ORCHESTRA

Connecting European Cohorts
to Increase Common
and Effective Response to
SARS- CoV-2 Pandemic

DELIVERABLE TEMPLATE

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Systematic review of the literature on determinants of COVID-19 manifestation/progression

SAS

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Executive summary

This document is the deliverable of “D2.1 - Systematic review of the literature on determinants of COVID-19 manifestation/progression” of of the European project “ORCHESTRA – Connecting European Cohorts to Increase Common and Effective response to SARS-CoV-2 Pandemic: ORCHESTRA”.

The purpose of the document is to provide an overall view of predictors of COVID-19 disease presentation, progression, and sequelae by SARS-CoV-2 variants and patients immunity function status. This task was carried out by means of a systematic review of published literature on clinical studies reporting on clinical presentation and/or progression of SARS-CoV-2 infection in humans. PICO questions were developed according to the Cochrane recommendations.

A second part of this study was a systematic review that was designed to summarize existing evidence on clinical evolution of SARS-CoV-2 in hematological patients compared to non-hematological and identify major risk factors for disease progression.

Core content

Background.

By end of January 2022, the COVID-19 pandemic, caused by the new coronavirus SARS-CoV-2, has caused more than 350.000 million cases and more than 5,5 million deaths worldwide, according to data from the World Health Organization. Importantly, the severity of COVID-19 ranges from asymptomatic or mild infection to a severe or critical illness and death. Identification of factors predicting the progression to severe forms of COVID-19 is paramount for timely intervention to prevent fatal outcomes (4-8). Advanced age and several comorbidities such as hypertension, diabetes mellitus (DM), or cardiovascular diseases (CVD) has been associated to adverse outcomes (5-12). Other comorbidities such as obesity, kidney disease (KD), liver disease (LD) or malignancies have been associated with severe SARS-CoV-2 infection is (13, 14), but the estimations for the relative impact of each of these conditions are heterogeneous across the different published studies.

Many studies that have explored the predictors for adverse outcomes in patients with COVID-19 have important limitations for generalizability including potential selection bias caused by limited geographic focus, populations and sample size, and information bias caused by diversity in inclusion and outcome criteria (14). As a consequence, the estimated risk data are not rarely significantly different when not contradictory (15-20). Finally, some published systematic reviews and meta-analyses are focused on single condition assessment but do not establish overall risk measures of cases for different conditions (21-23). In fact, the causal association of the different previous conditions of the patients with a negative outcome in COVID-10 patients may be over-or under-

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estimated due to residual confounding or other biases (24-26). Accurate knowledge of the risk estimates is critical for delineating specific prevention measures, including prioritizing vaccination or treatments.

An umbrella systematic review is a compilation of the evidence obtained from systematic reviews and meta-analyses (27), with the objective of proposing recommendations for clinical practice and research (27,28). The aim of this study was to conduct an umbrella review to identify the strength and validity of associations between patients' pre-existing determinants and severity or mortality in patients diagnosed with COVID-19. The results of this review will provide decision-makers with a consolidated source of high-quality studies on the topic.

Methods.

Design, data sources and search strategy

An umbrella literature review was conducted according to the principles of the Cochrane Handbook for Systematic Reviews of Interventions and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). In addition, this review was conducted using the elements of the Joanna Briggs Institute review methodology. The study protocol was registered in the PROSPERO (CRD42021267368) and approved by the local ethic committee. Patients were not involved in the design, conduct, interpretation, and writing up of the results of this study; he participation of the public and other experts will take place at a later stage.

We searched PubMed/MEDLINE, EMBASE, Web of Science, Scopus, Cochrane Library databases, JBI database of systematic reviews and implementation, and PROSPERO for systematic reviews and meta-analyses published between December 2019 and August 2021, with no language or country restrictions, for systematic reviews and meta-analyses of studies that investigated the associations between determinants and severity or mortality in patients with COVID-19. The initial search was conducted on August 1, 2021, and the final search was conducted on September 30, 2021. In the initial review, primary analysis was focused on studies presenting the best available evidence across studies. The search strategy used is presented in appendix 1. Then initial keywords were identified, followed by analysis of words contained in the title, abstract, and keywords. Subsequently, specific search filters were constructed for each database, and, finally, the reference list of all included reviews was searched. In addition, a manual citation search of retrieved eligible articles was performed to identify additional publications. We did not include preprint websites because of concerns about the quality of articles prior to the peer review process.

Inclusion and exclusion criteria, and extraction of variables

Systematic reviews investigating the association of comorbidities with hospitalization, development of severe or critical COVID-19, and death were considered. The predisposing conditions and comorbidities were grouped into categories including age,

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sex, hypertension, DM, CVD (arrhythmia, chronic heart failure), chronic pulmonary diseases (CPD) (any chronic lung disease, chronic obstructive pulmonary disease, acute respiratory distress syndrome, tuberculosis), malignancies (hematological cancer, solid cancer, any malignant tumor), cerebrovascular diseases (CBD) (stroke, transient ischemic attack), KD (chronic kidney or urinary disease) and LD (chronic liver disease, cirrhosis, hepatitis B).

Articles were eligible if they contained a meta-analysis for the association of pre-existing determinant conditions with the severity/mortality of patients with COVID-19. Studies had to meet the following criteria: (a) were conducted in patients diagnosed with COVID-19 and evaluated at least three pre-existing conditions among the selected primary studies; and (b) showed sick/survivor and sick/non-survivor counts among patients with or without pre-existing conditions, or risk, risk ratio or survival chance for the various types of conditions; all studies should include a comparison group of controls with outcomes and report sufficient data to perform the analyses were needed. Studies in which severity or mortality was not the primary outcome and narrative reviews and meta-analyses that included fewer than 5 studies were excluded. Systematic reviews reporting outcomes in vaccinated patients or in pregnant women and children (aged <18 years) were also excluded, as these groups have additional and specific conditions or morbidities.

All identified citations were managed with a reference management program, and duplicates were removed. The full text of the articles was then independently reviewed for eligibility. The full texts of potentially eligible articles were independently reviewed by two investigators. A third coauthor resolved any disagreement that could not be resolved by consensus. The data extracted included: author, year of publication, number of participants, number and type of studies included, assessment instrument used, method of analysis, outcomes assessed, heterogeneity, and the estimated associations for the conditions and the outcomes.

Quality evaluation

We assessed the strength and quality of data from the included meta-analyses using the AMSTAR 2 tool, which uses 11 criterion items to measure the methodological quality of systematic reviews; when the specific criterion is met, one point is allocated, and an overall score is then calculated using the sum of the individual scores. A review scoring above 8 is considered high quality, 4 to 7 is a review of moderate quality, and below 4 is low quality.

Data analysis

Systematic reviews and meta-analyses meting the inclusion criteria formed the final unit of analysis. The measures of effect size of the association between each factor and COVID-19 severity/mortality were: incidence rate ratio, odds ratio, and hazard ratio. Primarily, the effect size measure and its 95% confidence interval were used. The first step was to correct the measurements by estimating a more accurate value and 95% confidence interval in which the lower and upper limits were symmetrical

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around the measurement. This approach minimized dependence produced by sharing the unexposed sample while allowing estimation of heterogeneity among exposed samples. A graphical cross-tabulation (citation matrix) of the overlapping systematic reviews (in columns) and primary studies included (in rows) was created. A citation matrix allows the degree of overlap to be quantified with a measure known as the corrected covered area (CCA). Overlap is categorized as very high (>15%), high (11–15%), moderate (6–10%), or slight (0-5%). CCA is a validated method of quantifying the degree of overlap between two or more reviews, and it helps guide the decision process on how to deal with overlap when it is present.

The characteristics and results of the included studies were abbreviated as narrative synthesis and presented in tables and forest diagrams. The evidence provided was summarized for each identified study. Where proper meta-analyses were performed, generic inverse variance method random effects models with DerSimonian and Laird random-effects model, which accounts for inter- and intra-study variance, were used (36). To calculate the effects of the determinant conditions, which were presented as pooled odd ratios (pOR) with a 95% confidence interval in dichotomous variables, summary estimates were made using the logarithmic scale to maintain symmetry in the analysis. An estimate of publication bias was also calculated with Egger's regression test (37). A p value <.1 was considered significant for this test.

Results.

The initial search identified 411 potentially eligible studies. After discarding duplicates, 225 were screened and finally 16 were included (Figure 1). These systematic reviews included 568 primary studies, with a range between 7 and 77.

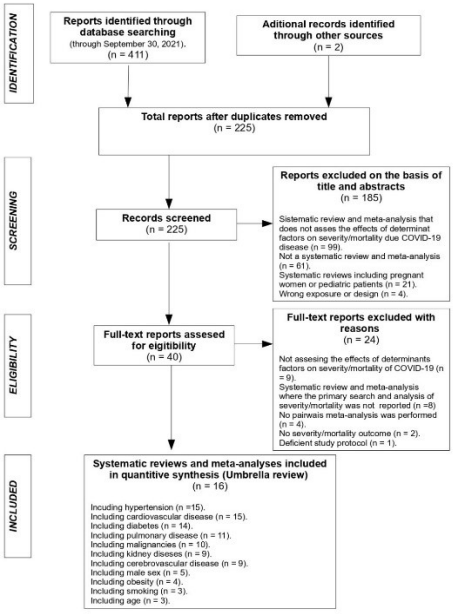

Figure 1. *Flow chart of research according to PRISMA.*

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The characteristics of the selected studies are shown in Table 1. Overall, risk estimates of the association of 12 underlying conditions with severity/mortality in patients diagnosed with COVID-19 were available. Five systematic reviews included information on the risk of hospitalization for 11 conditions (age, male sex, smoking status, cancer, hypertension, DM, obesity, CVD, CPD, and CBD), 8 reported the risk of severe/critical illness from 10 determinants (male sex, smoking habit, LD, neoplasms, obesity, KD, CVD, CBD, and CPD), and 3 reported risk estimates for mortality ratio of 11 factors (smoking, male sex, LD, obesity, CPD, neoplasms, DM, hypertension, KD, CBD, and CVD).

The quality assessment showed that only 3 reviews (20%) provided prior information on the design of the studies. Differences between reviewers were found in 41 indicators (32.8%) of 7 meta-analyses. All 16 studies (100%) met publication status as inclusion criteria, list and characteristics of included studies. Three studies had shortcomings in the selection of duplicate studies and data extraction, comprehensive literature search, and methods used to combine appropriate. Only six studies (40%) clearly reported conflicts of interest. Finally, 14 studies scored above 8 points (high quality) and 2 reviews scored 7 points (medium quality) (appendix 2).

Figure 2 shows the general characteristics of systematic reviews with overlapping associations. When analyzing overlapping associations, 266 primary studies appeared in at least two reviews. Overall, the CCA showed a degree of overlap of 2.05%, which is considered low. The degree of overlap ranged from 0% to 16%. One study showed high values of overlap with four studies and moderate values with another study. Another two studies showed cross-overlap with values reaching 14%.

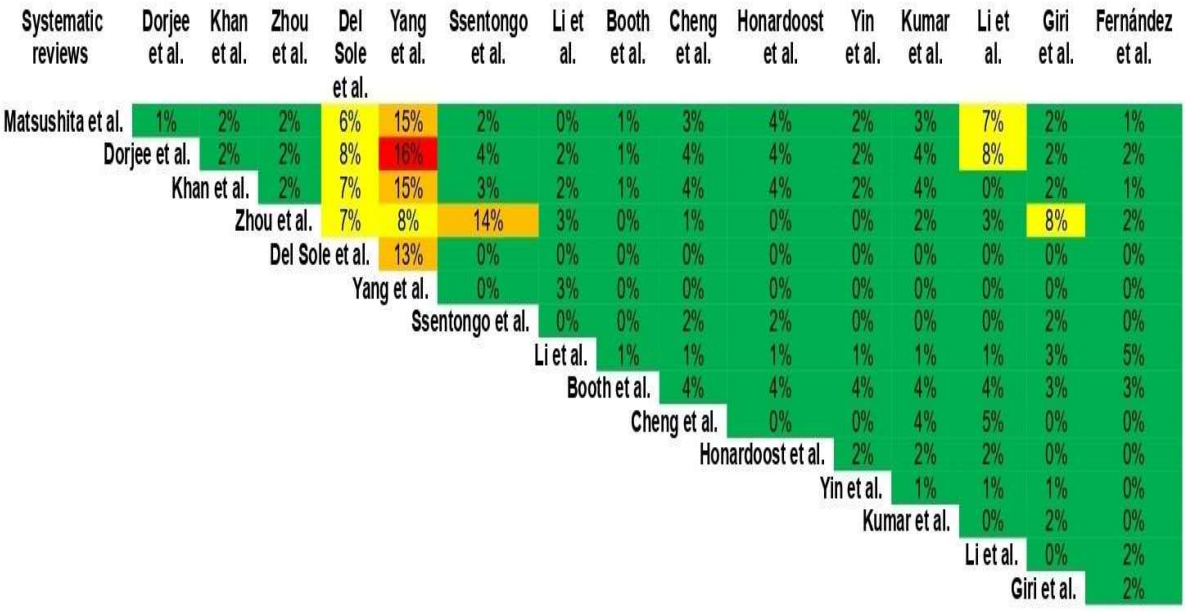

Figure 2. Overlapping graph.

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When considering p<.05 as trend of statistical significance, random effects estimates were significant for all outcomes. Of the 15 selected studies, 14 reported significant association of 12 determinant conditions with combined increased risk for hospitalization, severity/criticism, and disease mortality (38, 39, 42-48, 50-53). On the other hand, only two studies found no significant increase in risk for severity/critical disease or mortality of LD. When COVID-19 hospitalization odd ratios were analyzed (table 2), the conditions that showed the strongest association were CBD (pOR 4.05; 95%CI 3.20-5.12), age over 60 years (pOR 3.50; 95%CI 2.97-4.36) and CPD (pOR 2.94; 95%CI 2.14-4.04). Eight conditions showed significant association with the outcome (p<.0001), with the lowest value for the male sex (pOR 1.48; 95%CI 1.19-1.86).

Analysis of determinants for the risk of severe/critical illness showed that factors most strongly associated with this outcome were CPD (pOR 2.82; 95%CI 1.92–4.14), CBD (pOR 2.74; 95%CI 1.59–4.74), and CVD (pOR 2.44; 95%CI 1.97–3.01). The rest of the factors evaluated showed lower but significant odd ratio values for the outcome (p<.0001) (table 3).

CVD was the condition with the highest odd ratios for mortality in patients diagnosed with COVID-19 (pOR 3.59; 95% CI 2.83–4.56), followed by CBD (pOR 3.11; 95% CI 2.35–4.11) and KD (pOR 3.02; 95% CI 2.61–3.49). Other determinant factors also showed significant odd ratios for the resultant (p < .0001) (table 4).

About a third of the 16 selected systematic reviews and meta-analyses had significant heterogeneity, and 69% had I2 > 50%. Individual studies in each meta-analysis differed in terms of geographic location, ethnicity of selected subjects, frequency of diagnosis of the determinant condition, method of diagnosis, COVID-19 classification, duration of follow-up, and outcome assessment. The main problem is that these studies did not publish the heterogeneity of the primary studies included in the specific risk comparison.

We were unable to establish possible publication bias according to Egger's regression test. The test in 60% of meta-analyses in reanalysis of the remaining 40% had insufficient data. In those we reanalyzed, 50% had statistical evidence of publication bias. For the meta-analyses that could not be reanalyzed, none reported significant publication bias or did not perform or publish any statistical test of publication bias for the specific exposure comparison. This could have been due in part to sampling differences in the included studies. However, it is possible that unmeasured publication bias exists in many of the estimates summarized.

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TABLE 1.
CHARACTERISTICS OF THE SYSTEMATIC REVIEWS INCLUDED IN THE UMBRELLA REVIEW.

REFERENCE	LAST DATE OF SEARCH	SOURCE DATABASE	NO. OF PRIMARY INCLUDED ARTICLES	NO. OF INCLUDED PATIENTS	UNDERLYING CONDITIONS STUDIED	OUTCOMES RELATED TO COVID-19	INSTRUMENT OF QUALITY APPRAISAL USED	ADJUSTED POOLED ESTIMATES
Matsushita et al. (38)	April 3, 2020	PubMed and Embase	25	76638	Age, Male sex, Hypertension, DM, CVD	Death	Newcastle Ottawa Quality Assessment Scale	Considered
Dorjee et al. (39)	August 31, 2020	Medline, Embase, Web of Science and the WHO COVID-19 database	77	38906	Age, Male sex, Smoking, KD, Hypertension, LD, DM, CPD, CVD.	Death, severity	Newcastle Ottawa Quality Assessment Scale	Considered
Khan et al. (40)	May 1, 2020	Medline, Web of Science, Scopus, and CINAHL	41	27670	Malignancies, KD, Hypertension, LD, DM, CPD, CVD, CBD.	Death	Newcastle Ottawa Quality Assessment Scale	Not considered
Zhou et al. (41)	April 25, 2020	PubMed, Embase, and Cochrane Library	34	16110	Obesity, Malignancies, KD, Hypertension, LD, DM, CPD, CVD, CBD.	Severity / Death	Not reported	Not considered
Del Sole et al. (42)	May 28, 2020	PubMed, ISI Web of Science, SCOPUS and Cochrane databases	12	2794	Male sex, Smoking, Hypertension, DM, CPD, CVD, CBD,	Severity	Not reported	Not considered
Yang et al. (43)	February 25, 2020.	PubMed, EMBASE, and Web of Science	7	1576	Hypertension, CPD, CVD,	Severity	Not reported	Not considered
Ssentongo et al. (44)	July 7, 2020	MEDLINE, SCOPUS, OVID, and Cochrane Library databases, and medrxiv.org	25	484	Malignancies, KD, Hypertension, DM, CVD.	Mortality	Newcastle Ottawa Quality Assessment Scale	Considered
Li et al. (45)	February 28, 2021	PubMed, Embase, Web of science and Cochrane Library for epidemiological studies	41	21060	Male sex, Smoking, Obesity, malignancies, KD, Hypertension, LD, DM, CPD, CVD, CBD.	Severity	Newcastle Ottawa Quality Assessment Scale	Not considered
Booth et al. (46)	July 9, 2020	PubMed and SCOPUS	66	1786001	Age, Male sex, Obesity, Malignancies,	Severity	Newcastle Ottawa Quality Assessment Scale	Not considered

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Cheng et al. (47)	April 1, 2020	PubMed, Embase, China National Knowledge Infrastructure (CNKI), and Wanfang Database	22	3286	Malignancies, Hypertension, DM, CPD, CVD, CBD.	Severity	Newcastle Ottawa Quality Assessment Scale	Not considered
Honardoost et al. (48)	February 2021	Electronic literature	28	6270	Hypertension, DM, CPD, CVD, CBD.	Severity	Newcastle Ottawa Quality Assessment Scale	Not considered
Yin et al. (49)	January 18, 2021.	PubMed, Web of Science, and CNKI	41	12526	Malignancies, KD, Hypertension, LD, DM, CPD, CVD, CBD.	Severity	Not reported	Not considered
Sahu et al. (50)	May 24, 2020	PubMed, Embase, and Web of Science	22	4380	Obesity, Malignancies, KD, Hypertension, DM, CPD, CVD,	Severity	Not reported	Not considered
Li et al. (51)	April 14, 2020	PubMed, Embase, and Cochrane Library	12	2445	Malignancies, Hypertension, DM, CPD, CVD, CBD.	Severity	Newcastle Ottawa Quality Assessment Scale	Not considered
Giri et al. (52)	November 20, 2020	PubMed, Scopus, Embase, and Web of Sciences	41	16495	Malignancies, Hypertension, DM, CVD, CBD,	Severity	Methodological Index for Non-Randomized Studies	Not considered
Fernández et al. (53)	May 28, 2020	MEDLINE, bioRXiv, and MedRXiv,	74	44672	RD, Hypertension, CVD, CBD.	Severity (One parameter for mortality)	ROBINS-I tool	Considered

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TABLE 2.
HOSPITALIZATION.

STUDY	NUMBER OF PRIMARY STUDIES	ODDS RATIO	IC 95%	Z	p	WEIGTH (%)
MALE SEX						
De sole et al.	12	1.22	1.01 – 1.49	2.02	0.04348	36.67
Xinyian Li et al.	41	1.51	1.33 – 1.71	6.44	0.00000	43.82
Booth et al.	66	2.05	1.39 – 3.04	3.59	0.00033	19.51
COMBINED	**119**	**1.48**	**1.19 – 1.85**	**3.51**	**0.00045**	**100.00**
AGE						
Dorjee et al	77	3.60 (Age > 60 years)	2.97 – 4.36	13.14	0.00000	65.34
Booth et al.	66	2.65 (Age > 75 years	1.81 – 3.90	4.98	0.00000	34.66
SMOKING HISTORY						
Del Sole et al.	12	1.54	1.07 – 2.22	2.32	0.02045	100
OBESITY						
Booth et al.	66	2.57	1.25 – 5.27	2.58	0.00992	100
MALIGNANCIES						
Booth et al.	66	1.46	1.04 – 2.04	2.20	0.02757	35.18
Cheng et al.	22	3.18	2.09 – 4.82	5.43	0.00000	32.21
Yin et al.	41	2.63	1.75 – 3.93	4.66	0.00000	32.61
COMBINED	**129**	**2.27**	**1.40 – 3.33**	**3.33**	**0.00006**	**100.00**
RENAL DISEASES						
Yin et al.	41	3.60	2.18 – 5.94	5.01	0.00000	100
HYPERTENSION						
Del sole et al.	12	2.24	1.63 - 308	4.96	0.00000	32.78
Cheng et al.	22	2.79	1.66 – 4.69	3.72	0.00020	11.36
Honardoost et al.	28	2.37	1.80 – 3.13	6.12	0.00000	43.49
Yin et al.	41	2.13	1.81 – 2.51	2.86	0.00426	12.36
COMBINED	**103**	**2.34**	**1.95 – 2.81**	**9.13**	**0.00000**	**100.00**
DIABETES						
Del Sole et al.	12	2.78	2.09 – 3.72	6.96	0.00000	34.41
Cheng et al.	22	1.64	1.30 – 2.08	4.12	0.00004	36.34
Honadoost et al.	28	3.18	2.09 – 4.82	5.43	0.00000	29.25
COMBINED	**62**	**2.39**	**1.56 – 3.64**	**4.03**	**0.00005**	**100.00**
PULMONARY DISEASES						

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Del Sole et al.	12	2.39	1.10 – 5.19	2.20	0.02768	12.54
Cheng et al.	22	1.98	1.26 – 3.12	2.95	0.00314	24.53
Honadoost et al.	28	4.19	2.84 – 6.19	7.21	0.00000	28.19
Yin et al	41	3.14	2.35 – 4.19	7.75	0.00000	34.74
COMBINED	**103**	**2.94**	**2.14 – 4.04**	**6.63**	**0.00000**	**100.00**
CARDIOVASCULAR DIEASE						
Del Sole et al.	12	2.84	1.59 – 5.10	3.51	0.00045	19.51
Cheng et al.	22	1.79	1.08 – 2.96	2.26	0.02365	21.94
Honadoost et al.	28	4.81	3.43 – 6.74	9.11	0.00000	27.60
Yin et al.	41	2.76	2.18 – 3.49	8.46	0.00000	30.95
COMBINED	**103**	**2.94**	**2.00 – 4.33**	**5.46**	**0.00000**	**100.00**
CEREBROVASCULAR DISEASES						
Del Sole et al.	12	3.66	1.73 – 7.72	3.40	0.00067	9.93
Cheng et al.	22	3.92	2.45 – 6.28	5.69	0.00000	25.05
Honardoost et al	28	4.85	3.11 – 7.57	6.96	0.00000	28.06
Yin et al.	41	3.70	2.51 – 5.45	6.62	0.00000	36.96
COMBINED	**103**	**4.05**	**3.20 – 5.12**	**11.63**	**0.00000**	**100.00**

TABLE 3.
SEVERE AND CRITICAL DISEASE.

STUDY	NUMBER OF PRIMARY STUDIES	ODDS RATIO	IC 95%	Z	P	WEIGTH (%)
MALE SEX						
Dorjee et al.	77	1.30	1.21 – 1.42	6.77	0.00000	100
SMOKING HISTORY						
Dorjee et al.	77	1.28	1.06 – 1.55	2.63	0.00663	100
OBESITY						
Zhou et al.	34	1.72	1.04 – 2.85	2.11	0.03491	74.85
Kumar et al.	22	2.84	1.19 – 6.77	2.35	0.01860	25.15
COMBINED	**56**	**1.95**	**1.26 – 3.02**	**3.01**	**0.00265**	**100.00**
MALIGNANCIES						
Zhou et al.	34	2.73	1.73 – 4.21	4.43	0.00001	17.93
Ssentongo et al.	25	1.47	1.01 – 2.14	2.01	0.04432	22.96
Kumar et al.	22	2.38	1.25 – 4.52	2.64	0.00818	9.80
Li et al.	12	2.21	1.04 – 4.72	2.06	0.03987	7.34

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Giri et al.	41	1.75	1.40 – 2.18	4.95	0.00000	41.97
COMBINED	**134**	**1.91**	**1.54 – 2.37**	**5.88**	**0.00000**	**100.00**
RENAL DISEASES						
Dorjee et al.	77	2.5	2.09 – 2.99	10.06	0.00000	28.81
Zhou et al	34	3.02	2.23 – 4.08	7.18	0.00000	22.70
Ssentongo et al.	25	3.25	1.13 – 9.28	2.19	0.02821	4.89
Kumar et al.	22	1.46	1.06 – 2.02	2.30	0.02151	21.69
Fernadez et al.	74	2.5	1.82 – 3.44	5.65	0.00000	21.92
COMBINED	**232**	**2.35**	**1.83 – 3.03**	**6.66**	**0.00000**	**100.00**
LIVER DISEASES						
Dorjee et al.	77	2.65	1.88 – 3.75	5.54	0.00000	34.84
Zhou et al.	34	1.54	0.95 – 2.49	1.76	0.07894	29.29
Yin et al	41	1.32	0.96 – 1.82	1.70	0.08870	35.86
COMBINED	**115**	**1.76**	**1.12 – 2.78**	**2.43**	**0.01499**	**100.00**
DIABETES						
Dorjee et al.	77	1.5	1.36 – 1.65	8.11	0.00000	19.82
Zhou et al.	34	2.63	2.08 – 3.33	8.06	0.00000	17.10
Ssentongo et al.	25	1.82	1.43 – 2.23	5.29	0.00000	17.42
Kumar et al	22	2.29	1.56 – 3.39	4.18	0.00003	13.29
Li et al.	12	3.17	2.26 – 4.45	6.67	0.00000	14.50
Giri et al.	41	2.04	1.67 – 2.50	6.92	0.00000	17.88
COMBINED	**211**	**2.13**	**1.68 – 2.70**	**6.21**	**0.00000**	**100.00**
PULMONARY DISEASES						
Dorjee et al.	77	1.7	1.4 – 2.0	5.82	0.00000	23.06
Zhou et al.	34	3.56	2.87 – 4.41	11.59	0.00000	22.55
Yang et al.	7	2.46	1.76 – 3.44	5.27	0.00000	20.48
Kumar et al.	22	2.92	1.70 - 5.02	5.41	0.00000	19.43
Li et al.	12	5.08	2.68 – 9.63	4.98	0.00000	14.48
COMBINED	**152**	**2.82**	**1.92 – 4.14**	**5.30**	**0.00000**	**100.00**
CARDIOVASCULAR DISEASES						
Dorjee et al.	77	2.1	1.82 – 2.43	10.10	0.00000	17.57
Zhou et al	34	3.13	2.65 – 3.70	13.45	0.00000	17.10
Ssentongo et al.	25	2.25	1.60 – 3.17	4.65	0.00000	12.76
Kumar et al.	22	1.61	1.31 – 1.98	4.52	0.00001	16.18
Li et al.	12	2.66	1.71 – 4.15	4.32	0.00002	10.39
Giri et al.	41	2.78	2.00 – 3.86	6.10	0.00000	13.09
Fernández et al	34	3.20	2.29 – 4.48	6.80	0.00000	12.92
COMBINED	**245**	**2.44**	**1.97 – 3.01**	**8.26**	**0.00000**	**100.00**

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CEREBROVASCULAR DISEASE						
Zhou et al.	34	2.74	1.59 – 4.74	3.62	0.00030	100

TABLE 4.
Mortality.

STUDY	NUMBER OF PRIMARY STUDIES	ODDS RATIO	IC 95%	Z	P	WEIGTH (%)
MALE SEX						
Matsushita et al.	25	1.73	1.50 – 2.01	7.32	0.00000	100
SMOKING HISTORY						
Xinyang et al.	41	1.40	1.06 – 1.85	2.37	0.01791	100
OBESITY						
Xinyang et al.	41	1.89	1.44 – 2.46	4.66	0.00000	100
MALIGNANCIES						
Ali Kahn et al.	41	2.22	1.63 – 3.03	5.04	0.00000	42.26
Xinyang et al.	41	2.60	2.00 – 3.40	7.06	0.00000	57.74
COMBINED	**82**	**2.43**	**1.99 – 2.97**	**8.65**	**0.00000**	**100.00**
KIDNEY DISEASES						
Ali Khan et al.	41	3.02	2.60 – 3.51	14.39	0.00000	94.08
Li et al.	41	2.97	1.63 – 5.41	3.56	0.00038	5.92
COMBINED	**82**	**3.02**	**2.61 – 3.49**	**14.82**	**0.00000**	**100.00**
HYPERTENSION						
Matsushita et al.	25	2.87	2.09 – 3.93	6.54	0.00000	23.53
Li et al.	41	2.42	2.03 – 2.88	9.88	0.00000	76.47
COMBINED	**66**	**2.52**	**2.16 – 2.94**	**11.81**	**0.00000**	**100.00**
LIVER DISEASES						
Ali Kahn et al.	41	2.35	1.50 – 3.6	3.82	0.00013	46.04
Li et al.	41	1.51	1.06 – 2.17	2.22	0.02629	53.96
COMBINED	**82**	**1.85**	**1.20 – 2.85**	**2.79**	**0.00522**	**100.00**
DIABETES						
Matsushita et al.	25	3.20	2.26 – 4.53	6.55	0.00000	12.55
Ali Kahn et al.	41	2.46	2.03 – 2.85	10.39	0.00000	48.61
Li et al.	41	2.40	1.98 – 2.91	8.94	0.00000	38.34
COMBINED	**107**	**2.52**	**2.22 – 2.85**	**14.50**	**0.00000**	**100.00**
PULMONARY DISEASES						
Ali Khan et al.	41	1.94	1.72 – 2.19	10.75	0.00000	63.52
Li et al.	41	2.88	1.89 – 4.38	4.93	0.00000	36.48

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COMBINED	**82**	**2.24**	**1.54 – 3.25**	**4.24**	**0.00002**	**100.00**
CARDIOVASCULAR DISEASES						
Matsushita et al.	25	4.97	2.76 – 6.58	11.23	0.00000	26.51
Ali Khan et al.	41	3.42	2.86 – 4.09	13.50	0.00000	33.90
Yang et al.	7	3.41	1.88 – 6.22	4.02	0.00006	11.47
Li et al.	41	2.87	2.22 – 3.71	8.04	0.00000	28.13
COMBINED	**114**	**3.59**	**2.83 – 4.56**	**10.55**	**0.00000**	**100.00**
CEREBROVASCULAR DISEASES						
Ali Khan et al.	41	4.12	3.04 – 5.58	9.14	0.00000	38.86
Li et al.	41	2.47	1.54 – 3.97	3.74	0.00018	23.35
Giri et al.	41	2.68	1.29 – 5.57	2.64	0.00824	12.05
Fernández et al.	75	2.70	1.74 – 4.19	4.42	0.00001	25.74
COMBINED	**198**	**3.11**	**2.36 – 4.11**	**8.01**	**0.00000**	**100.00**

Conclusions.

This umbrella review provides a comprehensive summary of the body of published systematic reviews and meta-analyses examining the determinants and severity/mortality of COVID-19. The results of this research indicate that:

Determinants (demographics and co-morbidities) are variably (but significantly) associated with these outcomes. These factors represent a starting point of knowledge that can be used to advance research and improve patient prediction. Identification of risk factors associated with severity or mortality risk may aid in the identification of patient groups that could benefit from prevention strategies to modify potential risks.

Future research needs to actively investigate unstudied protective factors that are not reciprocal to certain risk factors, such as individual or family characteristics that increase the likelihood of finding protective factors.

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Attachments	
1.	Abstract “Association of patients’ pre-existing determinants and severity/mortality in patients diagnosed with COVID-19: results of an umbrella systematic review and meta-analysis” accepted to ECCMID 2022
2.	Preprint of "Predictors of clinical evolution of SARS-CoV-2 infection in hematological patients: a systematic review and meta-analysis"
3.	Preprint of “Clinical outcome in solid organ transplant recipients affected by COVID-19 compared to general population: a systematic review and meta-analysis”

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