Clinical characteristics and risk for severe COVID-19: a systematic review

Características clínicas e risco para COVID-19 grave: uma revisão sistemática

DOI:10.34119/bjhrv5n6-042

Recebimento dos originais: 10/10/2022
Aceitação para publicação: 08/11/2022

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ABSTRACT
COVID-19 has evolved into a serious clinical condition, especially in patients with comorbidities. However, the literature has diverged in relation to the main characteristics of patients prone to severe evolution. Objective: This study aimed to understand different variables that may be associated with the clinical management of COVID-19 for a better clinical response and prognosis. Methods: This is a systematic review in which the search in PubMed, Cochrane, EMBASE and LILACS databases. A manual and gray literature search on Google Scholar was also conducted. There was no country or region restriction and only studies in Portuguese, English and Spanish were included. Results: Of the 21 studies included in Primary Health Care (PHC) for eligibility, five studies from five countries involving 27,754 patients were analysed and, of the four eligible studies, one study was included for secondary care. Overall, the mean age of the COVID-19 population in PHC was around 41 years old, the number of cases was higher for females and, there was no difference between the groups without and with exposure, sex (p=0.322) and age (p=0.395). More than half of the patients had symptoms and, 47% had comorbidities. Heart diseases were the most prevalent among them. Approximately 79% of those infected had non-essential occupation. There was evidence that non-essential occupation was associated with infected individuals (p=0.002). Conclusions: This review identified that there may be greater vulnerability to contamination and aggravation of COVID-19 in female individuals, with adult age in non-essential activity, presence of chronic non-communicable diseases.

Keywords: COVID-19, patient care management, palliative care, primary health care, secondary care.
RESUMO
A COVID-19 evoluiu para uma condição clínica grave, especialmente em pacientes com comorbidades. Entretanto, a literatura tem divergido em relação às principais características dos pacientes propensos a uma evolução severa. Objetivo: Este estudo visou compreender diferentes variáveis que podem estar associadas ao manejo clínico da COVID-19 para uma melhor resposta clínica e prognóstico. Métodos: Esta é uma revisão sistemática na qual a busca nas bases de dados PubMed, Cochrane, EMBASE e LILACS. Também foi realizada uma pesquisa manual e literatura cinzenta no Google Scholar. Não houve restrição de país ou região e apenas estudos em português, inglês e espanhol foram incluídos. Resultados: Dos 21 estudos incluídos na Atenção Primária à Saúde (PHC) para elegibilidade, cinco estudos de cinco países envolvendo 27.754 pacientes foram analisados e, dos quatro estudos elegíveis, um estudo foi incluído para a atenção secundária. Em geral, a idade média da população COVID-19 em APS era de aproximadamente 41 anos, o número de casos era maior para as mulheres e, não houve diferença entre os grupos sem e com exposição, sexo ($p=0.322$) e idade ($p=0.395$). Mais da metade dos pacientes tinha sintomas e, 47% tinham comorbidades. As doenças cardíacas foram as mais prevalentes entre eles. Aproximadamente 79% dos infectados tinham ocupação não essencial. Havia evidências de que a ocupação não essencial estava associada a indivíduos infectados ($p=0.002$). Conclusões: Esta revisão identificou que pode haver maior vulnerabilidade à contaminação e agravamento da COVID-19 em indivíduos do sexo feminino, com idade adulta em atividade não essencial, presença de doenças crônicas não transmissíveis.

Palavras-chave: COVID-19, gerenciamento de cuidados ao paciente, cuidados paliativos, cuidados de saúde primários, cuidados secundários.

1 INTRODUCTION
Severe acute respiratory disease coronavirus 2 (SARS-CoV-2) is the cause of the disease called COVID-19, characterized by non-specific symptoms such as fever, cough, pharyngitis, difficulty breathing or chest pain, headache, nausea, fatigue, nasal constipation, coryza, pain in the eyes and, loss of smell and taste[1]. Transmission occurs through contact with respiratory droplets and expelled aerosols in both asymptomatic and symptomatic populations. The population of non-communicable chronic diseases may be more susceptible to aggravations. It is noteworthy that some identifiable factors in the population can contribute to the progression of the disease[2].

According to Stokes et al.[3], age is a risk factor for the worsening of the disease, as well as the presence of specific comorbidities such as: chronic kidney disease, chronic obstructive pulmonary disease (COPD), obesity, immunocompromised status, serious heart problems (heart failure, coronary artery disease or cardiomyopathies), type 2 diabetes mellitus and sickle cell disease. Many patients with these pre-existing conditions become seriously ill and die from secondary causes. To avoid the aggravation of these underlying diseases and the complication of the health condition, primary health care (PHC) plays a fundamental role, as it promotes
health education, guiding preventive measures such as social isolation, behaviours, and hygiene. In addition, PCH and also Secondary Care (SC) to enabling a rigorous evaluation and analysis of all original comorbidities of individuals with COVID-19 to carry out an individualized therapeutic plan to control health conditions[4].

The World Health Organization (WHO) estimates that PHC is an essential basis for the global response to COVID-19 since it is able to identify and track cases, make an early diagnosis, offer support to the population and reduce the demand for tertiary care[5]. Since most people diagnosed with COVID-19 develop mild symptoms, follow-up and support for them can be performed at the primary and secondary level of health care, without requiring referral to higher levels of care[5]. In order to obtain the most appropriate care for COVID-19 patients, it is essential to establish a holistic approach in the management of these patients[6] and, if necessary, PHC can refer the patient to the tertiary or quaternary level.

The structures tertiary health care offers specialized services, with different technological densities, and support for PHC and SC. However, according to an international analysis of health care systems, these systems are fragmented, focused on care for exacerbations of chronic conditions, and are usually organized through a set of isolated health care points that are incommunicado with each other in several countries. Consequently, they are unable to provide continuous attention to the population in a rational way to the health resources and the epidemiological control[7].

The analysis of clinical features that are related to a worse prognosis can aid to stratify patients’ risk and adjust appropriate management strategies during the COVID-19 pandemic[6]. The research question of this review was reasoned to know which clinical variables are correlated with the clinical management of COVID-19 in primary and secondary care, aiming to understand and relate different variables that may be associated with the clinical management of COVID-19 for a better clinical response and prognosis.

2 METHODS

This study is a systematic review that was based on the Joanna Briggs Institute method <https://jbi.global>, conducted following the Cochrane recommendations for systematic reviews and meta-analyses and based on the transparency and clarity criteria of the PRISMA checklist. The review question was defined as: What are clinical variables related to the clinical management of COVID-19 in primary and secondary care?

The search strategy was run by two independent researchers in four electronic bibliographic databases: MEDLINE by PubMed, Cochrane Library by Cochrane Central
Register of Controlled Trials (CENTRAL), Excerpta Medica database (EMBASE) by Elsevier, and Latin American Literature and Caribbean in Health Sciences (LILACS), on October 24, 2021. It was structured and organized according to the PICOS acronym.

2.1 SEARCH STRATEGY

The PICOS acronym was related to the following characteristics: P - patients diagnosed with COVID-19; I – support/treatment in primary health care or secondary care; C – disease progression and prognosis; O - not applicable, S - observational studies. The comparator was not considered for secondary care, only the population and the intervention, a strategy to provide a broader search.

Outcomes were not considered in the search strategy, since COVID-19 is an emerging disease, little known and described in the literature, for this reason, clinical trials were not selected. In addition, the response to this review includes the search for clinical outcomes.

The Boolean operators used were: “OR” for the expansion of words and terms into the categories and, “AND” for the combination between categories, PICOS. No search filters were used. Terms and keywords were extracted from controlled vocabularies, Emtree thesaurus for EMBASE, Descriptors in Health Sciences (DeCS) in Portuguese/Spanish/English for LILACs; MeSH (Medical Subject Headings) for PubMed and Cochrane (Supplemental file I).

The domain of this review was defined through the search for studies that evaluated the management of COVID-19 developed in PHC and SC, as well as the proposed treatments and the respective clinical variables relevant to the domain of this theme. The research was guided by a protocol (Systematic Review Protocol) registered in the database of PROSPERO - International Prospective Registry of Systematic Reviews - for systematic review, ID number 256450[8].

Search strategies were run for each database. The studies were retrieved and the file was generated for inclusion in the Rayyan systematic review database (https://www.rayyan.ai). Additionally, duplicates were removed and two researchers were selected for blind analysis. Initially, the first step through the system consisted of analysing the title and abstract of the studies. Those that did not include according to our protocol criteria were not eligible and were removed if there was consensus between the two researchers.

The articles selected after reading the title and abstract were analysed in full for inclusion of those studies that could respond to the questioning of the systematic review and that would meet the inclusion, exclusion and eligibility criteria. Conflicts in the selection of articles were mutually resolved between the researchers, when there was discordance, a third
researcher had the decision-making power. The following inclusion and exclusion criteria are listed (Supplemental file II).

2.2 INCLUSION CRITERIA

Studies with patients diagnosed with SARS-CoV-2 on pharmacological or non-pharmacological treatment for COVID-19 with clinical management for the disease at primary, secondary levels of health care.

2.3 EXCLUSION CRITERIA

Studies published in the form of narrative or integrative reviews, dissertations or theses, editorials, news, comments, letters to the editor, abstracts published in the annals of scientific journals or congresses and guidelines; studies that did not include the PICOS strategy, those that also did not consider the treatment of patients diagnosed with COVID-19; studies that analysed non-reproducible variables for interventions in the clinical management of COVID-19; studies that did not point to variables correlated with the care of patients with COVID-19; and those in which variables described in the clinical management were unclear as to their correlation with the disease.

Randomized and non-randomized clinical trials were also excluded, since in contrast to observational studies, in this type of study the researcher plans and actively intervenes in factors that influence the outcomes. Furthermore, COVID-19 is an emerging disease, there is no acceptable precision for outcomes in long term.

Studies with patient populations with specific disease conditions such as patients with myasthenia gravis, cancer, migraine, inflammatory bowel disease, haemodialysis patients, and paediatric patients were not considered.

2.4 DATA EXTRACTION

Data were extracted into predetermined worksheets reasoned on the standardized protocol. It was essential for the extracted data: title, authors, year, population, objectives, study design, inclusion criteria, database, evaluated outcomes, statistical analysis, population characteristics, symptoms and virological remission. To assess the quality of the studies, the validated instrument by Downs and Black\(^{[29]}\) was used, which comprises a 28-item checklist that allows verifying the general quality of the study, the internal and external validity, biases, confusion and power of the analyses.
2.5 DATA ANALYSIS

The analysis of results was performed using classical statistics. Thus, considering a significance level of 5% and a test power equal to 80%. The classical inferential statistical analysis was performed by the MINITAB version 18. The agreement between researches was analysed by the Kappa coefficient, with acceptability for values up to 0.70, the same was developed for quality score consensus. Otherwise, there would be a need to restructure a new search strategy. The Kappa coefficient was interpreted according to the classification by Landis and Koch.

The scores calculated by the Downs and Black instrument were measured in percentages from 0 to 100%. The interpretation of the evaluated scores was summarized as: up to 50% considered flawed or irrelevant studies; those between 50% and 69% considered to have weak evidence; 70–79% considered good evidence; and 80–100% considered with high scientific evidence.

Another classification was built on the Cochrane risk criteria applied to the Downs and Black instrument, which was proposed to classify in a quasi-quantitative way the quality of the studies retrieved in the review. Thus, predicting the type of domain that is more prone to bias and its percentage of risk of bias, which applies to the main problems interfering with the scores of the studies.

The t-student test was performed to test the hypothesis that continuous variables are equivalent for both exposure and non-exposure groups. To test the same hypothesis for categorical variables, the chi-square tested the association of contingency analysis between groups for categorical variables.

3 RESULTS

The results of the peer review at the selection stage were consistent as agreement between researchers [Kappa= 0.82; 95%CI, 0.72-1.0; (p<0.001)]; [Kappa=0.87; 95%CI, 0.78-1.0;(p<0.001)], for PHC, SC respectively. It was retrieved 3815 records without duplicates for PHC and 172 records for Secondary Care (SC), it being included five and one respectively (Figure 1) (Table 1).
Figure 1 - PRISMA flowchart for strategy in the Primary Health care and Secondary Care.

Table 1 - Presents the characteristics of the studies included in the final review of primary health care and secondary care

<table>
<thead>
<tr>
<th>Primary Health Care</th>
<th>Author (citation)</th>
<th>Year</th>
<th>Country</th>
<th>Study design</th>
<th>Eligible patients</th>
<th>Time of study</th>
<th>Confidential allocation</th>
<th>Sample number</th>
<th>Sample losses</th>
<th>Survivals with exposition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mayer et al.,32</td>
<td>2021</td>
<td>Spain</td>
<td>Retrospective observational</td>
<td>23844</td>
<td>170</td>
<td>No</td>
<td>Non-exposition= 324752 Exposition = 23844 Non-exposition = NI Exposition = NI</td>
<td>-</td>
<td>855</td>
</tr>
<tr>
<td></td>
<td>Krishnasamy et al.,33</td>
<td>2021</td>
<td>India</td>
<td>Prospective observational</td>
<td>1263</td>
<td>32</td>
<td>No</td>
<td>Non-exposition= NI Exposition = 1263 Non-exposition = NI Exposition = NI</td>
<td>-</td>
<td>304</td>
</tr>
<tr>
<td></td>
<td>Leal et al.,34</td>
<td>2020</td>
<td>Brazil</td>
<td>Prospective observational</td>
<td>496</td>
<td>52</td>
<td>No</td>
<td>Non-exposition= 1136 Exposition = 496 Non-exposition = NI Exposition = NI</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Lee et al.,35</td>
<td>2020</td>
<td>South Korea</td>
<td>Retrospective observational</td>
<td>632</td>
<td>29</td>
<td>No</td>
<td>Non-exposition= NI Exposition = 632 Non-exposition = NI Exposition = NI</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Alsofayan et al.,36</td>
<td>2020</td>
<td>Saudi Arabia</td>
<td>Sectional multicentric</td>
<td>1519</td>
<td>31</td>
<td>No</td>
<td>Non-exposition= 63481 Non-exposition = NI Exposition = NI</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Overall of five articles included in the review for PHC, four (80%) presented the classification of quality as good evidence, and one with weak evidence. The mean score of twenty-seven points was equivalent to 18.6.

Of the twenty-seven questions of the instrument, sixteen had a low risk of bias for the included studies. In terms of methodological quality, with the exception of the issue of differentiating the confounding variables between the groups, there was good representation for low risk of bias. All studies had a low risk of bias for the external validity. Regarding the internal validity and the confounding domain, of thirteen questions, five had a high risk of bias and one question had a medium risk, which was already expected since in observational studies it is not common to blind subjects to receive the intervention, as occurs in randomized clinical trials (Figure 2).

Figure 2 - Classification of the quality of the studies according to the domains of the Downs and Black instrument associated with risk bias of Cochrane.
Regarding the general characteristics of the studies included for PHC, three studies were published in 2020, one in Brazil, one in South Korea, and one in Saudi Arabia, and the other two published in 2021, one in Spain and the other in India. The studies by Krishnasamy et al.\cite{33} and Lee et al.\cite{35} had as clinical scenarios the COVID-19 Care Clinics, which are facilities for the isolation of positive COVID-19 patients and community treatment (Table 2).
Table 2 - Identification of the included studies and qualification of the clinical management of COVID-19 patients for the PHC

<table>
<thead>
<tr>
<th>Author citation (Country)</th>
<th>Monitoring time (days)</th>
<th>Number of consultations (rounds or contact with the patient)</th>
<th>Period or time of infection (mean or total days)</th>
<th>Clinical Scenario (Clinic, Basic Health Unit, Emergency, Specific for COVID-19 or Data base)</th>
<th>Multiprofessional support (yes or no)</th>
<th>Investigated symptoms</th>
<th>Travel history percentage (yes/no)</th>
<th>Average duration of isolation</th>
<th>Disease remission rate (cures)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayer et al., 32 2021 (Brazil)</td>
<td>167</td>
<td>Not informed</td>
<td>Not informed</td>
<td>Basic Health Unit (public)</td>
<td>No</td>
<td>Not informed</td>
<td>Not informed</td>
<td>Not informed</td>
<td>Not informed</td>
</tr>
<tr>
<td>Krishnasamy et al., 33 2021 (India)</td>
<td>30</td>
<td>Three times per day.</td>
<td>Not informed</td>
<td>Specific for COVID-19 (Public - Nandambakkam Central of Care)</td>
<td>Yes</td>
<td>Fever, dry cough, generalized body pain, difficulty breathing, fatigue, anosmia, ageusia, sneezing and coryza, pharyngitis, headache, productive cough, vomiting, joint pain, non-specific chest pain, back pain, abdominal pain, vertigo, anorexia, wheezing, hemoptysis, myalgia, anginal chest pain, eye itching and discharge, rash.</td>
<td>Yes: 9.2% of patients</td>
<td>8 days</td>
<td>Not informed</td>
</tr>
<tr>
<td>Leal et al., 34 2020 (Spain)</td>
<td>52</td>
<td>One to each two days: 14 days with phone calls (a maximum of seven phone calls)</td>
<td>Not informed</td>
<td>Basic Health Unit (public)</td>
<td>Yes</td>
<td>Headache, myalgia, cough, fatigue, anosmia, ageusia, coryza, fever, arthralgia, diarrhea, nausea, vomiting, anorexia, constipation, pharyngitis.</td>
<td>Not informed</td>
<td>Not informed</td>
<td>Not informed</td>
</tr>
<tr>
<td>Lee et al., 35 2020 (South Korea)</td>
<td>42</td>
<td>Two times per day.</td>
<td>Mean of 12 days.</td>
<td>Clinic (Korea Centers for Disease Control and Prevention - KCDC)</td>
<td>Yes</td>
<td>Cough, expectoration, rhinorrhea, pharyngitis, dyspnea, abdominal pain, diarrhea, headache, fever.</td>
<td>Not informed</td>
<td>7.8 days</td>
<td>59.1% of virological remission in 21 days. Symptomatic patients a mean of 11.7 days and asymptomatic of 23.1 days.</td>
</tr>
<tr>
<td>Alsofayan et al., 36 2020 (Saudi Arabia)</td>
<td>31</td>
<td>Not informed</td>
<td>Not informed</td>
<td>Data base</td>
<td>No</td>
<td>Fever, cough, pharyngitis, coryza, myalgia, headache, gastrointestinal symptoms.</td>
<td>Yes: without the percentage</td>
<td>Not informed</td>
<td>Not informed</td>
</tr>
</tbody>
</table>
The mean age of the group without exposure was 45.89 years, and there was a homogeneous distribution between the sexes, with males 50.17% and females 49.83%. In the exposed group, the mean age was 41.16 years and most patients were female (56.15%). Additionally, most patients had a non-essential occupation, 59.89% in the non-exposed group and 79.79% in the exposed group.

Regarding the progression of the disease and the presence or absence of morbidity, it was not possible to relate it to the unexposed group, as there was no data from this group in the articles included. It can be seen that 18.90% of the patients progressed to more severe disease and practically half of them (47.38%) had comorbidities (Table 3).

Of the most prevalent symptoms, shortness of breath was predominant in 172 patients (80.0%), affecting 77.5% of survivors and 83.7% of non-survivors. Cough showed signs of a symptom that affects survivors and non-survivors differently, being more prevalent among survivors. Of comorbidities, hypertension and cardiovascular diseases had a prevalence of 53.0% and 43.3% among patients. It highlights evidence of a higher prevalence of cardiovascular disease among non-surviving patients. It is noteworthy that angiotensin-converting enzyme (ACE) inhibitors had a higher prevalence of infected patients and that mechanical ventilation was predominant among the management of clinical conditions. For laboratory results, it was evident between neutrophils and lymphocytes of survivors and non-survivors and the relationship between them, albumin, C-reactive protein, D-dimer, glomerular filtration rate and acute kidney disease (Table 3).
Table 3 - Sociodemographic and clinical profile of patients of patients with and without exposure included in this review

<table>
<thead>
<tr>
<th>Variables</th>
<th>PRIMARY HEALTH CARE</th>
<th>SECONDARY CARE</th>
<th>p-value</th>
<th>Characteristics</th>
<th>Total of Patients</th>
<th>Surviving group</th>
<th>Non-surviving group</th>
<th>Statistical significance related by the authors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-exposition group (n=389,369)</td>
<td>Exposition group (n=27,754)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (Mean ± SD)</td>
<td>45.89 ± 13.98</td>
<td>41.16 ± 11.27</td>
<td>0.395</td>
<td>Sociodemographic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Man</td>
<td>163.216 (50.17%)</td>
<td>12.169 (43.85%)</td>
<td>0.322</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Woman</td>
<td>162.088 (49.83%)</td>
<td>15.585 (56.15%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Essential occupation (%)</td>
<td>221 (40.11%)</td>
<td>407 (20.21%)</td>
<td>0.002</td>
<td>Retirement home (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-essential occupation (%)</td>
<td>330 (59.89%)</td>
<td>1,607 (79.79%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with disease progression (%)</td>
<td>- 729 (18.90%)</td>
<td>-</td>
<td></td>
<td>Shortness of breath (%)</td>
<td>172 (80.0)</td>
<td>100 (77.5)</td>
<td>72 (83.7)</td>
<td>No</td>
</tr>
<tr>
<td>Patients without disease progression (%)</td>
<td>- 3,129 (81.10%)</td>
<td>-</td>
<td></td>
<td>Fever (%)</td>
<td>98 (45.6)</td>
<td>66 (51.2)</td>
<td>32 (37.2)</td>
<td>No</td>
</tr>
<tr>
<td>Comorbidities (%)</td>
<td>- 1,318 (47.38%)</td>
<td>-</td>
<td></td>
<td>Cough (%)</td>
<td>122 (56.7)</td>
<td>92 (71.3)</td>
<td>30 (34.8)</td>
<td>Yes</td>
</tr>
<tr>
<td>Comorbidities Absence (%)</td>
<td>- 1,464 (52.62%)</td>
<td>-</td>
<td></td>
<td>Weakness (%)</td>
<td>110 (51.2)</td>
<td>41 (37.3)</td>
<td>69 (62.7)</td>
<td>Yes</td>
</tr>
<tr>
<td>Risk factors</td>
<td>Mean Weight Kg (deviation)</td>
<td>78 (67.0–92.0)</td>
<td></td>
<td></td>
<td>84 (71.6–100)</td>
<td>70 (63–84)</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Smoking</td>
<td>46,659 (92.36%)</td>
<td>3,857 (7.64%)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Obesity</td>
<td>64,472 (92.40%)</td>
<td>5,303 (7.60%)</td>
<td>-</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td><strong>Comorbidites</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Morbidities</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Heart disease (%)</td>
<td>82,984 (39.74%)</td>
<td>6,769 (40.2%)</td>
<td>-</td>
<td></td>
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<td></td>
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<tr>
<td>Cerebrovascular disease (%)</td>
<td>1,658 (0.79%)</td>
<td>178 (1.06%)</td>
<td>-</td>
<td></td>
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<td></td>
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<tr>
<td>Diabetes (%)</td>
<td>27,418 (13.13%)</td>
<td>2,400 (14.25%)</td>
<td>-</td>
<td></td>
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<td></td>
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<tr>
<td>COPD (%)</td>
<td>8,247 (3.95%)</td>
<td>841 (4.99%)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Asthma (%)</td>
<td>-</td>
<td>67 (0.4%)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>66,675 (31.92%)</td>
<td>4,769 (28.32%)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cancer (%)</td>
<td>21,785 (10.43%)</td>
<td>1,778 (10.56%)</td>
<td>-</td>
<td></td>
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<td></td>
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<tr>
<td>Chronic Renal Disease (%)</td>
<td>3 (0.014%)</td>
<td>22 (0.13%)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hypothyroidism (%)</td>
<td>-</td>
<td>13 (0.08%)</td>
<td>-</td>
<td></td>
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<tr>
<td><strong>Medicines’ use</strong></td>
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<td></td>
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<tr>
<td>ACEi</td>
<td>-</td>
<td>1,714 (70.16%)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARB</td>
<td>-</td>
<td>729 (29.84%)</td>
<td>-</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>BMI kg/m² (deviation)</strong></td>
<td>28 (24.0 – 32.0)</td>
<td>29.4 (26.0 – 34.0)</td>
<td>26 (23.0 – 29.0)</td>
<td></td>
<td></td>
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<tr>
<td><strong>Treatment</strong></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEi</td>
<td>54 (25.0)</td>
<td>37 (28.7)</td>
<td>17 (19.8)</td>
<td></td>
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<tr>
<td>immunosuppressants</td>
<td>12 (5.6)</td>
<td>6 (4.6)</td>
<td>6 (7.0)</td>
<td></td>
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<tr>
<td><strong>Labs</strong></td>
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<tr>
<td>Hemoglobin (g/L)</td>
<td>133 (120.0–146.0)</td>
<td>134 (122.0–148.0)</td>
<td>129 (118.0–143.0)</td>
<td></td>
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<tr>
<td><strong>Hypertension (%)</strong></td>
<td>114 (53.0)</td>
<td>62 (48.1)</td>
<td>52 (60.5)</td>
<td></td>
<td></td>
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<tr>
<td>Diabetes mellitus (%)</td>
<td>65 (30.2)</td>
<td>42 (32.5)</td>
<td>23 (26.7)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Cardiovascular disease (%)</td>
<td>93 (43.3)</td>
<td>43 (33.3)</td>
<td>50 (58.1)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ischemic heart disease</td>
<td>53 (24.7)</td>
<td>28 (21.7)</td>
<td>25 (29.1)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Stroke</td>
<td>30 (14.0)</td>
<td>11 (8.5)</td>
<td>19 (22.1)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CKD (stage 3-5)</td>
<td>42 (19.5)</td>
<td>24 (18.6)</td>
<td>18 (20.9)</td>
<td></td>
<td></td>
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<tr>
<td>Breath disease (%)</td>
<td>65 (30.2)</td>
<td>32 (24.8)</td>
<td>33 (38.4)</td>
<td></td>
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<td></td>
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<tr>
<td>Cancer (%)</td>
<td>19 (8.8)</td>
<td>13 (10.1)</td>
<td>6 (7.0)</td>
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<tr>
<td>Hypothyroidism (%)</td>
<td>13 (0.08%)</td>
<td>-</td>
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<tr>
<td><strong>Clinical management at the hospital</strong></td>
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<tr>
<td>Mechanical ventilation (%)</td>
<td>24 (11.2)</td>
<td>12 (9.3)</td>
<td>12 (13.9)</td>
<td></td>
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<td></td>
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<tr>
<td>Non-invasive ventilation (%)</td>
<td>16 (7.5)</td>
<td>9 (7.0)</td>
<td>7 (5.4)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Intubation and Ventilation (%)</td>
<td>8 (3.7)</td>
<td>3 (3.5)</td>
<td>5 (5.8)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Patients admitted to hospital (days)</td>
<td>5 (2.0–10.0)</td>
<td>5 (2.0–10.0)</td>
<td>5 (3.0–9.0)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>133 (120.0–146.0)</td>
<td>134 (122.0–148.0)</td>
<td>129 (118.0–143.0)</td>
<td></td>
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<tr>
<td></td>
<td>Group 1 (Mean ± SD)</td>
<td>Group 2 (Mean ± SD)</td>
<td>Group 3 (Mean ± SD)</td>
<td>P-Value</td>
<td></td>
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<tr>
<td>Neutrophils (× 10⁹/L)</td>
<td>6 (4.0 – 9.0)</td>
<td>6 (4.0 – 8.0)</td>
<td>7 (4.0 – 9.0)</td>
<td>Yes</td>
<td></td>
<td></td>
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<tr>
<td>Lymphocytes (× 10⁹/L)</td>
<td>0.9 (0.6 – 1.3)</td>
<td>0.9 (0.6 – 1.4)</td>
<td>0.8 (0.5 – 1.2)</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Neutrophil: Relation of lymphocytes</td>
<td>7 (4.0 – 13.0)</td>
<td>6 (4.0 – 11.0)</td>
<td>9 (5.0 – 18.0)</td>
<td>No</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Platelet count (× 10⁹/L)</td>
<td>217 (161.0–270.0)</td>
<td>223 (162.0–270.0)</td>
<td>210 (155.0–265.0)</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Albumin (g/L)</td>
<td>30 (27.0–34.0)</td>
<td>31 (28.0–35.0)</td>
<td>29 (26.0–32.0)</td>
<td>Yes</td>
<td></td>
<td></td>
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<tr>
<td>Bilirubin (µmol/L)</td>
<td>12 (8.0–17.0)</td>
<td>12 (8.0–18.0)</td>
<td>11 (8.0–16.0)</td>
<td>No</td>
<td></td>
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<tr>
<td>Alkaline Phosphatase (U/L)</td>
<td>81 (63.0–109.0)</td>
<td>79 (62.0–107.0)</td>
<td>85 (65.0–109.0)</td>
<td>No</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>107 (56.0–177.0)</td>
<td>90 (41.0–164.0)</td>
<td>123 (72.0–189.0)</td>
<td>Yes</td>
<td></td>
<td></td>
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<tr>
<td>D-Dimer (ng/L)</td>
<td>610 (297.0–809.0)</td>
<td>559 (412.0–748.0)</td>
<td>775 (701.0–848.0)</td>
<td>Yes</td>
<td></td>
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<tr>
<td>GFR (mL/min/1.73m²)</td>
<td>67 (42.0–90.0)</td>
<td>77 (56.0–90.0)</td>
<td>48.5 (28.0–74.0)</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Acute Kidney Injury</td>
<td>65 (30.2)</td>
<td>25 (19.4)</td>
<td>40 (46.5)</td>
<td>Yes</td>
<td></td>
<td></td>
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<tr>
<td>Chest X-ray</td>
<td></td>
<td></td>
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<tr>
<td>Result suggestive of COVID-19</td>
<td>166 (79.8)</td>
<td>98 (77.8)</td>
<td>68 (82.9)</td>
<td>No</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Bilateral Infiltrators</td>
<td>117 (56.2)</td>
<td>67 (53.2)</td>
<td>50 (61.0)</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral Consolidation</td>
<td>48 (23.1)</td>
<td>31 (24.0)</td>
<td>17 (19.8)</td>
<td>No</td>
<td></td>
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</tbody>
</table>

Caption: SD = Standard Deviation;
When comparing the groups, the Student t-test was run for two independent samples in the age variable and the chi-square test for association in the gender and essential service variables, with a significance level of 5% for analysis of the results.

Weakness: prostration and body pain; BMI: Body Mass Index. Cardiovascular Diseases: Includes at least one of the following diseases - Ischemic Heart Disease, Myocardial Infarction, Congestive Heart Failure (CHF), Chronic Kidney Disease (CKD). Respiratory diseases include: Asthma, Chronic Obstructive Pulmonary Disease and Pulmonary Fibrosis. Albumin: Absent in 32 of 215 patients; C-reactive protein: Absent in 5 of 215 patients; D-dimer: Present in only 15 patients; GFR: Glomerular Filtration Rate; Thorax radiography was absent in 7 patients. Estimated glomerular filtration rate calculated by the CKD-EPI equation, U/L = units/lit.
4 DISCUSSION

During the pandemic, PHC has been essential in the clinical management of patients, preventing other levels of care from becoming overcrowded and, thus being able to deal with the demands of severe cases\textsuperscript{[37]}. PHC can be considered the most comprehensive component, in view of its centrality to the care and guarantee of the population's health. In this sense, it is recognized, especially in the pandemic, for having the operational capacity to detect mild and moderate cases of COVID-19 in a timely manner, as well as referring the most critical cases to referral hospitals\textsuperscript{[38]}.

However, about 80\% of cases are considered mild and do not use specialized services, being assisted by primary services\textsuperscript{[39,40]}. Therefore, this justifies the low number of studies retrieved in the search for SC, and the inclusion of only one, even when searching the gray-literature. In addition, there are few countries that divide the health system at the level of secondary care, for this reason, we did not find many studies specific to this level of care.

The studies included in this review showed a low bias for methodological quality in general, which means that the studies were designed according to what they were intended to assess, but they had limitations of the type of study regarding the evidence of the results, as they were not trials randomized clinical trials with triple blinding, for example. This fact infers the internal validity of the studies and the interference in the results by confounding variables. However, they proved to be studies that meet the necessary quality to answer this review question.

The mean age in the group with exposure was 41.16 (±11.27) years and in the group without exposure 45.89 years (13.98), which is close to the data reported by some studies that had been evaluated COVID-19 patients, in special in primary care and secondary care. The median age of COVID-19 patients appears to be around 47-59 years, and typically higher among severe cases and non-survivors who reach the tertiary level of care\textsuperscript{[41,42]}.

The lower mean age found in this review can be explained by the study of patients with mild COVID-19 in primary care, and therefore younger, as older patients progress to a more severe condition and are referred to tertiary care. Note that for this variable there was no difference between the groups without exposure and with exposure, which is also observed for the variable gender. Mayer et al.\textsuperscript{[32]} found in their study that there was no significant difference in age between patients with and without COVID-19, a conclusion similarly demonstrated by our study. Most of the studies included in this review showed that advanced age, together with underlying diseases, are associated with greater disease progression and, consequently, higher mortality\textsuperscript{[32]}. This finding is in agreement with the literature\textsuperscript{[41,43-46]}. 
Progression to severe disease has also been analysed by some authors, Krishnasamy et al.\[33\], for example, identified that symptomatic\[36\] patients with comorbidities and a higher proportion of neutrophil-lymphocytes (NLR) were more likely to progress to severe disease, requiring referral to tertiary care. All studies had demographic and clinical characteristics as outcomes and studied the presence of comorbidities, such as hypertension, diabetes, asthma, COPD, and chronic kidney disease and in relation to symptoms, fever, cough, myalgia, headache, and gastrointestinal symptoms were evaluated by most authors, except for Mayer et al.\[32\] who did not consider symptoms in their study. All comorbidities and all symptoms may be visualized at the Supplemental file III and Supplemental file IV, respectively.

Although there is no difference for contamination according to sex\[41,42\], our results showed a higher percentage of women (56.15%) in the exposure group. This can be explained by the fact that women use to take care of their health, seeking health services even in the absence of symptoms or with mild symptoms. Occupation was a preponderant factor among infected individuals, as the group without exposure had no difference between essential and non-essential occupation categories.

It was observed in this review that 47.4% of patients with COVID-19 had comorbidities, with heart disease being the most common (40.2%). The literature shows that 48% of patients with COVID-19 have at least one comorbidity, and hypertension together with coronary heart disease, accounts for approximately 38% of these patients\[44\]. Dyslipidaemia (28.32%), diabetes (14.25%), cancer (10.56%), COPD (4.99%) have also been prevalent diseases in this population\[44\].

Patients with a history of dyslipidaemia may be at an increased risk of serious COVID-19 infections, and this comorbidity may have a potential effect on disease severity\[47\]. Our results presented that 28.32% were dyslipidaemia patients, it was similar to a North American study with a prevalence of dyslipidaemia of 32.5% and a French study with 28%\[46,48\].

Diabetes is among the most frequent comorbidities in infected people, in this review this condition was the third most prevalent, with 14.25%. In a meta-analysis of 2,108 Chinese patients with confirmed COVID-19 infection, Fadini et al.\[49\] showed that the prevalence of diabetes was 10.3%. Patients with pre-existing cardiovascular disease, diabetes, chronic respiratory disease, and cancer who become infected with COVID-19 are known to have worse outcomes than patients without these diseases, with a mortality of 10.5%, 7.3%, 6.3%, and 5.6%, respectively, compared to 2.3% in the general population\[50\].

Obesity is an established risk factor for several infections and is well recognized as a pro-inflammatory condition\[51\]. In this study, that of the total obese patients, 7.6% had COVID-
19. COVID-19 disease in an obese patient may represent an amplification of inflammatory processes and worse prognosis\cite{46,51-53}. According to Hoong et al.\cite{54} hospitalized obese patients had a 50% higher chance of mortality compared to non-obese patients, however, the study by Mayer et al.\cite{32} included in this review did not find an increased risk of mortality in COVID-19 patients.

Another important risk factor for the progression of COVID-19 is smoking. It can be inferred that smokers are at greater risk of contamination by COVID-19, as they take electronic or traditional devices to their mouths, without adequate hand hygiene. Our result showed that 7.64% of smokers had COVID-19, a slightly higher result than Patanavanich and Glantz\cite{55} noted, of 9,025 COVID-19 patients, 5.5% had a history of smoking.

It is important to highlight that the studies by Lee et al.\cite{35} and Krishnasamy et al.\cite{33} had as clinical scenarios the COVID-19 Care Clinic, which are facilities for the isolation of COVID-19 positive patients and community treatment. Patients in these centers had frequent professional support, such as monitoring of respiratory symptoms and vital parameters three times a day, and when they had significant symptoms or abnormal vital signs or abnormal radiological findings, they were immediately transferred to tertiary hospitals by ambulance.

A systematic review that included 24,410 adults with laboratory-confirmed COVID-19 from nine countries found that the main symptoms of fever (78%) and persistent cough (57%) are in fact the most prevalent symptoms of COVID-19 worldwide, as shown in our study\cite{56}.

It is noteworthy that fever was less common in patients in relation to respiratory symptoms and cough was less frequent in patients who died. In this sense, the literature shows that fever has been more frequently observed in studies involving hospitalized patients with COVID-19 with a severe course of the disease, with cough being a milder symptom and a sign for prevention\cite{57}.

The literature has discussed that COVID-19 is not just a respiratory disease, but a systemic disease with an extensive spread in the human body, since the presence of pathogenic mechanisms and complications in vital organs has already been identified in studies\cite{39,58,59}. As shown in our study, conditions such as kidney disease are preponderant in the death of patients.

COVID-19 complications, post-covid disease, may have an important impact on the population's quality of life, possibly increasing the demand for medium to high complexity care\cite{60}. According to Avelar et al.\cite{39}, the effects of COVID-19 on the body affect several systems, such as respiratory, cardiovascular, urinary, central nervous system, sensory, digestive, male reproductive.
Therefore, it is expected that in the post-COVID-19 phase there will be a demand for outpatient services, thus increasing the demand on health systems for diagnosis, treatment, and rehabilitation of recovered patients, but still with complications, specifically: due to respiratory complications, overload of cardiologists’ care due to the accumulation of consultations postponed in the control protocol to avoid contamination and increase in the incidence of heart diseases from COVID-19, worsening of the drug therapy scenario, medical consultations and elective surgeries for non-communicable chronic diseases, as a result of rescheduling appointments, without renewing prescriptions\textsuperscript{[61]}.

5 CONCLUSION

Through the studies, it was possible to describe the main clinical variables that are related to the clinical management of COVID-19 in primary and secondary care, such as the presence of comorbidities, disease progression, most prevalent symptoms. In addition, is important highlights that some clinical sequelae that have occurred in most patients and, with proper patient management may be preventable. In this way, answering the study question, diabetes and cardiovascular disease were important variables associated with a worse prognosis. When identified in primary care, they are important factors in decision-making care for these patients to avoid severe COVID-19 progression.

As a determinate point, the results of this review tend to help identify different profiles of patients prone to the complications of COVID-19, considering early interventions regarding the need for oxygenation and intubation with mechanical ventilation. Additionally, these results are important to the prediction for referral to the hospital care level of patients with cardiovascular disease, previously hypertension, and comorbidities such as diabetes, dyslipidaemia, elevated neutrophil and lymphocyte ratio, as well as plasma D-dimer and C-reactive protein rates, exams that can be introduced in primary care with elaboration of specific protocols.
REFERENCES


