Clinical characteristics and predictors of hospitalization among 7,108 ambulatory patients with positive RT-PCR for SARS-CoV-2 during the acute pandemic period

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ABSTRACT

Objective: To describe baseline characteristics of outpatients with a positive RT-PCR for SARS-CoV-2 and to define whether "red flags" (new-onset fever, dyspnea, and chest pain) can predict clinical worsening during the isolation period. **Methods:** This was an epidemiological, observational, descriptive study. Between March and September of 2020, all outpatients who tested positive for SARS-CoV-2 at a tertiary medical center located in Santiago de Chile were included. Demographic variables, comorbidities, red flags, and other symptoms were compiled using follow-up surveys at specific time points. The risk of clinical worsening (hospitalization) and adjusted hazard ratios (HRs) were calculated. **Results:** A total of 7,108 patients were included. The median age was 38 years (range, 0-101), and 52% were men. At baseline, 77% of the patients reported having characteristic symptoms of SARS-CoV-2 infection. The most prevalent onset symptoms were headache (53%), myalgia (47%), and fever (33%). According to the follow-up surveys, the incidence of symptoms decreased during the isolation period; however, 28% of the patients still presented with symptoms on day 14. The risk of hospitalization for patients with new-onset fever and dyspnea during the follow-up period was HR = 7.43 (95% CI, 3.85-14.3, p<0.01) and HR = 5.27 (95% CI, 1.52-18.30; p < 0.01 for both), respectively. New-onset chest pain showed no association with clinical worsening. **Conclusions:** In this sample of outpatients with a recent diagnosis of SARS-CoV-2 infection, a survey-based monitoring of symptoms was useful to identify those at risk of clinical worsening. New-onset fever and dyspnea during the isolation period were considered as red flags associated with clinical worsening and warrants prompt medical evaluation.

Keywords: Ambulatory care; COVID-19; Follow-up studies; Hospitalization; Outpatients.

INTRODUCTION

The first confirmed case of COVID-19 in Latin America was reported in Brazil on February 26, 2020.[1] In Chile, the first patient was diagnosed on March 3, 2020, and the infection rate rapidly increased in the following months.

In most cases, the clinical presentation of COVID-19 is mild (81%), the symptoms are generally self-limiting, and recovery usually occurs within 14 days (mean = 11.5 days).[2,3]

Active monitoring of outpatient cases (and close contacts) is essential as a measure to contain the pandemic. Knowing the evolution of symptoms and the characteristics of patients who worsen during the isolation period may improve monitoring planning and optimize health resources. Of the few studies that have evaluated the symptomatology and evolution of these patients, two have reported that up to 30% of patients continue having symptoms at 14-21 days after infection.[4,5] Additionally, prompt recognition of

patients with an increased risk of hospitalization is strongly needed.

The objective of the present study was to describe the characteristics of outpatients who tested positive for SARS-CoV-2 at a tertiary health care center in Chile and to define whether "red flags" (new-onset fever, dyspnea, and chest pain) can predict clinical worsening.

METHODS

This study followed the current recommendation from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Table S1).[6] This was an epidemiological, observational, analytical study of a prospective cohort of outpatients with a positive SARS-CoV-2 RT-PCR test at the *Clínica Las Condes*, a private center located in the urban area of Santiago de Chile, between March 26 and September 30 of 2020. Both adult and pediatric patients who tested positive for SARS-CoV-2 by RT-PCR performed on an outpatient basis

were included regardless of the indication for the exam. Hospitalized patients who underwent RT-PCR testing and those who were hospitalized upon performing the test were excluded. Data were obtained from the institutional COVID-19 Research Registry approved by the institutional research ethics committee (April 6, 2020), as was the study. Management and analysis of the anonymized data were performed in accordance with the Declaration of Helsinki.

Baseline demographic and clinical information

A baseline online survey using the institutional Research Electronic Data Capture (REDCap) platform was conducted at the time of the examination and was completed by the patients, which included demographic (age and sex) and clinical variables (onset symptoms related to COVID-19, comorbidities, smoking status, and pregnancy). A summary of the survey is shown in Table S2.

Follow-up surveys

As of June 17, 2020, four follow-up surveys were included in the information collection protocol during the isolation period (14 days since the SARS-CoV-2 RT-PCR test was performed): at 24 h after the positive result and on days 6, 10, and 14 after the test being performed. Participants were consulted regarding their current condition (isolation at home or hospitalized) and the evolution of symptoms related to COVID-19. If a patient reported fever, dyspnea, or chest pain in any of the follow-up surveys conducted during the isolation period, an alert was generated (a red flag for hospitalization), and the patient was contacted by phone by a doctor or nurse from the COVID-19 Surveillance Team. Symptom identification was performed according to the COVID-19 Task Force from the *Clínica Las Condes* based on expert opinions due to the lack of literature on COVID-19. Finally, when the follow-up isolation period was finished (day 17 after the test was performed), a survey was sent by e-mail to each patient to determine perceived compliance with isolation during the period (a scale from 0 to 100, in which 0 corresponded to "I did not comply with the isolation recommendations at all" and 100 corresponded to "I strictly complied with the isolation recommendations, remaining isolated in a room at home"). In addition, people who continued to self-isolate were asked about symptoms related to COVID-19 as well as whether they had been retested (RT-PCR) and, if so, the result.

Statistical analysis

An initial descriptive analysis of all patients during the study period was performed, and the following variables were analyzed: demographic variables, comorbidities, onset symptoms, and information obtained from isolation compliance and contact tracing surveys. In a second analysis, the evolution of the patients surveyed during the isolation period was described, detailing symptoms related to COVID-19 and the symptom alerts that were generated.

Categorical variables are presented as absolute and relative frequencies. Continuous variables are expressed as medians and ranges when the data presented non-normal distribution and as means and standard deviations when the data presented normal distribution. Continuous variables were compared using the Mann-Whitney test, and the chi-square test was used for categorical variables.

Predictors associated with hospitalization risk

We determined the associations between the proposed red flags (new-onset fever, new-onset dyspnea, or new-onset chest pain) at any point during the follow-up period and incident hospitalization during the first 14 days after RT-PCR. The Kaplan-Meier survival analysis was used, along with the log-rank test (Mantel-Cox) and calculation of the Cox proportional hazard ratio (HR). We included the following covariables on the basis of clinical relevance: age, sex, diabetes, hypertension, obesity, asthma, cardiovascular disease, smoking history, and number of comorbidities, as well as fever, chest pain, and dyspnea at baseline (https://academic.oup.com/aje/article/177/4/292/147738).

Statistical significance was set at $p < 0.05$. Statistical analyses were performed using the R Commander software (https://cran.r-project.org/) and the IBM SPSS Statistics software package, version 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Between March 26 and September 30, 2020, a total of 35,327 SARS-CoV-2 RT-PCR tests were performed at the *Clínica Las Condes*, and 7,683 patients tested positive (21.7%). Of those, 575 (7.4%) were hospitalized and, therefore, excluded from the analysis. In the first descriptive analysis, 7,108 patients were included. For the second analysis, a subgroup of 1,617 patients (22.7%) who completed all of the online surveys during the isolation period (14 days) was included. Figure 1 shows a flow chart of the patients included in the study.

The number of outpatients with a positive SARS-CoV-2 RT-PCR test result by sampling date during the study period is shown in Figure S1, which peaked at 338 daily cases on May 25, 2020.

General characteristics and onset symptoms of the patients

Table 1 shows the general characteristics of the overall sample. In summary, 52.2% of the patients were male; the median age was 38 years (range, 0-101 years); 6.3% of the patients were under 18 years of age; and 10.6% were over 60 years of age. The most prevalent comorbidities were hypertension (10.3%), diabetes (4.2%), and obesity (4.2%). At baseline, 77% of the patients had symptoms at the time of the SARS-CoV-2 RT-PCR test. The most prevalent symptoms were headache (53%), myalgia (47%), fever (33%), and
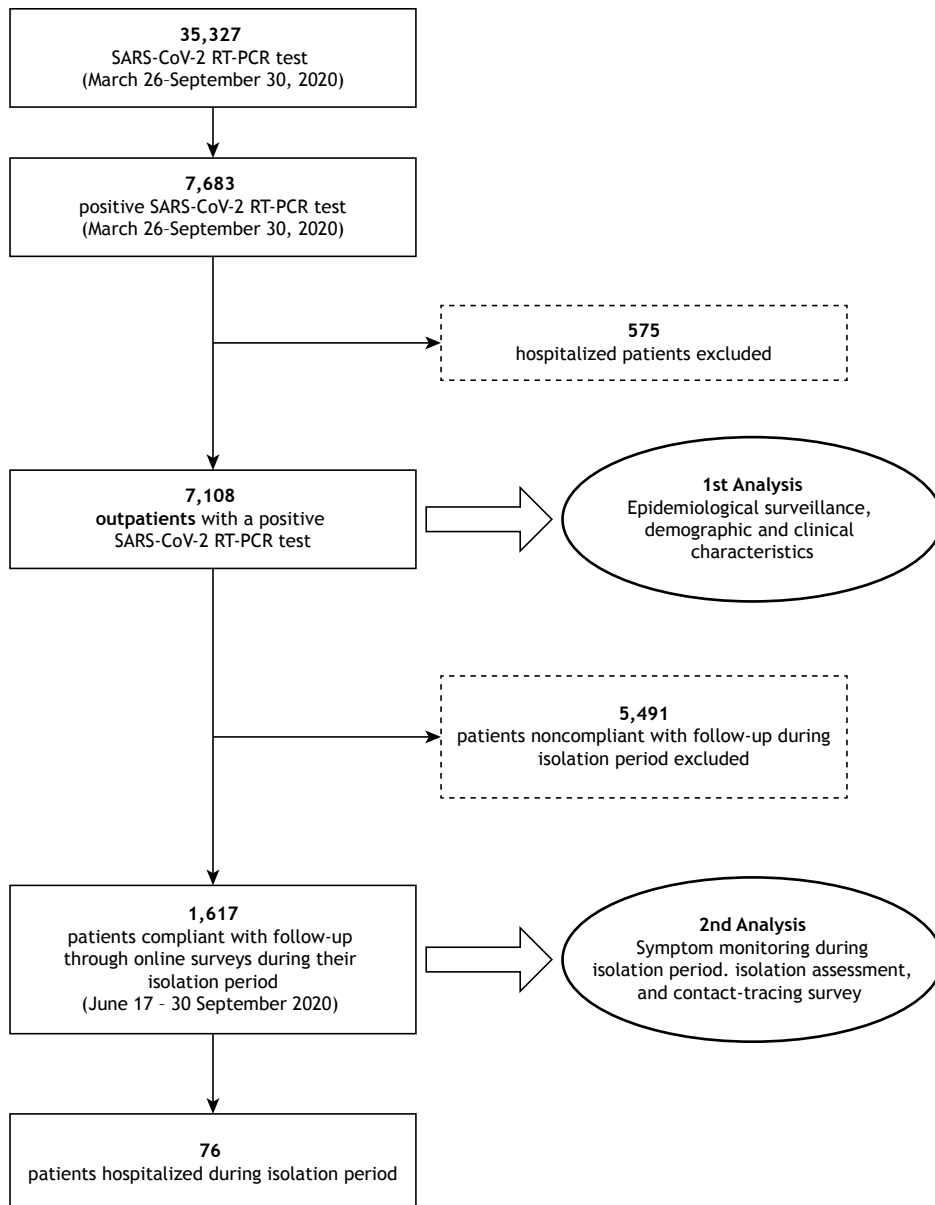
Figure 1. Flow chart of the patients included in the study.

cough (33%). In Table 2, onset symptoms are compared by sex and age. A higher proportion of symptoms was noted in females than in males (80% vs. 74%; p < 0.001). Regarding the frequency of onset symptoms, statistically significant differences were found for all symptoms when compared by sex. In men, the most common symptoms were headache (50%), myalgia (46%), and fever (39%), and, in women, headache and myalgia were more prevalent (57% and 47%, respectively), followed by cough (34%). When compared by age group, patients between 19 and 59 years of age had the highest proportion of symptoms (78%). Regarding onset symptoms, patients under 18 years of age most commonly presented with fever (49%), headache (39%), and cough (24%). In contrast, for the 19-to-59-year-old group, the most common onset

symptoms were headache (56%), myalgia (49%), and cough (33%); the onset symptoms for the group older than 60 years of age were similar, but the frequencies of headache and myalgia were lower (42% and 39%, respectively), and the frequency of cough was higher (40%).

Symptom monitoring

Most of the patients completed the follow-up survey at 24 h after the positive test result (82%), as well as at day 6 (79%), day 10 (75%), and day 14 (75%). When comparing the completion rate of the follow-up surveys by age, a significantly lower percentage of responses was noted in the ≥ 60-year-old group than in the ≤ 18-year and 19-to-59-year groups (66% vs. 78% vs. 80%; p < 0.0001).

Table 1. General characteristics of the patients with a positive SARS-CoV-2 RT-PCR test result.[a]

Characteristic	Group			p
	Total sample (N = 7,108)	No follow-up (n = 5,491)	Follow-up (n = 1,617)	
Age, years	38 [0-101]	38 [0-101]	37 [0-100]	0.04
Sex				
Male	3,713 (52.2)	2,827 (51.5)	841 (52.0)	0.71
Female	3,395 (47.8)	2,619 (48.7)	776 (48.0)	0.83
Comorbidities				
Hypertension	729 (10.3)	517 (9.4)	212 (13.1)	< 0.01
Diabetes	299 (4.2)	219 (4.0)	80 (4.9)	0.09
Obesity	298 (4.2)	188 (3.4)	110 (6.8)	< 0.01
Asthma	264 (3.7)	196 (3.6)	68 (4.2)	0.23
Cardiovascular disease	54 (0.8)	40 (0.7)	14 (0.9)	0.57
Immunosuppression	50 (0.7)	28 (0.5)	22 (1.4)	< 0.01
Chronic neurologic disease	34 (0.5)	21 (0.4)	13 (0.8)	0.03
Chronic kidney disease	27 (0.4)	14 (0.3)	13 (0.8)	< 0.01
Chronic lung disease	20 (0.3)	13 (0.2)	7 (0.4)	0.19
Chronic hepatic disease	8 (0.1)	3 (0.1)	5 (0.3)	< 0.01
Without comorbidities	5,194 (73.1)	4,282 (78.0)	1,100 (68.0)	< 0.01
Current smoking habit	501 (7.0)	307 (5.6)	194 (12.0)	< 0.01
Pregnancy	46 (1.4)	33 (0.6)	13 (0.8)	0.37

[a]Values expressed as median [range] or n (%).

Table 2. Presence/absence of symptoms at SARS-CoV-2 RT-PCR testing and onset symptoms by sex and age.[a]

Characteristic	Total sample (N = 7,108)	Sex		p	Age bracket, years			p
		Male (n = 3,713)	Female (n = 3,395)		≤ 18 (n = 447)	19-59 (n = 5,903)	> 60 (n = 758)	
Asymptomatic	1,645 (23)	957 (26)	688 (20)	< 0.001	134 (30)	1,270 (22)	241 (32)	< 0.001
Symptomatic	5,463 (77)	2,756 (74)	2,707 (80)		313 (70)	4,633 (78)	517 (68)	
Onset symptoms								
Headache	2,918 (53)	1,380 (50)	1,538 (57)	< 0.001	121 (39)	2,578 (56)	219 (42)	< 0.001
Myalgia	2,546 (47)	1,270 (46)	1,276 (47)	0.0029	65 (21)	2,277 (49)	204 (39)	< 0.001
Fever	1,786 (33)	1,069 (39)	717 (26)	< 0.001	153 (49)	1,458 (31)	175 (34)	< 0.001
Cough	1,807 (33)	877 (32)	930 (34)	< 0.001	74 (24)	1,525 (33)	208 (40)	< 0.001
Sore throat	1,313 (24)	574 (21)	739 (27)	< 0.001	64 (20)	1,163 (25)	86 (17)	< 0.001
Anosmia	1,271 (23)	589 (21)	682 (25)	< 0.001	32 (10)	1,175 (25)	64 (12)	< 0.001
Congestion	1,038 (19)	471 (17)	567 (21)	< 0.001	50 (16)	922 (20)	66 (13)	< 0.001
Dysgeusia	962 (18)	428 (16)	534 (20)	< 0.001	26 (8)	890 (19)	46 (9)	< 0.001
Weakening	925 (17)	441 (16)	484 (18)	0.0029	43 (14)	753 (16)	129 (25)	< 0.001
Dyspnea	389 (7)	170 (6)	219 (8)	< 0.001	14 (4)	332 (7)	43 (8)	0.0798
Diarrhea	609 (11)	282 (10)	327 (12)	0.0021	45 (14)	511 (11)	53 (10)	0.1537
Fatigue	540 (10)	239 (9)	301 (11)	< 0.001	19 (6)	461 (10)	60 (12)	0.0221
Chest pain	439 (8)	178 (6)	261 (10)	< 0.001	12 (4)	391 (8)	36 (7)	< 0.001
Nauseas/vomiting	346 (6)	109 (4)	237 (9)	< 0.001	38 (12)	279 (6)	29 (6)	< 0.001
Anorexia	341 (6)	152 (6)	189 (7)	0.0036	25 (8)	256 (6)	60 (12)	< 0.001
Conjunctivitis	218 (4)	96 (3)	122 (5)	0.0130	6 (2)	199 (4)	13 (3)	0.0041

[a]Values expressed as n (%).

The presence of symptoms decreased during the isolation period. At 24 h after the result, 88% of the patients reported symptoms attributable to COVID-19, whereas 76%, 62%, and 28% reported such symptoms at days 6, 10, and 14, respectively. The most prevalent symptoms at 14 days of self-isolation were anosmia (47%), headache (40%), and cough (38%). Figure 2 shows the symptomatology evolution in relation to the total number of patients with positive SARS-CoV-2 tests. Details of the symptoms for the total number of symptomatic patients are provided in Table S3.

No significant differences regarding sex, age, or comorbidities were found between symptomatic and asymptomatic patients during the isolation period (Table S4). Of the asymptomatic patients who underwent SARS-CoV-2 RT-PCR tests (n = 436), 243 (55.7%) developed symptoms during the follow-up period on different days; 195 (45.0%) developed symptoms in the first 24 h; 36 (15.0%), at day 6; 10 (5.0%), at day 10; and 2 (1.0%), at the end of the isolation period. The most common symptoms at 24 h after the result were headache (36%), nasal congestion (29%), and cough (26%).

Hospitalization and symptom alerts

During the follow-up period, 5% of the patients reported having been hospitalized during the isolation period. The median age of hospitalized patients was

54 years (range, 0-88 years), and most were male (64%). Table 3 shows the baseline characteristics of the patients who were and were not hospitalized during the isolation period.

A total of 698 symptom alerts were generated for 235 patients during the follow-up period. A total of 47% of the alerts was reported during the first 24 h of follow-up, followed by 29% on day 6, 17% on day 10, and 7% on day 14. The most common warning symptom was chest pain throughout the follow-up period. Table S5 provides the data for hospitalization reports and symptom alerts.

Predictors associated with hospitalization risk

We found an increased risk of hospitalization in patients with new-onset fever and dyspnea, respectively (HR = 7.43 [95% CI, 3.85-14.30]; and HR = 5.27 [95% CI, 1.52-18.30], p < 0.01 for both), during

follow-up (Figure 3). A summary of non-adjusted and adjusted HRs of the red flags is shown in Table 4.

Survey at the end of isolation period

Of the total number of outpatients, 64% completed the survey at the end of the isolation period. During this period, 9% of patients reported having visited an emergency service. On average, 87% of the patients surveyed reported that they had complied with self-isolation. The patients were isolated at home with households (median of 3 people [IQR, 2-4]); 52% of household contacts presented with symptoms attributable to COVID-19 after being infected.

DISCUSSION

Prompt identification of patients with a worse prognosis is important to reduce the rate of complications and, therefore, reduce the number of severe cases of COVID-19 in the ambulatory setting. In the present study,
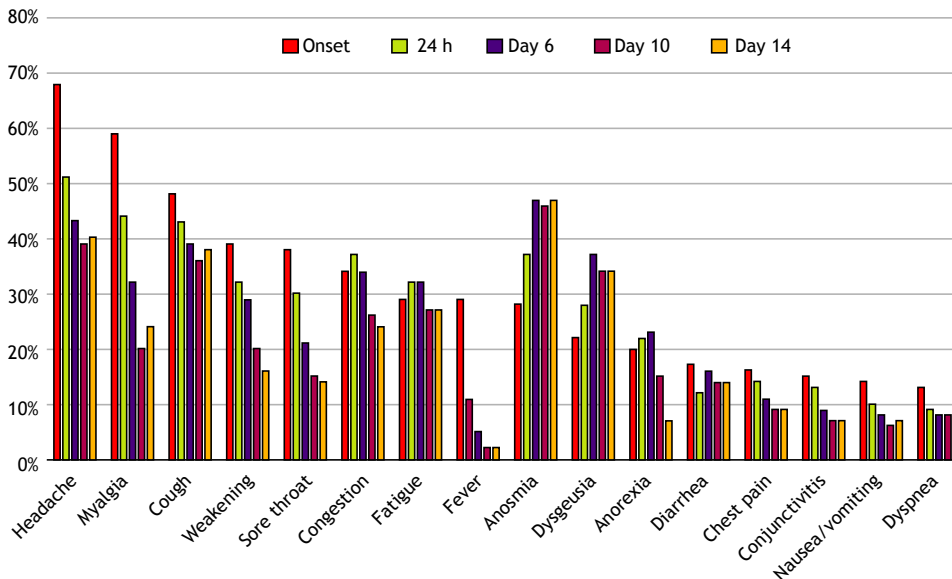

Figure 2. Symptom monitoring during the isolation period in symptomatic outpatients with a positive SARS-CoV-2 RT-PCR test result.

Table 3. Baseline characteristics of hospitalized and non-hospitalized patients during the isolation period.[a]

Characteristic	Group		p
	Hospitalized (n = 76)	Non-hospitalized (n = 1,541)	
Age, years	54 [0-88]	38 [0-100]	< 0.01
Sex			
Male	49 (64.5)	792 (51.4)	0.02
Comorbidities			
Hypertension	19 (25.0)	193 (12.5)	< 0.01
Diabetes	8 (10.5)	72 (4.7)	0.21
Obesity	5 (6.6)	105 (6.8)	0.93
Asthma	7 (9.2)	61 (4.0)	0.25
Cardiovascular disease	1 (1.3)	13 (0.8)	0.49
Current smokers	8 (10.5)	299 (19.4)	0.05
Onset symptoms	67 (88.2)	1114 (72.3)	< 0.01

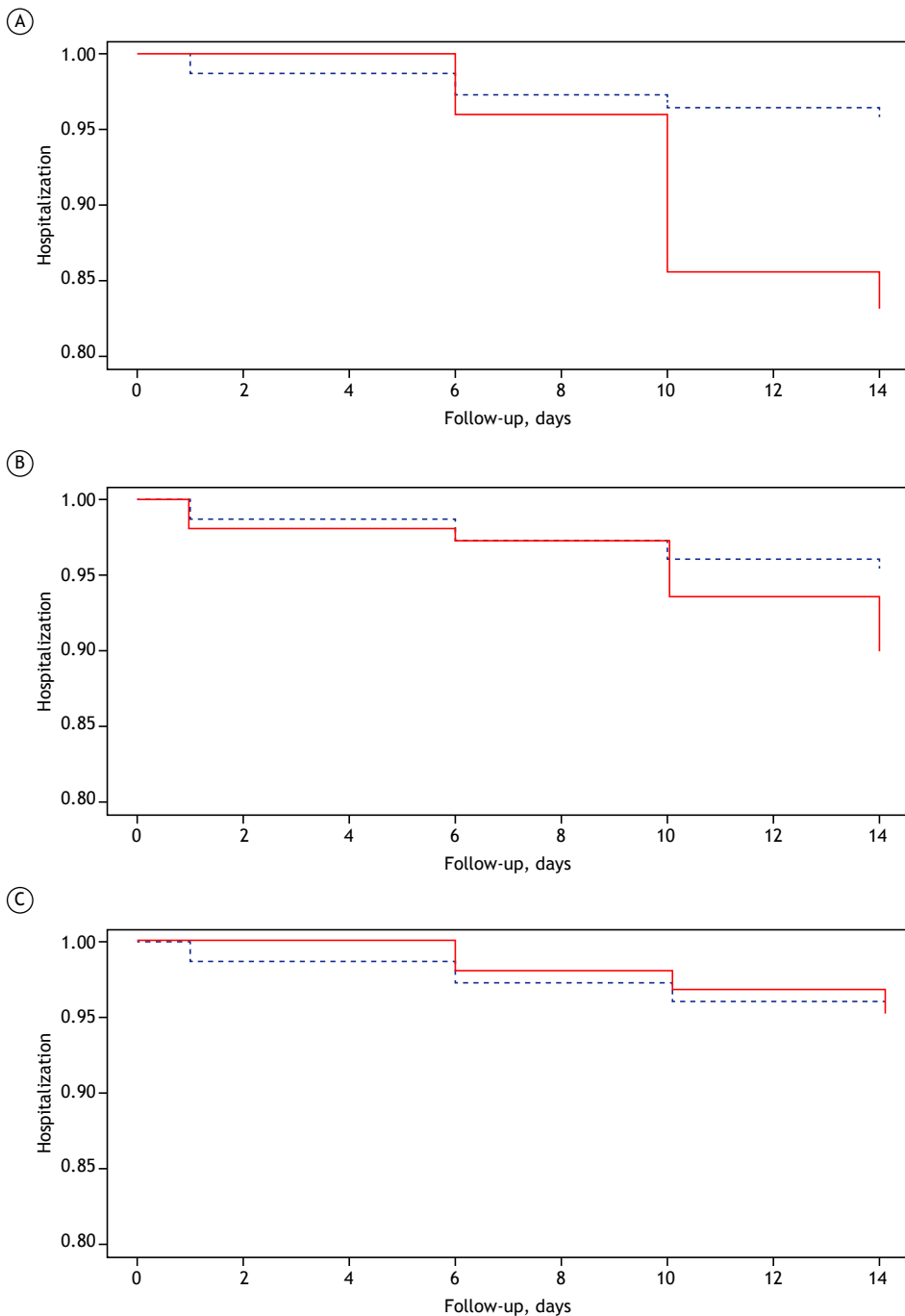[a]Values expressed as median [range] or n (%).

Figure 3. Survival analysis of the associations of new-onset fever (3A), new-onset dyspnea (3B), and new-onset chest pain (3C) with hospitalization.

Table 4. Summary of the association between red flags during follow-up and risk of hospitalization.

Variable	Unadjusted HR (95% CI)	p	Adjusted HR (95% CI)	p*
New-onset fever	4.18 (2.30-7.60)	< 0.01	7.43 (3.58-14.31)	< 0.01
New-onset dyspnea	2.33 (1.23-4.41)	< 0.01	5.27 (1.52-18.30)	< 0.01
New-onset chest pain	0.94 (0.43-2.06)	0.89	1.01 (0.46-2.21)	0.98

HR: hazard ratio. *Cox proportional hazard model adjusted by age, gender, diabetes, hypertension, obesity, asthma, cardiovascular disease, smoking history, number of comorbidities, fever, chest pain, and dyspnea at baseline.

we developed a survey-based follow-up intervention for 2 weeks including 7,108 outpatients infected with SARS-CoV-2 in Chile during the first 6 months of the pandemic. The main contribution of the present study

was the evaluation of three different "red flags" during the follow-up period and their associations with the risk of hospitalization. Although we found unadjusted associations between the three red flags and incident hospitalization, our adjusted analysis identified new-onset fever as the major risk factor. We found these results valuable, and further research, including a machine learning approach with training and validation datasets, is necessary.

Clinical characteristics, onset symptoms, and evolution of the patients during the isolation period have been described, thus contributing to knowledge regarding the natural history of this disease in its mild form to improve prevention measures and early detection of complications. In the overall sample, 7.6% of the patients were hospitalized at the time of testing, which is consistent with the results by Lechien et al.[3] that reported that 8% of the patients required hospitalization in a European cohort. Others have reported higher percentages (close to 20%), which were influenced by the smaller numbers of subjects studied.[7,8] In our study, the clinical characteristics were similar to those in previous studies.[7,9-12] The median age was 38 years (< 18 years of age = 6.3%), which is similar to a Chilean study including 1,125 outpatients (median age = 36 years [IQR, 28-50 years])[13] and other studies in Europe and North America.[3,8]

Regarding the onset symptoms attributable to COVID-19, the proportion of asymptomatic outpatients was higher than was that reported in other cohorts,[9] which may be explained by the massive testing performed in Chile regardless of symptomology, where only a medical order is required for the test. The most prevalent symptoms in outpatients were headache, myalgia, fever, and cough, which is consistent with other studies.[4,10]

The symptoms reported by the outpatients decreased as the isolation period progressed; however, on day 14, 28% of the patients still had symptoms attributable to COVID-19, which was also observed by Tenforde et al.,[8] who reported that 36% of the patients were symptomatic at 14-21 days after a positive SARS-CoV-2 test. Conversely, Bi et al.[5] estimated that the median recovery time from symptom onset was 20.8 days, which may imply that the isolation period should be increased, consequently resulting in further absences from work. This group of patients must be evaluated over a longer period to determine the impact of persistent symptoms and the long-term health repercussions for recovered patients.[14] Moreover, 56% of the asymptomatic patients who underwent testing developed symptoms during the isolation period, the vast majority of whom presenting symptoms between 1 and 6 days after testing.

During the isolation period, 5% of the patients reported having been hospitalized, most of whom were male, confirming reports from other studies that stated that the hospitalization rate for males was twice or three times higher than that for women.[15,16] In a retrospective multicenter study in the USA in which patients with a positive SARS-CoV-2 test result were contacted by telephone between 14 and 21 days after diagnosis, 8% of the patients reported requiring hospitalization during their isolation period.[8] Our smaller proportion of hospitalization cases during the period of isolation may be due to the greater number of asymptomatic patients (23% vs. 4% in that study[8]).

Virtual patient monitoring and counseling were possible in our center, which proved to be effective for investigating warning symptoms in 15% of the patients during the follow-up period. In the first stage, follow-up was conducted by phone; however, with the increase in the number of cases, telephone contact could not be maintained with all patients. Therefore, follow-up was continued via email. Surprisingly, this change decreased the patient response rate by only 9% (from 92% to 83%). This result shows that the follow-up of patients treated on an outpatient basis via email using an automated platform is possible, including continuous support from a health team that responds to the needs of patients, resolves concerns, and ensures timely referrals if warning symptoms emerge.[5] Special attention should be directed towards patients older than 60 years of age because the response rate in this age group was significantly lower (66% vs. 80% in those < 60 years) and because this age group has higher risks of complications and need for hospitalization.[10]

Our study has limitations. First, all the information in relation to symptoms and comorbidities was self-reported by the patients, which may result in information bias. Information about clinical outcomes during the isolation period (ICU admission and mortality) was not considered in the study protocol. Second, the results reflect the experience of a single center at the national level, which were acquired by analyzing 2% of RT-PCR-confirmed SARS-CoV-2 cases reported in Chile in the same period. Third, the proportion of patients lost to follow-up after a positive RT-PCR result was high, and this group of patients reported different characteristics when compared with those included in the cohort analysis, decreasing the applicability of the results. Further studies, including big data analyses, are necessary to validate our results. Despite the abovementioned limitations, a large cohort of outpatients was described and incorporated into an innovative virtual health monitoring system (REDCap platform), with a response rate close to 80%.

Knowing the demographic and clinical characteristics of patients in different populations is essential to address this pandemic. Email contact with outpatients with SARS-CoV-2 infection during self-isolation is possible and effective. This strategy allows continuous contact with patients and facilitates evaluations of risk symptoms in a timely manner, thus optimizing human resources in hospitals during a period of high health care demand. New-onset fever or dyspnea during the isolation period warrants a prompt medical evaluation.

AUTHOR CONTRIBUTIONS

DS, MM, MC, and MR: study design and execution. DS, MM, MR, JD and GL: data extraction and analysis.

DS, MM, JD and GL: drafting the manuscript. DS, MM, MC, MR, JD and GL: critical revision and final approval of the manuscript.

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