

Outpatient management or hospitalization of patients with proven or suspected SARS-CoV-2 infection: The HOME-CoV rule.

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Abstract

In the context of the COVID-19 pandemic and overloaded hospitals, a central issue is the need to define reliable and consensual criteria for hospitalization or outpatient management in mild cases of COVID-19. Our aim was to define an easy-to-use clinical rule aiming to help emergency physicians in hospitalization or outpatient management decision-making for patients with suspected or confirmed SARS-CoV-2 infection (the HOME-CoV Rule). The Delphi method was used to reach a consensus of a large panel of 51 experts: emergency physicians, geriatricians, infectious disease specialists, and ethical consultants. A preliminary list of eligible criteria was compiled based on a literature review. Four rounds of anonymized expert consultations were performed. The experts were asked to score each item as relevant, possibly relevant and non-relevant, as major or minor, and to choose the cut-off. They were also able to make suggestions and remarks. Eight criteria constituting the HOME-CoV were selected: six correspond to the severity of clinical signs, one to the clinical course (clinically significant worsening within the last 24 hours), and the last corresponds to the association of a severe comorbidity and an inadequate living context. Hospitalization is deemed necessary if a patient meets one or more of the criteria. In the end, 94.4% of the experts agreed with the defined rule. Thanks to the Delphi method, an absolute consensus was obtained of a large panel of experts on the HOME-CoV rule, a decision-making support mechanism for clinicians to target patients with suspected or confirmed COVID-19 requiring hospitalization.

Trial registration: NCT04338841

Introduction

The novel coronavirus (SARS-CoV-2) has spread worldwide and the coronavirus disease (COVID-19) is responsible for more than 2,5 million cases globally (04/23/2020) [1]. The classification of COVID-19 as a pandemic by the World Health Organization on 11 March 2020 alerted every country-specific health care system to the need for an urgent response to the requirements and challenges of this unprecedented situation. Because the spectrum of forms of the disease varies from asymptomatic to severe, public health systems have been mobilized at all levels [2]. Most cases during the outbreak of COVID-19 in China were reported by the Chinese Center for Disease Control and Prevention (CDC) team in a large cohort of 72,314 patients and 81% were classified as mild (non-pneumonia and mild pneumonia) and 14% were severe [3]. There is growing concern that the healthcare system, and intensive care units (ICU) and emergency departments (ED) in particular, will not be able to cope with the scale of the outbreak. Many models have predicted demand would rapidly exceed hospital capacities in most countries [4–6]. The excessive hospitalization of patients with only mild symptoms may lead to overloaded hospitals. In this context, the decision between hospitalization or outpatient management in cases of mild COVID-19 in ED is crucial.

In pneumonia patients or in patients with sepsis, many riskassessment score matrices and decision-making tools, such as thePulmonary Severity Index (PSI), CRB 65, CURB65, sequential organfailure assessment (SOFA) and quick sequential organ failureassessment (qSOFA), exist to identify low-risk patients [7–10].However, most of them cannot be used to quickly identify low-riskpatients in ED because they incorporate biological or imagingparameters (PSI, CURB-65, SOFA). In addition, they do not integrateall pragmatic elements that are taken into account in anorientation decision such as decompensated comorbidity or inabilityto take medication or inadequate follow-up care once the patienthas been discharged.

Our aim was to define an easy-to-use clinical rule aiming tohelp emergency physicians decide between hospitalization oroutpatient management for patients with suspected or confirmedSARS-CoV-2 infection (the HOME-CoV Rule:**H**ospitalization or **O**utpatient**M**anag**E**ment of patients with**SARS-CoV-2** infection).

Methods

A Delphi method was used to develop a list of items that willconstitute the HOME-CoV rule. In short, the Delphi method consistsof a multiple-round questionnaire sent to a panel of experts who,through participating in a series of rounds, collectively identifyrelevant candidate items [11]. After each round, the experts aregiven results of the group trends and are asked to reconsider theirinitial opinion for items with low agreements (<75%) in thelight of these trends. A consensus for decision making is usuallyobtained by four rounds. We used an electronical survey through thebuilt-in tools GoogleForms® website with the aim to finish theprocess in less than two weeks.

Preliminary phase

The main investigators (DD, RM and PMR) began by reviewing theliterature on the characteristics of COVID-19 patients at high riskof progression to a severe illness. Because of the limitedpublished data, pre-print studies were also considered. A preliminary list of pre-existing conditions and clinicalcharacteristics associated with a greater risk of diseaseprogression to a severe illness was defined by the study'sscientific committee composed of 7 experts in emergency medicine,infectious diseases, geriatrics, and ethics. The preliminary listincluded 10 clinical and disease course criteria, 22 comorbiditiesand treatments, and 3 living conditions (table 1).

Preliminary list of criteria

characteristics and course	Thresholdvalue			
rryrate	≥22/min	≥25/min	≥30/min	
al oxygensaturation	≤90%	≤92%	≤94%	
talk without stopping th	< 5sec	< 8sec	< 10sec	
ssure	SystolicBP ≤ 100mmHg	SystolicBP ≤ 90mmHg	SystolicBP≤90mmHg & diastolic BP ≤ 60mmHg	
le	≥ 110bpm	≥ 120bpm	≥ 125bpm	
n or consciousness	NA			
emia	≤35°C	≤36°C		
ermia	≥39°C	≥40°C	≥41°C	
r significant worsening elast 24 hours.	NA			
n the onset of initial s and admission 7 days to10 days	-	-	-	-
dities				
	≥ 65y*	≥ 70y*	≥ 75y*	≥ 80y*
ss Index	≥30kg/m ²	≥35kg/m ²	≥40kg/m ²	
edisorder	mild	moderate	severe	-
	Anystage	StageIII/IV	-	-
ory failure with us oxygentherapy	-	-	-	-
	Anystage	Controlled with systemic glucocorticoidtherapy	unstable	-
enal failure	Moderate(GFR<60 mL/min)	Severe(DFG< 30ml/min)	Terminal	dialysis
	Anystage	StageChild B or C	StageChild C	-
heart failure	Anystage	NYHA ≥III	-	-
ypertension	-	-	-	-
	-	-	-	-

vascular disease	-	-	-	-
artery disease	-	-	-	-
history of VTE†	-	-	-	-
ancer	History of cancer	Active cancer	Cancer receiving chemotherapy	-
immunodeficiency Virus	History of HIV	Uncontrolled HIV	-	-
immunodeficiency	-	-	-	-
cy	Any term	3rd trimester	-	-
itor or ARB	-	-	-	-
oidal anti-tubercular drug	-	-	-	-
glucocorticoid therapy	Any dosage	Dosage > 10 mg/d		
uppressed drug	-	-	-	-
Conditions				
riate dwelling (e.g., frail relative at long-term institution)	-	-	-	-
upport person (family or friend)	-	-	-	-
low-up impossible (no practitioner, telephone not possible, etc.)	-	-	-	-

*y : years †VTE: Venous Thrombo-Embolism

Delphi Panel

An invitation to participate to the Delphi method was sent to 64 French and Belgian physicians working in ED, infectious diseases departments, ICU and geriatric medicine and two experts in ethics. They were selected according to their clinical experience in rule-based decision-making and their interest in the field of COVID-19. The main investigators were not included in the panel of experts for the subsequent Delphi method questionnaire. The experts were asked to respond to each item in regard to the purpose of the HOME-CoV rule.

Data collection

The four-round Delphi method took place between April 4 and April 16, 2020. Experts were asked to rate each criterion for its relevance (relevant, possibly relevant, non-relevant), for the best cut-off value (1 to 4 proposed cut-off value if applicable) and for its level of significance (major or minor criteria) (table 1). One major criterion or two combined minor criteria will require hospitalization.

For the first round, a questionnaire was sent through an electronic survey with the preliminary list of criteria selected by the scientific committee. The experts were asked to score each item into 3 categories of relevance (relevant, possibly relevant, and non-relevant) and 2 categories of significance (major or minor). For non-binary items (ordinal or continuous variables), the experts had to select a “cut-off value” among 1 to 4 proposals sourced from research literature. They could also propose additional criteria or other cut-off values and make anonymous comments. The duration of each round was 72 hours with an electronic reminder every 24 hours. The results were analyzed by the main investigators, with details of the experts who made suggestions or comments anonymized. At the end of the first and the second rounds, items considered as relevant with a strong agreement between experts ($\geq 75\%$) were selected and incorporated in the rule. Items considered as non-relevant or facultative by 75% of the experts were excluded. The same rule was applied to consider each item as major or minor and to define the cut-off. Values that achieved an agreement $\geq 75\%$ were selected. Criteria that did not fulfill these conditions were subjected to the next round. On the basis of the comments of the experts, the main investigators proposed some groupings and/or clarifications and submitted them to the experts again.

In the second round, the experts were asked to reconsider their opinions and to score the new proposals taking into account the results of the last step, the group trends, and the anonymized comments of the others.

In the third round, the option “possibly relevant” was removed as well as the cut-off value with the lowest agreement for those items concerned. The experts were so asked to make a choice between only two options for the remaining criteria: relevant or non-relevant; major or minor; cut-off 1 or cut-off 2.

Finally, in the last round, the experts were asked to validate or reject the overall criteria constituting the HOME-CoV rule.

Ethics

This research project is part of an important trial that obtained approval from the *Comité de Protection des Personnes Ouest IV – Nantes* on 4th March 2020 (36/20_2). The sponsor of the study is CHU d'Angers (Angers University Hospital), Delegation for Clinical Research and Innovation. Approval for this study was obtained from all participants who gave their written informed consent.

Results

Among the 64 who were approached to participate, 51 experts agreed (80%). Among them, 47 experts participated in the first and the second rounds (92%), 42 (82%) in the third, and 37 (72.5%) in the fourth

round of the Delphi method.

In the first round, among the 35 items of the preliminary list, seven items were classified as relevant (i.e. respiratory rate, peripheral capillary oxygen saturation, ability to speak, blood pressure, consciousness or confusion, home follow-up impossible, and clinically significant worsening within 24 hours). Twelve items were rejected. Details, and particularly those pertaining to the classification as major or minor and the cut-off values, are mentioned (Supplementary Table 1).

In the second round, 18 unclassified items were proposed to the experts and 3 more items were classified as relevant (i.e. chronic severe respiratory disease, inappropriate dwelling in which containment is complicated, and lack of support person), and 3 items were rejected (Supplementary Table 2).

Table 2. HOME-CoV rule
Respiratory rate ≥ 25 /min
Pulse oxygen saturation $\leq 94\%$ in ambient air
Ability to talk without breathing < 8 sec
Systolic blood pressure ≤ 90 mmHg
Heart rate ≥ 120 beats/min
Confusion or impaired consciousness
Clinically significant worsening within the last 24 hours
Severe comorbidity* AND inadequate living conditions [†]

* Severe chronic respiratory disease (unstable asthma, COPD stage III or IV, respiratory failure with continuous oxygen therapy), chronic heart failure (NYHA \geq III), severe cognitive disorder, or immunodepression (primary immunodeficiency, uncontrolled HIV, immunosuppressive drug, chemotherapy)

[†] Inappropriate dwelling (homeless, frail relative at home, long term care institution), lack of support person (family member or friend), or home follow-up impossible.

In the third round all remaining items were classified: 3 as relevant (i.e. severe cognitive disorder, chronic heart failure, and immunodepression); and 1 was rejected. Grouping severe comorbidity and inadequate living conditions together in one criterion was proposed. Severe comorbidity includes severe chronic respiratory disease (unstable asthma, chronic obstructive pulmonary disease (COPD) stage III or IV, and respiratory failure with continuous oxygen therapy), chronic heart failure (NYHA \geq III), severe cognitive disorder, or immunodepression (primary immunodeficiency, uncontrolled HIV, immunosuppressive drug, or chemotherapy). Inadequate living conditions include inappropriate dwelling (homeless, frail relative at home, long term care institution), lack of support person (family member or friend), or home follow-up impossible (Supplementary Table 3).

The final rule includes 8 criteria: 6 items correspond to clinical signs of severity, 1 to the disease course and the last 1 to the association of a severe comorbidity and an inappropriate living condition. (table 2). The presence of one or more criteria should lead the physician to consider hospitalization.

In the last round, the final HOME-CoV rule was submitted to the experts and achieved an agreement of 94.4% of the experts (n=34/36).

Discussion

Using a Delphi method, the panel of 51 experts designed the HOME-CoV rule based on 8 clinical criteria to help physicians decide between hospitalizing patients with mild COVID-19 symptoms or treating them as outpatients. Hospitalization is deemed necessary if a patient with COVID-19 meets one or more criteria consisting of 6 major clinical signs, has experienced clinically significant worsening within the last 24 hours, or has a severe comorbidity and inadequate living conditions. Conversely, when no criteria of the rule are met, outpatient management should be considered. For example, a 54-year-old man presenting to the ED with symptoms consistent with COVID-19 (ageusia, myalgia, and fever) and unable to speak or to count without taking a breath more than 6 seconds should need hospitalization. A 78-year-old woman with chronic heart failure (NYHA III) presenting mild dyspnea but no desaturation or other clinical signs of severity and who lives with her husband in a reassuring environment can be treated on an outpatient basis with instructions on warning signs to watch.

Due to the rapid spread of the novel coronavirus SARS-CoV-2, no high-grade recommendation is yet available for management of COVID-19 patients. Most guidelines are based on expert opinion with a very low certainty of evidence. Almost all suggest that the decision to manage a patient as an inpatient or an outpatient should be made on a case-by-case basis or recommend applying a triage tool all the while without specifying which one to use [12–14]. SOFA score on admission, age, gender, d-dimer, serum lactate dehydrogenase, C-reactive protein level, the coefficient of variation of red blood cell distribution width, lymphocyte count, blood urea nitrogen, direct bilirubin, albumin, and quantitative evaluation on CT scan have all been associated with severe forms of COVID-19 and mortality [3, 15–19]. However, these risk factors were identified in cohorts of patients with COVID-19 who had been hospitalized and none of them has been evaluated to guide the management of suspected COVID-19 patients on admission in the ED. Moreover, like most previous risk assessment scores for sepsis or pneumonia incorporating biological or imaging parameters, they cannot be used to quickly identify low-risk patients in ED [7–9].

The best methodology for developing a decision rule is to perform multivariate logistic regression on a derivation important cohort of patients and to validate the rule in another important cohort. This was not possible for our purpose in lack of large database of COVID-19 patients including patients hospitalized as well as patients managed at home. The Delphi method is widely used to provide an expert consensus based on available data and expert experiences through a multiple-round questionnaire [20]. This method is recommended when scientific data are limited. For example, it has been previously used for building SEPSIS-3 consensus, for the definition of appropriate management of outpatient parenteral antimicrobial

therapy, and for elaborating a consensual definition of de-escalation of beta-lactams [21–23]. The use of an Internet-based version of the Delphi process allowed us to complete the fourth round in less than two weeks. This “electronic Delphi” method was motivated by the sanitary context of containment and the urgent need for COVID-19 management guidelines while allowing for the recruitment of a large panel of experts. Despite the exceptional sanitary situation, the high level of participation and the almost absolute expert consensus on the final rule (94.4%) are a pledge of quality and may assure a high level of acceptance of this guideline by physicians.

The HOME-CoV rule incorporates 6 major clinical signs, 3 concerning respiratory status, 2 hemodynamic status, and one neurological status. Most of them were taken into account in previous severity rules for sepsis and/or pneumonia (respiratory rate, pulse oxygen saturation, systolic blood pressure, heart rate, confusion, or impaired consciousness). Nevertheless, the cut-offs were debated between experts. Most of the time, the consensus was reached on an attitude that should be adopted with care with the aim to apply the rule as a guide for the majority of patients but not as an absolute decision-making rule. For example, SpO₂ at 94% in ambient air is a severity criterion for a young person without comorbidity but may be a usual feature for an old person or a patient with chronic respiratory disease. The cut-off for the respiratory rate decided upon (≥ 25 /min) may appear as a mid-mid choice in comparison to other rules [7,9,21]. However, it corresponds to the value found in the epidemiological study of COVID-19 patients in China [17]. The ability to talk or to count without breathing is a less common criterion but currently used in the informal assessment of dyspneic patients [24,25]. By defining 8 seconds as the time cut-off, the HOME-CoV rule proposes a standardization of this criterion. From the outset, the experts considered a clinically significant worsening within the last 24 hours to be a major criterion. This criterion may appear, at least partly, subjective. However, the clinical course of COVID-19 may be a good indicator of the short-term risk of complication, as rapid progressions to severe hypoxemia have been observed [26].

The HOME-CoV rule may be an important help decision making for physicians. Faced with a lack of reliable criteria and recommendations, physicians use their individual gestalt perception to decide whom to hospitalize or to manage as an outpatient. However, gestalt evaluation is associated with a great variability among physicians and an overestimation of patients' short-term risk of adverse outcome [27, 28]. In the specific field of the COVID-19 pandemic, gestalt accuracy may be even lower than expected in other circumstances and hospitalizing patients when there is “any concern for rapid deterioration or an inability to return promptly to hospital” may underestimate the number of patients who can be managed at home and lead to hospitals becoming overcrowded. Indeed, among 1,099 patients hospitalized in China for COVID-19, 6.1% required mechanical ventilation and 41.3% needed oxygen therapy, indicating that a significant proportion would not have required specific in-hospital care [2]. In cases of pneumonia, the use of a clinical prediction rule has been proven to improve the identification of low-risk patients, to increase the rate of patients managed at home, and to reduce costs of medical care [27,28]. At least the same benefit could be expected as a result of deploying the HOME-CoV rule in ED. This rule could be also useful for general practitioners and physicians in older nursing home.

Nevertheless, our study has some limitations. Most of the experts consulted were French and their personal experiences in COVID-19 management were recent and varied. The rule does not apply to patients with rare and/or very specific comorbidity or inspecific clinical situations. It does not take into account some criteria that appear, in recent data, to be death risk factors for SARS-CoV-2 infection, such as obesity, diabetes, and hypertension [29–30]. Indeed, the real direct impact of these factors is still unknown, as there has still been no large-scale international epidemiological study providing multivariate analysis of all possible risk factors. The decision of the expert panel may facilitate the deployment of the rule in many countries and for other viral pneumonia. Finally, in the absence of systematic screening, the rule may only apply to symptomatic patients for whom the search for infection has been carried out in the ED or prior to admission, and not to all asymptomatic patients or those without suggestive symptoms.

The HOME-CoV rule achieved by a Delphi method provides an easy-to-use clinical tool for physicians in deciding between hospitalization or outpatient management for patients with suspected or confirmed SARS-CoV-2 infection.

Declarations

Declaration of interests

We declare no conflicts of interest.

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Supplementary Tables

entary table1. First round results

Criteria	Firstround ruling
Characteristics and disease course	
oxygen rate	Relevant and major
oxygen saturation	Relevant and major
talk without stopping for a breath	Relevant
oxygen pressure	Relevant
oxygen level	No consensus
oxygen not impaired consciousness	Relevant
oxygen significant worsening within the last 24 hours.	Relevant
oxygen time from the onset of initial symptoms and admission between 7 days to 10 days	Non-relevant
Comorbidities	
oxygen disorder	No consensus
oxygen respiratory failure with continuous oxygen therapy	Threshold: stage III, IV
oxygen renal failure	No consensus
oxygen cardiac failure	No consensus
oxygen hypertension	Non-relevant
oxygen heart failure	Threshold: NYHA III
oxygen diabetes	Non-relevant
oxygen peripheral vascular disease	Non-relevant
oxygen history of VTE†	Non-relevant
oxygen immunodeficiency Virus (HIV)	No consensus
oxygen immunodeficiency	No consensus
oxygen chronic kidney disease	Non-relevant
oxygen statin or ARB	Non-relevant
oxygen oral anti-inflammatory drug	Non-relevant
oxygen glucocorticoid therapy	No consensus
oxygen immunosuppressive drug	No consensus
Other conditions	
oxygen unaccompanied	No consensus
oxygen support person	No consensus
oxygen follow-up impossible	Relevant

entary table2. Second round results

Criteria	Secondround ruling
Characteristics and disease course	
Oxygen saturation	Relevant, major, no consensus on threshold value
SpO2	Relevant, major, no consensus on threshold value
Talk without stopping for a breath	Relevant, major, no consensus on threshold value
SpO2	Relevant, major, no consensus on threshold value
No impaired consciousness	No consensus
Significant worsening within the last 24 hours.	Relevant, major
From the onset of initial symptoms and admission between 7 days	Relevant, major
3	No consensus
Conditions	
Respiratory disorder	Non-relevant
Disease: COPD, Respiratory failure with continuous oxygen	No consensus
Asthma	Validated as grouped
Renal failure	Non-relevant
Heart failure	Relevant, threshold: NYHA III
Disease: primary immunodeficiency, uncontrolled	No consensus
Immunosuppressive drug, chemotherapy	
Glucocorticoid therapy	Non-relevant
Conditions	
Unilateral swelling	Relevant and minor
Support person	Relevant and minor
Follow-up impossible	Relevant and minor

entarytable 3. Third round results

Criteria	Thirdround ruling
Characteristics and disease course	
Oxygen saturation	Relevant, major, threshold value: $\geq 25/\text{min}$
SpO2	Relevant, major, threshold value: $\leq 94\%$
Talk without stopping for a breath	Relevant, major, threshold value: 8 sec
Diastolic blood pressure	Relevant, major, threshold value: SBP $\leq 90\text{mmHg}$
Heart rate	Relevant, major, threshold value: $\geq 120\text{ bpm}$
Not impaired consciousness	Relevant, major
No significant worsening within the last 24 hours.	Relevant, major
Onset of initial symptoms and admission between 7 days	Non-relevant
Exclusions	
Respiratory failure	Relevant, minor, threshold value: severe
Disease: COPD, Respiratory failure with continuous oxygen	Validated as grouped, minor
Asthma	
Heart failure	Relevant, minor, threshold: NYHA III
Disease: primary immunodeficiency, uncontrolled immunosuppressive drug, chemotherapy	Validated as grouped, minor
Additional conditions	
Isolated swelling	Relevant and minor
Support person	Relevant and minor
Follow-up impossible	Relevant and minor