Elevation of Cardiac Biomarkers in COVID-19 As a Major Determinant for Mortality: A Systematic Review

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ABSTRACT

Aim: *To summarize the prognosis of Corona Virus Disease 2019 (COVID-19) patients with elevated troponin and N-terminal pro brain natriuretic peptide (NT-proBNP) levels and demonstrate the involvement of myocardial injury as a complication in COVID-19.* ***Methods:*** *A systematic literature search was performed using several databases (PubMed, MEDLINE, PROQUEST and SCOPUS) for studies published up to August 2020. Observational studies about the mortality outcome of COVID-19 patients who experienced cardiac injury, as defined by the elevation of serum levels of troponin, brain natriuretic peptide (BNP), with NT-proBNP or only BNP or only NT-proBNP, were included. In addition, a critical appraisal was conducted for all included studies using the Critical Appraisal for Prognostic Studies checklist published by the Centre for Evidence-Based Medicine by the University of Oxford.* ***Results:*** *Seven retrospective observational studies fulfilled the inclusion criteria. This study found that there is a higher risk of death in COVID 19 patients with higher levels of troponin and NT-proBNP, indicating the importance of these biomarkers as determinant factors to predict in-hospital deaths.* ***Conclusion:*** *Based on the analysis, elevation of troponin and NT-proBNP levels plays an essential role in determining the patient prognosis because it is shown to be associated with in-hospital mortality. This also supports the involvement of myocardial injury as a prominent fatal complication in COVID-19.*

Keywords: *COVID-19, myocardial injury, troponin, BNP, NT-proBNP, prognostic factors.*

INTRODUCTION

In early 2020, a pandemic state was reported in relation to the coronavirus disease-2019 (COVID-19), a novel strand of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). [1,2] By August 21, 2020, the global number of confirmed cases had reached more than 4 million, with over 780,000 deaths having occurred in 213 different countries.[3]

Although the major complication of COVID-19 infection is respiratory failure, there have been reports of myocardial injury defined by elevated biomarker values in patients, with troponin I as the main biomarker used.[1,4-8] The use of troponin I is based on its unique regulatory protein encoded by a specific gene that is only found in the myocardium, making it a fundamental aspect to clinically define the diagnosis of myocardial injury.[9-10] Other biomarkers, such as troponin T (TnT), brain natriuretic peptide (BNP), and N-terminal brain natriuretic peptide (NT-proBNP), are also used to further support the determination of any myocardial damage.[11]

To date, the most plausible cause of the myocardial injury found in COVID-19 is the presence of ACE2 receptors in the myocardium; these receptors allow the binding of SARS-Cov2 structural protein, leading to a direct viral infection of the heart. Furthermore, infection-mediated vasculitis by COVID-19 may also contribute to causing direct myocardial injury because of the ACE2 receptor expressions in the arterial and venous endothelial cells. Both events may lead to an indirect immunological response resulting in a hypersensitivity reaction, which manifests as the myocardial injury and dysfunction seen in COVID-19. Such occurrences often lead to a fatal outcome.[1]

Many studies have found that intensive care unit (ICU) admissions and in-hospital mortality may also be associated with elevated biomarkers, further supporting the essential determinant factor of patients' prognosis in clinical settings.[12] Thus, many clinicians have drawn their attention to the role of troponin and NT-proBNP elevation in determining the prognosis of patients with COVID-19.

METHODS

As a foundation for performing an extensive literature search, this study chose a relevant clinical question using a patients/intervention/comparison/outcome (PICO) model to define suitable terms for use in the search. The chosen terms derived from the following question: *Could the elevation of troponin and BNP/NT-proBNP determine the prognosis of patients with COVID-19 myocardial injury?* The selected keywords comprised of P (patients), I (intervention) and O (outcome), whereas C (comparison) was not considered as the main focus and therefore, excluded (**Table 1**).

We used the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines for this review. A literature search was performed using four databases (PubMed, MEDLINE, PROQUEST and SCOPUS) from April 24 to August 26, 2020, using a combination of Medical Subject Headings (MeSH) terms based on the PICO keywords derived from the clinical question (**Table 2**). Only longitudinal cohort studies or randomized controlled trials that observed death as the main outcome for COVID-19 patients with elevated NT-proBNP and/or troponin were included in this study.

Table 1. PICO.

Patient (P)	Intervention (I)	Comparison (C)	Outcome (O)
COVID-19 Myocardial Injury Patients	Elevation of Troponin and BNP/NTpro-BNP	-	Mortality/Death Case

BNP/NTproBNP, Brain Natriuretic Protein/N-terminal pro brain natriuretic peptide ;COVID-19, Coronavirus Disease 2019;

Table 2. Literature search strategy.

Database	Search Terms	Hits
PubMed	(((((("COVID-19"[Title/Abstract]) OR (CORONAVIRUS[Title/Abstract])) AND (MYOCARDIAL INJURY [Title/Abstract]) AND ((TROPONIN[Title/Abstract]) OR (BNP [Title/Abstract]) OR (NT-PROBNP[Title/Abstract])) AND (MORTALITY [Title/Abstract])	178
PROQUEST	((COVID-19) OR (CORONAVIRUS)) AND (MYOCARDIAL INJURY) AND ((TROPONIN)) OR (BNP) OR (NT-PROBNP)) AND (MORTALITY)	45
SCOPUS	((COVID-19) OR (CORONAVIRUS)) AND (MYOCARDIAL INJURY) AND ((TROPONIN)) OR (BNP) OR (NT-PROBNP)) AND (MORTALITY)	17
Medline	((COVID-19) OR (CORONAVIRUS)) AND (MYOCARDIAL INJURY) AND ((TROPONIN)) OR (BNP) OR (NT-PROBNP)) AND (MORTALITY)	215
Total		455

Critical Appraisal

A critical appraisal was conducted thoroughly by the author for all included studies using the Critical Appraisal for Prognostic Studies checklist published by the University of Oxford (www.cebm.net). Any uncertainties for inappropriate topics was then consulted to the second reviewer. Study design, patient demographics, value changes in troponin and BNP and/or NT-proBNP value, mortality rate, risk ratio/odd ratio, hazard ratios and other outcomes from adjusted statistical (if stated) were extracted from the included studies for further analysis.

RESULTS

Search Selection

A total of 455 papers were identified from the four databases. After the deduplication process, 450 different papers were screened based on their titles and abstracts (**Figure 1**). As a result, 216 articles were excluded from the initial screening, leaving 234 articles to undergo a full review and further selection process. Seven articles were selected as the final sample for this study. A summary of the selection process according to the PRISMA statement can be seen in the PRISMA diagram on **Figure 1**.[13]

The characteristics of the baseline study can be seen in **Table 3**. All chosen studies varied from a single-center or multicenter observational cohort and observed the relationship between the elevation of myocardial biomarkers of COVID-19 patients and the mortality outcome. Zhou et al[14]., Chen et al.[15], and Stefanini et al.[16] focused on the association of patients' clinical outcomes with troponin and NT-proBNP as myocardial markers. Guo et al.[17], Gao et al.[18], Zhang et al.[19], and Shi et al.[20] included other myocardial injury biomarkers, such as Creatinine Kinase Myocardial Band (CKMB), myohemoglobin, or myoglobin. These studies underwent critical appraisal as presented in **Table 4**.

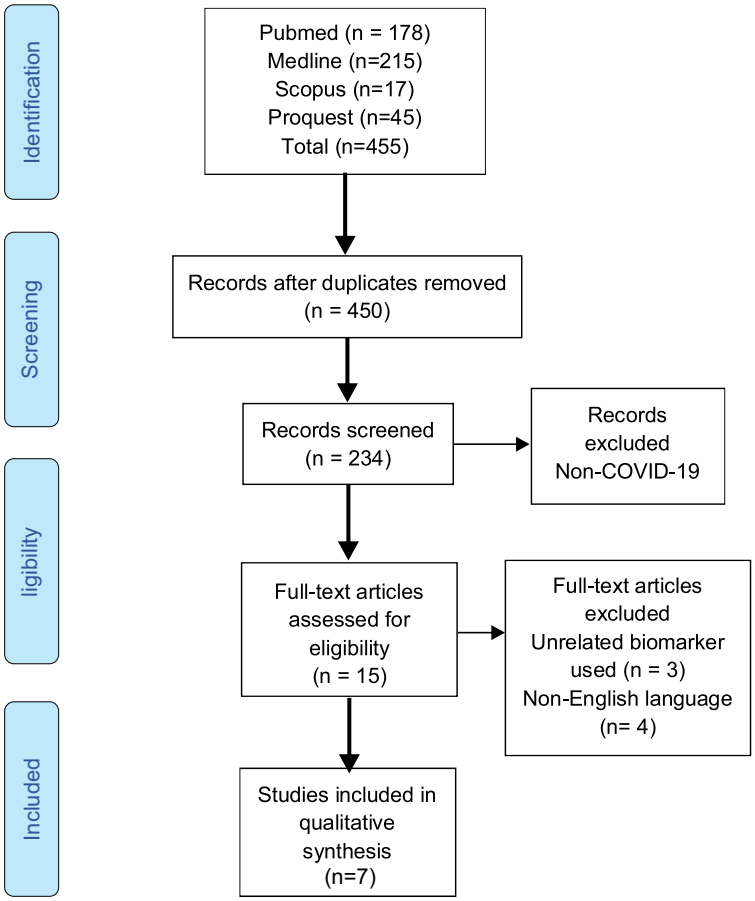

Figure 1. Prisma Flow Diagram of search and selection process

Table 3. Characteristic of included studies

Author	Institution/ Country Study Conducted	Design	Inclusion Criteria	Exclusion Criteria	Participants	Myocardial biomarker tested	Other biomarker tested	Primary endpoints	Secondary endpoint(s)	Results
Zhou et al	Jinyintan Hospital and Wuhan Pulmonary Hospital (Wuhan, China	Retrospective Cohort Study	Confirmed COVID-19 inpatients who died or discharged between 29th Dec 2019 and 31st Jan 2020	Non COVID-19 Inpatients, Patients without accessible medical records	191 Patients	Hs-cTnI	White blood cell, Lymphocyte count, Haemoglobin, Platelet count, Albumin, ALT, Creatinine, Lactate dehydrogenase, Creatinine kinase, serum ferritin, Il-6, Procalcitonin, , Prothrombin time, d-dimer	Death, Discharged	N/a	Hs-cTnI : 3.0 pg/ml survivor (54/191) vs 22.2pg/ml non survivor (137/191) OR Hs-cTnI 80.07 (CI 10.34 – 620.36)
Guo et al	Seventh Hospital of Wuhan City, China	Retrospective Cohort Study	Confirmed COVID-19 inpatients who died or discharged between 23rd Jan 2020 and 23rd Feb 2020	COVID-19 inpatients without a complete medical record	187 Patients	Troponin T, CKMB fraction, Myoglobin, NT-proBNP	White blood cell, Lymphocyte count, Neutrophil, Albumin, ALT, Creatinine, Aminotransferase (alanine, aspartate), hsCRP, Globulin, Procalcitonin, Prothrombin time, d-dimer, APTT, Cholesterol (total, triglyceride, HDL, LDL), Serum potassium, Serum Calcium	Death, Discharged	N/a	Mortality in Normal TnT (12[8.9%]) vs Elevated TnT (31[59.6%]) [p<0.001] Both TnT and NT-proBNP levels increased significantly during the course of hispitalization in those who ultimately died [p<0.001], but no such dygnamic changes in those biomarkers were evident in survivors
Shi et al	Renmin Hospital of Wuhan Universit	Retrospective Cohort Study	Confirmed COVID-19 inpatients between 20th Jan 2020 and 10th Feb 2020	COVID-19 inpatients without cardiac biomarkers data	416 Patients	Hs-cTnI, NT-proBNP, CKMB, NT pro-BNP, Myohemoglobin	Leukocyte, Lymphocyte, Platelet, Erythrocyte, Haemoglobin, C-reactive protein, Procalcitonin, Creatinine, Aminotransferase (alanine, aspartate), Serum potassium, Serum Calcium	Death, discharged, remained in hospital	N/a	Hs-cTnI : cardiac injury (0.19[0.08-1.12] p<0.001) vs without (<0.006) [<0.006-0.009] p<0.001] Death of Patient with cardiac injury (42/82) vs without (15/334) [p<0.001]

										Discharged patients with cardiac injury (2/82) vs without (38/334) [p<0.001] Patient remained in the hospital with cardiac injury (38/82) vs without (281/334) [p<0.001]
Chen et al	Tongji Hospital, Wuhan, China	Retrospective Cohort Study	Confirmed COVID-19 critically ill inpatients between 13th Jan 2020 and 28th Feb 2020	Not specified	274 Patients	Hs-TnI, NT-proBNP	White blood cell count, Neutrophil, Lymphocyte, Monocyte, Platelet, Haemoglobin, C-reactive protein, Procalcitonin, Creatinine, Aminotransferase (Alanine, Aspartate), Total Bilirubin, Alkaline phosphatase, gamma glutamyl transpeptidase, Triglycerides, Serum potassium, Serum Calcium, Blood Urea Nitrogen, Creatine Kinase, Lactate dehydrogenase, Prothrombin time, activated partial thromboplastine time, D-dimer, ferritin, erythrocyte, thyroid stimulating hormone, free triiodothyroxine, free thyroxin, Immunoglobulin (A,G,M), C3, C4, Il-1B, IL-1 receptor, Il-6, Il-8, Il-10, Tumor necrosis factor alpha, Urinary protein, Urinary Occult blood	Death, Recovered	N/a	Elevated Hs-TnI in deceased patients (68/94 [72%]) vs recovered patients 15/109[14%] Elevated NT-proBNP in deceased patients(68/80 [85%]) vs recovered patients (17/93 [18%])

Gao et al	Hubei General Hospital, China	Retrospective Observational Study	COVID-19 patients with severe conditions (respiratory rate ≥ 30/ min or rest oxyhemoglobin saturation (SPO2) ≤93% or oxygenation index (arterial oxygen tension/ inspired oxygen fraction, PaO2/ FiO2) ≤300 mmHg)	Patients lacking NT-proBNP results, Patients with stroke, acute myocardial infarction, malignant tumor, and pregnancy	54 participants	N-terminal pro-B-type natriuretic peptide (Nt-proBNP), High sensitive troponin I (Hs-TnI), Creatinine kinase-myocardial band (CKMB)	Myohaemoglobin, Urea, Creatinine, White blood cell count, Lymphocyte, CRP, Procalcitonin	Death, survived	N/a	NT-proBNP Area under the curve (AUC) for in-hospital mortality was 0.909 (95%CI 0.799–0.970, P < 0.001). using the cut-off 88.64 pg/mL	
Zhang et al	Wuhan No.1 Hospital, China	Retrospective Observational Study	Confirmed or Suspected COVID-19 inpatients admitted between 25th Dec 2019 and 15th Feb 2020, who underwent hs-cTni test within 48 hours after admission	Non COVID-19 Inpatients, did not undergo hs-cTnI within 48 hours after admission	48 patients	High sensitive troponin I (Hs-cTnI), Creatinine kinase-myocardial band (CKMB)	White blood cell count, Lymphocyte count, Neutrophil, Haemoglobin, Platelet, Thrombocyte Creatinine kinase, Aminotransferase (alanine, aspratate), Lactate dehydrogenase, serum creatinine, CRP, Fibrogen, d-dimer	Death, survived	Discharged, Transferred	Mortality: patients with elevated hs-cTnI 76.9% vs normal hs-cTnI 20% [p<0.001]	
Stefanini et al	Humanitas Clinical and Research Hospital (Rozzano-Milan, Lombardy, Italy)	Retrospective Observational Study	confirmed COVID-19 patients with available data on cardiac biomarkers	No exclusions were applied	397 patients	High-sensitivity troponin I (hs-TnI), B-type natriuretic peptide (BNP)	D-dimer, Fibrinogen, CRP, IL-6, Ferritin, Creatinine, White cell count, Neutrophils, Lymphocytes, Platelet baseline, Haemoglobin baseline, Procalcitonin, ALT, ALP, Total bilirubin baseline, PT ratio baseline, PTT ratio baseline, INR baseline	N/a	all-cause mortality	admission in intesive care unit (ICU), acute respiratory distress syndrome (ARDS) and shock	Mortality rate: elevated hs-TnI (22.5%, OR 4.35 [95% CI 1.72-11.04]) vs elevated BNP (33.9%, OR 7.37,

[95%CI 3.53 to 16.75]) vs both (55.6%, OR 18.75, [95%CI 9.32 to 37.71]) vs without elevated cardiac biomarkers (6.25%).

ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; ARDS, Acute Respiratory Distress Syndrome; CI, Confidence Interval; CKMB, Creatinine kinase-myocardial band; COVID-19, Coronavirus Disease 2019; CRP, C-Reactive Protein; hs-cTnI, high sensitivity cardiac troponin I; INR, International Normalized Ratio; ICU, Intensive Care Unit; IL, Interleukin; NT-proBNP, N-terminal pro brain natriuretic peptide; OR, Odds Ratio ; N/A, Not Applicable; PT, Ptothrombin Time; PTT, Partial prothrombin time; TnT, Troponin T.

Table 4. Critical Appraisal of the included studies using Prognosis Studies Questionnaire of Oxford CEEBM

	Criteria	Shi et al (2020)	Guo et al (2020)	Zhang et al (2020)	Zhou et al (2020)	Gao et al (2020)	Chen et al (2020)	Stefanini et al (2020)
Validity	**Was the defined representative sample of patients assembled at a common (usually early) point in the course of their disease**	Yes. Recruited participants were patients confirmed with COVID 19 according to WHO interim guidance and originated from Wuhan	Yes. Recruited participants were patients confirmed with COVID 19 according to WHO interim guidance and originated from Wuhan	Unclear. Recruited participants were patients suspected and confirmed with COVID 19 according to WHO interim guidance and originated from Wuhan. All patients who underwent hs-cTnI test within 48 hours after admission were included	Yes. Recruited participants were patients confirmed with COVID 19 according to WHO interim guidance and originated from Wuhan	Yes. Recruited participants were patients confirmed with COVID 19 according to WHO interim guidance and originated from Wuhan	Yes. Recruited participants were patients confirmed with COVID 19 according to Guidance for Corona Virus disease 2019 by the national health commission of China and originated from Wuhan	Yes. Yes. Recruited participants were patients confirmed with COVID 19 according to WHO interim guidance and originated from Italy
	Was patient follow-up sufficiently long and complete	Yes	Yes	Yes	Yes	No. biomarkers were only collected on a single test at admission	Yes	Yes
	Were outcome criteria either objective or applied in a 'blind' fashion?	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
	If subgroups with different prognoses are identified, did adjustment for important prognostic factors take place?	Yes. Age, comorbidities, creatinine levels and pro-BNP were taken account into the analysis	No	Yes. Age, Spo2, serum creatinine, and d-dimer value were taken account into the analysis	No	Yes. Sex, age, hypertension, coronary heart disease, myoglobin, CK-MB, troponin I, urea, creatinine, white blood cell, lymphocyte and procalcitonin is taken account into the analysis	No	Yes. Age, lymphocyte counts and D-dimer elevation were taken account into the analysis

Importance	**What were the results?**	Mortality rate was 51.2% among patients with cardiac injury.	Mortality rate was 59.6% among patients with cardiac injury.	Mortality rate was 76.9% among patients with cardiac injury.	Univariate OR of in-hospital death with elevation of hs-cTnI value 80.07	The AUC for in-hospital death was 0.909	Mortality rate was 72% and 85% in patients with increased troponin and Nt-proBNP concentrations consecutively	The AUC for all-cause mortality predictor is 0.938
	How precise are the prognostic estimates?	HR of death time from symptom onset was 4.26 [95% CI, 1.92-9.49] HR of death time from admission to study end point 3.41 [95% CI, 1.62-7.16]	Unclear (no CI was stated)	HR of death in elevation of hs-cTnI value 10.9 [95% CI, 1.28 -92.93]	95% CI, 10.34-620.36	95%CI, 0.79-0.97	Unclear (no CI was stated)	95%CI 1.06 to 9.93
Applicability	**Can I apply this valid, important evidence about prognosis to my patient?**	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Using a multivariable adjusted Cox proportional hazard regression model, Shi et al.[21] reported a hazard ratio of death of 3.4 in patients with cardiac injury (95% confidence interval [CI], 1.62–7.16). Zhang et al.[19] reported a hazard ratio of death among patients with high-sensitivity cardiac troponin I (hs-cTnI) elevation of 10.902 (95% CI, 1.279–92.927). Zhou et al.[14] calculated the odds ratio of death in COVID-19 patients with elevated hs-cTnI levels with a univariate regression analysis, and they reported a value of 80.07 (95% CI, 10.34–620.36).[19] Guo et al.[17] reported a higher mortality rate in patients with elevated serum troponin T levels (59.6%) than in those with normal levels (8.9%).

A single-center study conducted by Gao et al.[18] stated there is a significantly higher mortality rate in COVID-19 patients with high NT-proBNP compared with those with lower values (with a cut-off of 88.64 pg/ml); shown by the area under the curve (AUC) value of 0.909 (95% CI, 0.799–0.97) and hazard ratio of 1.373 (95% CI, 1.118–1.586, $p<0.001$) after adjusting for other risk factors (i.e sex, age, hypertension, coronary heart disease, myoglobin, CKMB, hs-TNI, urea and creatinine value. Both Chen et al.[15] and Stefanini et al.[16] reported higher concentrations of hs-cTnI (78% and 22.5%, respectively) and NT-proBNP markers (85% and 33.9%, respectively) in deceased patients compared with those who survived.

In deceased patients (85% and 33.9%, respectively) compared to those who survived.[15]

DISCUSSION

The World Health Organization (WHO) declared COVID-19 a global pandemic in early 2020.[2] This novel strain of coronavirus disease has various clinical manifestations: It can be asymptomatic in some people or result in a severe condition, with acute respiratory distress syndrome (ARDS) or other organ failures, in others.[3] Recent reports have shown evidence of myocardial injury involvement in COVID-19 patients, supported by the finding of elevated biomarkers, abnormal echocardiograph, and electrocardiograph in some hospitalized patients.[1-2,,6] Outcomes of patients with such conditions are often undesirable, and there is a high association with death.[1,6]

The finding of this study suggests that a higher risk of death can be found in COVID-19 patients with elevated cardiac biomarkers, consistent with previous reviews on the risk of mortality outcomes from COVID-19, especially for troponin I and BNP.[14,17,19-20.] Shi et al. reported a higher mortality rate in patients with higher levels of hs-cTnI (42/82) compared with those without such elevated levels (15/334).[11] This result was also in concordance with Zhang et al.'s finding, where the mortality rate was higher (up to 76.9%) among patients with hs-cTnI elevation compared with those without such biomarker elevation (20%).[20] Zhou et al. reported a similar finding of a higher chance of death in patients with elevated hs-cTnI levels, using a specific cut-off of 28 pg/ml.[14] This supports the hypothesis of myocardial injury involvement in COVID-19 related to SARS-CoV-2 structural S protein that binds to the ACE2 receptor of the myocardium, leading to possible cardiac injury and immune reactions throughout the body.

Hs-cTnI has mainly been used to determine troponin levels in many studies. Only Guo et al. used a slightly different biomarker component, TnT, to assess patients' troponin levels. Although this biomarker is less specific to define myocardial injury as a whole, other biomarkers of myocardial damage were also significantly elevated (CKMB, myoglobin, NT-proBNP), providing supporting evidence of myocardial injury in patients.[17] Moreover, this study showed similar results to other studies that used hs-cTnI, underlining that the elevation of any troponin increases patients' risk of death.

The complex mechanism of the clinical manifestation and limited information regarding disease progression indicate the need for other biomarkers to be considered when assessing patients' prognoses. Gao et al.[18] reported that procalcitonin and white blood cells also make a significant contribution to predicting in-hospital deaths. Stefanini et al.[15] and Chen et al.[16] reported that the values of Nt-proBNP and BNP were also shown to be increased in accordance with the elevation of troponin levels. This highlighted the essential need for further investigation of biomarkers' roles in myocardial

injury in COVID-19 patients and the associated prognoses, which should be conducted with better quality controls.

Only Gao et al.[18] included a bias control for the outcome analysis in the studies in this review, but an insufficient patient follow-up process was employed. All the other studies did not clearly state whether they were using blind assessment for the patients outcome or not. Blinding is crucial because unblinded investigators may search more aggressively for outcomes in people with known elevated cardiac biomarkers. Deciding on the underlying factors of mortality is a bit more complicated in patients with systematic diseases and requires blinding of the risk factors to ensure that it is unbiased. Moreover, Guo et al[17], Chen et al[15], Zhou et al[14] did not make any adjustment for other prognostic factors so it may pose a significant threat to the validity of the study.

Limitation the Study

The sources we used in this systematic review have potential bias and flaws due to the limited time and resources in this pandemic condition. Pre-prints articles were also used due to the as-yet limited information regarding COVID-19. However, the author only included studies with relevant information. Under current pandemic circumstances, we believe our study may be beneficial to the medical society and general public.

CONCLUSION

Although limited, there is evidence of higher mortality rate in COVID-19 patients with elevated troponin and NT-proBNP levels. Our findings highlight the importance of evaluating myocardial injury biomarkers, especially in terms of the early analysis of troponin and NT-proBNP levels. This may guide clinicians in considering the required preventive measures against further deterioration in patients' condition and avoiding fatal outcomes.

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