A Study Of D-Dimer And Its Corelation With Severity Of Covid-19 Infection In A Tertiary Care Hospital In South Gujrat

[1]Dr. Krimal Patel, [2]Dr. Deepak Shukla, [3]Dr. Rakesh Raval, [4]Dr. Dhaval korat,[5]Dr. Chintan Patel
[1]Third year Resident Doctor, [2]Professor, [3]Assistant Professor, [4]Senior Resident,
[5]Second Year Resident Doctor,
Department of General Medicine,
SMIMER, Surat.

*Corresponding Author:
Dr. Krimal Patel
Third Year Resident Doctor, Department of General Medicine, SMIMER, Surat.

Type of Publication: Original Research Paper
Conflicts of Interest: Nil

Abstract
Keywords: NIL

Introduction

On 31 December 2019, WHO was informed of cases of pneumonia of unknown cause in Wuhan City, China. A novel coronavirus was identified as the cause by Chinese authorities on 7 January 2020 and was temporarily named "2019- nCoV". Coronaviruses (CoV) are a large family of viruses that cause illness ranging from the common cold to more severe a new strain that has not been previously identified in diseases. A novel coronavirus (nCoV) is humans. The new virus was subsequently named the "Severe Acute Respiratory Syndrome Coronavirus 2 (SARS–CoV-2)". On the 31st of January 2020, the WHO announced that COVID-19 was labeled as Public Health Emergency of International Concern (PHEIC).[1]

On 11 March 2020, the rapid increase in the number of cases outside China led WHO Director- General Dr Tedros Adhanom Ghebreyesus to announce that the outbreak could be characterized as a pandemic. By then more than 118 000 cases had been reported in 114 countries, and 4291 deaths had been recorded.By mid-March 2020, the WHO European Region had become the epicentre of the epidemic, reporting over 40% of globally confirmed cases. As of 28 April 2020, 63% of global mortality from the virus was from the Region.[1]

Based on the current epidemiological survey, most individuals had a history of close contact to a patient who had 2019-nCoV infection or a history of travel from Wuhan City or Hubei province, China. The incubation period is generally 3–7 days (within 14 days).[2-4]

Plasma D-dimer is a hypercoagulabilty and fibrinolytic system marker, which is formed when factor XIIIa (a cross-linked fibrin) is degraded by plasmin. It is increased in various solid tumour patients including breast cancer. D-Dimer is the only test that directly tells about both thrombin and plasmin generation i.e.generation of thrombin resulting in a cross-linked fibrin clot and of plasmin resulting in the lysis of cross-linked fibrin clot. Extracellular remodeling of fibrin is essential for angiogenesis in tumors, and activation of intravascular fibrin formation and degradation has been shown to occur in the plasma of breast cancer patients.[5]

D-dimer is widely used as a biomarker for thrombotic disorders. A D-dimer value less than 0.5 µg/mL is usually considered normal, and values increase with increasing age and in pregnancy. The level of D-dimer rises with increased severity of community-acquired pneumonia. Following the outbreak sof the COVID-19 pandemic, D-dimer has been identified as a potential indicator for its prognosis in COVID-19 patients.

171

Admission day D-dimer has shown promise for predicting the disease severity in multiple studies.[6]

Accurate and widely available prognostic biomarkers can be very useful in the management of COVID-19. This multi-center study aims to assess elevation in D-dimer at the time of admission as a possible prognostic indicator of mortality in COVID-19 patients. The cutoff value used for D-dimer shows significant variation between the published studies, and there seems to be no consensus yet on what the best cutoff value is to predict severity or mortality.[6]

Hence; under the light of above-mentioned data, the present study was undertaken for assessing the D-Dimer levels and their correlation of severity of COVID infection in a tertiary care hospital in south Gujarat.

Aims & Objectives: To determine correlation of D – dimer level with severity and outcome in COVID-19 infection.

Methodology: A prospective observational study was conducted among 112 patients who were infected with COVID-19 infection and admitted at Department of General Medicine, SMIMER, Surat.

Sample size calculated by considering the proportion of raised D-dimer among COVID-19 patients who 9.

were positive by RDT/RTPCR/HRCT(CORADS 5 or 6) and got admitted at department of medicine is 20% by data record during study period.P=proportion of raised D-dimer among COVID-19 positive patients= 20% Q= 1-P,L=allowable error=6%,Z = level of significance =95% n = z2α/2 p q/ l = 110

Inclusion Criteria:

1. Patients who have admitted in covid ward/ICU in tertiary care hospital of south Gujarat,
2. Patients' diagnosis of Covid-19 infection confirmed either by RDT or RTPCR or HRCT (CORADS 5 or 6)

Exclusion Criteria:

Patients' having elevated D-dimer level due to any causes other than covid-19 like:

1. Pathological
2. Heart failure,
3. Malignancy,
4. Atrial fibrillation,
5. Eclampsia,
6. Sickle cell disease, Trauma,
7. Thrombolytic use,
8. Upper GI bleed.

Results:

Table 1: Age-wise distribution of the patients

Age group (years)	Number of patients	Percentage
Less than 30	3	2.72
30 to 40	8	7.27
41 to 50	12	10.91
51 to 60	35	31.82
More than 60	52	47.27
Total	110	100
Mean ± SD	59.95 ± 13.08	

Total 31.82 percent of the patients belonged to the age group of 51 to 60 years while 47.27 percent of the patients belonged to the age group of more than 60 years. Around 10.91 percent patients were in the age group of 41-50 years and 7.27% were between 30-40 years. Rest of the patients were younger than 30 years. Mean age of the patients was 59.95 years. [table 1]

Graph 1: Gender-wise distribution of the patients
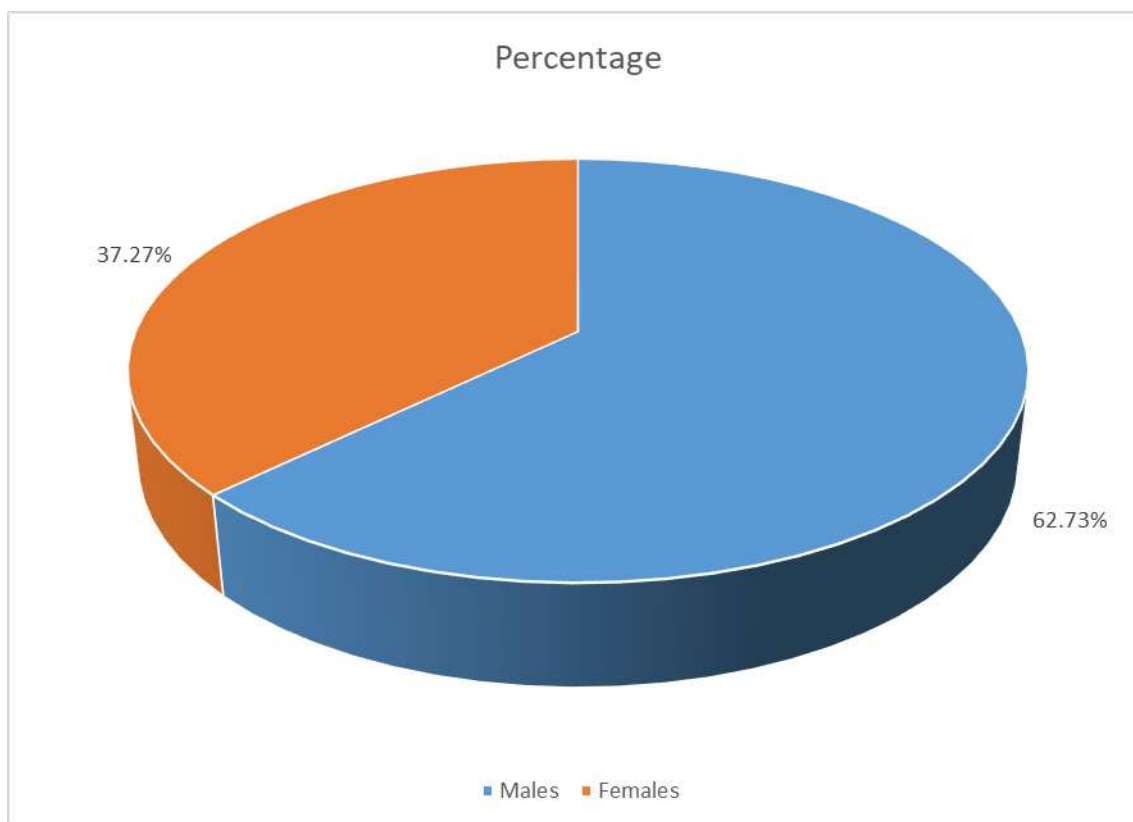
In the present study, 62.73 percent of the patients were male while the remaining were female.[Graph 1]

Table 2: Clinical symptoms of the study group

Clinical profile	Number of patients	Percentage
Fever	96	87.27
Cough	64	58.18
Breathlessness	23	20.91
Headache	8	7.27
Confusion	1	0.91
Diarrhea	1	0.91
Body ache	5	4.55
Malaise	6	5.45

Fever, cough and breathlessness were seen in 87.27 percent, 58.18 percent and 20.91 percent of the patients respectively. Headache, confusion, diarrhea, body ache and malaise were seen in 7.27 percent, 0.91 percent, 0.91 percent, 4.55 percent and 5.45 percent of the patients respectively.[Table 2]

**Graph 2: Disease severity of the study group**
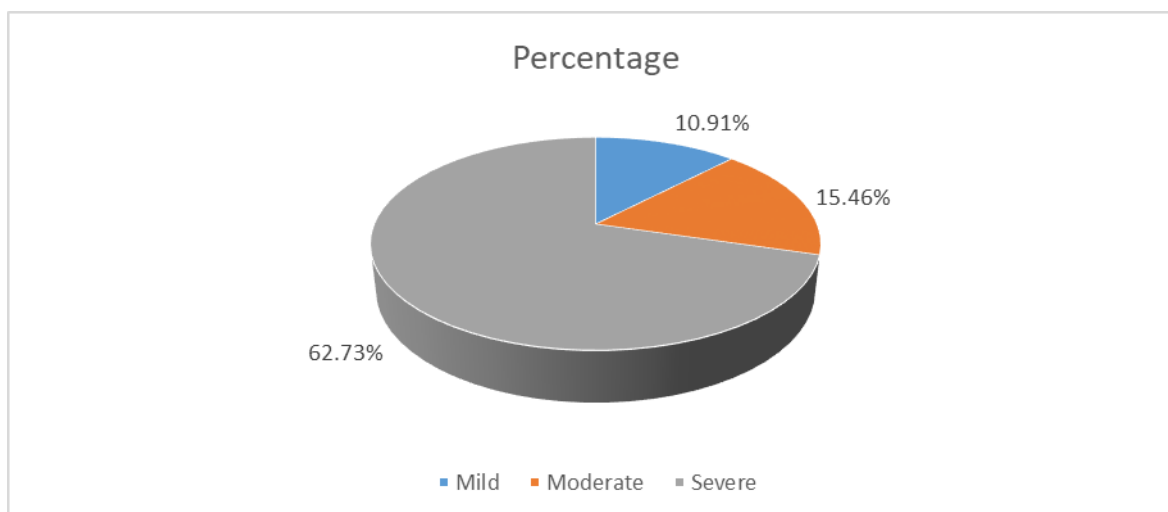
62.73 percent of the patients were affected by severe type of COVID while 10.91 percent and 15.46 percent of the patients were affected by mild and moderate type of COVID. [Graph 2]

Table 3: Disease outcome of the study group

Disease outcome	Number of patients	Percentage
DAMA	3	2.73
Expired	95	86.36
Survived	12	10.91
Total	110	100

While assessing the outcome, mortality was seen in 86.36 percent of the patients while DAMA was seen in 2.73 percent of the patients. 10.91 percent of the patients were discharged. [table 3]

Graph 3: Distribution of D-Dimer Levels in the study group
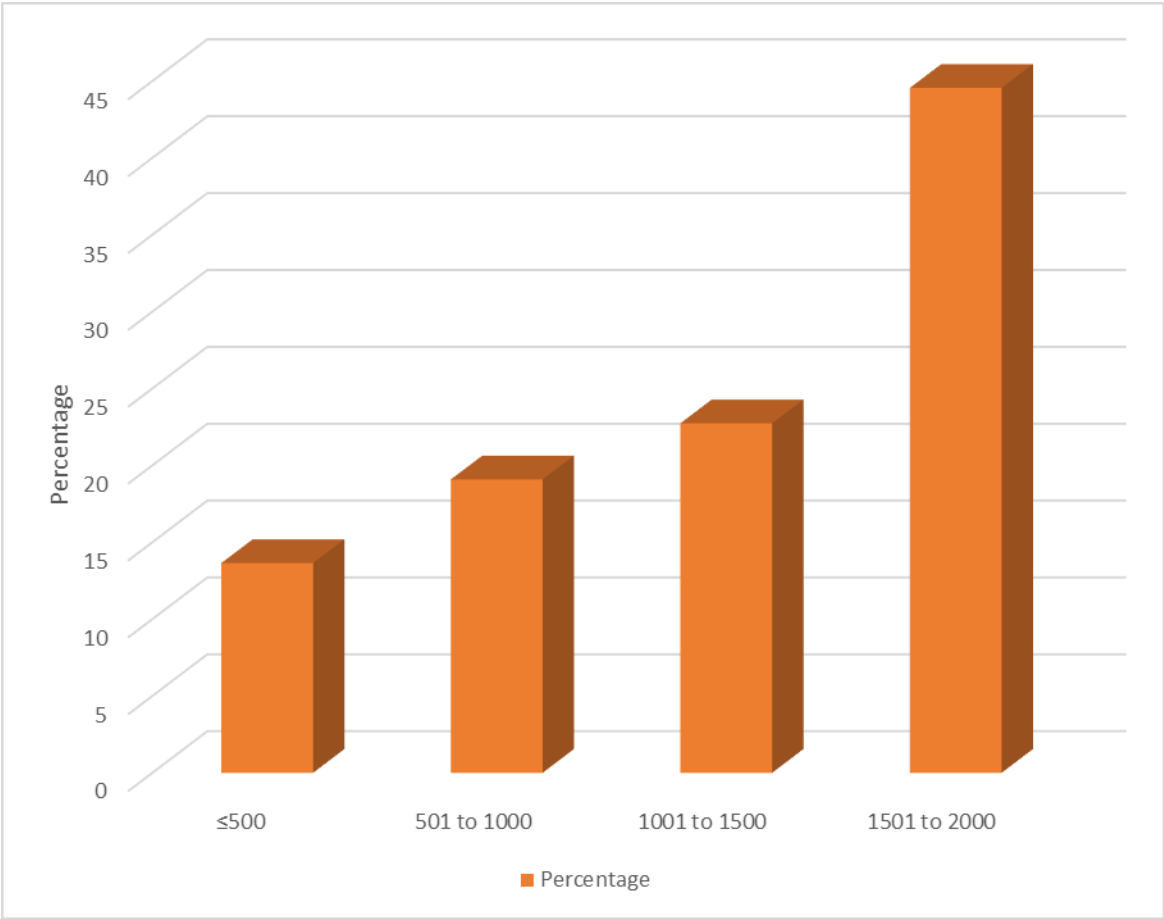
Mean D-Dimer levels were found to be 2104.76 ng/mL. In 44.55 percent of the patients, the D-Dimer levels were between 1501 to 2000 ng/mL. in 22.73 percent and 19.08 percent of the patients, D-Dimer levels were between 1001 to 1500 ng/mL and 501 to 1000 ng/mL respectively. In the remaining 13.64 percent of the patients, the D-Dimer levels were ≤500 ng/mL. [Graph 3]

Table 4: Correlation of disease severity with D-Dimer levels

Disease Severity	Mean	SD	p- value
Mild	1112.48	846.31	0.00014 (Significant)
Moderate	1912.37	1128.48	
Severe	2642.16	1486.22	

Mean D-Dimer levels among patients with mild, moderate and severe COVID was found to be 1112.48 ng/mL, 1912.37 ng/mL and 2642.16 ng/mL respectively. Significantly higher D-Dimer levels were found to be associated with patients with higher severity of COVID infection. [table 4]

Table 5: Correlation of disease outcome with D-Dimer levels

Disease outcome	Mean	SD	p- value
Expired	2744.47	1549.81	0.001 (Significant)

Survived	1046.52	813.52	

Mean D-Dimer levels among patients who expired and survived was found to be 2744.47 ng/mL and 1046.52 ng/mL respectively. Significantly higher D-Dimer levels were found to be associated with patients with mortality. [table 5]

Discussion: The present study was the single center study with study population of 110 whose severity of covid-19 patients correlated with their D dimer levels. We also tried to find out correlation between age, gender, comorbidities, clinical profile, biochemical profile, inflammatory markers (Il-6, procalcitonin) of study the population with severity and outcome of covid 19 disease.

Mean age of the patients was 59.95 years. Our results were in concordance with the results obtained by previous authors who also reported similar findings. In the study conducted by Yu HH et al, mean age of the patients was 62 years.[7] Lehmann A et al, in another study reported the mean age of the patients to be 48.9 years.[8] Poudel et al, in another study reported the mean age of the patients to be 58.16 years.[9] This suggests that most of the critically sick patients were older in age which may be because of decrease immunity or presence of comorbidities.

Around 62.73 percent of the patients were males while the remaining were females. Our results were in concordance with the results obtained by previous authors who also reported similar findings. In other studies, conducted by Saeed GA et al and Wu J et al, 85.3 percent and 52 percent of the subjects respectively were males.[10,11] Poudel et al, in another study reported that 62.1 percent of the patients were males.[9] Males were affected more than females because of higher expression of angiotensin-converting enzyme-2 (ACE 2; receptors for coronavirus) in male than female, sex-based immunological differences driven by sex hormone and X chromosome.

Fever, cough and breathlessness were seen in 87.27 percent, 58.18 percent and 20.91 percent of the patients respectively. Headache, confusion, diarrhea, body ache and malaise were seen in 7.27 percent, 0.91 percent, 0.91 percent, 4.55 percent and 5.45 percent of the patients respectively. Our results were in concordance with the results obtained by previous authors who also reported similar findings. In a similar study conducted by Hefeda MM et al, fever, cough,

breathlessness, sore throat, GIT symptoms and muscle pain was seen in 88.1 percent, 84.06 percent, 45.27 percent, 38.46 percent, 15.05 percent and 57.36 percent of the patients respectively.[12]

Total 62.73 percent of the patients were affected by severe type of COVID while 15.46 percent and 10.91 percent of the patients were affected by moderate and mild type of COVID-19 disease. In a study conducted by Banga V et al, Out of total 60 patients, 33 (55 percent) were in mild, 23 (38.33 percent) in moderate and 4 (6.67 percent) were in severe category.[13] In a study conducted by Saeed GA et al, mild, moderate and severe COVID-19 severity scoring was seen in 36.5 percent, 34.3 percent and 6.8 percent of the patients respectively.[10] In the present study only admitted patients were included at the peak of the covid pandemic, that may be the reason for such a large number (62.73%) of critically sick patients.

Mean D-Dimer levels among patients with mild, moderate and severe COVID was found to be 1112.48 ng/mL, 1912.37 ng/mL and 2642.16 ng/mL respectively. Significantly higher D-Dimer levels were found to be associated with patients with higher severity of COVID infection. In a similar study conducted by Berger JS et al, patients with elevated presenting baseline D-dimer were more likely than those with normal D-dimer to have critical illness (43.9% versus 18.5%; adjusted odds ratio, 2.4 [95% CI, 1.9–3.1]; P<0.001).[14]

In a similar study conducted by Banga V et al, in mild cases D Dimer varied from 43 ng/ml to 183 ng/ml with mean 97.4. In moderate cases D Dimer varied from 270 ng/ml to 991 ng/ml with mean 641.1. In severe cases D Dimer varied from 1043 ng/ml to 2463 ng/ml with mean 1609.5.[13] Abnormalities in D-dimer in patients with COVID-19 is associated with an increased risk of critical illness and death. A meta-analysis of 18 studies with 3682 patients noted a higher D-dimer in patients with severe versus non-severe infection. In a subgroup of 4 studies that reported critical illness (n=1218) and death (n=795), there was a 2-fold and 4-fold higher risk with of

critical illness and death, respectively, among patients with D-dimer <500 versus ≥500 ng/mL. In one study of 191 patients from Wuhan, China with 54 deaths, Zhou et al found that D-dimer >1000 ng/mL at baseline was associated with an 18-fold increased risk of mortality after multivariable adjustment.[15, 16]

Conclusion: D-dimer levels were independently associated with a higher risk of critical illness and all-cause mortality among patients with COVID-19. The present study provides additional support that COVID-19 is a coagulopathic condition with D-dimer representing a direct link between COVID-19 infection and adverse outcomes.Hence; it helps in identifying the high-risk group and providing early management to prevent mortality. Thus, D dimer can be used as an essential biomarker in developing the management protocol for COVID 19 patients.

References:

1. WHO. https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/novel-coronavirus-2019-ncov. [online] [accessed on 19/06/2020]

2. National Health Commission of the People's Republic of China. Diagnosis and treatment of new coronavirus pneumonia (version 5) http://www.nhc.gov.cn/. Accessed 30 Jan 2020.

3. Chan Jasper FW, Yuan SF, Kok KH, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. 2020 doi: 10.1016/s0140-6736(20)30154-9.

4. Memish ZA, Al-Tawfiq JA, Makhdoom HQ, et al. Respiratory tract samples, viral load, and genome fraction yield in patients with Middle East respiratory syndrome. J Infect Dis. 2014;210:1590–1594.

5. Valapala VNG, Dasari N, Kolli VK, Mandapaka M. Clinical and biochemical profile of COVID-19 patients admitted in a tertiary care hospital in Visakhapatnam, India during post unlock 2.0 - a retrospective study. J Med Life. 2022 Feb;15(2):264-268.

6. Olivia MPAY, Erawati S, Hutagalung MHP. Analysis factor - factor transmission covid-19. Journal Ilmiah Pannmed. 2021; 16(1): 143- 149

7. Yu HH, Qin C, Chen M, Wang W, Tian DS. D-dimer level is associated with the severity of COVID-19. Thromb Res. 2020 Nov;195:219-225.

8. Lehmann A, Prosch H, Zehetmayer S, Gysan MR, Bernitzky D, Vonbank K, Idzko M, Gompelmann D. Impact of persistent D-dimer elevation following recovery from COVID-19. PLoS One. 2021 Oct 28;16(10):e0258351

9. Poudel A, Poudel Y, Adhikari A, Aryal BB, Dangol D, Bajracharya T, Maharjan A, Gautam R. D-dimer as a biomarker for assessment of COVID-19 prognosis: D-dimer levels on admission and its role in predicting disease outcome in hospitalized patients with COVID-19. Plos one. 2021 Aug 26;16(8):e0256744

10. Saeed GA, Gaba W, Shah A, Helali AAA, Raidullah E, Al Ali AB, Elghazali M. Correlation between Chest CT Severity Scores and the Clinical Parameters of Adult Patients with COVID-19 Pneumonia. Radiology Research and Practice. 2021; 6697677.

11. Wu J, Wu X, Zeng W, Guo D, Fang Z, Chen L, Huang H. Chest CT Findings in Patients With Coronavirus Disease 2019 and Its Relationship With Clinical Features. Investigative Radiology. 2020; 55(5): 257- 261

12. Hefeda MM, Elsharawy DE, Dawoud TM. Correlation between the initial CT chest findings and short-term prognosis in Egyptian patients with COVID-19 pneumonia. Egypt J Radiol Nucl Med. 2022; 53:9

13. Banga V, Jain S. D-Dimer–Prognostic indicator for disease severity in patients hospitalised with COVID19. Indian Journal of Pathology and Oncology 2021;8(4):461- 464.

14. Berger JS, Kunichoff D, Adhikari S, Ahuja T, Amoroso N, Aphinyanaphongs Y, Cao M, Goldenberg R, Hindenburg A, Horowitz J, Parnia S, Petrilli C, Reynolds H, Simon E, Slater J, Yaghi S, Yuriditsky E, Hochman J, Horwitz LI. Prevalence and Outcomes of D-Dimer Elevation in Hospitalized Patients With COVID-19. Arterioscler Thromb Vasc Biol. 2020 Oct;40(10):2539-2547

15. Shah S, Shah K, Patel SB, Patel FS, Osman M, Velagapudi P, Turagam MK, Lakkireddy D, Garg

J. Elevated D-Dimer Levels Are Associated With Increased Risk of Mortality in Coronavirus Disease 2019: A Systematic Review and Meta-Analysis. Cardiol Rev. 2020 Nov/Dec;28(6):295-302.

16. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 395:1054–62.