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Predictors of adverse prognosis in COVID-19: A systematic review and meta-analysis

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Abstract

Background: Identification of reliable outcome predictors in coronavirus disease 2019 (COVID-19) is of paramount importance for improving patient's management.

Methods: A systematic review of literature was conducted until 24 April 2020. From 6843 articles, 49 studies were selected for a pooled assessment; cumulative statistics for age and sex were retrieved in 587 790 and 602 234 cases. Two endpoints were defined: (a) a composite outcome including death, severe presentation, hospitalization in the intensive care unit (ICU) and/or mechanical ventilation; and (b) in-hospital mortality. We extracted numeric data on patients' characteristics and cases with adverse outcomes and employed inverse variance random-effects models to derive pooled estimates.

Results: We identified 18 and 12 factors associated with the composite endpoint and death, respectively. Among those, a history of CVD (odds ratio (OR) = 3.15, 95% confidence intervals (CIs) 2.26-4.41), acute cardiac (OR = 10.58, 5.00-22.40) or kidney (OR = 5.13, 1.78-14.83) injury, increased procalcitonin (OR = 4.8, 2.034-11.31) or D-dimer (OR = 3.7, 1.74-7.89), and thrombocytopenia (OR = 6.23, 1.031-37.67) conveyed the highest odds for the adverse composite endpoint. Advanced age, male

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sex, cardiovascular comorbidities, acute cardiac or kidney injury, lymphocytopenia and D-dimer conferred an increased risk of in-hospital death. With respect to the treatment of the acute phase, therapy with steroids was associated with the adverse composite endpoint (OR = 3.61, 95% CI 1.934-6.73), but not with mortality.

Conclusions: Advanced age, comorbidities, abnormal inflammatory and organ injury circulating biomarkers captured patients with an adverse clinical outcome. Clinical history and laboratory profile may then help identify patients with a higher risk of in-hospital mortality.

KEYWORDS

COVID-19, meta-analysis, outcomes, predictors

1 | INTRODUCTION

Since December 2019, a novel coronavirus (2019-nCoV),[1] named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread throughout China and into several countries.[2,3] As of 5 May 2020, more than 3.6 million patients have been diagnosed with SARS-CoV-2 infection (COVID-19), with more than 250 000 deaths.[4] Patients typically present with fever, myalgia, respiratory symptoms such as nonproductive cough and dyspnoea, decreased lymphocyte counts and radiographic evidence of bilateral interstitial pneumonia.[2,5-7] The clinical presentation of COVID-19 ranges from very mild [8] to critical cases requiring admission to the intensive care unit (ICU).[7] COVID-19-associated mortality has been reported to vary broadly according to geographic areas and patients' age, sex and comorbidities.[2,5-7] There are scattered data about the specific contribution of pre-existing chronic conditions and COVID-19-driven acute organ damage to the clinical outcome. For instance, history of cardiovascular disease (CVD) may facilitate COVID-19 infection and predispose to worse clinical outcomes,[9] but it is less known whether virus-induced cardiac damage further aggravates the trajectory of the disease. Defining the relative contribution of patient-related factors or disease-specific manifestations to patient outcome is of great importance for implementing risk stratification and patient management. To that end, we reviewed available evidence and provided pooled estimates on predictors of clinical outcomes in patients with COVID-19.

2 | MATERIALS AND METHODS

2.1 | Systematic review

2.1.1 | Search strategy

A systematic review of literature using PubMed/MEDLINE and Scopus was conducted. Aiming to summarize all available sources, we used broad terms during our search strategy: Covid-19, novel coronavirus, 2019nCoV, novel coronavirus 2019, SARS-CoV-2 (Table S1). In addition, we sought to retrieve national-based information on age and sex distribution of COVID-19 cases in countries with the highest numbers of confirmed cases at the time of our search (Appendix S1). The last search was performed on 24 April 2020.

2.1.2 | Eligibility criteria

We included published peer-reviewed, pre-proof articles and papers published ahead of print which reported COVID-19 cases (mainly confirmed by real-time reverse transcriptase-polymerase chain reaction as evinced in Table S2) until 24 April 2020. Articles both in English and in non-English language were selected. Eligibility criteria and identification of eligible studies are described in the Appendix S1.

2.2 | Meta-analysis

2.2.1 | Protocol

The meta-analysis was performed in accordance with the checklist of the PRISMA statement for systematic reviews and meta-analyses[10] and registered in the PROSPERO database (CRD42020181873). Reporting of the study conforms to broad EQUATOR guidelines.[11]

2.2.2 | Data extraction and outcomes

From eligible studies, we extracted numeric data on patients' demographics, comorbidities, laboratory findings, symptoms at presentation, complications of COVID-19, type of empiric therapies received and occurrence of

clinical outcomes. For the quantitative analysis, we only considered studies reporting at least one of the following outcomes: death, severe COVID-19 infection, hospitalization in ICU and/or use of mechanical ventilation and progression of the disease. The primary endpoint corresponded to the composite of the events above. In-hospital mortality was considered as a secondary endpoint in a dedicated sensitivity analysis.

The definition of severe COVID-19 infection was heterogeneous across the studies (Table S3). When fatal cases were provided per age decade with different boundaries (ie 65-74 instead of 60-69 years), we assumed an equal distribution over this age range. Definitions of cardiac damage, acute kidney injury (AKI) and acute liver injury are reported in the Table S3. Two independent authors (SF and NA) extracted data according to a pre-specified form, while a third senior investigator (GG) checked data integrity and ensured there were no duplicates.

2.2.3 | Quality assessment and quality of evidence

Description of the quality assessment and quality of evidence is provided in the Appendix S1.

2.2.4 | Data synthesis and analysis

We implemented inverse variance random-effects models with the Sidik-Jonkman two-step heterogeneity estimator and the Hartung and Knapp (HK) correction[12] separately for each predictor and a) the primary composite endpoint and b) death. We conducted random-effects meta-regression to assess the mediating effect of age on the association of comorbidities with unfavourable prognosis in patients with COVID-19. Finally, we implemented trial sequential analysis (TSA) to assess whether the optimal information size for a series of predictors has been reached. Statistical analysis was performed with Stata v12.1 (StataCorp). Detailed information on data synthesis is provided in the Appendix S1.

3 | RESULTS

3.1 | Literature search

The process of study selection is reported in Figure S1. From 6843 articles initially identified, we discarded 6454 through screening of the title and abstract. We further evaluated 389 full-text articles and found 49 studies to be eligible for quantitative analysis.

3.2 | Selected studies

The meta-analysis included 49 studies and a total of 20 211 patients (Tables 1 and S2). We added 2 ad hoc reports from the United States (n = 6637)[13] and France (n = 2805)[14] with aggregate data on hospitalizations/ICU admission and underlying comorbidities. Twenty-two studies reported data on case fatality, seven investigated ICU hospitalizations, one focused on the need for mechanical ventilation and 17 compared patients with or without severe clinical presentation or progression. Finally, two studies reported a combined outcome (ICU admission or mechanical ventilation or death; Table S3). Nonproductive cough and fever were the most common symptoms at presentation, while hypertension was the most frequent cardiovascular comorbidity (Table S2). 23 studies reported data about therapies during the acute phase, namely steroids (21 studies), antibiotics (16 studies) and antiviral agents (23 studies; Tables 1 and S4). For estimates of age classification and the risk of adverse prognosis, an expanded database was used with 587 790 cases from China (n = 44 672, as of 11 February 2020), the United States (n = 2449, as of 16 March 2020), South Korea (n = 10 450, as of 12 April 2020), Italy (n = 177 173, as of 24 April 2020), France (n = 29 721, as of 17 April 2020), Germany (n = 150 383, as of 24 April 2020), the Netherlands (n = 30 164, as of 24 April 2020) and Spain (n = 142 278, as of 24 April 2020). A dedicated database with 482,224 subjects was used to derive the pooled association of sex with unfavourable clinical outcomes in COVID-19 (Table S5). Detailed information on available descriptive characteristics, laboratory parameters and treatment strategies of eligible studies (n = 49) is summarized in Tables 1 and S2-S6. We calculated or extracted estimates for the association of underlying neoplastic disease with COVID-19 in 20 studies (Table S6); on the contrary, we did not find data about the prevalence of autoimmune diseases. Six studies were adjudicated of fair quality, while the remaining ones were considered of good quality (Table S7). The main findings of our analysis are summarized in Table 2.

3.3 | Patient characteristics and comorbidities

When patients above 70 years were compared to younger subjects in pooled data from 587,790 individuals, a 13-fold increase in the odds of death was observed (OR 13.19, 7.72-22.55; Figure 1A). After excluding cases from France or Germany due to noncompatible data tabulation, we found a gradual increase in mortality with increasing age (OR 23.46, 13.58-40.52, as compared to patients younger than 60 years, n = 558 069; OR = 33.75, 16.17-70.46, as compared to patients younger than 50 years, n = 407 686). Overall, there

TABLE 1 Main characteristics, treatments and complications in the studies included in the meta-analysis

Author, Year, N	Median/Mean Age (IQR/SD)	Male, N (%)	Elevated CRP, N (%)	Elevated D-dimer, N (%)	Antivirals, N (%)	Antibiotics, N (%)
Zhou, Yu et al, 2020, 191	56 (46-67)	119 (62)	-	72/172 (42)	41 (21)	181 (95)
Huang, Wang et al, 2020, 41	49 (41-58)	30 (73)	-	-	38 (93)	41 (100)
Wang, Hu et al, 2020, 138	56 (42-68)	75 (54)	-	-	124 (90)	138 (100)
Zhang, Dong et al, 2020, 140	57 (25-87)	71 (51)	125/136 (92)	35/81 (43)	-	-
Yang, Yu et al, 2020,52	60	35 (67)	-	-	23 (44)	49 (94)
Guan, Yu Hu et al, 2020, 1099	47 (35-58)	640 (58)	481/793 (61)	260/560 (46)	393 (36)	637 (58)
Liu, Tao et al, 2020,78	38 (33-57)	39 (50)	-	-	-	-
Chen, Chen et al,2020, 150	59	84 (56)	-	-	-	-
Ruan, Yang et al, 2020, 150	58	102 (68)	-	-	88 (59)	143 (95)
Wu, Chen et al, 2020, 201	51 (43-60)	128 (64)	-	-	170 (85)	196 (98)
Chen, Qi et al, 2020, 249	51 (36-64)	126 (51)	-	-		
Mo, Xing et al, 2020, 155	54 (42-66)	86 (56)	-	-	45 (29)	-
Xu, Dong et al, 2020,50	-	29 (58)	26 (52)	-	-	-
Gao, Li et al, 2020,43	44 (12)	43 (100)	-	-	-	-
Shi, Qin et al, 2020, 416	64 (21-95)	205 (49)	-	-	403 (97)	235 (57)
Luo, Liu et al, 2020, 15	62-80	12 (80)	13 (87)			
Wang, Fang et al, 2020, 102	50 (39-58)	524 (52)	-	-	-	-
Cao, Tu et al, 2020, 102	54 (37-67)	53 (52)	52 (51)	21 (21)	100 (98)	101 (99)
Chen, Wu, Guo et al, 2020, 21	56 (50-65)	17 (81)	-	-	-	-
Li, Peng et al, 2020, 25	60-2 ± 5-6	10 (77)	8 (62)	9 (69)	-	-
Wang, He et al, 2020, 39	69 (65-76)	166 (49)	339 (100)	339 (100)	-	-
Wang, Li et al, 2020, 116	54 (38-69)	67 (58)	-	-	-	-
Zhang, Zhang et al, 2020, 95	49 (39-58)	53 (56)	87 (92)	63 (66)	-	-
Yuan, Yin et al, 2020, 27	60 (47-69)	12 (45)	-	-	-	-
Shi, Yu et al, 2020, 487	46 (19)	259 (53)	-	-	-	-
Grein et al,2020, 53	67 (56-72)	27 (79)	-	-	61 (100)	-
Lighter et al, 2020, 3,615	Stratified analysis for age below and above 60 years	-	-	-	-	-
Simonnet et al, 2020, 124	60 (51-70)	90 (73)	-	-	-	-
Feng, Ling et al, 2020, 476	53 (40-46)	271 (57)	266 (64)	476 (100)	286 (60)	319 (67)
Du, Liang et al, 2020, 179	58 ± 14	97 (54)	179 (100)	179 (100)	-	-
Ji, Qin et al, 2020, 202	45 (35-54)	-	-	-	-	-
Yang, Shi et al, 2020, 273	53-5 ± 1-9	33 (47)	-	-	-	-
Chen, Dai et al, 2020, 55	54 (20-91)	108 (53)	110 (54)	26 (13)	131 (65)	-
Cai, Huang et al, 2020, 318	47 (33-60)	198 (48)	-	-	147 (35)	47 (15)
Chen, Wu, Chen et al, 2020, 274	62 (44-70)	171 (62)	80 (33)	37 (15)	236 (86)	249 (91)
Fan, Wang et al, 2020, 21	63 ± 13	11 (52)	21 (100)	-	7 (33)	-
Gao, Jiang et al, 2020, 54	60 ± 17	24 (44)	54 (100)	-	-	-
Goyal et al, 2020, 393	62 (49-74)	238 (61)	63 (16)	44 (36)	17 (4)	-
Myers et al, 2020, 377	61 (50-73)	212 (56)	-	-	-	-
Pan, Mu et al, 2020, 204	53 ± 16	107 (53)	-	-	184 (90)	141 (69)
Richardson et al, 2020, 5700	63 (52-75)	3437 (60)	4517 (79)	3169 (56)	-	-
Wei, Wang et al, 2020, 167	42 (15)	95 (57)	107 (64)	-	166 (99)	-

Steroids, N (%)	Cardiac injury, N (%)	AKI, N (%)	ARDS N (%)	ICU, N (%)	Oxygen Therapy, N (%)	Invasive Mechanical ventilation, N (%)	Death, N (%)
57 (30)	24/145 (17)	8/186 (4)	59 (31)	50 (26)	41 (21)	32 (17)	-
9 (22)	5/41 (12)	4/41 (10)	12 (29)	13 (32)	37 (90)	4 (10)	6 (15)
62 (45)	10 (7)	-	-	36 (26)	106 (77)	17 (12)	6 (4)
-	-	15 (29)	-	-	-	-	-
30 (58)	12 (23)	6 (1)	35 (67)	52 (100)	33 (64)	22 (42)	28 (54)
204 (19)	-	12/752 (2)	37 (3)	55 (5)	454 (41)	25 (2)	15 (1)
-	-		20 (26)	-	-	0	2 (3)
-	22 (15)	23 (15)	-	-	-	-	11 (7)
53 (35)	-		62 (41)	41 (27)	-	25 (17)	68 (45)
62 (30)	-		84 (42)	53 (27)	165 (82)	5 (3)	44 (22)
	-		-	-			-
79 (51)			-	-	102 (66)	36 (23)	-
-	-	-	-	-	-	-	-
-	-		-	-	-	-	-
304 (73)	82 (20)	8 (2)	97 (23)	-	316 (76)	32 (8)	57 (14)
							3 (20)
-	-	-	-	-	-	-	-
51 (50)	15 (15)	20 (20)	20 (20)		76 (75)	14 (14)	17 (17)
-	-	-	-	-	-	-	
-	-	-	-	-	-	-	5 (39)
-	70 (21)	27 (8)	71 (21)	-	-	-	65 (19)
-	-	-	-	-	-	-	-
-	-	22 (23)	-	-	-	-	-
-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-
-	-	2 (6)	1 (3)	-	-	-	7 (13)
-	-	-	-	431 (12)	-	-	-
-	-	-	-	-	-	-	18 (15)
127 (27)	-	-	-	-	433 (91)	39 (8)	38 (8)
-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-
107 (53)	3 (5)	-	18 (33)	-	-	39 (19)	26 (13)
-	-	-	-	-	-	-	-
217 (79)	89 (44)	29 (11)	196 (72)		251 (92)	17 (6)	113 (41)
3 (14)	-	-	-	-	8 (38)	4 (19)	4 (19)
-	-	-	-	-	-	-	
46 (12)	50 (13)	-	-	-	263 (67)	130 (33)	40 (10)
34 (9)	-	-	-	-	170 (45)	110 (29)	-
80 (39)	-	-	-	16 (8)	-	-	36 (18)
-	-	523 (22)		373 (14)	1584 (28)	320 (12)	553 (21)
42 (25)	-	-	-	-	133 (80)	4 (2)	-

(Continues)

TABLE 1 (Continued)

Author, Year, N	Median/Mean Age (IQR/SD)	Male, N (%)	Elevated CRP, N (%)	Elevated D-dimer, N (%)	Antivirals, N (%)	Antibiotics, N (%)
Zhang, Liu, et al, 2020, 19	73 (38-91)	11 (58)	11 (58)	11 (58)	-	-
Zheng, Fang, et al, 2020, 96	55 (44-65)	58 (60)	-	-	96 (100)	33 (34)
Zheng, Gao et al, 2020,66	47	49 (74)	47 (71)	-	-	-
Zhou, Han et al, 2020, 21	66 + 14	13 (62)	18 (95)	15 (75)	21 (100)	20 (95)
Yao, Wang et al, 2020, 108	52 (37-58)	43 (40)	69 (64)	40 (37)	108 (100)	48 (44)
Wang, Zhang et al, 2020, 548	63 (46-78)	279 (51)	460 (84)	227 (41)	548 (100)	-
Yang Yang et al, 2020, 1476	57 (47-67)	-	-	-	-	-

Abbreviations: AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CRP, C-reactive protein; CT, computer tomography; ICU, intensive care unit; IQR, interquartile range; N, number of patients; RT PCR, real-time polymerase chain reaction.

was a signal of association between increasing age and worse prognosis (pooled OR = 1.027 per year, 95% confidence intervals 1.00-1.06, $P = .069$). In 602 234 cases, male sex was associated with an increased risk of death (OR 1.71, 1.39-2.09, $P < .001$; Figure 1B).

With respect to comorbidities, smoking was associated with a greater likelihood of the composite adverse outcome (OR 2.24 per comparison to nonsmokers, 1.40-3.58, $P = .003$, n = 11), but was not a predictor of mortality (OR 3.14, 0.48-20.56, n = 4). History of DM (OR 2.34, 95% CI 1.64-3.33, $P < .001$) or HTN (OR 2.25, 1.80-2.82, $P < .001$) more than doubled the odds of the combined adverse outcome (Figure 2A,B). Similarly, history of COPD (OR 2.63, 1.55-4.44, $P < .001$) or CVD (OR 3.15, 2.26-4.41) significantly correlated with the composite outcome (Figure 2C,D). In parallel, patients with COVID-19 and cerebrovascular disease (OR 2.93, 1.64-5.24) or history of cancer (OR 2.32, 1.13-4.28) at baseline had increased risk of experiencing the adverse composite outcome. The association of moderate or severe obesity with the composite clinical outcome in the 4 non-Chinese cohorts (OR 2.32, 1.14-4.74, $P = .024$) was attenuated after the HK correction (OR 2.28, 0.76-6.90, $I_2 = 81\%$).

When the analysis was repeated for death, DM (OR 1.74, 1.22-2.48, n = 13), history of CVD (OR 1.95, 1.08-3.54, n = 7) or cerebrovascular disease (OR 2.93, 1.84-4.26, n = 5), HTN (OR 2.71, 1.99-3.69, n = 15) and COPD (OR 2.98, 1.38-6.44, n = 8) conveyed an increased risk of mortality.

3.4 | Acute organ injury and outcome

Acute kidney injury (AKI) (Figure 2E) and acute liver injury were associated with the combined adverse outcome (OR 5.13, 1.78-14.83, $P = .001$ and OR = 3.25, 2.28-4.63, $P < .001$, respectively) and death (OR 12.1, 2.336-62.4, $P = .01$, n = 7 and OR 5.32, 1.04-27.39, respectively). Remarkably, cardiac damage conferred the highest risk of worse outcome (OR = 10.58, 95% CI 5.00-22.40, $P < .001$) and death (OR 16.55, 4.76-57.51, n = 7; Figure 2F).

3.5 | Inflammatory markers, leucocyte count, D-dimer and outcome

Patients experiencing the combined adverse outcome had more often increased CRP (OR 3.87, 2.26-6.63, $P < .001$) and procalcitonin levels (OR 4.8, 2.03-11.31, $P = .002$; Figure 3A), while no association was found with IL-6 (OR 1.76, 0.24-12.69, $P = .429$, n = 3). Nonetheless, increased CRP (OR 5.82, 0.60-56.88, $P = .08$, n = 3) or procalcitonin (OR 4.39, 0.85-22.75, $P = .067$) did not predict mortality. In parallel, increased D-dimer was related to adverse combined outcome (OR 4.39, 1.85-10.41, $P = .003$; Figure 3B) and death (OR 4.40, 1.10-17.58, $P = .04$, n = 6). Lymphocytopenia (OR 3.62, 2.01-6.51, $P < .001$) and thrombocytopenia (OR 6.23, 1.03-37.67, $P < .001$) were associated with the combined adverse outcome but only the former yielded an increased odd of dying (OR 2.87, 1.09-7.6, $P = .037$, n = 9). Plasma ferritin was reported only in 3 studies, without any significant association with the combined outcome or death.

3.6 | Therapies during the acute phase and outcomes

Steroids (OR 3.61, 1.93-6.73, $P = .001$, n = 15 studies) were associated with the composite adverse outcome, but not with mortality (OR 1.80, 0.48-6.72, $P = .302$, n = 6 studies). In view of heterogeneous categories of antibiotics and antivirals (Table S4) used across studies which could not synthesized per class, no pooled estimates were provided for this type of therapy.

3.7 | Meta-regression, trial sequential analysis and publication bias

Increasing age decreased the strength of the association between CVD ($P = .037$) and DM ($P = .027$) and the composite outcome. Details on trial sequential analysis and publication bias are provided in the Appendix S1.

Steroids, N (%)	Cardiac injury, N (%)	AKI, N (%)	ARDS N (%)	ICU, N (%)	Oxygen Therapy, N (%)	Invasive Mechanical ventilation, N (%)	Death, N (%)
-	-	-	-	-	-	7 (37)	8 (42)
78 (81)	-	-	-	30 (31)	-	10 (10)	-
-	-	-	-	-	-	-	-
-	-	-	-	-	21 (100)	8 (38)	3 (14)
30 (28)	8 (7)	16 (15)	45 (42)	17 (16)	35 (32)	10 (9)	12 (11)
341 (62)	119 (22)	-	207 (38)	-	102 (19)	25 (5)	78 (14)
-	-	-	-	-	-	-	-

4 | DISCUSSION

In this meta-analysis, we synthesized available evidence on COVID-19 and prognosis by identifying 18 and 12 predictors of unfavourable composite outcome and death, respectively (Table 2). History of CVD, acute virus-related organ injury, increased procalcitonin and D-dimer conveyed the highest odds of developing the composite adverse outcome. CVD and DM displayed a stronger independent association with the adverse composite outcome in younger than older patients. When considering in-hospital mortality, increased age (from 50 years onwards), male sex, comorbidities (hypertension, diabetes, COPD and history of CVD), acute organ injury, lymphocytopenia and raised D-dimer levels conferred an increased risk of death. Finally, use of steroids correlated with the occurrence of the composite adverse outcome but not with mortality.

4.1 | Demographic features, comorbidities, cardiovascular risk factors and prognosis in COVID-19 patients

Our results show that increased age is the strongest predictor of death in patients with COVID-19. We also report a proportional increase in the risk of death with age. Older age distribution paralleled the increased mortality rate observed in Italy (7.2%) vs China (2.3%), whereas the fatality rate turned out to be similar among patients with comparable age. Thus, the discordant age distribution might partly explain the different mortality rates across countries.[15] Importantly, most European countries (ie Italy, Germany, Spain and the Netherlands) demonstrated a stronger association between age > 70 years and mortality in COVID-19, with ORs ranging from 11 to 34, whereas non-European populations (apart from South Korea) showed a smaller risk attributed to older cases (ORs ranging from 8 to 9). These findings expand the prior evidence indicating advanced age as a major predictor of poor outcome in COVID-19 patients. Notably, increased age attenuated the association between history of CVD or DM and adverse prognosis. This highlights that the contribution of age to the adverse outcomes might be independent from the comorbidities or risk factors. This could be explained by the fact that ageing per se is associated with an impairment of the immune response alongside increased level of chronic inflammation.[16] On one hand, the less efficient immune system cannot effectively control SARS-CoV-2 replication during the acute phase of the infection. On the other hand, the presence of chronic inflammation associated with ageing is likely to burst the cytokine storm syndrome in later stages of the infection. Indeed, ageing is associated with immune dysregulation, of which the most evident characteristics are high blood levels of pro-inflammatory mediators in the absence of evident triggers and, in parallel, reduced capacity to mount an effective inflammatory response to adequate immunogenic stimulations.[17] Importantly, DM, history of CVD or COPD conveyed an increased risk of dying in patients affected by COVID-19. Men presented more often with severe complications of COVID-19 disease. This may be partly attributed to the higher prevalence of CVD, HTN, DM and COPD in comparison with females. COPD patients have increased likelihood to develop severe disease in case of respiratory infection due to intrinsic chronic lung injury and impaired bronchial clearance.[18] Overall, these findings may pave the way to the creation of a risk score based on demographics and comorbidities to improve outcome prediction in COVID-19.

4.2 | Acute organ injury and prognosis in COVID-19 patients

Acute kidney, liver or cardiac injury was associated with the composite adverse outcome and death. Remarkably, cardiac injury, defined as increased serum cTn, conveyed the highest odds of death. This finding corroborates a prior smaller meta-analysis,[19] which reported worse clinical outcome in COVID-19-positive patients and abnormal cTn. The mechanisms underpinning cardiac injury in COVID-19 are debated. First, ACI may indirectly reflect

TABLE 2 Synopsis of the main findings of the meta-analysis on predictors of COVID-19

Predictor	Effect estimate	Effect estimate after statistical correction for small number of studies	Total population	Data from outside China	Adjustment for other patients' characteristics	Composite endpoint/ Mortality	Quality of evidence[e]
Age (continuous)	OR = 1.03, 95% CI 1.003-1.057	OR = 1.027, 95% CI 0.997-1.059	1,285	Yes	Yes[a]	Composite outcome	Weak/Medium
Age ≥ 50	OR = 34.02, 95% CI 19.21-60.23	OR = 33.75, 95% CI 16.17-70.46	407,686	Yes	No	Mortality	Strong
Age ≥ 60	OR = 23.12, 95% CI 14.8-36.12	OR = 23.46, 95% CI 13.58-40.52	558,069	Yes	No	Mortality	Strong
Age ≥ 70	OR = 13.18, 95% CI 8.37-20.76	OR = 13.19, 95% CI 7.72-22.55	587,790	Yes	No	Mortality	Strong
Male sex	OR = 1.70, 95% CI 1.413-2.032	OR = 1.71, 95% CI 1.39-2.091	602,234	Yes	No	Mortality	Strong
Smoking	OR = 2.38, 95% CI 1.449-3.897	OR = 2.24, 95% CI 1.399-3.58	9,262	Yes	Yes[a]	Composite outcome/ Mortality[b]	Weak/Medium
Hypertension	OR = 2.05, 95% CI 1.792-2.35	OR = 2.25, 95% CI 1.796-2.816	9,360	Yes	No	Composite outcome/ Mortality	Strong
DM	OR = 2.33, 95% CI 1.848-2.936	OR = 2.34, 95% CI 1.64-3.328	15,953	Yes	Yes[a]	Composite outcome/ Mortality	Strong
Obesity	OR = 2.32, 95% CI 1.137-4.74	OR = 2.28, 95% CI 0.756-6.895	5,184	Yes	Yes[d]	Composite outcome	Medium
Cardiovascular disease	OR = 3.13, 95% CI 2.27-4.302	OR = 3.15, 95% CI 2.26-4.41	12,717	Yes	Yes[a]	Composite outcome/ Mortality	Strong
Cerebrovascular disease	OR = 2.8, 95% CI 1.842-4.26	OR = 2.93, 95% CI 1.636-5.24	2,595	No	No	Composite outcome/ Mortality	Medium
Cancer	OR = 2.3, 95% CI 1.472-3.602	OR = 2.32, 95% CI 1.367-3.946	4,176	No	Yes[a]	Composite outcome/ Mortality[b]	Medium
COPD	OR = 2.65, 95% CI 1.665-4.21	OR = 2.63, 95% CI 1.55-4.44	13, 544	Yes	No	Composite outcome/ Mortality	Medium/Strong
Acute cardiac injury	OR = 10.58, 95% CI 5.476-20.45	OR = 10.58, 95% CI 4.996-22.4	2,069	No	Yes[a]	Composite outcome/ Mortality	Medium/Strong
Acute kidney injury	OR = 5.13, 95% CI 2.104-12.54	OR = 5.13, 95% CI 1.78-14.83	5,324	No	Yes[a]	Composite outcome/ Mortality	Medium/Strong
Acute liver injury	OR = 3.79, 95% CI 2.206-6.516	OR = 3.79, 95% CI 2.124-6.77	5,528	No	Yes[a]	Composite outcome/ Mortality	Medium/Strong

(Continues)

TABLE 2 (Continued)

Predictor	Effect estimate	Effect estimate after statistical correction for small number of studies	Total population	Data from outside China	Adjustment for other patients' characteristics	Composite endpoint/ Mortality	Quality of evidence[e]
C-reactive protein	OR = 3.96, 95% CI 2.631-5.971	OR = 3.87, 95% CI 2.263-6.63	2,507	No	No	Composite outcome/ Mortality[c]	Weak/Medium
Procalcitonin	OR = 5.26, 95% CI 1.741-15.91	OR = 4.8, 95% CI 2.034-11.312	2,730	No	No	Composite outcome/ Mortality[c]	Weak/Medium
Lymphocytopenia	OR = 3.62, 95% CI 2.15-6.105	OR = 3.62, 95% CI 2.010-6.51	3,744	No	No	Composite outcome/ Mortality	Medium
Thrombocytopenia	OR = 6.23, 95% CI 1.402-27.7	OR = 6.23, 95% CI 1.031-37.67	2,437	No	No	Composite outcome/ Mortality[c]	Weak
IL-6	NP	OR = 1.76, 95% CI 0.244-12.69	456	No	No	Composite outcome	Weak
Ferritin	NP	OR = 5.3, 95% CI 0.665-42.29	609	No	No	Composite outcome	Weak
D-dimer	OR = 3.85, 95% CI 1.516- 9.78	OR = 3.7, 95% CI 1.736-7.894	3,270	No	Yes[a]	Composite outcome/ Mortality	Medium/Strong
Steroids	OR = 3.63, 95% CI 2.03-6.49	OR = 3.61, 95% CI 1.934-6.728	3,465	No	Yes[a]	Composite outcome/ Mortality[b]	Weak/Medium

Note: Hazard ratio instead of OR was used in 4 studies.

Abbreviations: CI, confidence intervals; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; IL, interleukin; NP, not performed; OR, odds ratio.

[a]Adjusted estimates were provided in 10 out of 35 studies.

[b]Significance was attenuated when studies assessing only mortality were used in the meta-analysis.

[c]Significance was lost when studies assessing only mortality were used in the meta-analysis.

[d]Separate estimates for different age groups.

[e]As estimated by Authors.

Colors give a visual message on the quality of evidence regarding the association of variables with worse prognosis in Covid-19

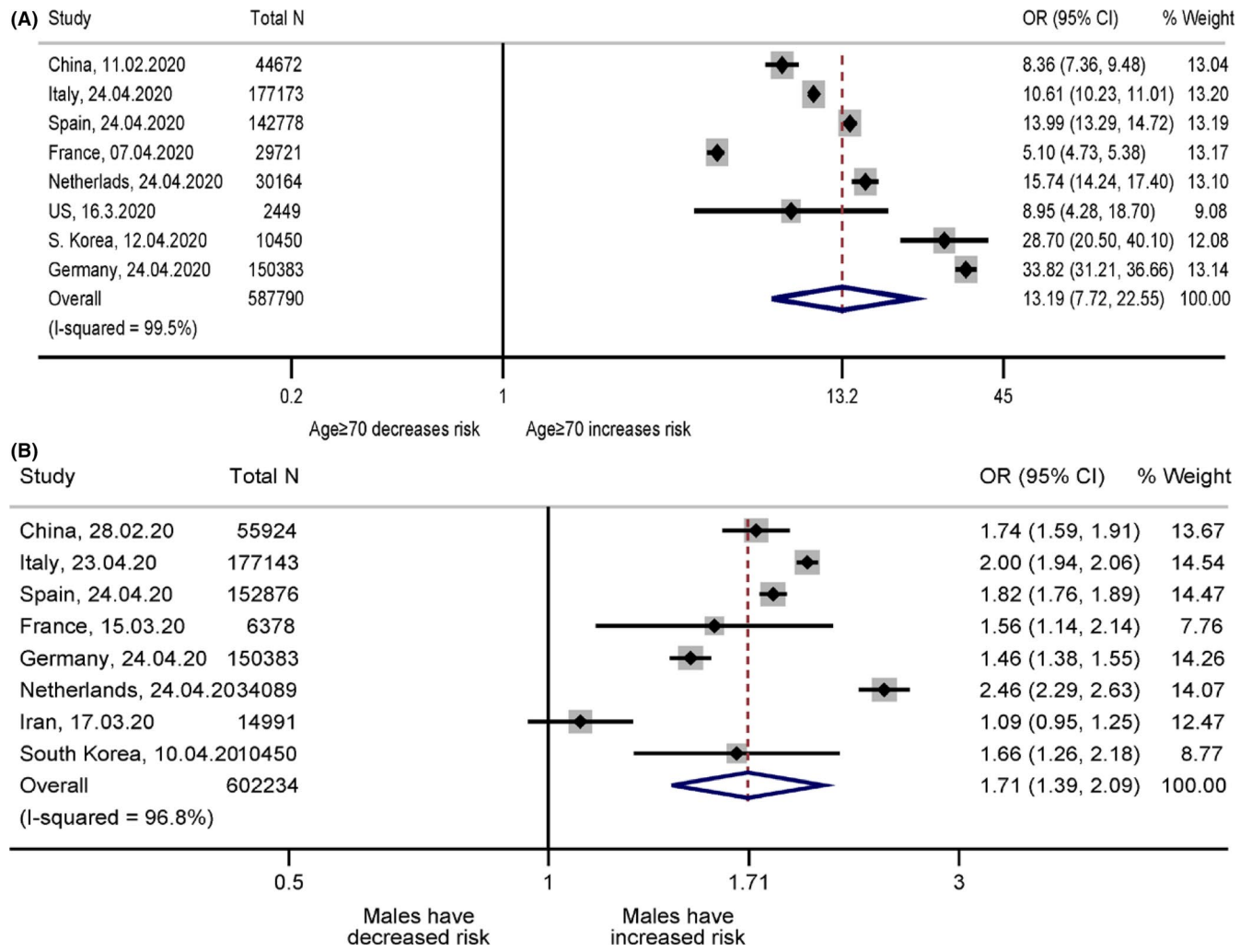

FIGURE 1 OR and 95% CIs for A, increased age ≥ 70years old and B, male sex and adverse prognosis in patients with COVID-19. Boxes represent the OR, and lines represent the 95% CIs for individual studies. The diamonds and their width represent the pooled ORs and the 95% CIs, respectively. Pooled estimates are derived from a random-effects model with the HK correction to overall 95% CIs. CIs, confidence intervals; HK, Hartung and Knapp correction; OR, odds ratio

severe pulmonary infection, which characterizes critical patients with COVID-19.[20] Notably, cardiac complications occur in up to 26.7% patients with community-acquired pneumonia (CAP) and have been associated with poor outcomes.[21] Severe pulmonary infections, irrespective of the aetiological agent, may prompt an intense systemic inflammatory response syndrome. This condition is associated with cytokine storm syndrome,[22,23] which promotes pro-thrombotic state predisposing to coronary thrombosis and acute coronary syndromes (ACS).[24] In fact, ACS due to coronary plaque destabilization has been reported in as many as 11% of hospitalized CAP patients [21,25] and this may account for ACI in critically ill patients with COVID-19. Interestingly, increased D-dimer levels are associated with poor outcome. Elevated D-dimer may reflect an activation of the coagulation cascade, which in turn could trigger ACS and acute pulmonary embolism. Intrapulmonary shunts and ventilation-perfusion mismatching in COVID-19 lead to hypoxaemia. At the same time, reflex sinus tachycardia increases myocardial oxygen needs and shortens diastole, facilitating myocardial ischaemia due to an imbalance of cardiac metabolic supply-to-demand ratio.[26-28] Consistently, higher serum CRP characterized poor outcomes of COVID-19 in individual studies and in our pooled analysis. Second, direct myocardial infection in SARS-CoV-2 has been postulated to also cause ACI. Indeed, SARS-CoV-2 entry to alveolar epithelial cells is mediated by angiotensin-converting enzyme-2 (ACE2),[29-31] the functional receptor of SARS-CoV-2, which is widely expressed also in cardiomyocytes.[29] In physiological conditions, ACE-2 has a vital role in the cardiovascular and immune systems, counteracting renin-angiotensin-aldosterone system (RAAS) [32] and protecting against lung injury.[33]

Based on anecdotal descriptions of transitory impairment of LV systolic function in COVID-19 with normal coronary

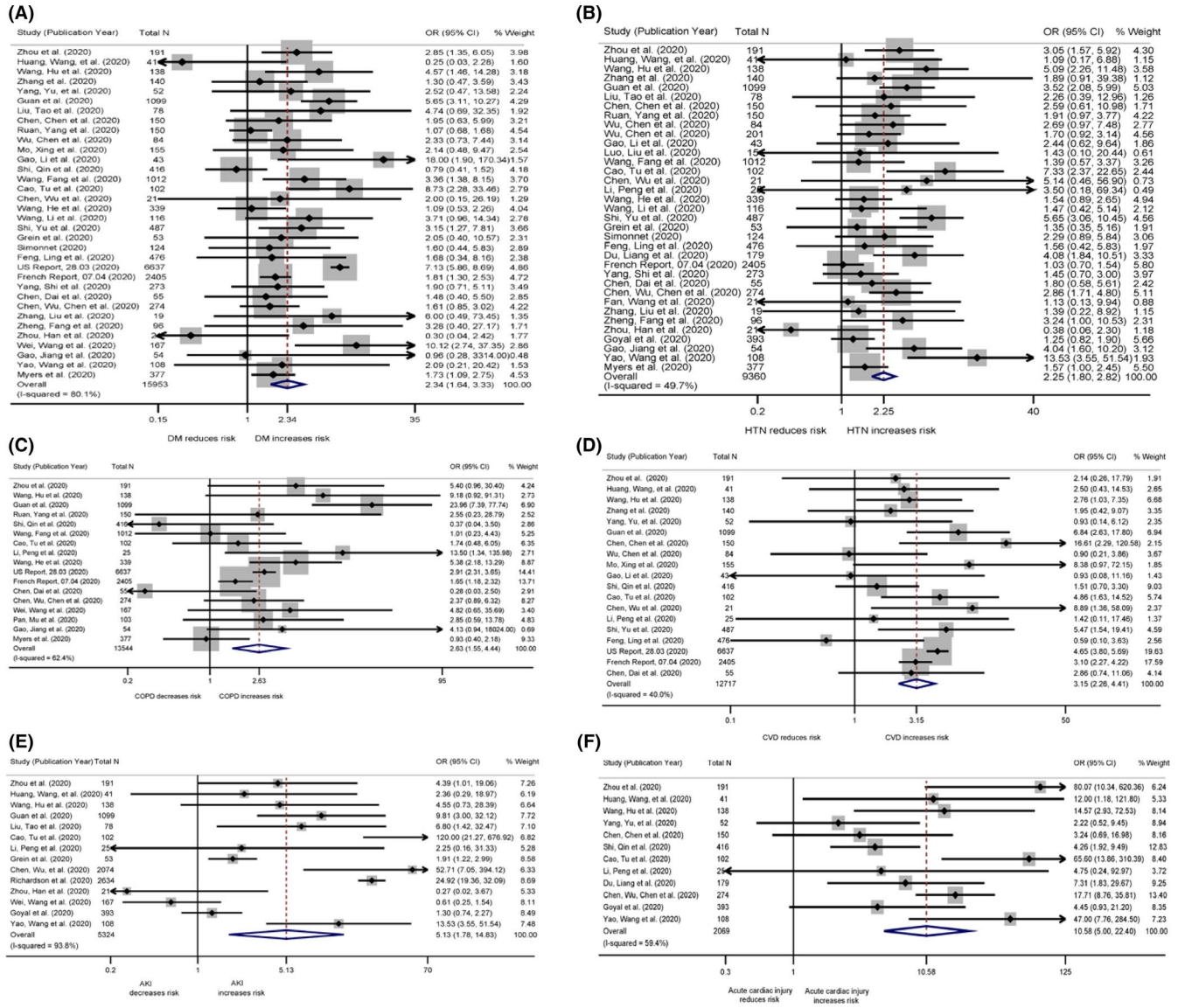

FIGURE 2 OR and 95% CIs for A, DM; B, HTN; C, COPD; D, history of CVD; E, AKI and F, ACI and adverse prognosis in patients with COVID-19. Boxes represent the OR, and lines represent the 95% CIs for individual studies. The diamonds and their width represent the pooled ORs and the 95% CIs, respectively. Pooled estimates are derived from a random-effects model with the HK correction to overall 95% CIs. ACI, acute cardiac injury; AKI, acute kidney injury; CIs, confidence intervals; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DM, diabetes mellitus; HK, Hartung and Knapp correction; HR, hazard ratio; HTN, arterial hypertension; OR, odds ratio

arteries, it has been speculated that SARS-CoV-2 is an aetiological agent of fulminant myocarditis.[34-36] Clinically suspected acute myocarditis, according to the European Society Cardiology definition,[37] without histological confirmation, has been described in few cases (38-40). So far, there is no definitive histopathological evidence of biopsy- or autopsy-proven acute myocarditis caused by COVID-19.[34,35,38-42] Nevertheless, the proof that COVID-19 is a new cause of viral myocarditis would require histologic findings of active myocarditis (ie inflammatory lymphomonocytic infiltrates plus myocyte necrosis not typical of ischaemic injury) plus the identification of the SARS-CoV-2 genome in heart tissue and/or identification of viral particles in cardiomyocytes, and exclusion of known cardiotropic viruses.[37] SARS-CoV-2 is not a known cardiotropic virus, and cardiotropic viruses that are known to be associated with myocarditis (eg enterovirus, which is associated with diarrhoea and parvovirus B19, which is associated with a pseudo-infarct presentation) were not searched for in most of the reported cases and might be involved. The anecdotal autopsy reports of lymphocytic[41] or eosinophilic cell infiltrates[42] may be due to immune-mediated virus-negative myocarditis unrelated to COVID-19, as proposed by the authors.[42] Additional autopsy-based studies and endomyocardial biopsy in living patients with COVID-19 with application of molecular detection methods for SARS-CoV-2 genome/particles are warranted.

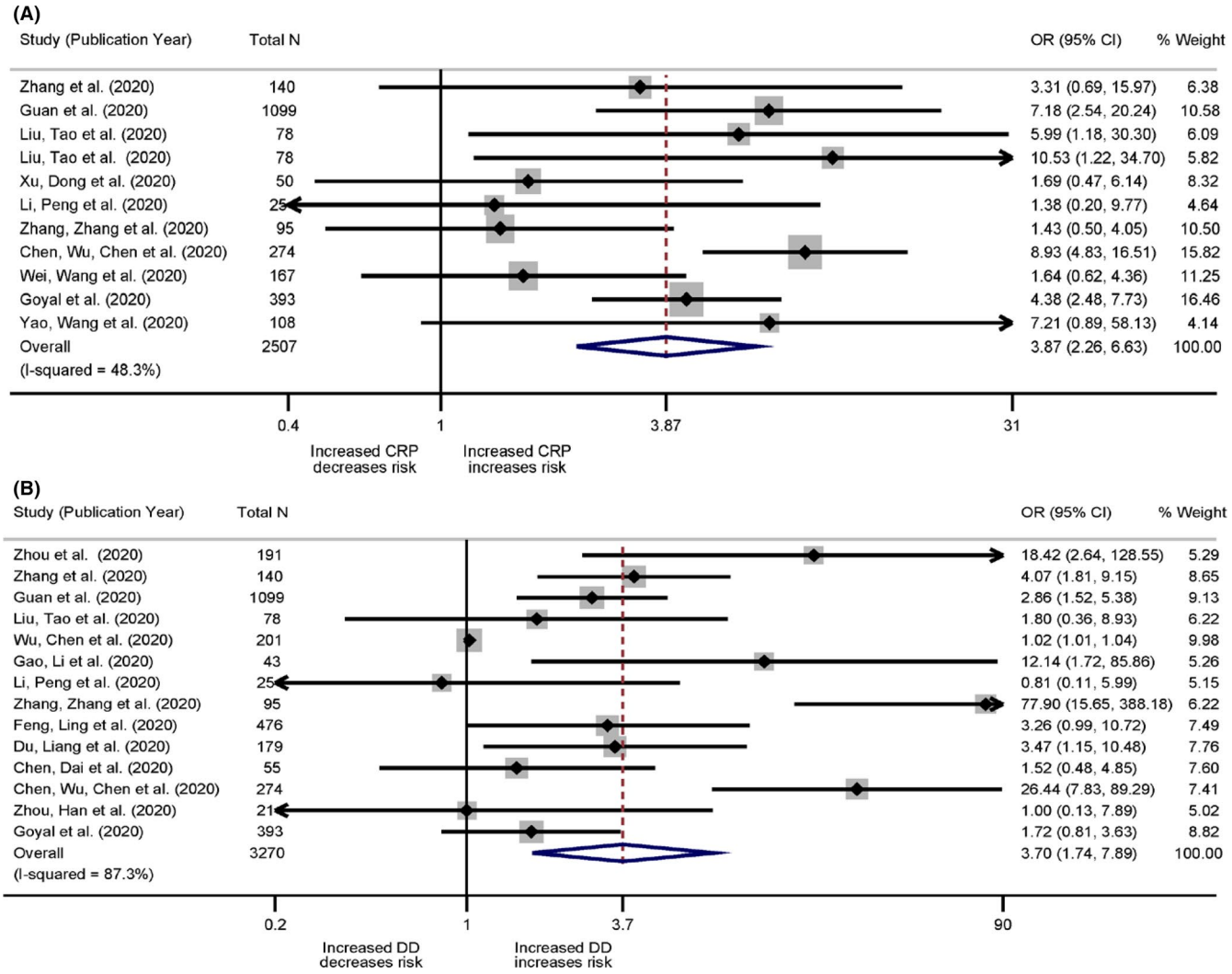

FIGURE 3 OR and 95% CIs for increased A, CRP and B, D-dimer and adverse prognosis in patients with COVID-19. Boxes represent the OR, and lines represent the 95% CIs for individual studies. The diamonds and their width represent the pooled ORs and the 95% CIs, respectively. Pooled estimates are derived from a random-effects model with the HK correction to overall 95% CIs. CIs, confidence intervals; CRP, C-reactive protein; HK, Hartung and Knapp correction; OR, odds ratio

4.3 | Treatment and prognosis in COVID-19 patients

In our meta-analysis, administration of steroids was associated with the adverse composite outcome. Nonetheless, in two studies indirect evidence on a treatment bias was identified. In specific, Wu Chen et al[20] showed that patients presenting with acute respiratory distress syndrome had higher prevalence of therapy with steroids in comparison with milder forms of pulmonary disease. Respectively, Ruan, Yang et al[43] found that fatal cases of COVID-19 had been treated with steroids early after hospital admission as compared to patients who survived. Despite no statistical inference could be drawn, those results support the concept of selective treatment with steroids in more severe cases of COVID-19 and raise the possibility of bias-driven spurious association of this therapy with worse outcomes. Emerging potentially effective drugs are under intense investigations, and several multicentre studies have been promoted by pharmaceutical industry, academy and regulatory agencies.[44]

As for antivirals, an open-label randomized clinical trial (RCT) reported that the combination of lopinavir and ritonavir was associated neither with clinical improvement nor with viral clearance in hospitalized patients with severe COVID-19.[45] Of interest, compassionate-use remdesivir resulted in clinical improvement in the majority of patients (68%, total n = 53) with severe COVID-19, in a preliminary nonrandomized and no placebo-controlled study.[46] Chloroquine and azithromycin induced significant viral load reduction in a small, nonrandomized study.[47] However, these drugs do not seem to be effective in critically ill patients, and safety concerns have been raised as they both prolong QT-interval, possibly inducing ventricular

tachyarrhythmias.[48] In patients with sepsis-induced coagulopathy or with markedly elevated D-dimer levels, low-molecular-weight heparin has been associated with decreased mortality[49] although it is not established whether COVID-19 patients benefit from an extensive use of anticoagulation. Tocilizumab, a monoclonal antibody-binding IL-6 receptor, appeared successful in improving clinical status in a small series of severe COVID-19 patients, although RCTs are needed to certify its effectiveness. The promising results of a recent in vitro trial[50] suggest a potential role of human recombinant soluble ACE2 in blocking early stages of SARS-CoV-2 infection.

4.4 | Limitations

Our meta-analysis has several limitations. First, due to the recent outbreak of COVID-19, the majority of cohorts of patients included in the analysis come from China. We sought to incorporate data for age and sex distribution of COVID-19 from other countries as well; we also used reports of aggregate data from the United States and France and also included all available studies outside China. Still, the possible difference in age distribution between China and other countries might also magnify inter-population discrepancies with respect to risk factors and abnormal laboratory findings on COVID-19 outcomes and our inference should be cautiously extrapolated. Second, the suspicion of overlapping populations from several Chinese studies[51] has been recently raised. Third, we pooled together mortality, mechanical ventilation and severe forms of COVID-19 disease in a combined outcome. However, a dedicated sensitivity analysis was feasible for most predictors towards mortality alone. Fourth, only 10 out of 35 studies included in the quantitative analysis provided adjusted effect estimates; respectively, the association of increasing age and male sex with adverse prognosis from nationwide data was not controlled for possible confounding factors. Fifth, levels of inflammatory markers were evaluated at diagnosis and we cannot exclude whether later measurements of IL-6 or other biomarkers might correlate with COVID-19 outcomes. Sixth, the quality of evidence could not be adjudicated strictly on GRADE[52] recommendations and classification of each predictor in terms of supporting data was partially based on authors' judgement. Finally, the analysis of mortality might be underpowered for several predictors due to smaller number of available studies.

5 | CONCLUSION

To the best of our knowledge, this is the first meta-analysis to provide a detailed evaluation of the prognostic significance of patient- and disease-related factors in patients affected by COVID-19. Advanced age, male sex, comorbidities, including history of CVD, DM, HTN or COPD, acute organ injury, with particular respect to ACI, increased levels of specific circulating biomarkers, namely CRP and D-dimer, and lymphocytopenia captured patients with the highest odds of mortality. The empirical therapeutic approaches do not appear to modify the natural history of the disease.

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CONFLICT OF INTEREST

None reported.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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