Should laboratory markers be used for early prediction of severe and possibly fatal COVID-19?

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This rapid review summarizes the available evidence on laboratory markers for early prediction of severe and possibly fatal COVID-19. This may change as new evidence emerges.

KEY FINDINGS

Several laboratory tests are found to be associated with disease severity and mortality in COVID-19, and may be used to prognosticate patients and guide management.

- Around 20% of COVID-19 patients develop severe illness that may require intensive care and lead to fatal complications. (1)This necessitates prioritization of patients requiring urgent medical care before disease progression.
- Certain laboratory markers (biomarkers) may reflect the processes involved in the clinical deterioration of infected patients. Hence, their use in the identification of patients at high risk of progression to severe disease or death has been investigated.
- Current available evidence shows that the following laboratory abnormalities in a person with COVID-19, especially when found early during hospitalization, are associated with severe or critical disease or mortality:
    1. Markers of organ dysfunction
        a. Reduced oxygen saturation
        b. Elevated lactic dehydrogenase (LDH)
        c. Elevated blood urea nitrogen (BUN) or serum creatinine
        d. Elevated cardiac troponin (cTnI)
        e. Elevated direct bilirubin, elevated aspartate transaminase (AST), reduced serum albumin
        f. High radiographic score or CT severity score, or consolidation on CT scan
    2. Marker of abnormal coagulation – D-dimer, protime
    3. Markers of immune dysfunction
        a. Elevated IL-6
        b. Elevated C-reactive protein (CRP)
        c. Elevated leukocytes or neutrophils
        d. Reduced lymphocyte percentage
        e. Reduced $CD4^+$ T lymphocytes, $CD3^+CD8^+$ lymphocytes
    4. Secondary bacterial infection – Elevated procalcitonin
- Proposed prediction models utilizing these markers, however, need further validation before they can be recommended for routine clinical use.

RESULTS

As of April 1, 2020, 17 articles fulfilled the inclusion criteria. A meta-analysis on the association of IL-6 with acute respiratory distress syndrome did not study other prognostic factors but this was the largest study on IL-6 and we decided to include it. (2) The rest were retrospective cohorts published in February or March of this year. One cohort study was from Japan (3) and the rest were from China. The sample size of the cohort studies ranged from 78 to 701. The systematic review and meta-analysis included 6 studies that enrolled 1302 patients.

Seven additional studies were found and included in the updates of this rapid review. **(See Appendix 1, Literature Search)**

The cohorts included hospitalized adults with moderate to critical COVID-19. Most studies included demographic and clinical characteristics and laboratory results in their analysis. The outcome of interest was death in 13 studies (4–16) identification of severe or critical disease on admission in five (3,6,17–19), disease progression in four (14,20–22), a composite of death or disease progression in two (23,24), or unimprovement in one (25). **(See Appendix 2, Characteristics of Included Studies)**

Guide questions from Painless Evidence-Based Medicine were used to critically appraise the included studies.(26) Some studies had high or unclear risk of bias with regards to the objective definition of outcome (admission to the intensive care unit) (22) and incomplete follow-up (observation period too short and some patients had not yet developed the outcomes under study on the date of assessment) (14,21–24). Most studies lacked internal validation of the identified risk factors; all the studies had no or insufficient external validation.

Studies included both adult male and female patients of Asian race who were symptomatic and required hospital admission. This selection bias results in larger representation of patients with moderate to critical disease. Some of the studies enrolled patients from the same hospitals during the same period of time, and it is possible that data from the same patients may have been used in more than one study. **(See Appendix 3, Critical Appraisal of Included Studies)**

CONCLUSION

Several laboratory tests were found to be associated with severe COVID-19, and these may be used to prognosticate and guide management. Limitations of current available evidence include small sample sizes, the absence of laboratory cut-off points for reference and inclusion of only severe cases in some studies, and the lack of validation of proposed predictive models.

Declaration of Conflict of Interest

No conflict of interest

REFERENCES

1. Jin Y, Yang H, Ji Wangquan, Wu Weidong, Chen S, Zhang W, Guangcai D. Virology, Epidemiology, Pathogenesis, and Control of COVID-19. Viruses. 2020;12(372):1–17.
2. Coomes E, Haghbayan H. Interleukin-6 in COVID-19: a systematic review and meta-analysis. Vol. 2842. 2020.
3. Tabata S, Imai K, Kawano S, Ikeda M, Kodama T, Miyoshi K, et al. Non-severe vs severe symptomatic

COVID-19: 104 cases from the outbreak on the cruise ship “Diamond Princess” in Japan. medRxiv [Internet]. 2020;2020.03.18.20038125. Available from: https://www.medrxiv.org/content/10.1101/2020.03.18.20038125v1

4. Tan L, Kang X, Ji X, Wang Q, Li Y, Wang Q, et al. Validation of reported risk factors for disease classification and prognosis in COVID-19: a descriptive and retrospective study. medRxiv Prepr. 2020;1–9.
5. Xie J, Hungerford D, Chen H, Abrams ST, Li S. Development and external validation of a prognostic multivariable model on admission for hospitalized patients with COVID-19. 2020;1–22.
6. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol (2020), doi https// doi.org/101016/j.jaci202004006.
7. Chen Ti, Dai Z, Mo P, Li X, Ma Z, Song S, et al. Clinical characteristics and outcomes of older patients with coronavirus disease 2019 (COVID-19) in Wuhan, CHina (2019): a single-centered, retrospective study. Downloaded from https//academic.oup.com/biomedgerontology/advance-article-abstract/doi/101093/gerona/glaa089/5819242. 2020;
8. Wang L, He W, Yu X, Hu D, Bao M, Liu H, et al. Coronavirus Disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. J Infect [Internet]. 2020; Available from: https://doi.org/10.1016/j.jinf.2020.03.019
9. Yan L, Zhang H, Goncalves J, Xiao Y, Wang M, Guo Y, et al. A machine learning-based model for survival prediction in patients with severe COVID-19 infection. medRxiv Prepr. 2020;
10. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney impairment is associated with in-hospital death of COVID-19 patients. medRxiv [Internet]. 2020;2020.02.18.20023242. Available from: https://www.medrxiv.org/content/10.1101/2020.02.18.20023242v1
11. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. JAMA Cardiol [Internet]. 2020;1–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32211816
12. Li K, Chen D, Chen S, Feng Y, Chang C. Radiographic Findings and other Predictors in Adults with Covid-19. 2020;2.
13. 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 [Internet]. 2020;6736(20):1–9. Available from: http://dx.doi.org/10.1016/S0140-6736(20)30566-3
14. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated with Acute Respiratory Distress Syndrome and Death in Patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020;1–10.
15. Chen R, Liang W, Jiang M, Guan W, Zhan C, Wang T, et al. Risk factors of fatal outcome in hospitalized subjects with coronavirus disease 2019 from a nationwide analysis in China. Chest [Internet]. 2020; Available from: http://www.ncbi.nlm.nih.gov/pubmed/32304772
16. Du R-H, Liang L-R, Yang C-Q, Wang W, Cao T-Z, Li M, et al. Predictors of Mortality for Patients with COVID-19 Pneumonia Caused by SARS-CoV-2: A Prospective Cohort Study. Eur Respir J [Internet]. 2020; Available from: http://www.ncbi.nlm.nih.gov/pubmed/32269088%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC7144257
17. Zhang X, Cai H, Hu J, Lian J, Gu J, Zhang S, et al. Epidemiological, clinical characteristics of cases of SARS-CoV-2 infection with abnormal imaging findings. Int J Infect Dis [Internet]. 2020; Available from: http://www.ncbi.nlm.nih.gov/pubmed/32205284
18. Gong J, Ou J, Qiu X, Jie Y, Chen Y. A Tool to Early Predict Severe 2019-Novel Coronavirus Pneumonia (COVID-19) : A Multicenter Study using the Risk Nomogram in Wuhan. medRxiv. 2020;
19. Feng Z, Yu Q, Yao S, Luo L, Duan J, Yan Z, et al. Early Prediction of Disease Progression in 2019 Novel Coronavirus Pneumonia Patients Outside Wuhan with CT and Clinical Characteristics. medRxiv Prepr. 2020;(138).
20. Huang H, Cai S, Li Y, Li Y, Fan Y, Li L, et al. Prognostic factors for COVID-19 pneumonia progression to severe symptom based on the earlier clinical features: a retrospective analysis. medRxiv Prepr. 2020;1–13.
21. Zeng L, Li J, Liao M, Hua R, Huang P, Zhang M. Risk assessment of progression to severe conditions for patients with COVID-19 pneumonia : a single-center retrospective study. medRxiv Prepr. 2020;
22. Chen J, Qi T, Liu L, Ling Y, Qian Z, Li T, et al. Clinical progression of patients with COVID-19 in Shanghai, China. 2020;(January).
23. Hu L, Chen S, Fu Y, Gao Z, Long H, Ren H, et al. Risk Factors Associated with Clinical Outcomes in 323 COVID-19 Patients in Wuhan, China. medRxiv [Internet]. 2020;2020.03.25.20037721. Available from: http://medrxiv.org/content/early/2020/03/26/2020.03.25.20037721.abstract
24. Liu W, Tao Z-W, Lei W, Ming-Li Y, Kui L, Ling Z, et al. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Chin Med J (Engl). 2020;0:1.
25. Zhang J, Wang X, Jia X, Li J, Hu K, Chen G, et al. Risk factors for disease severity, unimprovement, and mortality of COVID-19 patients in Wuhan, China. Clin Microbiol Infect [Internet]. 2020; Available from: http://www.ncbi.nlm.nih.gov/pubmed/32304745

26. Dans AL, Dans LF, Silvestre MAA (editors). Painless Evidence-based Medicine. Wiley. 2017;

Appendix 1. Literature Search

We searched PubMed, MEDLINE, Cochrane Library, and grey literature database medRxiv on 01 April 2020 for articles published between 01 December 2019 and 01 April 2020 using the keywords "coronavirus infections", "coronavirus", "novel coronavirus", "NCOV", "COVID-19", "COVID-2019", "2019-nCoV", "Wuhan", "severe acute respiratory syndrome coronavirus 2", "SARS-COV-2"; and "death", "mortality", "severe", "critical", "intensive care unit", "prediction", "prognosis", "heart", "cardiac", "blood", "interleukin", "Troponin I", "TNNI1 protein", "transaminases", "complete blood count", "procalcitonin", "lactate dehydrogenase", "D-lactate dehydrogenase", "l-lactate dehydrogenase", "fibrin", "fibrin fragment D", "D-dimer", and "ferritin", without language restrictions. Reference lists of included studies were examined for other relevant reviews. The initial search yielded 1191 titles of articles. Two review authors (EOS and PPR) independently assessed the potential relevance of all titles and abstracts identified through the searches. We selected articles based on the following inclusion criteria:

- Population: COVID-19 patients aged 18 years and above, excluding pregnant patients
- Exposure: Laboratory markers, any type
- Outcomes: Severe COVID-19, critical COVID-19, or death
- Study designs: systematic reviews and meta-analyses, observational studies (prospective or retrospective cohort studies) with adjustments for confounding factors

After removal of duplicates and articles that did not meet our selection criteria, 17 articles were included in the first review and one new article was added during the update.

A search for new articles was done on 23 April 2020 using the same search terms above, with the new search yielding an additional 437 titles, leading to a total of 1628 titles of articles. From these, six cohort studies met the inclusion criteria and were included in the update of this review. The validity of eligible articles was independently appraised by the authors. Disagreements were resolved through consensus.

Appendix 2. Characteristics of Included Studies

Title/Author	Study design	Setting	Population	Outcome	Prognostic Factors
Interleukin-6 in COVID-19: A Systematic Review and Meta-Analysis Coomes, E and Haghbayan, H.(2)	Systematic review and meta-analysis Most included studies had moderate to high risk of bias.	Meta-analysis done in Canada; All included studies from China	6 studies 486 patients with complicated COVID-19 disease 816 with non-complicated disease	Complicated COVID-19 defined as needing hospitalization, admission to intensive care unit, acute respiratory distress syndrome (ARDS), invasive mechanical ventilation, renal replacement therapy and severe disease on clinical scoring tools, or death.	Mean IL-6 is 2.9 fold higher in complicated COVID-19 compared to non-complicated disease. Ratio of means 2.9 (95% CI: 1.17, 7.19) Note: The effect of other factors on outcome was not considered.
Non-severe vs severe symptomatic COVID-19: 104 cases from the outbreak on the cruise ship “Diamond Princess” in Japan Tabata S et al (3)	Single-center Retrospective cohort	Japan	104 patients from cruise ship who were hospitalized, enrolled from February 11 to 25, 2020;	Severe symptomatic disease: dyspnea, tachypnea, SpO2<93%, needing oxygen therapy 28 patients with severe COVID-19	Consolidation detected by chest CT scan [adjusted OR 3.24 (95% CI: 1.04-10.40; p = 0.04)] and Lymphopenia [adjusted OR 4.30 (95% CI: 1.50-13.75; p <0.01)] were found to be significantly higher in severe cases
Validation of reported risk factors for disease classification and prognosis in COVID-19: a descriptive and retrospective study Tan, L, Kang X et al.(4	Single-center, retrospective cohort	Wuhan, China	132 inpatients with COVID-19 hospitalized between January 14 and March 14, 2020,	Death/severe disease 15 critical-died 21 severe-cured 96 moderate-cured	Those who died or had severe or critical disease had significant decrease in % of lymphocytes starting day 1-2 of hospitalization and significant increase in levels of IL-6 and CRP starting on day 2-4.These changes were consistent through the patients’ clinical course. % lymphocyte was most consistently able to distinguish severe or critical disease.

Development and external validation of a prognostic multivariable model on admission for hospitalized patients with COVID-19 Xie J, Hungerford D, et al. (5)	Single-center retrospective cohort study	Wuhan, China	444 inpatients with confirmed COVID-19 who were admitted in January to February 2020 who were discharged or had died	Death 155 (51.83%) died 289 discharged	Lymphocyte count, LDH, and SpO2 were independent predictors of mortality No cut-offs defined
Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan Li XC, Xu SY et al. (6)	Single-center, retrospective cohort	Wuhan, China	548 inpatients admitted between 26 January and 05 February 2020 and followed up until 03 March 2020	Severe COVID-19 and death 269 (49%) were severe cases on admission 46/269 severe cases (17%) had critical disease requiring ventilatory support 87 (15.8%) died	Risk factors for severe disease on admission Age ≥ 65 [OR 2.2 (95% CI: 1.5, 3.5)] Hypertension [OR 2.0 (95% CI 1.3, 3.2)] LDH > 445 U/L [OR 4.4 (95% CI 2.6, 7.6)] D-dimer > 1 mg/L [OR 2.2 (95% CI: 1.4, 3.3)] Risk factors for death among severe cases Male sex [adjusted HR 1.7 (95% CI: 1.0, 2.8) Age ≥ 65 [adjusted HR 1.7 (95% CI 1.1, 2.7)] Blood leukocyte count > 10 cells per mm3 [adjusted HR 2.00 (95% CI: 1.3, 3.3)] LDH > 445 U/L [adjusted HR 2.0 (95% CI: 1.2, 3.3)] at admission; Cardiac injury (serum hypersensitive cardiac troponin I > 15.6 pg/mL without acute coronary symptoms or abnormal electrocardiogram) [adjusted HR 2.9 (95% CI: 1.8, 4.8)] Hyperglycemia [adjusted HR 1.8 (95% CI: 1.1, 2.8)] High-dose corticosteroids (prednisone equivalent ≥ 1 mg/kg/day) [adjusted HR 3.5 (95% CI: 1.8, 6.9)] Lower risk of death in severe cases: Lopinavir/ritonavir [adjusted HR 0.4 (95% CI: 0.2, 0.9)] Umifenovir [adjusted HR 0.5 (95% CI: 0.3, 0.8)]
Clinical characteristics and outcomes of older patients with coronavirus diseases 2019 (COVID-19) in Wuhan, China (2019): a single-centered, retrospective study Chen TL, Dai Z, et al. (7)	Single-center, retrospective study	Wuhan, China	203 inpatients with confirmed COVID-19 admitted from 01 January to 10 February 2020, and followed up until 20 February 2020 48 out of 55 (87.3%) older patients were severely or critically ill	Death in older patients (≥ 65 years)	Risk factors for death among older patients: crea >105 umol/L [OR 4.82 (95% CI 1.16, 16.96), p = 0.03); shortness of breath [OR 12.9 (95% CI 1.8, 94.4) p = 0.01]; any comorbidities [OR 16.1 (95% CI 1.9, 133.8), p = 0.02]; and male sex [OR 13.8 (95% CI 1.41, 136.1), p = 0.02]

Coronavirus disease 2019 in elderly patients: characteristics and prognostic factors based on a 4-week follow-up Wang L, He W, et al.(8)	Single-center, retrospective cohort	Wuhan, China	339 inpatients with COVID-19 (> 60 years old) admitted from 01 January to 06 February 2020, followed up until 05 March 2020 80 (23.6%) critical 159 (46.9%) severe 100 (29.5%) were moderate cases	Death 65/339 (19.2%) died 183/339 (54%) remained in-hospital 91/339 (26.8%) discharged	After correction for age, the following were found to predict death: cardiovascular disease [HR 1.86 (95% CI 1.06, 3.26), p = 0.031]; COPD [HR 2.24 (95% CI: 1.12, 4.50), p = 0.023]; ARDS [HR 29.33 (95% CI 12.37, 69.58), p < 0.001]; WBC count [HR 1.16 (95% CI: 1.14, 1.20), p <0.001)]; protime [HR 1.17 (95% CI: 1.13, 1.24), p < 0.001] Laboratory tests predicting poor outcomes: Low lymphocytes HR 0.10 (95% CI: 0.04, 0.22), p <0.001 No specified laboratory cut-offs
A machine learning-based model for survival prediction in patients with severe COVID-19 infection Yan L, Zhang HT, et al. (9)	Single-center retrospective cohort study	Wuhan, China	404 inpatients with COVID-19 with medical information collected between January 10 to February 20, 2020	Death 191 (47.28%) died	High LDH levels (>365 U/L), low lymphocyte count (<14.7%), and high-sensitivity CRP (41.2 mg/L) levels can predict mortality risk in severe COVID-19 with >90% accuracy around 9 days in advance of the event.
Kidney impairment is associated with in-hospital death of patients with COVID-19 Cheng Y, Luo R, et al. (10)	Single-center prospective cohort study	Wuhan, China	701 inpatients with COVID-19, admitted between January 28 and February 11, 2020; outcomes monitored until February 29, 2020.	In-hospital death 89 (12.5%) died	High baseline serum creatinine or BUN, proteinuria or hematuria of any degree, peak serum creatinine > 133 umol/L, and AKI stages 1 to 3 were independent risk factors for in-hospital death. serum creatinine, HR 2.04 (95% CI: 1.32, 3.15) BUN, HR 4.20 (95% CI: 2.74, 6.45) Proteinuria ≥2+, HR 6.80 (95% CI: 2.97, 15.56) Proteinuria 1+ , HR 2.47 (95% CI: 1.15, 5.33) Hematuria ≥2+, HR 8.89 (95% CI: 4.41, 17.94) Hematuria 1+, HR 3.05 (95% CI: 1.43, 6.49) Peak serum creatinine > 133 umol/L, HR 3.09 (95% CI: 1.95, 4.87)] AKI Stage 1, HR 1.9 (95% CI: 0.76, 4.75) AKI Stage 2, HR 3.53 (95% CI: 1.5, 8.27) AKI Stage 3, HR 4.72 (95% CI: 2.55, 8.75)
Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 Shi S, Qin M, et al. (11)	Single-center retrospective cohort study	Wuhan, China	416 inpatients with COVID-19 confined between January 20 to February 10, 2020; 82 with cardiac injury 334 without. Cardiac injury definition: hsTnI>99th percentile of upper reference range	In-hospital mortality 57 (13.7%) died	Risk of death was higher if with cardiac injury HR 4.26 (95% CI:1.92, 9.49)] from symptom onset; HR 3.41 (95% CI:1.62, 7.16)] from admission to end point Risk of death for ARDS, HR 7.89 (95% CI: 3.73, 16.66) from symptom onset; [HR 7.11 (95% CI: 3.31, 15.25) from admission.

Radiographic Findings and other Predictors in Adults with Covid-19 Li K, Chen D et al.(12)	Single-center retrospective cohort	Wuhan, China	128 confirmed COVID-19 hospitalized between January 31 to March 5, 2020 and observed up to March 20, 2020	Death 15 (11.7%) died 5 remained hospitalized	Age ≥ 65 years [OR 1.063 (95% CI:1.006, 1.124)] LDH >225 U/L [OR 1.010 (95% CI: 1.005, 1.015)]
Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Zhou F, Yu T et al. (13)	Multi-center retrospective cohort	Wuhan, China	191 inpatients with confirmed COVID-19 who died or were discharged between December 29, 2019-January 31, 2020	Death 54 (28.3%) died	Older age [OR 1.10 (95% CI: 1.03–1.17, per year increase; p=0·0043), higher Sequential Organ Failure Assessment (SOFA) score [OR 5.65 (95% CI: 2.61–12.23; p<0·0001), and D-dimer greater than 1 µg/L [OR 18.42 (95% CI: 2.64, 128.55; p=0·0033)] on admission.
Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. Wu C, Chen X et al (14)	Single-center retrospective cohort	Wuhan, China	201 inpatients with confirmed COVID-19 ddmitted from December 25, 2019-January 26, 2020 and with outcomes by February 13, 2020	Development of ARDS and death ARDS defined according to WHO Interim guidance. 84 (41.8%) had ARDS 44 (21.9%) died	Risk factors for ARDS: older age [HR 3.26 (95% CI: 2.08, 5.11)]; neutrophilia [HR 1.14 (95% CI 1.09, 1.19)]; and organ and coagulation dysfunction (eg, higher LDH [HR 1.61 (95% CI: 1.44-1.79; and D-dimer [HR 1.03 (95% CI: 1.01, 1.04)]; high fever (≙39 °C) [HR 1.77 95% CI: 1.11,2.84)] Risk factors for progression to death: older age [HR 6.17 (95% CI, 3.26, 11.67)]; neutrophilia [HR 1.08 (95% CI: 1.01, 1.17)]; and organ and coagulation dysfunction (eg, higher LDH) [HR 1.30 (95% CI: 1.11, 1.52)] and D-dimer [HR 1.02 (95% CI: 1.01, 1.04)]. High fever (≙39 °C) was associated with lower likelihood of death [HR 0.41 (95% CI: 0.21-0.82)].
Risk factors of fatal outcome in hospitalized subjects with coronavirus diseases 2019 from a nationwide analysis in China Chen R, Liang W et al. (15)	Multicenter, retrospective cohort	575 hospitals in China	1590 inpatients with confirmed COVID-19 with data collected until 31 January 2020	Death 50 (3.14%) died	Age≥75 [HR 7.86 (95% CI: 2.44-25.35)]; age between 65-74 years [HR 3.43 (95%CI:1.24-9.5)]; CHD [HR 4.28 (95%CI: 1.14-16.13)]; CVD [HR 3.1 (95%CI:1.07-8.94)]; dyspnea [HR 3.96 (95%CI: 1.42-11)]; procalcitonin >0.5 ng/ml [HR 8.72 (95%CI: 3.42-22.28)]; AST >40 U/liter [HR 2.2 (95% CI: 1.1- 6.73)] A nomogram* for 14-day, 21-day, and 28-day overall survival probability based on the final multivariate model showed a C-index for prediction of overall survival was 0.91 (95% CI: 0.85, 0.97)
Predictors of Mortality for Patients with COVID-19 Pneumonia Caused by SARS-CoV-2: A Prospective Cohort Study	Single-center, prospective cohort	Wuhan, China	179 inpatients admitted between 25 December 25 2019 and 07 February 2020, followed up until 24 March 2020	Death 21 (12%) died 158 (88%) discharged	Age ≥ 65 years [OR 3.765 (95% CI: 1.146-17.394) p = 0.023], CD3+ CD8+ T cells ≤ 75 cells/uL [OR 3.982 (95% CI: 1.132-14.006), p < 0.001], and cardiac troponin I ≥ 0.05 ng/mL [OR 4.077 (95% CI: 1.166-14.253), p < 0.001].

Du RH, Liang LR et al. (16)			136 (76%) with confirmed COVID-19 and 43 (24%) with probable COVID-19 (clinically diagnosed)		
Epidemiological, clinical characteristics of cases of SARS-CoV-2 infection with abnormal imaging findings Zhang X, Cai H et al. (17)	Single-center retrospective cohort	Zhejiang, China 1 center	645 patients confirmed with COVID-19 infection between January 17 to February 8, 2020	Severe or critical COVID-19 64 (9.92%) had severe or critical disease	Muscle ache [OR 4.67 (95% CI: 1.75, 12.46)]; Shortness of breath [OR 9.02 (95% CI: 2.2, 37.01)] Nausea and vomiting [OR 15.5 (95% CI: 2.86, 84.5)] Higher serum creatinine [OR 1.03 (95% CI: 1.0-1.05)] Lymphocytes [OR 0.26 (95% CI: 0.09, 0.7)] Higher total radiograph score [OR 6.28 (95% CI: 3.9, 10.1)]
A Tool to Early Predict Severe 2019-Novel Coronavirus Pneumonia (COVID-19): A Multicenter Study using the Risk Nomogram in Wuhan and Guangdong, China Gong J, Ou J, et al. (18)	Multicenter retrospective cohort study	Wuhan and Guangdong Province, China	372 inpatients with COVID-19 with data between January 20 to March 2, 2020 Training cohort of 189 patients 2 independent validation cohorts with 165 patients and 18 patients each	Severe COVID-19* 72 (19.35%) had severe COVID-19	Prognostic normogram including: older age, higher LDH and CRP, direct bilirubin, higher RDW, higher BUN, and lower albumin correlated with higher odds of severe COVID-19. Area under the curve (AUC) values: • Training cohort = 0.912 (95% CI: 0.846, 0.978); sensitivity (Sn) 85.71%, specificity (Sp) 87.58% • First validation cohort = 0.853 (95% CI: 0.846, 0.978); Sn 77.50%, Sp 78.40% • Second validation cohort = Sn 75.00%, Sp 100%
Early Prediction of Disease Progression in 2019 Novel Coronavirus Pneumonia Patients Outside Wuhan with CT and Clinical Characteristics Feng Z, Yu Q, et al. (19)	Multi-center retrospective cohort study	Hunan Province, China (2 hospitals) January 17, 2020	141 inpatients with confirmed COVID-19 observed for at least 14 days from admission between January 17 to February 1, 2020	Severe 2019 novel coronavirus pneumonia (NCP), defined in this study as a composite of severe and critical NCP*† 15 (10.63%) had disease progression	Baseline neutrophil-to-lymphocyte ratio (NLR) and CT severity score [OR 1.25 (95% CI: 1.08, 1.46)] were independent predictors for progression to severe NCP [OR 1.26 (95% CI: 1.04, 1.53); p=0.018] in patients with history of contact with people from Wuhan or with local infected patients outside Wuhan. Age [OR 1.13 (95% CI: 1.04, 1.22)] was the only predictor for progression to severe NCP in patients who had recently been to Wuhan.
Prognostic factors for COVID-19 pneumonia progression to severe symptom based on the earlier clinical features Huang H, Cai S et al (20).	Single-center retrospective cohort	Guangzhou, China	125 of 298 patients admitted on January 20-February 29, 2020 with mild or ordinary COVID on admission, hospitalization >3 days, overall duration of disease >7 days.	Severe or critical COVID 3-7 days after admission Severe defined as RR≥30/min in resting state, O2sat ≤93% in resting state, paO2/FiO2 ≤300 mmHg 32 (25.6%) had poor outcome	Comorbidity, increased respiratory rate (>24/min), elevated CRP (>10mg/liter), and LDH (>250U/liter), were independently associated with the later development of severe disease. However, these factors could not confidently predict the occurrence of severe pneumonia individually. Combination of fast respiratory rate and elevated LDH significantly increased the predictive confidence (AUC= 0.944, Sn=0.941 and Sn= 0.902). A combination consisting of 3- or 4-factors further increase the prognostic value.

Risk assessment of progression to severe conditions for patients with COVID-19 pneumonia Zeng L, Li J et al.(21)	Single-center retrospective cohort	Shenzhe, China	338 (adult) inpatients with confirmed COVID 19, admitted between January 11-February 29, 2020 followed up until March 8, 2020 (45 still hospitalized at this date)	Progression to severe condition or death 76 progressed (31.9%) 3 died (0.8%)	Age, body mass index (BMI), fever symptom on admission, coexisting hypertension or diabetes are associated with progression to severe disease. The cohort is characterized with increasing cumulative incidences of severe progression up to 10 days after admission. A model incorporating CT imaging and baseline information predicted severity onset (mean time-dependent AUC of 0.880).
Clinical progression of patients with COVID-19 in Shanghai, China Chen J, Qi T (22)	Single-center retrospective cohort	Shanghai, China	249 patients with confirmed COVID=19 recruited from January 20-February 6, 2020	Admission to intensive care unit 22 admitted to ICU (8.8%), 2 died (0.8%)	Age [OR 1.06 (95% CI: 1.0, 1.12)] and $CD4^+$ T cell count [OR 0.55 (95% CI: 0.33, 0.92)] per 100 cells/ul increase) were independently associated with ICU admission.
Risk factors associated with clinical outcomes in 323 COVID-19 patients in Wuhan, China Hu L, Chen S et al. (23)	Single-center retrospective cohort	Wuhan, China	323 inpatients confirmed COVID enrolled on January 8-February 20, 2020, observed until March 10, 2020 (average observation period of 28 days, range 20-47 days)	Unfavorable outcome (disease progression, death, or non-improvement of severe or critical status) 63 (19.5%) had unfavorable outcome	Age over 65 years, smoking, critical disease status, diabetes, high hypersensitive troponin I (TnI) (>0.04 pg/mL), leukocytosis (>10 x 10^9/L) and neutrophilia (>75 x 10^9/L) predicted unfavorable clinical outcomes.
Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease Liu W, Tao ZW et al. (24)	Multicenter, retrospective cohort	Wuhan, China	78 inpatients with COVID-19 between December 30, 2019-January 15, 2020, hospitalized for 2 weeks or more, had died, recovered or discharged	Death/progression 11 in progression group (14.1%)	Risk factors for disease progression: Age [OR 8.546 (95% CI: 1.628, 44.864; P = 0.011)], history of smoking [OR 14.285 (95% CI: 1.577, 25.000; P = 0.018)], maximum body temperature on admission [OR 8.999 (95% CI: 1.036, 78.147, P = 0.046)], respiratory failure [OR 8.772 (95% CI: 1.942, 40.000; P =0.016)], albumin [OR 7.353 (95% CI: 1.098, 50.000; P =0.003)] and CRP [OR 10.53 (95% CI:1.224, 34.701; P = 0.028)]
Risk factors for disease severity, unimprovement, and mortality of COVID-19 patients in Wuhan, China Zhang J, Wang X, et al (25)	Single-center, retrospective cohort	Wuhan, China	663 inpatients with confirmed COVID-19 admitted from 11 January to 6 February 2020 94 (14.2%) critical 315 (47.5%) severe 251 (37.8%) moderate disease	"Unimprovement" defined as the absence of any of the following: continuously decreased temperature or normal temperature (below 37.3ºC); improved respiratory symptoms (disappeared or obviously relieved); gradual reduction of pulmonary inflammation upon imaging analysis (obviously reduced shadow area); and negative results of SARS-CoV-2 real-time RT-PCR detection .	Independent risk factors were determined only for unimprovement: Male sex [OR 0.486 (95% CI: 0.311, 0.758), p = 0.001]; severe COVID-19 [OR 0.129 (95% CI: 0.082, 0.201), p < 0.001]; expectoration [OR 1.796 (95% CI : 1.062, 3.026), p = 0.029]; muscle ache [OR 0.309 (95% CI: 0.153, 0.626), p = 0.001]; decreased serum albumin [OR 1.929 (95% CI: 1.199, 3.104), p = 0.007)] .

*Severe 2019 novel coronavirus pneumonia (NCP) defined as Severe type, having any 1 of the following: respiratory rate ≥30 breaths/minute; oxygen saturation ≤93% in the resting state; arterial blood PaO_2 ≤300 mmHg.
†Critical 2019 NCP defined as having any 1 of the following: respiratory failure requiring mechanical ventilation; shock; intensive care unit admission for combined organ failure.

Appendix 3. Critical Appraisal of Included Studies

Systematic Review

Author (Ref #)	Direct?	Criteria for inclusion of studies appropriate?	Search for eligible studies thorough?	Validity of included studies assessed?	Assessment of studies reproducible?	Valid?
Coomes E, Haghbayan H (2)	Yes	Yes	Yes	Yes	Yes	Yes

Observational Studies on Prognosis

Author (Ref #)	Direct?	All prognostic factors included?	Objective study outcomes?	Follow-up complete?	If testing prediction model, was validation done?	Valid?
Tabata S et al (3	Yes	Yes	Yes	Not clear	n/a	Yes
Tan L et al (4)	Yes	Yes but Adjustment for confounders not done	Yes	Yes	n/a	Yes
Xie J et al (5)	Yes	Yes	Yes	Yes	Yes	Yes
Li XC, Xu SY et al (6.	Yes	Yes	Yes	Yes	n/a	Yes
Chen TL, Dai Z, et al (7).	Yes	Yes	Yes	Yes	n/a	Yes
Wang L, He W, et al. (8)	Yes	Yes	Yes	Yes	n/a	Yes
Yan L et al (9)	Yes	Yes	Yes	Yes	Yes	Yes
Cheng Y et al (10)	Yes	Yes	Yes	Yes	n/a	Yes
Shi S et al (11)	Yes	Yes	Yes	Yes	n/a	Yes
Li K et al (12)	Yes	Yes	Yes	Yes	n/a	Yes
Zhou F et al(13)	Yes	Yes	Yes	Yes	n/a	Yes
Wu C et al (14)	Yes	Yes	Yes	No	n/a	Yes
Chen R, Liang W et al. (15)	Yes	Yes	Yes	Yes	Internal validation only	Yes

Du RH, Liang LR et al. (16)	Yes	Yes	Yes	Yes	n/a	Yes
Zhang X et al (17)	Yes	Yes	Yes	Yes	n/a	Yes
Gong J et al(18)	Yes	Yes	Yes	Yes	Yes	Yes
Feng Z et al (19)	Yes	Yes	Yes	Yes	n/a	Yes
Huang H et al (20)	Yes	Yes	Yes	Yes	n/a	Yes
Zeng L et al (21)	Yes	Yes	Yes	No	No	Yes
Chen J et al (22)	Yes	Yes	Maybe not	No	n/a	Yes
Hu L et al (23)	Yes	Yes	Yes	No	n/a	Yes
Liu W et al (24)	Yes	Yes	Yes	No	n/a	Yes
Zhang J, Wang X, et al. (25)	Yes	Yes for the outcome of "unimprovement"	Yes	Yes	n/a	Yes