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Influence of risk factors on mortality by COVID-19

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Summary

Introduction: The main risk factors studied that influence COVID-19 mortality have so far been inconclusive in the world literature, mainly in relation to the male sex.
Objective: to determine the main risk factors influencing increased mortality from COVID-19.
Material and methods: A case-control study was conducted, including 1190 patients with positive CRP-RT. The risk factors studied were: sex, age, presence of systemic arterial hypertension (SAH), diabetes mellitus (DM), obesity, chronic obstructive pulmonary disease (COPD), asthma, smoking, patients taking immunosuppressants, human immunodeficiency virus (HIV) carriers and influenza vaccination. In the case group they died from COVID-19 (*n* = 576), while in the control group they survived (*n* = 614). The statistical plan included cross-tabulations and multivariate logistic regression modelling to determine the influence of these risk factors on COVID-19 mortality.
Results: we found no statistically significant differences between cases and controls in relation to sex. However, cases presented: age > 60 years, HAS, DM and obesity, compared to controls. **Conclusions:** male sex was not a risk factor for COVID-19 mortality; however, other risk factors such as age over 60 years, hypertension, diabetes and obesity were corroborated as risk factors for increased mortality from COVID-19.

Abstract

Background: The main risk factors studied that have an influence on mortality from COVID-19 have so far been inconclusive in the world literature, mainly in relation to the male gender.
Objective: To determine which are the main risk factors that influence a higher mortality from COVID-19.
Material and methods: A case-control study was conducted, including 1190 patients with positive RT-PCR. The risk factors studied were: gender, age, systemic arterial hyper- tension (SAH), Diabetes mellitus (DM), obesity, Chronic Obstructive Pulmonary Disease (COPD), asthma, smoking, im- munosuppressants, Human Immunodeficiency Virus (HIV), influenza vaccine. In the Group of Cases: they died from CO- VID-19 (*n* = 576), while in the Controls group: they survived (*n* = 614). The statistical plan included cross-tables and mul- tivariate logistic regression model to determine the influence of these risk factors on mortality from COVID-19.
Results: We found no statistically significant differences between cases and controls in relation to gender. However, the cases were aged >60 years, SAH, DM, obesity compared to controls.
Conclusions: Male gender was not a risk factor for mortality from COVID-19, however, other risk factors such as age over 60 years, being hypertensive, diabetic and obese, were corroborated as such for a higher mortality from COVID-19.

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Introduction

In December 2019, a group of patients with viral neumony were confirmed to be infected with a new coronavirus in Wuhan, China.[1] It was named *Severe Acute Respiratory Syndrome Severe Coronavirus Type 2* (SARS-CoV-2), producing coronavirus disease (COVID-19).[1,2] On 11 March 2020, the World Health Organization (WHO) declared a COVID-19 pandemic.[2]

The WHO has emphasised that one of the most important concerns about COVID-19 is to identify risk factors, severity and mortality,[3] because it has been observed that communicable diseases do not affect all members of our society equally.[4] Most cases of COVID-19 are mild and moderate, however 14% are severe and 5% are critical.[5] The mortality rate in patients with COVID-19 was 5% in Wuhan, close to the global percentage (4.2%),[6] however, in Mexico this percentage has been higher.

According to the number of comorbidities that each patient with COVID-19 has, the prognosis could be determined.[7] The main risk factors studied worldwide and associated with greater mortality are: age,[8,9,10,11,12,13,14] sex,[1,2,5,6,15] presence of systemic arterial hypertension (HAS),[16,17] diabetes mellitus (DM)[8,9,10,11,12,13,14,15,16,17,18,19,20] and obesity.[21] The combination of DM- HAS is common,[22] however, there are other comorbidities such as smoking,9 as well as the presence of human immunodeficiency virus (HIV),[23] immunosuppression[24] and previous influenza vaccination,[25] for which the risk factor for increased mortality from COVID-19 has not yet been defined.

Given these inconclusive results, the purpose of the present study was to determine which risk factors have the greatest influence on COVID-19 mortality in a concentration hospital in the city of Puebla, Mexico.

Material and methods

Case-control study, conducted at the Hospital General de Zona No. 20 of the Instituto Mexicano del Seguro Social, in Puebla City, Mexico. The study was authorised by the Local Research and Ethics Committees with national registration number: R-2021-2108-001. To define the total number of patients to be studied, both for the case and control groups, the database of the National Epidemiological Surveillance System (SINO) was accessed.

LAVE), obtaining the information contained therein, taking into account the selection criteria: hospitalised patients, of any age, of either sex, with a positive result for SARS-CoV-2 by PCR-RT test and who had a discharge diagnosis, either death (case group) or improvement (control group), excluding those patients who were transferred to another hospital, from 1 March to 2 November 2020. The sample was not randomised, as all patients seen by COVID-19 were included. A total of 1190 patients admitted to the hospital during the aforementioned time period were divided into two groups: group 1 (cases) consisted of 576 patients who died of COVID-19, and group 2 (controls) consisted of 614 patients who discharged due to improvement. The variables studied were the same as those recorded in the SINOLAVE platform and identified as risk factors: sex, age, HAS, DM, obesity, COPD, asthma, smoking, immunosuppressant intake, presence of HIV and influenza vaccination. Matching between the two groups was by age, controls were matched to case age ± 5 years. Cross-tabulations were performed to obtain the *odds ratio* (OR) with 95% confidence interval (95%CI), multivariable logistic regression analysis was used to determine the association between sex, age, HAS, DM, obesity, COPD, asthma, smoking, immunosuppressant intake, HIV, influenza vaccination and COVID-19 mortality. A *p-value* of less than 0.05 was statistically significant. Data were processed in IBM SPSS Statistics for Windows, version 23.0.

Results

The sample consisted of 1190 patients, which were divided into: group 1 (cases) 576 patients and group 2 (con- troles) 614 patients. The mean age was 57 years (SD ± 15.6), with a range from 6 to 96 years of age. A total of 704 patients were male (representing 59.1%); with HSA, 795 patients (66.8%); with DM, 398 patients (66.8%); and with DM, 398 patients (66.8%).
patients (33.4%); with obesity, 264 patients (22.1%);
with COPD, 48 patients (4%); with smoking, 48 patients (4%); patients taking immunosuppressants,
42 (3.5%); patients with a history of asthma, 12 patients (1%); HIV carriers, 9 patients (0.7%); and 14 patients with influenza vaccination (1.1%) (tables I and II).

We found that of the 11 risk factors we included in our study, only 4 were statistically significant and increase the odds of dying from COVID-19 when we calculated their OR 95%CI, which are: age > 60 years (57.9 vs. 31.4%; OR: 2.07.), age > 60 years (57.9% vs. 31.4%; OR: 2.07.) and age > 60 years (57.9% vs. 31.4%; OR: 2.07.),

Table I Clinical characteristics studied of the patients admitted to the study

Variable	Cases		Controls		*N* = 1190	
	n	%	*n*	%	*n*	%
Male sex	345	59.8	359	58.4	704	59.1
Age (> 60 years)	334	57.9	193	31.4	527	44.2
HAS	442	76.7	353	57.4	795	66.8
DM	222	38.5	176	28.6	398	33.4
Obesity	143	24.8	121	19.7	264	22.1
COPD	23	3.9	25	4	48	4
Asthma	6	1	6	0.9	12	1
Smoking	24	4.1	24	3.9	48	4
Immunosuppressant intake	25	4.3	17	2.7	42	3.5
HIV	3	0.5	6	0.9	9	0.7
Influenza vaccine	5	0.8	9	1.4	14	1.1

HAS: systemic arterial hypertension; DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease; HIV: human immunodeficiency virus; HIV: human immunodeficiency virus.

Table II Variables studied between case and control groups

Variable	Cases *n* = 576		95%CI (LI-LS)	Controls *n* = 614		95%CI (LI-LS)	p*
	n	%		*n*	%		
Male sex	345	59.8	0.72-1.58	359	58.4	0.67-1.36	0.362
Age (> 60 years)	334	57.9	1.54-1.95	193	31.4	0.50-0.65	0.000
HAS	442	76.7	1.29-1.39	353	57.4	1.52-1.59	0.000
DM	222	38.5	1.41-1.48	176	28.6	1.51-1.61	0.000
Obesity	143	24.8	1.44-1.50	121	19.7	1.48-1.60	0.034
COPD	23	3.9	1.46-1.51	25	4	1.33-1.66	0.945
Asthma	6	1	1.46-1.51	6	0.9	1.17-1.83	0.911
Smoking	24	4.1	1.45-1.51	24	3.9	1.35-1.65	0.821
Immunosuppressant intake	25	4.3	1.45-1.51	17	2.7	1.44-1.75	0.142
HIV	3	0.5	1.46-1.51	6	0.9	0.95-1.72	0.364
Influenza vaccine	5	0.8	1.46-1.51	9	1.4	1.07-1.64	0.339

CI95%, 95% confidence interval; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HIV, human immunodeficiency virus; HAS, systemic arterial hypertension; LL, lower limit; UL, upper limit; LL, lower limit; HIV, human immunodeficiency virus; SD, SDI, SDI, SDI, SDI, SDI, SDI, SDI, SDI, SDI, SDI, SDI, SDI, SDI.
**P* < 0.05 was considered statistically significant.

95%CI: 1.80-2.39, *p* = 0.000), HAS (76.7 vs 57.4%; OR: 2.43, 95%CI: 1.89-3.13, *p* = 0.000), MD (38.5 vs. to 28.6%; OR: 1.56, 95% CI: 1.22-1.98, *p* = 0.000) and obesity (24.8 vs. 19.7%; OR: 1.34, 95%CI: 1.02-1.77), *p* = 0.000). Also, being male (59.8 vs. 58.4%; OR: 1.06, 95%CI: 0.84-1.33, *p* = 0.617), being a patient (59.8 vs. 58.4%; OR: 1.06, 95%CI: 0.84-1.33, *p* = 0.617), being a COPD (3.9 vs. 4%; OR: 0.98, 95%CI: 0.55-1.74, *p* = 0.945), asthma (1 vs. 0.9%; OR: 1.06, 95% CI: 0.34-3.32, *p* = 0.911), having a history of smoking (4.1 vs. 3.9%; OR: 1.06, 95%CI: 0.60-1.90, *p* = 0.821), immunosuppressant intake (4.3 vs 2.7%; OR: 1.59, 95%CI: 0.85-2.98, *p* = 0.142), HIV carriers (0.5 vs.

to 0.9%; OR: 0.53, 95%CI: 0.13-2.13, p = 0.364) and vaccine

The results of the study (0.8 vs. 1.4%; OR: 0.58, 95%CI: 0.19-1.76; p = 0.339) (table III), were not statistically significant in increasing the odds of death from COVID-19, and therefore, according to this study, should not be considered as risk factors.

Discussion

In our study, we analysed the risk factors that have the greatest influence on mortality in patients with a high risk of death.

Table III *Odds ratio* of the variables studied by univariate analysis (Chi-square)

Variable	OR	95%CI (LI-LS)	p*
Male sex	1.06	0.84-1.33	0.617
Age (> 60 years)	2.07	1.80-2.39	0.000
HAS	2.43	1.89-3.13	0.000
DM	1.56	1.22-1.98	0.000
Obesity	1.34	1.02-1.77	0.034
COPD	0.98	0.55-1.74	0.945
Asthma	1.06	0.34-3.32	0.911
Smoking	1.06	0.60-1.90	0.821
Immunosuppressant intake	1.59	0.85-2.98	0.145
HIV	0.53	0.13-2.13	0.372
Influenza vaccine	0.58	0.19-1.76	0.345

COPD, chronic obstructive pulmonary disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HAS, systemic arterial hypertension; CI95%, 95% confidence interval; HIV, human immunodeficiency virus; LI, lower limit; OR, *Odds ratio;* UL, upper limit; OR, Odds *Ratio.*

**P* < 0.05 was considered statistically significant.

tes with COVID-19. We observed that people of all ages are susceptible to death from SARS-CoV-2 infection. Children have a variety of virus-specific memory T-cells due to frequent exposure to a variety of viruses in childhood, and it is possible that this may cross-react after SARS-CoV-2 infection. In addition, the immune system of children is still developing and inadequate immune defence may prevent excessive immune damage to the host.[26] In our study, people over 60 years of age are part of the age group with the highest mortality from COVID-19, which is in line with the findings of Sousa *et al*, who found that this risk group is 3.7 times more likely to die from COVID-19 than those under this age.[11] The possible explanation for this is based on immunosenescence,[12] as patients over 60 years of age experience age-dependent defects in T- and B-lymphocyte function, as well as a decrease in cell-mediated immune function, which reduces the function of humoral immunity. On the other hand, increased production of type 2 cytokines may weaken the control of viral replication and prolong the proinflammatory response and lead to worse outcomes, according to other findings.[2,11] COVID-19-associated mortality is influenced by age.[12,13,14,16]

Several authors agree that a risk factor for severity and mortality from COVID-19 is being of the male sex.[1,5,10] This situation may be explained by the lower sensitivity of women to viral infections, because the X chromosome and female sex hormones play an important role in innate and adaptive immunity, acting as protective factors.[21] However, in our study being male was not associated with an increased risk of COVID-19 mortality.

HAS has been defined as one of the comorbidities associated with increased mortality from COVID-19,[20] similar to the findings of our study, as we observed that people with a history of HAS have a higher risk of dying from COVID-19 than patients without this pathology. In order to understand the role of HAS as a risk factor associated with high COVID-19 mortality, the pathophysiology of SARS-CoV-2 infection must be analysed. This virus infects respiratory epithelial cells by binding to angiotensin-converting enzyme 2 (ACE2) receptors. In the human body, ACE2 levels are known to be higher in the heart, kidney, intestinal tract, gall bladder, adipose tissue and testes than in the lung, leading to increased cytokine release and hyperinflammatory state, leading to multi-organ failure.[12,21] For this reason, COVID-19 may worsen pre-existing chronic inflammatory conditions such as HAS,[12] which may explain the high prevalence of severe COVID-19 in patients with this comorbidity.[6] However, our findings differ from those of Smith in the United States,[18] and Grasselli in Italy,[16] who in 2020 did not find that HAS could be a risk factor associated with increased mortality. In contrast, we agree with these same authors that DM is another risk factor influencing increased mortality from COVID-19. DM is the most consistent comorbidity for predicting disease severity and has been linked to other viral respiratory diseases. Rod *et al*.[3] mention that this condition may be attributable to impaired innate immunity, the function of which would serve as the first line of defence against SARS-CoV-2.[2] From

According to our research, the risk of mortality in people with DM was higher when compared to patients without this condition, in contrast to Sousa *et al.* who showed that the risk of mortality in people with DM was lower.[11] In our study, obesity was presented as another of the risk factors associated with mortality in patients with COVID-19. Patients with high body mass index are more likely to develop severe pneumonia and are associated with elevated ACE2 expression in adipose tissue, which is higher in obese patients,[21] which is similar to the findings of Palaiodimos *et al.* who concluded that obesity was associated with higher in-hospital mortality.

There is evidence that patients with a history of chronic respiratory diseases are at increased risk of death from COVID-19.[3,15] In this study we analysed asthma and COPD, finding no differences between cases and controls. Our findings are contradictory to those of other reports, which concluded that asthma and COPD are risk factors for increased mortality from COVID-19.[19] In our study, this may be due to the low number of patients included with these pathologies.

Smoking was not associated with increased mortality, similar to that identified by other authors,[9] but which differs from the results of Alqahtani *et al.* who identified smoking as a risk factor.[27]

In this study, patients with asthma and COPD, those living with HIV, as well as those taking immunosuppressants and patients without vaccination against influenza were not associated with higher mortality due to COVID-19, perhaps due to the low number of patients included, which did not allow these variables to be adequately assessed. However, our findings are consistent with those of other authors who concluded that HIV-positive patients with an adequate CD4 lymphocyte count do not have a worse prognosis than those without the disease.[23] Likewise, influenza vaccination was not associated with an increased risk of death, probably because the vaccine stimulates the immune system, leading to early activation to counteract SARS-CoV-2, specifically mediated by Toll-like receptor 7.[25] Comorbidities such as having HAS, DM and being obese, as well as being older than 60 years, are the best defined risk factors that increase the chances of death from COVID-19. The rest of the factors studied in the The results were not statistically significant in the different studies around the world, such as being male, having COPD, asthma, smoking, taking immunosuppressants, living with HIV and not being vaccinated against influenza, and did not represent statistically significant results.

The main limitations of our research were: the total number of patients studied, as there are series with a much larger number of study subjects, which contributes to the results being more reliable; another limitation of our study was that in some of the comorbidities we included we obtained a very low number of patients, which may have contributed to the results we presented being discordant with those of the literature consulted, this being the main bias of our study; We also failed to take into account other possible confounding factors (the time of evolution of the disease, the degree of severity of the disease on arrival at the hospital, the treatment received previously, as well as the time of delay in treatment, etc.), variables that have been taken into account.), variables that have been taken into account in other studies.

Conclusions

We conclude that being male is not a risk factor for COVID-19 mortality; however, the other risk factors studied, such as HAS, DM and obesity, were corroborated as risk factors for increased COVID-19 mortality. Other factors that we included in our study, such as COPD, asthma, smoking, immunosuppressant intake, living with HIV and influenza vaccination, were not statistically significant enough to be considered risk factors for increased COVID-19 mortality, perhaps due to the small number of patients included in this study with such characteristics. Larger studies including these clinical characteristics, mainly being male, may be needed to determine their actual influence on COVID-19 mortality.

Declaration of conflict of interest: the authors have completed and submitted the International Committee of Medical Journal Editors' declaration of potential conflicts of interest, and no conflicts of interest were reported in relation to this article.

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