IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

ASSESSMENT OF MORTALITY RISK IN COVID19 PATIENTS: A SYSTEMATIC REVIEW

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ABSTRACT

Background

Coronavirus or COVID-19 is a highly infectious diseases which was first reported in Hubei province of Wuhan city, China and subsequently spread to other countries of world. There were limited studies available in the database on risk of mortality was not well summarized. Current review of observational studies was done to summarize the findings on the association between age, gender, comorbidities and laboratory investigations and risk of death from COVID-19 infection.

Methodology

PubMed, PubMed Central, EMBASE, MEDLINE were searched for the studies in English language and date specified to after 2020.

Results

In total, 10 studies were included in this review. A total of 1469 patients included in Non-survivor group, while 22675 patients were included in survivor group. In meta-analysis, significant associations were found between Age (p-value <0.0001), comorbidities like Diabetes (p-value <0.00001), Hypertension (p-value 0.05), Cardiovascular diseases (p-value <0.00001) and risk of death from COVID 19.

Additionally, it was also observed that those patients included in non-survivor had elevated levels of D-dimer (MD, -2.73, 95% CI, -5.73 to 0.28), CRP (MD, -66.10, 95% CI, -97.01 to -35.20), Interleukin-6 (MD, -4.70, 95% CI, -7.59 to -1.81), WBC count (MD, -3.88, 95% CI, -5.80 to -1.96) and decreased Albumin levels Albumin (MD, 3.98, 95% CI, 1.66 to 6.29) compared to survivor group.

Conclusion

Elder age more than 65 years, Hypertension, Diabetes, Cardiovascular diseases, elevated D-dimer, Interleukin-6, WBC count and CRP were mostly associated with mortality in patients with COVID-19.

Keywords

COVID-19, Mortality, D-dimer, Interleukin-6, CRP.

Introduction

In the year of 2019 late in the month of December there were maximum number of cases in the province of China resembling pneumonia but of unknown etiology characterized by Fever , dry cough , occasional gastro intestinal issues and fatigue which was spotted among highest number of people who visited the sea food wholesale wet market named “The Hunan Sea food Whole sale Market” which is located in the Wuhan city of China resulted in an emergence of an outbreak of an unknown cause which compelled the Government and authorities to take stringent action i.e.; Completely shutting down of the city where the outbreak originated. (1) Initially it was observed that 66% of Staffs from the market were characterized with the same symptom which resulted the onset of the outbreak.(2) After the declaration of an epidemiological notice by the health administration of the local Government, the market was forced to cease operating from January 1st, 2020. However, in afterwards of January thousands of people around China which includes many domains like Hubei, Guangdong, Zhejiang, Hunan, Henan etc. along with the main cities of china Shanghai and Beijing which was attacked by the rapidly wide spreading infection.(3) Moreover, the disease did not remain in the country’s boundary and took a plunge to other nations robustly, such as, Republic of Korea, Vietnam, United States, Germany, Thailand, Japan etc.

World Health Organization (WHO) confirmed a total confirmed case of 28276 with 565 deaths globally by the infection as of 6th February, 2020 which included no less than 25 countries becoming major Global Health concern.(4) As the disease had respiratory characteristics but no confirmed cause and source of the disease was known, the local centres from Disease Control and Prevention collected Blood, Stool and Respiratory samples from the infected persons then the samples were transferred to designated laboratory authority for pathogen detection.(5) 41 cases were confirmed from 59 suspected cases to be affected by the infective 2019-nCOV. The virus was detected by Real-Time Polymerase Chain Reaction (RT-PCR) or next generation sequencing methods.(5)

Investigating current data on COVID-19 pandemic, there were almost 213 countries affected. There were 14562550 confirmed cases and 607781 people died across the globe.(6) Among all affected countries, USA (United states of America) have highest number of cases (3748248 confirmed cases and 139964 deaths) compared to the other countries worldwide.(6) Looking forward to India, the first case was detected on 2nd March 2020 and first death was encountered on 22nd March 2020.(7) Initially, in India this outbreak slowly progressed, but at present there were 1194888 confirmed cases and 28771 deaths.(7) With this, India has now become second most affected country by coronavirus in the world. Initially, the case fatality rate was 11- 12%, but as of now it was decreased to 4.03%.(6)

COVID-19 has spread so wildly as there is no specific antiviral treatment available. Isolation and supportive treatment are available as per symptoms such as oxygen therapy, antibody treatment and fluid management respectively.(8) It was seen that some COVID-19 patients symptoms advanced to Acute Respiratory Distress Syndrome (ARDS), Sepsis advancing to shock further advancing to Multiple organ failure.(8) Currently neither any specific treatment nor any vaccines are available. Drugs are been continuously evaluated for therapeutic treatment and some combined medicines are also been given to COVID-19 patients but the efficacy and safety is yet to be demonstrated against the infection. But some remaining antiviral drugs are also been constantly evaluated in clinical trial against COVID-19.(8)

Initial laboratory investigations which included Complete Blood Count (CBC) , Liver Function Test (LFT), Renal Function Test (RFT) , coagulation profile , lactate dehydrogenase (LDH) and Serum electrolytes , creatine kinase were also done to identify the real cause of the disease along with Respiratory samples like Nasal and Pharyngeal swabs , aspirates from the bronchial cavity, bronchoalveolar lavage fluid were tested for common viruses to rule out the probable cause of the disease which includes avian influenza, Influenza, adenovirus, Para influenza virus, respiratory syncytial virus , SARS- CoV, MERS -CoV, using Real Time Polymerase Chain Reaction (RT-PCR) test which was approved by Food and Drug Administration (FDA) in China.(2) Routine examination was carried out for the presence of any Fungus and Bacteria in the System of Infected Persons.

There were limited studies available in the database on possible risk factors for mortality in patients infected with COVID-19. Moreover, there was seen much discrepancy of findings in between these limited studies. To conclude or find out the exact association of risk with mortality in patients with COVID-19 infection this review was planned.

Methods

Study protocol

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to plan, smooth conduction and reporting of this review and meta-analysis.

Search strategy

Studies were systematically searched on risk of mortality in patients with COVID-19, with English as language barrier and publication year restricted to 2020 only. Initially searched for the studies included all observational studies for this systematic review. Articles searched in the PubMed, PubMed central, MEDLINE, EMBASE, SCOPUS databases using following search string: (“novel coronavirus” OR “severe acute respiratory syndrome coronavirus 2” OR “SARS-CoV-2” OR “COVID-19” OR “2019-nCoV”) AND (“death” OR “mortality” OR “survival” OR “fatal outcome”) AND (COVID19 OR "Novel coronavirus" OR coronavirus) AND (observational OR cohort OR “case control” OR prospective OR Retrospective). In addition, to ensure comprehensiveness, articles were also examined from the reference list of all searched articles for any supplementary relevant study.

Eligibility criteria

In meta-analysis, eligible studies were included if those met the following inclusion criteria: (1) all studies assessed the association between age, gender, comorbidities, laboratory investigations and mortality risk from COVID-19 infection as the primary outcomes; (2) All observational studies whether it may be of retrospective or prospective study design; (3) those studies reported hazard ratios (HRs) or odds ratios (ORs) or relative risks (RRs) along with 95% confidence intervals (CIs) for association between risk factors and COVID-19 mortality; (4) All studies published in 2020 and English language. Review articles, expert opinion articles, abstracts, thesis, books and those were not in full text were excluded.

Data extraction and assessment for study quality

All required data for this meta-analysis were extracted from the included studies like study design, the first author’s name, the publication year, age and gender of included patients, total sample size, exposure (risk factors), outcome (the risk of mortality), Methods of assessment the association of exposure with outcome, risk estimate (HRs, ORs, RRs) with 95% confidence intervals.

For assessment of publication bias, Newcastle–Ottawa Scale (NOS)(9) was used. This method was used for assessing the quality of all included observational studies based on following three major components: selection, comparability, and outcome. Selection refers to how the study population is selected and its representativeness of the actual population (maximum, 4 points). Comparability refers to how well the exposed and unexposed cohorts can be compared, based on the design or analysis (maximum, 2 points). Outcome refers to the quality of the assessment of the outcome (maximum, 3 points). The total score is the sum of the scores assigned to each category. If the articles had NOS score ≥5, then that were considered as high-quality publications.**SUPLIMENTARY TABLE 1**

Study selection

From databases total 643 articles were jotted down. After reviewing the title and abstract of all the articles, 31 articles were excluded due to non-availability of full text, 93 articles were excluded as the study was conducted before 2020, 11 articles were excluded because it was not in English, Furthermore, 470 were excluded because they were not observational studies, 25 were excluded as mortality was not mentioned, further, 2 were excluded because of non-adherence to eligibility criteria, and finally 1 article was excluded as the study did not include risk of mortality. So total of 633 articles were excluded, and 10 studies were taken into consideration for this review.(10,11,20,12–19) The flow diagram of the systematic literature review is depicted in flow diagram. **Figure 1**

Study Characteristics

The studies included in our meta-analysis comprised all observational studies. All studies included risk of mortality in patients infected with COVID-19. All studies were published in 2020 and in English language. **SUPLIMENTARY TABLE 2**

Statistical analysis

In this review and meta-analysis, HRs, ORs, and RRs (and their 95% confidence intervals) were used for finding the association between risk factors and mortality from COVID-19 infection. Then, the overall effect size for mortality in relation to risk factors was calculated using fixed-effects model. For examining the between-study heterogeneity, we performed the Cochran's Q test ($I^2 \geq 50\%$ were considered between-study heterogeneity). To identify potential sources of heterogeneity, we did separate analysis according to the predefined criteria as follows: age, gender (male vs. female), hypertension (Survivor vs. Non-survivor), diabetes (Survivor vs. Non-survivor), COPD (Survivor vs. Non-survivor), CVDs (Survivor vs. Non-survivor), Laboratory investigation (White blood cells, Albumin, C-reactive protein, D-dimer, Interleukin-6). In addition to the main analysis, we carried out sensitivity analysis to find if the overall estimate depended on the effect size from a single study. Assessing the publication bias was done by forest plot. All studies were statistically analyzed using Review Manager (RevMan version 5.3, The Cochrane collaboration, 2014). *p*-values were considered significant at level of <0.05.

Results

There were observed significant association of Age, comorbidities (like Diabetes, Hypertension and Cardiovascular diseases), Laboratory investigations (WBC count, Albumin, D-dimer and Interleukin-6) with mortality in patients infected with COVID-19 or coronavirus.

Meta-analysis

Our meta-analysis comprised total of 10 studies. In the pooled analysis, the association of age was seen significant difference in non-survivor group compared to survivor group with an adjusted pooled mean difference of -8.19 (95% CI, -9.43 to -6.95, p value – <0.00001). Considerable substantial heterogeneity was observed (I^2= 69%) among the included studies. It was observed that mean age in all included studies were higher in the non-survivor group compared to survivor group. **Figure 2**

Likewise, Gender was also found no significant association with mortality in patients infected with COVID-19. In pooled analysis, there were 15687 males and 8340 females, among them 5649 males and 727 females were died. But this association was not statistically significant (OR – 1.04, 95% CI, 0.93 – 1.16, p-value – 0.49). **Figure 2**

Moving on to the Comorbidities, a significant association is seen between Diabetes and mortality due to COVID-19 with OR - 3.49 (95% CI, 3.12 - 3.91, p-value - <0.00001). A considerable substantial heterogeneity is also observed with I^2 = 98%. **Figure 3**

This pooled analysis showed that most of the patients died were also diabetic. Moreover, it was also observed that cardiovascular disease is an important risk factor of mortality in patients due to COVID-19. In the pooled analysis a statistical significance was also observed (OR – 3.76, 95% CI, 3.44-4.10, p-value - < 0.00001). **Figure 3**

A statistical significance was also observed for hypertension (OR – 1.15, 95%CI, 1.00 – 1.34, p-value – 0.05) with considered substantial heterogeneity I^2 = 96%. **Figure 3**

However, respiratory disease had no significant association with mortality (OR – 0.83, 95% CI, 0.63-1.08, p-value – 0.17) and marked considered heterogeneity (I^2 = 90%). **Figure 3**

Additionally, we have considered WBC count, Albumin, CRP, D-dimer and Interleukin-6 for pool analysis, which yielded significant association with mortality except D-dimer with p value <0.00001, 0.00008, <0.00001, 0.08 and 0.001 respectively. In pooled analysis, it was observed that those COVID-19 patients died were having higher value of WBC count (MD, -3.88, 95% CI, -5.80 to -1.96), Albumin (MD, 3.98, 95% CI, 1.66 to 6.29), CRP (MD, -66.10, 95% CI, -97.01 to -35.20), D-dimer (MD, -2.73, 95% CI, -5.73 to 0.28) and Interleukin-6 (MD, -4.70, 95% CI, -7.59 to -1.81) compared to the survivor group.**Figure 4**

Discussion

There were limited studies available in database on assessment of risk associated with mortality in patients infected with COVID-19 or Novel coronavirus. I have included all observational studies for the meta-analysis. Journal of Korean Medical science (JKMS)(13) published an article considered analysis of 54 patients died in coronavirus infection in Korea, observed from January 19 to March 10, 2020. They have found that average age at death was 75.5 years. They have also found that among 54 patients, most of them were men (61.1%) and Hypertension followed by heart diseases were associated with mortality. But this study has drawbacks like, this study was having sample size very less, so it could not be generalized.

Du et al(12) published a prospective cohort study to analyze the most possible predictors of mortality in patients infected with COVID-19. They have included 179 patients, of them 21 died. The patients in non-survivor group were much older than patients in survivor group (70.2 ± 7.7 years in non-survivor vs. 56.0 ± 13.5 years in survivor, p-value < 0.001). They have also noted more patients in non-survivor group had Hypertension followed by cardiovascular diseases with p value 0.005 and <0.001 respectively.

Wu et al(18) did a retrospective cohort study on associated risk factors with mortality in patients with coronavirus infection. They have included 201 patients, of them 84 developed acute respiratory syndromes (ARDS). Among 84 ARDS patients, 44 were died. Further, they have analyzed demographic and clinical details of each died patients. On analysis, they have found that those patients died with ARDS were older in comparison to non-ARDS group (mean difference, 12.0 years; 95% CI, 8.0-16.0 years; p-value < 0.001). Apart from that, they have also observed that among the patients died with ARDS, maximum of them were having significant elevation of coagulation profile like D-dimer (difference, 2.10 µg/mL; 95% CI, 0.89- 5.27 µg/mL; p-value 0.001) and inflammatory related indicator like Interleukin-6 (difference, 3.88 pg/mL; 95% CI, 2.20-6.13 pg/mL; p-value < 0.001).

Mandeep et al(14) did an observational data base analysis from 169 hospitals in Asia, Europe and North

America. They had taken 8910 patients, of them 515 (5.8%) died and 8395 patients survived. They observed that most of the non-survivors were older (difference, −7.1, 95% CI, −8.4 to −5.7) and most of them were male. They also had reported higher prevalence of Coronary artery disease (difference, −9.2, 95% CI, −12.8 to −5.7) followed by Diabetes (difference, −4.8, 95% CI, −8.3 to −1.3) and COPD (difference, −3.9, 95% CI, −6.1 to −1.8).

Zhang et al(19) published an article in 2020. They had taken 663 COVID-19 patients for analysis, of them 25 patients died. They had observed same as Mandeep et al(14), that most of the non-survivors were having age more than 60 years (Median age, 69.3 years; Interquartile range (IQR), 61-78). Additionally, they analyzed that those patients died, they had increased WBC count (p-value < 0.001), increased CRP (p-value, 0.014), decreased Albumin (p-value, 0.005) compared to survivor group.

Tu et al(16) did a study of 25 fatal cases of COVID-19 in Wuhan, china observed the average age was 70 years, which was much higher than survivors (70 years in non-survivor vs. 51 years in survivor). They were disproportionately male (19 [76%] in non-survivor vs 60 [40.3] survivor, p-value <0.001) and most of them were suffered from Cardiovascular diseases (32% in non-survivor vs. 7.4% in survivor, p-value <0.001) compared to survivors. They also observed the serum level of Interleukin-6 (100% in non-survivor vs 77.2% in survivor, p-value 0.017), D-dimer (96% in non-survivor vs 59.7% in survivor, p-value <0.001), and CRP (100% in non-survivor vs 63.8% in survivor, p-value <0.001) were higher in all fatal cases.

Chen et al(11) conducted a retrospective cohort study on 1590 hospitalized patients infected with COVID-19 throughout China. They had used multivariate cox regression which showed that age more than 75 years (Hazard ratio (HR), 7.86; 95% CI, 2.44- 25.35), coronary heart disease (Hazard ratio, 4.28; 95% CI, 1.14-16.13), Procalcitonin > 0.5ng/ml (Hazard ratio, 8.72; 95% CI, 3.42-22.28) were independent risk factors associated with mortality. On admission, they had observed those were died due to COVID-19 had elevated levels of CRP (100%), D-dimer (87.2%), Lactate dehydrogenase (91.4%).

Another study published by Wang et al(17) in 2020, enrolled 296 patients with COVID-19 infection in training cohort, 22 (7.28%) of them were died. On analysis, observed that the mean age of non-survivor group had remarkably greater than that of survivor group (46.0 ± 14.4 vs 65.6 ± 12.6, p-value <0.001). Medical history showed that the non-survivor group had higher proportion of comorbidities like Hypertension (33 [11.9%] vs 9 [47.4%], p-value <0.001), Diabetes (24 [8.7%] vs 6 [31.6%], p-value 0.001). In training cohort, they had observed elevated WBC count (4.7[3.4 – 6.4] vs 7.8 [4.7 – 11.9], p-value <0.001), CRP level (11.4 [2.2 – 27.9] vs 88.6 [59.7 - 118], p-value <0.001), D-dimer (0.2 [0.1 – 0.3] vs 0.5 [0.4 – 1.4], p-value <0.001) than survivor group. But there was no significant association of gender disproportion with mortality.

Zhou et al(20) did retrospective cohort study among 191 patients infected with coronavirus, of them 54 were died. Among those, most had a comorbidity, Hypertension (26 [48%] vs 32 23%, p-value 0·0008) most common followed by Diabetes (17 [31%] vs 19 [14%], p-value 0·0051) and coronary heart disease (13 [24%] vs 2 [1%], p-value <0·0001). In non-survivor group most of them had elevated D-dimer level and older (69.0 [63.0–76.0] vs 52.0 [45.0–58.0], p-value <0.0001) in comparison to survivor group. Further, these finding were also supported by a study conducted on patients infected with coronavirus in New York city by Richardson et al(15) in 2020, observed 282 (24.5%) patients died. Of them who died, most of them were older (> 65 years) and having Diabetes. Those patients had history of Hypertension on admission, were more requiring on Invasive mechanical ventilation than non-hypertensive patients.

Summarizing risk of mortality in patients with COVID-19 The risk included demographic and clinicolaboratory details of mortality in patients infected with COVID-19 were examined. Meta-analysis comprises of all observational studies. It was observed that most of the studies were mentioned those patients were died with COVID-19 were older than the survivor group.(11–20) But there was no clear evidence yielded about which gender was mostly associated with mortality, only few studies mentioned the differences.(13,14,16) Looking into associated comorbidities Hypertension was mostly associated with mortality followed by Diabetes and cardiovascular diseases. Likewise, D-dimer, Interleukin-6, CRP levels in blood were elevated in the non-survivor group, whereas albumin level in blood decreased compared to survivor group.

Limitations

The result of this meta-analysis could not be generalized due to a smaller number of studies available in the databases.

Conclusion

Age more than 65 years, Hypertension, Diabetes and Cardiovascular diseases were associated with higher risk of death from COVID-19 infection. Additionally, it was also concluded that those patients were died in COVID-19 had elevated level of CRP, D-dimer, Interleukin-6 and decreased Albumin level. This demographic and clinicolaboratory risk factors will help physicians to find out high risk population groups that should receive medical care as soon as possible.

Ethical Approval and Consent to participate

Ethical approval was taken from Institutional Ethics Committee before starting of the study.

Consent for Publication

Not applicable

Availability of supporting data

Not applicable

Competing of interest

Authors declare to have no competing of interest.

Funding

Not applicable

Authors' contributions

Dr. E. Shantanu Kumar Patra, Dr. Shakti Bedanta Mishra and Dr. Pratap Jena had full access to all of the data in the study and taken responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: S.B.M, S.K.P
Acquisition, analysis, or interpretation of data: All Authors
Drafting of the manuscript: S.K.P, Alice
Critical revision of the manuscript for important intellectual content: S.B.M, P.J
Statistical analysis: S.K.P
Study supervision: S.B.M, S.K.P, P.J

Acknowledgement

We would like to be thankful Dr. Subhra Mallisha, all staffs of department of Critical Care Medicine, IMS and SUM Hospital, Bhubaneswar and KIIT school of public Health, BBSR for contributing in this study.

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Figure 1. PRISMA flow Diagram

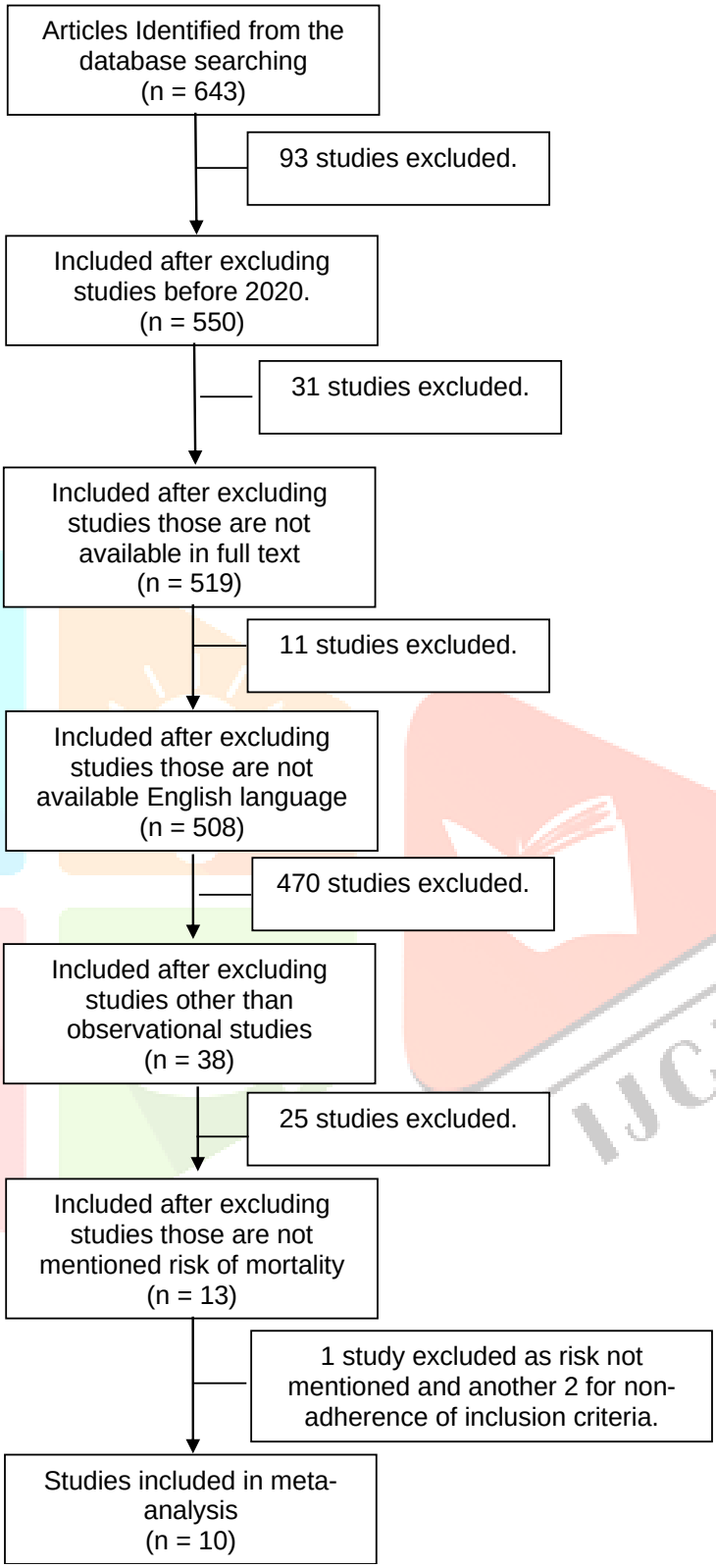
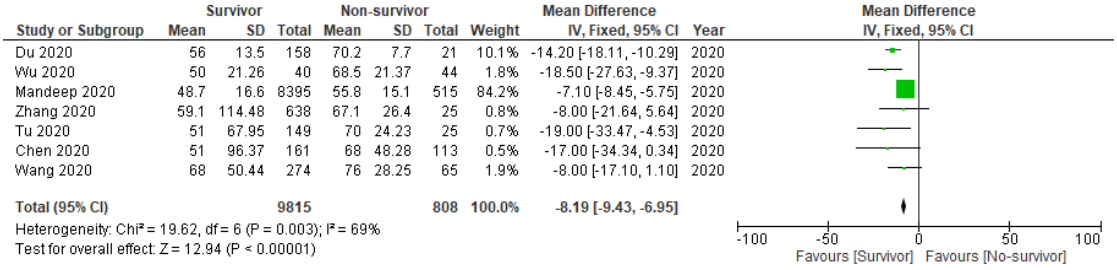


Figure 2. Association of demographics with mortality

(a) Association of Age with mortality



(b) Association of gender with mortality

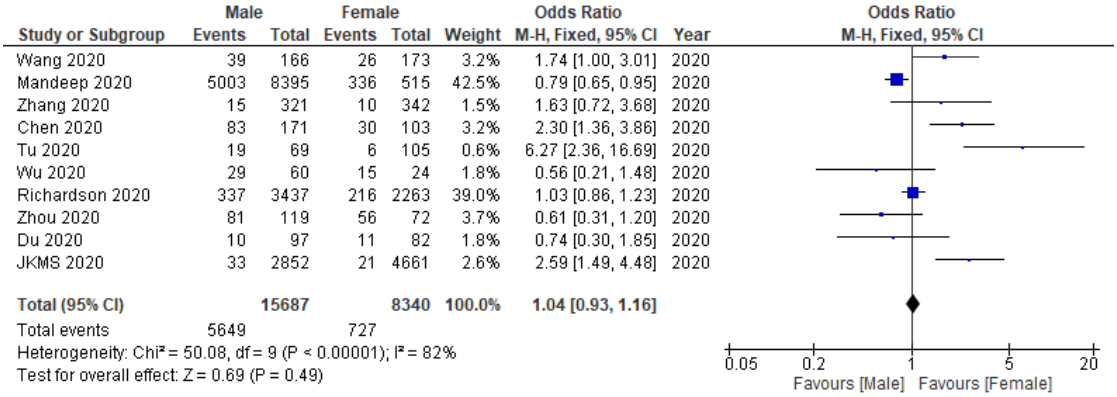
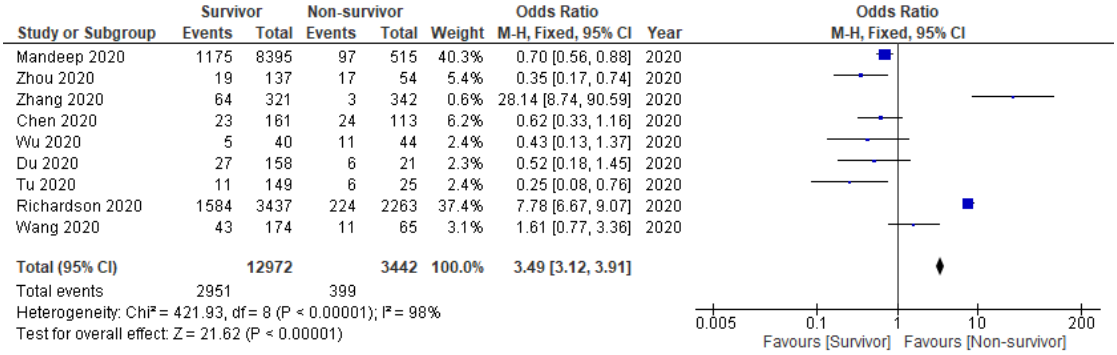
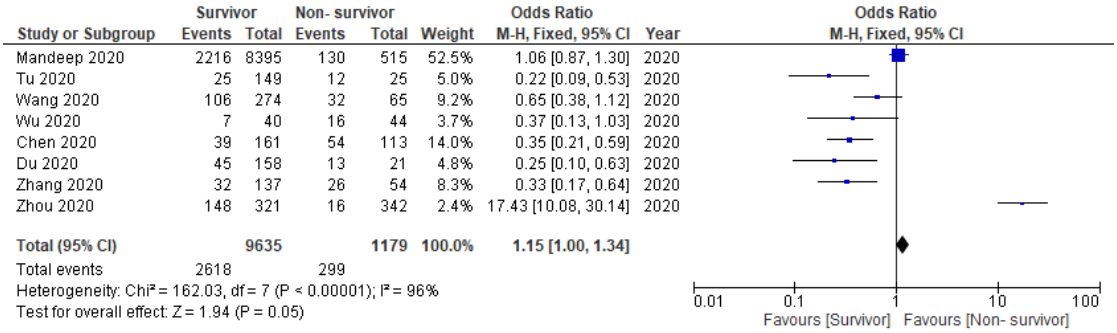


Figure 3. Association of comorbidities with mortality.

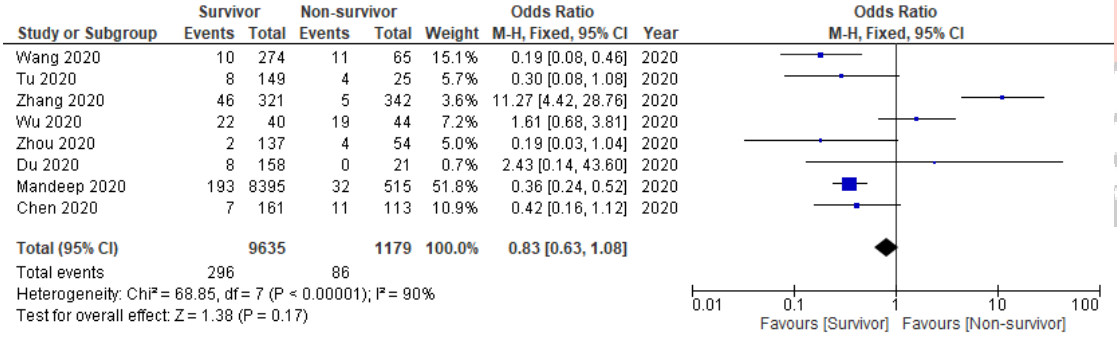
(a) Diabetes



(b) Hypertension



(c) Respiratory diseases



(d) Cardiovascular disease

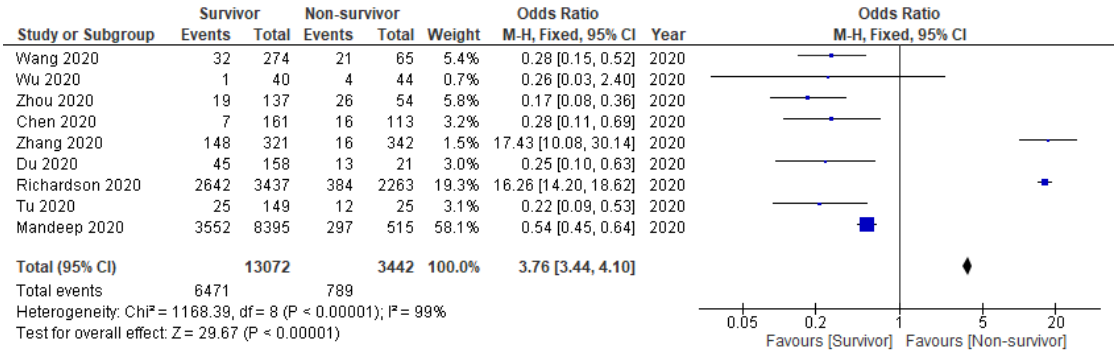
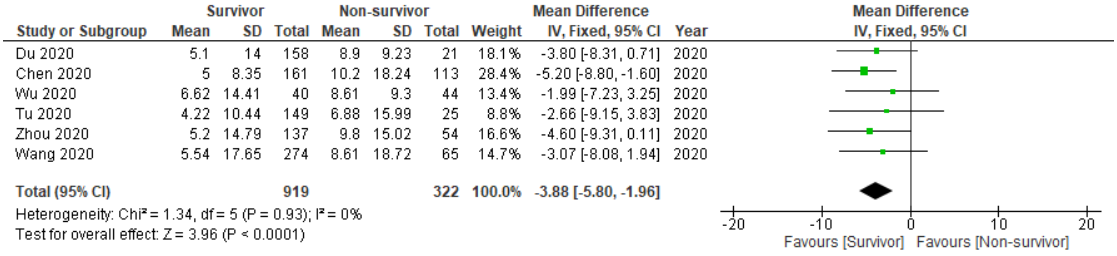
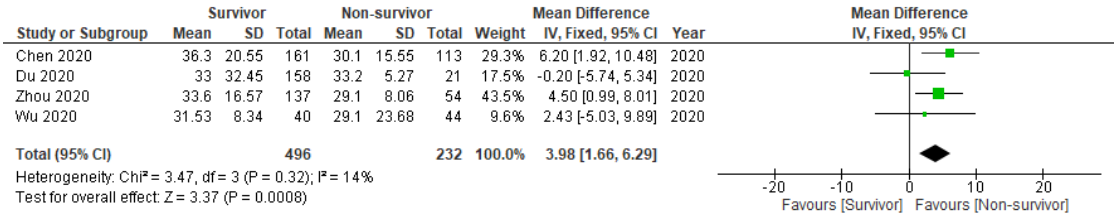


Figure 4. Association of Laboratory parameters with mortality

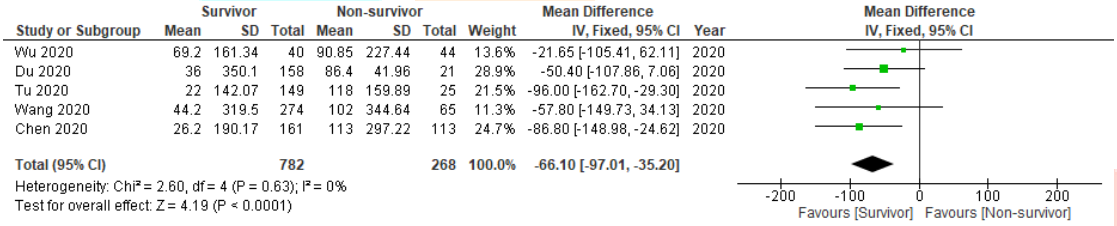
(a) WBC count



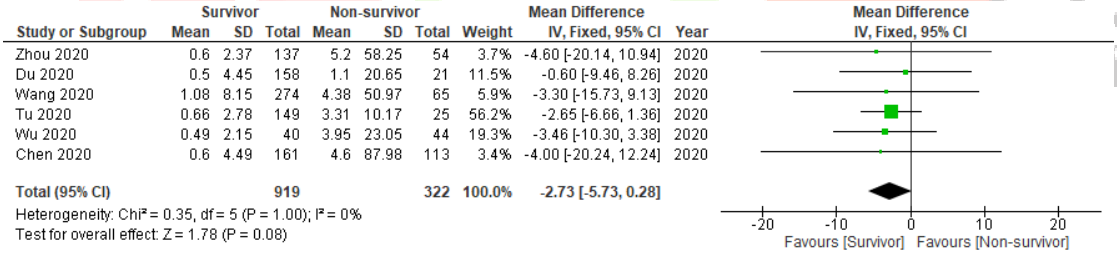
(b) Albumin



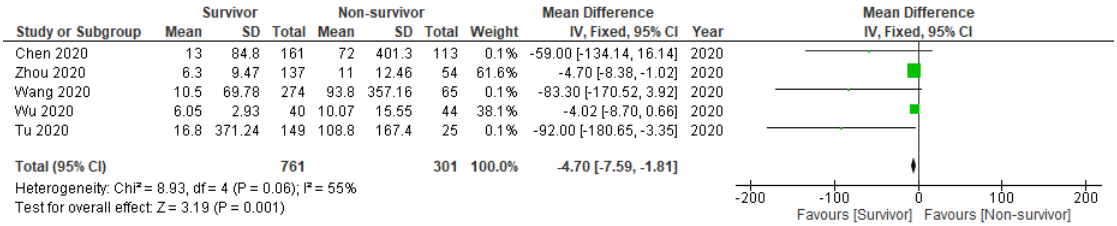
(c) CRP



(d) D-dimer



(e) Interleukin-6



SUPLIMENTARY TABLE 1. Newcastle - Ottawa Scale (NOS)

Study	Subject selection Max 4	Study Comparability Max 2	Assessment of Outcomes Max 3	Total Score
JKMS 2020	2	1	2	5
DU 2020	2	2	3	7
Chen 2020	2	2	3	7
Mandeep 2020	2	2	2	6
Richardson 2020	2	1	3	6
Wang 2020	3	2	3	8
Wu 2020	3	2	3	8
Tu 2020	2	2	2	6
Zhou 2020	3	2	3	8
Zhang 2020	3	1	2	6

[i] The Newcastle-Ottawa scale is a measure of study quality of cohort studies, in which a score is assigned to each of three categories: selection, comparability, and outcome. Selection refers to how the study population is selected and its representativeness of the actual population (maximum, 4 points). Comparability refers to how well the exposed and unexposed cohorts can be compared, based on the design or analysis (maximum, 2 points). Outcome refers to the quality of the assessment of the outcome (maximum, 3 points). The total score is the sum of the scores assigned to each category.

SUPLIMENTARY TABLE 2. Study Characteristics

Authors	Year	Study design	Country	sample size	Deaths
JKMS et al	2020	Retrospective	Korea	7513	54
DU et al	2020	Prospective	China	179	21
Chen et al	2020	Retrospective	China	274	113
Mandeep et al	2020	Retrospective	Asia Europe North America	8910	515
Richardson et al	2020	Retrospective	New York	5700	553
Wang et al	2020	Retrospective	China	339	65
Wu et al	2020	Retrospective	China	201	44
Tu et al	2020	Retrospective	China	174	25
Zhou et al	2020	Retrospective	China	191	54
Zhang et al	2020	Retrospective	China	663	25