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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ORIGINAL ARTICLE

A Multimodal Strategy to Reduce the Risk of Hospitalization/death in Ambulatory Patients with COVID-19

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Background. Different interventions have been implemented worldwide for the household monitoring of patients with mild COVID-19 to reduce the burden of healthcare systems and guarantee quality of care. Telephone follow up and treatment kits have not been evaluated in the context of a national-wide primary care program.

Aim of the study. To compare the risk of hospitalization and death for COVID-19 between ambulatory patients who received and those who did not receive a treatment kit and telephone follow-up in a developing country

Methods. A two-group comparative analysis was conducted using data from the medical information systems of the Mexican Institute of Social Security. We included a total of 28,048 laboratory-confirmed SARS-CoV-2 patients: 7,898 (28.2%) received a medical kit and 20,150 (71.8%) did not. The incidence rates of hospitalization and death combined were calculated. To identify significant associations between hospitalization or death and treatment medical kits, we calculated the risk ratios using a multivariate logistic model.

Results. The incidence of hospitalization was 6.14% in patients who received a kit and 11.71% in those who did not. Male sex, age, and a medical history of obesity, hypertension, diabetes, immunosuppression, or kidney disease were associated with increased risk of hospitalization or death. The risk rates were reduced in patients who received a medical kit or telephone follow-up. In the multivariate model, receiving a medical kit was associated with a lower risk of hospitalization or death from COVID-19: adjusted risk ratio 0.41 (95% confidence interval 0.36–0.47).

Conclusion. Use of a multimodal strategy may reduce the risk of hospitalization and death in adult outpatients with mild COVID-19.

Key Words: COVID-19, SARS-Cov-2, Ivermectin, Ambulatory management, Telemedicine.

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Abbreviations

IMSS, Mexican Institute of Social Security; MARSS, *Módulos de Atención Respiratoria del Seguro Social*; SARS-Cov-2, Severe acute respiratory syndrome coronavirus 2.

Introduction

The widespread dissemination of COVID-19 (Coronavirus disease 2019) has reached unprecedented pandemic proportions with more than 270 million confirmed cases and over 5 million deaths since its beginning in March 2020 (1) Health care systems around the world have been overwhelmed by COVID-19 and face not only historical medical challenges but also the social and economic consequences of the pandemic. Thus, the timely identification of patients who could be managed remotely at home is of paramount importance to unburden hospitals, allowing them to concentrate in the care of severely ill patients. Most people infected with the novel SARS-CoV-2 virus (severe acute respiratory syndrome coronavirus 2) present a rather mild form of the disease that can easily be managed at home with general supportive care. Yet, a variable proportion of patients will develop more severe forms of the infection that range from mild oxygen-requiring interstitial pneumonia to a devastating respiratory distress syndrome with multiorgan failure, whereby hospital or even intensive care unit admission is necessary to provide invasive mechanical ventilation as well as hemodynamic support (2). Telemedicine strategies to follow COVID-19 patients include telephone (3–5) or video calling (6), smartphone applications (7), robotic calls based on artificial intelligence technology (8) and home-based patient units that enable real-time monitoring of clinical parameters such as oxygen saturation, heart rate, body temperature, and peak expiratory flow (9,10).

Much of the burden of the COVID-19 pandemic in Mexico has fallen on the Mexican Institute of Social Security (Instituto Mexicano del Seguro Social, IMSS) because it provides health care to 19 million workers and their families, which equates to approximately 68 million people or 54% of the Mexican population (11). The IMSS operates around 1,400 primary care medical units, 270 general community hospitals, and 25 tertiary and quaternary care medical centers distributed throughout the 32 Mexican states. At the beginning of the pandemic, IMSS implemented respiratory care modules (in Spanish *Módulos de Atención Respiratoria del Seguro Social* or MARSS), with the intention of classifying patients with respiratory symptoms, providing medical attention at the primary care setting. In these modules, patients classified as having mild COVID-19 without any evidence of respiratory failure, are offered a treatment kit that included, besides an information brochure and a pulse oxymeter, medications such as azithromycin, ivermecin, acetaminophen and aspirin. This study was design to evaluate the hospitalization and mortality rates of many adults who received this primary treatment kit in comparison with an equally large cohort of individuals who declined it yet, continued monitoring by phone call-based telemedicine.

Materials and Methods

Study Population and Description of the Primary Care Strategy

Adult patients (18 years and older) presenting to the MARSS with symptoms and signs suggestive of COVID-19 were evaluated clinically and a nasopharyngeal swab was obtained to confirm SARS-CoV-2 infection by either the polymerase chain reaction (PCR) test or the rapid antigen test. Patients testing positive and classified as having moderate or severe disease were referred to one of the COVID-19-converted hospitals of our system, whereas those with mild disease (O2 saturation >93%, no evidence of respiratory failure or hemodynamic compromise) were sent home and instructed to isolate themselves from the rest of the family and to identify and report early signs of worsening. As of October 2020, a family physician would contact each patient with confirmed COVID-19 daily for 10 days. As of December 2020, patients diagnosed with mild COVID-19 were offered a treatment kit consisting of an information brochure, face masks, a pulse oximeter, a three-day course of azithromycin (500 mg on day 1, 250 mg on days 2 and 3), a two-day course of ivermectin 6 mg daily and several acetaminophen and aspirin tablets.

Study Design

A retrospective, two-group comparative study was conducted using secondary data from the National Family Medicine Information System of the IMSS. This database contains the personal and clinical records of every patient, including their diagnosis and prescribed medications. All data are captured in real time by the family physician while attending the patient. From February 1–May 16, 2021, a secondary database was prepared by the epidemiological surveillance system at the IMSS. A total of 28,048 records without personal identifiers were analyzed. They corresponded to ambulatory patients aged 18 years and older and over with confirmed COVID-19 diagnosis and with information about the treatment kit delivery. Only records from the second epidemic wave from January 1–August 30, 2021, were analyzed. (Figure 1). Information regarding sex, age, medical conditions (e.g., obesity, hypertension, diabetes, cardiovascular disease), follow-up by telephone, and whether they agreed to use the treatment kit was obtained for each patient, as well emergency room visits and hospitalization. Information regarding death was obtained and verified using the hospital and mortality registries.

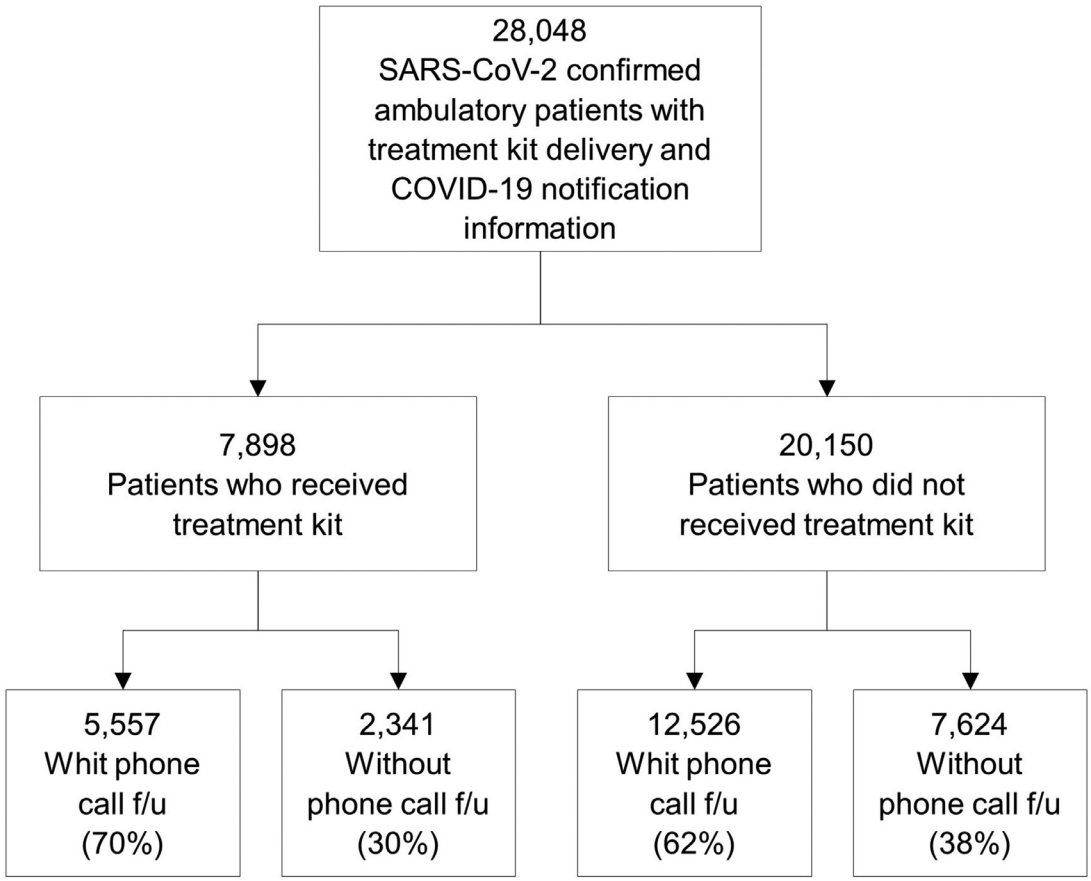

Figure 1. Flow diagram depicting the number of patients who received the treatment kit and those who did not, as well as those with and without treatment kit who were followed up by phone call.

Statistical Analysis

Quantitative variables are presented as either means ± SD (standard deviations) or as medians with interquartile ranges (IQR), depending on their distribution. The Shapiro-Wilk test was used to ascertain data distribution. Qualitative variables such as the baseline demographical and clinical characteristics of the patients were analyzed using the χ^2 test. The rate of hospitalization or death was calculated. Using bivariate analysis, we calculated the crude relative risk (RR) with 95% confidence interval (95% CI) to assess the relationship between patients' characteristics and hospitalization or death. A multivariate logistic model was used to evaluate the association between the delivery of treatment kits and hospitalization or death by including the variables that were significant in the bivariate analysis. Statistical analysis was performed using Stata (version 14).

Ethics Statement

Given that the analyses in this report used anonymized data from medical information systems as part of our institutional epidemiological surveillance, ethics review and informed consent were not required by the institutional review board. All procedures were in accordance with the ethical standards of the institutional research committee, national laws, and the 1964 Helsinki Declaration and its later amendments.

Results

A total of 28048 records of ambulatory patients with laboratory-confirmed SARS-CoV-2 were analyzed. The median age of patients was 38 years (IQR 29–48); 13613 (48.5%) were women and 14435 (51.5%) were men. Information about occupation was available in 27932 (99.5%) patients: 24,430 (87.4%) patients were formally employed, 2241 (8%) were housekeepers (97% of them were women), 649 (2.3%) were unemployed, and 612 (2.19%) were retired. Of the 24430 formally employed patients, 822 (3.3%) were health care professionals (44.3% of them female nurses). Of the total cohort, 9246 reported having one or more comorbidities; 3551 (12.6%) were obese, 3301 (11.8%) had arterial hypertension, 2348 (8.4%) had been diagnosed with type 2 diabetes and 1716 (6.1%) were smokers (Table 1).

Table 1. Comparison of demographic, clinical and outcome characteristics of patients who received the treatment kit (wK) and those who did not (woK)

Characteristics	With Treatment kit	Without Treatment kit	Both groups	*p*
Number of subjects	7,898	20,150	28,048	
Sex				
Female	3863 (48.9%)	9750 (48.4%)	13613 (48.5%)	
Male	4035 (51.1%)	10400 (51.6%)	14435 (51.5%)	0.430
Age group				
20–39	4405 (55.8%)	10725 (53.2%)	15130 (53.9%)	
40–59	3035 (38.4%)	8027 (39.8%)	11062 (39.4%)	
60 or more	458 (5.8%)	1398 (6.9%)	1856 (6.6%)	<0.001*
Occupation				
Employee	4595 (58.2%)	11196 (55.6%)	15791 (56.3%)	
Housekeeper	571 (7.2%)	1473 (7.3%)	2044 (7.3%)	
Other	2732 (34.6%)	7481 (37.1%)	10213 (36.4%)	<0.001*
Previous medical conditions				
Obesity	1013 (12.8%)	2538 (12.6%)	3551 (12.7%)	0.677
Hypertension	901 (11.4%)	2400 (11.9%)	3301 (11.8%)	0.202
Diabetes	621 (7.9%)	1727 (8.6%)	2348 (8.4%)	0.045*
Tobacco consumption	480 (6.1%)	1236 (6.1%)	1716 (6.1%)	0.804
Asthma	147 (1.9%)	280 (1.4%)	427 (1.5%)	0.004*
COPD	29 (0.4%)	95 (0.5%)	124 (0.4%)	0.230
Cardiovascular disease	49 (0.6%)	127 (0.6%)	176 (0.6%)	0.908
Immunosuppression	25 (0.3%)	66 (0.3%)	91 (0.3%)	0.872
HIV infection	32 (0.4%)	53 (0.3%)	85 (0.3%)	0.053
Chronic kidney disease	26 (0.3%)	96 (0.5%)	122 (0.4%)	0.089
Any medical condition	2343 (29.7%)	6139 (30.5%)	8482 (30.2%)	0.134
Outcomes				
Emergency room admission	435 (5.51%)	1906 (9.46%)	2341 (8.35%)	<0.001*
Hospitalization	485 (6.14%)	2360 (11.71%)	2845 (10.14%)	<0.001*
Endotracheal intubation	77 (0.97%)	216 (0.107%)	293 (1.04%)	0.472
Death	101 (1.27%)	303 (1.5%)	404 (1.4%)	0.155

The total cohort was divided into those who received and used the treatment kit (wK group, $n = 7898$, [28.2%]) and those who declined using it (woK group, $n = 20150$, [71.8%]). Table 1 depicts the demographical and clinical characteristics of the total cohort and of each of the groups. Median age of the wK group and the woK group was 37 and 38 years, respectively. Stratifying both groups by age, 55.8 and 53.2% of patients in the wK and in the woK groups were between 20 and 39 years old, respectively; slightly more patients in the woK group than in the wK group were 60 years or older (6.9 vs. 5.8%, $p < 0.001$). The prevalence of diabetes was higher in the woK group than in the wK group (8.6 vs. 7.9%, $p = 0.045$), whereas the proportion of patients with a history of asthma was higher among the wK than in the woK group (1.9 vs. 1.4%, $p = 0.004$). Other comorbidities such as obesity, hypertension, chronic obstructive pulmonary disease (COPD), immunosuppression, HIV disease and renal insufficiency were equally frequent in both groups. The diagnosis of SARS-CoV-2 infection was confirmed by a rapid antigen test in 88.3 and 81% of the patients in the wK and woK groups, respectively. SARS-CoV-2 PCR testing was carried out in only 7.5 and 11.4% of the patients in the wK and woK groups, respectively. Regarding outcomes, a significantly higher proportion of patients who did not use the treatment kit had to visit the emergency room (woK 9.46 vs. wK 5.51% $p < 0.001$) and required hospitalization (woK 11.7 vs. wK 6.14%). The proportion of patients requiring endotracheal intubation and the mortality rate were similar among the two groups (Table 1).

Daily phone call surveillance was carried out in 18083 of the 28048 (64%) who tested positive for SARS-CoV-2 infection. Significantly more patients were followed by phone call in the wK group than in the woK group (70.4 vs. 62.2%, $p < 0.001$). When we analyzed outcomes considering this variable, 303 out of 5557 (5.4%) subjects who used the treatment kit and who underwent phone-call surveillance required hospitalization and 63 of them (1.13%) died. In contrast, 1337 out of the 7624 (17.5%) subjects who declined using the treatment kit and did not undergo phone-call follow up ended up being hospitalized and 150 of them (1.96%) died ($p < 0.001$).

Upon univariate analysis, comorbidities such as age older than 60 years, COPD, immunosuppression, chronic kidney disease, obesity, hypertension, and diabetes, as well as admission to the emergency room, were found to be significantly associated with the risk of hospitalization or death (Table 2). Having used the treatment kit and hav-

Table 2. Uni and multivariate analysis assessing the relative risk of hospitalization or death

Variable	Univariate analysis		Multivariate analysis	
	RR	95% CI	RR	95% CI
Age >60 years	8.37	7.61–9.20	7.86	6.52–9.48
COPD	4.40	3.60–5.38	1.89	1.12–3.20
Cardiovascular disease	3.10	2.48–3.86	1.63	1.02–2.61
Immunosuppression	3.25	2.42–4.36	1.54	0.75–3.16
Chronic kidney disease	4.97	4.15–5.96	2.60	1.47–4.62
Obesity	1.62	1.48–1.76	1.27	1.09–1.48
Hypertension	2.78	2.58–3.00	1.07	0.91–1.25
Diabetes mellitus	2.99	2.77–3.24	1.51	1.28–1.78
Emergency room admission	19.54	18.34–20.83	74.51	65.62–84.60
Treatment kit (wK)	0.53	0.48–0.58	0.41	0.36–0.47
Phone call	0.48	0.45–0.52	0.40	0.32–0.50
wK and phone call	0.31	0.28–0.35	0.29	0.25–0.35

ing been followed by phone were significantly associated with a lower risk of hospitalization or death (Table 2). Upon multivariate analysis, only age, COPD, cardiovascular disease, chronic kidney disease, obesity, diabetes mellitus, emergency room admission, treatment kit and phone call follow up, remained statistically significant (Table 2).

Discussion

This study demonstrates that an intervention for the ambulatory treatment of mild COVID-19 is effective in reducing the hospitalization rate of these patients with a tendency, albeit not statistically significant, towards a reduction in mortality rate. The intervention consisted of an information brochure with instructions for the proper use of a pulse oximeter (also included in the kit), as well as for the early detection of symptoms and signs of deterioration. The medications included in the package were aspirin and acetaminophen for symptomatic relief, as well as ivermectin and azithromycin. The strategy conducted by the IMSS to treat COVID-19 at the first level of care started in March 2020. Triage filters were implemented at the entrance of each family medicine unit, where health personnel identified those patients with respiratory symptoms or suspected COVID-19 and referred them to the MARSS. The patients were examined by a family doctor, a rapid antigen test was performed, or a nasopharyngeal sample was obtained for a PCR test, and the patients were sent home or to a second-level hospital if required. The telephone follow-up of patients began in July 2020 and was fully operational by October 2020. In December 2020, the rapid testing and delivery of treatment kits started in Mexico City and was operating in all family medicine units by February 2021.

Previous studies have reported that monitoring of outpatients with COVID-19 is effective in identifying patients with alarming symptomatology. Remote follow-up of ambulatory patients has been evaluated during the acute phase of illness, both in adult (3) and pediatric patients (4) with mild SARS-CoV-2 infection after being discharged from the hospital and in some patients with pneumonia even with moderate risk of progression to acute respiratory distress (12), and remote monitoring has been associated with a reduction in hospital readmission (13). However, a systematic review of remote monitoring concluded that the real effectiveness of the different interventions could not be determined reliably. Additionally, this review found that the follow-up strategies based on telephone calls were more inclusive with patients, especially with those without internet access or with technological illiteracy (14).

The inclusion of ivermectin and azithromycin in the treatment kits was agreed by a group of IMSS experts, who made this decision based on the information available at that time (December 2020). Azithromycin was discontinued by July 2021, when information about its lack of effectiveness to treat COVID-19 emerged, except in cases of suspicion of bacterial coinfection (15). However, during the second epidemic wave, the use of ivermectin was controversial with sufficient evidence in favor of its effectiveness. The use of ivermectin in the different COVID-19 settings, from primary prevention to treatment of severe disease, continues to be controversial (16). There is only one formally published placebo-controlled study evaluating the use of ivermectin in ambulatory COVID-19 patients in terms of hospitalization rate (17). Although in this study there was a tendency favoring ivermectin, there was not a statistically significant difference between the placebo and the intervention groups.

The strengths of our study are the number of patients included, the personalized follow-up of each patient and the strong indication that the treatment kit and the telephone follow-up together reduced the risk for hospitalization and death. However, the results should be carefully contextualized in view of its limitations. The study analyzed a strategy implemented by IMSS to treat COVID-19, and it was not designed as a clinical trial. Therefore, it has the biases inherent to observational studies that decrease its validity. In addition, the two study groups were determined based on the delivery of the treatment kit, and delivery was based

on the kit's availability in the medical units and not on the patients' clinical conditions. Because the intervention was not randomly assigned, we observed an imbalance in the distribution of age, previous medical conditions, and type of test performed between the comparison groups. To assure that the results were not modified by these variables, a multivariate model was carried out in order to adjust the RRs for hospitalization and death. Unfortunately, the intervention program did not include the registration of medications consumed by patients. Therefore, information regarding the specific use of each kit component was not available, and the data considering only the use of ivermectin could not be retrieved.

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