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

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

Adrielle Pereira Cordeiro
Bachelor of Pharmacy for School of Pharmacy, Federal University of Juiz de Fora, Brazil
Institution: School of Pharmacy, Federal University of Juiz de Fora, Brazil
Address: Rua José Lourenço Kelmer, S/N, São Pedro, Juiz de Fora - MG, CEP: 36036-900
E-mail: adrielle-cordeiro@hotmail.com

Pâmela Santos Azevedo
MSc Medicines and Pharmaceutical Services for School of Pharmacy,
Federal University of Minas Gerais, Brazil
Institution: School of Pharmacy, Federal University of Minas Gerais, Brazil
Address: Av. Pres. Antônio Carlos, 6627, Pampulha, Belo Horizonte - MG, CEP: 31270-901
E-mail: pamela.azevedo43@gmail.com

Estael Luzia Coelho da Cruz-Cazarim
MSc. Pharmaceutical Science for School of Pharmaceutical Sciences of Ribeirao Preto,
University of Sao Paulo, Brazil
Institution: School of Pharmacy, Federal University of Juiz de Fora, Brazil
Address: Rua José Lourenço Kelmer, S/N, São Pedro, Juiz de Fora - MG, CEP: 36036-900
E-mail: estaelcruz@gmail.com

Damaris Salgueiro da Silva
Undergraduate of Pharmacy for School of Pharmacy, Federal University of
Juiz de Fora, Brazil
Institution: School of Pharmacy, Federal University of Juiz de Fora, Brazil
Address: Rua José Lourenço Kelmer, S/N, São Pedro, Juiz de Fora - MG, CEP: 36036-900
E-mail: damaris.salgueirod@gmail.com

Altacílio Aparecido Nunes
Ph.D. Tropical Medicine and Infectology for Department of Social Medicine of Ribeirão
Preto Medical School, University of Sao Paulo, Brazil
Institution: School of Medicine of Ribeirão Preto, University of Sao Paulo, Brazil
Address: Av. Bandeirantes, 3900, Ribeirão Preto - SP, CEP: 14049-900
E-mail: altacilio@fmrp.usp.br

Alessandra Ésther de Mendonça
PhD in Sciences and Biotechnology in the Department of Pharmaceutical Sciences, School of
Pharmacy from Universidade Federal de Juiz de Fora
Institution: Faculdade de Farmácia da Universidade Federal de Juiz de Fora, MG
Address: Rua José Lourenço Kelmer, S/N, São Pedro, Juiz de Fora - MG,
CEP: 36036-900
E-mail: alessandra.mendonca@ufjf.br

Marcelo Silva Silvério
PhD in Health in the Department of Pharmaceutical Sciences Faculty of Pharmacy from
Universidade Federal de Juiz de Fora, Brasil
Institution: Faculdade de Farmácia da Universidade Federal de Juiz de Fora, MG
Address: Rua José Lourenço Kelmer, S/N, São Pedro, Juiz de Fora - MG,
CEP: 36036-900
E-mail: marcelo.silverio@ufjf.br

Maurilio de Souza Cazarim
PhD in Pharmaceutical Sciences at the Department of Pharmaceutical Sciences, Faculty of
Pharmacy pela Universidade Federal de Juiz de Fora
Institution: Faculdade de Farmácia da Universidade Federal de Juiz de Fora, MG, Brasil
Institution: Rua José Lourenço Kelmer, S/N, São Pedro, Juiz de Fora - MG,
CEP: 36036-900
E-mail: maurilio.cazarim@ufjf.br

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 ($\rho=0.322$) and age ($\rho=0.395$). 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 ($\rho=0.002$). 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 (ρ=0,322) e idade (ρ=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 (ρ=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 INTRODUTION

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%[30]. 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[31].

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[29].

Another classification was built on the Cochrane risk criteria applied to the Downs and Black instrument, which was proposed to classify in a quali-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.
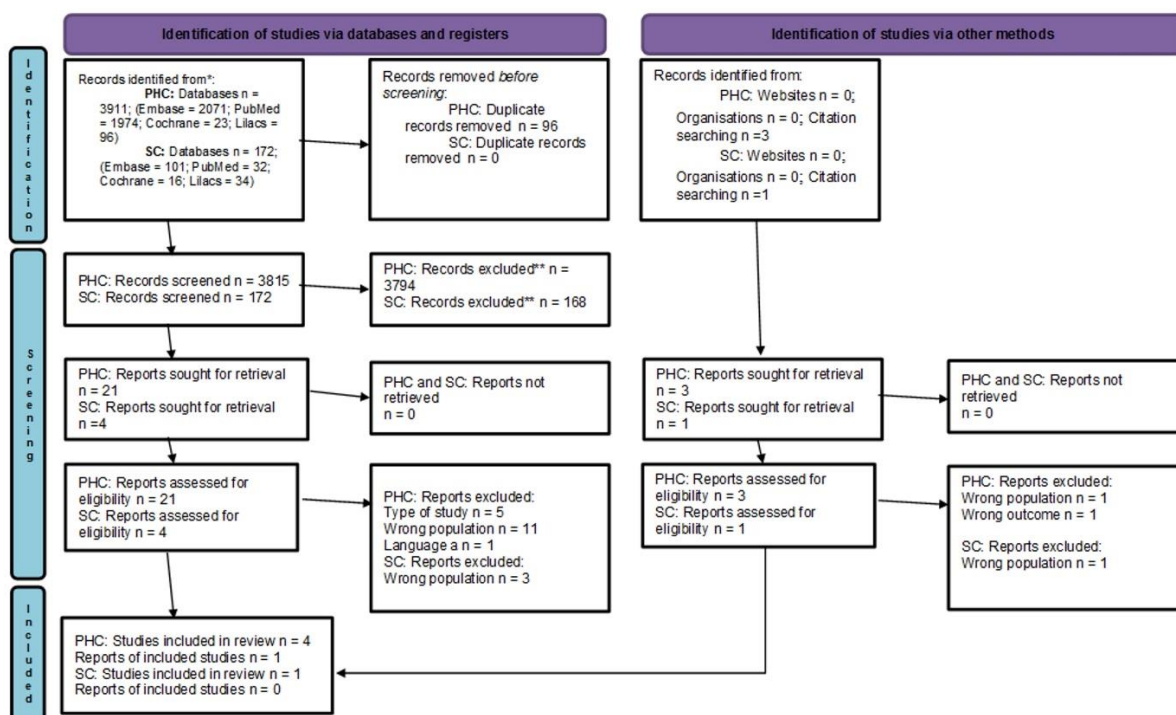

Table 1 - Presents the characteristics of the studies included in the final review of primary health care and secondary care

Primary Health Care

Author (citation)	Year	Country	Study design	Eligible patients	Time of study	Confidential allocation	Sample number	Sample losses	Survivals with exposition
Mayer et al.,[32] (2021)	2021	Spain	Retrospective observational	23844	170	No	Non-exposition= 324752 Exposition = 23844	Non-exposition = NI Exposition = NI	855
Krishnasamy et al.,[33] (2021)	2021	Índia	Prospective observational	1263	32	No	Non-exposition = NI Exposition = 1263	Non-exposition = NI Exposition = NI	304
Leal et al.,[34] (2020)	2020	Brazil	Prospective observational	496	52	No	Non-exposition= 1136 Exposition = 496	Non-exposition = 532 Exposition = NI	-
Lee et al.,[35] (2020)	2020	South Korea	Retrospective observational	632	29	No	Non-exposition = NI Exposition = 632	Non-exposition = NI Exposition = NI	-
Alsofayan et al.,[36] (2020)	2020	Saudi Arabia	Sectional multicentric	1519	31	No	Non-exposition= 63481	Non-exposition = NI	-

							Exposition = 1519	Exposition = NI	
Secondary Care									
Author (citation)	**Year**	**Country**	**Study design**	**Eligible patients**	**Time of study**	**Confidential allocation**	**Sample number**	**Sample losses**	**Survivals with exposition**
Chinnadurai *et al.*,[6] (2020)	2020	United Kingdom	Observational study, sectional	215	39	No	Non-exposition= 308 Exposition = 215	Non-exposition = NI; Exposition = 86	129

NI = Not informed.

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.
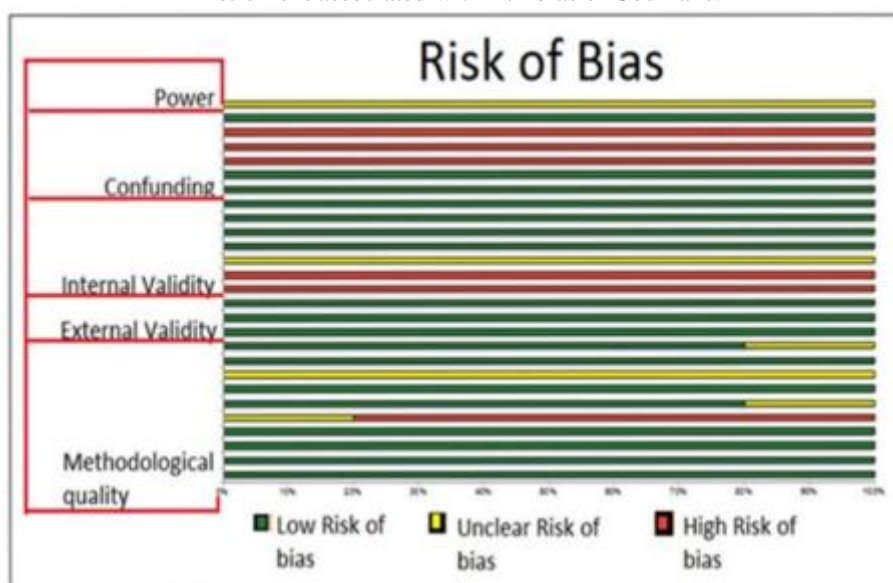
Regarding the general characteristics of the studies included for PHC, three studies were published in 2020, one in Brazil, one in South Korea, and one in Saudi Arabia, and the other two published in 2021, one in Spain and the other in India. The studies by Krishnasamy et al.[33] and Lee et al.[35] had 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

Author citation (Country)	Monitoring time (days)	Number of consultations (rounds or contact with the patient)	Period or time of infection (mean or total days)	Clinical Scenario (Clinic, Basic Health Unit, Emergency, Specific for COVID-19 or Data base)	Multiprofessional support (yes or no)	Investigated symptoms	Travel history percentage (yes/no)	Average duration of isolation	Disease remission rate (cures)
Mayer *et al.*,[32] 2021 (Brazil)	167	Not informed	Not informed	Basic Health Unit (public)	No	Not informed	Not informed	Not informed	Not informed
Krishnasamy *et al.*,[33] 2021 (India)	30	Three times per day.	Not informed	Specific for COVID-19 (Public - Nandambakkam Central of Care)	Yes	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.	Yes: 9.2% of patirnts	8 days	Not informed
Leal *et al.*,[34] 2020 (Spain)	52	One to each two days: 14 days with phone calls (a maximum of seven phone calls)	Not informed	Basic Health Unit (public)	Yes	Headache, myalgia, cough, fatigue, anosmia, ageusia, coryza, fever, arthralgia, diarrhea, nausea, vomiting, anorexia, constipation, pharyngitis.	Not informed	Not informed	Not informed
Lee *et al.*,[35] 2020 (South Korea)	42	Two times per day.	Mean of 12 days.	Clinic (Korea Centers for Disease Control and Prevention - KCDC)	Yes	Cough, expectoration, rhinorrhea, pharyngitis, dyspnea, abdominal pain, diarrhea, headache, fever.	Not informed	7.8 days.	59.1% of virological remission in 21 days. Symptomatic patients a mean of 11.7 days and asymptomatic of 23.1 days.
Alsofayan *et al.*,[36] 2020 (Saudi Arabia)	31	Not informed	Not informed	Data base	No	Fever, cough, pharyngitis, coryza, myalgia, headache, gastrointestinal symptoms.	Yes: without the percentage	Not informed	Not informed.

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

PRIMARY HEALTH CARE				SECONDARY CARE				
Variables	Non-exposition group (n= 389,369)	Exposition group (n= 27,754)	p-value	Characteristics	Total of Patients (n=215)	Surviving group (n=129)	Non-surviving group (n=86)	Statistical significance related by the authors
Age (Mean ± SD)	45.89 ± 13.98	41.16 ± 11.27	0.395	**Sociodemographic**				
Sex (%)				Age (years)	74 (60.0 – 82.0)	67 (57.0-79.0)	80 (73.0-86.0)	Yes
Man	163,216 (50.17%)	12,169 (43.85%)	0.322	Gender masculine (%)	133 (61.9)	82 (63.5)	51 (59.3)	No
Woman	162,088 (49.83%)	15,585 (56.15%)		Caucasian Ethnicity (%)	188 (87.4)	111 (86.0)	77 (89.5)	No
Essential occupation (%)	221 (40.11%)	407 (20.21%)	0.002	Retirement home (%)	60 (27.9)	23 (17.8)	37 (43.0)	Yes
Non-essential occupation (%)	330 (59.89%)	1,607 (79.79%)	-	**Clinic** Symptoms on hospital admission				
Patients with disease progression (%)	-	729 (18.90%)	-	Shortness of breath (%)	172 (80.0)	100 (77.5)	72 (83.7)	No
Patients without disease progression (%)	-	3,129 (81.10%)	-	Fever (%) Cough (%)	98 (45.6) 122 (56.7)	66 (51.2) 92 (71.3)	32 (37.2) 30 (34.8)	No Yes
Comorbidities (%)	-	1,318 (47.38%)	-	**Risk factors**				
Comorbidities Absence (%)	-	1,464 (52.62%)	-	Weakness (%) Smoking (%)	110 (51.2) 120 (55.8)	41 (37.3) 65 (50.4)	69 (62.7) 55 (63,9)	Yes Yes
Risk factors				Mean Weight Kg (deviation)	78 (67.0–92.0)	84 (71.6–100)	70 (63–84)	Yes

Smoking	46,659 (92.36%)	3,857(7.64%)	-
Obesity	64,472 (92.40%)	5303 (7.60%)	-
Morbidities			
Heart diseases (%)	82,984 (39.74%)	6,769 (40.2%)	-
Cerebrovascular disease (%)	1,658 (0.79%)	178 (1.06%)	-
Diabetes (%)	27,418 (13.13%)	2,400 (14.25%)	-
COPD (%)	8,247 (3.95%)	841 (4.99%)	-
Asthma (%)	-	67 (0.4%)	-
Dyslipidemia (%)	66,675 (31.92%)	4,769 (28.32%)	-
Cancer (%)	21,785 (10.43%)	1,778 (10.56%)	-
Chronic Renal Disease (%)	3 (0.014%)	22 (0.13%)	-
Hypothyroidism (%)	-	13 (0.08%)	-
Medicines' use			
ACEi		1,714 (70.16%)	-
	-		
ARB	-	729 (29.84%)	-

BMI kg/m2 (deviation)	28 (24.0 – 32.0)	29,4 (26.0 – 34.0)	26 (23.0 – 29.0)	No
Comorbidites				
Hypertension (%)	114 (53.0)	62 (48.1)	52 (60.5)	No
Diabetes mellitus (%)	65 (30.2)	42 (32.5)	23 (26.7)	No
Cardiovascular disease (%)	93 (43.3)	43 (33.3)	50 (58.1)	Yes
Ischemic heart disease	53 (24.7)	28 (21.7)	25 (29.1)	No
FH	39 (18.1)	15 (11.6)	24 (27.9)	Yes
Stroke	30 (14.0)	11 (8.5)	19 (22.1)	Yes
CKD (stage 3-5)	42 (19.5)	24 (18.6)	18 (20.9)	No
Breath disease (%)	65 (30.2)	32 (24.8)	33 (38.4)	Yes
Cancer (%)	19 (8.8)	13 (10.1)	6 (7.0)	No
Treatment				
ACEi	54 (25.0)	37 (28.7)	17 (19.8)	No
immunosuppressants	12 (5.6)	6 (4.6)	6 (7.0)	No
Drugs' clinical trials participants	39 (18.1)	27 (20.9)	12 (13.9)	No
Clinical management at the hospital				
Mechanical ventilation (%)	24 (11.2)	12 (9.3)	12 (13.9)	No
Non-invasive ventilation (%)	16 (7.5)	9 (7.0)	7 (5.4)	No
Intubation and Ventilation (%)	8 (3.7)	3 (3.5)	5 (5.8)	No
Patients admitted to hospital (days)	5 (2.0–10.0)	5 (2.0–10.0)	5 (3.0–9.0)	No
Labs				
Hemoglobin (g/L)	133 (120.0–146.0)	134 (122.0–148.0)	129 (118.0–143.0)	No

					Neutrophils (× 109/L)	6 (4.0 – 9.0)	6 (4.0 – 8.0)	7 (4.0 – 9.0)	Yes
					Lymphocytes (× 109/L)	0.9 (0.6 – 1.3)	0.9 (0.6 – 1.4)	0.8 (0.5 – 1.2)	Yes
					New lymphopenia	85 (39.5)	49 (37.9)	36 (41.9)	No
					Neutrophil: Relation of lymphocytes	7 (4.0 – 13.0)	6 (4.0 – 11.0)	9 (5.0 – 18.0)	Yes
					Platelet count (× 109/L)	217 (161.0–270.0)	223 (162.0–270.0)	210 (155.0–265.0)	No
					Albumin (g/L)	30 (27.0 - 34.0)	31 (28.0 - 35.0)	29 (26.0 - 32.0)	Yes
					Bilirubin (umol/L)	12 (8.0–17.0)	12 (8.0–18.0)	11 (8.0–16.0)	No
					Alanine transaminase (U/L)	27 (18.0–45.0)	28 (18.0–48.0)	27 (19.0–39.0)	No
					Alkaline Phosphatase (U/L)	81 (63.0–109.0)	79 (62.0–107.0)	85 (65.0–109.0)	No
					C-reactive protein (mg/L)	107 (56.0 - 177.0)	90 (41.0 - 164.0)	123 (72.0 - 189.0)	Yes
					D-Dimer (ng/L)	610 (297.0 - 809.0)	559 (412.0 - 748.0)	775 (701.0 - 848.0)	Yes
					GFR (mL/min/1.73m2)	67 (42.0 - 90.0)	77 (56.0 - 90.0)	48,5 (28.0 - 74.0)	Yes
					Acute Kidney Injury	65 (30.2)	25 (19.4)	40 (46.5)	Yes
					Chest X-ray				
					Result suggestive of COVID-19	166 (79.8)	98 (77.8)	68 (82.9)	No
					Bilateral Infiltrators	117 (56.2)	67 (53.2)	50 (61.0)	No
					Unilateral Consolidation	48 (23.1)	31 (24.0)	17 (19.8)	No

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[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[38].

However, about 80% of cases are considered mild and do not use specialized services, being assisted by primary services[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[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.[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[32]. This finding is in agreement with the literature[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[46,51-53]. According to Hoong et al.[54] hospitalized obese patients had a 50% higher chance of mortality compared to [non-obese patients, however, the study by Mayer et al.[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[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.[35] and Krishnasamy et al.[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[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[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[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[60]. According to Avelar et al.[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[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.

ACKNOWLEDGMENT

article are responsibility of the authors and do not necessarily reflect the viewpoint of FAPEMIG. It is noted that the funders had no role in study design, data collection and analysis, the decision to publish, or the preparation of the manuscript.

REFERENCES

1.   Moreira RS. Análises de classes latentes dos sintomas relacionados à COVID-19 no Brasil: resultados da PNAD-COVID19. Cadernos de Saúde Pública. 2021;37(1):1–14.

2.   Carvalho ARVS, Cezarotti-Filho ML, Azevedo PCP, Silveira-Filho RN, Barbosa FT, Rocha TJM, et al. Epidemiology, diagnosis, treatment, and future perspectives concerning SARS-COV-2: a review article. Revista da Associação Médica Brasileira. 2020;66(3):370–4.

3.   Stokes EK, Zambrano LD, Anderson KN, Marder EP, Raz KM, el-Burai Felix S, et al. Coronavirus Disease 2019 Case Surveillance — United States, January 22–May 30, 2020. MMWR Morbidity and Mortality Weekly Report. 2020;69(24):759–65.

4.   Costa JA, Silveira JA, Santos SCM, Nogueira PP. Implicações Cardiovasculares em Pacientes Infectados com Covid-19 e a Importância do Isolamento Social para Reduzir a Disseminação da Doença. Arquivos Brasileiros de Cardiologia. 2020;114(5):834–8.

5.   World Health Organization. Regional Office for the Western Pacific. Role of primary care in the COVID-19 response. https://apps.who.int/iris/handle/10665/331921. Licença: CC BY-NC-SA 3.0 IGO 2021.

6.   Chinnadurai R, Ogedengbe O, Agarwal P, Money-Coomes S, Abdurrahman AZ, Mohammed S, et al. Older age and frailty are the chief predictors of mortality in COVID-19 patients admitted to an acute medical unit in a secondary care setting- a cohort study. BMC Geriatrics. 2020;20(1):409.

7.   Mendes EV. As redes de atenção à saúde. Ciência & Saúde Coletiva. 2010;15(5):2297–305.

8.   Cruz-Cazarim ELC, Azevedo PS, Cordeiro AP, Araújo MS, Silva DS, Landim MJN, et al. Systematic Review Protocol: Main Clinical Variables for the COVID-19 Patients' Management at the Comprehensive Health Care in Brazil. CPQ Medicine. 2021;11(6):1–18.

9.   Zhu L, Wang J, Huang R, Liu L, Zhao H, Wu C, Zhu C. Clinical characteristics of a case series of children with coronavirus disease 2019. Pediatric Pulmonology. 2020;55(6):1430-2.

10.   Zhu J, Chen C, Shi R, Li B. Correlations of CT scan with high-sensitivity C-reactive protein and D-dimer in patients with coronavirus disease 2019. Pakistan Journal of Medical Sciences. 2020;36(6):1397-1401.

11.   Zhou Y, Zheng Y, Yang Q, Hu L, Liao J, Li X. Cohort study of chest CT and clinical changes in 29 patients with coronavirus disease 2019 (COVID-19). European Radiology. 2020;30(11):6213-20.

12.   Zhao W, He L, Tang H, Xie X, Tang L, Liu J. The relationship between chest imaging findings and the viral load of COVID-19. Frontiers in Medicine. 2020;7:558539.

13.   Xi X, Guo Y, Zhu M, Wei Y, Li G, Du B, Wang Y. Higher expression of monocyte chemotactic protein 1 in mild COVID-19 patients might be correlated with inhibition of Type 1 INF signaling. Virology Journal. 2021;18(1):12.

14.   Wu WS, Li YG, Wei ZF, Zhou PH, Lyu LK, Zhang GP, Zhao Y, He HY, Li XY, Gao L, Zhang XM, Liu H, Zhou N, Guo Y, Zhang XM, Zhang D, Liu J, Zhang Y. Investigation and analysis on characteristics of a cluster of COVID-19 associated with exposure in a department store in Tianjin. Zhonghua Liu Xing Bing Xue Za Zhi. 2020;41(4):489-93.

15.   Tian M, Li H, Yan T, Dai Y, Dong L, Wei H, Song X, Dong J, Cheng F, Li W. Clinical features of patients undergoing hemodialysis with COVID-19. Seminars in Dialysis. 2020;34(1):57-65.

16.   Singh S, Khan A. Clinical characteristics and outcomes of coronavirus disease 2019 among patients with preexisting liver disease in the United States: a multicenter research network study. Gastroenterology. 2020;159(2):768-71.

17.   Mahajan NN, Mathe A, Patokar GA, Bahirat S, Lokhande PD, Rakh V, Gajbhiye R, Rathi S, Tilve A, Mahajan K, Mohite SC. Prevalence and clinical presentation of COVID-19 among healthcare workers at a dedicated hospital in India. The Journal of the Association of Physicians of India. 2020;68(12):16-21.

18.   Liu W, Liu Y, Xu Z, Jiang T, Kang Y, Zhu G, Chen Z. Clinical characteristics and predictors of the duration of SARS-CoV-2 viral shedding in 140 healthcare workers. Journal of Internal Medicine. 2020;288(6):725-36.

19.   Li J, Long X, Zhang Q, Fang X, Li N, Lin Z, Li J, Xiong N. Mild manifestations of COVID-19 in healthcare workers. Plos Neglected Tropical Disease. 2020;14(12):e0008950.

20.   Lechien JR, Chiesa-Estomba CM, Place S, Laethem YV, Cabaraux P. Mat Q, Huet K, Plzak J, Horoi M, Hans S, Barillari MR, et al. COVID-19 Task Force of Yo-IFOS. Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus disease 2019. Journal of Internal Medicine. 2020;288(3):335-44.

21.   Lechien JR, Chiesa-Estomba CM, Siati DRD, Horoi M, Bon SDL, Rodriguez A, Dequanter D, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. European Archives of Oto-Rhino-Laryngology. 2020;277(8):2251-61.

22.   Krajcar N, Stemberger Maric L; Surina A, Kurecic Filipovic S, Trkulja V, Roglic S, Tesovic G. Epidemiological and clinical features of Croatian children and adolescents with a PCR-confirmed coronavirus disease 2019: differences between the first and second epidemic wave. Croatian Medical Journal. 2020;61(6): 491-500.

23.   Kong W, Wang Y, Hu J, Chughtai A, Pu H, Clinical Research Collaborative Group of Sichuan Provincial People's Hospital. Travel Medicine and Infectious Diseases. 2020;37:101754.

24.   Kalicinska E, Szymczak D, Andrasiak I, Bogucka-Fedorczuk A, Zinczuk A, Szymanski W, Biernat M, Rymko M, et al. Lymphocyte subsets in haematological patients with COVID-19: multicenter prospective study. Translational Oncology. 2021;14(1):100943.

25.   Cao C, Chen M, He L, Xie J, Chen X. Clinical features and outcomes of COVID-19 patients with gastrointestinal symptoms. Critical Care. 2020;24(1):340.

26.   Caneppele AH, Cucolo DF, Mininel VA, Meireles E, Silva JAM. Colaboração interprofissional em equipes da rede de urgência e emergência na pandemia da COVID-19. Escola Anna Nery Revista de Enfermagem. 2020;24(spe):e20200312.

27.   Herrmann J, Adam EH, Notz Q, Helmer P, Sonntangbauer M, Ungemach-Papenberg P, Sanns A, Zausig Y, Steinfeldt T, Torje I, et al. Covid-19 induced acute respiratory distress syndrome – a multicenter observational study. Frontiers in Medicine. 2020;18(7):599533.

28.   Passos R, Cardoso F, Alves D, Romano M, Silva F, Braga J, et al. High flow oxygen therapy in the ICU-a secondary care center experience. Intensive Care Medicine Experimental. 2020;8(Suppl 2):73.

29.   Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. 1998;52:377–84.

30.   Pegano M, Gauvreau K. Princípios da Bioestatística. 2nd ed. Learning C, editor. São Paulo; 2012.

31.   Landis JR, Koch GG. The Measurement of Observer Agreement for Categorical Data. Biometrics. 1977;33(1):159.

32.   Mayer MA, Vidal-Alaball J, Puigdellívol-Sánchez A, Marín Gomez FX, Leis A, Mendioroz Peña J. Clinical Characterization of Patients With COVID-19 in Primary Care in Catalonia: Retrospective Observational Study. JMIR Public Health and Surveillance. 2021;7(2):e25452.

33.   Krishnasamy N, Natarajan M, Ramachandran A, Vivian Thangaraj JW, Etherajan T, Rengarajan J, et al. Clinical Outcomes among Asymptomatic or Mildly Symptomatic COVID-19 Patients in an Isolation Facility in Chennai, India. The American Journal of Tropical Medicine and Hygiene. 2021;104(1):85–90.

34. Leal FE, Mendes-Correa MC, Buss LF, Costa SF, Bizario JCS, Souza SRP, Thomaz O, Tozetto-Mendoza TR, Villas-Boas LS, et al. Clinical features and natural history of the first 2073 suspected COVID-19 cases in the Corona São Caetano primary care programme: a prospective cohort study. BMJ Open. 2021;11(1):e042745.

35. Lee Y-H, Hong CM, Kim DH, Lee TH, Lee J. Clinical Course of Asymptomatic and Mildly Symptomatic Patients with Coronavirus Disease Admitted to Community Treatment Centers, South Korea. Emerging Infectious Diseases. 2020;26(10):2346–52.

36. Alsofayan YM, Althunayyan SM, Khan AA, Hakawi AM, Assiri AM. Clinical characteristics of COVID-19 in Saudi Arabia: a national retrospective study. Journal of Infection and Public Health. 2020;13(7):920-5.

37. Farias LABG, Colares MP, Barreto FKA, Cavalcanti LPG. O papel da atenção primária no combate ao Covid-19. Revista Brasileira de Medicina de Família e Comunidade. 2020;15(42):2455.

38. Cabral ERM, Melo MC, Cesar ID, Oliveira REM, Bastos TF, et al. Contribuições e desafios da Atenção Primária à Saúde frente à pandemia de COVID-19. InterAmerican Journal of Medicine and Health. 2020;3:1–12.

39. Avelar FG, Emmerick ICM, Muzy J, Campos MR. Complications of Covid-19: developments for the Unified Health System. Physis: Revista de Saúde Coletiva. 2021;31(1).

40. Rodrigues R, Jardim Mendonça Cardinali D. A COVID-19 na Atenção Primária à Saúde: mais um desafio. Health Residencies Journal - HRJ. 2021;2(9):3–10.

41. Hussain A, Bhowmik B, Moreira NCV. COVID-19 and diabetes: Knowledge in progress. Diabetes Research and Clinical Practice. 2020;162:108142.

42. Zhang J, Dong X, Cao Y, Yuan Y, Yang Y, Yan Y, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020;75(7):1730–41.

43. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. The Lancet Respiratory Medicine. 2020;8(5):475–81.

44. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet. 2020;395(10229):1054–62.

45. Guo L, Shi Z, Zhang Y, Wang C, do Vale Moreira NC, Zuo H, et al. Comorbid diabetes and the risk of disease severity or death among 8807 COVID-19 patients in China: A meta-analysis. Diabetes Research and Clinical Practice. 2020;166:108346.

46. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ. 2020;369:m1966.

47. Rossi-Neto JM, Drager LF, Maia LN. Fatores de risco cardiovascular e a COVID-19 cardiovascular risk factors and COVID-19. Revista da Sociedade de Cardiologia do Estado de São Paulo. 2020;30(4):444–52.

48. Simonnet A, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A, et al. High Prevalence of Obesity in Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) Requiring Invasive Mechanical Ventilation. Obesity. 2020;28(7):1195–9.

49. Fadini GP, Morieri ML, Longato E, Avogaro A. Prevalence and impact of diabetes among people infected with SARS-CoV-2. Journal of Endocrinological Investigation. 2020;43(6):867–9.

50. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China. JAMA. 2020;323(13):1239.

51.   Schmidt FM, Weschenfelder J, Sander C, Minkwitz J, Thormann J, Chittka T, et al. Inflammatory Cytokines in General and Central Obesity and Modulating Effects of Physical Activity. PlosOne. 2015;10(3):e0121971.

52.   Petrakis D, Margină D, Tsarouhas K, Tekos F, Stan M, Nikitovic D, et al. Obesity a risk factor for increased COVID 19 prevalence, severity and lethality (Review). Molecular Medicine Reports. 2020;22(1):9–19.

53.   Ryan DH, Ravussin E, Heymsfield S. COVID 19 and the Patient with Obesity – The Editors Speak Out. Obesity. 2020;28(5):847–847.

54.   Hoong CWS, Hussain I, Aravamudan VM, Phyu EE, Lin JHX, Koh H. Obesity is Associated with Poor Covid-19 Outcomes: A Systematic Review and Meta-Analysis. Hormone and Metabolic Research. 2021;53(02):85–93.

55.   Patanavanich R, Glantz SA. Smoking Is Associated With COVID-19 Progression: A Meta-analysis. Nicotine & Tobacco Research. 2020;22(9):1653–6.

56.   Grant MC, Geoghegan L, Arbyn M, Mohammed Z, McGuinness L, Clarke EL, et al. The prevalence of symptoms in 24,410 adults infected by the novel coronavirus (SARS-CoV-2; COVID-19): A systematic review and meta-analysis of 148 studies from 9 countries. PlosOne. 2020;15(6):e0234765.

57.   Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. New England Journal of Medicine. 2020;382(18):1708–20.

58.   Sun J, Aghemo A, Forner A, Valenti L. COVID-19 and liver disease. Liver International. 2020;40(6):1278–81.

59.   Zhang C, Shi L, Wang F-S. Liver injury in COVID-19: management and challenges. The Lancet Gastroenterology & Hepatology. 2020;5(5):428–30.

60.   Castro CS, Holzgrefe-Júnior JV, Reis RB, Andrade BB, Quintanilha LF. Pandemia da COVID-19: cenário do sistema de saúde brasileiro para o enfrentamento da crise. Research, Society and Development. 2020;9(7):e516974383.

61.   Campos MR, Schramm JMA, Emmerick ICM, Rodrigues JM, Avelar FG, Pimentel TG. Carga de doença da COVID-19 e de suas complicações agudas e crônicas: reflexões sobre a mensuração (DALY) e perspectivas no Sistema Único de Saúde. Cadernos de Saúde Pública. 2020;36(11).