Outpatient Management of Patients With COVID-19

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Multicenter Prospective Validation of the Hospitalization or Outpatient Management of Patients With SARS-CoV-2 Infection Rule to Discharge Patients Safely

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BACKGROUND: The Hospitalization or Outpatient Management of Patients With SARS-CoV-2 Infection (HOME-CoV) rule is a checklist of eligibility criteria for home treatment of patients with COVID-19, defined using a Delphi method.

RESEARCH QUESTION: Is the HOME-CoV rule reliable for identifying a subgroup of COVID-19 patients with a low risk of adverse outcomes who can be treated at home safely?

STUDY DESIGN AND METHODS: We aimed to validate the HOME-CoV rule in a prospective, multicenter study before and after trial of patients with probable or confirmed COVID-19 who sought treatment at the ED of 34 hospitals. The main outcome was an adverse evolution, that is, invasive ventilation or death, occurring within the 7 days after patient admission. The performance of the rule was assessed by the false-negative rate. The impact of the rule implementation was assessed by the absolute differences in the rate of patients who required invasive ventilation or who died and in the rate of patients treated at home, between an observational and an interventional period after implementation of the HOME-CoV rule, with propensity score adjustment.

RESULTS: Among 3,000 prospectively enrolled patients, 1,239 (41.3%) demonstrated a negative HOME-CoV rule finding. The false-negative rate of the HOME-CoV rule was 4 in 1,239 (0.32%; 95% CI, 0.13%-0.84%), and its area under the receiver operating characteristic curve was 80.9 (95% CI, 76.5-85.2). On the adjusted populations, 25 of 1,274 patients (1.95%) experienced an adverse evolution during the observational period vs 12 of 1,274 patients (0.95%) during the interventional period: –1.00 (95% CI, –1.86 to –0.15). During the observational period, 858 patients (67.35%) were treated at home vs 871 patients (68.37%) during the interventional period: –1.02 (95% CI, –4.46 to 2.26).

INTERPRETATION: A large proportion of patients treated in the ED with probable or confirmed COVID-19 have a negative HOME-CoV rule finding and can be treated safely at home with a very low risk of complications.

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Take-home Points

Study Question: Is the HOME-CoV rule reliable for identifying a subgroup of patients with COVID-19 with a low risk of adverse outcomes who can be treated at home safely?

Results: Among patients with negative HOME-CoV rule findings who represented 41% of patients (1,239/3,000) seeking treatment at the ED with probable or confirmed COVID-19, 0.32% (4/1,239) experienced an adverse outcome (invasive ventilation or death) within the ensuing 7 days, the overall rate of complications being lower afterward vs before the implementation of the rule, but without significant difference in the rate of home treatment.

Interpretation: A large proportion of patients treated in the ED with probable or confirmed COVID-19 have negative HOME-CoV rule findings and can be treated safely at home with a very low risk of complications.

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The COVID-19 pandemic has led to significant increases in the demand for hospital beds and a shortage of medical equipment. To mitigate the burden on the health care system, while also providing the best possible care for patients, emergency physicians have to identify low-risk patients who can be treated at home and high-risk patients who require hospitalization and, in some cases, admission to an ICU.

Several risk assessment models for COVID-19 have emerged,[1-4] and pre-existing scores designed for pneumonia or sepsis also were evaluated for this purpose.[5,6] However, all these models seem to be at high risk of bias, and none has been validated in an implementation study.[7] Moreover, all of them were based on hospitalized patients and focused on the assessment of severity, rather than the identification of a subgroup of low-risk patients seeking treatment at the ED who can be discharged home safely.[7] Finally, for many patients treated at the ED with suspected COVID-19, the decision between hospitalization and home discharge needs to be made without waiting for biological confirmation with positive reverse-transcriptase polymerase chain reaction (RT-PCR) findings for SARS-CoV2.

Using a Delphi method, we previously developed the Hospitalization or Outpatient Management of Patients With SARS-CoV-2 Infection (HOME-CoV) rule aiming to help physicians in triaging patients with confirmed or probable COVID-19 for home treatment.[8] Eight clinical criteria precluding home treatment were selected, the HOME-CoV rule being deemed negative and allowing home discharge if none of them are met (Table 1).

To validate the HOME-CoV rule prospectively, we performed a pragmatic before-and-after study and hypothesized that the implementation of the HOME-CoV rule will be at least as safe as previous and current practices regarding the rate of patients with an adverse evolution at day 7 and will lead to a higher rate of patients being managed at home.

Methods

Study Design

The HOME-CoV study was a pragmatic prospective, multicenter before-and-after design trial conducted in the ED of 34 hospitals: 31 in France, 2 in Belgium, and 1 in the Principality of Monaco (e-Appendix 1).

Selection of Participants

Patients were eligible for inclusion if they provided informed consent, were at least 18 years of age, and had a symptomatic COVID-19 confirmed by positive RT-PCR results for SARS-CoV-2 or COVID-

TABLE 1] HOME-CoV Rule

The presence of one or more criteria corresponds to a patient at risk of pejorative evolution and should lead the physician to consider hospitalization:
Pulse oxygen saturation ≤ 94% in ambient air
Respiratory rate ≥ 25/min
Ability to talk without breathing < 8 s
Systolic BP ≤ 90 mm Hg
Heart rate ≥ 120 beats/min
Confusion or impaired consciousness
Clinically significant worsening within the last 24 h
Severe comorbidity[a] and inadequate living conditions[b]

HOME-CoV = Hospitalization or Outpatient Management of Patients With SARS-CoV-2 Infection.
[a]Severe chronic respiratory disease (unstable asthma, COPD stage III or IV, respiratory failure with continuous oxygen therapy), chronic heart failure (New York Heart Association class ≥ III), severe cognitive disorder, or immunodepression (primary immunodeficiency, uncontrolled HIV infection, immunosuppressive drug, chemotherapy).
[b]Inappropriate dwelling (homeless, frail relative at home, long-term care institution), lack of support person (family member or friend), or home follow-up impossible.

19 was the most likely hypothesis according to the physician in charge of the patient. Patients were excluded if they required care in an ICU or in a resuscitation unit, if a limitation decision of active therapies was made, if follow-up at day 28 would not be possible, and if they were an individual deprived of liberty by a judicial or administrative decision, under psychiatric care under duress, under a legal protection measure, or unable to express consent.

Study Procedures

The first period was observational and the decision between hospitalization and home treatment was left up to the emergency physicians according to their current practices. A transition period without inclusion of 4 days allows the HOME-CoV rule to be implemented in participating centers using telephone meetings, posters, and pocket cards (e-Appendix 2). During the interventional period, the physicians had to apply the HOME-CoV rule. Patients were selected for home treatment if all criteria were negative and for hospitalization otherwise (Table 1). The physician in charge could overrule this qualification in the case of imperative medical or social reasons.

During the two periods, data were collected prospectively. Patients were followed up with a standardized phone interview at day 7 and day 28 after inclusion in the study and their clinical status was recorded using the World Health Organization Ordinal Scale for Clinical Improvement (WHO OSCI)[9] for COVID-19 patients (e-Appendix 3). The date of each change in the WHO OSCI status, and especially the date of intubation, if applicable, also was recorded to allow analysis over time.

Methods of Measurement and Outcome Measures

HOME-CoV Rule Performance: The performance of the rule was assessed by the rate of patients with evolution to severe COVID-19 according to the WHO OSCI definition (stages 6-8), that is, requiring invasive ventilation, dying, or both, among patients with negative HOME-CoV rule findings within the 7 days after their inclusion (false-negative rate). The area under the receiver operating characteristic curve (AUC), sensitivity, specificity, negative and positive predictive value, and negative and positive likelihood ratio

also were calculated. A complementary analysis was performed at the 28-day follow-up, and a subgroup analysis was performed in patients with positive RT-PCR results for SARS-CoV-2.

Implementation of the HOME-CoV Rule: The impact of the implementation of the HOME-CoV rule was assessed by comparison between the observational period and the interventional period after adjustment using a weighting-based propensity score. The primary safety outcome was the rate of patients undergoing invasive ventilation or dying within the 7 days after inclusion. The primary efficacy outcome was the rate of patients treated at home, defined as patients discharged home within 24 h after presentation at the ED.

We performed subgroup analysis in patients treated at home and with negative or positive HOME-CoV rule findings and in hospitalized patients with negative or positive HOME-CoV rule findings. We performed sensitivity analyses with the following outcomes: (1) an adverse evolution (ie, invasive ventilation or death) within 28 days after inclusion and (2) a poor outcome defined as a patient hospitalized and requiring at least oxygen support (stages 4-8 of the WHO OSCI) within 7 days of inclusion.

Statistical Analysis

For descriptive analyses, quantitative variables were reported as mean ± SD when their distribution can be considered as Gaussian and otherwise as median and interquartile range. Qualitative variables were reported using numbers and proportions. Comparisons were performed using the Student or Mann-Whitney tests for quantitative variables and using the Fisher exact test for qualitative variables. We used a predefined threshold of ≥ 1 and considered that the upper limit of the 95% CI of the false-negative rate should be lower than 2% for validation of the HOME-CoV rule.[10]

For comparison between the observational period and the interventional period, weighting-based propensity scores (inverse probability weighting) were used to account for individual profile differences between the two periods. All major variables available at the time of ED presentation were considered in the model (e-Fig 1. As soon as the patient profiles were balanced between the two phases, a logistic regression was performed that included a random effect on the center enabling computation of the CI for the difference in event rates between the two periods.[11,12] We used a hierarchical approach. The first step was a noninferiority (one-sided) analysis on the primary safety outcome (ie, adverse evolution with invasive ventilation or death) with a prespecified noninferiority margin of 2%. The second step was a superiority analysis (two-sided) on the rate of patients treated at home. $P < .05$ was considered to be statistically significant.

The compliance with the HOME-CoV rule defined as the proportion of patients with negative HOME-CoV rule findings who were actually treated at home after ED presentation also was assessed.

The hierarchy of objectives allowed us to avoid the problem of multiplicity as much as possible. No imputation of missing data was performed.[13] Descriptive analysis of these data was performed using the naniar package and was compared with no missing data to consider a potential bias.

Considering a noninferiority margin of 2% and a 5% incidence rate of the primary end point in each period, and assuming a dropout rate of 5%, 1,542 patients per study period were needed to achieve 80% power using a one-sided α level of 5%.[14] Statistical analyses were performed using R software version 3.5.1 (R Foundation for Statistical Computing) and the following R packages: pec, WeigthIt package, and Survey.[15]

Ethical Considerations

The HOME-CoV study obtained approval from the Comité de Protection des Personnes Ouest IV—Nantes on March 4, 2020

Results

Characteristics of the Patients

A total of 3,133 patients with confirmed or probable SARS-CoV-2 infection were enrolled prospectively, 1,763 during the observational period from April 9 through April 18, 2020, and 1,370 during the interventional period from April 21 through May 11, 2020. The capacity rate of ICUs in France was 106% and 99% during the first and the second period, respectively. Among the patients included, 3,000 completed day 7 follow-up and 133 (1.02%) were lost to follow-up (no significant difference between the two periods) (Fig 1). Patient characteristics at baseline are presented in Table 2. The median age was 53.4 years, and 54.5% of patients were women. The median time between the onset of symptoms and the ED visit was 5 days (interquartile range, 2-12 days) and 45% of the patients (n = 1,409) experienced a clinically significant worsening within the last 24 h. Inadequate living conditions were observed for 414 patients (13.8%): 186 patients with inappropriate dwelling (homeless, frail relative at home, long-term care institution), 245

patients without a support person, 55 patients for whom follow-up was not possible, and 66 patients having several criteria of inadequate living conditions. COVID-19 was confirmed by RT-PCR analysis for SARS-CoV-2 in 529 patients (e-Table 1). CT scans showed strong evidence of COVID-19 infection in 581 patients, 234 patients showing positive RT-PCR results and chest CT scan findings suggestive of COVID-19. After ED assessment, 2,066 patients were treated at home (65.94%), and among them, 36 were admitted secondarily to hospital within the 7 days after the inclusion in the trial (1.74%). Among hospitalized patients (n = 1,067/3,133 [34.06%]), 491 (46.02%) were still hospitalized at day 7. In the overall population within the 7 days after ED presentation, 223 patients (7.4%) required oxygen therapy, 28 patients (0.9%) required noninvasive ventilation, and 57 patients (1.9%) met the primary outcome: 19 patients (0.6%) required intubation and invasive ventilation and 38 patients (1.3%) had died. At day 28, 85 of 2,912 patients (2.9%) had experienced an adverse evolution, 5 (0.2%) had been intubated, and 80 (2.7%) had died (e-Table 2).
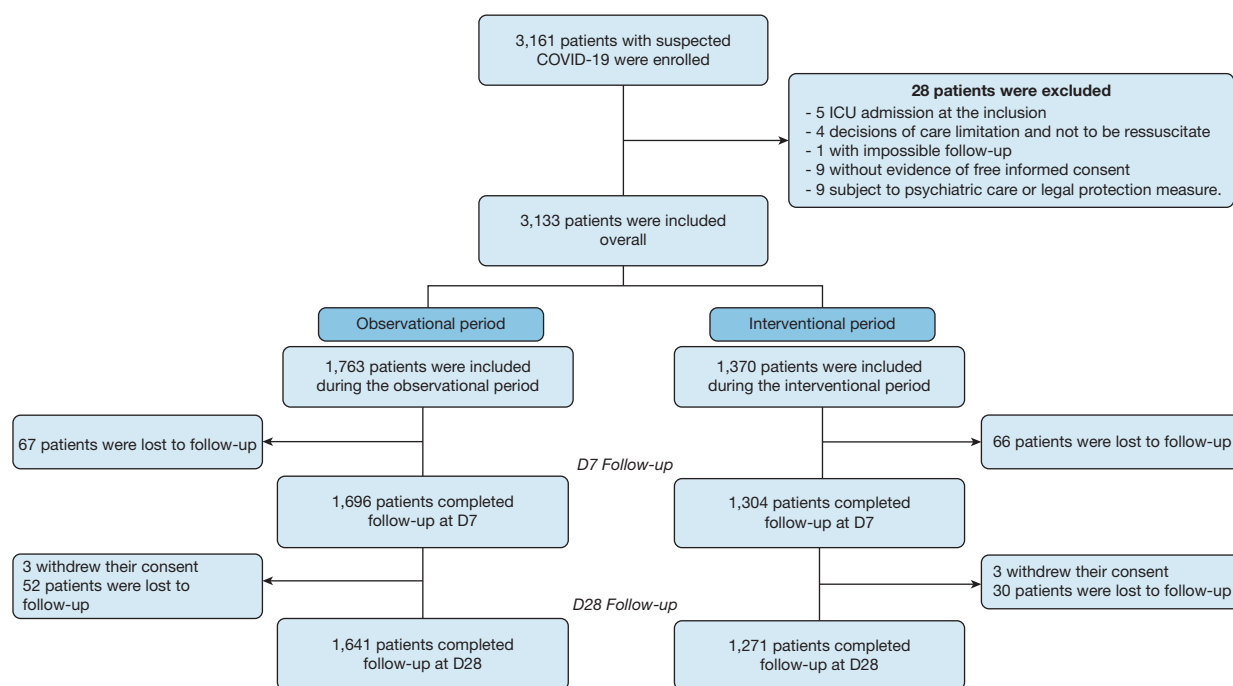

Figure 1 – Hospitalization or Outpatient Management of Patients With SARS-CoV-2 Infection Study flowchart.

TABLE 2] Baseline and Adjusted Characteristics of the Patients in the Observational and Interventional Periods

Patient Characteristic	Prior Weighting-Based Propensity Score		After Weighting-Based Propensity Score	
	Observational Period (n = 1,763)	Interventional Period (n = 1,370)	Observational Period (n = 1,274)	Interventional Period (n = 1,274)
Demographic characteristics				
Age, y	54.2 ± 19.8	52.3 ± 19.8	52.9 (19.7)	52.6 (19.9)
Female sex	952 (54)	757 (55.3)	704 (55.3)	705 (55.3)
Medical history				
Severe cognitive impairment	18 (1.0)	6 (0.4)	10 (0.8)	7 (0.5)
COPD stage III or IV	33 (1.9)	23 (1.7)	22 (1.7)	22 (1.7)
Chronic respiratory failure	27 (1.5)	18 (1.3)	18 (1.4)	17 (1.3)
Controlled or unstable asthma	181 (10.3)	151 (11)	148 (11.6)	140 (10.9)
Severe or end-stage renal disease (GFR < 30 mL/min)	38 (2.2)	18 (1.3)	18 (1.4)	17 (1.3)
Hepatic cirrhosis Child B or Child C	10 (0.6)	7 (0.5)	7 (0.5)	6 (0.5)
Chronic cardiac failure NYHA class III or IV	24 (1.4)	13 (0.9)	14 (1.1)	13 (1.0)
Hypertension	530 (30.1)	361 (26.4)	345 (27.1)	343 (26.9)
Diabetes	226 (12.8)	145 (10.6)	136 (10.7)	133 (10.4)
History of thromboembolism	96 (5.4)	71 (5.2)	65 (5.1)	66 (5.2)
Cancer history or active cancer	162 (9.2)	117 (8.5)	118 (9.3)	112 (8.8)
Immune deficiency and HIV	56 (3.2)	35 (2.6)	32 (2.5)	32 (2.5)
Inadequate living conditions	272 (15.4)	142 (10.4)	140 (11.0)	139 (10.9)
Signs and symptoms				
Anosmia, ageusia, dysgeusia	511 (29)	312 (22.8)	291 (22.8)	244 (19.2)
Cough	1,175 (66.6)	837 (61.1)	763 (59.9)	770 (60.4)
Dyspnea	1147 (65)	815 (59.5)	753 (59.1)	737 (57.8)
Diarrhea	481 (27.3)	385 (28.1)	320 (25.1)	346 (27.1)
Chest pain	635 (36.0)	513 (37.4)	463 (36.3)	462 (36.3)
Confusion, impaired alertness	92 (5.2)	44 (3.2)	43 (3.4)	43 (3.4)
Worsening in the last 24 h	869 (49.3)	540 (39.4)	500 (39.2)	498 (39.1)
Heart rate ≥ 120 beats/min	90 (5.1)	100 (7.3)	92 (7.2)	94 (7.4)
Systolic BP < 90 mm Hg	12 (0.7)	8 (0.6)	9 (0.7)	10 (0.8)
Temperature, °C	37.03 ± 1.0	36.8 ± 1.0	36.9 ± 0.9	39.9 ± 1.0
BMI ≥ 30 kg/m²	230 (13.0)	203 (14.8)	205 (16.1)	206 (16.2)
Pulse oxygen saturation ≤ 94% in ambient air or necessity of oxygen therapy	399 (22.6)	259 (18.9)	268 (21.0)	272 (21.4)
Respiratory rate ≥ 25/min	310 (17.6)	192 (14)	197 (15.5)	198 (15.5)
Ability to speak or count without resuming breathing < 8 s	209 (11.9)	99 (7.2)	103 (8.1)	105 (8.2)

Data are presented as No. (%) or mean ± SD. GFR = glomerular filtration rate; NYHA = New York Heart Association.

HOME-CoV Rule Performance

In the overall population, 1,239 of 3,000 patients (41.3%) had negative HOME-CoV rule findings. Among them, 3 patients required intubation and invasive ventilation and 1 patient died within the 7 days after ED presentation (n = 4/1,239) (Table 3). The false-negative rate of the HOME-CoV rule was 0.32% (95% CI, 0.13%-0.84%), meeting the predefined threshold of the upper limit of the 95% CI (< 2%). The AUC was 80.9 (95% CI, 76.5-85.2). At day 28, the AUC was 80.65 (95% CI, 76.41-84.88). Six of the 1,239 patients with initial negative HOME-CoV rule findings experienced an adverse evolution within the 28-day follow-up. The false-negative rate was 0.48 (95% CI, 0.22-1.08). In the subgroup of patients with positive RT-PCR results for SARS-CoV-2 (n = 529), the AUC was 78.47 (95% CI,

HOME-CoV Rule Findings	Total (N = 3,000)	Patients With Adverse Evolution (n = 57)	Patients Without Adverse Evolution (n = 2,943)
Positive	1,761	53	1,708
Negative	1,239	4	1,235

Data are presented as no. of patients. HOME-CoV = Hospitalization or Outpatient Management of Patients With SARS-CoV-2 Infection. Sensitivity, 0.93 (95% CI, 0.84-0.98). Specificity, 0.42 (95% CI, 0.40-0.44). Negative predictive value, 0.996 (95% CI, 0.98-1.00). Positive predictive value, 0.29 (95% CI, 0.13-0.35). Negative likelihood ratio, 0.16 (95% CI, 0.06-0.42). Positive likelihood ratio, 3.03 (95% CI, 2.56-3.58).

74.79-86.19) at day 7. The false-negative rate of the HOME-CoV rule in this subgroup was 0.28% (95% CI, 0.05%-1.58%).

Implementation of the HOME-CoV Rule

After using a weighting-based propensity score and excluding patients who could not be assessed at day 7, 1,274 patients were included in the adjusted population of each period (Table 2). Patient characteristics were similar between the two periods (Table 2). The evolution of the patients according to the WHO OSCI is noted in Figure 2.

In the adjusted population, 12 patients (0.95%) experienced an adverse evolution at day 7 during the interventional period vs 25 patients (1.95%) during the observational period. The absolute difference was –1.00 (95% CI, –1.86 to –0.15), meeting the noninferiority predefined criterion (P < .01 for noninferiority) and showing a statistically significant difference in favor of the interventional period (P = .004 for superiority). The difference between the two periods mainly depended on the difference observed in the subgroup of hospitalized patients with positive HOME-CoV rule findings: –4.4 (95% CI, –5.7 to –2.4) (Table 4). In the adjusted population, 89.3% of patients (560/627) with negative HOME-CoV rule findings were treated at home during the interventional period, and none of them was hospitalized subsequently.
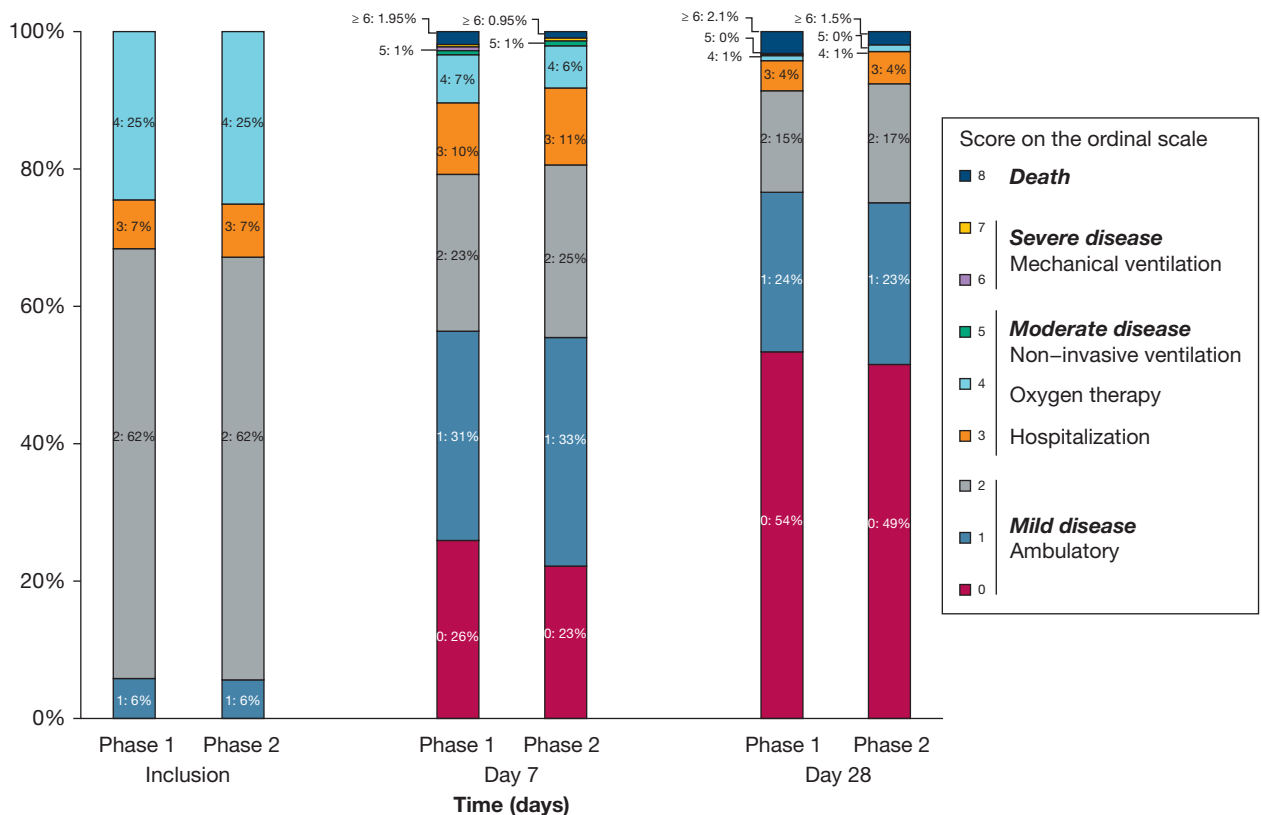
Figure 2 – Bar graph showing classification of patients according to the two periods and to the World Health Organization Ordinal Scale of Clinical Improvement of COVID-19 at inclusion, day 7, and day 28.

HOME-CoV Rule Findings	Management	Observational Period		Interventional Period		Comparison: Absolute Difference (95% CI)
		No. of Patients	%	No. of Patients	%	
Patient management						
Positive	Home treatment	374/1,243	30.1	296/1,235	24	−6.1% (−9.5% to −2.6%)
	Hospitalization	320/1,243	25.7	312/1,235	25.26	−0.4% (−3.9% to 3.0%)
Negative	Home treatment	474/1,243	38.1	560/1,235	45.3	+7.2% (3.3%-11.1%)
	Hospitalization	75/1,243	6.0	67/1,235	5.4	−0.6% (−1.2% to 2.5%)
Evolution toward severe COVID-19[a]						
Positive	Home treatment	1/374	0.3	1/296	0.3	0
	Hospitalization	31/320	9.8	17/312	5.4	−4.4% (−5.7% to −2.4%)
Negative	Home treatment	0/474	0	0/560	0	0
	Hospitalization	3/75	3.4	1/67	1.5	−1.9% (−3.2% to −0.8%)

HOME-CoV = Hospitalization or Outpatient Management of Patients With SARS-CoV-2 Infection.
[a]Severe COVID-19 was defined as cases in which patients were either undergoing mechanical ventilation or dead.

During the interventional period, 871 patients (68.38%) were treated at home vs 858 patients (67.33%) during the observational period without significant absolute difference: –1.02 (95% CI, –4.46 to 2.26). During the interventional period, compliance with the HOME-CoV rule was 90% (n = 618/687), and more patients with negative HOME-CoV rule findings were treated at home than during the observational period: +7.2 (95% CI, 3.3-11.1) (Table 4).

Sensitivity Analyses

At day 28 in the adjusted population, 21 of 1,235 patients (1.7%) experienced an adverse evolution during the interventional period vs 40 of 1,232 patients (3.2%) during the observational period. The absolute difference was –1.5 (95% CI, –0.4 to –2.6). The results were similar when using the rate of poor outcome at day 7 as a judgment criterion, that is, patients requiring oxygen therapy or noninvasive or invasive ventilation or who had died (e-Table 3).

Discussion

This prospective multicenter study validated the HOME-CoV rule as a helpful tool in deciding whether to opt for home treatment in patients treated in the ED with confirmed or probable COVID-19. Negative HOME-CoV rule findings qualified a large subgroup of patients at very low risk of adverse outcome. The rate of patients who required invasive ventilation or who died within the 7 days after ED presentation was lower with HOME-CoV rule implementation than in the previous observational period. More than two-thirds of patients were treated at home without significant difference between the two periods.

Several risk-stratification models are proposed for COVID-19 patients.[8] The goal of most of them is to identify high-risk patients requiring intensive care—ie, the Quick-COVID Severity Index,[1] the COVID-GRAM score,[16] and the score developed by Xie et al[17]—and all of these were based on hospitalized patients with COVID-19. As with the Pulmonary Severity Index for patients with community-acquired pneumonia,[18] the HOME-CoV rule was designed specifically to help emergency physicians in deciding whether to opt for home treatment over hospitalization in patients with COVID-19. Moreover, as in the ED, the RT-PCR results for SARS-CoV2 were unknown for many patients with suspected COVID-19; patients with typical signs of COVID-19 therefore were included, provided that the physician considered COVID-19 as the main diagnostic hypothesis. Although testing has become widespread, results still take time, and waiting for them will prolong patients' length of stay in the ED, and thus risk overburdening health care provisions. The HOME-CoV

Study was designed as a pragmatic trial dealing with the real issues at hand when deciding between outpatient care or hospitalization. This reinforces the applicability of our results.

During the interventional period, in the adjusted population, more than half of the patients showed negative HOME-CoV rule findings, and the emergency physician in charge complied with the rule for 90% of patients. As a result, 45% of the patients had negative rule findings and were discharged home after ED assessment. None of them experienced an adverse outcome. However, our study failed to show a significant increase in the rate of patients managed at home with the implementation of the HOME-CoV rule, with one-third of patients being hospitalized during each period, a rate in line with recent publications: 32% in a large cohort in New York City and 28% in the Danish nationwide cohort.[19,20] Indeed, the increase in the rate of patients with negative rule findings who were managed at home was balanced out by a decrease in the rate of patients with positive rule findings who were discharged to their homes. This result suggests that physicians, in their decision-making, took individual patient risk assessment into account to a greater extent when they applied the HOME-CoV rule than when they used their own judgment. However, it also suggests an overuse of the HOME-CoV rule. Indeed, the HOME-CoV rule was intended to define criteria for home treatment (if negative), rather than criteria for hospitalization (if positive). Our trial confirms that patients with negative rule findings had a very low risk of adverse outcome and could be treated at home safely, but it also shows that some patients with positive rule findings could be treated at home with a low risk of adverse outcome, also. This result could be explained by the organization of a close ambulatory follow-up of patients with probable or confirmed COVID-19 in many hospitals to increase home treatment. Another explanation could be the impact of the local caseload in the ED and in the hospital. Because of the before-and-after design of our study, a lower hospital caseload during the interventional period is likely and may have influenced the rate of hospitalization of patients with positive HOME-CoV rule findings. Indeed, a qualitative study of decision-making among emergency physicians shows that the extent to which the ED is busy has an influence on decisions to increase patient admissions.[21]

The rate of adverse outcomes defined as invasive ventilation or death was low as compared with previous studies and significantly lower during the interventional period than the observational period. This could be related to a decrease over time in the use of intubation for the benefit of noninvasive ventilation of patients with COVID-19.[22] However, a similar trend was observed when we considered hospitalization with oxygen therapy or all-cause mortality as a judgement criterion. It is notable that the difference in adverse outcome was observed only in hospitalized patients, for which the most likely explanation is a multifactorial improvement of care including corticoid and antiviral therapy, thromboprophylaxis, and respiratory failure management.[23]

The strength of our trial is its large panel of participating centers and patients and its prospective and pragmatic design. This reinforces the generalizability and applicability of our results. We included patients with confirmed or probable COVID-19, thus corresponding to the actual daily ED population that may benefit from the implementation of the HOME-CoV rule as a tool in decision-making.[24] Moreover, the same results were observed in the overall population and in the subgroup of patients with positive RT-PCR results for SARS-CoV2, reinforcing their validity. Finally, the HOME-CoV rule is based exclusively on clinical criteria that are easy to assess, even by phone, and may be a helpful tool not only for all frontline and emergency physicians, but also for general practitioners, geriatricians, and infectious disease consultants.

Our study has some limitations. First, we used a quasiexperimental before-and-after design by taking into account resource constraints (the EDs faced with the pandemic) and time constraints (the need to provide prospective validation of the HOME-CoV rule and practice guidelines as soon as possible). Our results optimally should be confirmed in a formal cluster randomized trial. Second, the rate of patients who experienced an unfavorable outcome and required invasive ventilation or who died was lower than expected at the time we designed the trial. Indeed, recent data have demonstrated mortality rates lower than those observed in the early phases of the epidemic in Wuhan.[14,25] Furthermore, and in contrast to previous studies, patients with severe cases of the disease at admission and requiring immediate intensive care were excluded. Indeed, the severity of these patients' symptoms was such that home treatment was not even an option.

Interpretation

Negative HOME-CoV rule findings qualified more than 40% of patients treated in the ED with probable or confirmed COVID-19 for home treatment, with a very low risk of adverse outcome.

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