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

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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.

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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., 2020). 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 (Ataoglu 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; Rehani 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 ≥30/min; (2) oxygen saturation ≤93% at resting state; and (3) partial pressure of arterial oxygen (PaO2)/oxygen concentration (FiO2) ≤300 mmHg (1 mmHg = 0.133 kPa). The quality of the

![Figure 1. PRISMA flow diagram of the literature search.](image-url)
studies was assessed using the Newcastle Ottawa Quality Scale (NOQS) for assessing non-randomized/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 I² 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,

| 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)  | Hebei 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)  | Shenzhen, 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|
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 v-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 NOQ < 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 mention 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 v-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). v-dimer is a degradation product of fibrin, which indicates abnormal haemostasis and intravascular thrombosis (Johnson et al., 2019). v-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 (Tersali 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 (Tersali 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 protease-activated 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 v-dimer. Increased levels of v-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 v-dimer elevation (Tersali 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.
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.

(Qin et al., 2020). 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) i-dimer.
Cardiac markers with the highest SMD values for predicting COVID-19 severity were NT-proBNP, followed by BNP and \( \alpha \)-dimer (1.90, 1.86, and 1.30, respectively). For predicting mortality, cardiac markers with the highest SMD value were NT-proBNP, followed by \( \alpha \)-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 \( \alpha \)-dimer is the best
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.

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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.

References

Abboud A, Januzzi JL. Heart failure biomarkers in COVID-19. Am Coll Cardiol 2020;.. [Accessed 28 July 2020] https://www.acc.org/latest-in-cardiology/articles/2020/07/27/09/25/heart-failure-biomarkers-in-covid-19.

Akikawa T, Takagi H, Ishikawa K, Kuno T. Myocardial injury characterized by elevated cardiac troponin and in-hospital mortality of COVID-19: an insight from a meta-analysis. J Med Virol 2020;93(1):51–5, doi:http://dx.doi.org/10.1002/jmv.26108.

Alessio E, Chhibreau M, Serafini L, Pasqualetti S, Falvella FS, Dolci A, et al. A comprehensive appraisal of laboratory biochemistry tests as major predictors of COVID-19 severity. Arch Pathol Lab Med 2020;144(12):1457–64, doi:http://dx.doi.org/10.5858/arpa.2020-0389-SA.

Arnett B. High-sensitivity procalcitonin (hs-PCT): A marker for identification of arteriovenous and myocardial infarction? Lab Med 2008;39:607–10, doi: http://dx.doi.org/10.1309/LM6E5BJZ2TQSCGHZ.

Atoğlu HE, Yılmaz F, Uzunhasan I, Çetin F, Temiz LU, Döventas YE, et al. Procalcitonin: A novel cardiac marker with prognostic value in acute coronary
Wang F, Qu M, Zhou X, Zhao K, Lai C, Tang Q, et al. The timeline and risk factors of clinical progression of COVID-19 in Shenzhen, China. J Transl Med 2020;18:1–11, doi: http://dx.doi.org/10.1186/s12967-020-03423-8.

Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2019. [Accessed 15 July 2020] http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

World Health Organization. WHO Coronavirus disease (COVID-19) dashboard. 2020. https://covid19.who.int/.

World Health Organization [WHO]. Clinical management of COVID-19. 2020.

Xu K, Zhou M, Yang D, Ling Y, Liu K, Bai T, et al. Application of ordinal logistic regression analysis to identify the determinants of illness severity of COVID-19 in China. Epidemiol Infect 2020;148:, doi: http://dx.doi.org/10.1017/S0950268820001533.

Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475–81, doi: http://dx.doi.org/10.1016/S2213-2600(20)30079-5.

Yao Y, Cao J, Wang Q, Shi Q, Liu K, Luo Z, et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. J Intensive Care 2020;8:1–11, doi: http://dx.doi.org/10.1186/s40560-020-00466-2.

Yuan X, Huang W, Ye B, Chen C, Huang R, Wu F, et al. Changes of hematological and immunological parameters in COVID-19 patients. Int J Hematol 2020;1–7, doi: http://dx.doi.org/10.1007/s12185-020-02530-w.

Zhang F, Xiong Y, Wei Y, Hu Y, Wang F, Li G, et al. Obesity predisposes to the risk of higher mortality in young COVID-19 patients. J Med Virol 2020a;92:2536–42, doi: http://dx.doi.org/10.1002/jmv.26039.

Zhang J-J, Cao YY, Tan G, Dong X, Wang B-C, Lin J, et al. Clinical, radiological and laboratory characteristics and risk factors for severity and mortality of 289 hospitalized COVID-19 patients. Allergy 2020b;76(2):533–50, doi:http://dx.doi.org/10.1111/all.14496.

Zhang Jin, Dong X, Cao Yysan, Yuan Ydong, Yang Ybin, Yan Qyin, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy Eur J Allergy Clin Immunol 2020c;75:1730–41, doi:http://dx.doi.org/10.1111/all.14238.

Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol 2020;17:259–60, doi: http://dx.doi.org/10.1038/s41569-020-0360-5.

Zou F, Qian Z, Wang Y, Zhao Y, Bai J. Cardiac injury and COVID-19: a systematic review and meta-analysis. CJC Open 2020;2:386–94, doi:http://dx.doi.org/10.1016/j.cjco.2020.06.010.b:issue+10.1016/j.cjco.2020.06.010.