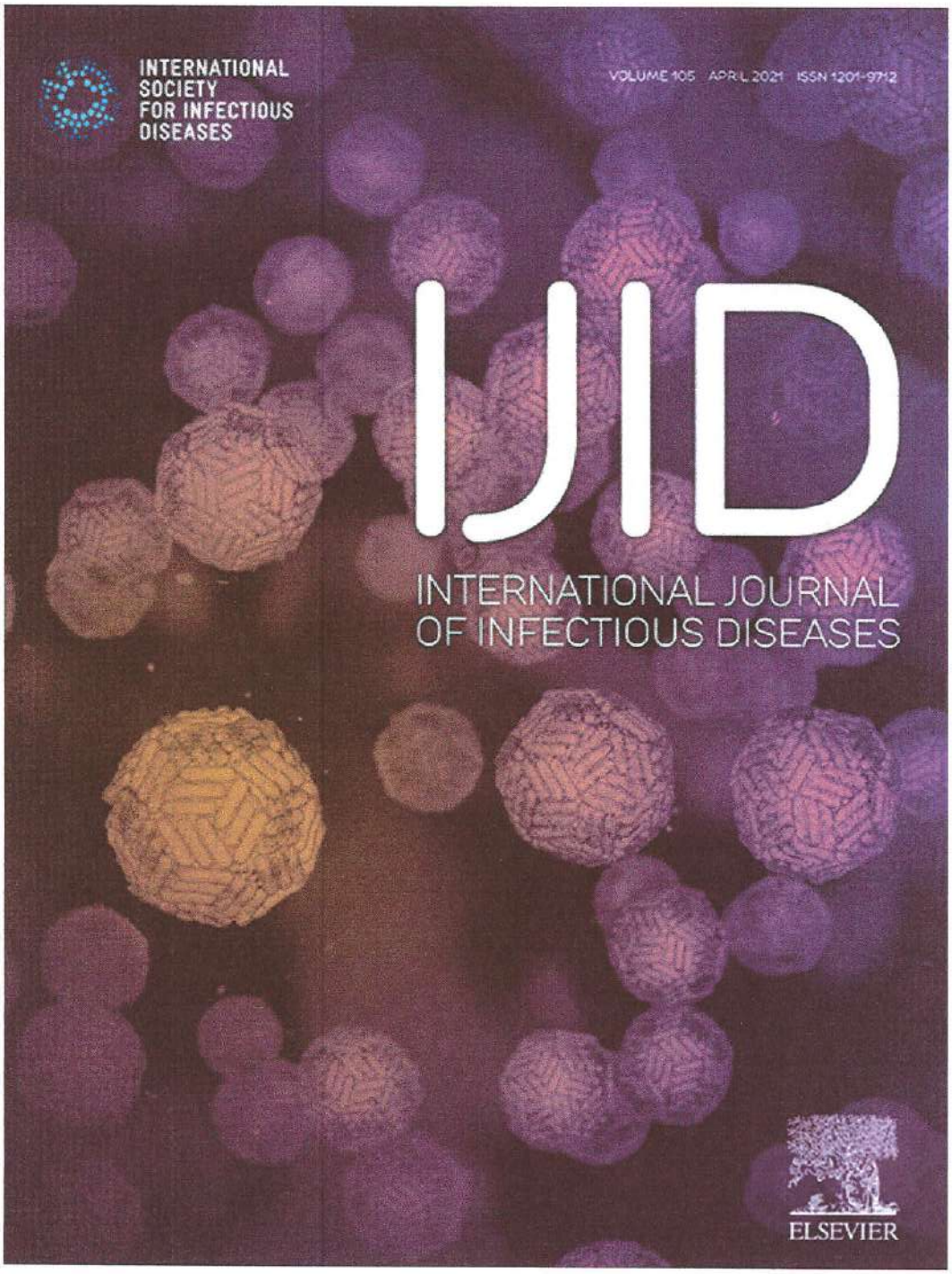
INTERNATIONAL
SOCIETY
FOR INFECTIOUS
DISEASES
VOLUME 105 APRIL 2021 ISSN 1201-9712
IJID
INTERNATIONAL JOURNAL
OF INFECTIOUS DISEASES
ELSEVIER

April 2021
Volume 105, p1-784
Open Access

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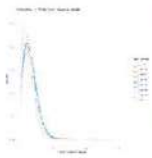

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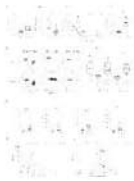

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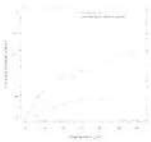

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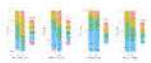

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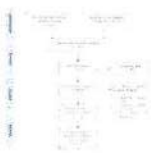

Prognostic performance of troponin in COVID-19: A diagnostic meta-analysis and meta-regression

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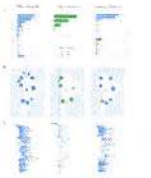

Characterizing SARS-CoV-2 genome diversity circulating in South American countries: Signatures of potentially emergent lineages?

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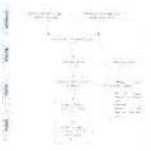

Tricuspid annular plane systolic excursion (TAPSE) measured by echocardiography and mortality in COVID-19: A systematic review and meta-analysis

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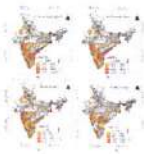

Geographic information system-based analysis of COVID-19 cases in India during pre-lockdown, lockdown, and unlock phases

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Surveillance of common respiratory infections during the COVID-19 pandemic demonstrates the preventive efficacy of non-pharmaceutical interventions

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The Grand Magal of Touba was spared by the COVID-19 pandemic

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Purple urine in a patient after recovery from a SARS-CoV-2 infection

Marcel Vetter, Matthias D. Kaufmann, Markus F. Neurath, Andreas E. Kremer

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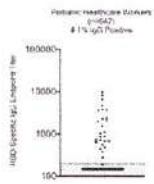

Prevalence of SARS-CoV-2 antibodies in pediatric healthcare workers

Claudia R. Morris, Patrick Sullivan, Grace Mantus, ... Mehul S. Suthar, Jens Wrammert, Miriam B. Vos

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Seroprevalence of SARS-CoV-2 antibody among healthcare workers in a university hospital in Mallorca, Spain, during the first wave of the COVID-19 pandemic

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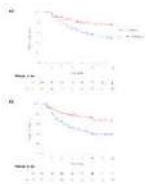

Combination therapy with tocilizumab and corticosteroids for aged patients with severe COVID-19 pneumonia: A single-center retrospective study

Francisco López-Medrano, María Asunción Pérez-Jacoiste Asín, Mario Fernández-Ruiz, ... José L. Pablos, José María Aguado on behalf of the H12O Immunomodulation Therapy for COVID-19 Group

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Efficacy and safety of pegylated interferon alfa-2b in moderate COVID-19: A phase II, randomized, controlled, open-label study

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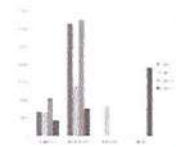

Soluble interleukin-2 receptor levels on admission associated with mortality in coronavirus disease 2019

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Efficacy evaluation of intravenous immunoglobulin in non-severe patients with COVID-19: A retrospective cohort study based on propensity score matching

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Risk and predictive factors of prolonged viral RNA shedding in upper respiratory specimens in a large cohort of COVID-19 patients admitted to an Italian reference hospital

Annalisa Mondi, Patrizia Lorenzini, Concetta Castilletti, ... Antonella Zanetti, Sara Zito For the INMI Recovery study group

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SARS-CoV-2 and immune-microbiome interactions: Lessons from respiratory viral infections

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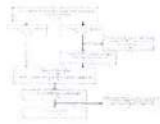

Factors affecting the survival of early COVID-19 patients in South Korea: An observational study based on the Korean National Health Insurance big data

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Effectiveness of a multidrug therapy consisting of Ivermectin, Azithromycin, Montelukast, and Acetylsalicylic acid to prevent hospitalization and death among ambulatory COVID-19 cases in Tlaxcala, Mexico

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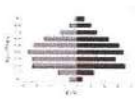

SARS-CoV-2 respiratory co-infections: Incidence of viral and bacterial co-pathogens

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CCR5Δ32 mutations do not determine COVID-19 disease course

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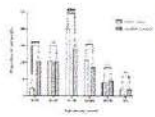

The high prevalence of asymptomatic SARS-CoV-2 infection reveals the silent spread of COVID-19

Marwa Ali Almadhi, Abdulkarim Abdulrahman, Sayed Ali Sharaf, ... Nigel J. Stevenson, Stephen L. Atkin, Manaf M. AlQahtani

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Serum amyloid A concentrations, COVID-19 severity and mortality: An updated systematic review and meta-analysis

Angelo Zinellu, Panagiotis Paliogiannis, Ciriaco Carru, Arduino A. Mangoni

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Temporal and spatial analysis of COVID-19 transmission in China and its influencing factors

Qian Wang, Wen Dong, Kun Yang, ... Dongqing Huang, Peng Zhang, Jie Wang

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Response to the comments received on article "Efficacy and safety of favipiravir, an oral RNA-dependent RNA polymerase inhibitor, in mild-to-moderate COVID-19: A randomized, comparative, open-label, multicenter, phase 3 clinical trial" by Udwadia et al

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Peculiar clinical presentation of COVID-19 and predictors of mortality in the elderly: A multicentre retrospective cohort study

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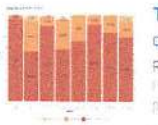

The COVID-19 pandemic is deepening the health crisis in South Kivu, Democratic Republic of Congo

René Ecochard, Patient Wimba, Justin Gengenya, ... Jean Iwaz, Jean-François Etard, Philippe Vanhems

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Coronavirus disease 2019 in pregnancy

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Letter to the editor on "Efficacy and safety of favipiravir, an oral RNA-dependent RNA polymerase inhibitor, in mild-to-moderate COVID-19: A randomized, comparative, open-label, multicenter, phase 3 clinical trial" by Udwadia et al

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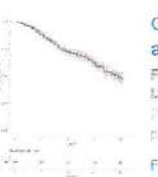

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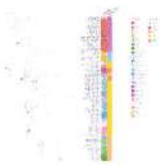

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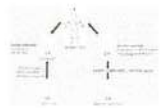

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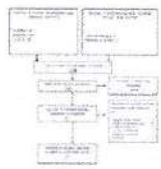

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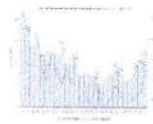

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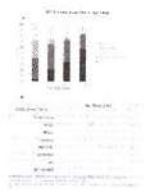

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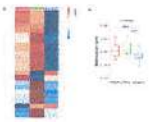

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INTERNATIONAL SOCIETY FOR INFECTIOUS DISEASES

International Journal of Infectious Diseases

OFFICIAL PUBLICATION OF THE INTERNATIONAL SOCIETY FOR INFECTIOUS DISEASES

International Journal of Infectious Diseases 105 (2021) 551–559

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Meta-analysis of cardiac markers for predictive factors on severity and mortality of COVID-19

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ARTICLE INFO

Article history:
Received 27 November 2020
Received in revised form 23 February 2021
Accepted 4 March 2021

Keywords:
COVID-19
Cardiac marker
Severity
Mortality

ABSTRACT

Objectives: Previous observational studies have suggested that increased cardiac markers are commonly found in COVID-19. This study aimed to determine the relationship between several cardiac markers and the severity/mortality of COVID-19 patients.

Methods: Several cardiac markers were analysed in this meta-analysis. RevMan 5.4 was used to provide pooled estimates for standardised mean difference (SMD) with 95% confidence intervals.

Results: Twenty-nine clinical studies were included in this meta-analysis. Significantly higher CK-MB (0.64, 95% CI = 0.19–1.09), PCT (0.47, 95% CI = 0.26–0.68), NT-proBNP (1.90, 95% CI = 1.63–2.17), BNP (1.86, 95% CI = 1.63–2.09), and D-dimer (1.30, 95% CI = 0.91–1.69) were found in severe compared with non-severe COVID-19. Significantly higher CK-MB (3.84, 95% CI = 0.62–7.05), PCT (1.49, 95% CI = 0.86–2.13), NT-proBNP (4.66, 95% CI = 2.42–6.91), BNP (1.96, 95% CI = 0.78–3.14), troponin (1.64 (95% CI = 0.83–2.45), and D-dimer (2.72, 95% CI = 2.14–3.29) were found in those who died from compared with survivors of COVID-19.

Conclusions: High CK-MB, PCT, NT-proBNP, BNP, and D-dimer could be predictive markers for severity of COVID-19, while high CK-MB, PCT, NT-proBNP, BNP, troponin, and D-dimer could be predictive markers for survival of COVID-19 patients.

Introduction

COVID-19 is a viral infectious disease that was first discovered in Wuhan, China, at the end of 2019 and caused by SARS-CoV2 infection (Jin et al., 2020). Until 26 September 2020 a total of 32,429,965 patients worldwide had been tested positive for COVID-19 and 985,823 had died (World Health Organization, 2020a). The clinical manifestations of COVID-19 include fever, cough, fatigue, muscle aches, diarrhoea, and pneumonia, which can develop into acute respiratory distress syndrome (ARDS), metabolic acidosis, and even liver, kidney or heart failure (Chen et al., 2020b; Huang et al., 2020; Wang et al., 2020a). Even though most COVID-19 cases have mild or moderate symptoms, up to 15% develop severe disease that require oxygen support (World Health Organization, 2020b).

COVID-19 patients with comorbidities such as hypertension, diabetes mellitus, coronary heart disease, cerebrovascular disease, chronic obstructive pulmonary disease, and kidney disorders have a worse clinical outcome (Ji et al., 2020a). Cardiovascular disease is a comorbid factor that can aggravate COVID-19 infection. This is due to the interaction of COVID-19 with the cardiovascular system at various levels, increasing morbidity in patients with previous underlying cardiovascular conditions, leading to injury and myocardial dysfunction (Clerkin et al., 2020). The percentage of global deaths from COVID-19 is almost 2% (Mahase, 2020; Yang et al., 2020). COVID-19 can cause direct and indirect damage to the myocardium through cytokine storm, systemic inflammation, myocardial cytotoxicity, free radical formation, dysregulated host-immune response, and loss of cellular homeostasis (Sattar et al., 2020).

Acute heart injury is the most commonly found cardiac abnormality in COVID-19 (about 8–12% of all cases). Direct myocardial injury caused by viral involvement in cardiomyocytes

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https://doi.org/10.1016/j.ijid.2021.03.008

and systemic inflammatory effects appear to be the most common mechanisms involved in cardiac injury (Bansal, 2020), although there are various other mechanisms, including: acute myocardial infarction, myocardial supply-demand mismatch, viral myocarditis, inflammation, and myocardial damage induced by oxidative stress (Shi et al., 2020). Troponin and natriuretic peptides (B-type natriuretic peptide (BNP) or N-terminal-pro hormone BNP (NT-proBNP)) in COVID-19 patients have been found to function for cardiac risk prediction and prognostic determination of severe COVID-19 patients (Mahajan et al., 2020). Higher concentrations of creatinine kinase-myocardial band (CK-MB), troponin, and NT-proBNP have also been associated with the severity of COVID-19. Therefore, close monitoring of cardiac biomarkers is essential in reducing complications and mortality of COVID-19 (Han et al., 2020a). Procalcitonin (PCT) is an inflammatory marker that can also serve as a marker for cardiac damage. It has prognostic value in acute coronary syndrome and heart failure (Ataoğlu et al., 2010; Möckel et al., 2017). Procalcitonin can be an indicator of disease severity and determine the severity of COVID-19 (Hu et al., 2020). About 94.44% of COVID-19 non-survivors showed high procalcitonin levels on the day of death (Shao et al., 2020). Another parameter that can also be a marker of the severity and mortality of COVID-19 is D-dimer (Yao et al., 2020). D-dimer is a marker of thrombus formation that increases in early myocardial infarction and acute coronary syndrome (Mansour and El-Sakhawy, 2020; Reihani et al., 2018).

To obtain more convincing results, a meta-analysis of cardiac biomarkers was performed to determine the increasing levels of several cardiac markers in COVID-19 cases: CK-MB, PCT, NT-proBNP, BNP, troponin, and D-dimer. The results were expected to be predictive factors of severity and mortality in patients with COVID-19.

Material and methods

Search strategy and eligibility criteria

An electronic search in PubMed, Proquest, and EBSCO/CINAHL was performed. The keywords were: "COVID-19", "Coronavirus", "SARS-CoV-2", "Cardiac injury", "CK-MB", "Creatine kinase-MB", "Procalcitonin", "PCT", "NT-proBNP", "BNP", "Brain Natriuretic Peptide", "Troponin", and "Cardiac troponin".

The electronic search was updated until August 2020. Inclusion criteria were: (1) studies involving measurement of either CK-MB, PCT, BNP, NT-proBNP, D-dimer, and/or troponin in COVID-19 patients cohort studies; (2) data about those parameters in severe/non-severe patients or dead/survived cases; (3) English language; (4) cohort study design; (5) included human subjects; (6) adult patients; (7) no specific population (obese, DM, kidney disease, etc); and (8) reported data in numerical values. The exclusion criteria were: (1) review articles, cross-sectional, case-control, case reports, case series, and meta-analysis; (2) duplicated studies; (3) paediatric patients; (4) specific population; (5) non-English articles; and (6) insufficient data. Mild cases were defined as mild symptoms absent of typical pneumonia changes on CT scan. Severe COVID-19 additionally met at least one of the following conditions: (1) respiratory distress, respiratory rate $\geq$30/min; (2) oxygen saturation $\leq$93% at resting state; and (3) partial pressure of arterial oxygen (PaO2)/oxygen concentration (FiO2 $\leq$ 300 mmHg (1 mmHg = 0.133 kPa). The quality of the

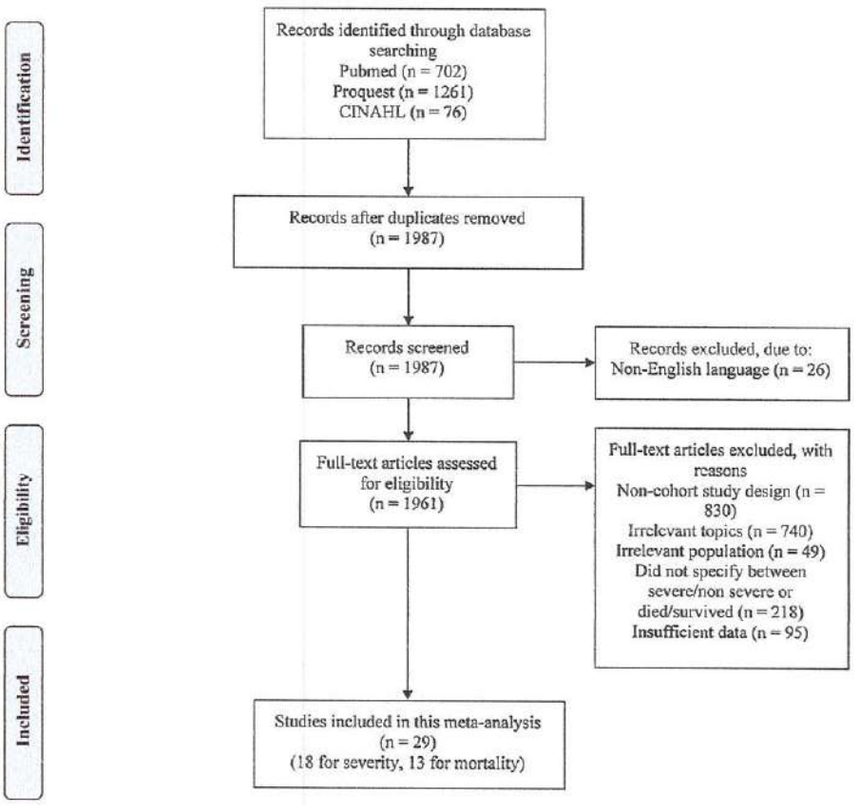

Figure 1. PRISMA flow diagram of the literature search.

studies was assessed using the Newcastle Ottawa Quality Scale (NOQS) for assessing non-randomised/observational studies (Wells et al., 2019) (Supplementary 1).

Data collection

Two investigators independently performed the search and extracted the articles. Two other investigators selected and filtered the studies. The investigators checked the article list and data extractions for duplicated articles. The full texts of relevant articles were then evaluated for eligibility criteria and included in this meta-analysis. The final inclusion of studies was decided based on the consensus of all investigators.

Statistical analysis

Heterogeneity between studies was evaluated with Q-test and I^2 test. The pooled estimated SMD was measured with models based on fixed effects or random effects assumptions. If $P < 0.05$, it indicated heterogeneity across the studies; thus, a random-effects model was used for analysis, otherwise a fixed-effect model was chosen. The 95% confidence interval (CI) of pool estimated SMD was also calculated. Begg's funnel plot of parameters with the number of studies >10 and Egger's test (Egger et al., 1997) for parameters with the number of studies >2 were performed to look for evidence of publication bias. The funnel plot was asymmetric and Egger's test was significant ($P < 0.05$) once publication bias was present. Data that were not shown as mean and standard deviation were extrapolated according to Hozo et al. (2005). Review Manager version 5.4 (The Cochrane Collaboration, Oxford, UK) and JASP version 0.13.1 (University of Amsterdam) were used for this meta-analysis.

Results

Study characteristics

In the literature search, 2039 studies were initially retrieved from database searching. After deleting duplicates, 52 articles were excluded. The studies were further reviewed and 26 of them were excluded due to non-English language. After screening the title and abstract, 1932 articles were excluded due to irrelevant study design, irrelevant topics, irrelevant population, and insufficient data or unqualified articles (Figure 1).

Finally, 29 studies consisting of 18 studies regarding COVID-19 severity and 13 regarding COVID-19 mortality were obtained. Studies by Zhang et al. and Cen et al. provided data about both COVID-19 severity and mortality. The included studies included 972 participants with severe COVID-19, 2590 with mild or non-severe COVID-19, 1386 deaths, and 4577 survived cases. Characteristics of all included studies are shown in Tables 1 and 2. For the studies of severity, almost all included studies took place in China, mainly in Wuhan, and one study took place in Switzerland. For the studies of mortality, 61.54% took place in China, 23.08% in Italy, and the rest took place in USA and Turkey. The study design of six of the 29 articles (20.69%) was a prospective cohort, while the majority were retrospective. The quality of the studies was checked using NOQS. It was found that almost all included studies had high quality, except three studies: Liu et al, Shaobo et al, and Violi et al, which had scores of 6 (possibly high risk of bias) (Supplementary 1).

Cardiac markers and COVID-19 severity and mortality

This meta-analysis examined the correlation between selected cardiac markers and COVID-19 severity/mortality. Patients with severe COVID-19 had significantly higher CK-MB (SMD = 0.64, 95% CI = 0.19–1.00, P = 0.006), PCT (SMD = 0.47, 95% CI = 0.26–0.68, P < 0.00001), NT-proBNP (SMD = 1.90, 95% CI = 1.63–2.20, P = 0.04), BNP (SMD = 1.86, 95% CI = 1.63–2.09, P < 0.0001), and D-dimer (SMD = 1.30, 95% CI = 0.91–1.69, P < 0.00001) compared with mild groups (Figure 2). When compared with mortality, COVID-19 patients who died had significantly higher biomarkers, including CK-MB (SMD = 3.84, 95% CI = 0.62–7.05, P = 0.02), PCT (SMD = 1.49, 95% CI = 0.86–2.13, P < 0.00001), NT-proBNP (SMD = 4.66, 95% CI = 2.42–6.91, P < 0.0001), troponin (SMD = 1.64, 95% CI = 0.83–2.45, P < 0.0001), and D-dimer (SMD = 1.30, 95% CI = 0.91–1.69, P < 0.00001) (Figure 3).

Publication bias and sensitivity analysis

In terms of publication bias evaluation, it was found that the studies by Zhang et al. and Cen et al. were the outliers. However,

Table 1
Characteristics of the included studies for severity.

No	Author	Study location	Sample size for severe cases (N = 972)	Sample size for mild cases (N = 2590)	Cardiac marker	Study design
1	Liu et al. (2020)	Henan Province, China	30	70	Procalcitonin	Retrospective cohort
2	Han et al. (2020a)	Wuhan, China	60	198	CK-MB, troponin I, NT-proBNP	Retrospective cohort
3	Han et al. (2020b)	Tianjin, China	30	155	CK-MB, troponin I, D-dimer	Retrospective cohort
4	Xu et al. (2020)	Shanghai, Hubei and Anhui provinces, China	85	400	CK-MB, procalcitonin, D-dimer	Cohort
5	Chen et al. (2020a)	Hubei Province, China	25	69	CK-MB, procalcitonin, D-dimer	Retrospective cohort
6	Yuan et al. (2020)	China	56	60	Procalcitonin, D-dimer	Retrospective cohort
7	Ji et al. (2020b)	Wuhan, China	55	88	Procalcitonin	Retrospective cohort
8	Gregoriano et al. (2020)	Switzerland	33	53	Procalcitonin	Retrospective cohort
9	Cao et al. (2020)	Beijing, China	27	53	Procalcitonin, troponin I	Cohort
10	Zhang et al. (2020b)	Wuhan, China	78	162	Procalcitonin, D-dimer	Retrospective cohort
11	Duan et al. (2020)	Chongqing, China	20	328	Procalcitonin, D-dimer	Retrospective cohort
12	Lu et al. (2020)	Shanghai, China	9	44	Procalcitonin, D-dimer	Retrospective cohort
13	Han et al. (2020c)	Wuhan, China	48	59	CK-MB, troponin I, D-dimer	Retrospective cohort
14	Hu et al. (2020)	Wuhan, China	21	62	Procalcitonin	Retrospective cohort
15	Cen et al. (2020)	Wuhan, China	200	409	Procalcitonin, D-dimer	Retrospective cohort
16	Deng et al. (2020b)	Wuhan, China	67	45	CK-MB, procalcitonin, troponin I, NT-proBNP, D-dimer	Retrospective cohort
17	Wang et al. (2020b)	Shenzen, China	70	253	CK-MB, procalcitonin, troponin T, D-dimer	Retrospective cohort
18	Zhang et al. (2020c)	Wuhan, China	58	82	Procalcitonin, D-dimer	Retrospective cohort

Table 2
Characteristics of the included studies on mortality.

No	Author	Study location	Sample size for deaths (N = 1386)	Sample size for survivors (N = 4577)	Cardiac marker	Study design
1	Aloisio et al. (2020)	Italy	35	63	Troponin T, D-dimer	Retrospective cohort
2	Shi et al. (2020)	China	62	609	CK-MB, procalcitonin, troponin I	Retrospective cohort
3	Wang et al. (2020a)	China	56	60	Procalcitonin, D-dimer	Cohort
4	Violi et al. (2020)	Italy	64	225	Troponin, D-dimer	Cohort
5	Bonetti et al. (2020)	Italy	70	74	Troponin I, D-dimer	Cohort
6	Zhang et al. (2020a)	Wuhan, China	11	27	Troponin I, D-dimer	Retrospective cohort
7	Zhang et al. (2020c)	Wuhan, China	49	240	Procalcitonin, D-dimer	Retrospective cohort
8	Du et al. (2020)	Wuhan, China	21	158	Procalcitonin, troponin I, BNP, D-dimer	Cohort
9	Barman et al. (2020)	Turkey	103	504	CK-MB, procalcitonin, troponin I, D-dimer	Retrospective cohort
10	Mikami et al. (2020)	USA	806	2014	Procalcitonin, troponin, D-dimer	Retrospective cohort
11	Deng et al. (2020a)	China	52	212	Troponin I, D-dimer	Retrospective cohort
12	Cen et al. (2020)	Wuhan, China	43	409	Procalcitonin, D-dimer	Retrospective cohort
13	Li et al. (2020c)	Wuhan, China	14	60	Procalcitonin, BNP, D-dimer	Retrospective cohort

when a study was omitted, it did not affect the pooled analysis. The Egger's test results were significant in CK-MB and PCT for severity and D-dimer for mortality groups (P = 0.021, P = 0.039, and P = 0.007, respectively). However, in the remaining groups, there was no evidence of publication bias (Table 3). Sensitivity analysis was performed for groups containing low-quality studies only, after excluding them from the analysis. According to the sensitivity analysis, despite excluding studies with NOQS <7 (high-quality studies only), the results remained stable. When one study in turn was sequentially excluded to assess the stability of the results, no study affected the pooled estimates. Most studies measured troponin I, except for Wang and Elena who measured troponin T. Two studies (Mikami and Violi) did not mentioned which troponin was measured. A sensitivity analysis for studies with troponin I only was performed; however, the pooled result was not much different.

Discussion

This meta-analysis showed that an increase in several cardiac markers was significantly associated with COVID-19 and mortality. Cases of death due to COVID-19 in patients with increased cardiac markers on admission, with or without prior history of heart disease, have been quite widely reported (Clerkin et al., 2020). Acute cardiac injury is characterised by elevated levels of cardiac markers, electrocardiographic abnormalities, or myocardial dysfunction occurring in about 60% of severe COVID-19 patients. Some of the possible causes of this include: (1) changes in myocardial demand and supply; (2) acute atherothrombosis due to inflammation and viral infection; (3) microvascular dysfunction due to microthrombus or vascular damage; (4) stress-related cardiomyopathy; (5) cytokine storm; and (6) direct toxicity by viruses (Lang et al., 2020). Angiotensin-converting enzyme (ACE) 2 receptor as viral entry is also thought to be associated with myocardial injury due to COVID-19 (Böhm et al., 2020).

In addition to classic cardiac markers such as troponin and CK-MB, which have been shown to have increased in previous studies, this meta-analysis also showed that PCT, NT-proBNP, BNP, and D-dimer were also increased in severe COVID-19 and deaths from it. NT-proBNP and BNP are markers of myocardial stretch injury used for diagnosis, prevention, and safe discharge planning in heart failure (Abboud and Januzzi, 2020). PCT is also an indicator of myocardial damage, as patients with myocardial damage have greater PCT levels than the 99th percentile of control patients (Arneth, 2008). Serum PCT is also a predictor of in-hospital biomarkers and 30-day outcomes for myocardial infarction patients as well as an indicator of cardiogenic shock (Patel and George, 2016). D-dimer is a degradation product of fibrin, which indicates abnormal haemostasis and intravascular thrombosis (Johnson et al., 2019). D-dimer levels are generally elevated in cardiac ischaemia (Reihani et al., 2018).

Several mechanisms explain the elevated cardiac markers in severe COVID-19: viral myocarditis, cytokine-driven myocardial damage, microangiopathy, and unmasked CAD. Myocardial ACE2 receptors are targets for SARS-CoV2 (Tersalvi et al., 2020). SARS-CoV2 can induce indirect cardiovascular damage through activation of the immune system. The virus attaches to the pattern recognition receptors (PRRs), which initiate host-immune defence. The host-immune system induces inflammatory responses, leading to cytokine storm. This causes myocardial damage through the release of reactive oxygen species (ROS), endogenous nitric oxide (NO), and damage-associated molecular proteins (DAMPs) by the injured myocardium (Sattar et al., 2020). Cytokines and host-immune dysregulation cause direct and indirect cardiac injury, leading to an increase in troponin and CK-MB (Tersalvi et al., 2020). Myocardial wall stress induced by COVID-19 causes the release of NT-proBNP and BNP. It can be worsened by renal failure as a complication, which impairs their clearance (Gao et al., 2020; Sorrentino et al., 2020). SARS-CoV2 can also cause direct cytotoxicity through 3C proteinase-mediated apoptosis, impaired host protein translation mechanisms, disbalance cellular homeostasis, and dysregulation of the host immune response (Sattar et al., 2020). Hypoxic conditions, respiratory distress, metabolic acidosis, fluid/electrolyte disturbances, and activation of the neurohormonal system can worsen heart damage, even triggering arrhythmias and cardiac arrest (Song et al., 2020). Cardiac inflammation occurring in this state can increase PCT levels (Unudurthi et al., 2020). In COVID-19, there can be an imbalance between coagulation and inflammation, leading to hypercoagulopathy. There is an interaction between the innate immune system and thrombosis, which can be seen from the increase in D-dimer. Increased levels of D-dimer can predict the severity and mortality of COVID-19 patients (Colling and Kanthi, 2020). Endothelial dysfunction, cytokine storm, Angiotensin II upregulation, and vasculitis promote coagulopathy, which results in D-dimer elevation (Tersalvi et al., 2020).

The results of this meta-analysis are in line with previous research. The meta-analysis conducted by Li et al. (2020b) also showed evidence of increased cardiac markers related to the severity and mortality of patients with COVID-19. The study found an increase in troponin, CK-MB, myoglobin, and NT-proBNP. This study also found that troponin I and NT-proBNP increased just before death from COVID-19 occurred (Li et al., 2020b). A study with a large sample by Qin et al. (2020) also showed that elevated troponin I, CK-MB, NT-proBNP, and myoglobin were closely associated with 28-day all-cause mortality due to COVID-19

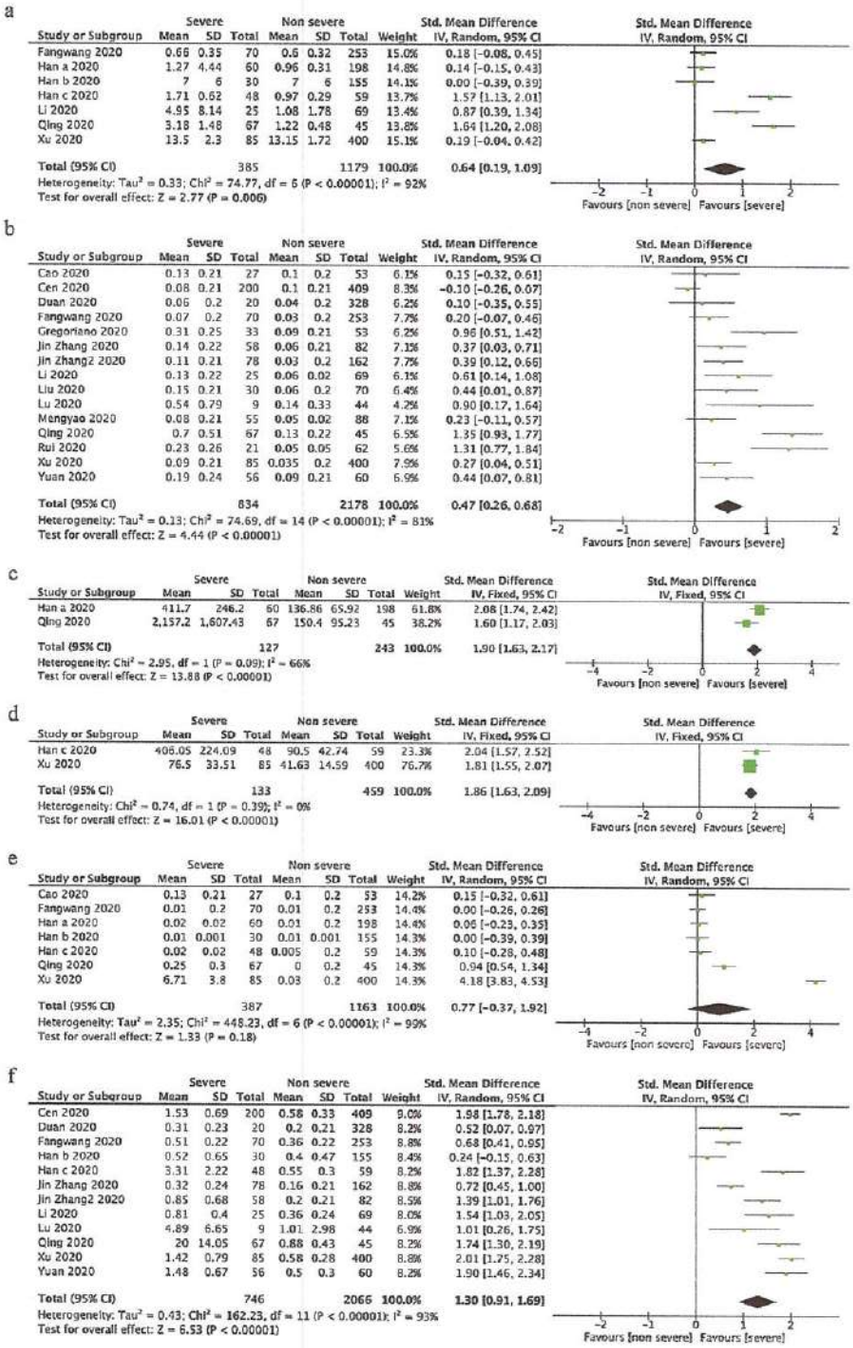

Figure 2. Forest plot for the pooled standardised mean difference (SMD) and 95% confidence interval (CI) in severe and non-severe COVID-19 patients: (a) CKMB; (b) PCT; (c) NT-pro BNP; (d) BNP; (e) troponin; (f) D-dimer.

(Qin et al., 2020). A longitudinal study also found that cardiac injury was an independent marker of mortality among critically ill COVID-19 cases (Li et al., 2020a). The previous studies mostly reported only elevated troponin as a marker of cardiac injury, for example Zou et al. (2020) and Aikawa et al. (2020), while this paper included several other cardiac markers. They also measured the outcome with Odds Ratio, which means that they only included studies with categorical data (number of patients with elevated cardiac troponin in cases and controls) but not all studies had such data; therefore, the current study used mean ± SD to ensure that studies showing only numerical data (mean/median) were included. Additionally, those papers were conducted in the earlier COVID-19 pandemic; therefore, the current study included more studies.

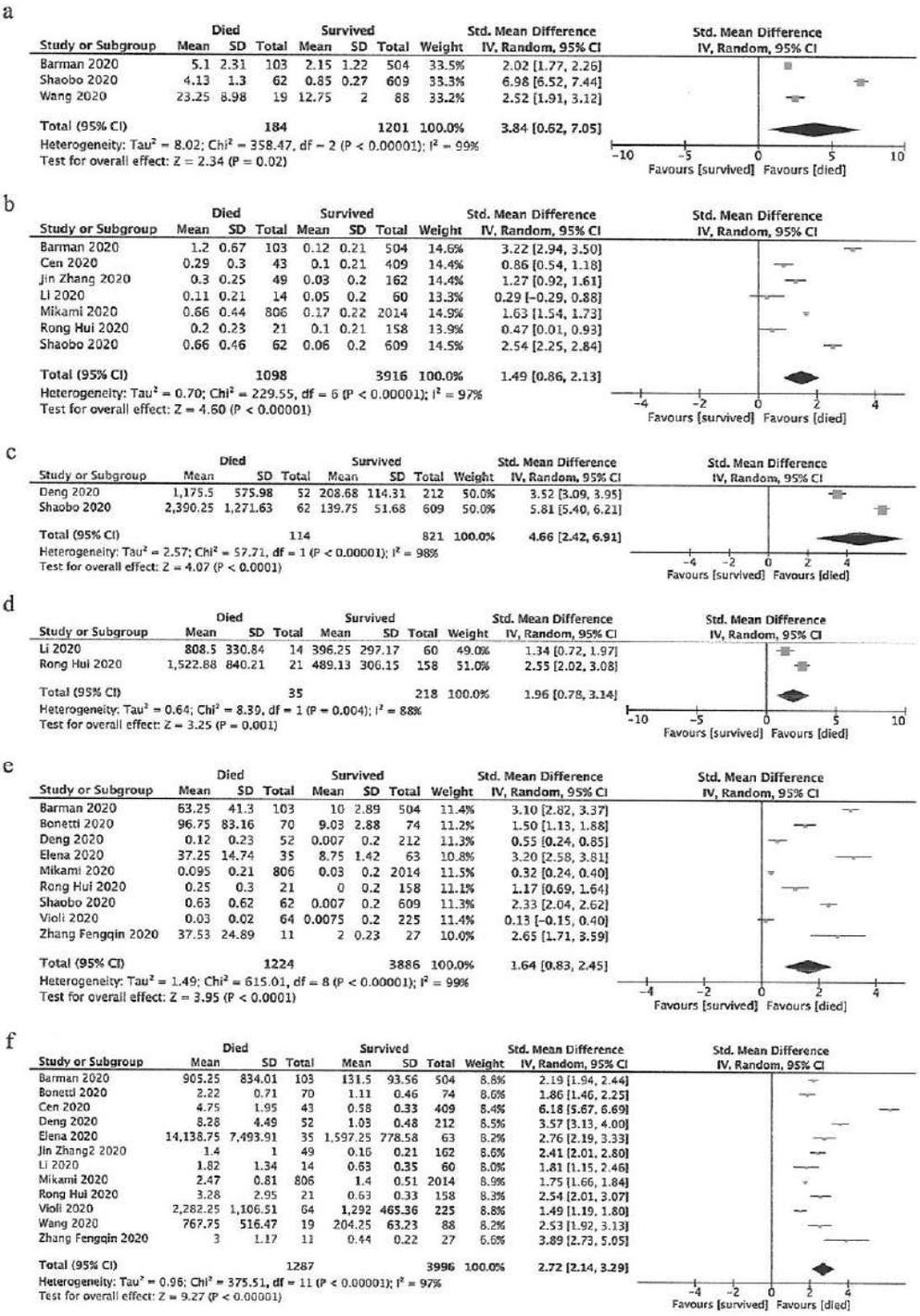

Figure 3. Forest plot for the pooled standardised mean difference (SMD) and 95% confidence interval (CI) in deaths and survivors of COVID-19: (a) CKMB; (b) PCT; (c) NT-pro BNP; (d) BNP; (e) troponin; (f) D-dimer.

Cardiac markers with the highest SMD values for predicting COVID-19 severity were NT-proBNP, followed by BNP and D-dimer (1.90, 1.86, and 1.30, respectively). For predicting mortality, cardiac markers with the highest SMD value were NT-proBNP, followed by D-dimer and BNP (4.66, 2.72, and 1.64, respectively). However, the number of included studies with NT-proBNP and BNP for both severity and mortality groups was relatively small (two studies for each biomarker/group). Thus, it is suggested that D-dimer is the best

Table 3
Summary of findings.

Groups	Number of cohorts	SMD	95% CI	I^2 (%)	P	Egger test
CK-MB severity	7	0.64	0.19–1.00	92	0.006	0.021
PCT severity	15	0.47	0.26–0.68	81	<0.00001	0.039
NT-proBNP severity	2	1.90	1.63–2.20	66	0.04	–
BNP severity	2	1.86	1.63–2.09	0	<0.0001	–
Troponin severity	7	0.77	−0.37–1.92	99	0.18	0.992
D-dimer severity	12	1.30	0.91–1.69	93	<0.00001	0.739
CK-MB mortality	3	3.84	0.62–7.05	99	0.02	0.832
PCT mortality	7	1.49	0.86–2.13	97	<0.00001	0.175
NT-proBNP mortality	2	4.66	2.42–6.91	98	<0.0001	–
BNP mortality	2	1.96	0.78–3.14	88	0.001	–
Troponin mortality	9	1.64	0.83–2.45	99	<0.0001	0.087
D-dimer mortality	12	2.72	2.14–3.29	97	<0.00001	0.007
Sensitivity analysis PCT severity	14	0.47	0.25–0.69	83	<0.0001	0.041
Sensitivity analysis troponin-I severity	5	0.24	−0.09–0.57	74	0.15	0.714
Sensitivity analysis PCT mortality	6	1.31	0.60–2.02	97	0.0003	0.147
Sensitivity analysis CK-MB mortality	2	2.19	1.72–2.66	57	<0.00001	–
Sensitivity analysis troponin mortality	7	1.76	0.75–2.77	99	0.0006	0.109
Sensitivity analysis troponin I mortality	6	1.87	0.99–2.74	97	<0.0001	0.646
Sensitivity analysis D-dimer mortality	11	2.84	2.20–3.48	97	<0.00001	0.017

predictor of severity and mortality in COVID-19, as it was found in many included studies (>10) and had high significance ($P < 0.00001$). Cardiac injury generally associated with COVID-19 is diagnosed from the presence of increased levels of cardiac enzymes, first detected electrocardiography, or echocardiography abnormality. However, this definition varies from study to study because there is no consensus that addresses COVID-19-associated cardiac injury (Kim et al., 2020). Early cardiac marker assessment in COVID-19 patients, especially during triage, is recommended so that it can prevent worsening and high mortality in COVID-19 patients.

Limitation

It is believed that this meta-analysis with 32 included different studies is the largest to evaluate the prognostic role of several cardiac markers on the severity and mortality of COVID-19 patients. However, this meta-analysis had several limitations. First, the laboratory markers were taken at baseline on admission, thus any shift of those markers in response to therapy could not be predicted. Although in some cases the administration of treatment in COVID-19 patients can normalise cardiac biomarkers (Kang et al., 2020), drug-related heart damage should be a concern in providing therapy (Zheng et al., 2020). Levels of these biomarkers can be increased through therapy and improved oxygenation, leading to reperfusion-injury ischaemia. The release of pro-inflammatory cytokines and free radicals through this process can cause further damage to organs, including the myocardium (Li et al., 2020d). Some antivirals such as chloroquine and azithromycin can even cause prolongation of the QT interval, which should be taken into consideration (Kang et al., 2020). Further clinical research is needed to determine the role of these cardiac markers as predictors of therapeutic response. Second, BNP and NT-proBNP studies were limited in number. In addition, most studies did not distinguish the involvement of prior cardiovascular disease in the elevation of those biomarkers; therefore, it is difficult to determine whether the cardiac injury was caused by COVID-19 induction or prior cardiovascular disease. Further studies should be performed to obtain more comprehensive understanding on the mechanism of cardiac injury in COVID-19.

Conclusion

In conclusion, there were significant differences in CK-MB, PCT, NT-proBNP, BNP, and D-dimer levels between severe and non-severe COVID-19 patients. Differences in CK-MB, PCT, NT-proBNP, BNP, troponin, and D-dimer level differences were also found between those who died and those who survived. This implies that cardiac markers (CK-MB, PCT, BNP, NT-proBNP, troponin, and D-dimer levels) are key laboratory parameters for diagnosis and prognosis, and with which to predict the severity and mortality of COVID-19. D-dimer is suggested to be the best predictor of severity and mortality in COVID-19, as it had been examined in many included studies and high significance ($P < 0.00001$). Further research is required to determine the role of more cardiac markers for predicting the prognosis of COVID-19 patients.

Conflict of interest

None declare.

Ethical approval

Not applicable.

Funding

None declare.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2021.03.008.

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