ASSOCIATION BETWEEN ELEVATED HIGH SENSITIVITY CARDIAC-TROPNON I LEVELS AND INCREASE IN LEVELS OF C-REACTIVE PROTEIN, INTERLEUKIN-6, D-DIMER, AND CONSEQUENT CARDIAC INJURY AND MORTALITY FOR PATIENTS WITH CORONAVIRUS DISEASE 2019: A META-ANALYSIS

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INTRODUCTION
Coronavirus disease 2019 (COVID-19) serious complications include respiratory failure or heart failure, stroke, dysfunction of other organs of body, and decease [1].

Following myocardial cell decay, unbound cytoplasmic troponin (Tn) is liberated from cardiac myocytes leading to elevation of Tn levels in blood [2].

Results found that C-reactive protein (C-RP) production in coronary smooth muscle cells was in reaction to inflammatory cytokines [3]. Interleukin-6 (IL-6) stimulates production of C-RP [4].

D-dimer (DD) is a soluble fibrin decaying output that comes from ordered collapse of thrombi by coagulative and fibrinolytic system [5]. Higher concentrations of circulating DD are existent in circumstances related to thrombosis [6].

METHODS
Search strategy
We suppose that we illustrated all required data sufficiently, please be accepted as it is. A systematic search was done by using "hs-cTnI" and "mortality" with each: "heart failure," "myocardial infarction," "myocarditis," "pericarditis," "cardiac injury," and "coronary artery disease."

Searched databases comprised PubMed-NCBI, PMC-NCBI, and Catholic University of America, university Libraries-Google Scholar.

The following original research articles were involved: Prospective observational, retrospective, retrospective observational, retrospective analysis, and case–control study.

The period of original research articles was from December 25, 2019 to April 20, 2020.

Criteria indicated for study selection
Studies met the following criteria were involved:
1. Studies mentioning characteristics of hospitalized COVID-19 affected individuals
2. COVID-19 affirmed by chest computed tomography scan, reverse transcriptase-polymerase chain reaction lab test, and hallmarks of illness
3. Cardiac injury was described as blood concentrations of cardiac biomarker cardiac troponin I (cTnI), elevated above 99th percentile upper reference limit
4. Studies documented higher high sensitivity-cardiac troponin I (hs-cTn I) concentrations, cardiac complications, and consequent deceases for COVID-19 hospitalized affected individuals
5. Altered biomarkers values of DD, C-RP, and IL-6 as a consequence of rise in hs-cTnI concentrations; measurement of these biomarkers was according to affirmed laboratory examinations.

The articles were excluded if they were: Meta-analysis, narrative reviews, reviews, review and meta-analysis, systemic reviews, editorial comment, case-based review, commentary, to the editor, editorial, letter to the editor, short communication, researches not dealing with COVID-19, case study, position statement complement, literature review, research article not in English, case presentation, and COVID-19 opinion.

Finally, the total number of uploaded articles with duplications was 557; the total number of articles met the criteria and with duplicated ones was 260; the number of duplicated articles that met the criteria was 174; the total number of original articles excluded after excluding duplications 109; the number of articles met the criteria after exclusion
of duplications was 86, and after all exclusions; and the total number of research articles enrolled in this meta-analysis was 11.

Statistical analysis
In all studies included in this meta-analysis; categorical variables were identified by frequency and percentages and continuous variables were mentioned as mean±standard deviation for normally distributed data and medians for non-normally distributed data. In addition, patient characteristic was compared using Chi-square tests or Fischer exact tests for categorical variables. Moreover, a two-sample t-test was used to assess whether there were significant differences in continuous variables when they were normally distributed. Further, univariate analysis was performed to describe significant variables correlated with cardiac injury and demise on hospital admission. Statistical analyses were considered significant if p<0.05.

Ethics considered
For all studies included in this meta-analysis oral consents of all patients were obtained. These studies were approved by Hospital Institutional Ethics Committee of each hospital enrolled in this meta-analysis. Written informed consent was waived due to rapid emergence of COVID-19 contagion.

RESULTS
Table 1 showed noticeable increase in number of death among COVID-19 affected patients and that males were more susceptible to be infected with this disease and more vulnerable to death in comparison with females.

Table 2 indicated that elderly COVID-19 affected individuals were significantly vulnerable to decease in comparison with other ages.

Table 3 revealed that hs-cTnI levels were considerably elevated among deceased COVID-19 contracted individuals compared to survivors.

Table 4 exhibited that hs-cTnI levels were considerably elevated among COVID-19 affected individuals experienced cardiac injury complications in comparison with those did not.

Tables 5-7 demonstrated noticeable increase in levels of C-RP, IL-6, and DD among deceased COVID-19 patients compared to survivors, respectively. Elevated levels of C-RP, IL-6, and DD were accompanied by noticeable elevation in levels of hs-cTnI in cases included in this meta-analysis.

DISCUSSION
Advantageous information propose high-rise predisposition of males to COVID-19 contagion in comparison with females [18]. A study, in Italy declared that COVID-19 decease average in males was 16.6% in males in comparison with 9.1% in females [19].

Elevated smoking percent is in male and it is correlated with COVID-19 seriousness [18]. Proofs presumed elevated hazard of contagion and retrieval of viral contagions in the upper respiratory tract among smokers in comparison with non-smokers [18]. Angiotensin-converting enzyme 2 (ACE2) is considered a principle regulatory component of renin angiotensin system (RAS) and participates noticeably in kidney, heart, and gastrointestinal tract physiology [18]. Smith et al. (2020) recognized change in ACE2 expression in different epithelial cells lining respiratory tract in reaction to tobacco [20]. Expression of ACE2 was noticed to be elevated in tobacco smoking persons in comparison with non-smokers [18]. Attachment of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) to ACE2 favors its entrance into host cells [18]. Therefore, upregulation of ACE2 effectiveness or expression may boost predisposition to SARS-CoV-2 contagion and seriousness of this illness [18].

Various literatures showed prevailing model of suppressed immune response in males attributed to existence of testosterone (T) hormone [18]. Activity of testosterone hormone results in decreased adaptive immune response attributing to suppressed action of associated type 2 T-helper cells and type 17 T-helper cells, and in consequence lowered antibody (Ab) responses and B cell propagation [18]. These circumstances attributed to decreased synthesis of efficient immunoglobulin G, in males as compared to females which might be predisposed to worst prediction [21].

Researches consider that noticeable populace of COVID-19 contracted persons complain cytokine storms [5] [18]. Proof describes that males are more susceptible for promoted synthesis of pro-inflammatory cytokines in comparison with females [22].

Table 1: Characteristics of patients in studies enrolled in this meta-analysis

| S. No. | Author | Place | Duration | Study type | Total patients’ number | Alive patients number | Dead patients number | Gender (%) |
|-------|--------|-------|----------|------------|------------------------|----------------------|---------------------|------------|
| 1.     | Heng et al. [7] | China | January 21, to April 18, 2020 | Prospective observational retrospective analysis | 51 | 39 | 12 (23.5%) | Male: 37 (72.50) |
| 2.     | Chen et al. [8] | Wuhan, China | December 25, 2019 to February 15, 2020 | Retrospective | 73 | 48 | 20 (27.40%) | Male: 42 (57.50) |
| 3.     | Zhang et al. [9] | Wuhan, China | January 25 to February 15, 2020 | Retrospective | 77 | 37 | 40 | Male: 50 (65.00) |
| 4.     | Lu et al. [10] | Wuhan, China | January 1 to February 23, 2020 | Retrospective | 671 | 609 | 62 | Male: 322 (48.00) |
| 5.     | Shi et al. [11] | Wuhan, China | February 7 to March 27, 2020 | Retrospective | 53 | 40 | 13 | NA |
| 6.     | Raad et al. [12] | South East Michigan, USA | March 9 to April 15, 2020 | Retrospective | 1020 | 840 | 180 | Female: 511 (50.00) |
| 7.     | Zhu et al. [13] | Wuhan, China | January 12 to February 28, 2020 | Retrospective analysis | 64 | 24 | 40 | Male: 36 |
| 8.     | Song et al. [14] | Wuhan, China | February 4 to March 3, 2020 | Retrospective observational analysis | 64 | 17 | 47 (73.40%) | Male: 42 (65.60) |
| 9.     | Pan et al. [15] | Wuhan, China | January 27 to March 19, 2020 | Case-control | 124 | 35 | 89 (71.80%) | Male: 85 (68.50) |
| 10.    | Barman et al. [16] | Istanbul, Turkey | March 20 to April 20, 2020 | Retrospective | 607 | 504 | 103 | Male: 334 |
Among COVID-19 contracted individuals, elderly ones have higher demise proportion due to raised case fatality rate and symptomatic contagion average [23]. It was found that about 80% and 90% of deceases happened in ill individuals aged more than 70 years and equal to or more than 60 years in Korea and Italy, respectively [23]. Age impacts time from hospitalization to decease and viral clearance [23]. In immuno-pathology, susceptibility to contagion in elderly persons is typically interpreted by immunosenescence [23]. In senility, production of naïve T and B cells lowers, and action of innate immune cells is declined; for this reason cells included in innate immunity do not get invigorated effectively during contagion, and development to adaptive immune response does not happen in regulated pattern [23]. These alterations decrease efficiency of viral clearance and elevate probability of provoking dysregulated immune response in a way that cytokines are released widely by activated immune cells, leading to CS [24]. Another recognizable characteristic of senile immunity is chronic subclinical systemic inflammation, also called inflammaging [23]. Inflammation is a basic pathogenic tool in COVID-19; thus, inflammaging has been predicted to contribute to worse result in elderly COVID-19 affected individuals [23]. In addition, mean measure of comorbid events steadily raise with age [23]. More than one-third of aged adults' raised decease hazard was mediated by bad lung function, hypertension, muscle weakness, and multiple long-term conditions (multiple LTCs) [25]. Among aged participants, these considerations were both more common and more potentially correlated with raised COVID-19 death percent [25].

Works by Huang et al. (2020) and Guo et al. (2020) not only described that recognizable number of hospitalized ill individuals identified with COVID-19 presented cardiac injury (exemplified by higher levels of cardiac biomarkers such as Tn), but that ones who progressed cardiac injury had noticeably raised death rate than those without [26,27].

Sick individuals with signals of cardiac injury were at raised hazard of demise both during period from symptom emergence and from admission to end point, assuming that associated biomarkers such as hs-cTn I may offer predictive information early on and throughout illness development [28]. Initial monitoring of cardiac injury-related biomarkers, involving hs-cTn I, may take part considerably in decreasing hazard of decease in grave circumstances [29]. Search articles shed light that cardiac deterioration happens with COVID-19-associated high Tn concentrations [30]. Tn I was regarded as primary considerable estimator of decease [30]. A valuable search article showed, in line with the previous literature, Tn concentrations were presented to be high-rise in aged sick persons and males [30]. A study conducted by Shi et al. (2020) recognized death rate was 51.2% in ill persons with elevated Tn concentrations and cardiac deterioration and 4.5% in ill ones without cardiac injury [31].

High-rise of Tn concentrations in COVID-19 affected individuals is interpreted by a number of potential mechanization [30]. These are first, viral myocarditis; second, cytokine-induced myocardial damage; third, microangiopathy; and fourth, unmasked coronary artery disease [30]. SARS-CoV-2 spike (S) glycoprotein attaches ACE2 receptors for entrance into target cell [30]. ACE2 is exceedingly found in pericytes of adult human hearts [30]. Further, for entrance target cell with ACE2, COVID-19 decreases return of angiotensin II (Ang II) to angiotensin 1-7 (Ang 1-7) by restraining ACE2 synthesis [30]. Ang 1-7 with ACE2, COVID-19 decreases return of angiotensin II (Ang II) to angiotensin 1-7 (Ang 1-7) by restraining ACE2 synthesis [30]. Ang 1-7 with ACE2, COVID-19 decreases return of Ang II to Ang 1-7 by restraining ACE2 synthesis [30]. Ang 1-7 generates protective cardiovascular (CV) influences in targeted organs of body [30]. In consequence, restrain of ACE2 synthesis and succeeding high-rise in Ang II concentrations may construct an impendence to heart and vessels in COVID-19 affected individuals [30]. Endothelial dysfunction, CSs, and Ang II upregulation can interpret usual incidence of coagulopathy in intense COVID-19 [30]. Oxidative stress, which is featured by raised production of reactive oxygen species and free radicals succeeded by lowered serum total antioxidant concentrations, can clarify usual incidence of coagulopathy in intense COVID-19 [30,32].

Yao et al. (2020) declared that ill individuals in male group and 60–79 years age groups incline to generate raised hs-cTn I levels than

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### Table 2: Distribution of COVID-19 patients' ages in enrolled studies according to alive versus death and cardiac injury versus non-cardiac injury

| S. No. | Author                           | Total No. | No. of Alive | No. of Dead | Age of Alive (Y) | Age of Dead (Y) | Age of Patients (Y) | Age of Patients with myocardial injury (Y) | Age of Patients with non-myocardial injury (Y) | p-value   |
|-------|---------------------------------|-----------|--------------|-------------|------------------|------------------|---------------------|---------------------------------------------|-----------------------------------------------|-----------|
| 1     | Zageer et al. [7]               | 51        | 39           | 12          | NA               | NA               | NA                  | NA                                          | NA                                             | <0.001    |
| 2     | et al. [8]                      | 48        | 37           | 12          | 67.6±13.3        | 60.9±12.5        | 60.9±13.3           | NA                                          | NA                                             | <0.001    |
| 3     | et al. [9]                      | 48        | 37           | 12          | 67.6±13.3        | 60.9±12.5        | 60.9±13.3           | NA                                          | NA                                             | <0.001    |
| 4     | et al. [10]                     | 77        | 61           | 16          | 65.9±13.3        | 60.9±12.5        | 60.9±13.3           | NA                                          | NA                                             | <0.001    |
| 5     | et al. [11]                     | 53        | 40           | 13          | 64 (61–73)       | 60 (58–70)       | 60.9±13.3           | NA                                          | NA                                             | <0.001    |
| 6     | et al. [12]                     | 64        | 47           | 17          | 69 (61–73)       | 60 (58–70)       | 60.9±13.3           | NA                                          | NA                                             | <0.001    |
| 7     | et al. [13]                     | 64        | 47           | 17          | 69 (61–73)       | 60 (58–70)       | 60.9±13.3           | NA                                          | NA                                             | <0.001    |
| 8     | et al. [14]                     | 64        | 47           | 17          | 69 (61–73)       | 60 (58–70)       | 60.9±13.3           | NA                                          | NA                                             | <0.001    |
| 9     | Pan et al. [15]                 | 124       | 99           | 25          | 66.6±14.3        | 60.9±13.3        | 60.9±13.3           | NA                                          | NA                                             | <0.001    |
| 10    | et al. [16]                     | 124       | 99           | 25          | 66.6±14.3        | 60.9±13.3        | 60.9±13.3           | NA                                          | NA                                             | <0.001    |
| 11    | et al. [17]                     | 124       | 99           | 25          | 66.6±14.3        | 60.9±13.3        | 60.9±13.3           | NA                                          | NA                                             | <0.001    |

S.: Sequence, No: Number, Y: Year, NA: None available, p-value: Probability value (p<0.05) were considered significant.
female and other age groups, which was in agreement with all raised percent of aged male deceased [5].

It was found that Tn concentrations were associated with concentrations of inflammatory biomarkers [33]. Plasma hs-Tn I concentrations were positively associated with plasma IL-6 concentrations, plasma high-sensitivity C-AP concentrations, plasma DD concentrations, and plasma brain natriuretic peptide concentrations [33]. It was demonstrated that for COVID-19 affected persons, in line with higher DD concentrations, high-rise Tn concentration, up to 36 pg/ml on hospital admission were prognostic of decease [33]. It was documented that higher lactate dehydrogenase (LDH), C-AP, and decreased lymphocytes counts were bound with raised death rates in infected persons with COVID-19 [34,35]. Higher values of cell death factors such as liver enzymes, LDH, DD, and Tn I refer to that COVID-19 CS is exemplified by pathological anomalies [36]. Besides pro-inflammatory action, IL-6 has anti-inflammatory characteristics and adjusts a number of features of immune system, involving hematopoiesis, aggregation of neutrophils, chemokines and their receptors [38]. Defensive action of IL-6 restricts the synthesis and secretion of adhesion components, and synthesis of heptapeptide [38]. The resulting decrease of ACE2 and high-rise in Ang II (Ang)II receptors’ induction [38]. A study revealed that mice contagion with SARS-CoV led to recognizably lowered ACE2 production in original articles recorded elevated concentrations of IL-6 in COVID-19 affected individuals: Viral contagion and angiotensin attributable causes can be presumed for elevated concentrations of IL-6 in COVID-19 cases [39]. There are two critical roles of cytokines from induced immune cells take part in antiviral immune response mechanism. Their raised and critical role in pathogenesis of a number of illnesses, involving viral contagions [38]. Many secreted cytokines from induced immune cells take part in antiviral immune response mechanism. Their raised and uncontrolled concentrations attribute to tissue injuries [38]. A number of original articles recorded elevated concentrations of IL-6 in COVID-19 contracted individuals with serious complications [39]. There are two attributable causes can be presumed for elevated concentrations of IL-6 in COVID-19 affected individuals: Viral contagion and angiotensin (Ang)II receptors’ induction [38]. A study revealed that mice contagion with SARS-CoV led to recognizably lowered ACE2 production in lungs [40]. ACE2 controls Ang II concentrations by converting it to heptapeptide [38]. The resulting decrease of ACE2 and high-rise in Ang II might drive IL-6 synthesis and release [38]. Much synthesis of IL-6 leads to pathological anomalies [38]. Besides pro-inflammatory action, IL-6 has anti-inflammatory characteristics and adjusts a number of features of immune system, involving hematopoiesis, aggregation of neutrophils, synthesis and secretion of adhesion components, and synthesis of chemokines and their receptors [38]. Defensive action of IL-6 restricts neutrophil recruitment and replacement of mononuclear cells [38]. Findings of this research clarified that neutrophil and monocyte counts had downward and upward slopes under 60 pg/ml of IL-6 while mechanism of neutrophil and monocyte changes reversed in COVID-19.

### Table 3: hs-cTnI levels in COVID-19 cases enrolled in the studies included in this meta-analysis distributed according to alive versus death

| S. No. | Author | Total cases No. | Reference or cut-off levels | hs-cTnI levels in total cases | Alive No. | hs-cTnI levels in alive | Dead No. | hs-cTnI levels in dead | p-value |
|-------|--------|----------------|----------------------------|-----------------------------|-----------|------------------------|---------|------------------------|--------|
| 1.    | Heng et al. [7] | 51 | NA | 0.07 ng/ml (0.02–0.23) ng/ml | 39 | 0.07 ng/ml (0.02–0.18) ng/ml | 12 | 0.20 ng/ml (0.03–0.54) ng/ml | 0.039 |
| 2.    | Chen et al. [8] | 73 | NA | 10.2 pg/ml (5.3–22.5) pg/ml | 53 | 7.2 pg/ml (5.0–15.2) pg/ml | 20 | 32.3 pg/ml (103–176.0) pg/ml | 0.000 |
| 3.    | Zhang et al. [9] | 48 | Upper reference limit: 0.026 ug/L | 31 | 0.006 ug/L | 17 | 0.034 ug/L | 0.001 |
| 4.    | Lu et al. [10] | 77 | Gut-off: ≤15.6 pg/ml | 13.0 pg/ml (3.4–11.3) pg/ml | 37 | 3.6 pg/ml (21–10.1) pg/ml | 40 | 41.5 pg/ml (121–308.6) pg/ml | <0.001 |
| 5.    | Shi et al. [11] | 671 | Normal reference: (0.0–0.04) ng/ml | 609 | 0.006 ng/ml (0.006–0.011) ng/ml | 62 | 0.235 ng/ml | <0.001 |
| 6.    | Zhang et al. [12] | 38 | NA | 2.10 pg/ml (1.90–4.45) pg/ml | 27 | 1.90 pg/ml (1.90–2.30) pg/ml | 11 | 19.45 pg/ml (12.55–98.67) pg/ml | 3.2X10⁻⁵ |
| 7.    | Zhu et al. [14] | 64 | NA | 24 | (0.02–0.03) ug/L | 40 | 0.03 ug/L | 0.007 |
| 8.    | Pan et al. [16] | 124 | <26.2 ug/L | 19.3 ug/L (8.4–96.4) ug/L | 35 | 9.9 ug/L (3.4–57.1) ug/L | 89 | 24.1 ug/L (9.8–155.8) ug/L | 0.006 |
| 9.    | Barman et al. [17] | 607 | Upper reference limit: 14 pg/ml | 504 | 10 pg/ml (5–15) pg/ml | 103 | 41 pg/ml (14–157) pg/ml | <0.001 |

*S.: Sequence, No.: Number, hs-cTn I: High sensitivity cardiac troponin I, NA: Non-available, ng/ml: Nanogram/milliliter, pg/ml: Pictogram/milliliter, ug/L: Microgram/liter, p-value: Probability value (p<0.05) were considered significant.*

### Table 4: hs-cTnI levels in cases with cardiac injury versus those with no cardiac injury in studies enrolled in this meta-analysis

| S. No. | Author | hs-cTnI levels in normal or cut-off levels | Total cases No. | No. of Cases with cardiac injury | hs-cTnI levels in cardiac injury cases | No. of cases with no cardiac injury | hs-cTnI levels in no-cardiac injury cases | p-value |
|-------|--------|-----------------------------------------|----------------|---------------------------------|-------------------------------------|-----------------------------------|----------------------------------------|--------|
| 1.    | Shi et al. [11] | Normal: 0–0.04 ng/ml | 671 | 106 | 0.159 ng/ml (0.075–0.695) ng/ml | 565 | 0.006 ng/ml (0.006–0.007) ng/ml | <0.001 |
| 2.    | Raad et al. [13] | Cut-off: ≤18 ng/L | 1020 | NA | 43 ng/L (27–87) ng/L | NA | 8.0 ng/L (2.3–14) ng/L | <0.001 |
| 3.    | Song et al. [15] | Normal: ≤34.2 ng/L | 64 | 34 | 276.1 ng/L (139.1–999.7) ng/L | 30 | 9 ng/L (4.7–18.9) ng/L | <0.001 |
| 4.    | Barman et al. [17] | Upper reference limit: 14 pg/ml | 607 | 150 | 97 pg/ml (42–300) pg/ml | 457 | 9 pg/ml (5–13) pg/ml | <0.001 |

*S.: Sequence, hs-cTn I: High sensitivity cardiac troponin I, No.: Number, ng/ml: Nanogram/milliliter, pg/ml: Pictogram/milliliter, p-value: Probability value (p<0.05) were considered significant.*
Table 5: High-sensitivity C-reactive protein levels for alive versus dead COVID-19 cases in the studies enrolled in this meta-analysis

| S. | Author          | Total No. of cases | C-RP levels in total cases       | Reference levels | Alive cases No. | C-RP Levels in alive cases | Dead cases No. | C-RP levels in dead | p-value |
|----|----------------|--------------------|----------------------------------|-----------------|----------------|--------------------------|----------------|---------------------|---------|
| 1. | Heng et al.    | 51                 | 66.26 mg/L (20.99–105.79) mg/L   | NA              | 39             | 42.67 mg/L (18.36–95.66) mg/L | 12             | 95.82 mg/L (74.92–114.95) mg/L | 0.024   |
| 2. | Chen et al.    | 73                 | 65.7 mg/L (28.7–134.5) mg/L      | NA              | 53             | 51.1 mg/L (20.4–86.3) mg/L   | 20             | 165 mg/L (90.2–220.8) mg/L | 0.000   |
| 3. | Zhang et al.   | 48                 | 4.32 mg/L (18.5–107.9) mg/L      | NA              | 31             | 23.8 mg/L (15.3–87.6) mg/L   | 17             | 65.5 mg/L (46.4–125.9) mg/L | 0.006   |
| 4. | Lu et al.      | 77                 | 7.25 mg/L (<1 mg/L)              | NA              | 37             | 52.1 mg/L (28.4–88.4) mg/L   | 40             | 120 mg/L (55.9–183.0) mg/L | <0.001  |
| 5. | Shi et al.     | 671                | 4.1 mg/L (12–81) mg/L            | NA              | 609            | 30 mg/L (8–59) mg/L          | 62             | 111 mg/L (<64–191) mg/L | <0.001  |
| 6. | Zhang et al.   | 53                 | 25.8 mg/L (7.23–57.73) mg/L      | NA              | 40             | 13.05 mg/L (4.70–47.68) mg/L | 13             | 58.40 mg/L (51.45–141.25) mg/L | 0.002   |
| 7. | Pan et al.     | 124                | 77.35 mg/L (43.13–111.94) mg/L   | (0.00–8.00) mg/L | 35             | 53.57 mg/L (30.28–78.56) mg/L | 89             | 85.8 mg/L | <0.001  |
| 8. | Barman et al.  | 607                | NA                               | NA              | 504            | 64 mg/dl (29–110) mg/dl      | 103            | 132 mg/dl (85–194) mg/dl |        |

S.: Sequence, No.: Number, C-RP: C-reactive protein, p-value: Probability value, (p<0.05) were considered significant, NA: Non-available, mg/L: Milligram/liter, ug/ml: Microgram/milliliter, p-value: Probability value, (p<0.05) were considered significant

Table 6: Interleukin-6 levels in alive versus dead COVID-19 cases measurements in studies enrolled in this meta-analysis

| S. | Author          | Cases total No. | Reference Levels | IL-6 levels in total cases | Alive No. | IL-6 levels in alive | Dead No. | IL-6 levels in dead | p-value |
|----|----------------|-----------------|-----------------|---------------------------|-----------|---------------------|----------|---------------------|---------|
| 1. | Heng et al.    | 51              | NA              | 39.81 pg/ml (10.0–674.38) pg/ml | 39        | 19.48 pg/ml (7.43–68.48) pg/ml | 12       | 1071.39 pg/ml (463.82–1820.50) pg/ml | <0.001  |
| 2. | Chen et al.    | 73              | NA              | 35.5 pg/ml (13.2–81.9) pg/ml | 53        | 27.2 pg/ml (12.6–62) pg/ml | 20       | 84.3 pg/ml (22.6–137.8) pg/ml | 0.011   |
| 3. | Zhang et al.   | 34              | NA              | 11.27 pg/ml (2.11–20.91) pg/ml | 27        | 9.50 pg/ml (1.79–18.09) pg/ml | 7        | 22.88 pg/ml (18.90–27.76) pg/ml | 0.117   |

S.: Sequence, No.: Number, NA: Non-available, IL-6: Interleukin-6, pg/ml: Pictogram/milliliter, p-value: Probability value, (p<0.05) were considered significant

Table 7: D-dimer levels for alive versus dead COVID-19 cases measurements in studies included in this meta-analysis

| S. | Author          | Patients total No. | Reference level | D-dimer levels in total patients | Alive No. | D-dimer levels in alive | Dead cases No. | D-dimer levels in dead | p-value |
|----|----------------|--------------------|-----------------|-----------------------------|-----------|------------------------|----------------|-----------------------|---------|
| 1. | Heng et al.    | 51                 | NA              | 2.44 mg/L (1.16–5.04) mg/L   | 39        | 2.01 mg/L (0.99–4.38) mg/L | 12             | 4.10 mg/L (2.20–10.95) mg/L | 0.024   |
| 2. | Chen et al.    | 73                 | NA              | 1.30 mg/L (0.88–6.32) ug/ml  | 53        | 1.13 mg/L (0.76–2.25) ug/ml | 20             | 9.68 ug/ml (1.82–21.0) ug/ml | 0.000   |
| 3. | Zhang et al.   | 48                 | NA              | 0.625 mg/L (0.325–2.035) mg/L | 31        | 0.565 mg/L (0.313–0.943) mg/L | 17             | 2.295 mg/L (0.413–17.05) mg/L | 0.025   |
| 4. | Lu et al.      | 77                 | <0.5 ug/ml      | 2.4 ug/ml (1.0–21.0) ug/ml   | 37        | 1.3 ug/ml (0.7–2.2) ug/ml | 40             | 18.2 ug/ml (3.0–21.0) ug/ml | <0.001  |
| 5. | Zhang et al.   | 51                 | NA              | 0.47 mg/L (0.36–1.09) ug/ml  | 40        | 0.44 mg/L (0.31–0.57) ug/ml | 11             | 2.42 ug/ml (1.55–5.59) ug/ml | 1.89X10−5 |
| 6. | Zhu et al.     | 64                 | NA              | 0.7 mg/L (0.4–2.0) mg/L      | 24        | 0.7 mg/L (0.4–2.0) mg/L | 40             | 2.0 mg/L (0.6–5.2) mg/L | NA      |
| 7. | Pan et al.     | 124                | <0.5 mg/L      | 3.06 mg/L (0.62–8.0) mg/L    | 35        | 1.12 mg/L (0.43–5.42) mg/L | 89             | 3.97 mg/L (0.78–8.0) mg/L | 0.010   |
| 8. | Barman et al.  | 607                | NA              | 67 ng/ml (34–358) ng/ml      | 504       | 67 ng/ml (34–358) ng/ml | 103            | 305 ng/ml (61.0–2950.0) ng/ml | <0.001  |

S.: Sequence, No.: Number, NA: Non-available, mg/L: Milligram/liter, ug/ml: Microgram/milliliter, p-value: Probability value, (p<0.05) were considered significant
infected persons with more than 60 pg/ml [ten-fold of normal range] of IL-6 [38]. Continuation of acute phase and neutrophil aggregation results in tissue deterioration [38]. Number of research articles proposed that lymphopenia and cytokine release syndrome (CRS) were combined with seriousness of illness; cytokine release syndrome (CRS) is systemic inflammatory response that can be provoked by different conditions, such as contangions, toxins, or idiosyncratic response to medication, and is exemplified by high-rise in concentrations of pro-inflammatory cytokines, involving IL-6 [41]. This known as CS may speedily result in single or multiple organ dysfunction syndromes (MODS) and is identified to specify not only acuteness but also predicting COVID-19 progression [41]. Elevated IL-6 concentrations were recognized among deceased cases from COVID-19 in comparison with survived cases [39].

Yao et al. (2020) administered that there was considerable association between atypical hs-cTn I levels and DD concentrations [5]. About half of affected individuals with COVID-19 have raised DD concentrations, which is correlated with illness gravity and elevated death averages [42]. Guo et al. (2020) reported that DD concentrations were considerably raised in group with elevated Tn concentrations than in group with normal Tn concentrations [27]. Huang et al. (2020) concentrated that imbalance of T helper 1 and T helper 2 immune responses in ill individuals with COVID-19 resulted in a CS and attributed to myocardial injury [30]. Cytokines, resulted from circulating systemic inflammation, generate type 1 myocardial infection (type 1 MI), causing thrombus formation, atherosclerotic plaque instability, and disruption [30]. Of interest, Guo et al. (2020) mentioned that no ill persons presented acute myocardial infarction (MI) findings at admittance to hospital [27]. Decrease levels of Ang 1-7 in consequence to ACE2 receptor downregulation resulted from COVID-19 elevates incidence of CSs, which can lead to intense inflammatory response associated with myocardial destruction and contagion [30]. In searches achieved by Shi et al. (2020) and Guo et al. (2020) and Lin et al. (2020), noticeable positive linear correlation was existent between plasma Tn and C-RP concentrations, assuming that myocardial destruction can be exceedingly correlated with inflammatory pathogenesis [27,31,43]. On the same, a notable study revealed that C-RP levels were noted to be elevated in high Tn lgroup [30]. In addition, Guo and Lin et al. declared that, in serious COVID-19 ill persons, ferritin, LDH, and DD values were elevated and lymphocyte counts were lowered in than cases without serious illness [31,43].

Biochemical markers take crucial role in precise diagnosis and also for estimating gravity and choosing therapy that boosts clinical outcome [44].

CONCLUSIONS
Male and elderly individuals with COVID-19 were more susceptible to poor outcomes and death than female and young individuals experienced COVID-19. hs-cTn I levels were significantly higher among COVID-19 individuals with cardiac injury compared with without cardiac injury ones. Higher hs-cTn I levels were accompanied by significant increase in levels of C-RP, IL-6, and DD among COVID-19 affected individuals. Death was significantly higher among patients with higher levels of hs-cTn I, C-RP, IL-6, and DD. hs-cTn I alone can be used as reliable biomarker in prognosis of COVID-19 and as predictor of death.

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