Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Value of leukocytosis and elevated C-reactive protein in predicting severe coronavirus 2019 (COVID-19): A systematic review and meta-analysis

Takayuki Yamada[a,c,*,1], Mako Wakabayashi[b,1], Takahiro Yamaji[c], Nitin Chopra[a], Takahisa Mikami[a], Hirotaka Miyashita[a], Satoshi Miyashita[a]

[a] Department of Medicine, Mount Sinai Beth Israel, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[b] Department of Medicine, Nippon Medical School, Tokyo, Japan
[c] Department of Medical Science and Cardiorenal Medicine, Yokohama City University Graduate School of Medicine, Yokohama, Japan

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ABSTRACT

Background: Since December 2019, coronavirus 2019 (COVID-19) has spread worldwide. Identifying poor prognostic factors is helpful for risk stratification. In this meta-analysis, we investigated the association between severe COVID-19 and a change in white blood cell (WBC) count, an elevation of C-reactive protein (CRP), and fever. Moreover, we aimed to evaluate the diagnostic accuracy of leukocytosis and an elevation of CRP.

Methods: We performed a systematic search of PubMed, EMBASE, Scopus, and the Cochrane Library through April 20th, 2020. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. A sensitivity analysis was conducted according to the study size (> 200 or < 200) and median age (> 55 or < 55). Meta-regression analyses were conducted to examine possible sources of heterogeneity. We calculated the diagnostic accuracy of leukocytosis and CRP.

Results: Eighteen studies with 3278 patients were selected. Fever, leukocytosis, and elevated CRP were associated with poor outcomes (OR (95% CI) 1.63 (1.06–2.51), 4.51 (2.53–8.04), and 11.97 (4.97–28.8), respectively). Leukopenia was associated with a better prognosis (OR 0.56, 95% CI 0.40–0.78). Sensitivity analyses showed similar tendencies. Meta-regression analysis for leukocytosis indicated that age, dyspnea, and hypertension contributed to heterogeneity. The pooled area under the leukocytosis and CRP curves were 0.70 (0.64–0.76) and 0.89 (0.80–0.99), respectively.

Conclusion: In patients with COVID-19, fever, leukocytosis, and an elevated CRP were associated with severe outcomes. Leukocytosis and CRP on arrival may predict poor outcomes.

1. Background

Coronaviruses are enveloped, non-segmented, positive-sense RNA viruses that cause diseases ranging from the common cold to more severe respiratory infections. In the past two decades, two highly-pathogenic human coronaviruses, severe acute respiratory syndrome coronavirus (SARS-CoV) [1,2] and Middle East respiratory syndrome coronavirus (MERS-CoV) [3,4] have caused epidemics, with mortality rates of 10% for SARS-CoV and 37% for MERS-CoV [5,6].

In December 2019, the first cases of acute respiratory illness caused by coronavirus 2019 (COVID-19) were identified in Wuhan, Hubei Province, China [7]. Since then, this pathogen has spread worldwide. In some cases, COVID-19 causes severe pneumonia that can progress to acute respiratory distress syndrome (ARDS) or multiple organ failure [8]. Since there is no established treatment for COVID-19, identifying poor prognostic factors is helpful for risk stratification.

As prior studies reported [9], the elevation of inflammatory markers is associated with severe disease. In this study, we performed a meta-analysis to investigate the association between severe COVID-19 and well-known markers of inflammation, including leukocytosis, the elevation of C-reactive protein (CRP), and fever. Moreover, we aimed to evaluate the diagnostic accuracy of leukocytosis and an elevation of CRP by conducting a meta-analysis of the data extracted from relevant studies.

2. Methods

The search strategy was conducted in accordance with PRISMA

* Corresponding author at: Department of Medicine, Mount Sinai Beth Israel, Icahn School of Medicine at Mount Sinai, 281 1st Avenue, New York, NY, 10003, USA.
E-mail address: Takayuki.Yamada@mountsinai.org (T. Yamada).
[1] These authors contributed equally to this work.

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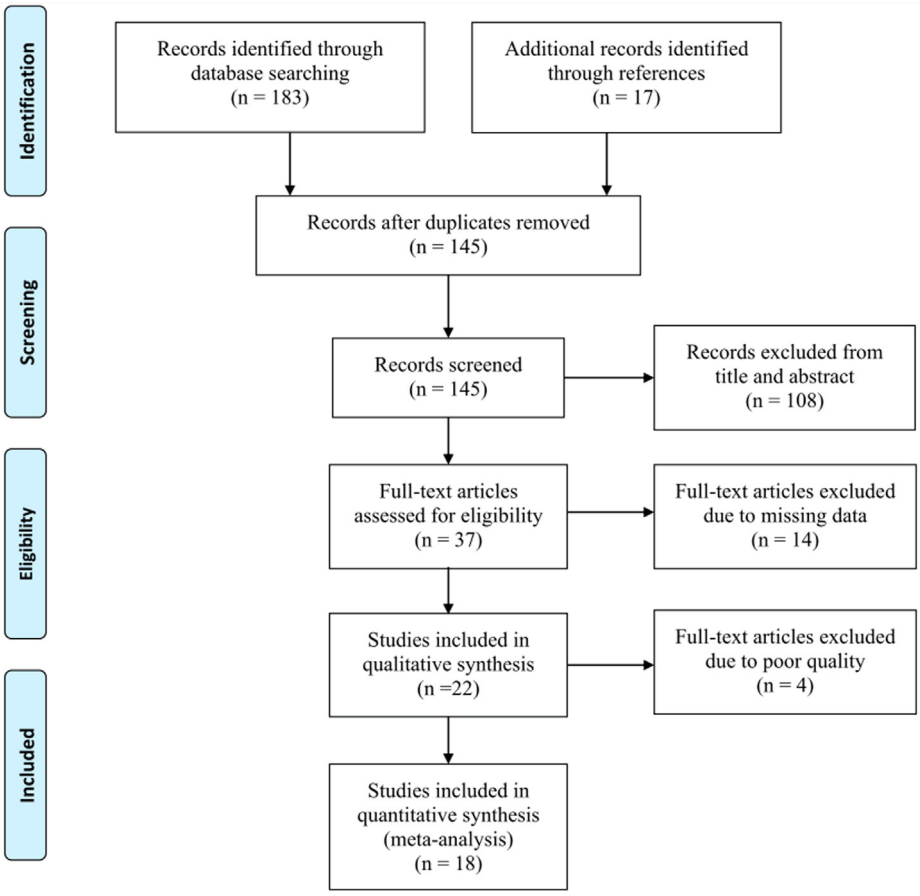

Fig. 1. Flow diagram for study selection.

(Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [10]. We performed a systematic search of PubMed, EMBASE, Scopus, and the Cochrane Library from inception to April 20th, 2020. The following keywords were applied: ("severe acute respiratory syndrome coronavirus 2" [MeSH] OR COVID-19 OR SARS-CoV-2 OR "novel coronavirus") AND ("blood cell count" [MeSH] OR CBC OR "complete blood count" OR leukocytes [MeSH] OR WBC OR "white blood cell" OR leukocytosis OR leukopenia OR fever OR febrile OR "body temperature") AND ("Intensive care units" [MeSH] OR ICU OR critical OR "critical illness" [MeSH] OR "critical care" [MeSH] OR "respiration, artificial" [MeSH] OR "mechanical ventilation" OR intubation OR ARDS OR "acute respiratory distress syndrome"). We restricted the search to human studies. Reference lists included in studies for meta-analysis were reviewed to minimize missing relevant studies. Two independent and blinded authors (TY and MW) reviewed the search results separately to select the studies based on inclusion and exclusion criteria. When a consensus was not reached between the two authors, a third author (TY) was consulted to reach a decision.

Studies were selected if they met the following criteria: (1) they included adult patients (> 18 years old); (2) they included COVID-19 patients confirmed by reverse transcription-polymerase chain reaction (RT-PCR); (3) they reported vital signs and laboratory data on admission; (4) they divided patients into two groups: those with poor outcomes, including hypoxia, intensive care unit (ICU) admission, mechanical ventilation, ARDS, or death, and a non-severe group; and (5) they investigated the association between various ranges of white blood cell counts (WBC), CRP, or body temperature (BT) on admission and poor outcomes. We selected studies that defined leukocytosis as WBC $> 9.5 \times 10^3/mm^3$ or more, leukopenia as WBC $< 4.0 \times 10^3/mm^3$ or less, and elevation of CRP as CRP > 8 mg/L or more. Studies were excluded if (1) they included non-human subjects; (2) they included patients who were not confirmed by RT-PCR; (3) they did not define severe diseases clearly; (4) there was insufficient data for estimating the odds ratio (OR) even after contacting the authors; and (5) the data was not available in English. The primary outcome was severe COVID-19 as defined in each study.

All data from eligible studies were abstracted independently by two investigators (TY and MW). Discrepancies were resolved by discussion among the authors and by referencing the original report. For each study, data regarding the differences in WBC/CRP/BT and poor outcomes in each cohort were abstracted. If the adjusted OR was reported, it was used. If the number of patients in each cohort were reported, we calculated the unadjusted OR, which was used in the analysis.

All analyses were conducted using Comprehensive Meta-Analysis version 3 (Biostat, Englewood, New Jersey, USA) and "mada" 0.5.9 package (R Foundation for Statistical Computing, Vienna, Austria). To detect an association in our meta-analysis, the ORs and 95% confidence intervals (CIs) were estimated using Mantel-Haenszel methods. A random-effects model was used to determine the association between WBC, CRP, or BT and poor outcomes. All reported probability values were 2-sided, with a significance set to < 0.05. Heterogeneity was assessed by the probability value of the χ^2 statistic and I^2 [11,12]. We regarded an I^2 of < 40% as "heterogeneity might not be important" and > 50% as "may represent substantial heterogeneity" based on the suggestion of the Cochrane Handbook for Systemic Review of Interventions [13]. To further detect clinically significant heterogeneity, a sensitivity analysis was conducted according to the study size (> 200 or < 200) and median age (> 55 or < 55).

Publication bias of studies with different sample sizes was assessed by the Begg and Mazumdar rank correlation test [14] and Egger's regression test [15]. Univariable meta-regression analyses were conducted to examine the effect of study-level variables: age, study size,

Table 1
Definitions of included studies. ICU, intensive care unit; ARDS, acute respiratory distress syndrome; WBC, white blood cell; N/A, not available.

Author (year)	Design	Outcome	Low temperature (°C)	High temperature (°C)	Low WBC ($\times 10^3/mm^3$)	High WBC ($\times 10^3/mm^3$)	High CRP (mg/L)
Chen G 2020	Retrospective case series	RR ≥ 30/min, SpO2 ≤ 93%, PaO2/FiO2 < 300	N/A	> 39.0	< 4	> 10	N/A
Chen J 2020	Retrospective case series	ICU admission	N/A	N/A	N/A	N/A	N/A
Chen T 2020	Retrospective case series	Mortality	N/A	N/A	< 4	> 10	N/A
Deng 2020	Retrospective case series	Mortality	N/A	N/A	N/A	N/A	N/A
Guan 2020	Retrospective case series	ICU admission/ventilation/mortality	< 37.5	> 38.0	< 4	> 10	> 10
Huang 2020	Prospective cohort	ICU admission	< 37.3	> 38.0	< 4	> 10	N/A
Li H 2020	Retrospective case series	Mechanical ventilation/septic shock/ICU admission	N/A	N/A	< 3.5	> 9.5	> 100
Li K 2020	Retrospective case series	Tachypnea, hypoxia, mechanical ventilation, shock, ICU admission	N/A	N/A	N/A	N/A	N/A
Liu W2020	Retrospective case series	Mechanical ventilation/septic shock/ICU admission	N/A	N/A	< 4	N/A	> 8.2
Liu Y 2020	Retrospective case series	Mechanical ventilation	N/A	N/A	< 4	> 10	> 10
Wan S 2020	Retrospective case series	RR ≥ 30/min, SpO2 ≤ 93%, PaO2/FiO2 < 300	< 37.3	> 38.0	< 3.5	> 9.5	N/A
Wang 2020	Retrospective case series	ICU admission	N/A	N/A	N/A	N/A	N/A
Wu 2020	Retrospective cohort study	ARDS	N/A	> 39.0	N/A	N/A	N/A
Yang 2020	Retrospective case series	Mortality	N/A	N/A	N/A	N/A	N/A
Zhang J 2020	Retrospective case series	ICU/mechanical ventilation/mortality	N/A	N/A	< 3.5	> 9.5	N/A
Zhang Y 2020	Retrospective case series	RR ≥ 30/min, SpO2 ≤ 93%, PaO2/FiO2 < 300	N/A	N/A	N/A	N/A	> 10
Zheng F 2020	Retrospective case series	RR ≥ 30/min, SpO2 ≤ 93%, PaO2/FiO2 < 300	N/A	N/A	< 4	> 10	> 8
Zhou 2020	Retrospective cohort study	Mortality	< 37.3	N/A	< 4	> 10	N/A

Table 2
Characteristics of included studies. HTN, hypertension; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; WBC, white blood cell; N/A, not available.

Author (year)	Patients	Age	Age > 60 (%)	Male (%)	Smoker (%)	Fever (%)	Cough (%)	Dyspnea (%)	Diarrhea (%)	HTN (%)	DM (%)	COPD (%)	CVD (%)	WBC (x $10^3/mm^3$)
Chen G 2020	21	56	N/A	81	N/A	100	80	52	20	24	14	N/A	N/A	5.7
Chen J 2020	249	51	N/A	50.6	N/A	87	37	7.6	3.2	N/A	10	2	21.7	4.7
Chen T 2020	274	62	56	62	6.9	91	68	44	28	34	17	7	8	5.9
Deng 2020	225	54	N/A	55	N/A	84	38	44	17	26	12	11	7.5	5.8
Guan 2020	1081	47	N/A	58.1	12.6	48.3	67.8	18.7	3.8	15	7.4	1.1	2.5	4.7
Huang 2020	41	49	N/A	73	7	98	76	55	2.6	15	20	2	15	6.2
Li H 2020	132	62	66	56.8	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	5.7
Li K 2020	83	46	N/A	53	N/A	87	78	11	N/A	6	7.8	6	1.2	5.3
Liu W2020	78	38	19	50	6.4	N/A	43.6	25.6	N/A	40	25	10	N/A	5.4
Liu Y 2020	12	63	58	67	N/A	83	92	N/A	17	25	17	8.3	33	5.1
Wan S 2020	135	47	N/A	53	N/A	89	77	13	13	9.7	8.9	0	5.2	5.4
Wang 2020	138	56	N/A	54	N/A	99	59	31	10	31	10	2.9	15	4.5
Wu 2020	170	51	N/A	64	N/A	94	81	40	N/A	19	11	2.5	N/A	5.9
Yang 2020	52	60	52	67	4	98	77	63.5	N/A	N/A	17	8	10	N/A
Zhang J 2020	120	57	N/A	51	6.4	92	75	37	13	30	12	1.4	5	4.7
Zhang Y 2020	115	50	30	43	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Zheng F 2020	161	45	N/A	50	N/A	76	63	14	11	14	4.3	3.7	2.5	4.36
Zhou 2020	191	56	N/A	62	6	94	79	29	5	30	19	3	N/A	6.2

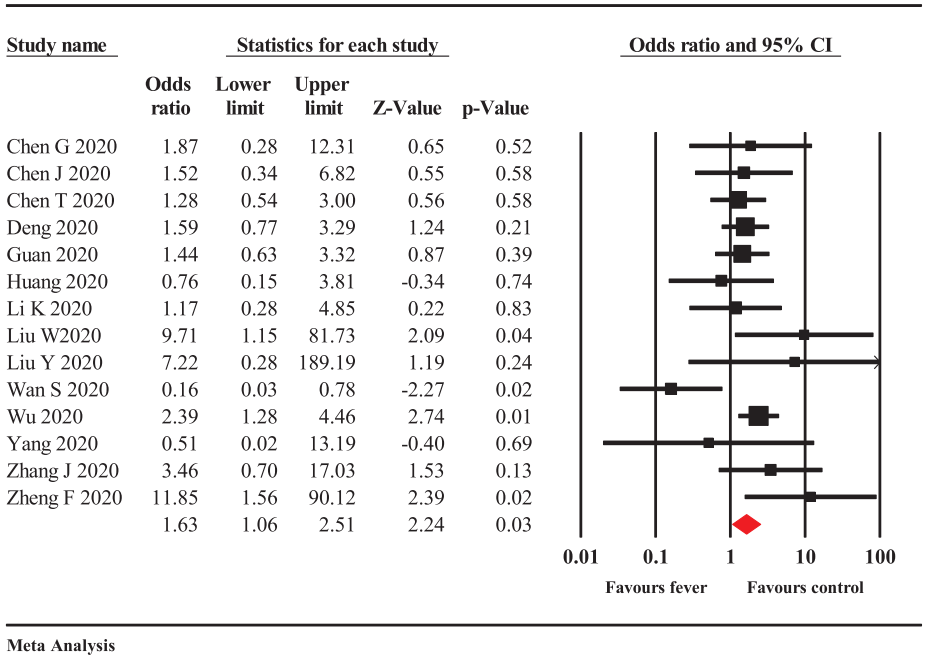

Fig. 2. Forest plot of the association between fever and severe disease in patients with COVID-19. Odds ratio was presented as mean and 95% confidence intervals.

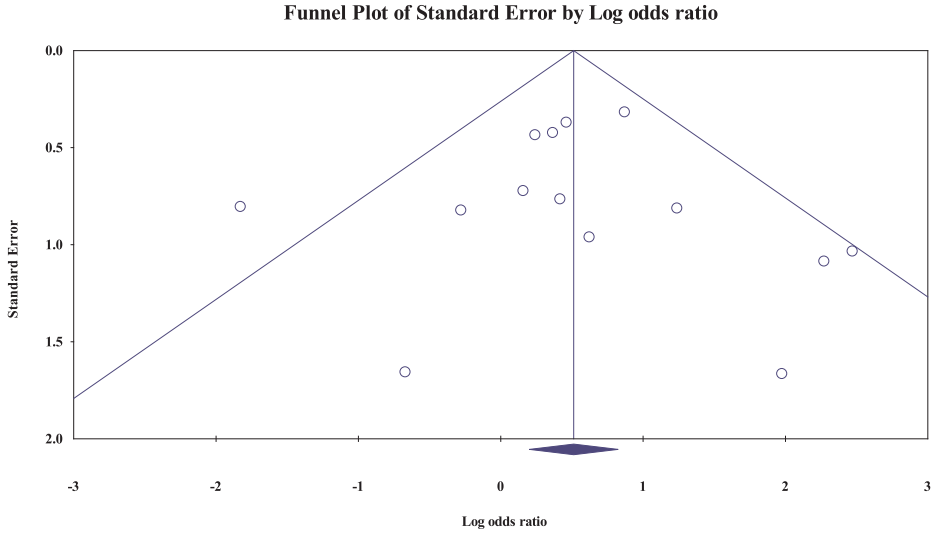

Fig. 3. Funnel plot of fever and severe COVID-19. COVID-19, coronavirus disease 2019.

sex, smoking status, fever, cough, dyspnea, and the presence of hypertension, diabetes, chronic obstructive pulmonary disease (COPD), and cardiovascular disease (CVD). The general linear method was used for meta-regression, weighted by study sample size.

For meta-analysis of diagnostic test accuracy, threshold effects were calculated by Spearman's correlation test, with significance represented by p-values < 0.05. Cochran's Q test and I^2 were used to measure the heterogeneity caused by non-threshold effects. I^2 values $\geq 40\%$ and p-values < 0.05 indicated that the heterogeneity from non-threshold effects was significant. The cut-off of values of WBC and CRP were $> 9.5 \times 10^3/mm^3$ and 8 mg/L, respectively. We calculated the pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), area under the curve (AUC), and corresponding 95% CIs using a bivariate random-effects model.

3. Results

A diagram of the study selection is shown in Fig. 1. Initially, a total of 183 studies were obtained in the primary search from databases, and 17 studies were identified through references. After removing duplicates, 145 studies were screened. By screening titles and abstracts, 108 papers were excluded because they did not meet the inclusion criteria. By assessing full-text articles, 15 studies were excluded due to missing data. By assessing quality, four studies were excluded due to missing definitions of COVID-19 diagnosis and severe disease. Ultimately, 18 studies published up to April 20th, 2020, were selected for our meta-analysis according to the inclusion and exclusion criteria [16–33]. The pooled population consisted of 3278 patients, including 732 patients with poor outcomes.

The definitions of terms and characteristics of the included studies are listed in Tables 1 and 2, respectively. Four studies defined poor outcomes as mortality [17,18,25,27], three studies as ICU admission [16,20,28], one study as mechanical ventilation [23], one study as the

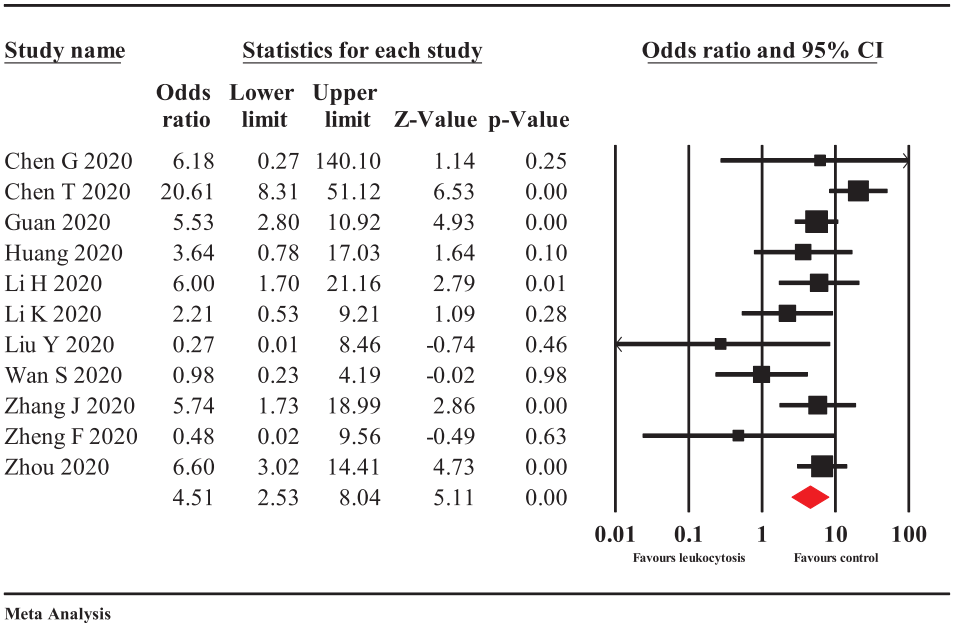

Fig. 4. Forest plot of the association between leukocytosis and severe disease in patients with COVID-19. Odds ratio was presented as mean and 95% confidence intervals.

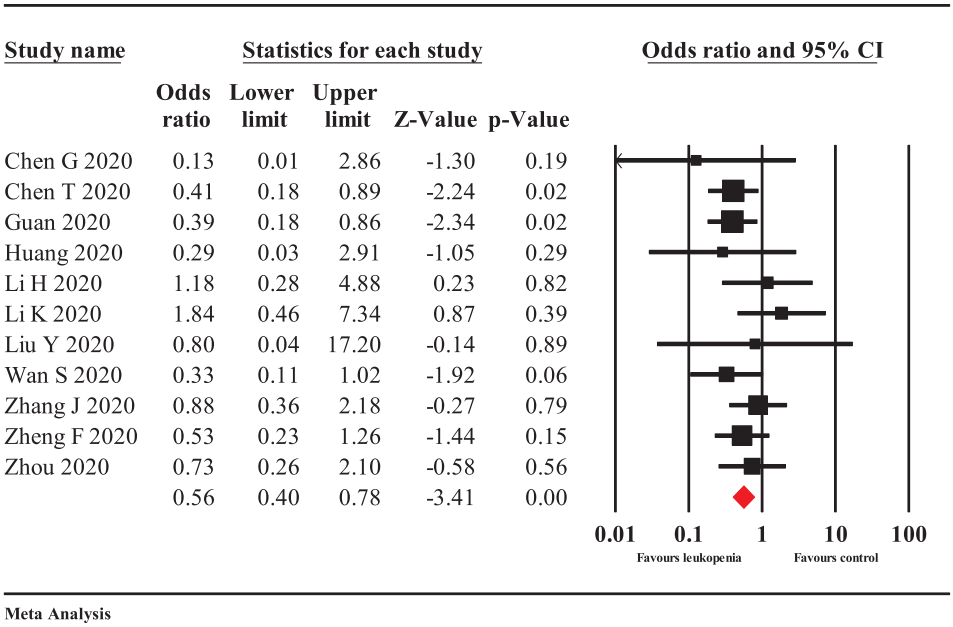

Fig. 5. Forest plot of the association between leukopenia and severe disease in patients with COVID-19. Odds ratio was presented as mean and 95% confidence intervals.

development of ARDS [24], four studies as the composite of tachypnea, hypoxia, and decreased oxygenation index [29,31–33], three studies as the composite of mechanical ventilation, septic shock, and ICU admission [21,23,30], and two studies as the composite of ICU admission, mechanical ventilation, and mortality [19,26]. All the studies except for Huang et al. [20] were retrospective studies. The median age ranged from 38 to 62.5. All the studies defined leukocytosis as WBC more than $10 \times 10^3/mm^3$ and leukopenia as WBC less than $4 \times 10^3/mm^3$, except for two studies that defined leukocytosis as $> 9.5 \times 10^3/mm^3$ and leukopenia as $< 3.5 \times 10^3/mm^3$ [30,31]. Three studies defined an elevated CRP as CRP > 10 mg/L [19,22,32], one study as > 100 mg/L [30], one as > 8.2 mg/L [23], and one as > 8 mg/L [33].

Fever was associated with poor outcomes (OR 1.63, 95% CI 1.06 to 2.51, $p = 0.025$; $I^2 = 34.0\%$) (Fig. 2). The associated Funnel plot was symmetric (Fig. 3). Begg and Mazumdar's rank correlation test and Egger's regression test also indicated no statistically significant publication bias (p = 0.66 and 0.91, respectively). Low BT was not associated with poor outcomes (OR 1.21, 95% CI 0.71–2.07, $p = 0.48$; $I^2 = 0.0\%$).

Next, we investigated leukocytosis, leukopenia, and elevated CRP. Leukocytosis was associated with poor outcomes (OR 4.51, 95% CI 2.53–8.04, $p < 0.001$; $I^2 = 52.6\%$) (Fig. 4). On the other hand, leukopenia was associated with a better prognosis (OR 0.56, 95% CI 0.40–0.78, $p = 0.001$; $I^2 = 0\%$) (Fig. 5). An elevated CRP was associated with severe disease (OR 11.97, 95% CI 4.97–28.8, $p < 0.001$; $I^2 = 47.7\%$) (Fig. 6).

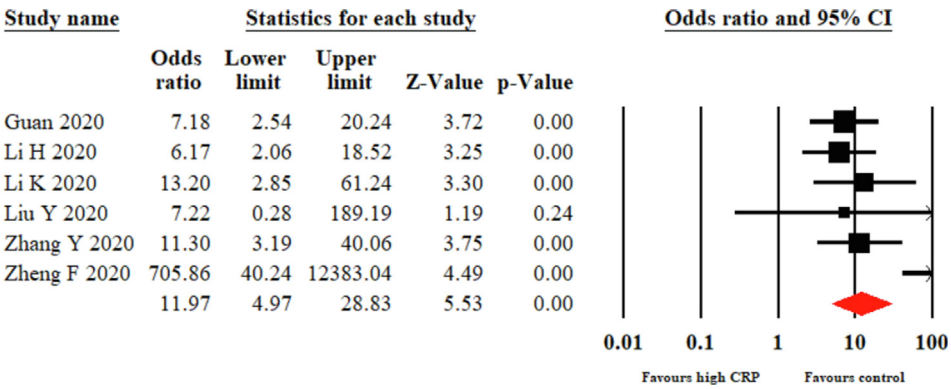

Fig. 6. Forest plot of the association between C-reactive protein (CRP) and severe disease in patients with COVID-19. Odds ratio was presented as mean and 95% confidence intervals.

Table 3
Diagnostic accuracy of WBC and CRP on arrival for severe COVID-19. WBC, white blood cell; CRP, C-reactive protein; LR, likelihood ratio; DOR, diagnostic odds ratio; AUC, area under the curve. Results are presented as mean and 95% confidence intervals.

	WBC	CRP
Sensitivity	0.33 (0.22–0.46)	0.87 (0.74–0.94)
Specificity	0.68 (0.54–0.79)	0.55 (0.30–0.78)
Positive LR	3.42 (2.28–4.83)	2.05 (1.30–3.56)
Negative LR	0.74 (0.61–0.86)	0.26 (0.16–0.38)
DOR	4.69 (2.68–7.64)	8.32 (4.12–15.1)
AUC	0.70 (0.64–0.76)	0.88 (0.79–0.99)

Table 4
Meta-regression analyses of leukocytosis for severe illness. HTN, hypertension; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease.

Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided P-value
Age	0.083	0.040	0.0053	0.16	2.09	0.036
Study size	0.0007	0.0010	−0.0012	0.0026	0.68	0.49
Male (%)	0.034	0.041	−0.047	0.11	0.81	0.42
Smoking (%)	−0.053	0.12	−0.29	0.18	−0.44	0.66
Fever (%)	0.006	0.016	−0.026	0.038	0.39	0.7
Cough (%)	−0.074	0.056	−0.18	0.036	−1.31	0.19
Dyspnea (%)	0.038	0.019	0.0008	0.076	2.0	0.045
HTN (%)	0.069	0.025	0.019	0.12	2.71	0.0066
DM (%)	0.089	0.065	−0.038	0.22	1.38	0.17
COPD (%)	0.087	0.14	−0.18	0.36	0.63	0.53
CVD (%)	−0.044	0.062	−0.17	0.078	−0.70	0.48

3.1. Sensitivity analysis

We performed sensitivity analysis according to study size (number of patients > 200 or < 200). In the four large studies, fever tended to be related with poor outcomes (OR 1.45, 95% CI 0.94 to 2.26, $p = 0.09$; $I^2 = 0\%$). Only one study analyzed low temperature and CRP. Leukocytosis was associated poor outcomes (OR 10.3, 95% CI 2.84 to 37.3, $p < 0.001$, $I^2 = 80.6\%$). Leukopenia was related to a better prognosis (OR 0.40, 95% CI 0.23–0.70, $p = 0.001$, $I^2 = 0\%$). These results were similar in small studies for fever (OR 1.82, 95% CI 0.85–3.90, $p = 0.12$; $I^2 = 0\%$), low BT (OR 0.77, 95% CI 0.34–1.76, $p = 0.53$; $I^2 = 0\%$), leukocytosis (OR 3.45, 95% CI 1.92–6.22, $p < 0.001$; $I^2 = 26.9\%$), and CRP (OR 15.3, 95% CI 4.73–49.3, $p < 0.001$; $I^2 = 56.9\%$). Leukopenia tended to be related to better prognosis (OR 0.68, 95% CI 0.44–1.03, $p = 0.07$; $I^2 = 0\%$).

Another sensitivity analysis according to median age (> 55 or < 55) was performed. In five studies with median age > 55, neither fever nor low BT showed significant association with severe disease (OR 1.65, 95% CI 0.85 to3.22, $p = 0.14$; $I^2 = 0\%$ and OR 0.87, 95% CI 0.25–3.25, $p = 0.82$; $I^2 = 0\%$, respectively). Leukocytosis and CRP were significantly associated with poor outcomes (OR 7.43, 95% CI 3.67–15.0, $p < 0.001$; $I^2 = 42.0\%$ and OR 6.27, 95% CI 2.21–17.8, $p = 0.001$; $I^2 = 0\%$, respectively). Leukopenia tended to be associated with a better prognosis (OR 0.63, 95% CI 0.39–1.01, $p = 0.06$; $I^2 = 0\%$). In nine studies with median age < 55, neither fever nor low BT were related to poor outcomes (OR 1.58, 95% CI 0.89–2.82, $p = 0.012$; $I^2 = 53.6\%$ and OR 1.31, 95% CI 0.72–2.37, $p = 0.38$; $I^2 = 0\%$, respectively). Leukocytosis and CRP showed significant association with poor outcomes (OR 2.65, 95% CI 1.18–5.90, $p = 0.018$; $I^2 = 41.0\%$ and OR 17.7, 95% CI 4.91–63.8, $p < 0.001$; $I^2 = 65.6\%$, respectively). Leukopenia was associated with a better prognosis (OR 0.50, 95% CI 0.30–0.84, $p = 0.009$; $I^2 = 12.0\%$).

3.2. Meta-regression analysis

Since meta-analyses of leukocytosis and CRP suggested heterogeneity, we conducted a univariable meta-regression analysis to examine study-level variables: age, study size, sex, smoking status, fever, cough, dyspnea, and the presence of hypertension, diabetes, COPD, and CVD. Meta-regression analysis studies for leukocytosis indicated that age (p = 0.036), dyspnea (p = 0.045), and hypertension (p = 0.0066) contributed to a source of heterogeneity (Table 4). Regarding CRP, meta-regression analysis did not indicate any source of heterogeneity.

3.3. Diagnostic accuracy of leukocytosis and elevated CRP

The Spearman correlation coefficient and p-value for leukocytosis and CRP were 0.25 and 0.42, and 0.33 and 0.66, respectively, which indicated that there was no significant threshold effect. Next, we evaluated the non-threshold effect using a DOR. The Cochrane-Q and p-value for leukocytosis and CRP were 11.0 and 0.36, and 7.4, 0.19, respectively, indicating minimal heterogeneity that cannot be explained by chance. The I^2 for leukocytosis and CRP were 9.2% and 32.8%, respectively.

The pooled sensitivity, specificity, DOR, AUC, and corresponding 95% CI of leukocytosis and CRP were 0.33 (0.22–0.46), 0.68 (0.54–0.79), 4.69 (2.68–7.64), and 0.70 (0.64–0.76); and 0.86 (0.73–0.94), 0.64 (0.42–0.82), 10.68 (4.57–24.9), and 0.89 (0.80–0.99), respectively (Table 3). Forest plots of sensitivity and specificity are shown in Fig. 7 (leukocytosis) and Fig. 8 (CRP), respectively. We plotted the summary receiver operating characteristic (SROC) curve, which is shown in Fig. 9.

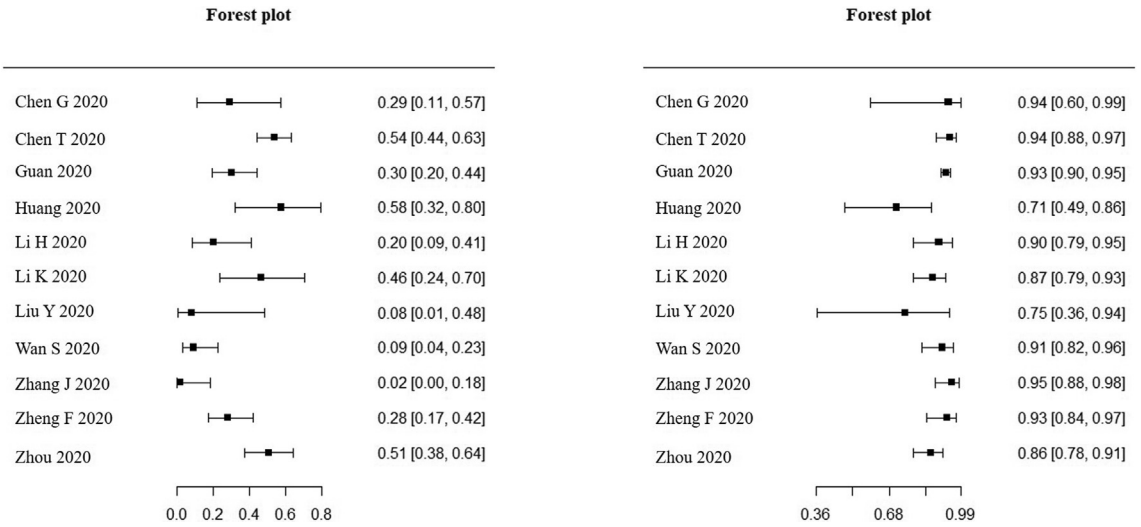

Fig. 7. Forest plot of sensitivity (left) and specificity (right) of leukocytosis. Odds ratio was presented as mean and 95% confidence intervals.

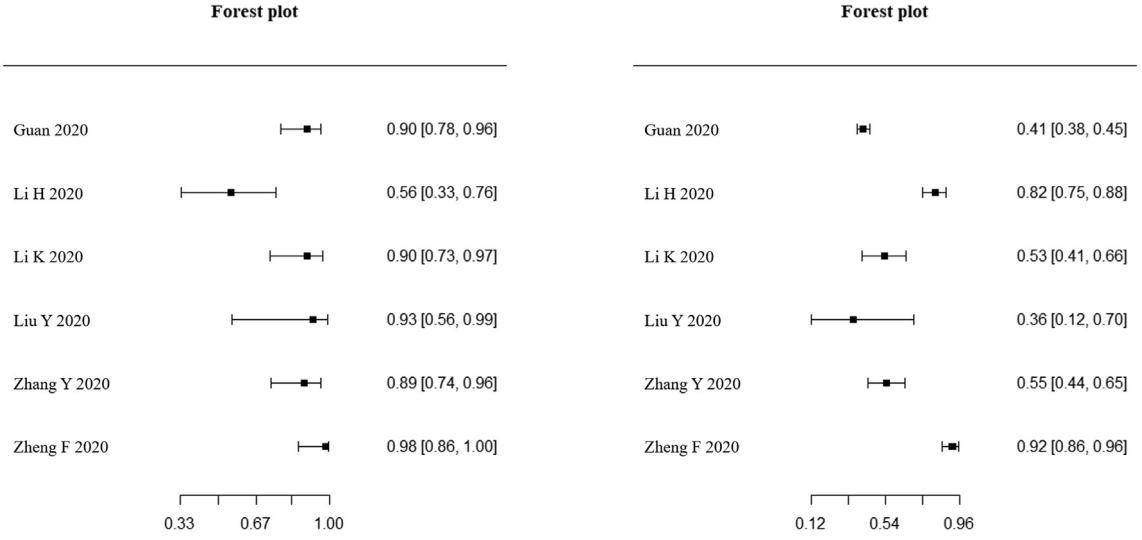

Fig. 8. Forest plot of sensitivity (left) and specificity (right) of C-reactive protein. Odds ratio was presented as mean and 95% confidence intervals.

4. Discussion

As far as we know, this is the first meta-analysis that investigated the potential value of leukocytosis and CRP elevation on the prediction of poor outcomes in COVID-19 patients. Our study revealed that fever, leukocytosis, and CRP elevation were associated with severe COVID-19 infection. Moreover, our study suggested that leukocytosis and CRP on arrival could be biomarkers to predict severe COVID-19.

It has been reported that roughly 5% of COVID-19 patients become critically ill [34]. Given the short time between hospital admission and disease progression [20], it is essential to identify patients who may develop critical illness early on.

COVID-19 and severe acute distress syndrome (SARS) share several clinical manifestations. First, fever is the most common symptom. Second, both high and low leukocyte count have been reported as presentations of SARS and COVID-19 [20,35,36].

It is believed that dysregulation of inflammatory cytokines and chemokines, also known as a cytokine storm, contributes to severe COVID-19 [37]. Vigorous proinflammatory cytokine/chemokine response to the virus induces apoptosis in lung epithelial and endothelial cells. Inflammatory cell infiltration induced by inflammatory cytokines causes apoptosis of airway and alveolar epithelial cells [38]. Apoptosis of endothelial cells and epithelial cells damages the pulmonary microvascular barriers and causes vascular leakage and alveolar edema, leading to ARDS. Therefore, inflammatory mediators play an important role in the pathogenesis of severe disease. CRP is an acute-phase protein that is stimulated by the release of cytokines. A prior study revealed that CRP on admission could be a predictive factor for respiratory failure in MERS-CoV infected patients [39]. Our study suggested that CRP might be useful to anticipate severe diseases in COVID-19 patients as well.

The present meta-analysis also suggested the association between WBC and poor outcomes. For SARS, elevated WBC counts have been reported to be associated with a poor prognosis [36]. Our results showed a similar tendency to SARS. In terms of blood cell differential, prior studies suggested that lymphopenia and elevated neutrophils were associated with refractory COVID-19 [28,40]. Owing to a lack of data thus far, the impact on prognosis of these differentials remains to be seen.

Our study provides insight into the prediction of severe COVID-19. Our data suggests that we can predict severe COVID-19 based on WBC and CRP on arrival, which can help with risk stratification of COVID-19 patients. Moreover, because we included 18 studies with 3278 patients, there was enough power to reveal statistically significant differences.

Our study has several limitations. First, most studies included were case series. Analyses of these unadjusted data were subject to selection

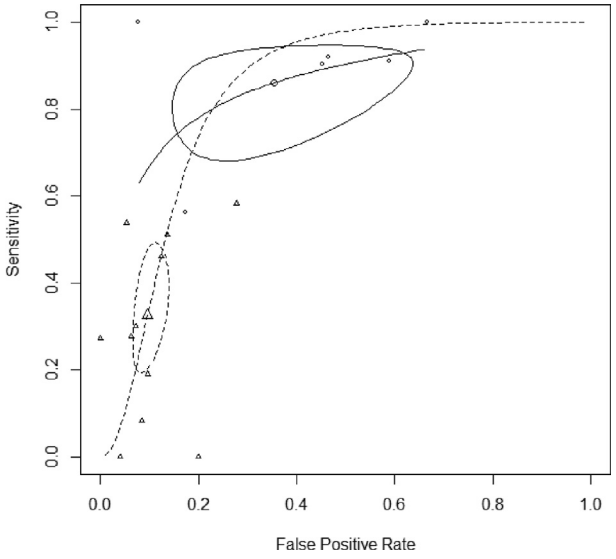

Fig. 9. Summary receiver-operating characteristic (SROC) curves for the prediction of severe coronavirus disease 2019. Solid line for CRP, dashed line for leukocytosis. CRP, C-reactive protein.

bias. Moreover, the included studies did not investigate the diagnostic accuracy of leukocytosis and elevated CRP, which could lead to bias as well. Second, most studies did not mention antipyretic medication use. These medications might mask the real change of BT, which can affect the association. Third, the definitions of disease severity varied among the studies, which could lead to bias as well. At the current time, there is a lack of individual patient data available for more in-depth analysis. Further studies with adjusted analyses are needed.

5. Conclusion

In patients with COVID-19, fever, leukocytosis, and elevated CRP were associated with critical outcomes. Leukopenia was associated with a better prognosis. Moreover, leukocytosis and elevated CRP on arrival may predict poor outcomes.

Human and animal rights

This article does not contain any studies with human participants or animals performed by any of the authors.

Contributions

T.Y.: Designed the study, collected the data, contributed to the statistical analysis, and served as the primary author of the manuscript.

M.W.: Collected the data, contributed to the statistical analysis, and served as an author of the manuscript (equivalent contributor).

T.Y.: Collected the data and contributed to the statistical analysis.

N.C.: Designed the study and served as an author of the manuscript.

T.M.: Collected the data and contributed to the statistical analysis.

H.M.: Collected the data and contributed to the statistical analysis.

S.M.: Collected the data, contributed to the statistical analysis, and served as an author of the manuscript.

CRediT authorship contribution statement

Takayuki Yamada: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Writing - original draft, Visualization. **Mako Wakabayashi:** Methodology, Validation, Investigation, Resources, Writing - original draft, Visualization. **Takahiro Yamaji:** Methodology, Validation, Resources. **Nitin Chopra:** Validation, Formal analysis. **Takahisa Mikami:** Software, Formal analysis, Resources. **Hirotaka Miyashita:** Conceptualization, Validation. **Satoshi Miyashita:** Conceptualization, Validation, Writing - original draft, Visualization.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cca.2020.06.008.

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