Prediction of Mortality With the Use of Noninvasive Ventilation for Acute Respiratory Failure

Francesca Innocenti, Laura Giordano, Simona Gualtieri, Arianna Gandini, Lucia Taurino, Monica Nesa, Chiara Gigli, Alessandro Becucci, Alessandro Coppa, Irene Tassinari, Maurizio Zanobetti, Francesca Caldi, and Riccardo Pini

BACKGROUND: In actuality, it is difficult to obtain an early prognostic stratification for patients with acute respiratory failure treated with noninvasive ventilation (NIV). We tested whether an early evaluation through a predictive scoring system could identify subjects at risk of in-hospital mortality or NIV failure. METHODS: This was a retrospective study, which included all the subjects with acute respiratory failure who required NIV admitted to an emergency department–high-dependence observation unit between January 2014 and December 2017. The HACOR (heart rate, acidosis [by using pH], consciousness [by using the Glasgow coma scale], oxygenation [by using P_{aO_2}/F_{IO_2}], respiratory rate) score was calculated before the NIV initiation (T0) and after 1 h (T1) and 24 h (T24) of treatment. The primary outcomes were in-hospital mortality and NIV failure, defined as the need for invasive ventilation. RESULTS: The study population included 644 subjects, 463 with hypercapnic respiratory failure and an overall in-hospital mortality of 23%. Thirty-six percent of all the subjects had NIV as the "ceiling" treatment. At all the evaluations, nonsurvivors had a higher mean ± SD HACOR score than did the survivors (T0, 8.2 ± 4.9 vs 6.1 ± 4.0; T1, 6.6 ± 4.8 vs 3.8 ± 3.4; T24, 5.3 ± 4.5 vs 2.0 ± 2.3 [all $P < .001$]). These data were confirmed after the exclusion of the subjects who underwent NIV as the ceiling treatment (T0, 8.2 ± 4.9 vs 6.1 ± 4.0 [$P = .002$]; T1, 6.6 ± 4.8 vs 3.8 ± 3.4; T24, 5.3 ± 4.5 vs 2.0 ± 3.2 [all $P < .001$]). At T24, an HACOR score > 5 (Relative Risk [RR] 2.39, 95% CI 1.60–3.56) was associated with an increased mortality rate, independent of age and the Sequential Organ Failure Assessment score. CONCLUSIONS: Among the subjects treated with NIV for acute respiratory failure, the HACOR score seemed to be a useful tool to identify those at risk of in-hospital mortality. *Key words: acute respiratory failure; noninvasive ventilation; prognosis; emergency department; organ failure.* [Respir Care 2020;65(12):1847–1856. © 2020 Daedalus Enterprises]

Introduction

Noninvasive ventilation (NIV) has been established as a useful and safe method to improve gas exchange in patients who are critically ill and with acute respiratory failure (ARF) of different etiologies. NIV decreases the work of breathing and improves arterial oxygenation and alveolar ventilation, with a consequent reduction in the use of invasive mechanical ventilation.[1-6] In the early 2000s, the main indication was the treatment of exacerbations of COPD and, at the time, NIV reduced the likelihood of endotracheal intubation and in-hospital mortality.[7,8] Although the weight of evidence favored a reduction in mortality and endotracheal intubation, further findings that supported NIV

Drs Innocenti, Giordano, Gualtiere, Gandini, Taurino, Nesa, Gigli, Becucci, Coppa, Tassinari, Zanobetti, Caldi, and Pini are affiliated with the High-Dependency Unit, Department of Clinical and Experimental Medicine, Careggi University Hospital, Florence, Italy.

The authors have no conflict of interest to declare.

Correspondence: Francesca Innocenti MD, High-Dependency Unit, Department of Clinical and Experimental Medicine, Careggi University Hospital, Lg. Brambilla 3, 50134 Florence, Italy. E-mail: innocenti.fra66@gmail.com.

DOI: 10.4187/respcare.07464

for acute cardiogenic pulmonary edema were not conclusive.[9,10] Little evidence supports the use of NIV for other causes of ARF, for example, pneumonia.[11]

Despite the potential harm from the overuse of NIV among patients who are unlikely to benefit from it, the use of NIV has dramatically increased in the past 2 decades in the United States, even in cases that lacked strong supporting evidence.[12] NIV can be performed outside the ICU and could be a good alternative for patients who are not candidates for invasive mechanical ventilation.[13] Among such a diverse population, the early identification of patients at increased risk of a poor outcome remains challenging. Duan et al[14] recently proposed a score for the identification of patients with hypoxemic ARF at high risk of NIV failure. The HACOR (heart rate, acidosis [by using pH], consciousness [by using the Glasgow coma scale], oxygenation [by using P_{aO_2}/F_{IO_2}], respiratory rate) score is based on parameters easily obtainable at bedside. Therefore, it can be repeated after the NIV initiation to monitor the patient's response to treatment. The present study aimed to test the prognostic value of the HACOR score among the subjects with ARF, treated with NIV in the emergency department.

QUICK LOOK

Current knowledge

Noninvasive ventilation (NIV) is an established treatment option for patients with an exacerbation of COPD. Among these patients, NIV, in conjunction with usual care, has proved to be beneficial for reducing the likelihood of in-hospital mortality and endotracheal intubation. The HACOR (heart rate, acidosis, consciousness, oxygenation, and respiratory rate) score was recently developed to predict the failure of NIV among patients with hypoxemic respiratory failure: its simplicity and the ability to perform serial evaluations makes it a useful clinical tool.

What this paper contributes to our knowledge

In subjects with hypoxemic or hypercapnic acute respiratory failure, treated with NIV, the HACOR score was significantly higher in those with an adverse outcome. A score >5 was associated with an increased risk of NIV failure and in-hospital mortality. The trend over the first 24 h added prognostic information to the earliest evaluations, with persistently high values in the subjects with an adverse prognosis. Increasing age and higher degree of organ failure were independent predictors of an unfavorable prognosis among subjects who are critically ill. After adjusting the HACOR score with these 2 parameters, we confirmed the independent association with an increased mortality rate.

Methods

Study Design and Setting

This was a retrospective study, performed in the emergency department–high-dependence unit at the Careggi University Hospital. The ethics committee and institutional review board approved this study (13731_oss). The Careggi University Hospital is an urban academic hospital and a tertiary care center (1,300 beds, 130,000 emergency department visits per year). We are accustomed to limited ICU and sub-ICU beds; therefore, between the emergency department and the ICU, we created an area in which patients who are critically ill could be managed and stabilized for 24–48 h to reduce ICU admissions. The emergency department–high-dependence observation unit is a sub-ICU, with equipment for advanced monitoring, NIV, and the possibility to administer vasoactive drugs, managed by emergency physicians. All the subjects were admitted from the emergency department, according to bed availability.[15] Due to the absence of invasive mechanical ventilators, patients already intubated in the emergency department or those with a high probability of intubation in the first 24 h are admitted directly into the ICU.[16]

Selection of Participants

All consecutive patients, who were admitted to the emergency department–high-dependence observation unit for respiratory failure in the period January 2014 to December 2017, who were either hypoxemic or hypercapnic, were included in the study. No dedicated respiratory therapist was available in the unit during the study period. The decision to initiate NIV (Philips Respironics Model V680, Respironics, Carlsbad, California) was made by the attending emergency physician based on the guidelines of the American Thoracic Society[17] and the British Thoracic Society.[18] Whenever possible, a management plan was made before initiating an NIV trial with regard to what to do in case of failure. The options were to intubate and mechanically ventilate the patient or to consider the NIV trial as a "ceiling" treatment when taking into account the stage of the underlying disease and the wishes of the patient about advanced life support. NIV was initially provided in the emergency department and continued in the emergency department–high-dependence observation unit as soon as a bed became available.

The attending emergency physicians managed the NIV without the presence of respiratory therapists, Pressure support was increased from 5 up to 20 cm H_2O to obtain an exhaled tidal volume of 6–8 mL/kg of predicted body weight. The breathing frequency setting was driven by the

attenuation of the activity of respiratory accessory muscles and the achievement of the comfort of the subject (target rate, <30 breaths/min). PEEP was initiated at 5 cm H_2O and increased in steps of 2 to 3 cm H_2O up to 12 cm H_2O, until the F_{IO_2} requirement was ≤ 0.60 in subjects with hypoxemic respiratory failure. Bi-level pressure support was the most commonly used mode of ventilation; CPAP was used for subjects with pulmonary edema without hypercapnia. We defined NIV failure as the need for endotracheal intubation and invasive mechanical ventilation. When adhering to current guidelines, the attending physician decided to intubate the subjects.

Measurements and Outcomes

The subjects were identified according to emergency department–high-dependence observation unit admission diagnosis from electronic medical records. For each subject, basic demographic data and previous medical conditions were collected from medical records by using a standardized collection template; the variables needed to construct the score were collected at emergency department admission (T0), after 1 h (T1), and after the first 24 h (T24) from the beginning of NIV. The Sequential Organ Failure Assessment (SOFA) score was calculated at T0 and T24; the APACHE II (Acute Physiology and Chronic Health Evaluation) score was calculated based on the worse values in the first 24 h of staying in the emergency department–high-dependence observation unit. The HACOR score was calculated as indicated in Table 1; it was analyzed as a continuous value and dichotomized as ≤ 5 or as > 5, based on the original study.[14] At all the evaluations, the HACOR scores were available in 95% of the whole population; because every subject had one missing HACOR value out of 3, we decided not to delete them from the study. The primary outcomes were in-hospital mortality and NIV failure. NIV failure was evaluated only among patients, who were candidates to invasive mechanical ventilation.

Statistical Analysis

Due to the retrospective design of the study, we included all the patients who underwent NIV in the study period. However, based on the reported mortality in the original study (21% in the subjects with a T0 HACOR score ≤ 5 and 65% in those with a HACOR score > 5), the required population size was 60 subjects (power, 95%; $\alpha = 5\%$); we included >600 subjects.[14] Continuous variables were reported as mean ± SD, and comparisons between the 2 groups were performed with the Student *t* test for unpaired data. Categorical data were analyzed by using contingency tables and the chi-square test. All score comparisons between different groups were performed by using the Mann-Whitney test for nonparametric data. Discrimination ability was tested by building receiver operating characteristic curves and calculating the areas under the curves with 95% CI. Differences in trend among different scores were evaluated by using analysis of variance, we performed a survival analysis by using the Cox logistic regression analysis (input for values < 0.05, output for ≥ 0.10). A *P* value of <.05 was considered significant. All statistical analyses were carried out by using SPSS software package, v. 25 (IBM, Armonk, New York).

Table 1. The HACOR Score

Parameter Range	Score
Heart rate	
<120 beats/min	0
≥120 beats/min	1
pH	
≥7.35	0
7.30–7.34	2
7.25–7.29	3
<7.25	4
Glasgow coma scale score	
15	0
13–14	2
11–12	5
≤10	10
P_{aO_2}/F_{IO_2}	
≥201 mm Hg	0
176–200 mm Hg	2
151–175 mm Hg	3
126–150 mm Hg	4
101–125 mm Hg	5
≤100 mm Hg	6
Breathing frequency	
≤30 breaths/min	0
31–35 breaths/min	1
36–40 breaths/min	2
41–45 breaths/min	3
≥46 breaths/min	4

HACOR = heart rate, acidosis, consciousness, oxygenation, respiratory rate

Results

Characteristics of the Study Participants

From January 2014 to December 2017, 644 subjects underwent NIV during their emergency department–high-dependence observation unit stay. A total of 181 subjects (28%) had hypoxemic ARF, whereas 463 subjects (72%) had hypercapnic ARF. NIV was the ceiling treatment for 223 subjects (35%). The admission diagnoses and the previous medical conditions in our subjects with hypoxemic and hypercapnic ARF are shown in Table 2. Compared with the survivors, in both groups, nonsurvivors were older, whereas

Table 2. Clinical Characteristics of the Whole Study Population and Based on the Type of Respiratory Failure

Characteristic	All Subjects ($N = 644$)	Subjects With Hypoxic Respiratory Failure ($n = 181$)			Subjects With Hypercapnic Respiratory Failure ($n = 463$)		
		Survivors ($n = 117$)	Nonsurvivors ($n = 64$)	P	Survivors ($n = 377$)	Nonsurvivors ($n = 86$)	P
Age, mean ± SD y	78 ± 11	73 ± 14	79 ± 11	.01	78 ± 11	82 ± 9	.001
Men, *n* (%)	332 (52)	48 (41)	23 (36)	.61	216 (57)	45 (52)	.47
Body mass index, mean ± SD kg/m^2	27 ± 7	26 ± 5	24 ± 4	.07	28 ± 8	23 ± 5	< .001
Admission diagnosis, *n* (%)							
COPD exacerbation	273 (57)	7 (6)	3 (5)	.99	197 (54)	30 (35)	.003
Pneumonia	371 (58)	72 (62)	40 (63)	.99	206 (55)	53 (62)	.30
Heart failure	233 (36)	52 (44)	22 (34)	.25	136 (36)	23 (27)	.13
Sepsis	121 (19)	35 (30)	30 (45)	.04	30 (8)	26 (31)	<.001
Pulmonary embolism	11 (2)	5 (4)	3 (5)	.99	1 (0.3)	2 (2)	.16
Chest trauma	19 (3)	5 (4)	0		13 (4)	1 (1)	.44
PMC, *n* (%)							
Diabetes	193 (30)	48 (41)	16 (25)	.04	112 (30)	17 (20)	.08
COPD	339 (53)	17 (15)	8 (13)	.89	267 (73)	47 (55)	.003
CAD	147 (23)	40 (34)	17 (27)	.37	74 (20)	16 (19)	.93
CKD	91 (14)	23 (20)	9 (14)	.46	45 (12)	14 (16)	.37
Cancer	94 (15)	20 (17)	23 (36)	.01	37 (10)	14 (16)	.13
NIV parameters							
Bi-level modality, *n* (%)		93 (79)	48 (75)	.72	372 (99)	83 (99)	.92
T0, mean ± SD							
PEEP		6.6 ± 1.6	6.6 ± 1.5	.29	6.0 ± 1.4	6.2 ± 1.5	.48
PS		9.8 ± 3.4	10.6 ± 3.1	.25	12.6 ± 3.6	12.2 ± 4.1	.42
T24, mean ± SD							
PEEP		7.1 ± 2.0	7.6 ± 1.8	.24	6.1 ± 1.5	6.2 ± 1.3	.74
PS		10.1 ± 4.1	1.9 ± 3.7	.42	12.8 ± 4.1	12.2 ± 1.4	.37

PMC = previous medical conditions; CAD = coronary artery disease; CKD = chronic kidney disease; NIV = noninvasive ventilation; T0 = emergency department admission; PS = pressure support; T24 = first 24 h from the beginning of NIV

the sex distribution was comparable, regardless of prognosis. Among the subjects with hypercapnic ARF, the nonsurvivors had a lower body mass index than did the survivors. Among the most frequent admission diagnoses, COPD exacerbation was more frequent in the subjects with hypercapnic ARF (50% vs 6%, $P < .001$). However, pneumonia (62% vs 56%; $P = .21$) and cardiac failure (41% vs 34%; $P = .15$) showed a similar prevalence in both groups. COPD exacerbation as an admission diagnosis, with a normal chest radiograph, was associated with a lower in-hospital mortality. Sepsis was the admission diagnosis in 19% of our subjects, and it was more frequent among those with hypoxemic versus hypercapnic ARF (36% vs 12%; $P < .001$) as well as among the nonsurvivors compared with the survivors. The sepsis source was pulmonary in 77% of cases, and in 60 subjects who were septic, NIV was used as the ceiling treatment.

The presence of diabetes among patients with hypoxemic ARF and the presence of COPD among those with hypercapnic ARF, were associated with a lower mortality rate. As expected, a significantly higher number of the subjects with hypoxemic ARF were treated with CPAP (17% vs 1%; $P < .001$) compared with those with hypercapnic ARF. T0 and T24 ventilation pressures were similar in the survivors as well as in the nonsurvivors, both in the subjects with hypoxemic and those with hypercapnic ARF (Table 2). The degree of organ failure, expressed by the SOFA score, was more severe in the nonsurvivors than in the survivors in both groups. As we predicted, a higher APACHE II score was associated with a higher mortality rate (Tables 3 and 4).

In Figure 1, we reported the outcome of our subjects according to the ARF etiology and the use of NIV as the ceiling treatment. In the whole study population, in-hospital mortality was 23% and the subjects with hypoxemic ARF exhibited a higher mortality versus subjects with hypercapnic ARF (35% vs 19%; $P < .001$). This difference was confirmed among the subjects who were candidates for invasive mechanical ventilation in the case of NIV failure (overall mortality rate, 11%, 19% among the subjects with hypoxemic ARF, and 9% among those with hypercapnic

Table 3. Prognostic Scores in the Subjects With Successful or Failed NIV and in Survivors or Nonsurvivors With Hypoxemic or Hypercapnic ARF, Respectively: NIV Failure

Score	NIV Failure					
	Hypoxemic ARF ($n = 181$)			Hypercapnic ARF ($n = 463$)		
	Yes ($n = 22$)	No ($n = 159$)	P	Yes ($n = 21$)	No ($n = 442$)	P
SOFA, mean ± SD						
T0	6.0 ± 3.3	5.8 ± 3.4	.70	5.0 ± 3.0	4.1 ± 2.2	.23
T1	6.1 ± 3.0	5.4 ± 3.3	.11	4.6 ± 2.6	3.8 ± 2.1	.23
T24	6.3 ± 3.4	5.2 ± 3.2	.08	4.8 ± 2.8	3.6 ± 2.0	.041
APACHE II, mean ± SD	18 ± 5	18 ± 6	.93	16 ± 5	17 ± 5	.32
HACOR, mean ± SD						
T0	7.3 ± 3.4	6.3 ± 4.1	.16	6.8 ± 4.3	6.6 ± 2.5	.58
T1	6.2 ± 3.0	4.7 ± 4.5	.01	4.4 ± 2.4	4.3 ± 2.8	.38
T24	5.5 ± 2.2	4.0 ± 3.6	.02	4.6 ± 3.0	2.1 ± 2.9	<.001
HACOR > 5, *n* (%)						
T0	15 (75)	96 (65)	.52	12 (57)	211 (50)	.73
T1	14 (64)	53 (33)	.02	7 (33)	126 (29)	.83
T24	8 (36)	36 (22)	.07	7 (33)	34 (8)	<.001

NIV = noninvasive ventilation; ARF = acute respiratory failure; SOFA = Sequential Organ Failure Assessment score; T0 = before beginning of NIV; T1 = first 1 h after beginning NIV; T24 = first 24 h after beginning NIV; APACHE = Acute Physiology and Chronic Health Evaluation; HACOR = heart rate, acidosis, consciousness, oxygenation, respiratory rate

Table 4. Prognostic Scores in the Subjects With Successful or Failed NIV and in Survivors or Nonsurvivors With Hypoxemic or Hypercapnic ARF, Respectively: In-Hospital Mortality

Score	In-Hospital Mortality					
	Hypoxemic ARF ($n = 181$)			Hypercapnic ARF ($n = 463$)		
	Yes ($n = 61$)	No ($n = 120$)	P	Yes ($n = 86$)	No ($n = 377$)	P
SOFA, mean ± SD						
T0	7.0 ± 3.5	5.3 ± 3.1	<.001	5.7 ± 2.9	3.8 ± 2.0	<.001
T1	6.8 ± 3.4	4.9 ± 2.9	<.001	5.4 ± 2.7	3.5 ± 1.9	<.001
T24	6.8 ± 3.6	4.8 ± 2.8	<.001	5.1 ± 2.7	3.3 ± 1.7	<.001
APACHE II, mean ± SD	21 ± 6	16 ± 5	<.001	20 ± 2	16 ± 5	<.001
HACOR, mean ± SD						
T0	8.0 ± 4.9	5.8 ± 3.3	.002	8.4 ± 5.0	6.2 ± 4.2	<.001
T1	6.9 ± 5.2	3.9 ± 3.4	<.001	6.4 ± 4.6	3.8 ± 3.3	<.001
T24	6.0 ± 4.1	3.3 ± 2.7	<.001	4.8 ± 4.7	1.6 ± 2.0	<.001
HACOR > 5, *n* (%)						
T0	48 (79)	70 (58)	.031	55 (64)	173 (46)	.006
T1	32 (50)	40 (35)	.061	44 (51)	91 (24)	<.001
T24	21 (34)	19(16)	.005	24 (28)	16 (4)	<.001

NIV = noninvasive ventilation; ARF = acute respiratory failure; SOFA = Sequential Organ Failure Assessment score; T0 = before beginning of NIV; T1 = first 1 h after beginning NIV; T24 = first 24 h after beginning NIV; APACHE = Acute Physiology and Chronic Health Evaluation; HACOR = heart rate, acidosis, consciousness, oxygenation, respiratory rate

ARF; $P = .008$) and in subjects with NIV as the ceiling treatment (overall, 44%; 59% vs 37% among the subjects with hypoxemic and hypercapnic ARF; $P = .003$).

Predictors of Adverse Outcome

Among the subjects who were candidates for invasive mechanical ventilation ($n = 421$), NIV failure had occurred in 48 (11% [21% among the subjects with hypoxemic ARF vs 8% among those with hypercapnic ARF]; $P = .001$). When comparing the subjects successfully treated with NIV versus those who underwent endotracheal intubation, we found that they were of a similar mean ± SD age (73 ± 13 vs 75 ± 12 y $P = .32$). Among T0 and T1 arterial blood gas parameters, only the mean ± SD P_{aO_2}/F_{IO_2} was lower with NIV failure (T0, 150 ± 88 mm Hg vs 204 ± 86 mm

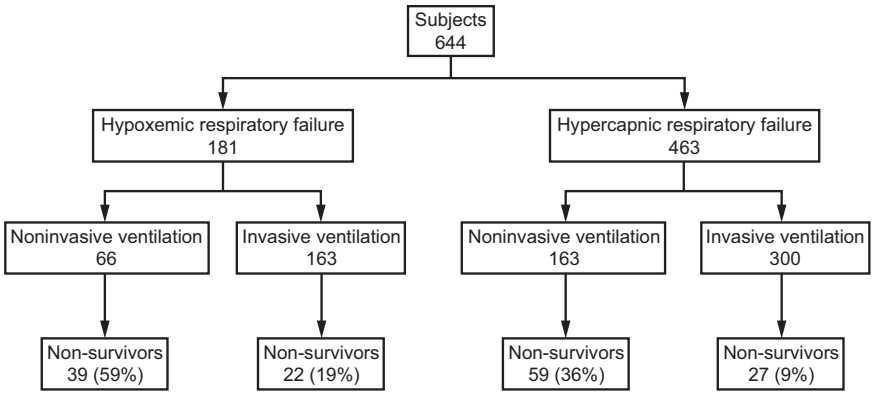

Fig. 1. Flow chart.

Hg [$P < .001$]; T1, 192 ± 107 mm Hg vs 233 ± 116 mm Hg [$P = .03$]). Prognostic scores did not show a significant difference between the subjects with a successful or unsuccessful NIV (Tables 3 and 4). In the subgroups with hypoxemic and hypercapnic ARF, the absolute and dichotomized value of the HACOR score was higher in the subjects who underwent endotracheal intubation at T1 and T24 evaluations (Table 3).

As we followed up the serial evaluations, we found that those who underwent endotracheal intubation showed a consistently high proportion of the subjects with a value > 5. We observed a rapid decrease in that percentage of the subjects with a successful NIV. The analysis for repeated measures confirmed a significantly different trend between the subjects with successful and unsuccessful NIV, both in those with hypoxemic and hypercapnic ARF (Fig. 2, A–C). We observed consistently high values among those who underwent endotracheal intubation. The Cox regression analysis showed that a higher HACOR score was associated with an increased risk of NIV failure in the subjects with hypoxemic ARF (T0, 1.22, 95% CI 1.06–1.40; T1, Relative Risk [RR] 1.41, 95% CI 1.18–1.68; T24, RR 1.59, 95% CI 1.18–2.14). Although, among those with hypercapnic ARF, the association was confirmed only at T24 (RR 1.59, 95% CI 1.33–1.90).

Compared with the survivors, the nonsurvivors showed significantly higher values of prognostic scores (Tables 3 and 4). At T0, although the arterial blood gas evaluation did not give any useful information, the Glasgow coma scale was significantly lower in the nonsurvivors, both in the subjects with hypoxemic and hypercapnic ARF. At T1, all the vital signs, along with the P_{aO_2}/F_{IO_2}, were more compromised in nonsurvivors than in the survivors. These data were confirmed at the T24 evaluation (Table 5). During the first 24 h, the HACOR score was significantly higher in the nonsurvivors than in the survivors in the whole population and in both subgroups (Fig. 2). In-hospital mortality increased in the subjects with a set of score values consistently > 5 (Fig. 2, Table 4). In the whole study population, the discrimination ability evaluated by receiver operating characteristic curves was fair to good, and it improved over the first 24 h (T0, area under the curve 0.64, 95% CI 0.58-0.69; T1, area under the curve 0.68, 95% CI 0.63–0.73; T24, area under the curve 0.75, 95% CI 0.70-0.80 [all $P <$ .001]) (Fig. 3). These data were confirmed in the subjects with hypoxemic and hypercapnic ARF (data not shown).

According to the univariate Cox regression analysis, the HACOR score value of >5 was associated with an increased mortality rate at all the evaluations in the whole population and in the subjects with hypercapnic ARF. In those with hypoxemic ARF, the association was confirmed at T24 (Table 6). We performed a multivariate Cox regression survival analysis in which we included the dichotomized HACOR score (≤5 or >5), together with the SOFA score and age, which were significantly different between the survivors and nonsurvivors. At T1 and T24, the HACOR score, adjusted by age and the SOFA score, was independently associated with an increased mortality in the subjects with hypercapnic ARF. In the subjects with hypoxemic ARF, this result was confirmed only at T24.

We repeated the analysis after the exclusion of the subjects who underwent NIV as the ceiling treatment. In the whole study population (T0, 8.2 ± 4.9 vs 6.1 ± 4.0 [$P =$ .002]; T1, 6.6 ± 4.8 vs 3.8 ± 3.4; T24, 5.3 ± 4.5 vs 2.0 ± 3.2 [all $P < .001$]) as well as in the subjects with hypercapnic ARF (T0, 8.6 ± 4.1 vs 5.8 ± 4.1 [$P = .005$]; T1, 6.4 ± 4.4 vs 3.3 ± 2.9; T24, 4.2 ± 4.1 vs 1.4 ± 1.8 [all $P < .001$]), the mean ± SD HACOR scores were significantly higher in the nonsurvivors compared with the survivors. In the whole population and in the subjects with hypercapnic ARF compared with survivors, a significantly higher percentage of the nonsurvivors had a HACOR score of >5 (whole population: T0, 70% vs 50%, T1, 47% vs 23%; T24, 23% vs 8% [P value are as follows: T0, $P = .02$; T1, $P = .001$; T24, $P = .004$]; hypercapnic ARF: T0, 62% vs 45%, $P = .17$; T1, 48% vs 20% [$P =$ .002]; T24, 20% vs 3% [$P < .001$]). We did not find

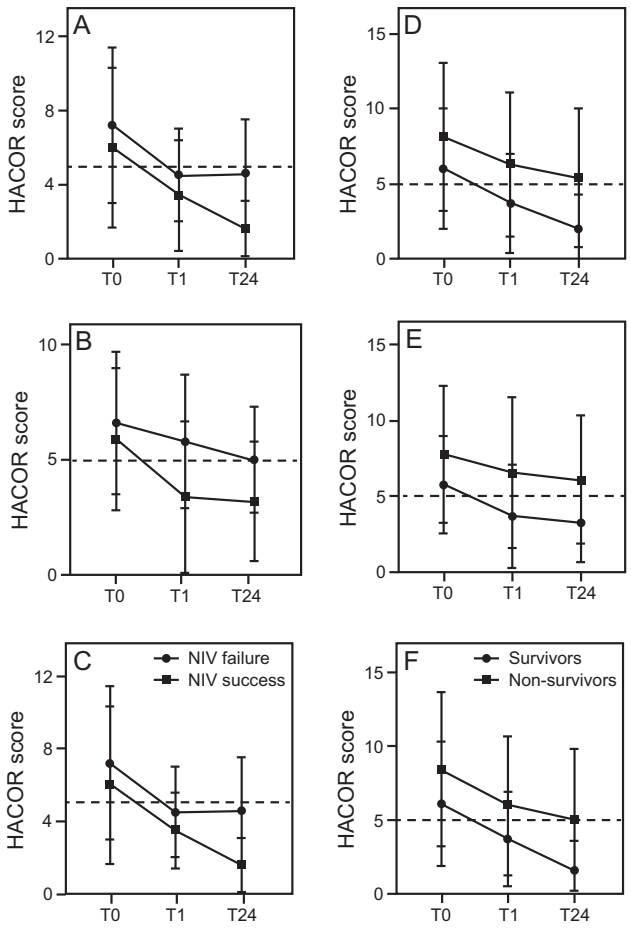

Fig. 2. Absolute values and trends of the HACOR (heart rate, acidosis, consciousness, oxygenation, respiratory rate) score during the first 24 h based on noninvasive ventilation (NIV) failure (A–C) and survival (D–F) in the whole study population (A: within subjects, $P = .062$, between subgroups $P = .004$; D: within subjects, $P = .004$, and between groups, $P < .001$), in subjects with hypoxemic ARF (B: within subjects, $P = .30$; between subgroups, $P = .02$; E: within subjects, $P = .20$; between survivors and nonsurvivors, $P = .001$) and hypercapnic ARF (C: within subjects, $P = .064$, between subgroups $P = .004$; F: within subjects $P = .067$, between survivors and nonsurvivors $P < .001$). The dotted line marks the level of 5, the cutoff value suggested by the investigators[14] who proposed the score.

evidence of a significant difference in the subjects with hypoxemic ARF (T0, 7.0 ± 3.0 vs 6.0 ± 3.0; T1, 4.8 ± 3.5 vs 3.8 ± 3.5; T24, 4.5 ± 3.9 vs 2.6 ± 3.8 [all P = not significant]). This result could be due to the small size of the group with hypoxemic ARF.

Discussion

In a population of subjects admitted to the emergency department with ARF, who underwent NIV, we demonstrated that the HACOR score was significantly higher and showed a blunted decrease in the nonsurvivors compared with the survivors. In the subjects with hypercapnic ARF, a HACOR score > 5 at 1-h and 24-h intervals after the initiation of NIV was independently associated with an increased in-hospital mortality. In the subjects with hypoxemic ARF, the independent association was confirmed only at T24. In the subjects on NIV without limitations to be promoted to invasive mechanical ventilation, a HACOR score > 5 was associated with a higher rate of endotracheal intubation.

In the past few years, NIV use has increased worldwide. Despite substantial differences in the evidence that supports the use of NIV to treat ARF from COPD or cardiogenic pulmonary edema compared with other etiologies, NIV use increased at similar rates, regardless of the potential etiology of respiratory failure.[12,19] Moreover, NIV has been increasingly delivered outside the ICU, in the high-dependence observation unit or general ward; due to this, the treatment has been used in a higher number of patients, compared to those admitted to the ICU.[20,21] Our subjects with ARF, who qualified for invasive mechanical ventilation, showed a mortality rate comparable with a previous study on subjects treated with NIV in high-dependence observation units.[22] When we considered the whole study population, which included a significant proportion of the subjects treated with NIV as the ceiling treatment, the mortality rate increased. Among candidates for invasive mechanical ventilation, the rate of NIV failure was low compared with previous studies: [23,24,25] this difference could be due to the characteristics of our clinical setting, where invasive mechanical ventilation is not feasible. As a result, only the subjects at low risk of deterioration in the very short-term were admitted to the high-dependence observation unit.

Most of the previous studies[11,12,20] that investigated the prognosis of patients treated with NIV focused their attention on the incidence and predictors of NIV failure, to identify patients early who needed invasive mechanical ventilation as the final treatment. All the investigators agree to identify NIV failure and delayed endotracheal intubation as predictors of an increased in-hospital mortality. However, for a "real world" study population like this, it is of utmost importance to find a feasible tool for the early identification of patients at high risk of an adverse prognosis. Previous studies[26,27] did not find reliable parameters to stratify the risk of death. Fiorino et al[26] in a population of patients with hypercapnic respiratory failure managed in an experienced general ward found that an increased age and a depressed Glasgow coma scale score were associated with an adverse prognosis. A higher APACHE score proved to be associated with a higher mortality rate.[27] However, the ability to predict NIV failure is low when based only on a single variable.

The HACOR score was recently developed by Duan et al,[14] for the prediction of NIV failure in patients with hypoxemic respiratory failure. The scale takes into account heart

Table 5. Arterial Blood Gas Parameters in the Whole Study Population and in Survivors and Nonsurvivors With Hypoxemic and Hypercapnic ARF

Parameter	All Subjects ($N = 644$)	Subjects With Hypoxemic Respiratory Failure ($n = 181$)			Subjects With Hypercapnic Respiratory Failure ($n = 463$)		
		Survivors ($n = 117$)	Nonsurvivors ($n = 64$)	P	Survivors ($n = 377$)	Nonsurvivors ($n = 86$)	P
Data at NIV beginning, mean ± SD							
Heart rate, beats/min	97 ± 23	99 ± 22	101 ± 26	.55	95 ± 22	98 ± 25	.09
SBP, mm Hg	134 ± 63	136 ± 30	124 ± 84	.16	139 ± 72	119 ± 30	.01
Breathing frequency, breaths/min	28 ± 8	29 ± 7	31 ± 7	.29	27 ± 8	28 ± 8	.81
Glasgow coma scale score	13.9 ± 2.4	14.6 ± 1.2	13.7 ± 2.9	.03	14.0 ± 2.2	13.0 ± 3.4	<.001
pH	7.34 ± 1.09	7.39 ± .09	7.36 ± .12	.053	7.27 ± .9	7.27 ± .11	.97
P_{CO_2}, mm Hg	61 ± 22	36 ± 6	36 ± 9	.80	70 ± 17	70 ± 19	.68
P_{aO_2}/F_{IO_2}, mm Hg	188 ± 93	141 ± 77	131 ± 92	.43	213 ± 86	187 ± 99	.01
Data after 1 h with NIV, mean ± SD							
Heart rate, beats/min	91 ± 18	91 ± 18	95 ± 21	.26	89 ± 17	92 ± 18	.16
SBP, mm Hg	125 ± 24	124 ± 27	112 ± 22	.003	128 ± 23	119 ± 23	.002
Breathing frequency, breaths/min	23 ± 6	24 ± 6	26 ± 6	.03	22 ± 6	24 ± 7	.041
Glasgow coma scale score	14.3 ± 1.6	14.6 ± 1.0	13.8 ± 2.4	.001	14.5 ± 1.2	13.6 ± 1.3	<.001
pH	7.34 ± .08	7.39 ± .07	7.35 ± .10	.002	7.33 ± .07	7.31 ± .09	.12
P_{CO_2}, mm Hg	55 ± 18	37 ± 7	37 ± 8	.72	61 ± 16	62 ± 16	.87
P_{aO_2}/F_{IO_2}	217 ± 106	196 ± 109	162 ± 85	.032	236 ± 107	205 ± 92	.02
Data after 24 h with NIV							
Heart rate, beats/min	84 ± 17	84 ± 19	95 ± 18	.001	81 ± 15	89 ± 21	.006
SBP, mm Hg	129 ± 23	128 ± 25	119 ± 22	.03	132 ± 21	124 ± 25	.007
Breathing frequency, breaths/min	22 ± 9	22 ± 5	26 ± 12	.006	21 ± 8	25 ± 10	.009
Glasgow coma scale score	14.7 ± 1.5	14.8 ± .8	14.0 ± 2.2	.02	14.9 ± 1.2	13.9 ± 2.3	.001
pH	7.39 ± .07	7.42 ± .05	7.38 ± .09	.002	7.39 ± .06	7.35 ± .08	<.001
P_{CO_2}, mm Hg	51 ± 13	38 ± 5	39 ± 9	.20	54 ± 12	57 ± 13	.10
P_{aO_2}/F_{IO_2}	222 ± 81	184 ± 87	152 ± 67	.02	245 ± 71	210 ± 78	<.001

ARF = acute respiratory failure; NIV = noninvasive ventilation; SBP = systolic blood pressure

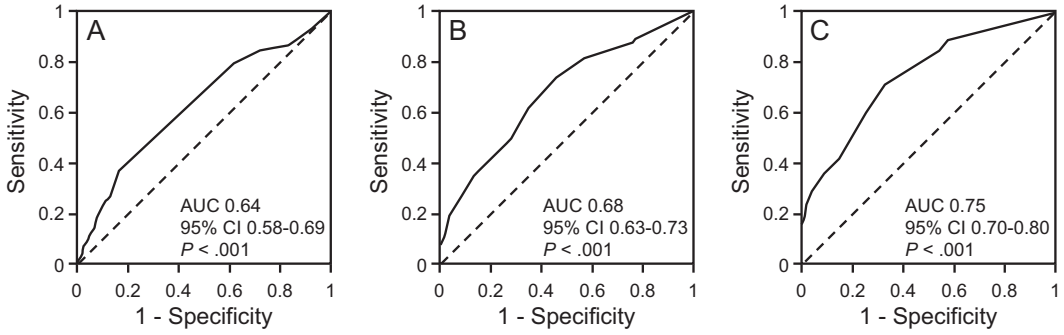

Fig. 3. Receiver operating characteristic curves of the HACOR (heart rate, acidosis, consciousness, oxygenation, respiratory rate) score in the whole study population at T0 (A), T1 (B), and T24 (C).

rate, acidosis, consciousness, oxygenation, and respiratory rate, variables that can be obtained by simple bedside measurements. Thus, the HACOR score is a feasible tool to assess baseline conditions and the patients' evolution over time because it can be easily repeated at short intervals. We decided to test the accuracy of the scale in predicting in-hospital mortality. The possibility to perform serial evaluations; the inclusion of parameters, which were significantly different between the survivors and nonsurvivors in hypoxemic and hypercapnic ARF; and the easy calculation of the score motivated our choice. The score demonstrated a fair-to-good prognostic accuracy; however, a value of the HACOR score of >5 according to the cutoff proposed in the original study,[14] proved to be independently associated with a higher mortality, after the adjustment for age and severity of co-existing organ damage.

Table 6. Cox Survival Analysis for In-Hospital Mortality, Including HACOR Score at Different Evaluations, Adjusted by Age and SOFA Score, in the Whole Study Population and in the Subjects With Hypoxemic and Hypercapnic ARF

Analysis	All Subjects ($N = 644$)			Hypoxemic ARF ($n = 181$)			Hypercapnic ARF ($n = 463$)		
	Relative Risk	95% CI	*P*	Relative Risk	95% CI	*P*	Relative Risk	95% CI	*P*
Univariate									
HACOR score > 5									
T0	2.02	1.41–2.91	<.001			.068	1.97	1.23–3.12	.004
T1	2.09	1.51–2.89	<.001			.24	2.85	1.85–4.41	<.001
T24	3.35	2.33–4.83	<.001	2.14	1.23–3.71	.007	4.75	2.91–7.78	<.001
Multivariate									
Age	1.05	1.03–1.07	<.001	1.05	1.02–1.08	.001	1.06	1.03–1.09	<.001
T0 SOFA score	1.18	1.13–1.24	<.001	1.13	1.05–1.22	.002	1.24	1.16–1.34	<.001
T0 HACOR score >5		–	.25		–	.71		–	
Age	1.05	1.03–1.07	<.001	1.05	1.02–1.07	<.001	1.06	1.03–1.09	<.001
T1 SOFA score	1.20	1.15–1.26	<.001	1.12	1.05–1.20	<.001	1.25	1.14–1.36	<.001
T1 HACOR score >5	1.45	1.02–2.04	.036		–	.60	1.83	1.16–2.89	.01
Age	1.05	1.03–1.07	<.001	1.05	1.02–1.08	.002	1.07	1.03–1.10	<.001
T24 SOFA score	1.13	1.07–1.20	<.001	1.16	1.05–1.27	.003	1.16	1.06–1.27	.001
T24 HACOR score >5	2.39	1.60–3.56	<.001	1.98	1.04–3.75	.037	2.69	1.49–4.85	.001

HACOR = heart rate, acidosis, consciousness, oxygenation, respiratory rate; SOFA = Sequential Organ Failure Assessment score; ARF = acute respiratory failure; T0 = before beginning of NIV; T1 = first 1 h after beginning NIV; T24 = first 24 h after beginning NIV

Before starting the treatment with NIV, the survivors and the nonsurvivors had shown similar values of the HACOR score, as if parameters collected before the initiation of NIV did not allow the subjects with an adverse prognosis. However, the 1- and 24-h values discriminated between the subjects with a good or an unfavorable prognosis because the early positive response to the treatment with NIV exerted a significant effect on the outcome. In fact, the trend over the first 24 h added prognostic information to the earliest evaluations, with persistently high values in those with an adverse prognosis, in terms of NIV failure or in-hospital mortality. To the best of our knowledge, for the first time, a feasible score was tested in a large "real-world" population, to predict the outcome of the subjects treated with NIV. The score showed an association with a higher mortality rate, independent of the severity of organ damage. We already demonstrated that a higher SOFA score was associated with an increased mortality rate in the whole population admitted to the high-dependence unit and in the subjects who were septic. In the subset of subjects affected by ARF and treated with NIV, the HACOR score added significant prognostic information, both for the need to increase the level of care and to identify subjects at a higher risk of in-hospital mortality.

From a clinical point of view, the utility of this evaluation was the early identification of the subjects at risk of an adverse prognosis: among the subjects with hypercapnic respiratory failure, a score value of >5 after 1 h of treatment was independently associated with increased mortality. A high score value could become a warning sign of an impending deterioration, especially for those treated with NIV outside the ICU. We need prospective studies to confirm the prognostic accuracy of this score in a clinical scenario. The retrospective and single-center study design represents a significant limitation. The emergency department–high-dependence observation unit clinical setting could limit the applicability of our results, especially outside of European countries, where this type of emergency department organization is uncommon. A significant proportion of our study population underwent NIV as the ceiling treatment and, from a certain point of view, this can be considered a major limitation. Due to this, we added data about the prognostic value of the HACOR score after the exclusion of the subjects who underwent NIV as the ceiling treatment. However, our study population represented the patients who undergo NIV in everyday clinical practice. With our subjects, we were able to test the prognostic tool to give clinicians useful information for the early identification of those at high risk of an adverse outcome.

Conclusions

Among the subjects treated with NIV for hypoxemic or hypercapnic ARF, the HACOR score proved to be a useful and feasible tool for an early identification of those at risk of an adverse prognosis. The evolution of the score over the first 24 h added prognostic information to the earliest evaluations. The persistence of high values during this period was associated with an increased risk of NIV failure and in-hospital mortality. The easy calculations at bedside make this score a promising tool for the prognostic

stratification of subjects treated with NIV because it allows the early identification of those at high risk of an adverse outcome.

REFERENCES

1. Nava S, Hill N. Non-invasive ventilation in acute respiratory failure. Lancet 2009;374(9685):250-259.
2. Quon BS, Gan WQ, Sin DD. Contemporary management of acute exacerbations of COPD - a systematic review and metaanalysis. Chest 2008;133(3):756-766.
3. Peter JV, Moran JL, Phillips-Hughes J, Graham P, Bersten AD. Effect of non-invasive positive pressure ventilation (NIPPV) on mortality in patients with acute cardiogenic pulmonary oedema: a meta-analysis. Lancet 2006;367(9517):1155-1163.
4. Vital FMR, Ladeira MT, Atallah AN. Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary oedema. Cochrane Database Syst Rev 2013(5):CD005351.
5. Rana S, Jenad H, Gay PC, Buck CF, Hubmayr RD, Gajic O. Failure of non-invasive ventilation in patients with acute lung injury: observational cohort study. Crit Care 2006;10(3):R79.
6. Hess DR. Noninvasive ventilation for acute respiratory failure. Respir Care 2013;58(6):950-972.
7. Mehta AB, Douglas IS, Walkey AJ. Hospital noninvasive ventilation case volume and outcomes of acute exacerbations of chronic obstructive pulmonary disease. Ann Am Thorac Soc 2016;13(10):1752-1759.
8. Osadnik CR, Tee VS, Carson-Chahhoud KV, Picot J, Wedzicha JA, Smith BJ. Non-invasive ventilation for the management of acute hypercapnic respiratory failure due to exacerbation of chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2017(7):CD004104.
9. Gray A, Goodacre S, Newby DE, Masson M, Sampson F, Nicholl J, 3CPO Trialists. Noninvasive ventilation in acute cardiogenic pulmonary edema. N Engl J Med 2008;359(2):142-151.
10. Weng CL, Zhao YT, Liu QH, Fu CJ, Sun F, Ma YL, et al. Meta-analysis: noninvasive ventilation in acute cardiogenic pulmonary edema. Ann Intern Med 2010;152(9):590-600.
11. Al-Rajhi A, Murad A, Li PZ, Shahin J. Outcomes and predictors of failure of non-invasive ventilation in patients with community acquired pneumonia in the ED. Am J Emerg Med 2018;36(3):347-351.
12. Walkey AJ, Wiener RS. Use of noninvasive ventilation in patients with acute respiratory failure, 2000–2009: a population-base study. Ann Am Thorac Soc 2013;10(1):10-17.
13. Davidson AC, British Thoracic Society Guideline Group For The Ventilatory Management of Acute Hypercapnic Respiratory Failure in Adults. Managing acute hypercapnic respiratory failure in adults. Where do we need to get to? Thorax 2016;71(4):297-298.
14. Duan J, Han X, Bai L, Zhou L, Huang S. Assessment of heart rate, acidosis, consciousness, oxygenation, and respiratory rate to predict noninvasive ventilation failure in hypoxemic patients. Intensive Care Med 2017;43(2):192-199.
15. Innocenti F, Bianchi S, Guerrini E, Vicidomini S, Conti A, Zanobetti M, Pini R. Prognostic scores for early stratification of septic patients admitted to an emergency department-high dependency unit. Eur J Emerg Med 2014;21(4):254-259.
16. Innocenti F, Caldi F, Tassinari I, Meo F, Gandini A, Noto P, et al. SOFA score prognostic performance among patients admitted to high-dependency units. Minerva Anestesiol 2019;85(10).
17. Rochwerg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, et al; Suhail Raoof Members Of The Task Force. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J 2017;50(2):1602426.
18. Davidson AC, Banham S, Elliott M, Kennedy D, Gelder C, Glossop A, et al; BTS Standards of Care Committee Member, British Thoracic Society/Intensive Care Society Acute Hypercapnic Respiratory Failure Guideline Development Group, On behalf of the British Thoracic Society Standards of Care Committee. BTS/ICS guideline for the ventilatory management of acute hypercapnic respiratory failure in adults. Thorax 2016;71(Suppl 2):ii1-35.
19. Mehta AB, Douglas IS, Walkey AJ. Evidence-based utilization of noninvasive ventilation and patient outcomes. Ann Am Thorac Soc 2017;14(11):1667-1673.
20. Sainaghi PP, Colombo D, Re A, Bellan M, Sola D, Balbo PE, et al. Natural history and risk stratification of patients undergoing non-invasive ventilation in a non-ICU setting for severe COPD exacerbations. Intern Emerg Med 2016;11(7):969-975.
21. Parker K, Perikala V, Aminazad A, Deng Z, Borg B, Buchan C, et al. Models of care for non-invasive ventilation in the acute COPD comparison of three tertiary hospitals (ACT_3) study. Respirology 2018;23(5):492-497.
22. Hukins C, Wong M, Murphy M, Upham J. Management of hypoxaemic respiratory failure in a respiratory high-dependency unit. Intern Med J 2017;47(7):784-792.
23. Agarwal R, Handa A, Aggarwal AN, Gupta D, Behera D. Outcomes of noninvasive ventilation in acute hypoxemic respiratory failure in a respiratory intensive care unit in north India. Respir Care 2009;54(12):1679-1687.
24. Chawla R, Mansuriya J, Modi N, Pandey A, Juneja D, Chawla A, et al. Acute respiratory distress syndrome: predictors of noninvasive ventilation failure and intensive care unit mortality in clinical practice. J Crit Care 2016;31(1):26-30.
25. Mehta AB, Douglas IS, Walkey AJ. Hospital noninvasive ventilation case volume and outcomes of acute exacerbations of chronic obstructive pulmonary disease. Ann ATS Vol 2016;13(10):1752-1759.
26. Fiorino S, Bacchi-Reggiani L, Detotto E, Battilana M, Borghi E, Denitto C, et al. Efficacy of non-invasive mechanical ventilation in the general ward in patients with chronic obstructive pulmonary disease admitted for hypercapnic acute respiratory failure and pH < 7.35: a feasibility pilot study. Intern Med J 2015;45(5):527-537.
27. Antro C, Merico F, Urbino R, Gai V. Non-invasive ventilation as a first-line treatment for acute respiratory failure: "real life" experience in the emergency department. Emerg Med J 2005;22(11):772-777.