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Primary care relevant risk factors for adverse outcomes in patients with COVID-19 infection: a systematic review

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Contributions of authors

The study was conceived and designed by MHE; CH and MB performed the search and summarized the data, supervised by MHE; initial analysis and interpretation of the data was by CH and MB, supervised by MHE; manuscript was drafted by MHE, critical revision of the manuscript for important intellectual content by MB and CH; no funding.

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Abstract

Background

The aim of this systematic review is to summarize the best available evidence regarding individual risk factors, simple risk scores, and multivariate models that use patient characteristics, vital signs, comorbidities, and laboratory tests relevant to outpatient and primary care settings.

Methods

Medline, WHO COVID-19, and MedRxIV databases were searched; studies meeting inclusion criteria were reviewed in parallel and variables describing study characteristics, study quality, and risk factor data were abstracted. Study quality was assessed using the Quality in Prognostic Studies tool. Random effects meta-analysis of relative risks (categorical variables) and unstandardized mean differences (continuous variables) was performed; multivariate models and clinical prediction rules were summarized qualitatively.

Results

551 studies were identified and 22 studies were included. The median or mean age ranged from 38 to 68 years. All studies included only inpatients, and mortality rates ranged from 3.2% to 50.5%. Individual risk factors most strongly associated with mortality included increased age, c-reactive protein (CRP), d-dimer, heart rate, respiratory rate, lactate dehydrogenase (LDH), and procalcitonin, as well as decreased oxygen saturation, the presence of dyspnea, and comorbid coronary heart and chronic kidney disease. Independent predictors of adverse outcomes reported most frequently by multivariate models include increasing age, increased CRP, decreased lymphocyte count, increased LDH, elevated temperature, and the presence of any comorbidity. Simple risk scores and multivariate models have been proposed, but are often complex and most have not been validated.

Conclusions

Our systematic review identifies several risk factors for adverse outcomes in COVID-19 infected inpatients that are often available in the outpatient and primary care settings: increasing age, increased CRP or procalcitonin, decreased lymphocyte count, decreased oxygen saturation, dyspnea on

presentation, and the presence of comorbidities. Future research to develop clinical prediction models and rules should include these predictors as part of their core dataset to develop and validate pragmatic outpatient risk scores.

Introduction

In December 2019, the first cases of novel coronavirus disease, later to become known as COVID-19, were reported.[1] Since this outbreak, the world has found itself facing a pandemic with total global cases exceeding 11 million as of October 21, 2020[2], including over 8 million confirmed cases in the United States[3]. Symptoms of COVID-19 include cough, fever, dyspnea, chills, myalgias, and loss of taste and smell. However, many individuals remain asymptomatic or have mild symptoms and do not seek testing, so the number of total cases is estimated to be approximately 10 times higher than the number of confirmed cases.[4,5] Currently, the treatment is primarily supportive for patients with non-severe illness[6], with respiratory support, remdesivir, and dexamethasone for more severely ill patients.[7,8]

COVID-19 has an infection mortality ratio estimated to be approximately 0.5 to 1.0%[9], and an accurate prognosis is important to help clinicians decide on the most appropriate site of care (hospital vs home) and the intensity of follow-up and monitoring for both inpatients and outpatients. However, our understanding of clinical risk factors and biomarkers that increase the likelihood of serious illness or death remains incomplete and in some cases is contradictory. Previous studies have found that risk factors for severe illness or mortality include increasing age, male sex, and comorbidities such as diabetes, renal failure, asthma, COPD, hypertension and cardiovascular disease.[10] A variety of biomarkers have also been reported to be associated with severe disease or mortality including c-reactive protein (CRP), lactate dehydrogenase (LDH), imaging findings, and the white blood cell count parameters.[11]

However, some of these biomarkers or imaging studies are not rapidly or widely available in outpatient settings, and physicians are increasingly having to make decisions via telehealth or in outpatient clinics. While the availability of tests varies in different countries and in different outpatient settings (urgent care vs primary care vs telehealth vs emergency department), tests like the complete blood count, c-reactive protein (CRP), d-dimer, and procalcitonin are increasingly available.[12,13,14,15] The goal of this systematic

review and meta-analysis is to summarize the best available evidence regarding individual risk factors, simple risk scores, and multivariate models that use patient characteristics, vital signs, comorbidities, and laboratory tests in inpatients, as a guide to testing their predictive utility in outpatient and primary care settings.

Methods

This systematic review was registered with the PROSPERO registry, registration number CRD42020193336. It was declared not human subjects research by the University of Georgia Institutional Review Board.

Inclusion Criteria

Risk factors were limited to demographics, vital signs, oxygen saturation, comorbidities, and laboratory tests judged to be available in at least some outpatient settings (white blood cell count and differential, c-reactive protein, d-dimer and procalcitonin). Studies were included that reported the association between at least one of these risk factors and at least one marker of serious illness in cohorts of adults with a confirmed diagnosis of COVID-19. Adverse outcomes for all patients were defined as death, intensive care unit (ICU) stay, or need for mechanical ventilation. Included studies also had to report sufficient data for calculation of relative risk, including the number of patients with and without the risk factor for both good and bad outcomes.

Studies were excluded if they enrolled cohorts of only children. They were also excluded if the study focused on a specialized population such as pregnant women, individuals with cancer, HIV positive, or post-operative patients. Studies that included less than 50 patients were also excluded from the meta-analysis. There were no limitations set on the country or language of the publications. Studies from preprint servers were also included.

Search Strategy

A search of the Medline database was used with multiple terms for COVID-19 such as “betacoronavirus”, “coronavirus”, “COVID-19”, and “SARS-CoV-2” as well as terms for prognostic studies such as “risk factor”, “validation”, “prediction rule”, and “prognosis”. All terms were linked by Boolean terms and the search is shown in Appendix A. The limits “has abstract” and “human” were applied to the search. Additionally, the WHO COVID-19 Database and the MedRxIV preprint server were searched to identify additional published and preprint studies using similar keywords.

Data Abstraction

All abstracts were reviewed for inclusion by the lead author (MHE) and at least one other co-author. For any abstract that was of interest, the full article was obtained and reviewed by the lead author and at least one other co-author. Studies meeting inclusion criteria were reviewed in parallel and variables describing study characteristics, study quality, and risk factor data were abstracted. Risk factor data included the number of individuals with and without the risk factor and how many observed the outcome of interest. We included continuous and categorical data. All discrepancies were discussed and resolved by consensus. If a study reported a simple risk score, clinical prediction rule, or multivariate model, data regarding them was abstracted separately.

Data preparation

Similar risk factors (e.g. lymphocyte count < 0.8 and < 1.0) were grouped where it was felt to be clinically reasonable by the lead investigator, a physician. Outcomes were similarly grouped into three outcome categories: 1) death, 2) severe disease (intensive care unit admission, mechanical ventilation, or disease progression), and severe disease or death. Where different units were reported, results were converted to a common set of units (e.g. mg/L for c-reactive protein). Original risk factors and outcome categories are available for the full dataset are available on request from the investigators.

In studies that did not report mean and standard deviation (SD) of continuous variables, these values were estimated using median and interquartile range (IQR). The mean was approximated by adding the lower ($q_{1)}$ and upper bound (q_3) to the median (m) and dividing but the constant of 3. The standard deviation was estimated by subtracting q_1 from q_3 dividing by $\eta(n)$ which was determined using the sample size and Table 2 in the publication by Wan et al. [16] These values were calculated with the equation $\eta(n) = 2E(Z_{(3Q+1)})$ for $Q \leq 50$ using the statistical software R. In cases where the sample size was large and Q was ≥ 50, 1.35 was used as the $\eta(n)$.

Assessment of Study Quality

The Quality in Prognostic Studies (QUIPS)[17] tool was adapted and used to determine the quality of included studies. Definitions of low, moderate, and high risk of bias were prespecified for each domain. The full adapted tool is included in Appendix C. Quality was assessed in parallel by at least two researchers and all discrepancies were discussed and resolved by consensus.

Analytic Strategy

Data were imported into STATA (version 15.1) and the metan procedure was used to perform the random effects meta-analysis of relative risks (categorical variables) and unstandardized mean differences (continuous variables). Forest plots were created for each risk factor, stratified by outcome (e.g. death, severe disease). The number of studies and patients for each summary estimate were also noted. To perform random effects meta-analysis of continuous variables median and interquartile ranges were converted to estimates of mean and standard deviation prior to calculation using the method of Wan et al.[16]

Results

A summary of our search process is outlined in Figure 1. Our initial search of PubMed was performed in May 2020 and a bridge search was performed on June 30, 2020. A total of 551 records were identified, and 56 full text articles were screened for inclusion. Ultimately, 22 studies were included in the quantitative synthesis.

The characteristics of included studies are summarized in Table 1. One study was set in the United States, one in Korea, and the remainder were set in China. All studies included adult inpatients with previously confirmed COVID-19 and reported outcomes of death, severe disease, or both; there were no studies of outpatient prognosis. The median or mean age ranged from 38 to 68 years with the majority of the participants being male in 16 of 22 studies. Mortality rates ranged from 3.2% to 50.5%.

Study quality was assessed for all included studies using the QUIPS tool. All 22 studies were considered to have moderate risk of bias for study participation because only inpatients were included, limiting generalizability to patients cared for outside of the hospital. Eight studies included patients who were still hospitalized at the time of data collection and were therefore considered to have high risk of bias for study attrition and ascertainment of the final outcome. Three studies did not provide a multivariate analysis and were considered to have high risk of bias for study confounding. All results and analytic strategies seemed to be clearly reported and were not considered to be a source of bias. Detailed results of the quality assessment including the adapted QUIPS tool are shown in Appendix C.

Table 2 includes summary estimates of the relative risks and their corresponding confidence intervals for each categorical risk factor reported by at least 3 studies using the same cutoff for abnormality (full data are available in Appendix B). Risk factors most strongly associated with mortality included increased procalcitonin, increased lactate dehydrogenase (LDH), decreased oxygen saturation, the presence of dyspnea, comorbid coronary heart disease, COPD and chronic kidney disease, and increased respiratory rate. Risk factors reported by at least 3 studies and most strongly associated with the outcome “severe

disease" included the presence of dyspnea, elevated procalcitonin, and comorbid chronic heart disease and chronic kidney disease. Cough and fever were not significantly associated with any of our adverse outcomes with relative risks for all risk categories near the null. Increased white blood cell count and increased neutrophil count were most strongly associated with the outcome "severe disease or death" (data not shown; no risk factor for this outcome was reported by more than 2 studies).

Risk factors reported as continuous variables are summarized in Table 3, showing the unstandardized weighted mean difference between patients with and without the risk factor for each risk factor. For the outcome of death, risk factors with clinically and statistically significant differences between patients dying and survivors included higher c-reactive protein (CRP), age, d-dimer, and white blood cell parameters, as well as lower oxygen saturation and lymphocyte count. Risk factors that that had significantly higher values in patients with the outcome of severe disease or death included CRP, age, neutrophil count, and white blood cell count; oxygen saturation and lymphocyte count were significantly lower. For the outcome of severe disease, CRP, and age were significantly higher while lymphocyte count was significantly lower. While d-dimer was higher, the difference was small and not clinically important.

Table 4 summarizes risk factors identified as independent predictors of adverse outcomes by multivariate models reported in 17 studies. Risk factors most often included in multivariate models included increasing age, increased CRP, decreased lymphocyte count, increased lactate dehydrogenase (LDH), elevated temperature, and the presence of any comorbidity.

Finally, Table 5 summarizes 11 clinical prediction rules reported in the literature to date. They used a variety of approaches, including risk scores, classification trees, full models in the form of online calculators, and nomograms. Only four of the clinical prediction rules have been externally validated[18,19] and only two have been externally validated outside of China (one in the United Kingdom and one in France).[52, 53]

Discussion

We have summarized the literature to date with regards to prognosis of inpatients with COVID-19, with a focus on clinical factors and tests that may be available in the outpatient or primary care setting during the initial evaluation of a patient with COVID-19. Thus, we did not abstract data regarding imaging studies or tests that are not widely available such as interleukin-6, lactate dehydrogenase, or serum albumin. Our systematic review identified several risk factors that are consistently and strongly associated with adverse outcomes based on univariate and multivariate analyses: increasing age, increased CRP, LDH, or procalcitonin, decreased lymphocyte count, decreased oxygen saturation, dyspnea on presentation, and the presence of comorbidities. Fever and cough were not strongly associated with severe disease or mortality, perhaps because almost all hospitalized patients had these symptoms, making them less helpful for discrimination. Future research to study prognosis in the North America and Europe and develop prediction models and clinical prediction rules should include these predictors as part of their core dataset. While the data are limited in several ways as noted below, they represent the best evidence currently available. Greater availability of tests like CRP, d-dimer, and procalcitonin at the point of care is desired by physicians and would facilitate more efficient evaluation of patients for COVID-19 and other important conditions such as community-acquired pneumonia.[20,21,13] Similarly, providing inexpensive oxygen saturation monitors to outpatients at risk for deterioration should be encouraged based on our findings.

Limitations

The studies that we identified had a number of important limitations that should be addressed by future research. These limitations can inform design of future studies of prognosis and risk models in North America and Europe. First, studies had variable definitions of serious illness. Standardization would assist in future analyses, although there is inherent subjectivity and between country variability in decisions to move a patient to the intensive care unit. The World Health Organization has identified 6 clinical severity

categories for patients with COVID-19: 1: Not hospitalized; 2: Hospitalized, not requiring supplemental oxygen; 3: Hospitalized, requiring supplemental oxygen; 4: Hospitalized requiring nasal high-flow oxygen, non-invasive mechanical ventilation, or both; 5: Hospitalized, requiring invasive mechanical ventilation, ECMO or both; and 6: Death.[22] For outpatients and patients being evaluated in primary care, the important clinical prediction is category 1 versus 2 or higher, or possibly 1 or 2 versus 3 or higher. All of the studies in our meta-analysis only included hospitalized patients, and in some cases excluded patients who had not yet died or been discharged. There was also a wide range in mortality rates, which likely reflects differences in health systems, hospital capacity, and the decision to admit, as well as declining case fatality rates as treatments emerge. In addition, timing of data collection was not always clearly reported, and in 8 of 22 studies outcome ascertainment was incomplete. Future studies should also include patients managed in the outpatient setting, to identify risk factors for deterioration and later hospitalization, as well as patients who are hospitalized. As the literature evolves, additional risk factors may also be identified such as red cell distribution width.[23]

Another limitation of the current literature is that many of the multivariate models and clinical prediction rules were quite complex, in some cases including 9 to 12 predictors including imaging.[19,24] They also often required laboratory tests such as lactate dehydrogenase, interleukin-6 and serum albumin that are not readily or rapidly available in outpatient settings. This places a high data collection and computational burden for those hoping to apply these tools in practice. We encourage researchers to create simpler clinical prediction rules and to provide online calculators.[19] The most widely used clinical prediction rules in current clinical practice such as the Ottawa Ankle Rules,[25] the Strep Score,[26,27] the CURB-65,[28] and the CRB-65[29] only require 4 or 5 pieces of clinical information. This reduces the implementation burden and facilitates memorization. In addition, since many patients are initially evaluated in the outpatient or even telehealth settings, clinical prediction rules that require few or no laboratory tests are needed. Fourth, most of the clinical prediction rules have not been externally validated. Prior to implementation, clinical

prediction rules require at a minimum internal validation using bootstrapping or split sample approaches, and ideally should be externally validated in a different population.

Finally, It is important that clinical prediction rules identify risk groups that are situated in the clinical context with an understanding of clinical decision-making. For example, the risk score proposed by Galloway and colleagues identifies a low risk group with 12.4% mortality and a high risk group with 40.7% mortality. Most physicians and their patients would consider both groups to be above the risk threshold for hospitalization. Similarly, Yu and colleagues identify a low risk group with 5.4% mortality and a high risk group with 22.8% mortality. What would be more helpful was a clinical prediction rule that identified three or more risk groups, with the lowest risk group clearly below the threshold for hospitalization, a moderate risk group that might be followed closely as an outpatient with oxygen saturation monitoring or that might be hospitalized, and a high risk group that would generally be hospitalized. More work is needed to determine these risk thresholds.

In conclusion, we have comprehensively reviewed the literature on risk factors for severe disease and mortality in COVID-19 and found it lacking. While this represents the best available evidence, studies to date have been in hospitalized patients; prognostic studies are needed in the outpatient setting where most patients are managed. Our research provides a starting point for outpatient studies, identifying several clinical variables and laboratory tests that are promising for predicting severe disease and mortality. There is a need for pragmatic clinical prediction rules with a low burden of data collection to identify patients who are at low, moderate, or high risk for severe disease or death to guide decision-making in the outpatient and primary care settings. Also, as more data are published in both inpatient and outpatient settings, it will also be important to update systematic reviews like this one. Because of their usefulness in determining prognosis, tests such as c-reactive protein, d-dimer, and procalcitonin should be made available and studied in outpatient settings, and home monitoring of oxygen saturation should be offered to identify patients at risk for a poor outcome.

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Figure Legends

Figure 1. PRISMA flow diagram of the search process

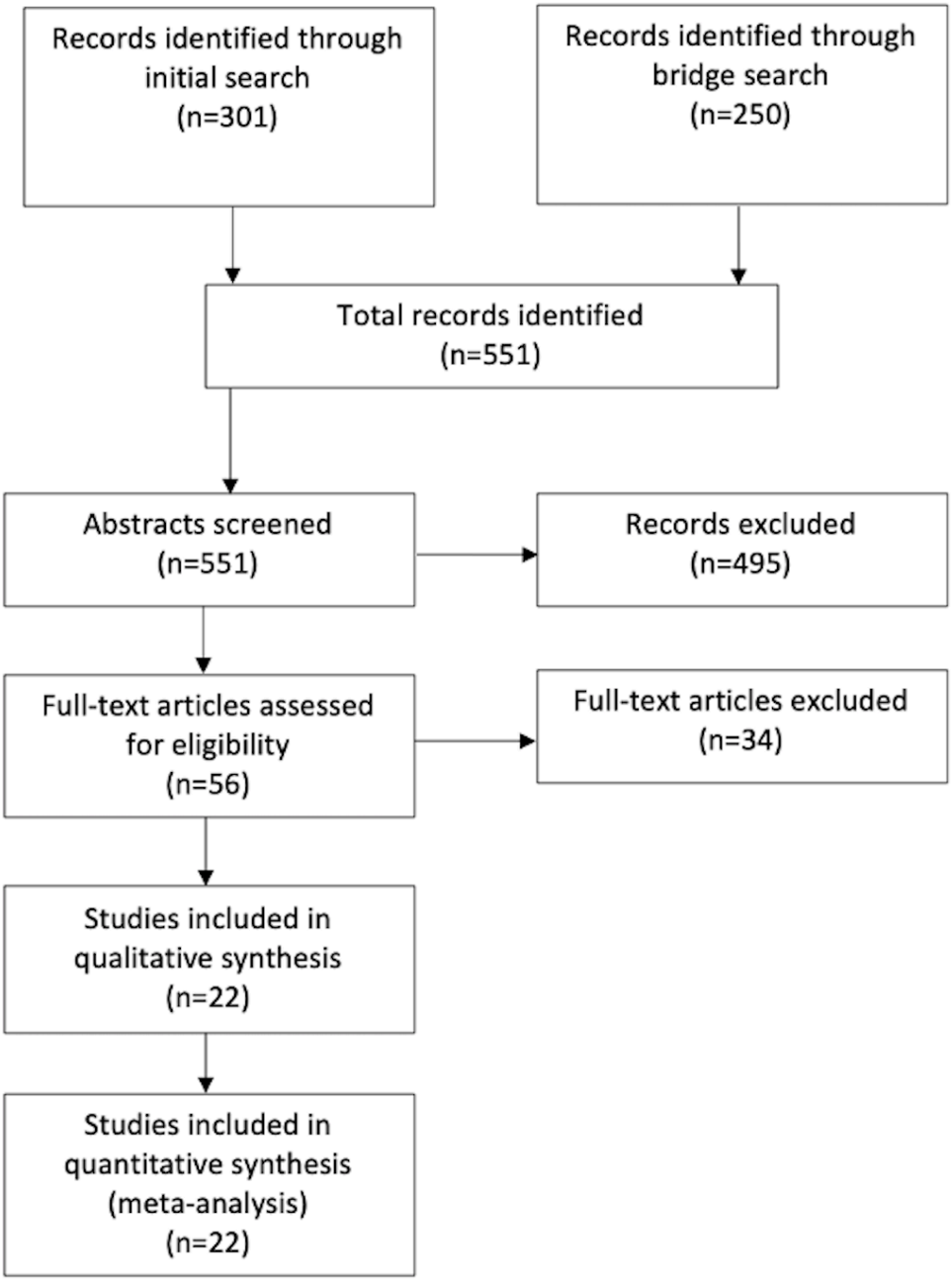

Table 1. Characteristics of included studies

Author, Year	Country	Patients studied	Mean or median age	% Male	Definition of bad outcome	Mortality rate
Yu, 2020[30]	China	Adults with COVID-19 from 27 hospitals in Jiangsu Province with a CT scan	48 (median)	53.0	Composite of ICU admission, acute respiratory failure occurrence, or shock during hospitalization	15.0%
Wang, 2020[31]	China	Adults with COVID-19 who were discharged from 2 hospitals (Wuhan and Hubei Province)	51 (median)	53.3	Death	17.8%
Chen, 2020[32]	China	Adults with COVID-19 classified as moderately, severely or critically ill in 1 hospital in Wuhan	68 (median)	62.4	Death	41.2%
Zhou, 2020[33]	China	Adults with COVID-19 who had been discharged or died in 2 Wuhan hospitals	56 (median)	62.3	Death	28.0%
Liu, 2020[34]	China	Adults with COVID-19 pneumonia in 3 tertiary hospitals in Wuhan	38 (median)	50	Clinical deterioration	14.1%
Liang, 2020[35]	China	Adults with COVID-19 from 575 hospitals in 31 regions of China	48.9 (mean)	57.3	Composite of admission to ICU, invasive ventilation, death	3.2%
Xie, 2020[36]	China	Adults with COVID-19 who had been discharged from or died in 2 hospitals in Wuhan	62 (median)	53.8	Death	50.5%
Yan, 2020[37]	China	Adults with COVID-19 in 1 hospital in Wuhan	58.83 (mean)	58.7	Death	46.4%
Cao, 2020[38]	China	Adults with COVID-19 in 1 hospital in Shanghai	50.1 (mean)	51	Admission to ICU	NR
Hu, 2020[39]	China	Adults with COVID-19 in 1 hospital in Wuhan	61 (median)	51.4	Death or progression	10.8%
Luo, 2020[40]	China	Adults with COVID-19 with a clinical outcome in 1 hospital in Wuhan	57 (median)	50.3	Death	28.2%
Petrilli, 2020[41]	United States	Adults with laboratory confirmed critical COVID-19 in 1 hospital in New York City	54 (median)	49.5	Composite of ICU, mechanical ventilation, discharge to hospice or death.	24.3%

Wu, 2020[42]	China	Adults with COVID-19 pneumonia in 1 hospital in Wuhan	51 (median)	63.7	Acute respiratory distress syndrome	21.9%
Li, 2020[43]	China	Adults with laboratory confirmed severe COVID-19 infection	57 (median)	58	Death	14.7%
Jang, 2020[44]	Korea	Adults with COVID-19 hospitalized at a tertiary hospital in Daegu, Korea	56.9 (mean)	43.6	Compositive of ARDS, ICU care, or death	7.3%
Xu, 2020[45]	China	Adults with laboratory confirmed COVID-19 admitted to 16 tertiary hospitals from 8 provinces in China	46.1 (mean)	54	Composite of death, ICU, or requiring mechanical ventilation.	4.7%
Zhou, 2020[46]	China	Adults with laboratory confirmed COVID-19 collected from 47 locations in Sichaun	43 (median)	56.6	Vasopressors or respiratory failure + 3 of: respiratory rate > 30, PaO2/FIO2 ≤ 250 mm Hg, infiltrates, confusion, BUN ≥ 20 mg/dl, leukopenia, hypothermia, thrombocytopenia, or hypotension.	NR
Hou, 2020[47]	China	Adults with laboratory confirmed COVID-19 hospitalized at Beijing hospitals	50.9 (median)	43.6	Progression defined as having a clinically advanced type of COVID-19, ICU admission, or death during hospitalization	5.0%
Zhang, 2020[48]	China	Adults with laboratory confirmed COVID-19 in 1 hospital in Wuhan, China	38.0 (median)	41.4	Disease deterioration including the transfer to ICU and death	13.5%
Liu, 2020[49]	China	Adults with laboratory confirmed COVID-19 in 1 hospital in Wuhan, China	65.5 (median)	35	Severe disease defined as having shortness of breath, RR ≥30 bpm, O2 sat ≤ 93%, PaO2/FIO2 ≤ 300 mmHg, and progression on imaging	NR
Zhu, 2020[50]	China	Adults with confirmed COVID-19 at 1 hospital in Zhejiang, China	50.9 (mean)	35.4	Severe disease defined as shortness of breath, RR >= 30 bpm, O2 sat <= 93%, PaO2/FIO2 <= 300 mmHg, or lesion progression	NR
Hu, 2020[51]	China	Adults with laboratory confirmed critical COVID-19 in 1 hospital in Wuhan, China	60.8 (mean)	50.9	Death	18.0%

RR = respiratory rate; O2 sat = oxygen saturation; BUN = blood urea nitrogen; ICU = intensive care unit; ARDS = acute respiratory distress syndrome.

Table 2. Association between categorical variables and mortality or severe disease in patients with COVID-19. Variables reported by fewer than 3 studies are not included but can be found in online Appendix B.

	Studies	Total Patients	RR (95% CI)
Outcome = death			
Demographics and vital signs			
Oxygen saturation < 90% – 93%	3	718	6.07 (4.27, 8.63)
Respiratory rate > 20 – 30 breaths/min	4	841	3.80 (2.13, 6.78)
Age >= 60 to 65 years	3	483	2.62 (1.91, 3.58)
Male sex	9	2213	1.24 (1.08, 1.43)
Comorbidities			
Coronary heart disease	9	2213	5.27 (2.89, 9.58)
Chronic kidney disease	5	1562	5.11 (2.18, 12.0)
Chronic obstructive pulmonary disease	9	2213	3.79 (2.51, 5.72)
Hypertension	9	2213	2.34 (1.80, 3.05)
Diabetes mellitus	9	2213	2.15 (1.46, 3.15)
Symptoms			
Dyspnea	3	1073	3.47 (1.67, 7.18)
Fever	6	1530	1.10 (0.95, 1.28)
Cough	5	1366	1.02 (0.93, 1.13)
Laboratory tests			
Procalcitonin >= 0.25 - 0.5 ng/mL	4	728	9.59 (3.71, 24.8)
Increased LDH	3	831	5.16 (0.72, 37.09)
D-dimer >= 1.0 mg/L	4	718	2.56 (2.10, 3.13)
D-dimer >= 0.5 mg/L	3	569	1.54 (1.32, 1.80)
D-dimer 0.5-1.0 mg/L	4	718	0.45 (0.31, 0.64)
D-dimer <= 0.5 mg/L	4	718	0.19 (0.12, 0.30)
Lymphocyte count < 0.8 - 1.1 x 10^9/ml	4	841	2.07 (1.51, 2.84)
WBC >= 4 x 10^9/ml	3	567	1.07 (0.81, 1.41)
WBC < 3.5 - 4 x 10^9/ml	3	567	0.34 (0.20, 0.56)
WBC 4-10 x 10^9/ml	3	567	0.65 (0.54, 0.78)
Outcome = severe disease			

Male sex	11	4582	1.30 (1.11, 1.53)
Comorbidities			
Coronary heart disease	9	4364	3.69 (1.75, 7.77)
Chronic kidney disease	3	3516	3.02 (0.63, 14.6)
Diabetes mellitus	11	4582	2.57 (1.59, 4.17)
COPD	7	1033	2.47 (1.34, 4.52)
Hypertension	11	4582	2.29 (1.61, 3.26)
Symptoms			
Dyspnea	7	1473	6.28 (3.10, 12.7)
Fever	10	4504	1.13 (1.05, 1.22)
Cough	9	1775	1.11 (0.87, 1.42)
Laboratory tests			
Procalcitonin > 0.05 ng/mL	3	448	4.06 (0.65, 25.3)
C-reactive protein > 5 -10 mg/L	3	448	1.68 (1.47, 1.93)

Table 3. Weighted mean differences (WMD) between patients with and without the outcome. Variables reported by fewer than 3 studies are not included but can be found in the online Appendix B.

Risk factor	Studies	Patients	WMD (95% CI)
Outcome = death			
CRP (mg/L)	4	1016	40.4 (27.4, 53.3)
Age (years)	7	1418	18.5 (15.4, 21.6)
D-dimer (mg/L)	4	870	7.8 (6.1, 9.4)
Heart rate (beats/minute)	3	486	5.3 (1.7, 8.9)
Neutrophil count (x 10^9/ml)	3	679	4.3 (2.7, 5.8)
WBC count (x 10^9/ml)	6	1314	4.0 (3.4, 4.6)
Respiratory rate	3	486	3.1 (1.5, 4.7)
Procalcitonin (ng/ml)	3	763	0.34 (0.27, 0.40)
Oxygen saturation (%)	4	823	-8.9 (-11.9, -5.9)
Lymphocyte count (x 10^9/ml)	6	1314	-0.41 (-0.50, -0.32)
Outcome = severe disease			
CRP (mg/L)	4	731	34.2 (15.4, 53.1)
Age (years)	8	2223	14.1 (10.9, 17.6)
Neutrophil count (x 10^9/ml)	5	752	0.94 (-0.42, 2.3)
WBC count (x 10^9/ml)	5	954	0.73 (-0.63, 2.1)
D-dimer (mg/L)	5	604	0.30 (0.06, 0.55)
Lymphocyte count (x 10^9/ml)	5	948	-0.44 (-0.52, -0.36)
Outcome = severe disease or death			
CRP (mg/L)	4	4531	60.5 (47.9, 73.2)
Age (years)	5	4641	15.9 (10.4, 21.3)
Neutrophil count (x 10^9/ml)	4	1912	2.6 (2.1, 3.2)
WBC count (x 10^9/ml)	3	322	2.0 (0.98, 3.0)
Procalcitonin (ng/ml)	3	4420	0.13 (-0.30, 0.56)
Oxygen saturation (%)	3	2940	-4.4 (-7.3, -1.4)
Lymphocyte count	5	4641	-0.63 (-1.0, -0.22)

Table 4. Summary of variables included in multivariate models to predict an adverse prognosis for COVID-19

Variable	Zhang, 2020 (J Clin Virol)	Zhou, 2020 (PLOS One)	Xu, 2020 (Theranostics)	Liu, 2020 (J Clin Virol)	Jang, 2020 (JKMS)	Hou, 2020 (Infectious Diseases)	Yu, 2020 (Theranostics)	Wang, 2020 (Critical Care)	Zhou, 2020 (Lancet)	Liu, 2020 (Chin Med J)	Liang, 2020 (JAMA IM)	Xie, 2020 (medRxIV)	Yan, 2020 (medRxiv)	Hu, 2020	Luo, 2020 (Clin Infect Dis)	Petrilli, 2020 (BMJ)	Li, 2020	Number of models including this variable
Demographics																		
Age (increasing)			x			x		x	x	x	x	x		x	x	x	x	11
Male sex	x							x										2
Vital signs																		
Temperature (elevated)		x			x					x								3
Oxygen saturation (decreased)					x							x						2
Comorbidities																		
Presence of comorbidities	x		x								x							3
Diabetes mellitus					x									x				2
Tobacco use										x				x				2
History of cancer											x					x		2

Hypertension		x															1
Cardiovascular disease		x															1
Heart failure															x		1
Chronic liver disease		x															1
Chronic kidney disease		x															1
Use of hypnotic													x				1
Symptoms																	
Dyspnea		x									x						2
Cough		x															1
Hemoptysis											x						1
Loss of consciousness											x						1
Labs																	
C-reactive protein (elevated)	x			x		x				x			x		x	x		7
Lymphocyte count (decreased)	x		x			x						x	x			x		6
Lactate dehydrogenase (increased)											x	x	x				x	4
WBC count (increased)			x											x				2
Neutrophil count (increased)														x	x			2
Troponin (increased)														x		x		2
Procalcitonin (increased)				x												x		2
D-dimer (increased)									x							x		2

Interleukin-6 > 32.1 pg.ml				x													1
CK-MB (elevated)					x												1
Albumin (decreased)										x							1
Neutrophil/lymphocyte ratio											x						1
Direct bilirubin (increased)											x						1
Serum creatinine (increased)															x		1

Table 5. Proposed clinical prediction rules (CPRs) in the medical literature.

Study	Predictor Variables	Outcome Predicted	Validation (Country)	Type of CPR With Outcome
Lu, 2020 *	Age, c-reactive protein (CRP)	Death	Internal validation (China)	Classification tree: Low: 0% mortality Mod: 6% mortality High: 33% mortality
Xie, 2020	Age, lactate dehydrogenase (LDH), lymphocytes, SpO2	Death	External validation in 1 hospital (China)	Probability assessment using full logistic model as nomogram
Yan, 2020	LDH, CRP, lymphocytes	Death	Internal validation (China)	Classification tree
Yu, 2020	Age, sex, diabetes mellitus, lymphocytes, procalcitonin	Death	Internal validation (China)	Risk score High risk (> 3 points): 22.8% Low risk (<= 3 points): 5.4%)
Shi, 2020	Age, sex, hypertension	Death or severe disease	Internal validation (China)	0 factors: 0% 1 factor: 6% 2 factors: 19% 3 factors: 40%
Galloway, 2020	Age, sex, race, oxygen saturation, chest radiograph, neutrophils, CRP, albumin, creatinine, diabetes	Death or critical care	Internal validation (UK)	Risk score High risk (>= 4 points): 40.7% Low risk (< 4 points): 12.4%

	mellitus, hypertension, chronic lung disease			
Petrilli, 2020	Age, SpO2, procalcitonin, troponin, CRP, hypertension	Severe disease	Internal validation (US)	Classification tree
Liang, 2020	Age, neutrophil/lymphocyte ratio, LDH, direct bilirubin, chest radiograph, hemoptysis, dyspnea, unconsciousness, comorbidities, cancer	Severe disease	External validation in 3 hospitals (China)	Logistic regression model requiring online calculator
Zhou, 2020	Temperature, cough, dyspnea, hypertension, chronic liver disease, chronic kidney disease, cardiovascular disease	Severe disease	Internal validation (China)	Nomogram
Kaeuffer, 2020 [52]	Age, BMI, sex, dyspnea, neutrophil count, lymphocyte count, CRP	Severe disease	External validation	Risk score: Low risk (≤ 6): 13% Moderate risk (6-14): NR High risk (> 14): 66%
Knight SR, 2020 [53]	Age, sex, number of comorbidities, respiratory rate, SpO2, level of consciousness, urea level, CRP	Mortality	External validation	Risk score from 0 to 21 points. Low risk (0-3): 1.2% Intermediate risk (4-8): 9.9% High risk (9-14): 31.4% Very high risk (≥15): 61.5%

*. Study included some patients with suspected but not confirmed COVID-19. Preprint at MedRxIV: Lu J, et al. ACP risk grade: a simple mortality index for patients with confirmed or suspected severe acute respiratory syndrome coronavirus 2 disease (COVID-19) during the early stage of outbreak in Wuhan https://doi.org/10.1101/2020.02.20.20025510.

Appendices

Appendix A: Search strategy

("betacoronavirus"[mh] OR "coronavirus"[tiab] OR "corona-virus"[tiab] OR "COVID-19"[tiab] OR "COVID19"[tiab] OR "2019-nCoV"[tiab] OR "nCoV"[tiab] OR "SARS-CoV-2"[tiab] OR "SARSCOV2"[tiab] OR "2019-nCov"[tiab] OR "2019 coronavirus"[tiab] OR "novel coronavirus"[tiab]) AND ("risk factor"[tiab] OR "validation"[tiab] OR "prediction rule"[tiab] OR "clinical prediction"[tiab] OR "risk model"[tiab] OR "prediction model"[tiab] OR "prognosis"[tiab] OR "prognostic"[tiab] OR "Predictive value of tests"[mh] OR "prognosis"[mh] OR "prognosis"[mh])

Appendix B: Full dataset

Association between categorical variables and mortality, severe disease, or both in patients with COVID-19. Full dataset.

Risk Factor	Studies	Patients	RR (95% CI)
Outcome = Death			
Age < 39-40	1	274	0.01 (0.00, 0.21)
Age < 45	1	107	0.21 (0.06, 0.79)
Age > 45	1	107	1.79 (1.38, 2.32)
Age > 75	1	107	10.42 (3.58, 30.33)
Age >= 40	1	274	1.49 (1.33, 1.66)
Age >= 60 - 65	3	483	2.62 (1.91, 3.58)
Age 40 - 60	1	274	0.55 (0.34, 0.89)
Age 45 - 59	1	107	0.19 (0.03, 1.34)
Age 60 - 75	1	107	2.03 (0.97, 4.23)
Any comorbidity	1	692	2.99 (2.37, 3.77)
Chronic kidney disease	5	1562	5.11 (2.18, 11.98)
COPD	9	2213	3.79 (2.51, 5.72)
Coronary heart disease	9	2213	5.27 (2.89, 9.58)
Cough	5	1366	1.02 (0.93, 1.13)
CRP > 100 mg/L	2	243	4.16 (2.71, 6.37)
CRP >= 3 mg/L	1	102	1.19 (1.04, 1.36)
CRP increased	1	581	1.42 (1.29, 1.55)
D-dimer <= 0.5 mg/L	4	718	0.19 (0.12, 0.30)
D-dimer > 21 mg/L	1	247	17.53 (5.54, 55.49)
D-dimer >= 0.5 mg/L	3	569	1.54 (1.32, 1.80)
D-dimer >= 1.0 mg/L	4	718	2.56 (2.10, 3.13)
D-dimer 0.5-1.0 mg/L	4	718	0.45 (0.31, 0.64)
D-dimer increased	1	371	2.63 (1.91, 3.63)
Diabetes mellitus	9	2213	2.15 (1.46, 3.15)
Dyspnea	3	1073	3.47 (1.67, 7.18)
Fever	6	1530	1.10 (0.95, 1.28)
Heart rate > 100	1	274	1.66 (1.23, 2.25)
Heart rate >= 125	1	191	12.55 (0.61, 257.13)
Hypertension	9	2213	2.34 (1.80, 3.05)
LDH increased	3	831	5.16 (0.72, 37.09)
Lymphocyte count < 0.5	1	274	7.84 (3.84, 16.00)
Lymphocyte count < 0.8 - 1.1	4	841	2.07 (1.51, 2.84)

Lymphocyte count >= 1	1	274	0.17 (0.09, 0.31)
Lymphocyte count 0.5 - 0.8	1	274	1.53 (1.07, 2.19)
Lymphocyte count 0.8 - 1	1	274	0.81 (0.46, 1.43)
Lymphocytes decreased	1	547	2.10 (1.87, 2.36)
Male sex	9	2213	1.24 (1.08, 1.43)
Neutrophil count > 6.3	1	274	6.29 (3.94, 10.04)
Neutrophils increased	1	544	6.12 (3.86, 9.70)
Oxygen saturation < 90 - 93	3	718	6.07 (4.27, 8.63)
Procalcitonin < 0.05 ng/mL	1	236	0.02 (0.00, 0.15)
Procalcitonin < 0.1 ng/mL	1	164	0.44 (0.31, 0.64)
Procalcitonin > 0.05 ng/ml	1	102	1.79 (1.45, 2.22)
Procalcitonin >= 0.1 - 0.25 ng/mL	1	164	2.53 (1.34, 4.79)
Procalcitonin >= 0.25 - 0.5 ng/mL	4	728	9.59 (3.71, 24.82)
Procalcitonin >= 2.0 ng/mL	1	236	24.71 (1.44, 423.13)
Procalcitonin 0.05 - 0.5 ng/mL	1	236	1.31 (1.04, 1.65)
Procalcitonin 0.5 - 2.0 ng/mL	1	236	13.13 (4.10, 42.04)
Procalcitonin increased	1	455	1.48 (1.18, 1.85)
Respiratory rate < 24	1	274	0.48 (0.38, 0.60)
Respiratory rate > 20 - 30	4	841	3.80 (2.13, 6.78)
Respiratory rate 24-30	1	274	3.02 (1.79, 5.10)
SBP < 90 mm Hg	2	274	5.70 (1.23, 26.34)
SBP >=140 mm Hg	1	274	2.16 (1.49, 3.12)
SBP 90-140 mm Hg	1	274	0.62 (0.51, 0.76)
Troponin > 34.2	1	101	6.96 (2.61, 17.17)
WBC < 3.5 - 4	3	567	0.34 (0.20, 0.56)
WBC >= 4	3	567	1.07 (0.81, 1.41)
WBC >= 9.5 - 10	3	567	5.73 (2.48, 13.27)
WBC 4-10	3	567	0.65 (0.54, 0.78)
WBC increased	1	630	16.08 (9.05, 28.58)
Outcome = Severe disease or death			
Age >= 40	1	323	1.13 (1.07, 1.19)
Age >= 60 - 65	1	323	2.06 (1.56, 2.74)
Chronic kidney disease	1	1590	4.45 (1.76, 11.29)
COPD	2	1913	5.63 (1.07, 29.69)
Coronary heart disease	1	1590	3.15 (1.75, 5.57)
Cough	2	1821	1.06 (0.96, 1.17)
CRP >= 3 mg/L	1	306	1.13 (1.07, 1.19)
Diabetes mellitus	2	1913	3.24 (2.41, 4.36)
Dyspnea	2	1717	3.09 (2.59, 3.68)

Fever	2	1859	1.01 (0.96, 1.07)
Hypertension	2	1913	2.00 (1.06, 3.78)
LDH increased	1	87	3.32 (1.75, 6.32)
Lymphocyte count < 2.0	1	305	1.57 (1.33, 1.84)
Male sex	2	1901	1.19 (1.06, 1.33)
Neutrophil count > 7.5	1	305	3.02 (2.28, 3.99)
WBC >= 9.5 - 10	1	305	9.14 (3.94, 21.24)
Outcome = Severe disease			
Age < 39-40	1	198	0.29 (0.08, 1.11)
Age > 75	1	2729	1.69 (1.49, 1.93)
Age >= 40	1	198	1.39 (1.15, 1.68)
Age >= 50	1	198	1.62 (1.23, 2.14)
Age >= 60 - 65	2	564	2.53 (1.89, 3.40)
Age >= 70	1	198	4.71 (2.33, 9.53)
Age 40 - 49	1	198	0.67 (0.17, 2.61)
Age 50 - 59	1	198	0.13 (0.01, 2.11)
Age 60 - 69	1	198	1.74 (0.90, 3.33)
Asthma or COPD	1	2729	1.05 (0.88, 1.24)
Chronic kidney disease	3	3516	3.02 (0.63, 14.60)
COPD	7	1033	2.47 (1.34, 4.52)
Coronary heart disease	9	4364	3.69 (1.75, 7.77)
Cough	9	1775	1.11 (0.87, 1.42)
CRP > 5 -10 mg/L	3	448	1.68 (1.47, 1.93)
D-dimer >= 0.5 mg/L	2	877	3.10 (1.45, 6.64)
Diabetes mellitus	11	4582	2.57 (1.59, 4.17)
Dyspnea	7	1473	6.28 (3.10, 12.74)
Fever	10	4504	1.13 (1.05, 1.22)
Heart rate >= 90	1	366	0.88 (0.43, 1.79)
Hypertension	11	4582	2.29 (1.61, 3.26)
LDH increased	1	110	2.65 (1.93, 3.63)
Lymphocyte count < 0.8 - 1.1	2	308	27.36 (0.96, 778.27)
Lymphocyte count > 3.2	1	198	0.13 (0.02, 0.90)
Male sex	11	4582	1.30 (1.11, 1.53)
Neutrophil count < 1.8	1	198	0.26 (0.02, 4.12)
Neutrophil count > 6.3	1	308	4.13 (2.31, 7.37)
Oxygen saturation < 88	1	2729	3.69 (3.06, 4.46)
Oxygen saturation < 96	1	366	1.39 (0.77, 2.52)
Procalcitonin > 0.05 ng/mL	3	448	4.06 (0.65, 25.29)
Respiratory rate > 20 - 30	2	477	2.11 (0.20, 22.05)

SBP >= 110 mm Hg	1	366	1.07 (1.01, 1.13)
WBC < 3.5 - 4	1	198	0.67 (0.17, 2.61)
WBC >= 9.5 - 10	2	308	5.52 (2.41, 12.66)

Association between continuous variables and mortality, severe disease, or both in patients with COVID-19. Full dataset

Risk factor	Studies	Patients	WMD (95% CI)
Outcome = death			
Age	7	1418	18.5 (15.4, 21.6)
Systolic blood pressure	1	105	12.5 (0.64, 24.3)
Mean arterial pressure	2	381	8.0 (4.3, 11.8)
D-dimer (mg/L)	4	870	7.6 (6.1, 9.4)
Heart rate	3	486	5.3 (1.7, 8.9)
CRP (mg/L)	4	1016	40.4 (27.4, 53.3)
Neutrophil count	3	679	4.3 (2.7, 5.8)
WBC count	6	1314	4.0 (3.4, 4.6)
Respiratory rate	3	486	3.1 (1.5, 4.7)
Procalcitonin	3	763	0.34 (0.27, 0.40)
Oxygen saturation	4	823	-8.9 (-11.9, -5.9)
Lymphocyte count	6	1314	-0.4 (-0.5, -0.3)
Outcome = severe disease or death			
CRP (mg/L)	4	4531	60.5 (47.9, 73.2)
Age	5	4641	15.9 (10.4, 21.3)
Systolic blood pressure	1	110	8.6 (0.07, 17.1)
Neutrophil count	4	1912	2.6 (2.1, 3.2)
WBC count	3	322	2.0 (0.98, 3.0)
Respiratory rate	2	211	1.5 (0.02, 3.3)
Heart rate	2	211	0.99 (-3.7, 5.5)
D-dimer (mg/L)	1	2729	0.31 (0.27, 0.36)
Procalcitonin	3	4420	0.13 (-0.30, 0.56)

Mean arterial pressure	1	101	-6.1 (-17.8, 5.6)
Oxygen saturation	3	2940	-4.4 (-7.3, -1.4)
Lymphocyte count	5	4641	-0.63 (-1.0, -0.22)
Outcome = severe disease			
CRP (mg/L)	4	731	34.2 (15.4, 53.1)
Age	8	2223	14.1 (10.9, 17.6)
Oxygen saturation	1	78	12.3 (2.6, 22.1)
Heart rate	1	78	7.3 (-21.4, 36.0)
Neutrophil count	5	752	0.94 (-0.42, 2.3)
WBC count	5	954	0.73 (-0.63, 2.1)
D-dimer (mg/L)	5	604	0.30 (0.06, 0.55)
Procalcitonin	2	276	0.05 (-0.08, 0.19)
Respiratory rate	1	78	0.00 (-15.6, 15.6)
Lymphocyte count	5	948	-0.44 (-0.52, -0.36)

Appendix C: Evaluation of study quality using the Quality of Prognostic Studies (QUIPS) Tool

Table 2. Study quality assessment using the QUIPS tool

	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting
Yu, 2020	M	L	L	L	L	L
Wang, 2020	M	L	L	L	L	L
Chen, 2020	M	H	L	L	H	L
Zhou, 2020	M	L	L	L	L	L
Liu, 2020	M	L	L	L	L	L
Liang, 2020	M	L	L	L	L	L
Xie, 2020	M	L	L	L	L	L
Yan, 2020	M	H	L	L	L	L
Cao, 2020	M	L	L	L	H	L
Hu, 2020	M	H	L	L	L	L
Luo, 2020	M	L	L	L	L	L
Petrilli, 2020	M	H	L	L	L	L
Wu, 2020	M	H	L	L	H	L
Li, 2020	M	H	L	L	L	L
Jang, 2020	M	L	L	L	L	L
Xu, 2020	M	H	L	L	L	L
Zhou, 2020	M	L	L	L	L	L
Hou, 2020	M	L	L	L	L	L

Zhang, 2020	M	H	L	L	L	L
Liu, 2020	M	L	L	L	L	L
Zhu, 2020	M	L	L	L	L	L
Hu, 2020	M	L	L	L	L	L

L = low risk of bias, M = moderate risk of bias and H = high risk of bias.

	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting
High risk of bias	Specialized population (ie pregnant, elderly) or subset of very ill patients only	Incomplete outcome ascertainment (some patients still hospitalized)	Unclear definition for prognostic factors	Outcome not defined	No multivariate analysis performed	Selective reporting of results, no clear analytic strategy
Moderate risk of bias	Only inpatients	Complete ascertainment but > 10% loss to follow-up	Post-hoc selection of cutpoints	Unclear definition		
Low risk of bias	Inpatient & outpatient	Complete ascertainment and <10% loss to follow-up	Typical cutoffs used, clearly defined	Clear and reproducible definition	Multivariate analysis reported	Full reporting, analytic strategy clearly described