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ORIGINAL ARTICLE

Clinical stability and in-hospital mortality prediction in COVID-19 patients presenting to the Emergency Department

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ABSTRACT

BACKGROUND: The Novara-COVID score was developed to help the emergency physician to decide which Coronavirus disease (COVID) patient required hospitalization at Emergency Department (ED) presentation and to which intensity of care. We aimed at evaluating its prognostic role.

METHODS: We retrospectively collected data of COVID patients admitted to our ED between March 16 and April 22, 2020. The Novara-COVID score was systematically applied to all COVID patients since its introduction in clinical practice and adopted to decide patients' destination. The ability of the Novara-COVID score to predict in-hospital clinical stability and in-hospital mortality were evaluated through multivariable logistic regression and cox regression hazard models, respectively.

RESULTS: Among the 480 COVID patients admitted to the ED, 338 were hospitalized: the Novara-COVID score was 0-1 in 49.7%, 2 in 24.6%, 3 in 15.4% and 4-5 in 10.3% of patients. Novara-COVID score values of 3 and 4-5 were associated with lower clinical stability with adjusted odds ratios of 0.28 (0.13-0.59) and 0.03 (0.01-0.12), respectively. When in-hospital mortality was evaluated, a significant difference emerged between scores of 0-1 and 2 *vs*. 3 and 4-5. In particular, the death adjusted hazard ratio for Novara-COVID scores of 3 and 4-5 were 2.6 (1.4-4.8) and 8.4 (4.7-15.2), respectively.

CONCLUSIONS: The Novara-COVID score reliably predicts in-hospital clinical instability and mortality of COVID patients at ED presentation. This tool allows the emergency physician to detect patients at higher risk of clinical deterioration, suggesting a more aggressive therapeutic management from the beginning.

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KEY WORDS: Coronavirus; Severe acute respiratory syndrome coronavirus 2; Emergency medicine.

The spread of the Coronavirus disease-19 (COVID-19) in northern Italy has put Emergency Departments (EDs) as well as all the Italian National Health System under an unprecedent pressure.[1-3]

Even though news on its diffusion was coming

from China since the end of December 2019,[4] such novel disease, almost completely unknown and for which no scientific foothold was available, took by surprise both patients and medical personnel.[5] As it often is, the ED was the first place to face the stress of this new situation.[6, 7]

Besides the usual flow of patients referring to the ED for varied complaints, emergency physicians, overwhelmed by a large flow of new patients,[8] had to rapidly determine the most appropriate destination (either hospital admission or quarantine home discharge) considering the relative lack of beds,[9-11] especially in the Intensive and Semi-Intensive Care Units.[12-14]

To accomplish this task, we proposed a clinical score, the Novara-COVID score, for rapid destination of COVID patients at Emergency Department presentation.[15] This score was developed and adopted since the very first days of COVID-19 pandemic in our University Hospital, to determine the intensity of care that should have been required by each COVID patient.

After the first month since its introduction and its description in the literature,[15] we aimed at evaluating its efficacy in terms of prognostic role in clinical practice.

Materials and methods

Patients

This study was approved by the Local Ethical Committee (Comitato Etico Interaziendale di Novara, C.E. 97/20). Due to the retrospective nature of the investigation, the need of an informed consent was waived. Patients aged ≥18 years admitted to the Emergency Department at Eastern Piedmont University Hospital with diagnosis of COVID-19 (defined by positive nasal swab for SARS-CoV-2 RNA) were included in this analysis.

The Novara-COVID score

Since its introduction in clinical practice, the Novara-COVID score was systematically applied to all COVID patients at ED presentation. After a 15-minute trial with oxygen at a fraction of inspired oxygen of 0.5, three clinical items were evaluated:

- peripheral oxygen saturation (SpO_2):
  - SpO_2 100% to 96% → 0 points;
  - SpO_2 95% to 90% → 1 point;
  - SpO_2 <90% → 2 points;
- respiratory rate:
  - ≤24 breaths/min → 0 points;
  - 24-35 breaths/min → 1 point;
  - >35 breaths/min → 2 points;
- presence of comorbidity (any disease on active therapy):
  - no → 0 points;
  - yes → 1 point.

According to the score obtained by the sum of each item, patients were either discharged or admitted to COVID-wards with different levels of care:

- 0-1 point: consider either discharge and home quarantine or admission to a low-intensity care ward;
- 1-2 point(s): consider admission to a low-intensity care ward;
- 3 points: consider admission to an intermediate-intensity care ward;
- 4-5 points: consider intensivist consult and intensive care unit (ICU) admission.

Study design

Data were systematically retrieved from COVID patients' ED clinical charts and collected after anonymization. The Novara-COVID score, demographic and destination data, as well as in-hospital transfers and in-hospital mortality were recorded.

In-hospital mortality and clinical stability were then analyzed. Clinical stability was defined as no need for transfer to a higher intensity of care (*e.g.* from low to intermediate intensity of care) and no in-hospital death. The percentage of ED readmissions over the following 14 days was evaluated among patients discharged at home in quarantine.

Statistical analysis

Data were summarized according to Novara-COVID score groups as median and (25^{th}-75^{th} percentile); whenever dichotomous or nominal they were reported as absolute frequencies and percentages. A multivariable logistic regression analysis was performed to evaluate the Novara-COVID score effects on the clinical stability

endpoint, adjusted for gender and age. The 0.632 bootstrap (1000 resamples) validation procedure was carried out to evaluate the predictive logistic regression model performance reporting the Harrell-C statistics corrected for over-optimism.

Kaplan-Meier estimation method was used to estimate the survival curves across Novara-COVID score groups. The log-rank test estimation method was used to compare the survival curves. A *post-hoc* analysis was performed on log-rank tests. Multiple comparisons across groups have been adjusted using a Benjamini-Hochberg correction. A Cox regression hazard multivariable model was estimated to evaluate the Novara-COVID score effects on the death Hazard, adjusted for gender and age. A restricted cubic spline component has been considered in the multivariable models to account for the nonlinear effects.

A two-tailed test was considered for the hypothesis testing procedure and statistically significant values were considered to reach a P value <0.05. Statistical analyses were conducted using R 3.5.2 and rms packages.

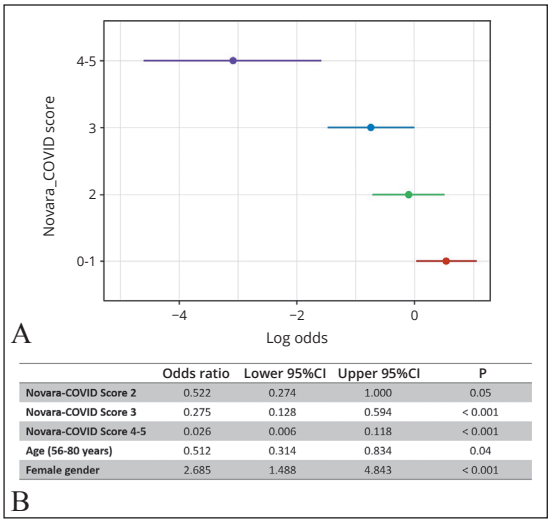
Results

Patients

Between March 16 and April 22, 2020, 480 patients with final diagnosis of COVID-19 were admitted to our ED and 338 were subsequently hospitalized. The median age was 68 (56-80) years and 208 (62%) were male. Ninety-six patients (28%) died during hospitalization. Among hospitalized patients, 168 (49.7%) had a score of 0-1, 83 (24.6%) of 2, 52 (15.4%) of 3 and 35 (10.3%) a score of 4-5. Patient characteristics are reported on Table I.

Prediction of clinical stability

High values of the EP-COVID score, notably 3 and 4-5, were significantly associated with lower clinical stability (Figure 1). At the multivariable logistic regression analysis, EP-COVID scores of 3 and 4-5 showed adjusted odds ratios of 0.28 (0.13-0.59) and 0.03 (0.01-0.12), respectively. Conversely, scores of 0-1 and 2 were not associated with a lowering in the clinical stability.



	Odds ratio	Lower 95%CI	Upper 95%CI	P
Novara-COVID Score 2	0.522	0.274	1.000	0.05
Novara-COVID Score 3	0.275	0.128	0.594	< 0.001
Novara-COVID Score 4-5	0.026	0.006	0.118	< 0.001
Age (56-80 years)	0.512	0.314	0.834	0.04
Female gender	2.685	1.488	4.843	< 0.001

B

Figure 1.—Multivariable logistic regression model for clinical stability. A) The age and gender-adjusted log odds have been reported in the graph together with the 95% confidence intervals; and B) the model estimated odds ratios have been also presented with 95% confidence intervals and P values. CI: confidence interval.

Similarly, patients aged 56 to 80 years showed a significantly lower probability of clinical stability, compared to the younger ones, with an odds ratio of 0.51 (0.31-0.83). Conversely, female gender was associated with a significant increase in clinical stability with an odds ratio of 2.69 (1.49-4.84) (Figure 1). The Harrell-C statistics for this predictive model was 0.81.

Prediction of in-hospital mortality

At the *post-hoc* adjusted log-rank test, for in-hospital mortality evaluation, scores of 0-1 and 2 were significantly different to scores of 3

TABLE I.—*Patient characteristics.*

Parameters	Novara-COVID Score 0-1 (N.=168)	Novara-COVID Score 2 (N.=83)	Novara-COVID Score 3 (N.=52)	Novara-COVID Score 4-5 (N.=35)
Age	60 [51–72]	74 [63–84]	77 [69–86]	75 [64–86]
Deaths (N. %)	20 (12%)	22 (27%)	25 (48%)	29 (83%)
Male/female	110/58	45/38	28/24	25/10

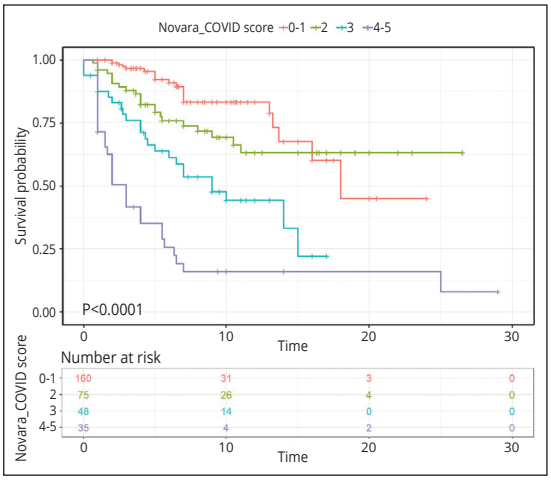
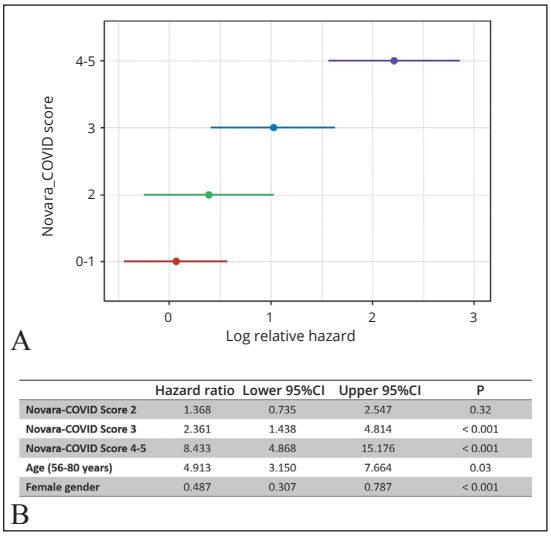


Figure 2.—Survival analysis. Kaplan Meier curve. The log rank test P value has been also reported.

(P<0.0001 and P=0.0100, respectively) and 4-5 (P<0.0001 for both) (Figure 2). Moreover, a significant difference was also observed between 3 and 4-5 (P=0.004). In particular, patients with a Novara-COVID score of 3 showed a death adjusted hazard ratio of 2.4 (1.4-4.8) that reached 8.4 (4.9-15.2) for those with a score of 4-5 (Figure 3).

Female gender emerged as an independent protective factor against in-hospital mortality, with an adjusted hazard ratio of 0.49 (0.31-0.77), whereas older age independently increased the risk of death (hazard ratio 4.9 [3.2-7.7]) (Figure 3). The Harrell-C statistics for this predictive model was 0.80.



	Hazard ratio	Lower 95%CI	Upper 95%CI	P
Novara-COVID Score 2	1.368	0.735	2.547	0.32
Novara-COVID Score 3	2.361	1.438	4.814	< 0.001
Novara-COVID Score 4-5	8.433	4.868	15.176	< 0.001
Age (56-80 years)	4.913	3.150	7.664	0.03
Female gender	0.487	0.307	0.787	< 0.001

B

Figure 3.—Cox Regression Hazard multivariable model. A) The age and gender-adjusted log hazard have been reported in the graph together with the 95% confidence intervals; and B) the model estimated hazard ratios have been also presented with 95% confidence intervals and P values.
CI: confidence interval.

ED readmission

One-hundred forty COVID patients were initially discharged at home. The median age was 45 (36-56) years and 69 (49%) were female. Among them, 15 (10.7%) were subsequently readmitted to the ED, with a median time of 5 (3-8) days. No difference was observed between male and female gender in terms of probability of ED readmission (P=0.09). All the 15 patients had still a Novara-COVID score of 0-1 at ED readmission and were subsequently hospitalized to a low-intensity of care ward.

Discussion

This study shows that the Novara-COVID score reliably predicts clinical stability and in-hospital mortality in COVID patients at ED presentation.

Most of the initial research on COVID-19 (besides searching for a valid therapeutic management)[16] has been focused on detailing the clinical characteristics of COVID patients and hypothesizing which factors could have been responsible for a worse prognosis.[17] In particular, the need of mechanical ventilation and ICU admission have been among the most commonly evaluated outcomes.[18]

However, as this scientific strategy is irreproachable, it is not as much pragmatic as emergency physicians may wish. Indeed, when the rapid choice among which patient should be hospitalized and which one could be safely discharged is needed, choosing whether one particular factor should be preferred over another to stratify the prognosis may become cumbersome. On the contrary, a rapid stratification score may be very helpful and more practical, in a context of extreme pressure for both EDs and COVID wards.

In this context, the Novara-COVID score, by evaluating the presence of comorbidities together with two simple physiologic variables, respiratory rate, and SpO_2 after a 15-minute trial

of oxygen therapy, seems to fit for such needs, as it helps emergency physicians to admit COVID patients to the most appropriate intensity of care ward. In addition, the Novara-COVID score allows the early detection of patients at higher risk of clinical deterioration, for whom a more aggressive therapeutic management may be considered from the beginning.

Of note, for the lowest scores (0-1) the Novara-COVID score leaves a certain degree of discretion to the emergency physician: according to other clinical elements and physician's judgement, the patient can be either discharged or admitted to a low-intensity care ward. In this regard, only 10% of patients discharged at home were subsequently readmitted to the ED.

Limitations of the study

The study presents some limitations. First, this is a monocentric retrospective study. Second, the Novara-COVID score evaluates the presence of comorbidities, without specifying neither their number nor their severity. However, we assumed that the fact of having at least one disease on active therapy reflects the presence of frailty, making a strong distinction with healthy patients. This is easy to detect and leaves less arbitrariness on the decision of giving or not one point to this item. Third, we did not evaluate the ratio of the arterial oxygen partial pressure over the fraction of inspired oxygen, which is commonly used to define both the need and the level of oxygen support. Nevertheless, SpO_2 and respiratory rate provide valid information regarding the patient's response to a trial of standard oxygen therapy. These physiologic parameters are easier to evaluate and less invasive, widening their utilization.

Conclusions

The Novara-COVID score reliably identifies patients at higher risk of in-hospital mortality and clinical instability. This score is easy to calculate, costless and can be performed in all the EDs, regardless of the level of resource settings. Even though a prospective validation on a large multicentric cohort may be desirable, we suggest its adoption by EDs that are facing the COVID-19 pandemic.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions.—Francesco Gavelli and Luigi M. Castello have given substantial contributions to data acquisition and analysis, and manuscript conception and writing, Mattia Bellan, Eyal Hayden, Michela Beltrame, Alessandra Galbiati, Clara A. Gardino, Maria L. Gastaldello, Francesca Giolitti, Emanuele Labella, Filippo Patrucco and Pier P. Sainaghi to data acquisition and data analysis, Danila Azzolina to data analysis and interpretation, and manuscript writing, Gian C. Avanzi to data analysis, and manuscript conception and writing. All authors read and approved the final version of the manuscript.

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