

Comorbidities increase the risk of severity and mortality in COVID-19 patients: a systematic review and meta-analysis

Comorbidades aumentam o risco de gravidade e mortalidade em pacientes com COVID-19: uma revisão sistemática e metanálise

Comorbilidades aumentan el riesgo de gravedad y mortalidad en pacientes con COVID-19: una revisión sistemática y metanálisis

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Edilson Leite de Moura

ORCID: <https://orcid.org/0000-0001-6216-6522>
Universidade Federal de Alagoas, Brasil
E-mail: edilsonleite17@hotmail.com

Jean Moises Ferreira

ORCID: <https://orcid.org/0000-0002-6554-0337>
Universidade Federal de Pernambuco, Brasil
E-mail: jean.moises@hotmail.com

Ana Caroline Melo dos Santos

ORCID: <https://orcid.org/0000-0003-0280-6107>
Universidade Federal de Alagoas, Brasil
E-mail: anacaroline12305@gmail.com

Denise Macedo da Silva

ORCID: <https://orcid.org/0000-0002-2294-6660>
Universidade Federal de Alagoas, Brasil
E-mail: denise.macedo15@hotmail.com

Maria Lidiane Ferreira da Silva

ORCID: <https://orcid.org/0000-0002-4679-1069>
Universidade Federal de Alagoas, Brasil
E-mail: lidianebiologia2018@gmail.com

Gleyce Kelly Marques de Oliveira Silva

ORCID: <https://orcid.org/0000-0003-1650-1718>
Universidade Federal de Alagoas, Brasil
E-mail: gleycekelly1844@gmail.com

Pedro Henrique Nobre Silva

ORCID: <https://orcid.org/0000-0003-1994-6480>
Universidade Federal de Alagoas, Brasil
E-mail: pehnobre@gmail.com

José Anderson dos Santos

ORCID: <https://orcid.org/0000-0002-4182-4693>
Universidade Federal de Alagoas, Brasil
E-mail: jose.anderson.s.2013@gmail.com

Marcos Antônio da Silva Barbosa Junior

ORCID: <https://orcid.org/0000-0002-7759-4981>
Universidade Federal de Alagoas, Brasil
E-mail: marcosantoniojunior.s15@gmail.com

Abel Barbosa Lira Neto

ORCID: <https://orcid.org/0000-0001-7597-3761>
Universidade Federal de Alagoas, Brasil.
E-mail: abel.neto@arapiraca.ufal.br

Aline Cristine Pereira e Silva

ORCID: <https://orcid.org/0000-0002-9620-5654>
Universidade Federal de Alagoas, Brasil
E-mail: aline_ufal@yahoo.com.br

Carlos Alberto de Carvalho Fraga

ORCID: <https://orcid.org/0000-0002-9564-9595>
Universidade Federal de Alagoas, Brasil
E-mail: carlos.fraga@arapiraca.ufal.br

Karol Fireman de Farias

ORCID: <https://orcid.org/0000-0003-1352-2513>
Universidade Federal de Alagoas, Brasil
E-mail: karolfireman@hotmail.com

Elaine Virginia Martins de Souza Figueiredo

ORCID: <https://orcid.org/0000-0001-9724-5861>

Universidade Federal de Alagoas, Brasil

E-mail: elainevms@yahoo.com.br

Abstract

Introduction: Several studies have shown that patients with comorbidities present a poor clinical outcome of COVID-19, but the conclusions are not yet consolidated. We conducted a meta-analysis to evaluate the relationship between the preexistent conditions (comorbidities) in patients infected with SARS-CoV-2 and the outcome of COVID-19. **Methods:** PubMed, Science Direct, ISI Web of Science and Scopus databases were examined up to November 2020. We calculated the pooled odds ratio (OR) with 95% confidence interval, using fixed-effects or random-effects models. **Results:** A total of 48 retrospective cohort studies with 344,290 COVID-19 patients were included in the meta-analysis. The pooled results showed that hypertension, diabetes, cardiovascular, chronic pulmonary, chronic kidney and cerebrovascular diseases increase the risk of severity and mortality in COVID-19 patients. Moreover, malignancy was associated with an increased risk of death from COVID-19. **Conclusions:** The comorbidities previously mentioned may be important predictors of poor outcome of COVID-19, contributing to the prognosis of severe cases of the disease. (TNR font 10 – simple space)

Keywords: Coronavirus; Comorbidities; Chronic disease; COVID-19 and SARS-CoV-2.

Resumo

Introdução: Vários estudos têm mostrado que pacientes com comorbidades apresentam um pobre desfecho clínica da COVID-19, mas as conclusões ainda não estão consolidadas. Nós conduzimos uma metanálise para avaliar a relação entre as condições preexistentes (comorbidades) em pacientes infectados com SARS-CoV-2 e o desfecho da COVID-19. **Métodos:** Os bancos de dados PubMed, Science Direct, ISI Web of Science e Scopus foram examinados até novembro de 2020. Nós calculamos o odds ratio (OR) com intervalo de confiança de 95%, usando modelos de efeitos fixos ou aleatórios. **Resultados:** Um total de 48 estudos de coorte retrospectivos com 344.290 pacientes com COVID-19 foram incluídos na metanálise. Os resultados combinados mostraram que hipertensão, diabetes, doenças cardiovasculares, pulmonares crônicas, renais crônicas e cerebrovasculares aumentam o risco de gravidade e mortalidade em pacientes com COVID-19. Além disso, a malignidade foi associada a um risco aumentado de morte por COVID-19. **Conclusões:** As comorbidades citadas anteriormente podem ser importantes preditores de pobre desfecho da COVID-19, contribuindo para o prognóstico de casos graves da doença.

Palavras-chave: Coronavírus; Comorbidades; Doenças crônicas; COVID-19 e SARS-CoV-2.

Resumen

Introducción: Varios estudios han demostrado que los pacientes con comorbilidades presenten un mal pronóstico clínico de COVID-19, pero las conclusiones aún no están consolidadas. Realizamos un metanálisis para evaluar la relación entre las condiciones preexistentes (comorbilidades) en pacientes infectados con SARS-CoV-2 y el resultado de COVID-19. **Métodos:** Se examinaron las bases de datos PubMed, Science Direct, ISI Web of Science y Scopus hasta noviembre de 2020. Nosotros calculamos el odds ratio (OR) con un intervalo de confianza del 95%, utilizando modelos de efectos fijos o de efectos aleatorios. **Resultados:** Se incluyeron en el metanálisis un total de 48 estudios de cohorte retrospectivos con 344,290 pacientes con COVID-19. Los resultados combinados mostraron que la hipertensión, la diabetes, las enfermedades cardiovasculares, pulmonares crónicas, renales crónicas y cerebrovasculares aumentan el riesgo de gravedad y mortalidad en los pacientes con COVID-19. Además, la malignidad se asoció con un mayor riesgo de muerte por COVID-19. **Conclusiones:** Las comorbilidades mencionadas anteriormente pueden ser importantes predictores de mala evolución del COVID-19, contribuyendo al pronóstico de los casos graves de la enfermedad.

Palabras clave: Coronavirus; Comorbilidades; Enfermedades crónicas; COVID-19 e SARS-CoV-2.

1. Introduction

In December 2019, an outbreak that started in Wuhan - China, gave rise to Coronavirus disease 2019 (COVID-19) (Lin et al., 2020a; Tian et al., 2020a). COVID-19 is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). SARS-CoV-2 shows a high transmission capacity and infected patients may be asymptomatic or develop a moderate (non-severe) to severe form of the disease (Lai et al., 2020; Tay et al., 2020).

The clinical conditions of patients may change rapidly, leading to severe pneumonia and, eventually, to acute respiratory distress syndrome, septic shock and/or multiple organ failure, which lead to a considerable number of deaths (Alhazzani et al., 2020; Moccia et al., 2020; Moore et al., 2020). COVID-19 mortality is a serious global problem today.

Several researches are focused on the development of vaccines and medicines, and recent discoveries may make treatment and prophylaxis a reality for the very near future (Abd El-Aziz & Stockand, 2020; Robson, 2020). Thus, understanding the dynamics of the virus, as well as the tendency of patients to develop a poor prognosis, is vital, and this information may provide better patient care and effectively reduce the mortality of the disease (Azkur et al., 2020; Zheng et al., 2020b).

Analysis of COVID-19 patients showed that susceptibility to severe SARS-CoV-2 infection varies between different groups of patients (Lee et al., 2020; Shi et al., 2020b). Some studies have shown that pre-existing conditions before symptomatic SARS-CoV-2 infection increase the severity of the disease, leading to poor patient prognosis (Li et al., 2020d; Yang et al., 2020a). Hypertension, chronic obstructive pulmonary disease (COPD), malignancy, diabetes, cardiovascular, renal, liver and cerebrovascular diseases have been described as possible factors of severity in patients with COVID-19 and in cases of fatality (Yang et al., 2020a; Yang et al., 2020c).

The literature on SARS-CoV-2 and COVID-19 has grown and changed rapidly in response to the need for new data on the virus (Harwood & Sinha, 2020; Lin et al., 2020b; Rando et al., 2020). For this reason, we performed a meta-analysis to affirm the relationship between pre-existing conditions (comorbidities) in patients infected with SARS-CoV-2 and the outcome of COVID-19. (TNR font 10 – justified – space 1,5).

2. Methodology

2.1 Search Strategy

To assess the association of pre-existing comorbidities with the severity and mortality of COVID-19, we performed a systematic review with a quantitative approach (meta-analysis), in which analyze the pooled data of the articles included (de Moura et al., 2020; Pereira et al., 2018). The review followed recommendations from Preferred Reporting Items for Systematic Reviews and Meta-analysis (Prisma) (Moher et al., 2009). The following databases were examined until November 2020: PubMed, Science Direct, ISI Web of Science and Scopus. The search keywords with the combinations used were “coronavirus”, “COVID-19”, “SARS-CoV-2” and “clinical characteristics”; using Boolean connectors “And”, “Or” and “And Not”. Descriptors were defined using the PICOS method (Santos et al., 2007). Participants (P): COVID-19 patients who have the severe form of the disease or who have died; the intervention (I): identification of comorbidities; control groups (C): COVID-19 patients without the severe form of the disease or who have recovered from the disease; outcome (O): presence or absence of comorbidities in the group of patients with non-severe or severe COVID-19 and patients who recovered or have died from COVID-19; Study design (S): a retrospective cohort. The surveys were not limited by the language or country of the primary studies. However, only articles published in English were qualified.

2.2. Eligibility criteria

The inclusion criteria to select studies in our meta-analysis were: (1) studies with a retrospective cohort design; (2) studies that assessed the association between comorbidities and severe COVID-19; (3) studies that assessed the association between comorbidities and death in COVID-19 patients. The exclusion criteria were: (1) systematic/integrative/narrative review; (2) letters to editors; (3) case reports; (4) editorials, (5) conference abstracts, and (6) duplicates articles.

2.3. Evaluation of studies

Titles, abstracts and full articles were independently assessed by three researchers (ELM, DMS and ACMS). Inconsistencies among the researchers were elucidated by discussion after re-evaluating the article. Three investigators separately assessed the quality of the included studies using the Newcastle–Ottawa Scale (NOS) standards (PHNS, JAS, and MASBJ) (Stang, 2010). The quality of the studies was classified as low quality (score < 4), medium quality (score 4-6) and high quality (score > 7). The authors' evaluation form is summarized in Supplementary 1.

2.4. Data extraction

The data of interest for each accepted study were extracted into a data extraction form developed specifically for this systematic review. We extracted the following variables: author, year of publication, sex, average age, number of participants, number of patients with comorbidities. Subsequently, they were categorized as patients with severe and non-severe COVID-19; patients who died and recovered from COVID-19. Two investigators collected information from each study, and a third investigator independently reviewed the extracted data for completeness and accuracy from the original studies (MLFS, GKMO, JMF).

2.5. Statistical analysis

Review Manager (version 5.3) software was used for statistical analysis, considering Odds Ratio (OR) and an estimate of the 95% confidence intervals (CIs) for each study and the pooled OR were established by Z test ($p < .05$). The results were calculated to assess the sensitivity. The I² statistic and Cochran's Q test (Higgins & Thompson, 2002) were used to assess statistical heterogeneity. We calculated the pooled ORs using fixed-effects model (when P heterogeneity > 0.05 or I² $< 50\%$) and random-effects model (when P heterogeneity < 0.05 or I² $> 50\%$). Egger's test was calculated to detect bias in comparisons, using the metafor package (Nicodemus, 2008) in the R Project for Statistical version 3.6.2. (TNR font 10 – justified – space 1,5).

3. Results

3.1 Search results

Searches in the four databases identified a total of 3,228 articles (PubMed: 1283, Scopus: 947, Web of Science: 755, Science Direct: 243). After removing duplicates, 1,546 articles were considered for the studies selection process. From the 1,546 articles, 1,421 were excluded after analysis of titles and abstracts. Thus, 125 full-text articles were carefully reviewed. Applying the inclusion and exclusion criteria, 48 studies were included in the qualitative and quantitative (meta-analysis) synthesis (Figure 1).

The data for all participants included in the meta-analysis (344,290 COVID-19 patients) were divided into subgroups, according to patient characteristics. The first subgroup included studies that analysed non-severe and severe cases of COVID-19 (2,501 severe and 6,567 non-severe patients) (Charlotte et al., 2020; Chen et al., 2020a; Dang et al., 2020; de la Rica et al., 2020; Fang et al., 2020; Feng et al., 2020; Guan et al., 2020; He et al., 2020a; He et al., 2020b; Huang et al., 2020; Jiang et al., 2020; Jin et al., 2020; Lee & Kim, 2020; Li et al., 2020a; Li et al., 2020b; Li et al., 2020c; Liao et al., 2020; Liu et al., 2020a; Liu et al., 2020b; Lv et al., 2020; Shi et al., 2020a; Shu et al., 2020; Wang et al., 2020a; Wang et al., 2020b; Wang et al., 2020c; Wu et al., 2020a; Xie et al., 2020; Yang et al., 2020b; Yao et al., 2020; Zhang et al., 2020a; Zhang et al., 2020b; Zhang et al., 2020c; Zheng et al., 2020a; Zhu et al., 2020).

The second subgroup was composed of studies that evaluated hospitalized COVID-19 patients who recovered or died (39,722 died and 295,500 recovered) (Chen et al., 2020b; Chen et al., 2020c; Chen et al., 2020d; Deng et al., 2020; Guisado-Vasco et al., 2020; Hu et al., 2020; Javanian et al., 2020; Li et al., 2020c; Morrison et al., 2020; Ñamendys-Silva et al., 2020; Parra-Bracamonte et al., 2020; Shang et al., 2020; Vena et al., 2020; Wu et al., 2020; Xie et al., 2020; Yao et al., 2020; Zhou et al., 2020). The characteristics of the studies included in the meta-analysis are shown in Tables 1A and 1B.

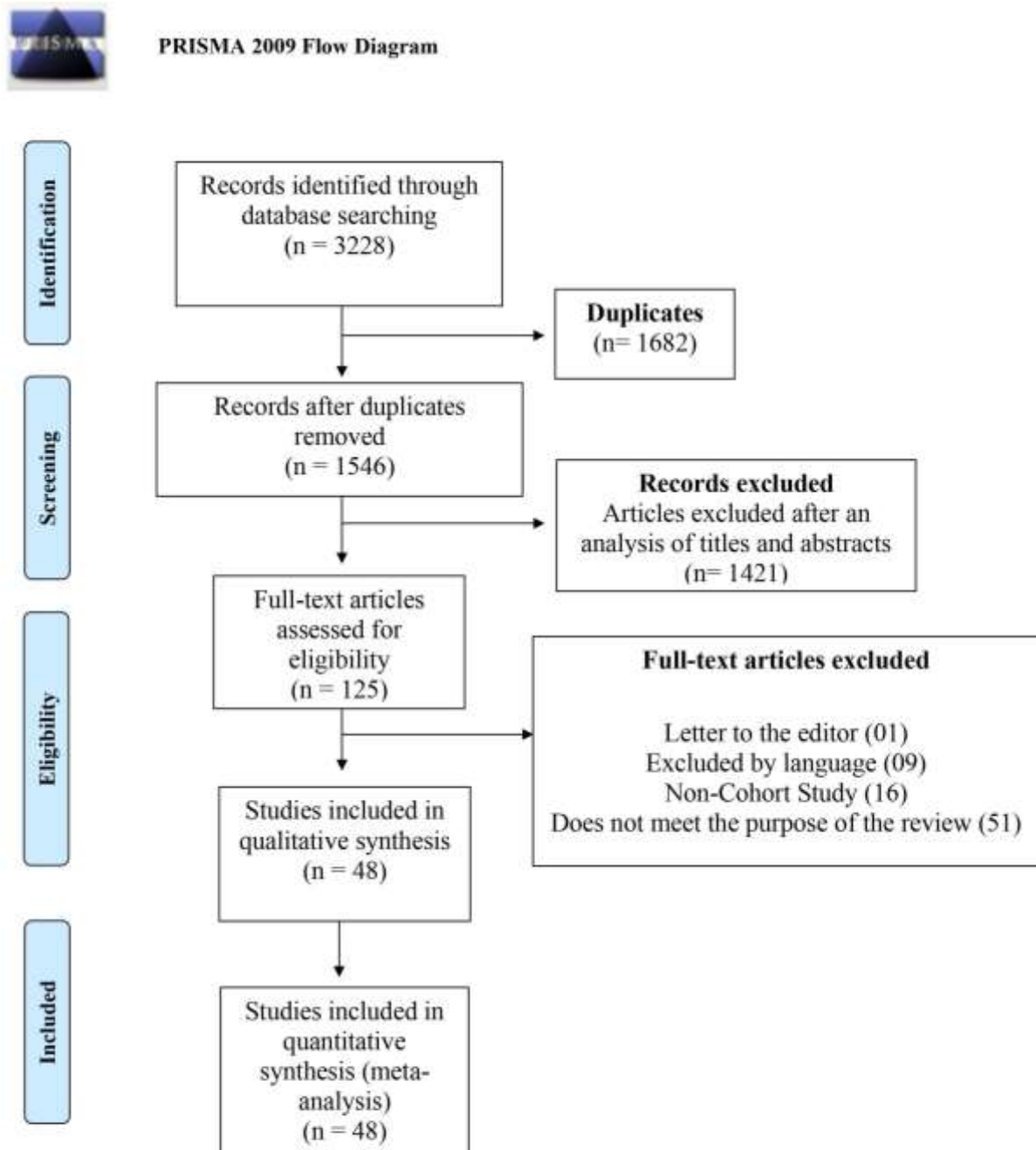
3.2 Meta-analysis

3.2.1 Hypertension

Thirty-four studies (2,501 severe and 6,567 non-severe COVID-19 patients) were included in the meta-analysis to assess susceptibility to severe COVID-19 in hypertensive individuals. The pooled ORs showed that patients with hypertension had a 2.38-fold increased risk of developing the severe form of COVID-19 (OR = 2.38 [95% CI = 1.91 - 2.96], $P < 0.00001$)

(Table 2). The forest plot of this association is shown in Figure 2A. In this analysis, the Egger test confirmed the presence of publication bias (Egger test: $Z = 6.9149$, $P < 0.0001$). Furthermore, heterogeneity was detected among the included studies ($\chi^2 = 86.94$, $P < 0.00001$, $I^2 = 62\%$) (Table 2).

Figure 1 - Process of selecting studies for meta-analysis.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Source: author of this research (2020).

Table 1A - Characteristics of the studies included in the meta-analyses.

Author	Patients			Country	Age (median)	Groups	Comorbidities							
	All	Female	Male				Hypertension	Diabetes	Cardiovascular disease	CPD	CKD	Cerebrovascular disease	CLD	Malignancy
Charlotte et al., 2020	196	77	119	Switzerland	70	Without ICU stay vs. With ICU stay	118 (60.2%)	52 (26.5%)	47 (24.0%)	16 (8.2%)	0	0	0	15 (7.6%)
Chen(1) et al., 2020	48	11	37	China	64.4	Severe/critically vs. Moderate	23 (49.7%)	12 (25%)	8 (16.7%)	2 (4.2%)	0	6 (12.5%)	4 (8.3%)	6 (12.5%)
Chen(2) et al., 2020	203	95	108	China	54	Died vs. Survived	43 (21.2%)	16 (7.9%)	16 (7.9%)	8 (3.9%)	8 (3.9%)	9 (4.4%)	8 (3.9%)	7 (3.4%)
Chen(3) et al., 2020c	274	103	171	China	62	Death vs. Recovered	93 (33.9%)	47 (17.1%)	23 (8.4%)	18 (6.6%)	4 (1.5%)	4 (1.5%)	0	7 (2.5%)
Chen(4) et al., 2020	681	319	362	China	65	Survivors vs. Non-survivors	293 (43.0%)	114 (16.7%)	80 (11.7%)	15 (2.2%)	27 (4.0%)	33 (4.8%)	0	0
Dang et al., 2020	17	5	12	China	88	Severe vs. Non-severe	9 (52.9%)	5 (29.4%)	8 (47.1%)	3 (17.6%)	6 (35.3%)	0	0	2 (11.8%)
Deng et al., 2020	225	101	124	China	NP	Death vs. Recovered	58 (25.8%)	26 (11.6%)	17 (7.6%)	25 (11.1%)	0	0	0	8 (3.6%)
Fang et al., 2020	1,280	665	615	China	NP	POTC vs. PSTC vs. PCTC	423 (33.0%)	184 (14.4%)	130 (10.2%)	36 (2.8%)	20 (1.6%)	13 (1.0%)	17 (1.3%)	13 (1.0%)
Feng et al., 2020	476	205	271	China	53	Severe/critically vs. Moderate	113 (23.7%)	49 (10.3%)	38 (8%)	22 (4.6%)	4 (0.8%)	17 (3.6%)	0	12 (2.5%)
Guan et al., 2020	1,099	459	640	China	47	Severe vs. Non-severe	165 (15%)	81 (7.4%)	27 (2.5%)	12 (1.1%)	8 (0.7%)	15 (1.4%)	23 (2.1%)	10 (0.9%)
Guisado-Vasco et al., 2020	607	212	394	Spain	69	Survivors vs. Non-survivors	276 (46.9%)	95 (16.2%)	133 (22.6%)	114 (19.4%)	22 (3.7%)	21 (3.6%)	24 (4.1%)	77 (13.1%)
He(1) et al., 2020	288	157	131	China	48.5	Severe vs. Non-severe	84 (29.2%)	24 (8.3%)	85 (29.5%)	5 (1.7%)	8 (2.8%)	0	10 (3.5%)	6 (2.1%)
He(2) et al., 2020	95	42	53	China	57.3	Common vs. Severe vs. Critical	33 (34.7%)	8 (8.4%)	13 (13.7%)	0	0	13 (13.7%)	0	0
Hu et al., 2020	105	43	62	China	NP	Survivors vs. Non-survivors	28 (26.7%)	4 (3.8%)	6 (5.7%)	12 (11.4%)	0	4 (3.8%)	0	6 (5.7%)
Huang et al., 2020	54	26	28	China	41	Common vs. Severe	8 (14.8%)	5 (9.3%)	8 (14.8%)	2 (3.9%)	0	3 (5.3%)	4 (7.4%)	0
Javaniyan et al., 2020	100	49	51	Iran	60.1	Deceased patients vs. Survivor patients	32 (32.0%)	37 (37.0%)	20 (20.0%)	12 (12.0%)	12 (12.0%)	3 (3.0%)	3 (3.0%)	4 (4.0%)
Jiang et al., 2020	60	25	35	China	41	Severe vs. Non-severe	5 (8.3%)	1 (1.7%)	0	1 (1.7%)	0	0	2 (3.3%)	0
Jin et al., 2020	45	27	18	China	58.8	Severe to critically vs. Mild to moderate	17 (37.7%)	5 (11.1%)	13 (28.8%)	3 (6.7%)	2 (4.4%)	0	0	2 (4.4%)
Lee and Kim, 2020	51	29	22	South Korea	58	Mild vs. Severe	14 (27.4%)	8 (15.7%)	7 (13.7%)	4 (7.8%)	1 (2.0%)	0		4 (7.8%)
Li(1) et al., 2020	548	269	279	China	60	Severe vs. Non-severe	166 (30.3%)	83 (15.1%)	34 (6.2%)	22 (4.0%)	10 (1.8%)	0	5 (0.9%)	24 (4.7%)
Li(2) et al., 2020	312	125	187	China	69.2	Severe vs. Non-severe	178 (57.1%)	121 (38.8%)	93 (29.8%)	27 (8.6%)	10 (3.2%)	20 (6.4%)	11 (3.5%)	12 (3.8%)
Li(3) et al., 2020	523	273	250	China	54.2	Non-ICU vs. ICU; ICU Survivors vs. ICU Non-survivors	130 (25.0%)	94 (18.0%)	38 (7.3%)	0	0	0	0	0
Liao et al., 2020	148	74	74	China	NP	Mild or moderate progressed to severe vs. Match mild or moderate	30 (20.3%)	7 (4.7%)	7 (4.7%)	3 (2.0%)	1 (0.7%)	4 (2.7%)	0	0
Liu(1) et al., 2020	140	91	49	China	65.5	Severe vs. Mild	63 (45%)	34 (24.3%)	35 (25%)	0	0	0	0	0

CPD: Chronic pulmonary disease; CKD: Chronic kidney disease; CLD: Chronic liver disease; ICU: intensive care unit; NP: no performed; POTC: Patients with ordinary type of COVID-19; PSTC: Patients with severe type of COVID-19; PCTC: Patients with critical type of COVID-19. Source: author of this research, 2020.

Table 1B - Characteristics of the studies included in the meta-analyses.

Author	Patients			Country	Age (median)	Groups	Comorbidities							
	All	Female	Male				Hypertension	Diabetes	Cardiovascular disease	CPD	CKD	Cerebrovascular disease	CLD	Malignancy
Liu(2) et al., 2020	72	33	39	China	46.2	Uncomplicated illness vs. Mild vs. Severe	7 (9.7%)	2 (2.8%)	7 (9.7%)	0	1 (1.4%)	0	0	0
Lv et al., 2020	354	179	175	China	62	Mild vs. Severe	74 (20.9%)	35 (9.9%)	18 (5.1%)	6 (1.7%)	0	0	0	2 (0.6%)
Morrison et al. 2020	81	25	56	EUA	64	Survivors vs. Non-survivors	60 (74.1%)	37 (45.7%)	23 (28.4%)	15 (18.5%)	1 (1.2%)	0	0	0
Ñamendys-Silva et al., 2020	164	50	114	Mexico	57.3	Alive vs. Dead	63 (38.4%)	53 (32.3%)	0	4 (2.4%)	6 (3.6%)	0	0	10 (6.0%)
Parra-Bracamonte et al., 2020	331,298	153,143	178,155	Mexico	44	Survivors vs. Non-survivors	66,170 (20%)	53,712 (16.2%)	7,351 (2.2%)	14,441 (4.4%)	6,895 (2.1%)	0	0	0
Rica et al., 2020	48	16	32	Spain	66	Non-ICU vs. ICU	33 (70.2%)	11 (24.4%)	14 (29.8%)	5 (10.6%)	8 (17.4%)	0	0	10 (21.3%)
Shang et al., 2020	113	40	73	China	66	Survivors vs. Non-survivors	50 (44.2%)	20 (17.7%)	28 (24.8%)	5 (4.4%)	9 (8.0%)	0	8 (7.1%)	8 (7.1%)
Shi et al., 2020	134	69	65	China	46	Severe vs. Non-severe	20 (14.9%)	9 (6.7%)	6 (4.5%)	0	0	6 (4.5%)	5 (3.7%)	5 (3.7%)
Shu et al., 2020	571	293	278	China	50	Transferred patients vs. Stable patients	55 (9.6%)	17 (3.0%)	12 (2.1%)	0	1 (0.2%)	0	0	0
Vena et al., 2020	317	104	213	Italy	71	In-hospital survivors vs. In-hospital non-survivors	149 (47%)	49 (15.5%)	63 (19.9%)	18 (5.7%)	22 (6.9%)	0	0	23 (7.2%)
Wang(1) et al., 2020	138	63	75	China	56	ICU vs. Non-ICU	43 (31.2%)	14 (10.1%)	20 (14.5%)	4 (2.9%)	4 (2.9%)	7 (5.1%)	4 (2.9%)	10 (7.2%)
Wang(2) et al., 2020	1,012	488	524	China	50	Patients with aggravation of illness during follow up vs. Patients without aggravation of illness during follow up	46 (4.5%)	27 (2.7%)	15 (1.5%)	0	0	0	0	0
Wang(3) et al., 2020	209	104	105	China	NP	Severe vs. Non-severe	27 (12.9%)	11 (5.3%)	5 (2.4%)	0	0	6 (2.9%)	0	0
Wu et al., 2020	201	73	128	China	51	With ARDS vs. Without ARDS Died vs. Alive	39 (19.4%)	22 (10.9)	8 (4.0%)	5 (2.5%)	2 (1.0%)	0	7 (3.5%)	1 (0.5%)
Xie(1) et al., 2020	79	35	44	China	60	Severe vs. Moderate	14 (17.7%)	8 (10.1%)	7 (8.9%)	0	0	0	0	0
Xie(2) et al., 2020	733	256	477	China	65	Survivors vs. Non-survivors	308 (42%)	138 (18.8%)	108 (14.7%)	37 (5.0%)	13 (1.8%)	34 (4.6%)	11(1.5%)	24 (3.3%)
Yang et al., 2020	136	70	66	China	56	Moderate vs. Severe and Critical	36 (27.1%)	20 (14.7%)	9 (6.6%)	0	4 (2.9%)	1 (0.7%)	8 (5.9%)	4 (2.9%)
Yao et al., 2020	108	65	43	China	NP	Severe vs. Non-severe Severe-alive vs. Severe-dead	16 (14.8%)	5 (4.6%)	4 (3.7%)	3 (2.8%)	0	0	2 (1.9%)	2 (1.9%)
Zhang(1) et al., 2020	140	69	71	China	57	Severe vs. Non-severe	42 (30.0%)	17 (12.1%)	7 (5.0%)	2 (1.4%)	2 (1.4%)	0	8 (5.7%)	0
Zhang(2) et al., 2020	111	65	46	China	38	Deterioration vs. Discharge	15 (13.5%)	14 (12.6%)	3 (2.7%)	3 (2.7%)	0	0	1 (0.9%)	8 (7.2%)
Zhang(3) et al., 2020	88	43	45	China	55	Moderate vs. Severe vs. Critical	23 (26.1%)	11 (12.5%)	8 (9.1%)	0	4 (4.5%)	5 (5.7%)	0	3 (3.4%)
Zheng et al., 2020	161	81	80	China	45	Severe vs. Non-severe	22 (13.7%)	7 (4.3%)	4 (2.5%)	6 (3.7%)	0	4 (2.5%)	4 (2.5%)	0
Zhou et al., 2020	191	72	119	China	56	Survivor vs. Non-survivor	58 (30.4%)	36 (18.8%)	15 (7.8%)	6 (3.1%)	2 (1.0%)	0	0	2 (1.0%)
Zhu et al., 2020	127	82	45	China	50.9	Severe vs. Non-severe	31 (24.4%)	10 (7.9%)	6 (4.7%)	6 (4.7%)	0	0	7 (5.5%)	5 (3.9%)

CPD: Chronic pulmonary disease; CKD: Chronic kidney disease; CLD: Chronic liver disease; ICU: intensive care unit; NP: no performed; POTC: Patients with ordinary type of COVID-19; PSTC: Patients with severe type of COVID-19; PCTC: Patients with critical type of COVID-19. Source: author of this research, 2020.

Seventeen studies involving 39,722 hospitalized COVID-19 patients who died and 295,500 hospitalized COVID-19 patients who recovered were included in the meta-analysis to assess the risk of death in hypertensive individuals. The pooled ORs showed that hypertensive patients hospitalized for COVID-19 had a 2.43-fold increased risk of dying (OR = 2.43 [95% CI = 1.90 - 3.11], $P < 0.00001$) (Table 2). The forest plot of this association is shown in Figure 3C. In this analysis, publication bias (Egger test: $Z = 46.2239$, $P > 0.0001$) and heterogeneity ($\chi^2 = 70.76$, $P < 0.00001$, $I^2 = 77\%$) were found (Table 2).

Table 2 - Meta-analysis of association between comorbidities and severity/mortality COVID-19.

Comorbidity	Teste of association			Model	Teste of heterogeneity			Egger test	
	OR (95% CI)	Z	p-value		χ^2	p-value	I ² (%)	Z	P
Severity									
Hypertension	2.38(1.91-2.96)	7.83	<0.00001	R	86.94	<0.00001	62	6.9149	<0.0001
Diabetes	2.08(1.67-2.60)	6.52	<0.00001	R	54.21	0.01	39	5.1688	<0.0001
Cardiovascular disease	2.36(1.98-2.80)	9.77	<0.00001	F	41.93	0.09	26	3.3947	0.0007
Chronic pulmonary disease	2.31(1.72-3.11)	5.53	<0.00001	F	19.18	0.57	0	0.8841	0.3766
Chronic kidney disease	2.55(1.11-5.84)	2.21	0.03	R	52.45	<0.00001	69	0.6908	0.4897
Cerebrovascular disease	2.51(1.68-3.76)	4.48	<0.00001	F	10.76	0.55	0	0.1614	0.8718
Chronic liver disease	0.99(0.64-1.52)	0.06	0.95	F	13.28	0.58	0	0.3035	0.7615
Malignancy	1.40(1.00-1.96)	1.94	0.05	F	23.51	0.22	19	0.1432	0.8861
Mortality									
Hypertension	2.43(1.90-3.11)	7.05	<0.00001	R	70.76	<0.00001	77	46.2239	<0.0001
Diabetes	1.93(1.35-2.76)	3.62	0.0003	R	104.44	<0.00001	85	36.2858	<0.0001
Cardiovascular disease	2.91(2.26-3.73)	8.38	<0.00001	R	30.39	0.01	51	10.4782	<0.0001
Chronic pulmonary disease	1.97(1.43-2.72)	4.15	<0.0001	R	23.19	0.04	44	13.3344	<0.0001
Chronic kidney disease	3.01(1.94-4.66)	4.94	<0.00001	R	20.05	0.04	45	13.0460	<0.0001
Cerebrovascular disease	2.40(1.60-3.60)	4.24	<0.0001	F	11.15	0.08	46	0.6710	0.5022
Chronic liver disease	1.72(0.87-3.39)	1.56	0.12	F	3.02	0.55	0	0.3098	0.7567
Malignancy	1.81(1.30-2.52)	3.52	0.0004	F	11.29	0.42	3	0.6944	0.4874

OR: odds ratio; CI: confidence interval. Source: author of this research (2020).

3.2.2. Diabetes

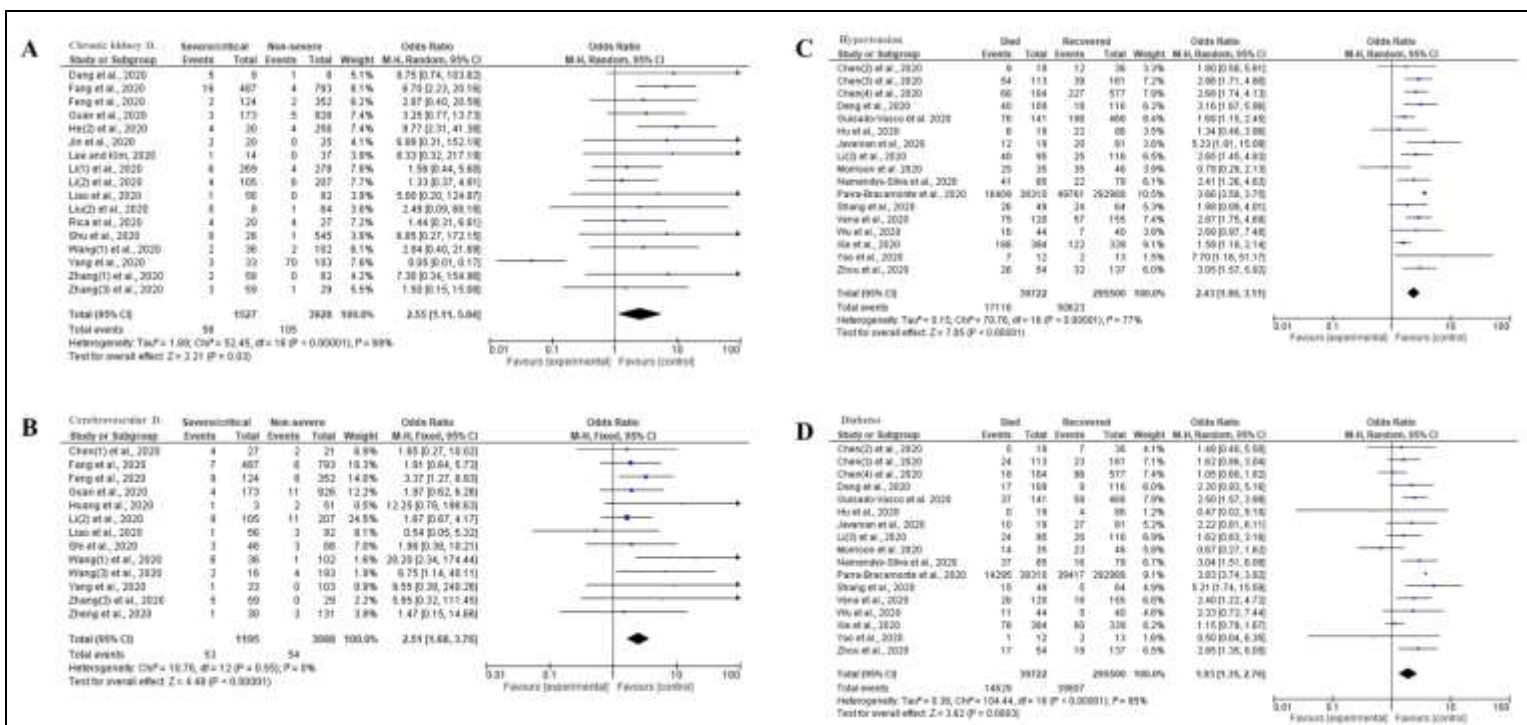
Thirty-four studies containing 2,501 severe and 6,567 non-severe COVID-19 patients were included in the meta-analysis to assess the susceptibility to severe form of the disease. The pooled ORs showed that diabetic patients were associated with a 2.08-fold increased risk of developing the severe COVID-19 (OR = 2.08 [95% CI = 1.67 - 2.60], $P < 0.00001$) (Table 2). The forest plot of this association is shown in Figure 2B. In this analysis, publication bias (Egger test: $Z = 5.1688$, $P < 0.0001$) and heterogeneity ($\chi^2 = 54.21$, $P = 0.01$, $I^2 = 39\%$) were detected (Table 2).

Seventeen studies were included in the meta-analysis to assess the risk of dying from COVID-19 in diabetics. Overall, 39,722 hospitalized COVID-19 patients who died and 295,500 hospitalized COVID-19 patients who recovered were analysed. The pooled ORs showed that COVID-19 patients with diabetes presented a 1.93-fold increased risk of dying (OR = 1.93 [95% CI = 1.35 - 2.76], $P = 0.0003$) during hospitalization (Table 2). The forest plot of this association is shown in Figure 3D. In this analysis, publication bias (Egger test: $Z = 36.2858$, $P < 0.0001$) and heterogeneity ($\chi^2 = 104.44$, $P < 0.00001$, $I^2 = 85\%$) were found (Table 2).

The pooled ORs showed that patients with chronic pulmonary disease had a 2.31-fold increased risk of developing the severe form of COVID-19 (OR = 2.31 [95% CI = 1.72 - 3.11], $P < 0.00001$) (Table 2). The forest plot of this association is shown in Figure 2D. Publication bias (Egger test: $Z = 0.8841$, $P = 0.3766$) and heterogeneity ($\chi^2 = 19.18$, $P = 0.57$, $I^2 = 0\%$) were not observed in this analysis (Table 2).

Fifteen studies comprising 39,583 hospitalized COVID-19 patients who died 295,344 hospitalized COVID-19 patients who recovered were included in the meta-analysis to assess the risk of death in individuals with chronic pulmonary disease. The pooled ORs showed that COVID-19 patients with chronic pulmonary disease were associated with a 1.97-fold increased risk of dying (OR = 1.97 [95% CI = 1.43 - 2.72], $P < 0.0001$) during hospitalization (Table 2). The forest plot of this association is shown in Figure 4B. Publication bias (Egger test: $Z = 13.3344$, $P < 0.0001$) and heterogeneity ($\chi^2 = 23.19$, $P = 0.04$, $I^2 = 44\%$) (Table 2) were detected.

Figure 3 - The Floret plots of comorbidities associated with severity and mortality by COVID-19.



(A) Floret plot of association between Chronic kidney disease and the risk of severe COVID-19. (B) Floret plot of association between Cerebrovascular disease and the risk of severe COVID-19. (C) Floret plot of association between Hypertension and the risk of COVID-19 death. (D) Floret plot of association between Diabetes and the risk of COVID-19 death. Source: author of this research (2020).

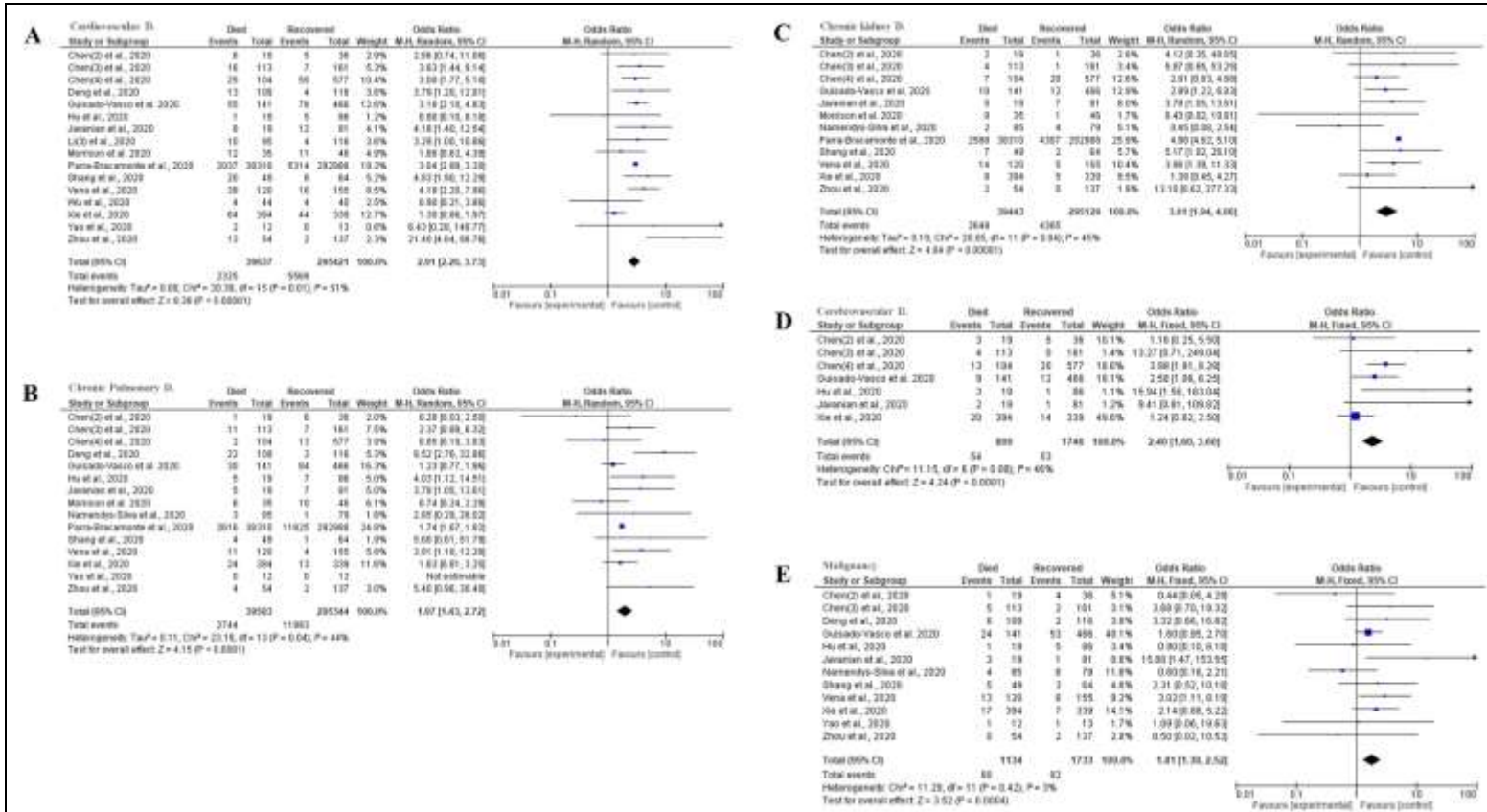
3.2.5. Chronic kidney disease

Seventeen studies containing 1,527 severe and 3,928 non-severe COVID-19 patients were included in the meta-analysis to assess susceptibility to severe form of the disease in individuals with chronic kidney disease. The pooled ORs showed that patients with chronic kidney disease had a 2.55-fold increased risk of developing severe COVID-19 (OR = 2.55 [95% CI = 1.11 - 5.84], $P = 0.03$) (Table 2). The forest plot of this association is shown in Figure 3A. No publication of bias (Egger test: $Z = 0.6908$, $P = 0.4897$) was found, but heterogeneity ($\chi^2 = 52.45$, $P < 0.00001$, $I^2 = 69\%$) was observed in this analysis (Table 2).

Twelve studies comprising 39,443 hospitalized COVID-19 patients who died and 295,129 hospitalized COVID-19 patients who recovered were included in the meta-analysis to assess the risk of death in individuals with chronic kidney disease. The pooled ORs showed that hospitalized COVID-19 patients with chronic kidney disease had a 3.01- fold increased

risk of dying (OR = 3.01 [95% CI = 1.94 - 4.66], $P < 0.00001$) (Table 2). The forest plot of this association is shown in Figure 4C. Publication of bias (Egger test: $Z = 13.0460$, $P < 0.0001$) and heterogeneity ($\chi^2 = 20.05$, $P = 0.04$, $I^2 = 45\%$) were detected in this analysis (Table 2).

Figure 4 - The Floret plots of comorbidities associated with COVID-19 mortality.



(A) Floret plot of association between Cardiovascular disease and the risk of COVID-19 death. (B) Floret plot of association between Chronic pulmonary disease and the risk of COVID-19 death. (C) Floret plot of association between Chronic kidney disease and the risk of COVID-19 death. (D) Floret plot of association between Cerebrovascular disease and the risk of COVID-19 death. (E) Floret plot of association between Malignancy and the risk of COVID-19 death. Source: author of this research (2020).

3.2.6. Cerebrovascular disease

Thirteen studies were included in the meta-analysis to assess susceptibility to severe COVID-19 in individuals with cerebrovascular disease. The sample was composed of 1,195 severe and 3,088 non-severe COVID-19 patients. The pooled ORs showed that patients with cerebrovascular disease were associated with a 2.51-fold increased risk of developing the severe COVID-19 (OR = 2.51 [95% CI = 1.68 - 3.76], $P < 0.00001$) (Table 2). The forest plot of this association is shown in Figure 3B. Publication of bias (Egger test: $Z = 0.1614$, $P = 0.8718$) and heterogeneity ($\chi^2 = 10.76$, $P = 0.55$, $I^2 = 0\%$) were not found in this analysis (Table 2).

Seven studies containing 809 hospitalized COVID-19 patients who died and 1,746 hospitalized COVID-19 patients who recovered were included in the meta-analysis to assess the risk of death in individuals with cerebrovascular disease. The pooled ORs showed that hospitalized COVID-19 patients with cerebrovascular disease had a 2.40-fold increased risk of death (OR = 2.40 [95% CI = 1.60 - 3.60], $P < 0.0001$) (Table 2). The forest plot of this association is shown in Figure 4D. Publication bias (Egger test: $Z = 0.6710$, $P = 0.5022$) and heterogeneity ($\chi^2 = 11.15$, $P = 0.08$, $I^2 = 46\%$) were not observed in this analysis (Table 2).

3.2.7. Chronic liver disease

Sixteen studies were included in the meta-analysis to assess susceptibility to severe COVID-19 in individuals with the chronic liver disease. These studies analysed 1,364 severe and 3,380 non-severe COVID-19 patients. There was no significant association between patients with the chronic liver disease and severe form of COVID-19 (OR = 0.99 [95% CI = 0.64 - 1.52], P = 0.95) (Table 2). Publication of bias (Egger test: Z = 0.3035, P = 0.7615) and heterogeneity ($\chi^2 = 13.28$, P = 0.58, I² = 0%) were not observed in this analysis (Table 2).

Five studies containing 240 hospitalized COVID-19 patients who died and 660 hospitalized COVID-19 patients who recovered were included in the meta-analysis to assess the risk of death in individuals with chronic liver disease. There was no significant association between patients with chronic liver disease and the risk of death for COVID-19 (OR = 1.72 [95% CI = 0.87 - 3.39], P = 0.14) (Table 2). Publication of bias (Egger test: Z = 0.3098, P = 0.7567) and heterogeneity ($\chi^2 = 3.02$, P = 0.55, I² = 0%) were not detected in this analysis (Table 2).

3.2.8. Malignancy

Twenty studies with 1,787 severe and 3,781 non-severe COVID-19 patients were included in the meta-analysis to assess susceptibility to severe COVID-19 in individuals with some type of cancer. No association was found between malignancy and severe form of COVID-19 (OR = 1.40 [95% CI = 1.00 - 1.96], P = 0.05) (Table 2). Publication of bias (Egger test: Z = 0.1432, P = 0.8861) and heterogeneity ($\chi^2 = 23.51$, P = 0.22, I² = 19%) were not detected in this analysis (Table 2).

Twelve studies containing 1,134 hospitalized COVID-19 patients who died and 1,733 hospitalized COVID-19 patients who recovered were included in the meta-analysis to assess the risk of death in individuals with malignancy. The pooled ORs showed that COVID-19 patients with malignancy had a 1.81-fold increased risk of death (OR = 1.81 [95% CI = 1.30 - 2.52], P = 0.0004) during hospitalization (Table 2). The forest plot of this association is shown in Figure 4E. Publication of bias (Egger test: Z = 0.6944, P = 0.4874) and heterogeneity ($\chi^2 = 11.29$, P = 0.42, I² = 3%) were not found in the analysis (Table 2). (TNR font 10 – justified – space 1,5).

4. Discussion

Currently, COVID-19 is the most important public health problem in the world, due to its capacity for global expansion. A major challenge for health authorities is to discover the main factors involved in the development of the severe form of the disease and risk of death. Studies have demonstrated a high prevalence of comorbidities in COVID-19 patients who progressed to the severe form of the disease and/or died. We investigated the impact of comorbidities in the susceptibility to severe COVID-19 and the risk of death through a systematic review with meta-analysis.

In our meta-analysis, patients with COVID-19 and with pre-existing cardiovascular disease were about 2-fold more likely to develop severe disease, and among hospitalized COVID-19 patients the risk of death was approximately 3-fold higher in cardiopathy patients when compared to patients without cardiovascular disease. Six recent meta-analyses have shown that COVID-19 patients with cardiovascular disease have approximately a 3- to 4-fold increased risk from developing severe COVID-19 (Aggarwal et al., 2020; Jain & Yuan, 2020; Liu et al., 2020c; Wang et al., 2020d; Wang et al., 2020e; Yang et al., 2020a). At the same time, the meta-analyses carried out by Tian et al. (2020) and Li et al. (2020) showed that patients with this comorbidity had a risk of death 3.80 and 4.85-fold higher in SARS-CoV-2 infection, respectively (Li et al., 2020e; Tian et al., 2020b). Thus, patients with pre-existing cardiovascular diseases infected with SARS-CoV-2 should be monitored more carefully by healthcare professionals, especially cardiologists, to obtain better clinical management.

Hypertension has been considered an important risk factor for severe COVID-19 and disease fatality (Deng et al., 2020; Zhu et al., 2020). In our meta-analysis, hypertensive patients infected with SARS-COV-2 were about 2-fold more likely to develop severe COVID-19 and/or death from this illness. Six previous meta-analysis revealed an association between

hypertensive patients and an increased risk of developing severe COVID-19, with an estimated risk of about 2- to 3-fold higher compared to non-hypertensive patients (Jain & Yuan, 2020; Liu et al., 2020c; Wang et al., 2020d; Wang et al., 2020e; Yang et al., 2020a; Zhang et al., 2020d). Additionally, three recent meta-analyses showed that hypertensive patients with COVID-19 also had a 2- to 3-fold increased risk of dying (Li et al., 2020e; Tian et al., 2020b; Zheng et al., 2020c).

Studies have reported diabetes as a risk factor for worse clinical outcome in patients with COVID-19 (Wang et al., 2020e; Wu et al., 2020b). Our meta-analysis showed that diabetic patients had nearly a 2-fold increased risk of developing the severe form and/or die of COVID-19. Corroborating with our finding, four previous meta-analyses identified that diabetic patients had about a 2.5-fold increased risk of developing the severe form of the disease (Liu et al., 2020c; Wang et al., 2020d; Wang et al., 2020e; Wu et al., 2020b). On the other hand, two meta-analyses found no association between diabetes and severe COVID-19 (Jain & Yuan, 2020; Yang et al., 2020a). Regarding the risk of mortality, similar results were observed in the meta-analyses conducted by Wu et al. (2020) and Tian et al. (2020), in which diabetic patients were associated with a 3- and 2-fold higher risk of mortality from COVID-19, respectively (Tian et al., 2020b; Wu et al., 2020b). In addition, a meta-analysis carried out by Zheng et al. (2020) revealed that diabetes was associated with a 3.68-fold higher risk of developing the critical form of COVID-19 or death from the disease (Zheng et al., 2020c). According to Yang et al. (2006), during the SARS infection, fasting plasma glucose levels were negatively associated with arterial oxygenation (SaO₂) and this condition was correlated with mortality and hypoxia (Yang et al., 2006d). Thus, diabetic patients are more susceptible to COVID-19, but this effect has not been fully elucidated yet.

Recent studies have reported that patients with pre-existing chronic pulmonary disease have a high risk of complications and worsening lung injury during the pathogenesis of COVID-19 (Daccord et al., 2020; Taghavi-Farahabadi et al., 2020). The clinical characteristics of COVID-19 demonstrated by some studies revealed that the majority of patients with pre-existing chronic pulmonary disease presented respiratory failure and require ICU intervention. Therefore, these patients appear to be the most susceptible to the development of severe COVID-19. We assessed the risk of severity and mortality in patients with chronic pulmonary disease, which included COPD and asthma. We observed that patients with chronic pulmonary disease had nearly a 2-fold increased risk of developing severe form and/or die of COVID-19. A previous meta-analysis revealed that patients with the chronic pulmonary disease also had nearly a 4-fold higher risk of developing the severe form of COVID-19 (Liu et al., 2020c). In addition, two recent meta-analyses showed that COPD patients had approximately a 6-fold increased risk of developing severe COVID-19 (Jain & Yuan, 2020; Wang et al., 2020d). Regarding the risk of death, Zhao et al. (2020) found that the risk of death from COVID-19 was almost 2-fold higher in patients with COPD (Zhao et al., 2020), similar result to our findings. However, this association was not observed in the meta-analysis by Tian et al. (2020) (Tian et al., 2020b).

Despite a few previous reports, chronic kidney disease has been associated with the severe form of COVID-19 (Adapa et al., 2020). We showed that patients with chronic kidney disease had a 2.55-fold increased risk to develop severe COVID-19. While, hospitalized COVID-19 patients with chronic kidney disease had a 3-fold increased risk of death when compared to patients without chronic kidney disease. Corroborating with our results, Wang et al. (2020) identified that patients with chronic kidney disease were associated with a 2.22-fold increased risk of developing severe COVID-19 (Wang et al., 2020e). Additionally, the meta-analysis conducted by Tian et al. (2020) revealed that patients with chronic kidney disease had a 9.40-fold higher risk of death from COVID-19 (Tian et al., 2020b). In contrast, a previous meta-analysis found no association between chronic kidney disease and severe COVID-19, but the small number of studies (4 studies) and patients (n = 15) included may have influenced this analysis (Wang et al., 2020d). Several mechanisms can be responsible for the susceptibility of patients with chronic kidney diseases to SARS-CoV-2 infection. First, ACE2 is highly expressed in renal tubular cells, and thus SARS-CoV-2 may directly affect this organ (Fan et al., 2020). Second, that studies have detected kidney injuries in

COVID-19 patients (Li et al., 2020f). Third, chronic kidney disease leads to a series of complications, such as high blood pressure, anemia, water retention and these complications may have a greater effect on SARS-CoV-2 infection (Babitt & Lin, 2012; Drawz et al., 2016). Fourth, chronic kidney disease has been linked to uncontrolled chronic inflammation that can affect the immune response during SARS-CoV-2 infection (Imig & Ryan, 2013; Raj et al., 2015).

Previous reports have suggested that cerebrovascular diseases may lead to a poor outcome in COVID-19 patients (Pranata et al., 2020). In our meta-analysis, patients with cerebrovascular diseases had a 2.51-fold increased risk to developing severe COVID-19. Among hospitalized COVID-19 patients with cerebrovascular disease the risk of death was 2.82-fold higher when compared to hospitalized COVID-19 patients without cerebrovascular disease. The meta-analysis conducted by Wang et al. (2020) revealed that cerebrovascular disease was associated with a 3.89-fold higher risk of developing severe COVID-19 (Wang et al., 2020d). In relation to the risk of death, Tian et al. (2020) and Pranata et al. (2020) showed that COVID-19 patients with cerebrovascular disease had an increased risk of death (Pranata et al., 2020; Tian et al., 2020b). The pathophysiological mechanism that explains the poor clinical evolution of COVID-19 in patients with cerebrovascular disease has not yet been reported. However, cerebrovascular disease seems to act in conjunction with other comorbidities, such as cardiovascular problems (Pranata et al., 2020).

Current studies have shown that cancer patients infected with SARS-CoV-2 were more likely to have intubation and mortality when compared to patients without cancer (Venkatesulu et al., 2020). Analysing severity and mortality, our meta-analysis showed that cancer patients had approximately a 2-fold increased risk of mortality during hospitalization for COVID-19. However, no association was found between cancer patients and severe COVID-19 in our analysis. Venkatesulu et al. (2020) reported that cancer patients were associated with a 2.58, 2.18, 2.43, 2.54-fold higher risk of severity, ICU admission, intubation and mortality during SARS-Cov-2 infection, respectively. Moreover, the authors found that hematologic cancer was associated with a 2.39-fold increased risk of death from COVID-19, but this association was not found in lung, gastrointestinal and breast cancers (Venkatesulu et al., 2020). Several factors may contribute to elevated complications during the pathogenesis of COVID-19 in cancer patients, such as anticancer therapy, immunocompromised state, and other physiologic alteration, depending on the type of cancer (Gosain et al., 2020; Zhang et al., 2020e). Chemotherapy, for example, affects cells of the immune system causing immunosuppression, favoring COVID-19 morbidity (Bersanelli, 2020).

Previous meta-analyses have evaluated the influence of comorbidities on susceptibility to COVID-19. However, our meta-analysis included a considerable number of studies (48 articles) and patients with COVID-19 (n = 344,290). The limitations of this study were: (1) presence of publication bias in some analysis; (2) detection of heterogeneity among the meta-analysed studies; (3) low sample number in some comorbidities; (4) lack of detailed information on patients' comorbidities in the included studies, and (5) the small sample size in some studies. (TNR font 10 – justified – space 1,5).

5. Conclusion

In conclusion, our meta-analysis showed sufficient evidence that hypertension, diabetes, cardiovascular, chronic pulmonary, chronic kidney and cerebrovascular diseases increase the risk of severity and mortality in COVID-19 patients. In addition, malignancy showed increase the risk of death by COVID-19. Therefore, we suggest that the mentioned comorbidities may be an important predictor of an unfavourable outcome for COVID-19, contributing to the prognosis of severe cases of the disease.

We suggest that future studies may assess the risk and severity of mortality in individuals who have two or more pre-existing comorbidities combined. The quantity of pre-existing comorbidity in an individual may be proportional to clinical complications caused by COVID-19. Therefore, it would be important to assess this condition to clarify which specific comorbidities combined can further increase the risk of the disease.

Conflicts of interest

All authors declare that there are no conflicts of interest.

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