



## REVIEW ARTICLE

### Available evidence on risk factors associated with COVID-19's poorer outcomes, worldwide and in Brazil

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#### GENERAL INFORMATION

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#### ABSTRACT

**Objectives:** Analyse availability and quality of existing evidence on COVID-19's risk factors and underlying health conditions that are associated with poorer outcomes, worldwide and in Brazil. **Methods:** EBMR (Ovid), Google Scholar, MEDLINE (OvidSP), PubMed, CINAHL (EBSCO) and Cochrane Library databases were screened, plus Brazilian government epidemiological reports. A body of 25 articles plus 1 report met the inclusion criteria. **Results:** Available data are still disconnected and several biases exist throughout literature, mainly due to COVID-19 novelty aspect. Hypertension was the most analysed risk factor, followed by diabetes and chronic obstructive pulmonary disease. Availability of Brazilian data is significantly scarce and only governmental reports are readily available. **Conclusion:** Further studies, with good methodological designs, are needed to provide good levels of evidence in order to provide solid background to help the pandemic's mitigation strategies.

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#### Introduction

In December of 2019, a novel coronavirus - SARS-CoV-2 - has been identified after a series of unknown viral pneumonia-like cases were reported in the city of Wuhan, Hubei province, China<sup>1</sup>. On March 11, 2020, the World Health Organization (WHO) declared the emerging disease (COVID-19) a pandemic<sup>2</sup>. By the last fortnight of April, it has been the cause of death of 182.808 persons, approximately 0.02% of the estimated world population from 2019, and has affected 180 countries<sup>3-6</sup>. At the time, all cause mortality was found to be 0.3%<sup>7</sup>.

Currently, a reliable and strong evidence concerning various aspects of COVID-19 is limited, despite the urge to thoroughly understand its pathophysiology, epidemiology, clinical manifestations and risk factors<sup>7</sup>. Identifying groups that are likely to have poorer outcomes is crucial to help in mitigation policies for this disease, and can only be done once observational evidence exists<sup>8</sup>.

In Brazil, the first case was confirmed - after retrospective analyses - on April 2, 2020<sup>9</sup>. In the country's scenario, the availability of tests is reduced due to

insufficient public laboratory testing capacity<sup>10</sup>. Overall, laboratories' bottlenecks and situations in which only severe cases are tested can result in misleading epidemiological indicators<sup>8</sup>. Therefore, mapping group risks in the national context is more than necessary as compensation for the lack of testing.

This review aims to analyse the quality and availability of evidence on risk factors for COVID-19's poorer outcomes, worldwide and in the Brazilian context.

#### Methods

##### Search strategy

Studies were retrieved from Evidence-Based Medicine Reviews (Ovid), Google Scholar, MEDLINE (OvidSP), PubMed, CINAHL (EBSCO) and Cochrane Library. Due to the novelty aspect of the disease and considering its starting point, results published before 2019 were excluded. Search terms were selected to identify risk factors that may be determinants for the severity of COVID-19. The terms were: "COVID-19", "novel coronavirus disease 19", "coronavirus", "prevalence", "determinants" and "risk factors". The terms and their combinations in the English language were used to conduct the comprehensive search.

The search string was then replicated in Brazilian databases, using the same search terms in the Portuguese language. Results from the 13<sup>th</sup> Brazilian epidemiological status report for COVID-19 were compiled and compared with existing literature.

Citation tracking and reference chaining were performed to identify additional articles. After removing

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duplicates, titles and abstracts were screened regarding relevance to the topic and copies of the remaining publications were obtained, for further analyses.

Due to time constraints and the need to quickly publish scientific evidence in the Brazilian context, no author was contacted.

The first search was performed on April 19, 2020. A second and last update of the same search methods was reproduced on April 25, 2020. The theoretical background to select studies was based on available literature on the subject<sup>11</sup>.

The reproducible search string was: ((((((COVID-19) OR (novel coronavirus disease 19)) OR (coronavirus)) NOT (MERS)) NOT (SARS)) AND (prevalence)) AND (determinants)) AND (risk factors).

#### *Inclusion criteria*

Articles published from December 2019 up until the date of the last search were included. To avoid potential bias when locating studies, no restrictions regarding geographical location of the publications were applied. Populations included were from all ages, of both biological sexes, of any educational level, and of whom tested positive for COVID-19, to create a compilation as comprehensive as possible and avoid selection bias. Outcomes had to be clearly stated to increase external validity of this review for the inclusion of articles<sup>12</sup>. Any cultures and populations that speak any languages were included due to the pandemic aspect of the disease.

Methodological quality of the published articles was one of the main inclusion criterion and was assessed with support from existing literature<sup>13,14</sup>.

#### *Exclusion criteria*

Due to this being a rapid review, and the allocation of time and money necessary to contact professional translators, publications in languages other than English were excluded<sup>15</sup>, except for the official Brazilian governmental COVID-19 report 13.

Pre-prints, books and book sections, thesis manuscripts, articles with limited relevance and/or limited presentation of findings and/or mainly demographic data were excluded from the final scope of included articles, in order to increase the methodological quality and internal validity of this review<sup>12,16</sup>. Reviews and meta-analyses were excluded to avoid duplication bias.

#### *Data assessment process*

The PRISMA statement guided the identification, screening, eligibility and final inclusion of articles in this review. To assess risk of bias in individual articles and overall quality, the Newcastle-Ottawa Scale (NOS) was applied to all included studies<sup>17</sup>.

## **Results**

The comprehensive search identified 734 publications. Of which, 701 from scientific databases, 32 from additional sources and 01 from Brazilian government. Duplicates and non-relevant articles were removed resulting in 177 articles. After a thorough screening of abstracts, 115 articles were excluded based

on the criteria previously established.

A total of 62 studies were then fully assessed for eligibility and methodological quality. Articles that scored 3 or lower at the NOS Scale<sup>17</sup> were excluded along with those with limited presentation of findings, limited relevance and that presented mainly demographic data. Finally, a total of 25 articles were assessed as eligible and, therefore, included in this review.

Figure 1 shows the PRISMA flowchart and step-by-step sampling visualisation<sup>15</sup>, whereas Table 1 shows the NOS Scale, arranged by scores in crescent, and alphabetical order for same score papers. As previously stated, NOS Scale had to be equal or higher than 4 because studies with lower values were considered methodologically weak and excluded.

Initial studies on the virus scored poorly on outcome and comparability<sup>18-22</sup>, mainly due to the lack of reporting on control group and the presence of only one composite endpoint. The initial researches that addressed a control group and stated more than one composite endpoint scored higher, despite the non-ideal follow-up time. A clear sampling method helped to increase the score<sup>1,23,24</sup>.

Chart 1 summarises sample populations, design and main findings of each of the 25 articles + 01 Brazilian government COVID-19 official report, in alphabetical order.

Sample size increased with time due to the exponential aspect of the pandemic, levelling up statistical power. Zhang *et al.* (2020) published the largest cohort amongst the articles ( $n = 8579$ ). The country with the largest number of publications was China (84.6%). The designs, and their frequency of usage, in parenthesis, were (Retrospective/Prospective) (57.7%), Case Series (Retrospective) (26.9%), Single-Centre (7.7%), Cross Sectional (3.8%) and Case Report (3.8%).

Comorbidities were not addressed during initial studies, up until population sampling began to occur from January 2020 onwards. Across all studies, chronic diseases increased hospitalisation period and severity of symptoms.

Global health status, such as the use of tobacco products, occupation and pregnancy were not extensively evaluated: 11.5%, 7.7% and 4.0%, respectively. Nutritional status was little investigated ( $n = 2$ ) but it shed a light on the need for healthcare professionals to pay more attention to patients diagnosed with COVID-19 who have either obesity or malnourishment<sup>21,25</sup>. Few authors considered in-hospital treatment options ( $n = 4$ ) and the least evaluated disorders were mental disorders ( $n = 1$ ).

Table 2 shows an overview of the sex incidence, epidemiological history, clinical manifestations, comorbidities, health status, incidence in occupations and in-hospital treatment of COVID-19. And the frequency of articles included in this review that accounted for each of the before-mentioned variables.

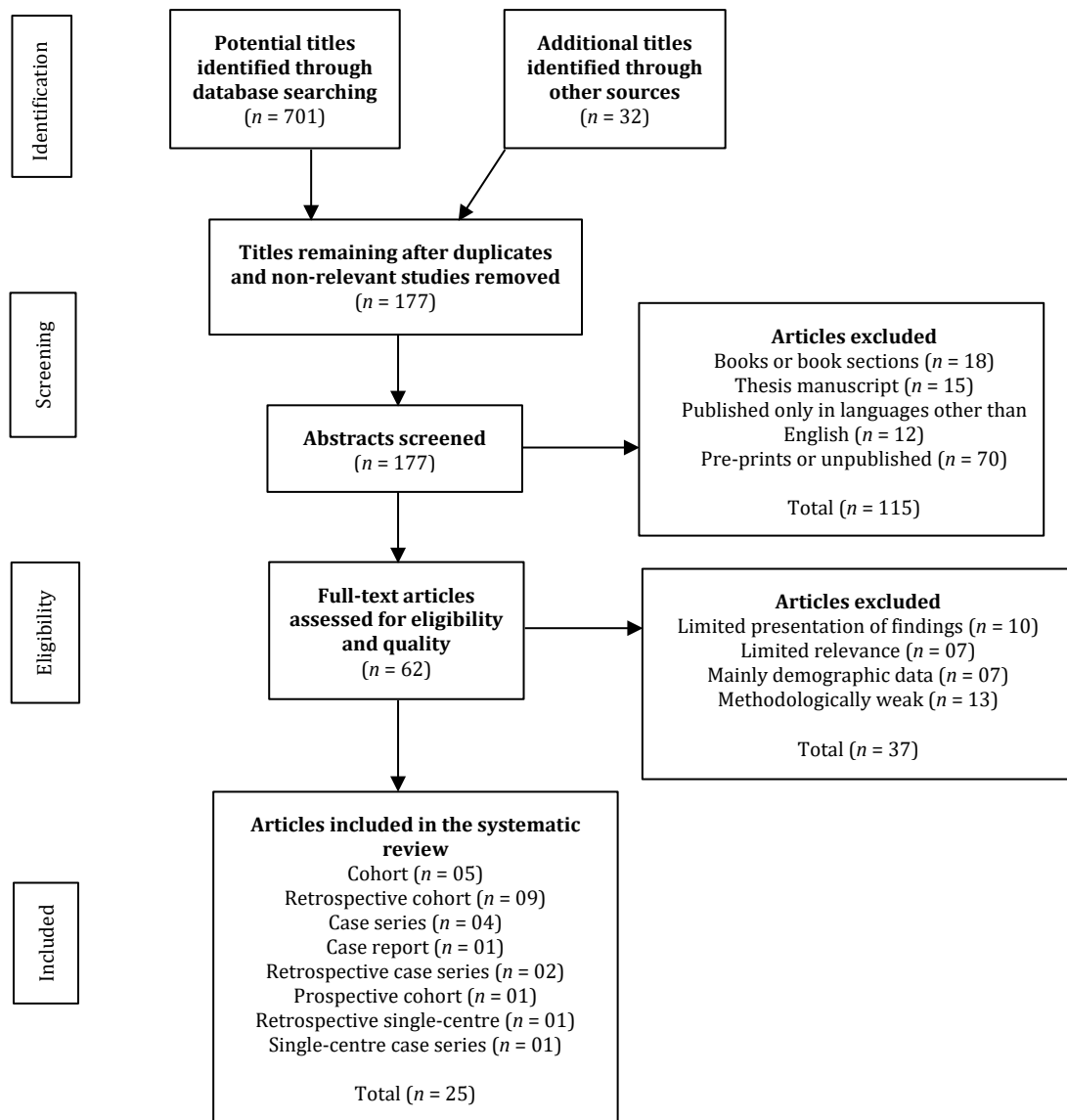
Males tended to experience more severe clinical manifestations when compared to females and 77.0% of the authors included sex related information on their papers. Epidemiological history of contacts ( $n = 10$ ) comprises close contact with a person with either COVID-19 or symptoms of it, sporadic travel to Hubei province in general, travel or sojourning to Wuhan itself, visits to or working at Wuhan Huanan Wholesale Seafood Market, visits to relatives living in the Chinese epicentre or

working with infected patients.

Regarding clinical manifestations, the three most frequently analysed variables were cough ( $n = 17$ ), fever ( $n = 16$ ) and diarrhoea ( $n = 14$ ). The list of comorbidities accounted for throughout the articles is long and rather

diverse. In these findings, comorbidities are organised, hence their grouping by systems with the exception of the three most frequently analysed ones: Hypertension ( $n = 14$ ), Diabetes ( $n = 13$ ) and COPD ( $n = 13$ ). Fatal cases were reported by 57.7% of the articles.

**Figure 1** – PRISMA flowchart and step-by-step sampling process.



## Discussion

There is a tendency for the poorer outcomes of COVID-19 to develop in males<sup>1,18,20,21,23-37</sup>, but these findings may not represent the relation between biological sex and the novel coronavirus, for all authors failed to present sex-disaggregated data, potentially skewing results<sup>38</sup>.

Ongoing epidemic diseases may limit appropriate data collection and the novelty aspect of the SARS-CoV-2 infection hinders this process and its subsequent assessment<sup>31,39</sup>. A direct consequence is the inadequate information or presentation of the findings concerning

follow-up or its loss. Not knowing the viral life cycle may lead to changes in some or all the measurement processes - E. g. diagnostic criteria - during the development of the article, leading to changes in instrumentation, thus threatening the paper's internal validity<sup>12</sup>.

Certain designs are more likely to suffer from selection bias and randomising the sample is essential to avoid it<sup>16</sup>. Research design might reduce or increase the possibility of randomising the population selection processes<sup>40</sup>. Authors who published case-series, single-centre, case reports and cross-sectional studies might have suffered from this type of bias<sup>1,19-23,32,35,41,42</sup>. The small size of some samples reduced the statistical power of the

studies and, later on, their external validity<sup>1,19,20,22,24,41</sup>. On the other hand, during recent phases of a novel disease, case reports help broaden the knowledge under construction<sup>22</sup>.

Recent articles on the topic should be able to avoid selection biases and population size problems once

the pandemic is no longer in its initial phase and the recruitment of larger and statistically powerful samples must be carried out. Initial COVID-19 guidelines may not have accounted for atypical clinical manifestations, therefore excluding patients without proper criteria<sup>43</sup>

**Table 1** – Newcastle-Ottawa Scale (NOS) for the articles included in this review.

First author	Year	Selection	Comparability	Outcome	NOS Score
Cao, C <sup>18</sup>	2020	2	1	1	4
Leung, C <sup>30</sup>	2020	2	1	1	4
Li, T <sup>21</sup>	2020	1	1	2	4
Yu, P <sup>22</sup>	2020	1	1	2	4
COVID-19 National Emergency Response Center, Epidemiology and Case Management Team (KCDC) <sup>20</sup>	2020	2	2	1	5
Chan, JF-W <sup>41</sup>	2020	2	2	2	6
Chang, Lin <sup>19</sup>	2020	2	1	3	6
Li, Q <sup>31</sup>	2020	3	1	2	6
Li, R <sup>32</sup>	2020	3	1	2	6
Zhang, J <sup>45</sup>	2020	3	1	2	6
Cheng, Y <sup>27</sup>	2020	3	2	2	7
Dong, Y <sup>28</sup>	2020	3	2	2	7
Guan, WJ <sup>29</sup>	2020	3	2	2	7
Yu, X <sup>36</sup>	2019	2	2	3	7
Chen, N <sup>23</sup>	2020	3	2	3	8
Garg, S <sup>25</sup>	2020	4	2	2	8
Huang, C <sup>1</sup>	2020	4	2	2	8
Liang, WH <sup>33</sup>	2020	4	2	2	8
MS <sup>26</sup>	2020	4	2	2	8
Nie, X <sup>34</sup>	2020	4	1	3	8
Qian, GQ <sup>42</sup>	2020	4	2	2	8
Qiu, H <sup>24</sup>	2020	3	2	3	8
Wang, D <sup>35</sup>	2020	3	2	3	8
Zhao, XY <sup>37</sup>	2020	3	2	3	8
Zhu, W <sup>43</sup>	2020	4	2	2	8
Wu, J <sup>46</sup>	2020	4	2	3	9

**Chart 1** – Sample populations, design and main findings of each of the 25 articles + 01 Brazilian government COVID-19 official report.

First author/ country	Year of publication	Type of design	n	Main findings
Cao, C <sup>18</sup> / China	2020	Cohort	135	The presence of positive cases both in urban and suburban areas indicates population is generally susceptible. Significant differences between cases with and without contact history indicates that human-to-human transmission was the main form of transmission
Chan, JF-W <sup>41</sup> / China	2020	Case Series	6	Human-to-human transmission exists and must be taken into account. Infection clusters within hospitals and families have to be acknowledged. Contact tracing might help mitigate the exponential spread.
Chang, Lin <sup>19</sup> / China	2020	Case Series	13	The late identification of the etiological source might be the cause of the higher number of infections. Even though the majority of cases had positive contact history, the existence of cases without any contact history indicates active viral transmission. Travel history might play an important role on the contamination and spread of the virus.
Chen, N <sup>23</sup> / China	2020	Retrospective single-centre	99	COVID-19 had a clustering onset and is more prevalent amongst males with cardiovascular and cerebrovascular diseases.
Cheng, Y <sup>27</sup> / China	2020	Prospective Cohort	701	First article that provided evidence of COVID-19 poorer outcome and kidney related disorders. Higher serum creatinine at baseline was related to higher risk of deterioration.
COVID-19 National Emergency Response Center, Epidemiology and Case Management Team (KCDC) <sup>20</sup> / South Korea	2020	Case Series	28	All initial cases in Korea were imported from individuals traveling from abroad. Residence cluster was an important infection cluster indicating close-contact transmission and a minor, but mostly infective, initial period. An early detection strategy is crucial for mitigation response.
Dong, Y <sup>28</sup> / China	2020	Retrospective Cohort	2135	The disease's spatial distribution indicated that it was rapidly spreading outside the initial epicentre: Hubei. Familial clustering, as has been seen in previous literature, confirms it is spreading from human-to-human. Children are less affected than adults and this may be due to their higher levels of antibodies (for they are more susceptible to seasonal respiratory infections), or ACE2 lower maturity and function. All ages of childhood, particularly infants, are susceptible to the disease.
Garg, S <sup>25</sup> / USA	2020	Cohort	1660	90% of the patients hospitalised in the U.S. had comorbidities. The most prevalent was obesity followed by hypertension. Black populations apparently are more affected, when controlling for confounders.

**Chart 1** – Sample populations, design and main findings of each of the 25 articles + 01 Brazilian government COVID-19 official report (cont.).

First author/ country	Year of publication	Type of design	n	Main findings
Guan, WJ <sup>29</sup> / China	2020	Retrospective Cohort	1590	Any comorbidity might yield poorer outcomes for patients with COVID-19. More than one comorbidity increased HR. Controlling for age and smoking status confirmed findings related to comorbidities.
Huang, C <sup>1</sup> / China	2020	Case Series	41	Exposure to the Wuhan Huanan Wholesale Seafood Market was present in the majority of cases. 98% of patients presented fever.
Leung, C <sup>30</sup> / Australia	2020	Retrospective Case Series	46	Comorbidities weighted down the disease's natural history, increasing severity, hospitalisation time and, as a result, more prevalent poorer outcomes.
Li, Q <sup>31</sup> / China	2020	Cohort	425	Initial cases that happened before January, had a clear connection with Wuhan Huanan Wholesale Seafood Market. The incidence of epidemiological connection reduced significantly over time.
Li, R <sup>32</sup> / China	2020	Case Series	225	Patients treated for COVID-19 in areas outside but near Wuhan, had clinical manifestations similar to those treated in Wuhan itself. Patients with COVID-19 without epidemiological connection with Wuhan Huanan Seafood Wholesale Market had lower mortality.
Li, T <sup>21</sup> / China	2020	Cross-sectional	182	Malnutrition had a high prevalence amongst elderly patients diagnosed with COVID-19. Patients who had diabetes had a higher risk for developing malnutrition.
Liang, WH <sup>33</sup> / China	2020	Retrospective Cohort	1590	Patients treated for COVID-19 in Hubei had more severe clinical manifestations and poorer outcomes attributed to prolonged time to hospitalisation. The majority of cases were related to the city of Wuhan.
MS <sup>26</sup> / Brazil	2020	Cohort	2575	Mortality projection is growing regionally indicating infection clusters. Case fatality rates are higher in regions with higher population density.
Nie, X <sup>34</sup> / China	2020	Retrospective Cohort	7015	A decrease in the number of imported cases showed an active human-to-human transmission. Strict containment measures are important and help reduce viral spread.
Qian, GQ <sup>42</sup> / China	2020	Retrospective Case Series	91	Infection clusters play an important role in the spread of the virus. Therefore, contact tracing is important to help stop the rapidly advancing progress of the disease.
Qiu, H <sup>24</sup> / China	2020	Retrospective Cohort	36	Children are susceptible and familial clustering is a constant. Fever was one of the main symptoms amongst children and also a risk factor for severity. Findings indicate that children are less likely to present upper respiratory tract infections. Gastrointestinal symptoms were more likely to be seen in children.

**Chart 1** – Sample populations, design and main findings of each of the 25 articles + 01 Brazilian government COVID-19 official report (cont.).

First author/ country	Year of publication	Type of design	n	Main findings
Wang, D <sup>35</sup> / China	2020	Single-centre case series	138	Nosocomial COVID-19 infection: 41.0% of cases. Findings suggested that COVID-19 may be associated with cellular immune deficiency, coagulation activation, myocardia injury, hepatic injury, and kidney injury. Cytokine storm is triggered by viral invasion.
Wu, J <sup>46</sup> / China	2020	Retrospective Cohort	80	The absence of contact history showed human-to-human infection. Treatment was mostly empirical and mainly polyvalent.
Yu, P <sup>22</sup> / China	2020	Case Report	4	The findings indicated that a person may be infectious during incubation period. Monitoring contacts was considered essential to control the spread of the disease.
Yu, X <sup>36</sup> / China	2019	Cohort	333	Strong preventive measures are effective due to the virus clustering aspect and its high infection rate. Children tend to travel less and socialise less, explaining why they were less severely affected. Overweight was a prevalent characteristic of people diagnosed with COVID-10.
Zhang, J <sup>45</sup> / China	2020	Cohort	8579	Outside Hubei, there were both active transmissions and transmissions with contact history. The estimated incubation period suggested that transmission is possible even before the onset of symptoms. Strict containment measures shortened the window period.
Zhao, XY <sup>37</sup> / China	2020	Retrospective Cohort	91	Injuries to other systems besides respiratory system exist. Especially liver, kidneys, digestive tract and heart. Severity of the disease is linked to higher age and presence of comorbidities.
Zhu, W <sup>43</sup> / China	2020	Retrospective Cohort	116	Human-to-human transmission appears to exist. Fever was the main clinical manifestation. The findings shed a light in the importance of strict medical quarantine and closely monitoring all suspected patients.

None of the articles established a follow-up time beforehand due to the lack of any available data on the SARS-CoV-2 infection, which might have introduced immortal-time bias. Future, longitudinally analysed observational researches are encouraged to determine the appropriate timeline of the disease, helping mitigation policies<sup>40</sup>.

Data collection processes were extensively described by only one author<sup>25</sup>. Proper description increases methodological quality and the consecutive reliability of findings, thus increasing overall external validity<sup>12</sup>. In contrast, other authors had problems with data collection due to unresponsiveness from potential data sources<sup>33</sup>. Self-reporting was somewhat present amongst the Chinese articles, specifically self-reporting comorbidities, and self-reporting bias must be taken into account<sup>29,33,44</sup>.

Diverging from policies adopted by China, South

Korea managed to trace its first cases to the country's patient zero. Rapid response and solid strategies have made it possible to trace the virus' route in the country adequately. Resulting in extremely reliable epidemiological projections, a lack of publication biases and significant reduction in selection ones. These findings explain, to some extent, the different evolution of COVID-19 in South Korea, when compared to its neighbouring countries<sup>20</sup>.

Not all authors included comorbidities, and Zhao *et al.* (2020) were the ones that accounted for more of them. Findings regarding these chronic diseases tend to be biased due to self-reporting<sup>29,33</sup>, unreasonable exclusion criteria<sup>23</sup>, missing information<sup>36,45</sup> and design limitations<sup>22,24,41</sup>.

Children tend to be less likely to develop upper respiratory symptoms, and more likely to experience gastrointestinal manifestations. Children are, by no means,

susceptible and fever is a sign of severity<sup>24,26,28</sup>. The reason why they are less affected may be due to their higher levels of antibodies (since they are more susceptible to seasonal respiratory infections), or the lower maturity and function of ACE2. Considering age, all childhood ages, particularly infants, may become ill<sup>28</sup>.

The spatial distribution of COVID-19 indicated that it was rapidly spreading outside Hubei province, its

initial epicentre<sup>18-20,25,26,33,34,36,42,43,45,46</sup>. The virus has a huge potential to create clusters of infections, hence the first documented and published articles had expressive familial clustering, indicating that the virus was spreading from human-to-human<sup>34,43,46</sup>. In addition to the clustering characteristic of the disease, there is potential to injure several systems<sup>37</sup>, and a higher serum creatinine at baseline may indicate poorer outcomes<sup>27</sup>.

**Table 2** – Summary of the pool of included articles.

Risk Factors	Articles reference numbers	Frequency of investigation
Sex		
Male	1, 18, 19, 20, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 45	77.0%
Epidemiological contact history	1, 18, 19, 20, 23, 28, 33, 42, 43, 45	38.4%
Symptoms		
Cough	1, 19, 23, 24, 25, 29, 30, 32, 33, 34, 35, 36, 37, 41, 42, 43, 46	65.3%
Fever	1, 19, 20, 23, 29, 30, 32, 33, 34, 35, 36, 37, 41, 42, 43, 46	61.5%
Diarrhoea	1, 19, 23, 24, 25, 33, 34, 35, 36, 37, 41, 42, 43, 46	54.0%
Comorbidities		
Hypertension	1, 20, 22, 25, 26, 27, 29, 30, 32, 33, 35, 41, 42, 43	54.0%
Diabetes	1, 20, 23, 25, 26, 27, 29, 33, 35, 37, 41, 42, 43	50.0%
COPD	1, 22, 23, 25, 26, 27, 29, 30, 33, 35, 37, 43, 46	50.0%
Cardiovascular disorders	1, 22, 23, 25, 26, 29, 30, 33, 35, 42, 43, 46	46.1%
Tumor	1, 23, 27, 29, 33, 35, 41, 43, 46	35.0%
Cerebrovascular disorders	23, 29, 30, 33, 35, 42, 43, 46	31.0%
Kidney disorders	25, 26, 27, 29, 33, 35, 43, 46	31.0%
Liver disorders	1, 25, 29, 33, 35, 43, 46	27.0%
Immunodeficiency	25, 26, 29, 33, 35, 46	23.0%
Nervous system disorders	23, 25, 26, 46	15.4%
Gastrointestinal disorders	23, 25, 46	11.5%
Obesity	25, 26, 36	11.5%
Endocrine disorders	23, 46	7.7%
Malnourishment	21, 36	7.7%
Mental disorders	43	4.0%
Smokers	36, 33, 43	11.5%
Profession	23, 36	7.7%
Pregnancy	25	4.0%
In-hospital treatment	23, 24, 32, 46	15.4%



The COE COVID-19 Report 13 by the Brazilian government is in accordance with Chinese and American findings within this review. Unlike the Chinese, the Brazilian report made a distinction between COPD and Asthma. Like the American study results, COPD controlling for asthma was more prevalent amongst fatal cases of COVID-19<sup>25,26</sup>.

Higher Case Fatality Rates (CFR) in regions with higher population density illustrate regional clusters and the importance of social distancing and contact tracing<sup>26</sup>.

Amongst occupations, staff from service industries appear to be more vulnerable, but findings are very limited<sup>36</sup>. Consequently, further research is encouraged once it may help create contingency plans to protect susceptible workers, so that economies can be reopened in an organised and controlled manner.

### Limitations

The main limitation of this review is the novelty literature. To establish a level of good methodological quality, only published articles were included. A total of 70 pre-prints and unpublished studies were excluded. Several could have been included had they were not pre-prints. Accordingly, publication bias has to be considered.

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Another important limitation was the identification of studies contextualising COVID-19 in Brazil, especially in the English language. Consequently, the only material included in a language other than English was the Brazilian government COVID-19 Epidemiological Report 13<sup>26</sup>. The authors are aware that the disruption of previously established inclusion criteria may have created synthesising bias, thus the importance of further observational analyses of COVID-19 in the Brazilian context.

### Conclusion

Comorbidities play an important role in the natural history of COVID-19 and must be taken into account because they may indicate future poorer outcomes. Children are not free from infection and paediatricians must consider atypical onset of the disease in this group. The lack of research in the Brazilian context is dangerous since research can guide the mitigation of the disease. Foreign data may apply only to some extent, in the national context. Additional Brazilian research is encouraged and of extreme importance.

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