Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Hypertension, Diabetes and Obesity, Major Risk Factors for Death in Patients with COVID-19 in Mexico

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Background. Mexico has reported high death and case fatality rates due to COVID-19. Several comorbidities have been related to mortality in COVID-19, as hypertension, diabetes, coronary heart disease, chronic obstructive lung disease and chronic kidney disease.

Aims. To describe the main clinical characteristics of COVID-19 in the major social security institution in Mexico, as well as the contribution of chronic comorbidities and the population attributable fraction related to them.

Methods. Data for all patients with a positive test for SARS-CoV-2 in the institutional database was included for analysis. Demographic information, the presence of pneumonia and whether the patient was hospitalized or treated at home as an outpatient as well as comorbidities were analyzed. Case fatality rate was estimated for different groups. Odds ratios with 95% confidence intervals from a logistic regression model were estimated, as well as the population attributable fraction.

Results. By November 13, 2020, 323,671 subjects with COVID-19 infection have been identified. Case fatality rate is higher in males (20.2%), than in females (13.0%), and increases with age. Case fatality rate increased with the presence of obesity, hypertension and/or diabetes. Age and sex were major independent risk factors for mortality, as well as the presence of pneumonia, diabetes, hypertension, obesity, immunosuppression, and end-stage kidney disease. The population attributable fraction due to obesity in outpatients was 16.8%.

Conclusions. Major cardiovascular risk factors and other comorbidities increase the risk of dying in patients with COVID-19. Identification of populations with high fatality in COVID-19, provides insight to deal with this pandemic by health services in Mexico.

Key Words: COVID-19, Diabetes mellitus type 2, Fatality, Hypertension, Obesity, Risk factors.

Introduction

Mexico has reported high death and case fatality rates due to coronavirus disease 2019 (COVID-19). Since the beginning of the epidemic on February 27, 2020, 997,393 cases have been reported, with over 96,624 deaths by November 14, 2020 (1,2).

From the genesis of the pandemic in China, several comorbidities have been related to mortality in COVID-19, as hypertension, diabetes, coronary heart disease, chronic obstructive lung disease and chronic kidney disease (3). This pattern has been also observed in other affected countries, as Italy (4), the United States (5,6) or the United Kingdom (7), among others. Fatal cases of COVID-19 are closely related to renin-angiotensin-aldosterone system

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imbalance an hyperinflammation (8). Hypertension, cardiovascular disease, and diabetes are associated with reduced baseline levels of angiotensin-converting enzyme 2 (ACE2) expression (8), while ACE 2 may protect against lung injury in infection (9). Obesity, hypertension, cardiovascular disease and diabetes are inflammatory diseases (10,11) that during COVID-19 infection may lead to a dysregulated immune response (12), promoting hyperinflammation, with subsequent endothelial cell activation and endothelial dysfunction, that may enhance a prothrombotic state (8).

While diabetes and extreme obesity (13−15), as well as cardiovascular diseases when there is myocardial injury, (16) seem to be commonly identified as risk factor for severe disease and death in COVID-19 infection, hypertension may not be a common feature as a risk factor for severity (13,17), and the need to assess its contribution in the severity and mortality of the infection, has been highlighted in a recent analysis of 17 million patients (17).

Given that the scientific community is struggling to cope with the burden of this new disease, the authors aimed to describe the main clinical characteristics of COVID-19 in the major social security institution in Mexico, as well as the contribution of chronic comorbidities that are frequent in the Mexican population estimating the population attributable fraction, to increase the knowledge of the occurrence of this disease in different countries.

Methods

The Mexican Social Security Institute (IMSS) is the country's major social security institution, covering nearly half of Mexico's population. IMSS covers over 70 million Mexicans and provided health care in 1,515 family medical units (first level of health care), 248 hospitals (second level of health care) and 36 hospitals in 10 National Medical Centers (third level of health care).

Each health care unit or hospital is covered by an epidemiologist, that registers and validates detailed information of major health problems included in the Epidemiologic Surveillance System at IMSS. Information regarding COVID-19 has been captured since the beginning of the epidemic in an electronic health record database. This information is sent to feed the national database on patients with a suspect, negative and definitive diagnosis of COVID-19, that manages the Directorate of Epidemiology of the Mexican Ministry of Health.

This analysis includes patients with a positive test for SARS-CoV-2 infection by real-time reverse transcription polymerase chain reaction. Only certified laboratories by the National Institute of Epidemiological Diagnosis and Reference of the Mexican Ministry of Health can test for diagnosis of COVID-19. Since October 7 case definition of COVID-19 changed. In spite of those patients with a positive reverse transcription-polymerase chain reaction, COVID-19 was also considered in patients with a clinical-epidemiological relation compatible with SARS-CoV-2 infection, as well as those deaths that sample test was not available or was not suitable for analysis, but clinical characteristics that led to death, were compatible with COVID-19. We analyzed data for the IMSS by reviewing the institutional database.

Information regarding age, sex, residence, and smoking status was retrieved. So was analyzed data on the presence of pneumonia and whether the patient was hospitalized or treated at home as an outpatient. Comorbidities were registered by self-report, and included hypertension, diabetes, obesity chronic obstructive pulmonary disease (COPD), cardiovascular disease (CVD), immunosuppression, asthma, and end-stage kidney disease (ESKD). Since obesity, diabetes and hypertension were the most frequent comorbidities, subjects were classified according to the absence of any of these three diseases, the independent presence of each of them and the simultaneous occurrence of two or all of them, in a single variable. Death was certified and registered for inpatients and outpatients.

Statistical Analysis

We analyzed data from the first reported cases (at the end of February and early days of March) to November 13, 2020. Data are presented as frequencies and percentages. Case fatality rate was estimated taking in the numerator the total number of COVID-19 deaths and in the denominator the population with COVID-19. Specific case fatality rates were estimated for each analyzed variable, taking in the numerator the number of COVID-19 deaths in each particular group divided by the population with COVID-19 for each analyzed variable (i.e., age group, sex, comorbidities).

Odds ratios with 95% confidence intervals were estimated for each risk factor related to mortality (i.e. age, sex, comorbidities). To control for potential confounders, and to assess the independent contribution on COVID-19 fatality, a logistic regression model was developed, and the strength of association with the studied risk factors was assessed with odds ratios and 95% confidence intervals (95% CI).

Attributable Fraction

To estimate the population attributable fraction (AFp), we used the Miettinen approach, since Levin's traditional formula fails to hold when RR adjustment is needed, as it was done in this analysis (18). The formula is $AFp = pcRFt = 1 - \{(1 - pc) + pc/RR\}$, where pc is the prevalence of the factor (target condition) among cases of the outcome event and $RFt = (RR-1)/RR = 1 - 1/RR$ is the risk fraction among all subjects with the analyzed risk factor. We estimated the population attributable fraction for diabetes, hypertension, and obesity, in both outpatients

and inpatients. To estimate the population attributable fraction (AF) we used the available estimated diabetes (12.8%) and hypertension (29.3%) prevalence for the population covered by IMSS, (19) and the obesity national prevalence estimate (36.5%) from a national survey of 15′165,621 subjects ≥18 years, randomly selected and assessed at Family Medical Units in 2019.

Results

In the nine months of the epidemic in Mexico, 323,671 subjects with COVID-19 infection have been identified at the Mexican Institute of Social Security (Table 1). While 31.5% of the diagnosed females have been hospitalized, 44.7% of all infected men have been so. More than half of the outpatients with COVID-19 are younger than 40 years, whereas the age distribution is shifted to older ages in hospitalized patients. Case fatality rate is higher in males (20.2%), than in females (13.0%), and increases with age, so that over half of those affected subjects aged 70 or above die (Table 1).

Among outpatients, 16.0% were obese, 13.3% had hypertension and 8.8% had diabetes (Table 2). The frequency of these comorbidities was higher in inpatients. The case fatality rate was higher in those with comorbidities when compared to the absence of them, mainly in outpatients. However, no difference was observed in mortality among those with asthma and those who smoke when compared to those with no asthma or no smoking (Table 2).

Assessing the independent and simultaneous occurrence of obesity, hypertension and/or diabetes, case fatality rate increased with the presence of any of these comorbidities, as well as with the concurrent presence of two or the three of them in a single variable, albeit no interaction was observed. This situation was observed in all age groups, both genders and in hospitalized and outpatients, although it was more evident in outpatients and at younger ages (Table 3).

Hypertension was the more frequent comorbidity associated to COVID-19 in hospitalized patients. Among male outpatients, 13.5% had hypertension, whereas 13.1% of females had a previous diagnosis of hypertension. These figures were 45.2 and 37.0% among inpatients, and the adjusted relative risk in the multivariate model was 1.96 (95% CI 1.60−2.39) in outpatients and 1.32 (95% CI 1.26−1.39) in hospitalized subjects, for hypertension alone. Diabetes and obesity were also commonly seen among patients with COVID-19. The prevalence of diabetes in outpatients was 9.0% in females and 8.6% in males, which increased to 37.2 and 30.3% in hospitalized patients. Regarding obesity, these figures were 16.5% (females) and 15.4% (males) in outpatients, and 25.4% and 19.0 respectively in inpatients.

Table 1. Inpatients and outpatients with COVID-19 infection, deaths and case fatality rate (CFR) according to age and sex

	Outpatients				Inpatients				Total			
	Female		Male		Female		Male		Female		Male	
Age-group (years)	*n* (%)	Deaths (CFR)	*n* (%)	Deaths (CFR)	*n* (%)	Deaths (CFR)	*n* (%)	Deaths (CFR)	*n* (%)	Deaths (CFR)	*n* (%)	Deaths (CFR)
<40	59,590 (56.1)	37 (0.1)	55,168 (57.3)	61 (0.1)	6,619 (13.6)	963 (14.5)	9,789 (13.5)	2,019 (20.6)	66,209 (42.8)	1,000 (1.5)	64,957 (20.1)	2,080 (3.2)
40−49	26,437 (24.9)	69 (0.3)	21,988 (22.8)	125 (0.6)	7,464 (15.3)	1,907 (25.5)	12,528 (17.3)	3,867 (30.9)	33,901 (21.9)	1,976 (5.8)	34,516 (10.7)	3,992 (11.6)
50−59	13,847 (13.0)	101 (0.7)	12,845 (13.3)	240 (1.9)	11,374 (23.4)	4,050 (35.6)	17,272 (23.8)	7,271 (42.1)	25,221 (16.3)	4,151 (16.5)	30,117 (9.3)	7,511 (24.9)
60−69	4,275 (4.0)	130 (3)	4,151 (4.3)	221 (5.3)	11,777 (24.2)	5,797 (49.2)	16,418 (22.6)	9,109 (55.5)	16,052 (10.4)	5,927 (36.9)	20,569 (6.4)	9,330 (45.4)
≥70	2,001 (1.9)	185 (9.2)	2,144 (2.2)	280 (13.1)	11,471 (23.6)	6,950 (60.6)	16,513 (22.8)	10,935 (66.2)	13,472 (8.7)	7,135 (53)	18,657 (5.8)	11,215 (60.1)
Total	106,150 (52.4)	522 (0.5)	96,296 (47.6)	927 (1.0)	48,705 (40.2)	19,667 (40.4)	72,520 (59.8)	33,201 (45.8)	154,855 (47.8)	20,189 (13.0)	168,816 (52.2)	34,128 (20.2)

n (%): Number of subjects in each age and sex group and percentage from the total.
Deaths: number of deaths.
CFR, case fatality rate in percentage.

Table 2. In-patients and out-patients with COVID-19 infection, deaths and case fatality rate (CFR), according to sex and co-morbidities

	Outpatients						Inpatients					
	Female			Male			Female			Male		
Comorbidity	***n***	**Deaths**	**CFR**	***n***	**Deaths**	**CFR**	***n***	**Deaths**	**CFR**	***n***	**Deaths**	**CFR**
Hypertension	13,948	276	2.0	12,995	376	2.9	22,019	10,916	49.6	26,850	14,671	54.6
No hypertension	92,202	246	0.3	83,301	551	0.7	26,686	8,751	32.8	45,670	18,530	40.6
Diabetes	9,516	223	2.3	8,319	315	3.8	18,097	8,763	48.4	21,974	11,794	53.7
No diabetes	96,634	299	0.3	87,977	612	0.7	30,608	10,904	35.6	50,546	21,407	42.4
Obesity	17,528	159	0.9	14,807	223	1.5	12,375	5,326	43.0	13,807	6,570	47.6
No obesity	88,622	363	0.4	81,489	704	0.9	36,330	14,341	39.5	58,713	26,631	45.4
ESKD	659	48	7.3	797	67	8.4	3,334	1,967	59.0	4,588	2,747	59.9
NO ESKD	105,491	474	0.4	95,499	860	0.9	45,371	17,700	39.0	67,932	30,454	44.8
CPOD	690	30	4.3	612	46	7.5	2,115	1,180	55.8	2,627	1,559	59.3
No CPOD	105,460	492	0.5	95,684	881	0.9	46,590	18,487	39.7	69,893	31,642	45.3
Cardiovascular disease	866	37	4.3	951	45	4.7	2,030	1,075	53.0	3,157	1,819	57.6
No cardiovascular disease	105,284	485	0.5	95,345	882	0.9	46,675	18,592	39.8	69,363	31,382	45.2
Immunosuppression	775	13	1.7	589	13	2.2	1,426	637	44.7	1,631	840	51.5
No Immunosuppression	105,375	509	0.5	95,707	914	1.0	47,279	19,030	40.3	70,889	32,361	45.7
Asthma	3,820	9	0.2	1,996	13	0.7	1,593	585	36.7	1,098	445	40.5
No asthma	102,330	513	0.5	94,300	914	1.0	47,112	19,082	40.5	71,422	32,756	45.9
Smoking	4,651	21	0.5	8,548	102	1.2	1,904	750	39.4	7,255	3,522	48.5
No smoking	101,499	501	0.5	87,748	825	0.9	46,801	18,917	40.4	65,265	29,679	45.5

n: Number of subjects in each category according to the presence or absence of the comorbidity.
Deaths: number of deaths.
CFR, case fatality rate in percentage (%).

Age and sex were major independent risk factors for mortality, as well as the presence of pneumonia, mainly in outpatients (Table 4). Aside from diabetes, hypertension and obesity, immunosuppression and end-stage kidney disease were independent ailments that increased the risk of mortality, both in hospitalized and in outpatients. In the multivariate analysis, while controlling for the presence of any comorbidity and other confounders, chronic obstructive pulmonary disease, asthma, smoking or cardiovascular disease, had no significative contribution on explaining mortality in COVID-19 (Table 4).

The estimated attributable fraction (AF) in hospitalized patients were 2.0% for diabetes, 7.1% for hypertension and 8.0% for obesity, whereas these figures were 1.1, 14.3 and 16.8% in outpatients. It could be said that up to 16.8% of COVID-19 deaths could have been avoided among outpatients, were the prevalence of obesity reduced.

Discussion

Mortality and case fatality rates depend on the incidence of the infection, the severity of the disease and the ability of health services to provide quality care on time. While mortality rates describe the number of deaths among the population, case fatality rates describe the frequency of deaths among confirmed cases. The incidence of the infection depends on general control measures related to social distancing, hygiene, testing and contact tracing. Case fatality rates depend on a mixture of health services capacity, the sensibility of the system for case detection, treatment opportunity and the mixture of severe and mild cases (20). Demographic characteristics of population affects CFR since mortality is higher in older population. Definition of COVID related deaths, differences in testing and preventing strategies, as well as differences in health care systems, also impact CFR (20). In the studied population, only a random sample of mild or asymptomatic cases of COVID-19, while almost all hospitalized patients were tested for SARS-CoV2 infection, so global CFR may have been overestimated. Nevertheless, CFR was substantially lower in milder cases (0.5% in females and 1.0% in males, outpatients), compared to CFR in hospitalized subjects (40.4% and 45.8% respectively), as shown in Table 1.

The higher risk of COVID-19 fatality in older ages and in men has consistently been reported (17). Older subjects are more prone to suffer chronic diseases that in turn are related to severe COVID-19, but overinduction of pro-inflammatory cytokines may also be related to age (21), increasing the risk of acute lung injury (8). While there is no clear functional relevance on the fact that the ACE2 gene is located on the X chromosome, (22) the truth is that soluble angiotensin-converting enzyme 2 (sACE2) levels seem to be higher in male and in older ages (23). sACE2 is the result of cleavage and shedding of membrane-bound angiotensin-converting enzyme 2 (mACE2), a process also associated to acute lung injury, (23) and it may thus increase severity of the disease in males and older patients. There is also progressive lymphopenia with CD4+ T-cell attrition and decreased regulatory T-cell function in

Table 3. Deaths (n) and total in-patients and out-patients with COVID-19 infection (N), and case fatality rate (CFR), according to age, sex and major co-morbidities

Age group (years)	None	Obesity	Diabetes	Hypertension	Diabetes and obesity	Hypertension and obesity	Diabetes and hypertension	Hypertension diabetes and obesity
Outpatient−Female								
<40	19/49,167 (0.04)	5/6,862 (0.07)	0/881 (0)	4/1,208 (0.33)	2/352 (0.57)	3/681 (0.44)	3/241 (1.24)	1/198 (0.51)
40−49	20/17,495 (0.11)	11/3,168 (0.35)	4/1,139 (0.35)	6/2,001 (0.3)	5/445 (1.12)	6/978 (0.61)	6/696 (0.86)	11/515 (2.14)
50−59	28/7,018 (0.4)	16/1,234 (1.3)	9/989 (0.91)	8/1,846 (0.43)	2/298 (0.67)	3/811 (0.37)	19/1,019 (1.86)	16/632 (2.53)
60−69	38/1,596 (2.38)	4/248 (1.61)	10/371 (2.7)	15/733 (2.05)	4/91 (4.40)	11/291 (3.78)	32/607 (5.27)	16/338 (4.73)
≥70	48/620 (7.74)	5/66 (7.58)	14/137 (10.22)	37/476 (7.77)	2/25 (8.00)	12/135 (8.89)	43/382 (11.26)	24/160 (15)
Total	153/75,896 (0.20)	41/11,578 (0.35)	37/3,517 (1.05)	70/6,264 (1.12)	15/1211 (1.24)	35/2,896 (1.21)	103/2,945 (3.5)	68/1,843 (3.69)
Outpatient−Male								
<40	30/44,903 (0.07)	15/6,275 (0.24)	4/737 (0.54)	3/1,640 (0.18)	1/280 (0.36)	5/947 (0.53)	1/195 (0.51)	2/191 (1.05)
40−49	53/14,536 (0.36)	21/2,452 (0.86)	11/1,101 (1)	9/1,772 (0.51)	2/303 (0.66)	12/883 (1.36)	7/604 (1.16)	10/337 (2.97)
50−59	96/6,952 (1.38)	27/979 (2.76)	31/1,025 (3.02)	21/1,694 (1.24)	4/211 (1.9)	20/627 (3.19)	27/939 (2.88)	14/418 (3.35)
60−69	80/1,772 (4.51)	13/200 (6.5)	25/440 (5.68)	24/697 (3.44)	6/72 (8.33)	4/182 (2.2)	49/613 (7.99)	20/175 (11.43)
≥70	95/814 (11.67)	12/66 (18.18)	22/168 (13.10)	60/496 (12.10)	3/15 (20.00)	12/90 (13.33)	56/391 (14.32)	20/104 (19.23)
Total	354/68,977 (0.51)	88/9,0.972 (0.88)	93/3,471 (2.68)	117/6,299 (1.86)	16/881 (1.82)	53/2,729 (1.94)	140/2,742 (5.11)	66/1,225 (5.39)
Age group (years)	None	Obesity	Diabetes	Hypertension	Diabetes and Obesity	Hypertension and Obesity	Diabetes and Hypertension	Hypertension Diabetes and Obesity
Inpatient−Female								
<40	454/4,323 (10.50)	160/981 (16.31)	66/355 (18.59)	115/391 (29.41)	33/135 (24.44)	41/160 (25.63)	61/155 (39.35)	33/119 (27.73)
40−49	607/3,303 (18.38)	220/940 (23.40)	202/712 (28.37)	183/626 (29.23)	99/319 (31.03)	143/430 (33.26)	285/693 (41.13)	168/441 (38.10)
50−59	1,065/3,709 (28.71)	338/998 (33.87)	440/1,222 (36.01)	459/1,282 (35.80)	172/437 (39.36)	310/795 (38.99)	789/1,851 (42.63)	477/1,080 (44.17)
60−69	1,322/2,949 (44.83)	278/610 (45.57)	556/1,134 (49.03)	837/1,780 (47.02)	205/375 (54.67)	422/797 (52.95)	1,395/2,716 (51.36)	782/1,416 (55.23)
≥70	1,682/2,843 (59.16)	200/322 (62.11)	518/801 (64.67)	1,609/2,634 (61.09)	134/218 (61.47)	459/735 (62.45)	1,696/2,851 (59.49)	652/1,067 (61.11)
Total	5,130/17,127 (29.95)	1196/3,851 (31.06)	1,782/4,224 (42.19)	3,203/6,713 (47.71)	643/1,484 (43.33)	1,375/2,917 (47.14)	4,226/8,266 (51.13)	2,112/4,123 (51.22)
Inpatient−Male								
<40	1,024/6,210 (16.49)	385/1,602 (24.03)	93/408 (22.79)	212/713 (29.73)	56/162 (34.57)	107/332 (32.23)	87/206 (42.23)	55/156 (35.26)
40−49	1,576/6,279 (25.10)	577/1,662 (34.72)	388/1,171 (33.13)	360/1,062 (33.90)	99/300 (33.00)	219/582 (37.63)	424/990 (42.83)	224/482 (46.47)
50−59	2,728/7,299 (37.37)	631/1,426 (44.25)	837/1,918 (43.64)	828/1,950 (42.46)	201/418 (48.09)	418/889 (47.02)	1,177/2,442 (48.20)	451/930 (48.49)
60−69	3,057/5,815 (52.57)	475/815 (58.28)	1,075/1,919 (56.02)	1,287/2,463 (52.25)	205/345 (59.42)	459/729 (62.96)	1,951/3,360 (58.07)	600/972 (61.73)
≥70	3,733/5,830 (64.03)	300/431 (69.61)	953/1,464 (65.10)	2,572/3,798 (67.72)	137/196 (69.90)	459/659 (69.65)	2,269/3,416 (66.42)	512/719 (71.21)
Total	12,118/31,433 (38.55)	2,368/5,936 (39.89)	3,346/6,880 (48.63)	5,259/9,986 (52.66)	698/1,421 (49.12)	1,662/3,191 (52.08)	5,908/10,414 (56.73)	1,842/3,259 (56.52)

n/N: n = number of COVID-19 deaths and N = total population at risk, for each age and co-morbidity category, with COVID-19.
(CFR): Case fatality rate in percentage (%).

Table 4. Risk factors for mortality in patients with COVID 19 infection

	Outpatients					Inpatients				
Risk factor	**Crude OR**	**95% CI**	**Adjusted OR**	**95% CI**	***p***	**Crude OR**	**95% CI**	**Adjusted OR**	**95% CI**	***p***
Age (years)	1.108	1.105−1.112	1.100	1.096−1.104	<0.001	1.047	1.046−1.047	1.045	1.044−1.046	<0.001
Male	1.97	1.76−2.19	2.00	1.78−2.23	<0.001	1.25	1.22−1.28	1.37	1.33−1.40	<0.001
Pneumonia	8.04	6.90−9.36				1.65	1.61−1.69	1.55	1.52−1.59	<0.001
Chronic Obstructive Pulmonary Disease	9.02	7.02−11.45				1.81	1.71−1.92			
Asthma	0.52	0.32−0.79				0.80	0.74−0.86			
Cardiovascular disease	6.89	5.42−8.66				1.67	1.58−1.77			
Immunosuppression	2.73	1.77−4.03	0.97	0.64−1.48	0.897	1.21	1.13−1.31	1.21	1.12−1.31	<0.001
End-stage Kidney Disease	12.83	10.44−15.71	3.51	2.79−4.41	<0.001	1.99	1.90−2.08	1.92	1.82−2.02	<0.001
Smoking	1.33	1.10−1.61	0.94	0.76−1.15	0.520	1.14	1.09−1.19			
No diabetes, obesity or hypertension			1.00[a]						1.00[a]	
Hypertension	1.71	1.40 −2.09	1.96	1.60−2.39	<0.001	1.04	0.99−1.09	1.32	1.26−1.39	<0.001
Obesity	5.40	4.41−6.58	1.85	1.51−2.27	<0.001	1.56	1.49−1.62	1.28	1.22−1.34	<0.001
Diabetes	4.30	3.62−5.11	1.09	0.90−1.30	0.379	1.86	1.80−1.93	1.19	1.15−1.24	<0.001
Hypertension and obesity	4.28	2.87−6.18	2.36	1.62−3.43	<0.001	1.56	1.44−1.68	1.52	1.40−1.64	<0.001
Diabetes and hypertension	4.53	3.56−5.7	2.01	1.58−2.54	<0.001	1.80	1.70−1.89	1.53	1.44−1.62	<0.001
Diabetes and obesity	12.71	10.85−14.89	2.08	1.75−2.48	<0.001	2.15	2.08−2.23	1.32	1.27−1.37	<0.001
Diabetes, obesity and hypertension	13.00	10.63−15.86	3.28	2.65−4.05	<0.001	2.09	1.99−2.20	1.57	1.49−1.65	<0.001

Variables included in the model: Age, sex, pneumonia, and the self-report of chronic obstructive pulmonary disease, asthma, cardiovascular disease, immunosuppression, end-stage kidney disease, smoking, hypertension, diabetes and obesity.

[a]Reference category.

aging, that leads to propensity for autoimmune and excessive inflammatory responses and could explain a higher severity of infection in older ages (22).

Hypertension seems to be a risk factor for a more severe clinical expression of the disease in this population. Hypertension is an inflammatory disease, (11) with an underlying endothelial dysfunction (8) that may increase the risk of severe and fatal COVID-19. In spite of having been identified as a risk factor of severity and mortality in the Chinese population, (24) it has not been a major risk in populations of Italy, (25,26) the United States, (27) or the United Kingdom (17). Therefore, identifying its contribution in different populations, may provide insights on its relationship with COVID-19 severity.

While the prevalence of diabetes in COVID-19 patients in other countries may be lower, (25) or similar, (17,27) than the observed prevalence in Mexico, the increased risk of severe infection and death is constant in most studied populations, similar to the herein reported. Obesity also increases the risk of death in COVID-19, (28) and together with diabetes result in a dysregulated immune response to respiratory infections. In animal models, it has been shown that this dysregulated immune response in diabetes, along with the inability to resolve inflammation and lung pathology, result in more severe and prolonged lung pathology in MERS-CoV infection, (12) a mechanism that could be shared in SARS-CoV2 infection.

The type 2 immune response that characterizes asthma, together with therapeutics for asthma, may explain the reduced mortality risk observed in this population with COVID-19. (29) HIV infection has not shown to increase the risk of dying due to COVID-19 infection, (30) contrary to was observed in this Mexican population with those with immunosuppression (mainly due to HIV infection), but few reports have addressed this topic so far. Regarding other analyzed risk factors, as ESKD, COPD, CVD, and smoking, only ESKD showed a significant contribution in the multivariate model. Whether the increased fatality in these diseases is related to pathological conditions or to an association with identified major risk factors (age, diabetes, hypertension, obesity), remains to be elucidated.

We analyzed the independent contribution of the three major risk factors of fatality in COVID-19, hypertension, obesity, and diabetes. Although we did not see interaction between them, the presence of two or the three of them showed stronger association with mortality, than each one alone, compared to the absence of them. Without the detailed analysis presented in this report, a couple of predictive models in Mexicans have been recently published, that support our findings on the importance of pneumonia, (31) and obesity and diabetes, (32−34) on explaining COVID-19 mortality in Mexico. The estimated attributable fraction highlights how crucial it is to reduce the prevalence of major cardiovascular risk factors.

One of the limitations of the current report is that we had to rely on secondary data. Even though epidemiologist review the completeness and pertinence of the data, accuracy depends on the knowledge of the patients of their own health problems (i.e., diabetes or hypertension), and the capacity of the interviewer. Nevertheless, the consequent misclassification bias ought to be non-differential and thus, an underestimation of the true relative risk should be expected. The high case fatality rate that in some instances was observed can hardly be compared with other populations or be explained, in the absence of additional data. Specifically, designed studies, aimed to analyze the underlying causes additional to the identified risk factors in this article, should be encouraged and developed in this studied population.

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