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Original Article

Semiquantitative ChestCT Severity Score Predicts Failure of Noninvasive Positive-Pressure Ventilation in Patients Hospitalized for COVID-19 Pneumonia

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Objective: Noninvasive positive-pressure ventilation (NPPV) emerged as an efficient tool for treatment of COVID-19 pneumonia. The factors influencing NPPV failure still are elusive. The aim of the study was to investigate the relationships between semiquantitative chest computed tomography (CT) scoring and NPPV failure and mortality in patients with COVID-19.

Design: Observational study.

Setting: Nonintensive care setting.

Participants: A total of 112 patients consecutively admitted for COVID-19 pneumonia.

Interventions: Usual care including various degrees of respiratory support.

Measurements and Main Results: The semiquantitative CT score was calculated at hospital admission. Subgroups were identified according to the ventilation strategy used (oxygen delivered by Venturi mask n = 53; NPPV-responder n = 38; NPPV-failure n = 21). The study's primary endpoint was the use of NPPV. The secondary endpoints were NPPV failure and in-hospital death, respectively. CT score progressively increased among groups (six *v* nine *v* 14, $p < 0.05$ among all). CT score was an independent predictor of all study endpoints (primary endpoint: 1.25 [95% confidence interval {CI} 1.1-1.4], p = 0.001; NPPV failure: 1.41 [95% CI 1.18-1.69], $p < 0.001$; in-hospital mortality: 1.21 [95% CI 1.07-1.38], p = 0.003). According to receiver operator characteristics curve analysis, CT score was the most accurate variable for prediction of NPPV failure (area under the curve 0.862 with $p < 0.001$; $p < 0.05$ *v* other variables).

Conclusions: The authors reported the common and effective use of NPPV in patients with COVID-19 pneumonia. In the authors' population, a semiquantitative chest CT analysis at hospital admission accurately identified those patients responding poorly to NPPV.

Key Words: COVID-19; chest computed tomography; non-invasive ventilation; intubation; pneumonia

COVID-19 IS a respiratory tract infection burdened by a significant rate of respiratory insufficiency, need for hospitalization, and mortality.[1] The novelty and wide spread of the COVID-19 pandemic raised questions on how to effectively manage patients with COVID-19 with worsening respiratory

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insufficiency, who, in a nonpandemic setting, would have been treated within intensive care units (ICUs). Noninvasive positive-pressure ventilation (NPPV), with continuous positive airway pressure or pressure support by helmet or facemask, was shown to be a reliable tool for treatment of COVID-19 patients even outside ICUs,[2-5] and was associated with substantial beneficial effect especially when used early during hospitalization.[6] On the other hand, the need for and timing of orotracheal intubation (OTI) and mechanical ventilation still are being debated.[7] Identification of patients with COVID-19 in whom NPPV approach will fail is of paramount importance, as it can aid optimal timing for OTI[2] or, conversely, palliative measures when a do-not-intubate indication is present and NPPV itself seems to be associated with lower efficacy.[8] Chest computed tomography (CT) is an effective technique for the diagnosis of COVID-19 pneumonia,[9] and the semiquantitative evaluation of chest CT findings provides useful prognostic information.[10] However, fewer data are available specifically regarding the influence of increasing lung parenchyma involvement on outcomes of different ventilatory strategies, and the semiquantitative CT assessment still has relatively little validation or widespread clinical use. The aim of the present study was to investigate the accuracy of a CT severity scoring assessment at hospital admission in predicting the response to oxygen therapy (Venturi mask or NPPV), as well as in-hospital outcome, in a cohort of patients hospitalized for COVID-19 pneumonia within a non-ICU setting.

Methods

Study population

This was a single-center observational study. Methodology of enrollment and baseline data acquisition in patients admitted for COVID-19 pneumonia at the authors' institution previously have been described in detail.[11] The authors enrolled all patients admitted for COVID-19 pneumonia at their COVID unit in Vannini hospital. Patients included in the final analysis all had an available chest CT, arterial blood gas, and venous blood examination performed within 24 hours of admission. Patients with COVID-19 having other prominent acute clinical conditions leading to the index hospital admission (eg, acute myocardial infarction), or those with no data regarding in-hospital ventilation or without timely chest CT analysis, were excluded (Supplementary Fig 1). The final sample consisted of N = 112 patients admitted to a mixed low- and medium-intensity care unit. For the purpose of the present study, the authors identified subgroups of patients according to the maximum ventilatory support required during hospitalization and its efficacy (oxygen delivered by Venturi mask n = 53; successful noninvasive ventilation n = 38; and failure of noninvasive ventilation n = 21). Devices used for noninvasive ventilation included face mask and helmet, with or without connection to the ventilator. Modality of NPPV deployment included continuous positive airway pressure, with or without pressure-support ventilation. The study complied with the Declaration of Helsinki; all patients provided written informed consent for the use of their data for research purposes. The study was approved by the Institutional Review Board.

Endpoints definition

The study's primary endpoint was the use of NPPV due to worsening respiratory insufficiency. Decision to initiate NPPV was made by the attending physician according to the current indications.[12] The secondary endpoints were failure of NPPV and in-hospital mortality, respectively. Failure of NPPV was defined as death or need of OTI and mechanical ventilation after initiation of NPPV. The decision to intubate was made by the consultant anesthesiologists on a case-by-case evaluation and largely guided by a simple algorithm available from the literature,[13] which considered oxygen saturation and respiratory rate as the main variables. In the authors' population, every patient who underwent OTI had a trial of NPPV before intubation. Clinicians recording outcome data were blinded to the semiquantitative radiologic evaluation. Outcome data are updated as of January 31, 2021.

Chest-CT analysis

The authors used two multidetector CT scanners (Philips Brilliance 16 and Brilliance 64) for all examinations. Scanning parameters were set as indicated by the manufacturer's standard recommended presetting for a thorax routine. The authors acquired images with a 1-mm slice thickness and a reconstruction increment of 0.5 mm in all patients using a soft tissue kernel of B20 and a lung kernel of B60. Coronal and sagittal multiplanar reconstructions (MPR) were performed in all cases. Infection prevention and control measures were guaranteed in all suspected CT cases (including sanitation of theCT room and patient's isolation). Radiologic findings consistent with SARS-CoV2 pneumonia included three kinds of CT patterns as follows: ground-glass opacity, crazy-paving, and consolidation.[9,14]

A semiquantitative severity score described in the literature[15] was used per each of the five lobes considering the degree of anatomic involvement (0: no involvement; 1: <5% involvement; 2: 5-25% involvement; 3: 26-50% involvement; 4: 51-75% involvement; and 5: >75% involvement). The involvement of each lobe was assessed by the identification of aforementioned abnormalities (ground- glassopacity, crazy-paving, and consolidation) and then visual estimation of their extent (eyeballing). The resulting global CT score was the sum of each individual lobar score (0-25). The image analysis, blinded to clinical data, was performed by a radiologist with experience in thoracic radiology by use of the institutional digital database system (Impax Client, Agfa, version 6.6.0.145, Belgium). A further experienced radiologist performed blinded rereading of images in a subgroup of patients to test for reproducibility of the score.

Statistical analysis

The distribution of data was assessed by Shapiro-Wilk test. The $\chi 2$, Fisher exact test, Mann–Whitney U test, or

Kruskall–Wallis test as appropriate were used to compare groups stratified by use and efficacy of ventilatory support. Between-group differences were assessed by post hoc analysis with Bonferroni correction. Biomarker values were reported as Log10-transformed in regression analysis to yield an approximate normal distribution. Univariate and multivariate linear regression analysis were used to investigate factors independently associated with increasing CT severity score. Univariate and multivariate logistic regression analysis were performed to investigate factors independently associated with primary and secondary endpoints, reporting for each variable the standardized beta coefficient (B). Collinearity was tested through correlation matrix, assuming a correlation closer than r = ±0.7 as a proxy of significant collinearity. Multivariate analysis was performed using stepwise method for linear regression and backward for binary logistic regression; this allowed the appropriate reduction of variables included in the final model.[16] Durbin–Watson test was performed, confirming the absence of autocorrelations. Homogeneity of variances was assessed by the Levene's test. All variables with $p < 0.05$ at univariate analysis were included in the multivariate models. Receiver operator characteristics (ROC) curves were built to assess the ability of different variables in predicting the primary and secondary endpoints; sensitivity and specificity were provided for each variable according to the Youden Index. Comparisons between different ROC curves were performed by Delong test. Interrater reliability of CT severity scoring was assessed in a subgroup of randomly selected patients (n = 32) through evaluation by a second expert operator and calculation of Cohen's kappa and interclass correlation coefficient. All analyses were carried out by using SPSS software version 25 (SPSS Inc, Chicago, IL) and MedCalc version 19.7 (MedCalc Software, Ostend, Belgium). A two-tailed $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics

Table 1 includes baseline characteristics within the overall population, as well as in the ventilation subgroups. Mean age was 67 ± 16 years and 62% were men. Comorbidities were common in the authors' population; more than half of the patients had known hypertension, and approximately one-fourth had preexisting cardiovascular diseases (11% atrial fibrillation, 10% coronary artery disease, and 8% heart failure). Venous blood samples analysis revealed increases of median C-reactive protein (CRP) (6.4 mg/dL, normal value <0.5 mg/dL) and D-dimer (827 ng/mL fibrinogen equivalent unit, normal value <500 ng/mL fibrinogen equivalent unit), as well as decreased lymphocytes count (0.9 per 10^9/L, normal value >1). On arterial blood gas analysis, mean PaO_2 was 77 ± 26 mmHg and median the ratio between blood partial pressure of Oxygen (PaO_2) and Oxygen fraction into inspired gas (F_IO_2) 310 (interquartile range 244-371). Median chest-CT score was 9 ± 5. In-hospital mortality rate in the authors' population was 25% (n = 28).

Characteristics of population according to ventilation strategy

On subgroups analysis, patients who experienced NPPV failure were significantly older as compared with other groups ($p = 0.001$ for trend); whereas no significant differences were recorded among groups regarding sex and comorbidities distribution. Laboratory tests showed higher CRP in the NPPV failure group as compared with both patients with successful NPPV or low-flow oxygen (10.6 mg/dL *v* 7.8 mg/dL *v* 3.7 mg/dL, $p < 0.001$ for trend, with $p < 0.05$ for difference between NPPV failure and the other groups, depicted in Figure 1A); whereas no significant D-dimer differences were found between groups ($p = 0.359$, depicted in Fig 1B). On blood gas analysis, the PaO_2/F_IO_2 was higher in patients who received oxygen by Venturi mask during hospital stay but similarly was reduced in those who underwent successful or unsuccessful NPPV (333 *v* 213 *v* 219 respectively, $p < 0.001$ for trend, $p < 0.05$ for difference between low-flow oxygen and the other groups, depicted in Fig 1C). A step-wise increase of CT severity score was observed among groups (6 *v* 9 *v* 14, $p < 0.001$ for trend), with significant differences detected among all groups according to post hoc analysis ($p < 0.05$, depicted in Fig 1D). Average time between symptoms onset to CT examination was seven ± four days, not significantly different among groups. No difference in medical therapy between patients with NPPV responder and failure were detected, whereas patients within the Venturi mask group had lower prescription rates of antibiotics and corticosteroids.

The duration of NPPV received was higher in NPPV-failure patients (seven days *v* 12 days, $p = 0.005$). OTI rate was 8% overall and 42% in the NPPV failure group. In-hospital death occurred in eight patients (15%) in the Venturi mask group and 20 (95%) in the NPPV failure group.

Predictors of CT severity score

Table 2 depicts results from linear regression analysis for predictors of increasing CT severity score. Multivariate analysis, CRP(Log10), PaO_2/F_IO_2, and history of chronic obstructive pulmonary disease remained independently associated with CT score (standardized beta coefficient (B) = 0.373, B = −0.329 and B = −0.223 with $p < 0.001$, $p = 0.001$, and $p = 0.007$, respectively) Figure 2, 3.

Reproducibility of CT scoring

The authors found excellent agreement between readers in the subset of patients that was reanalyzed by a different operator. Interclass correlation coefficient was 0.98 (95% confidence interval [CI] 0.96-0.99, $p < 0.001$), and Cohen's kappa was 0.831, $p < 0.001$.

Table 1
Characteristics of Study Population Overall and According to Cardiac Biomarkers Levels at Admission.

Variable	Overall (N = 112)	Venturi Mask (n = 53)	NPPV Responder (n = 38)	NPPV Failure (n = 21)	P
Age (y)	67 ± 16	63 ± 19†	65 ± 13*	78 ± 8*,‡	**0.001**
Sex (male)	69 (62)	32 (60)	24 (63)	13 (62)	0.964
Coexistent Conditions					
Hypertension (%)	67 (60)	26 (49)	27 (71)	14 (67)	0.051
Dyslipidemia (%)	26 (23)	8 (15)	11 (29)	7 (33)	0.102
Diabetes (%)	22 (20)	10 (19)	6 (16)	6 (29)	0.335
Previous CVD (%)	28 (25)	13 (25)	9 (24)	6 (29)	0.744
- Atrial fibrillation (%)	13 (11)	9 (17)	1 (3)	3 (14)	**0.046**
- Coronary artery disease (%)	12 (10)	3 (6)	8 (21)	1 (5)	0.065
- Heart failure (%)	10 (8)	6 (11)	1 (3)	3 (14)	0.134
COPD (%)	10 (9)	2 (4)	4 (10)	4 (18)	0.135
CKD (%)	6 (5)	3 (6)	1 (3)	2 (10)	0.448
Cancer (%)	5 (4)	4 (7)	1 (3)	0 (0)	0.212
Laboratory Tests					
Hb (g/dL)	13.2 ± 2	12.7 ± 2	13.6 ± 2	13.4 ± 2	0.099
Platelet (per 10^9/L)	214 ± 80	218 ± 87	219 ± 74	191 ± 71	0.383
WBC (per 10^9/L)	6.3 (4.9, 9.1)	5.9 (4.7, 8.7)	7.4 (4.8, 9.5)	7.6 (5.2, 13.3)	0.335
Neutrophil (per 10^9/L)	5 (3.3, 7.4)	4.3 (3, 6.7)	5.3 (3.4, 7.7)	6 (4, 12)	0.068
Lymphocyte (per $\mu 10^9$/L)	0.9 (0.6, 1.3)	1 (0.6, 1.3)	0.8 (0.6, 1.2)	0.8 (0.4, 1.3)	0.366
NLR	5.5 (3.1, 9.7)	4.7 (2.8, 8.1)	6.7 (3.7, 9.7)	7.8 (3.4, 17)	**0.047**
Creatinine (mg/dL)	0.9 (0.7, 1.2)	0.9 (0.6, 1.1)†	0.9 (0.8, 1.1)	1.1 (0.9, 1.4)‡	**0.019**
CRP (mg/dL)	6.4 (2, 10.8)	3.7 (0.5, 7.6)†	7.8 (5.2, 14.7)†	10.6 (5.7, 14.4)*†	< **0.001**
D-dimer (ng/mL FEU)	827 (561, 1,279)	868 (476, 1443)	772 (542, 974)	881 (614, 1320)	0.359
hs-troponin (pg/mL)	12 (8, 26)	10 (6, 21)†	11 (8, 17)†	27 (12, 56)*,‡	**0.002**
Blood Gas Analysis					
PaO_2/F_IO_2	288 (207, 353)	333 (280, 391)*,†	213 (172, 300) †	219 (155, 295)‡	< **0.001**
CT Findings					
Symptoms to CT (d)	7 ± 4	6 ± 5	7 ± 3	6 ± 2	0.347
CT score	9 ± 5	6 ± 4*,†	9 ± 3†,‡	14 ± 6*,‡	< **0.001**
In-hospital Medical Therapy					
Corticosteroid (%)	(87)	(76)	36 (95)	21 (100)	**0.007**
Antibiotic (%)	(87)	(76)	36 (95)	21 (100)	**0.011**
Tocilizumab (%)	3 (3)	0 (0)	2 (6)	1 (5)	0.138
Remdesivir (%)	11 (10)	3 (6)	6 (16)	2 (10)	0.320
Anticoagulation (profilaxis) (%)	111 (99)	52 (98)	38 (100)	21 (100)	0.547
In-hospital Outcome					
NPPV (%)	59 (53)	-	38 (100)	21 (100)	NA
- NPPV duration (d)	8 (5, 11)	-	7 (5, 8)	12 (7, 14)	**0.005**
- NPPV failure (%)	21 (19)	-	-	21 (100)	NA
OTI (%)	9 (8)	-	-	9 (42)	NA
In-hospital death (%)	28 (25)	8 (15)	0 (0)	20 (95)	< **0.001**

Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CVD, cardiovascular disease; FEU, fibrinogen equivalent unit; Hb, hemoglobin; OTI, orotracheal intubation; NA, not applicable; NIV, Non Invasive Ventilation; NPPV, noninvasive positive-pressure ventilation; URN, upper reference of normality; WBC, white blood cells.
*p < 0.05 *v* NIV responder.
† p < 0.05 *v* NIV failure.
‡ p < 0.05 *v* Venturi mask.

Outcome analysis

Results from outcome analysis are summarized in Table 3 (primary endpoint), Table 4 (secondary endpoints), and Table 5 (ROC analysis). Primary endpoint was met by 59 patients (53%). After multivariate analysis, PaO_2/F_IO_2 (odds ratio [OR] per 10-point increase 0.91, 95% CI 0.86-0.96, p = 0.001) and CT score (OR 1.25, 95% CI 1.1-1.4, p = 0.001) remained independently associated with the primary endpoint. Secondary endpoints were met by n = 21 (19%) and n = 28 (25%) for NPPV failure and in-hospital mortality, respectively. After multivariate analysis, age (OR 1.41, 95% CI 1.18-1.69, p = 0.019) and CT score (OR 1.41, 95% CI 1.18-1.69, p < 0.001) remained independently associated with NPPV failure. Factors independently associated with in-hospital mortality were age (OR 1.14, 95% CI 1.07-1.22, p < 0.001) and CT score (OR 1.21, 95% CI 1.07-1.38, p = 0.003).

ROC curves analysis

According to the ROC curves analysis, CT score showed at least moderate ability of predicting all study endpoints

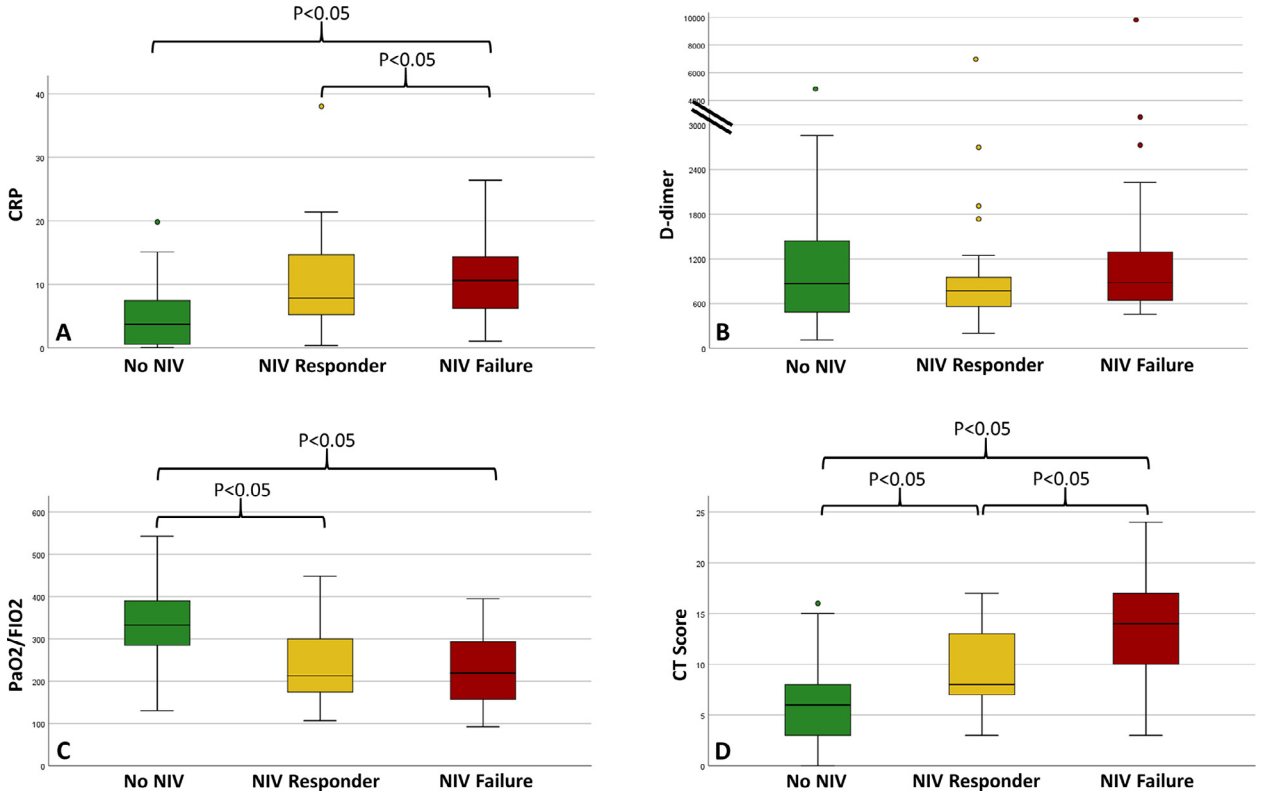

Fig. 1. Boxplots show median value of C-reactive protein (A), D-dimer (B), PaO_2/F_IO_2 (C), and computed tomography score (D) among study groups. Of note, computed tomography score was the only variable displaying stepwise increase with significant differences among all study groups. NIV, Non Invasive Ventilation; PaO_2/F_IO_2, .

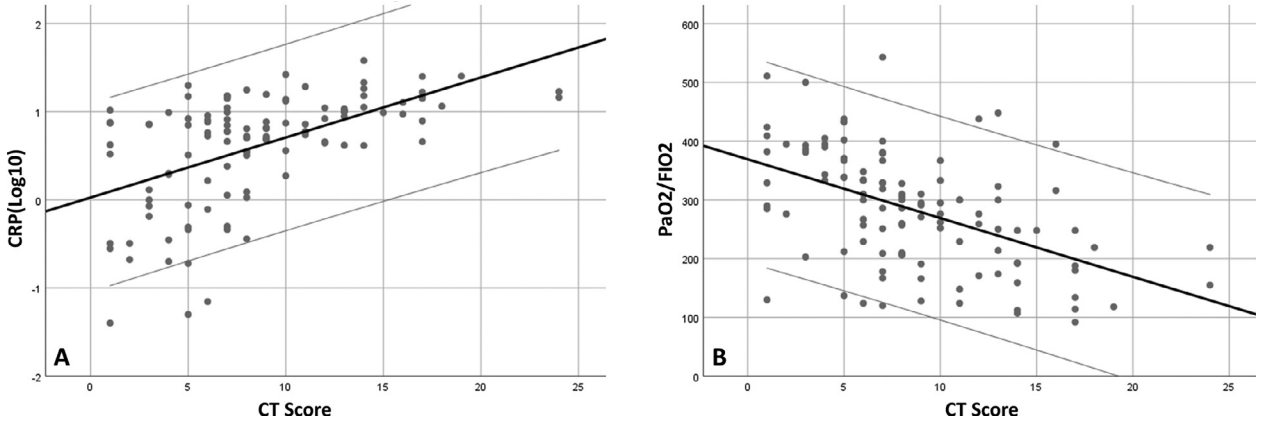

Fig 2. Scatter plots show significant correlation between computed tomography score and C-reactive protein(Log10) (A) and PaO_2/F_IO_2 (B). CRP, C-reactive protein; CT, computed tomography; PaO_2/F_IO_2.

(primary endpoint: area under the curve [AUC] 0.773 [95% CI 0.679-0.866], $p < 0.001$; NPPV failure: AUC 0.862 [95% CI 0.779-0.945], $p < 0.001$; in-hospital death: AUC 0.699 [95% CI 0.559-0.839], $p = 0.004$). ROC curves comparison showed relatively higher accuracy of PaO_2/F_IO_2 in predicting the primary endpoint ($p < 0.05$ *v* high sensitivity troponin (hs-troponin) and D-dimer, nonsignificant *v* other variables); CT score and age predicted with significantly higher accuracy NPPV failure and in-hospital mortality, respectively ($p < 0.05$ for both *v* all variables).

Discussion

In the present study, the authors described findings from a cohort of patients with COVID-19 pneumonia, having detailed data available regarding in-hospital ventilation strategy, radiologic evaluation, and outcome. In a mixed low- and medium-intensity care non-ICU setting, the authors reported the common use of NPPV, which in most of the patients was effective. The semiquantitative chest-CT assessment at hospital admission provided highly reproducible information, with significant

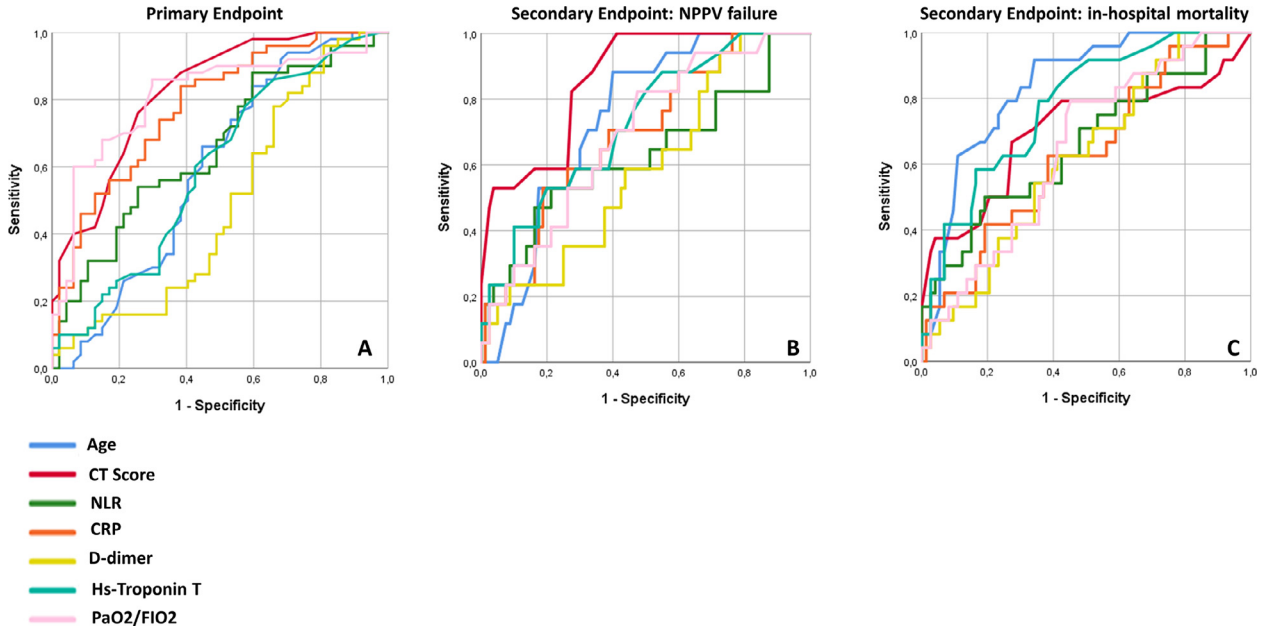

Fig 3. Receiver operator characteristics curves for prediction of study endpoints. (A) Primary endpoint. (B). Noninvasive positive- pressure ventilation failure. (C) In-hospital death. Full data reported within Table 5. CRP, C-reactive protein; CT, computed tomography; PaO_2/F_IO_2,; NLR, neutrophil-to-lymphocyte ratio; NPPV, noninvasive positive-pressure ventilation.

Table 2
Univariate and Multivariate Linear Regression for Factors Associated With Increasing CT Score

CT score				
Variable	Univariate		Multivariate*	
	Standardized B	**p**	**Standardized B**	**P**
Age	0.185	0.051	NS	NS
Sex	0.075	0.433	-	-
COPD	−0.161	0.089	−0.223	**0.007**
Previous CVD	−0.042	0.665	-	-
NLR	0.309	**0.001**	NS	NS
Creatinine	0.158	0.101	NS	NS
CRP(Log10)	0.536	< **0.001**	0.406	< **0.001**
D-dimer(Log10)	0.313	< **0.001**	NS	NS
hs-troponin (Log10)	0.239	**0.014**	NS	NS
PaO_2/F_IO_2	−0.492	< **0.001**	−0.326	**0.001**

NOTE. Bold indicates $p < 0.05$.
Abbreviations: COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CT, computed tomography; CVD, cardiovascular disease; NLR, neutrophil-to-lymphocyte ratio.
* Adjusted R Square 0.398.

prognostic relevance. Furthermore, among the study endpoints, CT score retained the best accuracy in discriminating failure of treatment in those patients allocated to NPPV.

NPPV increasingly is used in patients with COVID-19, even outside the ICUs in the context of increasing pressure on healthcare systems driven by the ongoing pandemic.[3] NPPV use in COVID-19 relies on its ability to recruit nonaerated alveoli, reducing extravascular lung water (highly represented within affected lung areas[17]), increasing functional residual capacity, and reducing work of breathing.[18] NPPV was effective in more than half of the patients allocated to this treatment in the authors' population, a rate comparable to previous studies,[18-20] which suggested that this strategy might significantly contribute to the clinical management of patients with COVID-19. Allocation to the NPPV strategy (primary endpoint) in the authors' population was not driven unexpectedly by worsening respiratory failure, as indicated by PaO_2/F_IO_2 being one of the most accurate predictors of the primary endpoint. PaO_2/F_IO_2 is a fundamental parameter to be assessed in patients with COVID-19, used as a measure of disease severity as well as outcome measure in studies testing novel treatments,[21,22] hence, it was likely one of the major variables guiding clinical decision-making as supported by previous evidence.[12] The independent association that the authors observed between CT score and the primary endpoint indicated that the radiologic evaluation potentially could integrate blood gas analysis to aid the identification of those patients who should be considered for early NPPV and closer monitoring.

Selection of patients with COVID-19 who will benefit most from a NPPV approach remains of paramount importance. Indeed, when NPPV is considered as a ceiling-of-care therapy, as in the presence of a do-not-intubate indication, this likely would provide fewer advantages as compared with the Venturi mask only.[8] On the other hand, Vaschetto et al., reporting data from a large sample of patients with COVID-19 managed in a non-ICU setting, observed how delayed OTI could be a risk factor for mortality.[2] In this context, the authors found that CT severity score was the most accurate predictor of NPPV failure in comparison to all other variables, including PaO_2/F_IO_2 or CRP. Moreover, the authors found higher CT scores in patients with NPPV failure as compared with those in whom it was effective, and PaO_2/F_IO_2 did not differ among these subgroups. Based on the authors' findings it could be speculated that, in the presence of respiratory failure of comparable

Table 3
Univariate and Multivariate Logistic Regression Analysis for Factors Associated With the Primary Endpoint.

Variable	Primary Endpoint			
	Univariate		Multivariate*	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**
Age	1.02 (1-1.05)	**0.05**	NS	NS
Sex (male)	1.1 (0.5 -2.4)	0.800	-	-
COPD	4 (0.8 - 19.8)	0.09	-	-
Previous CVD	1.1 (0.45-2.5)	0.879	-	-
NLR	1.04 (0.99-1.1)	0.123	-	-
Creatinine	2.17 (0.78-6)	0.138	-	-
CRP(Log10)	7.9 (3-20.1)	< **0.001**	-	-
D-dimer(Log10)	1.47 (0.46-4.69)	0.510	-	-
hs-troponin (Log10)	2.21 (0.88-5.59)	0.092	-	-
PaO_2/F_IO_2 (per 10 points decrease)	0.88 (0.83-0.93)	< **0.001**	0.91 (0.86-0.96)	**0.001**
CT score (per each point increase)	1.31 (1.17-1.48)	< **0.001**	1.25 (1.1-1.4)	**0.001**

NOTE. Bold indicates $p < 0.05$.
Abbreviations: COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CT, computed tomography; CVD, cardiovascular disease; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio.
* Nagelkerke R Square 0.455.

Table 4
Univariate and Multivariate Logistic Regression Analysis for Factors Associated With the Secondary Endpoints.

Variable	Secondary Endpoint: NPPV failure				Secondary Endpoint: In-hospital Mortality			
	Univariate		**Multivariate***		**Univariate**		**Multivariate†**	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Age	1.08 (1.03-1.13)	**0.001**	1.08 (1.02-1.15)	**0.011**	1.13 (1.07-1.19)	< **0.001**	1.15 (1.07-1.22)	< **0.001**
Sex	1.02 (0.38-2.7)	0.975	-	-	0.7 (0.3-1.6)	0.409	-	-
COPD	3.33 (0.85-13)	0.085	-	-	2.17 (0.56-8.32)	0.260	-	-
Previous CVD	1.52 (0.51-5.54)	0.450	-	-	2.76 (1.07-7.1)	**0.035**	NS	NS
NLR	1.04 (0.99-1.09)	0.062	-	-	1.08 (1.02-1.11)	**0.008**	NS	NS
Creatinine	4.94 (1.52-16)	**0.008**	NS	NS	4.32 (1.43-12.9)	**0.009**	NS	NS
CRP(Log10)	5.56 (1.43-21.6)	**0.013**	NS	NS	2.51 (1.03-.14)	**0.043**	NS	NS
D-dimer(Log10)	3.49 (0.77-15.83)	0.105	-	-	3.78 (0.96-15)	0.058	-	-
hs-troponin(Log10)	6.98 (2.18-22.3)	**0.001**	NS	NS	12.1 (3.34-43.2)	< **0.001**	NS	NS
PaO_2/F_IO_2 (per 10 points decrease)	0.93 (0.88-0.98)	**0.011**	NS	NS	0.96 (0.91-1)	0.056	-	-
CT score (per each point increase)	1.34 (1.17-1.52)	< **0.001**	1.43 (1.2-1.73)	< **0.001**	1.17 (1.07-1.28)	**0.001**	1.2 (1.04-1.32)	**0.009**

NOTE. Bold indicates $p < 0.05$.
Abbreviations: COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CT, computed tomography; CVD, cardiovascular disease; NLR, neutrophil-to-lymphocyte ratio; NPPV, noninvasive positive-pressure ventilation; PaO_2/F_IO_2, .
* Nagelke R Square 0.539.
† Nagelke R Square 0.475.

severity on admission, the anatomic substrate might condition responsiveness to NPPV.

The authors observed a nontrivial rate of in-hospital mortality in their cohort, partly explained by the characteristics of relatively elderly Italian COVID-19 patients,[23] and by inclusion of more severely affected individuals who were sent directly to a medium-intensity care setting. Though most of the deaths occurred in the context of worsening respiratory failure and after initiation of NPPV, others happened in patients who received oxygen delivered only by Venturi mask during hospital stay. Even though CT score remained independently associated with the secondary endpoint, in-hospital mortality, age had higher accuracy, further reiterating the role of preexisting underlying conditions of vulnerability portending significant influence on prognosis. Accordingly, the authors found CT severity score to be independently associated with PaO_2/F_IO_2 and CRP but not with age nor with markers of end-organ damage, such as hs-troponin or creatinine, which suggested that multiorgan damage in COVID-19 might not be entirely justified solely by higher disruption of lung

Table 5
ROC Analysis Findings.

	ROC analysis					
Variable	Primary Endpoint		Secondary Endpoint: NPPV Failure		Secondary Endpoint: In-hospital Mortality	
	AUC (95% CI)	**p**	**AUC (95% CI)**	**p**	**AUC (95% CI)**	**p**
Age	0.594 (0.478-0.710)	0.111	0.741(0.635-0.846)	**0.002**	0.839 (0.756-0.922)	**< 0.001**
CT score	0.826 (0.745-0.907)*	**< 0.001**	0.862 (0.779-0.945)†	**< 0.001**	0.699 (0.559-0.839)‡	**0.004**
NLR	0.658 (0.549-0.766)	**0.007**	0.629 (0.466-0.793)	0.095	0.660 (0.529-0.792)	**0.019**
CRP	0.781 (0.690-0.871)	**< 0.001**	0.693 (0.562-0.825)	**0.013**	0.626 (0.499-0.754)	0.065
D-dimer	0.488 (0.369-0.607)	0.837	0.589 (0.448-0.729)	0.072	0.616 (0.495-0.736)	0.090
hs-troponin	0.596 (0.482-0.710)	0.103	0.725 (0.598-0.851)	**0.004**	0.805 (0.724-0.886)	**< 0.001**
1/(PaO_2/F_1O_2)	0.811 (0.722-0.901)	**< 0.001**	0.692 (0.563-0.820)	**0.013**	0.646 (0.527-0.764)	**0.033**

NOTE. Bold indicates $p < 0.05$.
Abbreviations: AUC, area under the curve; CI, confidence interval; CRP, C-reactive protein; CT, computed tomography; NLR, neutrophil-to-lymphocyte ratio; ROC, receiver operator characteristics.
* Cut-off 7 points, sensitivity 76%, specificity 74%.
† Cut-off 10 points, sensitivity 81%, specificity 74%.
‡ Cut-off 9 points, sensitivity 64%, specificity 73%.

parenchyma and subsequent respiratory insufficiency, but also by systemic nonrespiratory involvement influencing prognosis.[24-26] Of note, after multivariate analysis, CRP failed to be independently associated with any of the study endpoints; however, given the present study's sample size and literature data indicating a prognostic role for CRP in COVID-19,[27] this result should be carefully interpreted.

The authors' findings might potentially carry clinical implications. In patients with an available chestCT at hospital admission, to routinely perform a semiquantitative evaluation could provide timely information on anatomic lung involvement, to be complemented by the assessment of end-organ damage markers and blood gas analysis in order to improve risk-stratification and provide treatment guidance (ie, by leading to a lower threshold for NPPV initiation). Optimal timing of OTI in patients with COVID-19 still is debated,[28-30] in which lung involvement by CT imaging might be considered as an adjunctive factor contributing to this evaluation.[7] Further studies are needed to fully assess if a more prominent role of semiquantitative chest CT evaluation in guiding ventilatory treatment approach, with early OTI in patients with major lung anatomic involvement, might be associated with improved prognosis. The usefulness of qualitative analysis, as well as a repeated CT scan during in-hospital stay, has been hypothesized,[15] likely providing more accurate information as compared with a semiquantitative evaluation only; however, limitations related to costs, reproducibility, and slowing workflow should be taken into account.

Limitations

The present study should be read in light of several limitations, including partly retrospective nature, limited sample size, and absence of a validation cohort. The authors acknowledge that their protocol, including routine chestCT at hospital admission, might not be transferred immediately to other settings with different resources and organization; thus, by limiting the generalizability and applicability of their findings. For such reasons, the authors' observational data should be considered as hypothesis-generating only, as targeted case-control prospective studies should be performed to effectively demonstrate an advantage of a CT score-guided clinical management in patients with COVID-19. Effect-size of CT scores for the association with the primary endpoint and in-hospital mortality were relatively lower if compared with the effect-size for prediction of NPPV failure, suggesting that other factors than extent of lung parenchyma disruption, including age and systemic involvement, highly contribute to determine prognosis in patients with COVID-19. In the authors' sample, all patients had a trial of NPPV before OTI; this likely was explained by the fact that more severely affected patients requiring immediate OTI at hospital admission were sent directly to higher intensity-of-care wards such as ICUs, being missed by the authors' analysis. Consequently, results from the authors' study might not be transferable immediately to the ICU setting, as well as to other populations with markedly different baseline demographic data.

Conclusions

In the authors' population, NPPV was an effective tool for the management of COVID-19 pneumonia-related respiratory insufficiency outside ICUs. Semiquantitative chest-CT analysis at hospital admission provided highly reproducible prognostic information, especially in terms of responsiveness to NPPV. Further studies are needed to fully assess if routine implementation of CT score to guide clinical management might bring advantages in the care of patients with COVID-19 pneumonia.

Author Agreement CT score

This statement is to certify that all authors have seen and approved the manuscript being submitted, have contributed significantly to the work, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to the *Journal of Cardiothoracic and Vascular Anesthesia*. The authors attest that the article is the authors' original work, has

not received prior publication and is not under consideration for publication elsewhere. On behalf of all coauthors, the corresponding author shall bear full responsibility for the submission. Any changes to the list of authors, including changes in order, additions or removals, will require the submission of a new author agreement form approved and signed by all the original and added submitting authors. All authors are requested to disclose any actual or potential conflict of interest. including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work. If there are no conflicts of interest, the COI should read: "The authors report no relationships that could be construed as a conflict of interest".

Conflict of Interest

None

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2021.09.010.

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