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ARTICLE

Score to identify the severity of adult patients with influenza A (H1N1) 2009 virus infection at hospital admission

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Abstract The objective of this paper was to develop a prognostic index for severe complications among hospitalized patients with influenza A (H1N1) 2009 virus infection. We conducted a prospective observational cohort study of 618 inpatients with 2009 H1N1 virus infection admitted to 36 Spanish hospitals between July 2009 and February 2010. Risk factors evaluated included host-related factors and clinical data at admission. We developed a composite index of severe in-hospital complications (SIHC), which included: mortality, mechanical ventilation, septic shock, acute respiratory distress syndrome, and requirement for resuscitation maneuvers. Six factors were independently associated with SIHC: age >45 years, male sex, number of comorbidities, pneumonia, dyspnea, and confusion. From the β parameter obtained in the multivariate model, a weight was assigned to each factor to compute the individual influenza risk score. The score shows an area under the receiver operating characteristic (ROC) curve of 0.77. The SIHC rate was 1.9 % in the low-risk group, 10.3 % in the intermediate-risk group, and 29.6 % in the high-risk group. The odds ratio for complications was 21.8 for the high-risk group compared with the low-risk group. This easy-to-score influenza A

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(H1N1) 2009 virus infection risk index accurately stratifies patients hospitalized for H1N1 virus infection into low-, intermediate-, and high-risk groups for SIHC.

Abbreviations

ARDS	Acute respiratory distress syndrome
AUC	Area under the receiver operating characteristic curve
BMI	Body mass index
CI	Confidence intervals
ED	Emergency department
ICU	Intensive care unit
OR	Odds ratio
Ref.	Reference group
RT-PCR	Real-time polymerase chain reaction
SD	Standard deviation
SIHC	Severe in-hospital complications

Introduction

The influenza A (H1N1) virus pandemic in 2009 shocked the health systems of many countries and raised great social alarm. Much of this alarm was due to the information emitted on the epidemiological and clinical characteristics of the infection: a high capacity for contagion and rapid spread [1, 2]. Unlike seasonal influenza, the infection affected mostly young people and fewer people aged >65 years [3]. Initially, it was regarded as a potentially severe disease, with a high mortality rate, above all in young people without comorbidities, who required intensive care [4–6]. Obesity and pregnancy were identified as risk factors [4, 7–9].

In this context, extraordinary measures were taken with respect to the care of hospitalized patients. For example, the isolation of patients together with thorough cleaning and protection of health care personnel, both steps aimed to limit contagion. Molecular microbiological determinations were used to provide an early diagnosis of the virus. The specific treatment of the virus was standardized for all infected patients admitted. Extraordinary resources were provided in order to increase intensive care unit (ICU) staff. However, we lacked specific tools for the early identification of adult patients hospitalized with a bad prognosis.

Although a large amount of information about the epidemiology and clinical management of influenza A (H1N1) 2009 virus infection has been obtained in a remarkably short period, a major gap exists in understanding disease severity and identifying at-risk populations. Most studies have focused on epidemiological aspects of the general population and on patients admitted to ICUs. Selecting the most seriously ill patients exclusively according to ICU admittance involves significant bias, due to the variability in ICU selection criteria [10, 11], especially if the initial alarm raised by the pandemic and the emphasis on critical care is taken into account. In addition, the information available on risk factors groups children and adults together. It is reasonable to suppose that serious risk factors could differ between children and adults and, in addition, the hospital care of children and adults is structured differently. No in-depth studies have been carried out to identify risk factors of severe evolution for adult patients hospitalized for influenza A (H1N1) 2009 virus infection in order to manage these patients.

The aim of this study was to identify risk factors present at admission in adult patients hospitalized due to influenza A (H1N1) 2009 virus infection during the period 2009–2010 that were independently associated with worse outcomes and, thereby, develop a prognostic influenza severity index.

Patients and methods

Setting and study design

A multicenter matched case–control study was carried out in 36 hospitals and primary care centers from seven Spanish regions (Andalusia, Catalonia, Castile and Leon, Madrid, Navarre, the Basque Country, and Valencia). Cases and controls were recruited between July 2009 and February 2010. A case was defined as a patient admitted to hospital

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for >24 h with influenza A (H1N1) virus infection laboratory-confirmed by real-time polymerase chain reaction (RT-PCR). Twenty-five patients aged ≥18 years were recruited from each of the 36 study hospitals, and were chosen by the systematic sampling of all patients admitted with laboratory-confirmed influenza A (H1N1) 2009 virus infection [12]. For the purpose of this article, only the prospective cohort of patients admitted to any of the participant hospitals were included (the cases) and the controls are not included. Therefore, for this study, based in our selection criteria, we included only adult cases (≥18 years) who were hospitalized selected from the 36 hospitals studied. We excluded patients who had nosocomial infection, defined as pandemic virus infection in a patient that appears ≥48 h after admission for another cause. All information collected was treated as confidential, in strict observance of legislation on observational studies. The study was approved by the Ethics Committees of the hospitals involved. Written informed consent was obtained from all patients included in the study.

Data collection

A structured questionnaire was administered to patients by specifically trained personnel. We collected information on sociodemographic characteristics, pre-existing medical conditions, vaccinations, toxic habits, previous medications, exposure to social environments which could contribute to contagion, and the adoption of measures to prevent influenza. Variables on pre-existing medical conditions and vaccination were completed and verified by review of the medical records.

Possible predictive variables considered

The following demographic variables and pre-existing medical conditions were considered for this study: age, sex, previous hospital admission, history of pneumonia in the previous two years, obesity [body mass index (BMI)≥30], morbid obesity (BMI≥40), pregnancy in women aged 15–49 years, smoking, alcoholism, comorbidities (chronic obstructive pulmonary disease, asthma, other chronic respiratory diseases, cardiovascular disease, renal failure, diabetes, liver disease, HIV infection, disabling neurological disease, rheumatologic diseases, cancer, immunodeficiency, asplenia), vaccination, previous treatment, and clinical data at admission. For each vaccine, a case was considered to be vaccinated if they had received the vaccine at least 15 days before the onset of symptoms.

Outcomes

Severe in-hospital complications (SIHC) were the primary outcome of interest. This was a composite variable including: hospital mortality or requirement for mechanical ventilation or the presence of septic shock or acute respiratory distress syndrome (ARDS) or a requirement for resuscitation maneuvers during hospitalization. Shock was defined as systolic blood pressure below 90 mmHg without anti-hypertensive drugs and the need for vasopressive agents. Mechanical ventilation was included when it was needed for at least 24 h and always after influenza A diagnosis in the Emergency Department (ED). We did not include patients who received non-invasive positive pressure ventilation.

Statistical analysis

Univariate and multivariate logistic regression models were then constructed to identify the statistical significance of each risk factor. The dependent variable was SIHC, and the independent variables were factors with a significance of $p<0.15$ in the univariate analysis. The odds ratio (OR) and 95 % confidence intervals (95 % CI) were calculated. The possible interaction between variables was also examined. The predictive accuracy of the model was determined by calculating the area under the receiver operating characteristic curve (AUC) for discrimination [13] and by comparing predicted and observed SIHC using the Hosmer–Lemeshow test for calibration [14]. Multilevel analysis with generalized estimated equations was carried out to determine whether the statistical significance of each predictive variable remained after adjusting for the Spanish regions.

To develop the influenza risk score, we first assigned a weight to each risk factor in relation to each β parameter based on the multivariate logistic regression model. Then, we added the weights of each of the risk factors presented by a patient. The predictive accuracy of the influenza risk score was determined by means of the AUC [13] and its calibration was tested by the Hosmer–Lemeshow test [14]. In addition, we attempted to validate the risk score by *K*-fold cross-validation [15, 16], which uses part of the available data to fit the model, and a different part to test it. That is, the model is validated in a random subsample which was not involved in the development of the model. This process is repeated sequentially for all partitions of the original sample. Thus, we split the data into $K=10$ roughly equal-sized parts, we fitted the model with $K-1$ parts of the data, and validated it by predicting the remaining *k*th part of the data. This procedure was repeated for each *K*th part, until the ten groups were all used in the validation, meaning that all cases were used once in the validation of the risk score [15].

Once the influenza risk score was developed, we created three categories (low, intermediate, and high risk) in relation to the predicted SIHC. The performance of the index score categories was studied using a logistic regression model and the AUC, and the Cochran–Armitage test for trend was used

Table 1 Characteristics and outcomes of patients hospitalized with influenza A (H1N1) virus infection (N=618)

	n (%)
Characteristics	
Age, years, mean (SD)	48.60 (15.7)
Age, groups, years	
≤45 years	275 (44.5)
46–65 years	242 (39.2)
>65 years	101 (16.3)
Female	320 (51.8)
Hospitalized during the last year	133 (22.1)
Previous hospitalization by influenza A (H1N1) virus infection	3 (0.5)
Pneumonia in the last two years	93 (16.3)
Obesity	
No	414 (78)
30≤BMI≤40	96 (18.1)
BMI ≥40	21 (4)
Pregnant women	48 (7.8)
Toxic habit	
Smoking	
No	308 (50.4)
Yes	176 (28.8)
Ex-smoker	127 (20.8)
Alcoholism	44 (7.1)
Drugs	13 (2.1)
Comorbidities	
Chronic obstructive pulmonary disease	72 (11.7)
Asthma	103 (16.8)
Others chronic pulmonary disease	74 (13.2)
Chronic respiratory insufficiency	54 (8.8)
Cardiovascular disease	89 (14.5)
Renal failure	40 (6.5)
Diabetes	89 (14.5)
Liver disease	33 (5.4)
AIDS	19 (3.1)
AIDS/symptomatic infection by HIV	21 (3.4)
Disabling neurological disease	20 (3.3)
Cognitive deterioration	8 (1.3)
Neuromuscular disease	8 (2.1)
Convulsive event	12 (3.1)
Rheumatologic disease	21 (3.5)
Neoplasia	62 (10.1)
Immunodeficiency	10 (1.6)
Asplenia	4 (0.7)
No. of comorbidities	
0	240 (38.8)
1	172 (27.8)
2	115 (18.6)
>2	91 (14.7)
Vaccination	
Pandemic vaccine	10 (1.8)
Seasonal influenza vaccine in last year	174 (28.8)
23-valent pneumococcal vaccine in last 5 years	35 (6.3)
7-valent conjugated pneumococcal vaccine in last 5 years	10 (1.8)
Previous treatment	
Previous antibiotics	229 (37.1)
Length of antibiotic treatment, days, mean (SD)	1.14 (4.9)
Systemic corticosteroids in last 90 days	94 (18)
Inhaled corticosteroids	134 (21.8)
Clinical status at admission	
Multilobar and/or bilateral involvement	35 (5.7)
Pneumonia	174 (28.2)
Confusion	37 (6.2)
Fever	565 (92.8)
Dyspnea	404 (67.9)
Outcomes	
Hospital mortality	5 (1.3)
Shock	22 (5.4)
Mechanical ventilation	33 (5.3)
Acute respiratory distress syndrome	19 (4.9)
Resuscitation maneuvers	5 (1.3)

SD, standard derivation

Data are given as frequency (percentage) unless otherwise stated. Percentages exclude patients with missing data

to study the trend of the proportion of SIHC according to risk categories.

All effects were considered to be significant at $p<0.05$, unless otherwise stated. All statistical analyses were performed using SAS for Windows statistical software, version 9.1 (SAS Institute, Inc., Carey, NC) and R© version 2.13.0 software.

Results

A total of 618 patients hospitalized with influenza A (H1N1) 2009 virus infection were included. Patient characteristics and outcomes are shown in Table 1. The mean age was 48.6 years [standard deviation (SD), 15.7], and 44.5 % were aged <46 years. Almost 40 % had no comorbidity, while 14.7 % had ≥3 comorbidities. Of the 320 women included, 48 (15 %) were pregnant. A total of 117 patients (22 %) were obese (BMI ≥ 30), of which 21 (17.9 %) were morbidly obese (BMI≥40). The SIHC rate was 9.9 % (61/618).

In the univariate analyses, several host-related factors, such as age, gender, smoking, comorbidities, and clinical

data at admission, were significantly associated with the likelihood of SIHC (Table 2). Obesity was not associated with SIHC (OR, 1.39; 95 % CI, 0.72–2.66; p=0.3275), and no pregnant woman developed SIHC.

In the multivariate analysis, six factors were independently associated with SIHC: age, sex, number of comorbidities, and the presence of pneumonia, confusion, and dyspnea at admission (Table 3). The logistic model showed good discrimination, with an AUC value of 0.77. The model was also well calibrated, with a Hosmer–Lemeshow p-value of 0.9618. The statistical significance of each predictive variable remained after adjustment for Spanish regions.

Based on the multivariate logistic model, a weight was assigned to each risk factor in relation to each β parameter (Table 3). By adding up the weights assigned to each predictive variable, an individual influenza risk score was given to each patient, ranging from 0 to 8, with a higher score corresponding to a higher likelihood of SIHC. The risk score was significantly associated with the likelihood of developing SIHC (OR, 2.11; 95 % CI, 1.68–2.64; p<0.0001), and was well calibrated (Hosmer–Lemeshow o-value, 0.9603). The influenza risk score showed good discrimination (AUC, 0.76; 95 % CI, 0.71–0.82), in addition to the good results showed by the K-fold cross-validation, which had an AUC (95 % CI) of 0.74 (0.68–0.80) (Fig. 1).

Three risk categories were assigned using the influenza risk score (Table 4): low risk (0–2 points); intermediate risk (3–4 points); high risk (>4 points). The percentage of SIHC

Table 2 Risk factors significantly associated with severe in-hospital complication in the univariate analyses (N=618)

Characteristics	Severe in-hospital complication, n (%)	Odds ratio (95 % CI)	p-value
Age, in groups			
≤45 years	15 (5.5)	Ref.	
46–65 years	32 (13.2)	2.6 (1.4–5)	0.003
>65 years	14 (13.9)	2.8 (1.3–6)	0.009
Sex			
Female	21 (6.6)	Ref.	
Male	40 (13.4)	2.2 (1.3–3.8)	0.005
Smoking			
No	20 (6.5)	Ref.	
Yes	22 (12.5)	2.1 (1.1–3.9)	0.03
Ex-smoker	17 (13.4)	2.2 (1.1–4.4)	0.02
No. of comorbidities			
0	19 (7.9)	Ref.	
1	15 (8.7)	1.1 (0.6–2.3)	0.77
2	9 (7.8)	1 (0.4–2.3)	0.98
>2	18 (19.8)	2.9 (1.4–5.8)	0.003
Clinical data at admission			
Multilobar and/or bilateral involvement			
No	54 (9.3)	Ref.	
Yes	7 (20)	2.5 (1–5.9)	0.04
Pneumonia			
No	37 (8.3)	Ref.	
Yes	24 (13.8)	1.8 (1–3)	0.04
Confusion			
No	49 (8.8)	Ref.	
Yes	10 (27)	3.9 (1.8–8.5)	0.0007
Fever			
No	9 (20.5)	Ref.	
Yes	49 (8.7)	0.4 (0.2–0.8)	0.01
Dyspnea			
No	6 (3.1)	Ref.	
Yes	53 (13.1)	4.7 (2–11)	0.0005

CI, confidence interval; Ref., reference group

Percentages exclude patients with missing data. Only factors with a significance of p<0.15 in the univariate analysis are presented

Table 3 Risk factors significantly associated with severe in-hospital complication in the multivariate analyses (N=618)

Risk factors	β parameter	Odds ratio (95 % CI)	p-value	Weight
Intercept	−4.91			
Age (years)				
>45 vs. ≤45	0.76	2.1 (1.1–4.2)	0.03	1
Sex				
Male vs. female	0.88	2.4 (1.3–4.4)	0.004	1
No. of comorbidities				
≥3 vs. <3	0.80	2.2 (1.2–44)	0.02	1
Pneumonia	0.65	1.9 (1.1–3.5)	0.03	1
Confusion	1.35	3.9 (1.6–9.1)	0.002	2
Dyspnea	1.50	4.5 (1.95–11)	0.0009	2
AUC		0.77		
Hosmer–Lemeshow p-value[a]		0.9618		

CI, confidence interval; β parameter=estimated β coefficient; AUC, area under the receiver operating characteristic curve

All risk factors were examined jointly

[a]A significant value for the Hosmer–Lemeshow statistic indicates a significant deviation between predicted and observed outcomes

ranged from 1.9 % (95 % CI, 0.1–3.7) in patients classified as low risk to 29.6 % (95 % CI, 19.7–39.5) in patients classified as high risk (trend test, p<0.001). The OR for the high-risk group was 21.8 compared with the low-risk group. The risk categories showed good discrimination, with an AUC value of 0.74.

Discussion

This study was able to derive and validate a 2009 H1N1 virus infection influenza risk score with acceptable validity, discriminative ability, and generalizability, using data from a large cohort of inpatients from 36 geographically distinct Spanish hospitals. The risk score has various strengths. We developed a clinical prediction tool with six variables using information on predictive factors, including host-related factors and clinical conditions. The tool can be readily assessed and computed by physicians using information readily available in the ED.

Our results suggest that males aged >45 years and those patients with more than two underlying chronic conditions have an increased risk. However, the greatest risk factors are associated with clinical factors at hospital admission, when a patient with dyspnea and confusion, and, for example, pneumonia, would have a probability of almost 30 % of developing SIHC. The main value of this predictive score is its ability to identify patients who need additional monitoring and more aggressive treatment after the first ED evaluation, either in the ICU, intermediate care units, or specialized regular wards, depending on the severity. The ED is the natural setting for the use of this severity score, but it could also be useful in outpatient services, as an adjunct to clinical judgment. It is easy and quick to apply. Patients with a score of >2 points should be taken to hospital and patients with a score of >4 points should be hospitalized on an emergency basis. However, in patients with a score of <3, the chances of severe complications would be slim and the patient could be managed at home.

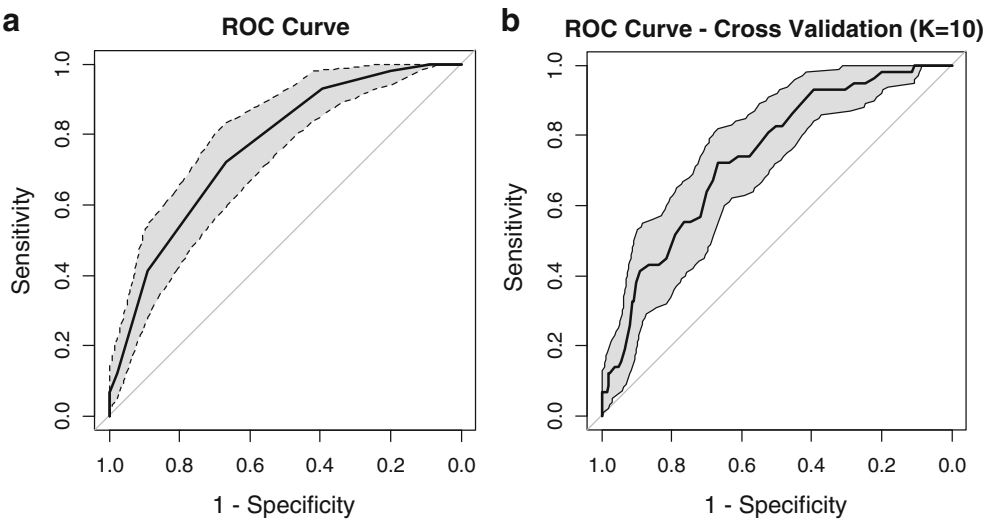

Fig. 1 Receiver operating characteristic curve of predicting severe in-hospital complication according to the individual influenza risk score (**a**) and according to the 10-fold cross-validation model (**b**). **a** Area under the curve (AUC) [95 % confidence interval (CI)], 0.76 (0.71–0.82); **b** AUC (95 % CI), 0.74 (0.68–0.80)

Table 4 Validation of the influenza risk score: severe in-hospital complication by index score categories

Risk group (points)	No. with SIHC/ no. at risk	Percentage (95 % CI)[a]	Odds ratio (95 % CI)
Low risk (0–2)	4/211	1.9 (0.1–3.7)	Ref.
Intermediate risk (3–4)	30/291	10.3 (6.8–13.8)	6 (2.1–17.1)
High risk (>4)	24/81	29.6 (19.7–39.5)	21.8 (7.3–65.3)
AUC			0.74

AUC, area under the receiver operating characteristic curve; CI, confidence interval; Ref., reference group

The low-risk group was considered as the reference group

[a] $p<0.001$ for the Cochran–Armitage test for trend

The strengths of the study include the relatively large cohort of patients recruited from different settings during the influenza A (H1N1) 2009 pandemic and the amount of clinical information collected. The main limitation of this study comes from its original design as a case–control study, where only 25 patients were recruited from each participating center and followed until discharge. Likewise, some laboratory parameters were not collected. Although we performed cross-validation, external validation of our score is still required.

Many of the predictors incorporated in our severity score have been established as risk factors for influenza A (H1N1)-associated complications in earlier studies. Comorbidities have been associated with an increased risk of complications both in seasonal influenza [17, 18] and in the influenza A (H1N1) 2009 pandemic [3, 7, 19–21]. We found that the risk of SIHC only increases in patients with >2 comorbidities. In contrast to seasonal influenza, where the greatest risk occurs in patients aged ≥70 years [18, 22], in both this study and other reports [19], severe outcomes occurred in patients aged >45 years.

We found that men had a higher risk of SIHC than women: similar results were reported by a Chinese study [7]. Another previous study showed that male sex was an independent risk factor for prolonged RT-PCR positivity in cases infected by influenza A (H1N1) virus [23]. Men have been found to be at a higher risk than women for death due to pneumonia [24, 25] and for sepsis [26]. Patterns of inflammation, coagulation, and fibrinolysis biomarkers in men may explain the reduced survival [27].

A preliminary report of 32 patients with influenza A (H1N1) 2009 virus infection hospitalized in a Spanish ICU showed that pneumonia was associated with a relatively high case–fatality rate [28]. The rate of patients hospitalized in wards and the ICU with pneumonia in the 2009 pandemic was higher [3, 4, 8, 19, 29]. We sought to confirm that pneumonia was an independent risk factor for SIHC.

Severe obesity has been identified as a risk factor for influenza A (H1N1) 2009 virus infection [4, 6–8]. However, in accordance with other studies [3, 30], we found that obesity was not associated with a higher risk of SIHC. In fact, obesity has not been identified as a risk factor for seasonal influenza complications [31, 32]. However, the prevalence of obesity in our series was similar to that of the general Spanish population [33], while a previous Spanish study found a high prevalence of obesity in patients hospitalized for 2009 H1N1 virus infection [34]. Obese patients may have been under-represented in our sample because the recruiting process of hospitalized cases collected 25 cases in each center during the pandemic period, but without trying to be representative of all cases seen in each hospital. Further investigation is needed in order to clarify the association between obesity and severe influenza.

In previous influenza epidemics and pandemics, pregnancy has been associated with an increased risk of severe disease [35, 36]. Likewise, recent reports suggest that there is an increased hospitalization rate and severity of illness in pregnant women infected by influenza A (H1N1) 2009 virus [8, 9, 19], while a Chinese study found that pregnancy was an independent risk factor associated with severe illness [7]. However, in our series, none of the pregnant women hospitalized for 2009 H1N1 virus infection developed SIHC, similar to the results of a previous Spanish study [34] and a Canadian study [20] that did not identify pregnancy as a risk factor for ICU admission or death. Preventive measures carried out in Spain, together with a fast diagnosis, early evaluation, and early antiviral treatment, may explain the relatively low rate of severity in pregnant women infected with the influenza A (H1N1) 2009 virus.

We did not use ICU admission as a criterion for determining SIHC because the decision to admit a patient to the ICU depends on individual clinical judgment and local hospital practices, differences that could account for much of the variability in ICU admission [10, 11]. On the other hand, the risk of death from influenza A infection is not the same as the need for inpatient care. We considered in-hospital death, mechanical ventilation, septic shock, ARDS, and resuscitation maneuvers as endpoints, given their more objective nature as variables [10]. This is a major strength of our study.

Conclusions

Although the 2009 pandemic is over, gaining deeper knowledge of influenza A (H1N1) 2009 remains essential, as it will plan for the next, unavoidable pandemic and because, as in the 2010–2011 seasonal influenza in Spain [37], the influenza A (H1N1) virus might be one factor responsible for future seasonal influenza epidemics.

We identified risk factors for severe in-hospital complications (SIHC) in patients hospitalized due to influenza A (H1N1) virus infection and developed a clinical severity score that is very easy and simple to apply. The use of this score at diagnosis, or at diagnostic presumption, even with ambulatory patients, could assist decisions on care management. Early identification of the sickest patients could allow earlier interventions and, thus, potentially improve outcomes.

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