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Development and Validation of a New Risk Score for Infection with Coronavirus (Ri.S.I.Co) Obtained from Treating Coronavirus Disease (COVID-19) Patients on the Field

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Abstract

Background: The Coronavirus Disease 2019 (COVID-19) pandemic has necessitated the alteration of the organization of entire hospitals to try to prevent them from becoming epidemiological clusters. The adopted diagnostic tools lack sensitivity or specificity.
Objectives: The aim of the study was to create an easy-to-get risk score (Ri.S.I.Co., risk score for infection with the new coronavirus) developed on the field to stratify patients admitted to hospitals according to their risk of COVID-19 infection.
Methods: In this prospective study, we included all patients who were consecutively admitted to the suspected COVID-19 department of the Bufalini Hospital, Cesena (Italy). All clinical, radiological, and laboratory predictors were included in the multivariate logistic regression model to create a risk model. A simplified model was internally and externally validated, and two score thresholds for stratifying the probability of COVID-19 infection were introduced.
Results: From 11th March to 5th April 2020, 200 patients were consecutively admitted. A Ri.S.I.Co lower than 2 showed a higher sensitivity than SARS-Cov-2 nucleic acid detection (96.2% vs. 65.4%; $P < 0.001$). The presence of ground-glass pattern on the lung-CT scan had a lower sensitivity than a Ri.S.I.Co lower than 2 (88.5% vs. 96.2%; $P < 0.001$) and a lower specificity than a Ri.S.I.Co higher than 6 (75.0% vs. 96.9%; $P < 0.001$).
Conclusions: We believe that the Ri.S.I.Co could allow to stratify admitted patients according to their risk, preventing hospitals from becoming the main COVID-19 carriers themselves. Furthermore, it could guide clinicians in starting therapies early in severe-onset cases with a high probability of COVID-19, before molecular SARS-CoV-2 infection is confirmed.

Keywords: Early Diagnosis, Score, Mass Casualty Incidents, Pandemic

1. Background

Coronavirus (SARS-CoV-2) disease (COVID19) (1, 2) has dramatically changed the world during the past few months, and disrupted our lives, daily routines, and relationships (3). As physicians, we had to react to the shock-wave: a large number of patients who required access to Emergency Departments (ED) in a short period of time. Oftentimes, these patients rapidly filled up the capacity of hospitals and overwhelmed local and regional resources. This scenario has a simple, well-known, but frightening name: Mass Casualty Incident (MCI). Unlike common MCIs (terrorist attacks, earthquakes, or accidents), COVID-19 lasts for months.

In Western countries, Italy was in the frontline of Coronavirus (SARS-CoV-2) infection from last days of February, especially in northern regions (Lombardy, Emilia-Romagna, Veneto); the COVID-19 pandemic required health national systems to change not only the type of work done in hospitals, but also the organization of the hospitals: move and/or reduce surgical departments, theoretically "cleans", create beds for medical and/or intensive care units, theoretically "dirty".

This number of patients with acute respiratory symptoms required that physicians and/or surgeons changed

their usual work and acquired new skills to cope with the situation.

This is even more important today in order to not expose patients and healthcare professionals to unnecessary biological risks and to prevent hospitals from becoming epidemiological clusters, as unfortunately happened in some cases (4).

M. Bufalini Hospital, Cesena Emilia-Romagna (Italy) is the hub for trauma, stroke, and burns patients; it covers about one million people, increasing dramatically during the summer. During the first days of the COVID-19 outbreak, one major problem was where and how to manage patients suspected of SARS-CoV-2 infection. While laboratory tests were under evaluation, often, patients needed treatment as basic as oxygen or close medical monitoring. In our hospital, Emergency Surgery Ward was used to solve these problems.

Anamnestic criteria for suspected COVID-19 (at least one of: fever, cough, breathing difficulties, contact with patients positive for COVID-19, and travel to endemic regions) lost their effectiveness. In a pandemic situation, there are no safe people or places, suspicious symptoms covered the vast majority of patients in EDs. Blood samples showed a heterogeneous variability between normal and strongly altered. SARS-Cov-2 nucleic acid detection in upper respiratory tract specimen did not show sufficient sensitivity, and radiologic exams, chest X-ray, particularly Thoracic High Resolution CT (HRCT), showed suspected, but not exclusive, signs related to interstitial involvement of the lungs.

2. Objectives

While managing suspected COVID-19 patients on the field, we prospectively collected data with the aim of creating an easy-to-get risk score to meet our need to stratify and separate patients according to their risk of COVID19 infection; the goal was to minimize the risk of intra-hospital SARS-CoV-2 infection and to provide the best treatment available to everyone, even during the emergency period.

3. Methods

We developed the new risk score for infection from the new coronavirus (SARS-CoV-2) [Ri.S.I.Co] on a construction sample of consecutive patients admitted from 11th to 23rd March 2020 in the suspected COVID-19 department of the Bufalini Hospital in Cesena (Italy). After excluding patients with missing data, we established the internal validity of the Ri.S.I.Co, based on the internal validation cohort. Finally, we externally validated the Ri.S.I.Co on a "external validation cohort" derived from validation sample formed by consecutive patients admitted to our department in a later time period (from 24th March to 5th April 2020).

3.1. Construction Sample

This prospective study included all patients who were consecutively admitted from 11th March 2020 to 5th April 2020 to the suspected COVID-19 department of the Bufalini Hospital in Cesena (Italy). During this period, all patients who accessed the Emergency Department (ED) with fever higher than 37.5°C and/or respiratory symptoms (on admission or in the last 10 days) or close contact with patients with confirmed infection with the COVID-19 in the last two weeks, underwent an upper respiratory tract specimen collection (swab) for COVID-19 testing by RT-PCR (SARS-CoV-2 swab test). Patients who could not be discharged from the ED (with indication for clinical observation by the territorial medicine) and did not need ventilatory support were admitted to the suspected COVID-19 department.

After admission, patients waited for a definitive confirmation or exclusion of an infection with the coronavirus. Patients were treated for COVID-19 infection if they had almost one positive SARS-CoV-2 swab test or if they had strongly suspected radiological and clinical signs, even with negative swabs. All the probable cases of COVID-19 infection with negative swabs were reviewed by a final diagnosis committee composed of internal medicine specialists and/or pneumologists. If a patient was defined COVID-19 infected, he/she was transferred to a COVID-19 department or, in case of permissive conditions, the patient was discharged with an indication for isolation and clinical observation by the Territorial Medicine. Otherwise, he/she was transferred to a non-COVID-19 department.

For the purpose of defining the outcome of the score, we considered a patient infected with COVID-19 if he was treated for COVID-19 infection and/or he was transferred to a COVID-19 department. The following data were extracted for each patient: age, sex, contact with patients with a confirmed infection with COVID-19, vaccine status for the last influenza virus, symptoms other than fever and respiratory symptoms (joint or muscle pain, gastrointestinal symptoms, asthenia, headache, anosmia, and ageusia), radiological findings in the thoracic HRCT report (presence of a ground-glass pattern, consolidations, interlobular septum thickening, pleural effusion, nodules, location of the pulmonary findings, and presence of monolateral or bilateral findings), findings of the thoracic US performed in ED (presence of B-lines or subpleural consolidations), blood and urine tests performed in the ED (Legionella and Pneumococcus urinary antigens, Chlamydia and Mycoplasma serology, influenza A/B virus swab test, lymphocytes and neutrophils count, reactive C protein [PCR], lactic dehydrogenase [LDH], creatinfosfochinasi [CPK], albu-

minemia, D-dimer, procalcitonin [PCT], troponin), respiratory rate [RR], oxygen saturation [SO_2], walking test result and blood gas numbers at ED (PO_2/FiO_2 ratio, PO_2, PCO_2), COVID-19 swab tests results, treatment for COVID-19 virus infection, and destination department/discharge. Any predictor recorded for < 50% of patients in the development data was not included in the modeling process.

After prospectively collecting the first 100 patients (construction sample), all clinical, radiological, and laboratory predictors were included in the univariate analysis, and then, after excluding non-significant factors, a multivariate logistic regression model was developed to create a risk score. We used multivariate logistic regression with backward stepwise selection with a P value greater than 0.07 for the removal of variables. We used the odds ratio (OR) to estimate the coefficients associated with each potential risk factor to create a regression model. A simplified model, called Ri.S.I.Co, was constructed based on the regression coefficients, which were approximated to coefficients directly proportional to the corresponding OR. The discriminating capacity of the simplified model was compared to the regression model through the average area under the ROC curve (AUC).

3.2. Sample Size

All available data on the database were used to maximize the power and generalizability of the results. We did not perform a formal sample size calculation because there are no generally accepted approaches to estimate the sample size requirements for derivation and validation studies of risk prediction models. On the basis of some empirical investigations (5), we followed the widely adopted rule to have at least 10 outcome events per variable, or more precisely, per parameter estimated in the logistic regression.

3.3. Internal Validation

We assessed internal validity and calculated performance measures in the internal validation cohort derived from the construction sample after excluding patients with missing information on any predictors in the risk model. The average AUC score was calculated and compared with the performance measures of the most commonly used diagnostic tests for COVID-19 infection, namely the SARS-CoV-2 swab test and thoracic HRCT.

3.4. External Validation

The accuracy of the model was externally validated on an external validation cohort derived from a validation sample made of the prospectively collected data of 100 patients consecutively admitted to the suspected COVID-19 department in a later time period (from 24th March to 5th April 2020).

The external validation cohort was derived from the validation sample after excluding patients with missing information on any of the predictors in the risk model. Similar to the internal validation process, the average AUC score was calculated and compared with the performance measures of the most commonly used diagnostic tests for COVID-19 infection, that is, the SARS-CoV-2 swab test and thoracic HRCT.

Once a final model was defined, patients were divided into risk groups. Score thresholds for stratifying the probability of COVID-19 infection were introduced based on clinically acceptable specificity and sensitivity.

3.5. Construction and Validation of a Model Without HRCT

As many of the hospitals most affected by the pandemic in Northern Italy excluded thoracic HRCT from the diagnostic path of patients with suspected COVID-19 infection to save resources, we created a second simplified score (score without HRCT) for the construction sample excluding HRCT predictors from the multivariable logistic regression model. Subsequently, we validated the model internally based on the internal validation cohort and externally based on the external validation cohort, similar to the model with HRCT.

3.6. Statistical Analysis

Student's *t*-test and Fisher's exact test were used for analyzing differences in continuous variables and proportions. Logistic regression analysis was used in the multivariate analysis for the construction of the scores. The ROC area was used for comparing the discriminating capacity of the scores. The new score's sensitivity and specificity were compared with those of other diagnostic tests using McNemars' test.

This work was performed according to TRIPOD Statements (5).

4. Results

4.1. Construction of the Model

From 11th March 2020 to 5th April 2020, 200 patients were consecutively admitted to the suspected COVID-19 department of the Bufalini Hospital in Cesena (Italy). Figure 1 reports the participants flow diagram.

The first 100 patients formed the construction sample. In Table 1, the characteristics of patients of the construction sample are reported with univariate analysis. Age lower than 60 years, LDH higher than 214 U/L, neutrophil

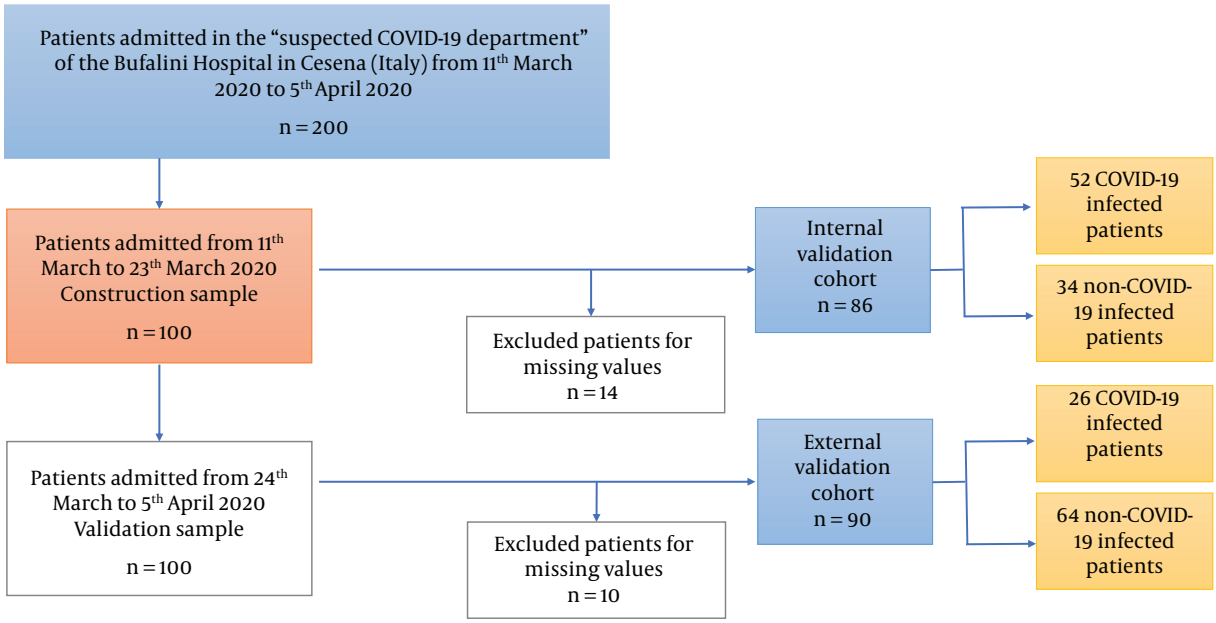

Figure 1. Participant flow diagram

count lower than 8×10^9/L, presence of ground-glass pattern at thoracic HRCT, presence of bilateral findings at thoracic HRCT, contact with confirmed COVID-19 infected patients, and positive first SARS-CoV-2 swab were the significant risk factors for COVID-19 infection in univariate analysis. As the SARS-CoV-2 swab is the accepted standard for COVID-19 diagnosis up to now, and all positive patients need isolated observation and/or treatment, we did not include this single item in the regression analysis.

The significant risk factors for COVID-19 infection in multivariate logistic regression analysis are reported in Table 2 with the corresponding regression scores. These variables (age lower than 60 years, LDH higher than 214 U/L, neutrophil count lower than 8×10^9/L, presence of ground-glass pattern at thoracic HRTC) and the relative OR made up the Regression score. A simplified score, Ri.S.I.Co, was constructed based on the regression coefficients, which were approximated to coefficients directly proportional to the corresponding OR.

The logistic regression analysis, excluding the HRCT finding, is reported in Table 2. These variables and the relative scores made up the regression score without HRCT. A simplified score without HRCT was constructed similar to the previous one.

4.2. Internal and External Validation

These two scores were internally and externally validated. The characteristics of patients in the internal and external validation cohorts are reported in Table 3. The discriminating capacity of the regression score (AUC 0.891, 95% CI: 0.825 - 0.958) and the simplified Ri.S.I.Co (AUC 0.892, 95% CI: 0.825 - 0.958) were very similar in the internal validation cohort. Likewise, the discriminating capacity of the regression score without HRCT (AUC 0.843, 95% CI: 0.762 - 0.924) and the score without HRCT (AUC 0.830, 95% CI: 0.746 - 0.914) were very similar (Figure 2).

The AUC of the Ri.S.I.Co calculated in the internal validation cohort was 0.892 (95% CI: 0.825 - 0.954), and it was significantly higher than the AUC of the presence of ground glass pattern on HRCT (AUC 0.701, 95% CI: 0.581 - 0.822). The AUC of the Ri.S.I.Co was not significantly different from the AUC of the first SARS-CoV-2 swab (AUC 0.933, 95% CI: 0.876 - 0.989) and the score without HRCT (AUC 0.830, 95% CI: 0.746 - 0.914). The ROCs and the relative AUCs of the internal validation cohort are reported in Figure 3 and Table 3.

The AUC of the RI.S.I.CO calculated in the external validation cohort was 0.754 (95% CI: 0.640 - 0.868), which was not significantly different from the AUC of the presence of ground-glass pattern on thoracic HRCT (AUC 0.817, 95% CI: 0.721 - 0.913) and the AUC of the first SARS-CoV-2 swab (AUC 0.827, 95% CI: 0.711 - 0.942). The AUC of the score without HRTC was not significantly different from 0.5. The ROCs and the relative AUCs of the external validation cohort are reported in Figure 3 and Table 4.

Table 5 reports the performance measures of the

Table 1. Characteristics of the Construction Sample

Characteristics (N = 100)	Missing Values	All Patients in the Construction Group	COVID-19 Infection (N = 56), No. (%)	Non-COVID-19 Infection (N = 44), No. (%)	P Value
Age	0	< 60	27 (81.8)	6 (18.2)	< 0.001
		≥ 60	29 (43.3)	38 (56.7)	
Gender	0	Female	25 (52.1)	23 (47.9)	0.546
		Male	31 (59.6)	21 (40.4)	
HRTC: consolidation	7	No	31 (57.4)	23 (42.6)	1.000
		Yes	23 (59.0)	16 (41.0)	
HRTC: interlobular septum thickening	7	No	36 (58.1)	26 (41.9)	1.00
		Yes	18 (58.1)	13 (41.9)	
HRTC: pleural effusion	7	No	51 (60.7)	33 (39.3)	0.158
		Yes	3 (33.3)	6 (66.7)	
HRTC: nodules	7	No	47 (61.0)	30 (39.0)	0.267
		Yes	7 (43.8)	9 (56.3)	
HRTC: location	9	Inferior	11 (57.9)	8 (42.1)	0.071
		Superior	3 (25.0)	9 (75.0)	
		Inferior + superior	39 (66.1)	20 (33.9)	
HRTC: mono/bilateral findings	10	Monolateral	5 (26.3)	14 (73.7)	0.002
		Bilateral	48 (67.6)	23 (32.4)	
HRTC: ground glass pattern	8	No	3 (15.0)	17 (85.0)	< 0.001
		Yes	52 (72.2)	20 (27.8)	
Contact with COVID+	0	No	43 (50.0)	43 (50.0)	0.003
		Yes	13 (92.9)	1 (7.1)	
Joint or muscle pain	0	No	50 (54.3)	42 (45.7)	0.460
		Yes	6 (75.0)	2 (25.0)	
Gastrointestinal symptoms	0	No	43 (53.8)	37 (46.3)	0.454
		Yes	13 (65.0)	7 (35.0)	
Astenia	0	No	44 (53.0)	39 (47.0)	0.283
		Yes	12 (70.6)	5 (29.4)	
Headache	0	No	54 (55.7)	43 (44.3)	1.000
		Yes	2 (66.7)	1 (33.3)	
Anosmia/Ageusia	0	No	54 (55.7)	43 (44.3)	1.000
		Yes	2 (66.7)	1 (33.3)	
Lymphocyte count	1	≥ $1*10^9$/L	28 (56.0)	22 (44.0)	1.000
		< $1*10^9$/L	28 (56.0)	22 (44.0)	
Neutrophil count	1	≥ $8.00*10^9$/L	5 (19.2)	21 (80.8)	< 0.001
		< $8.00*10^9$/L	51 (68.9)	23 (31.1)	
PCR	1	≥ 5.0 mg/L	50 (57.5)	37 (42.5)	0.553
		< 5.0 mg/dL	6 (46.2)	7 (53.8)	
LDH	6	> 214 U/L	47 (68.1)	22 (31.9)	0.001
		≤ 214 U/L	7 (28.0)	18 (72.0)	
RR > 20	10	> 20	17 (53.1)	15 (46.9)	0.503
		≤ 20	36 (62.1)	22 (37.9)	
SO_2[a]	16	< 95%	16 (51.6)	15 (48.4)	0.357
		≥ 95%	34 (64.2)	19 (35.8)	
P/F < 300	40	< 300	7 (41.2)	10 (58.8)	0.779
		≥ 300	20 (46.5)	23 (53.5)	
1° SARS-CoV-2 swab	0	Negative	8 (15.4)	44 (84.6)	< 0.001
		Positive	48 (110.0)	0 (0.0)	

Abbreviations: Ag, antigen; HRCT, high resolution computed tomography; LDH, lactic dehydrogenase; PCR, reactive C protein; P/F: PO_2/FiO_2; RR, respiratory rate; SO_2, oxygen saturation

[a] without oxygen supplement

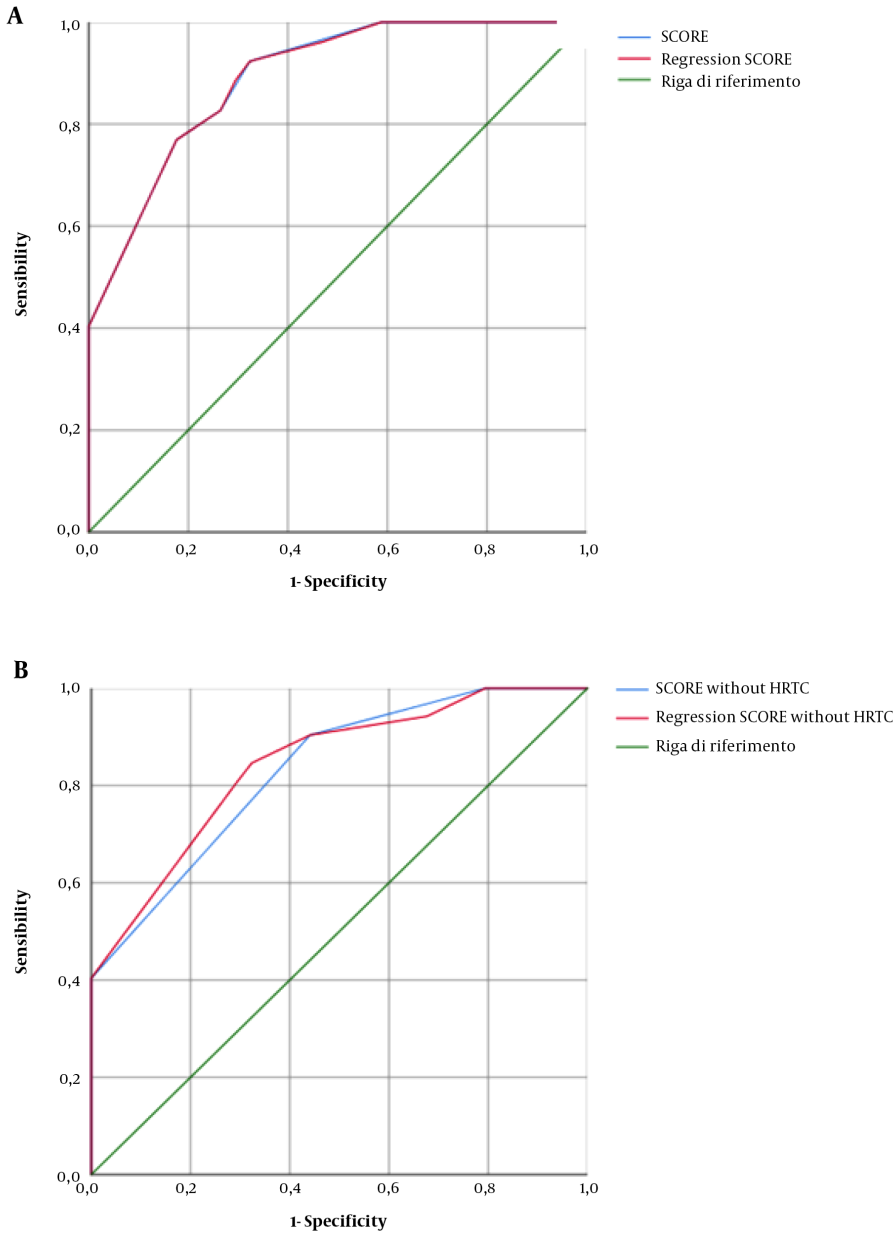

Figure 2. Discriminating capacity of regression scores and simplified scores with (A) and without (B) HRCT findings

Ri.S.I.Co with 2 score thresholds (> 2 and >6) and for the maximum value of the score (6) of the first SARS-CoV-2 swab and of the presence of ground glass on thoracic HRCT.

The Ri.S.I.Co. > 2 showed a higher sensitivity than the first SARS-CoV-2 swab and the presence of ground glass on thoracic HRCT (Ri.S.I.Co.: 96,2% vs. first SARS-CoV-2 swab: 65.4%, P < 0.001 vs. presence of ground glass on thoracic HRTC: 88.5%, P > 0.001), with the negative predictive value (PV-) of 95.5%.

The Ri.S.I.Co. > 6 showed a higher specificity than the presence of ground-glass pattern on thoracic HRTC (85.9% vs. 75.0%, P < 0.001), with the positive predictive value (PV+) of the Ri.S.I.Co. = 9 of 75.5% (higher than PV+ of ground glass presence on thoracic HRCT: 59.0%). There was no significant difference between the specificity of Ri.S.I.Co. > 6 and the specificity of the first SARS-CoV-2 swab

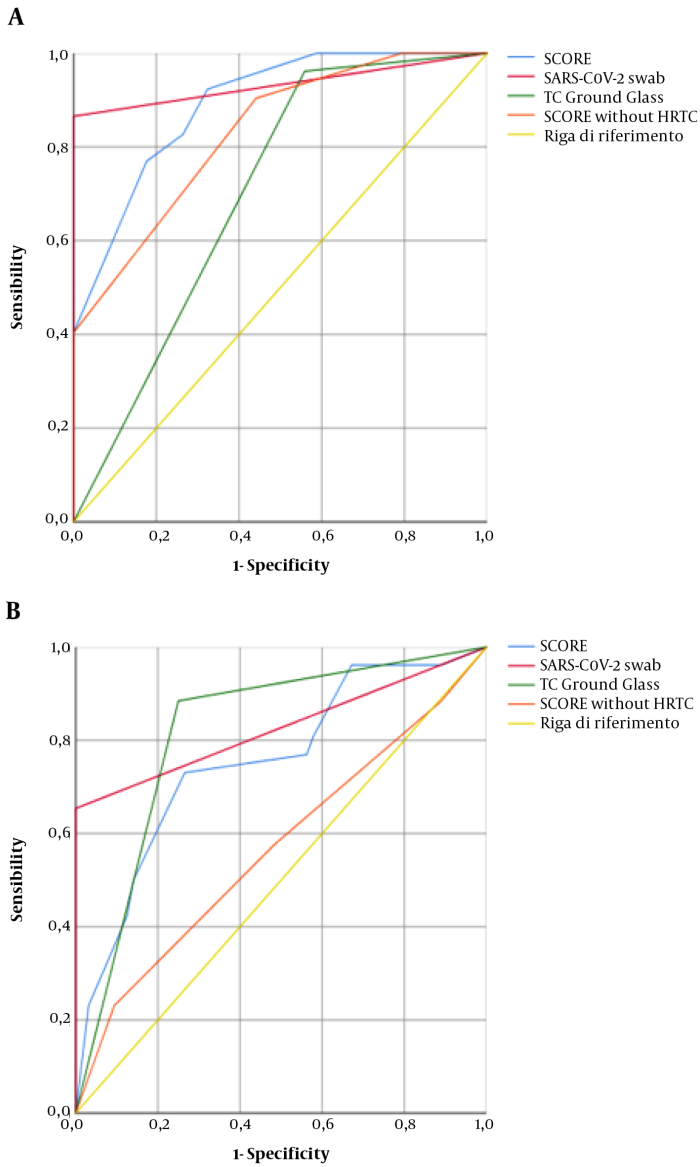

Figure 3. ROC of the internal validation cohort (A) and ROC of the external validation cohort (B)

(85.9% vs. 100.0%, P = 0.332).

Figure 4 reports the proposed Ri.S.I.Co and the related risk groups.

5. Discussion

The spread of COVID-19 on a global scale represents an epochal change in lifestyle and personal relationships and puts the world medical and scientific community in front of a unique challenge; for the first time, the whole of the world is faced with a disease still largely unknown with regard to the virus itself, its pathophysiological damages, and more than all, its treatment.

The contribution of all health systems, all health structures, and every single professional was necessary. In this scenario, some countries found themselves facing the emergency first, others had a few weeks to prepare and organize their defences. At present, however, despite the efforts of all, we still find ourselves having to chase a virus that runs faster than we do.

Table 2. Logistic Regression Model with and Without HRCT

Variables	P Value	OR (Regression Score)	Ri.S.I.Co.
With HRTC			
HRCT ground glass	0.004	13.107	3
Age < 60	0.062	3.825	1
LDH > 214 U/L	0.006	8.501	2
Neutrophil count < 8.00 * 10^9/L	0.001	12.489	3
Without HRTC			**Score Without HRCT**
Age < 60	0.001	8.485	1
LDH > 214 U/L	0.001	9.188	1
Neutrophil count < 8.00 * 10^9/L	0.003	8.903	1

Abbreviations: HRCT, high resolution computed tomography; LDH, lactic dehydrogenase; Ri.S.I.Co, risk score for infection with the new coronavirus

Variable	SCORE
HRCT Ground glass	3
Age < 60 years	1
LDH > 214U/L	2
Neutrophil count < 8.00*10^9/L	3

Ri.S.I.Co	RISK GROUPS
0-2	Low probability
3-6	Intermediate group
7-9	High probability

Figure 4. Scoring sheet with corresponding risk groups

Within the pandemic declared by the WHO last March (7), the primary role turns out to be early and definitive identification of patients positive for COVID-19 to start experimental therapies as soon as possible and to isolate positive cases to effectively counteract the spread of virus transmission. The massive influx of patients suffering from respiratory symptoms, risked tilting the emergency nets of many countries, even those with national health systems considered at the top of the world. The solution was to change the face of hospitals, to make them suitable for the management of these patients: to create dedicated pathways and often having to use professional resources normally employed in other activities.

Why should surgeons handle patients with a viral infection of the respiratory tract? We, as Trauma and Acute Care Surgeons (TACS), believe that as in other MCIs, surgeons should be the first choice. Because TACS are used to managing many patients from EDs and working closely with emergency physicians and/or ICU staff; they are prepared for these challenging clinical scenarios and have the adequate skills to manage suspected COVID19 post-triage patients.

During exceptional periods, Acute Care Surgery's staff (both medical and nursing staff) is crucial: it can relieve the pressure on the EDs and take care of the post-triage management, also they can be used for the management of complex surgical patients and their medical complications, and they are certainly more familiar with in network relationships of modern hospitals, as it is their daily routines (8).

Medical scores are widely used to help physicians in ranking patients with dubious medical diagnoses. Also, emergency surgeons frequently face these clinical scenarios: an example is lower right abdominal pain, suspected for acute appendicitis, which represents one of the most frequent conditions for which a surgical evaluation is required. In this clinical scenario, the use of risk scores, such as the AIR Score, is of great use; by collecting clinical information and laboratory data, it allows to group patients into subgroups at progressive risk for being affected by appendicitis (9).

COVID-19 outbreak started in early 2020 worldwide, and clinicians are fighting against a new largely unknown virus with a high virulence. Diagnostic tests are still perfectible and not always available. Diagnosis of COVID-19 is still difficult; symptoms appear compatible with flu-like ones, different and aspecific. Regarding the epidemiological history of the patients, between contact with positive cases and residence/traveling to endemic areas, in our opinion, the latter appears to be of limited utility: since the disease has spread worldwide and because of the high rate of asymptomatic positive patients is know.

False-negative results in SARS-CoV-2 nucleic acid detection are caused by various reasons, such as the quality of the samples taken, the number of viruses, and the stage of the disease. There are limited data on the rates of false-positive and false-negative results for the various RT-PCR tests available. If a negative result is obtained from a patient with a high suspicion for COVID-19, additional testing should be carried out, especially if only upper respiratory tract specimens were collected, as we do in our ED, prolonging the time needed for diagnosis (6).

Lung CT has been proposed as a diagnostic tool, but its findings dependend on the experience of radiologists and disease stage, and it needs specific dirty machines and results in more expensive and time-consuming procedures.

Table 3. AUC of Internal and External Validation Cohort

Diagnostic Test	AUC	Standard Error	P Value (for Difference with AUC = 0.5)	95% Confidence Interval
Internal Validation Cohort				
Ri.S.I.Co.	0.892	0.034	< 0.001	0.825 - 0.954
Score without HRCT	0.830	0.043	< 0.001	0.746 - 0.914
First SARS-CoV-2 swab	0.933	0.029	< 0.001	0.876 - 0.989
CT ground glass	0.701	0.062	0.002	0.581 - 0.822
External Validation Cohort				
Ri.S.I.Co.	0.754	0.058	< 0.001	0.640 - 0.868
Score without HRCT	0.569	0.070	0.310	0.431 - 0.706
First SARS-CoV-2 swab	0.827	0.059	< 0.001	0.711 - 0.942
CT ground glass	0.817	0.049	< 0.001	0.721 - 0.913

Abbreviations: Ri.S.I.Co., risk score for infection with the new coronavirus

The British Society of Thoracic Imaging (BSTI) recommends CT in seriously ill patients with suspected COVID-19 if the chest X-ray is uncertain or normal (10). On the other side of the Atlantic Ocean, the American College of Radiology recommends CT for hospitalised, symptomatic patients with specific clinical indications, but radiological findings appear not to exclude a priori diagnosis (11). Also, CT appears to be more specific in the later stages of COVID-19 or on disease progression (12).

Ai and colleagues (13) showed that the sensitivity of chest CT in suggesting COVID-19 was 97% (95% CI, 95 - 98%, 580/601 patients) in positive RT-PCR samples, but 308/413 (75%) patients with negative RT-PCR results had positive radiological findings.

The analysis of prospectively collected data of the first 100 patients admitted to our department and waiting for viral RNA RT-PCR confirmation highlighted four significant risk factors for COVID-19 infection, which have become part of the Ri.S.I.Co.: age lower than 60 years, presence of ground-glass pattern on lung-CT, increased serum LDH, and a normal neutrophil count. In order to maximize sensitivity and specificity of the score, we have identified two threshold values, allowing us to distinguish 3 groups of patients with a progressive increase in the risk of being affected by COVID-19: low risk (score 0 - 2), intermediate-risk (score 3 - 6), and high risk (7 - 9).

Ri.S.I.Co. appears easy to use in daily clinical practice; it consists of four variables; even in the evaluation of CT, only the radiological identification of the ground glass pattern is necessary, without any measurements or the need to evaluate multiple radiological parameters.

The variables used are normally recorded for any patient visiting the PS, therefore, they are widely reproducible.

In order to determine whether the Ri.S.I.Co. is advantageous, we compared its performance measures to the most adopted diagnostic tools for COVID-19 infection: the SARS-CoV-2 detection by RT-PCR in the first upper respiratory tract specimen collection (swab) and the presence of a ground-glass pattern on thoracic HRCT. Results showed that there was no significant difference between the AUC of Ri.S.I.Co. and that of the first SARS-COV-2 swab and the presence of ground-glass pattern on HRCT (Ri.S.I.Co: 0.754, 95% CI: 0.640 - 0.868; first SARS-CoV-2 swab: 0.827, 95% CI: 0.711 - 0.942; CT ground glass: 0.817, 95% CI: 0.721 - 0.913). However, although the SARS-Cov-2 swab had a high specificity (100%), its sensitivity was lower than a Ri.S.I.Co. lower than 2 (low risk group) (65.4% vs. 96.2%, $P < 0.001$). The presence of ground-glass pattern on HRCT had a lower sensitivity than a Ri.S.I.Co. lower than 2 (low risk group) (88.5% vs. 96.2%, $P < 0.001$) and a lower specificity than a Ri.S.I.Co. higher than 6 (high risk group) (75.0% vs. 96.9%, $P < 0.001$).

Because many hospitals, likely to save resources or due to inability to subject all patients to the examination, excluded lung CT as a diagnostic tool for COVID-19 infection, we created another score by eliminating the CT data; but, even if it performed well in the internal validation cohort, it showed low discriminating capacity in the external validation cohort. Therefore, in our opinion, lung CT is one of the first diagnostic steps in the suspicion of coronavirus (SARS-CoV-2) infection.

Since most hospitals do not have a large number of single rooms or beds with a real insulation capacity, the stratification of patients according to the risk groups based on the proposed Ri.S.I.Co, could be mainly used to separate admitted patients according to their risk. This could prevent low-risk patients from being infected from high-risk patients and could prevent hospitals from becoming the

Table 4. Comparison of Participant Characteristics in Construction and Validation Samples

Characteristic	Internal Validation Cohort (N = 86)	External Validation Cohort (N = 90)
Age < 60	31 (36.0)	20 (22.2)
Gender (Male)	45 (52.3)	43 (47.8)
HRCT: consolidation	38 (44.7)	39 (43.8)
HRCT: interlobular septum thickening	31 (36.5)	17 (18.9)
HRCT: pleural effusion	9 (10.6)	20 (18.9)
HRCT: nodules	13 (15.3)	13 (14.4)
HRCT: location		
Superior	17 (20.2)	30 (40.5)
Inferior	11 (13.1)	9 (12.2)
Superior + Inferior	56 (66.7)	43 (58.1)
HRCT: bilateral findings	67 (79.8)	44 (59.5)
HRCT: ground glass pattern	69 (80.2)	39 (43.3)
Contact with COVID+	12 (14.0)	11 (12.2)
Joint or muscle pain	8 (9.3)	4 (4.4)
Gastrointestinal symptoms	16 (18.6)	17 (18.9)
Astenia	16 (18.6)	9 (10.0)
Headache	2 (2.3)	0 (0.0)
Anosmia/Ageusia	2 (2.3)	5 (5.6)
Positive Pneumococcus Ag	7 (9.9)	8 (14.5)
Positive Legionella Ag	0 (0.0)	0 (0.0)
Positive Respiratory syncytial virus swab	0 (0.0)	0 (0.0)
Positive Influenza A/B virus swab	0 (0.0)	0 (0.0)
Neutrophil count < 8.00 * 10^9/L	66 (76.7)	58(64.4)
LDH > 214 U/L	65 (75.6)	60 (66.7)
RR > 20	26 (33.3)	35 (64.8)
SO_2[a] < 95%	27 (37.0)	36 (54.5)
P/F < 300	11 (22.0)	20 (26.3)
Positive 1° SARS-CoV-2 swab	45 (52.3)	17(18.9)
COVID-19 infected	52 (60.5)	26 (28.9)

Abbreviations: Ag, antigen; HRCT, high resolution computed tomography; LDH, lactic dehydrogenase; PCR, reactive C protein; P/F: PO_2/FiO_2; RR, respiratory rate; SO_2, oxygen saturation

[a]Without oxygen supplement

main COVID-19 carriers, as happened in many Italian hospitals. Furthermore, it could be a diagnostic tool used in addition to lung-TC and SARS-CoV-2 detection by RT-PCR, increasing diagnostic sensitivity, and specificity.

During the writing of the manuscript of this article, we read with interest a pre-print version of the COVID-19 early warning score (COVID-19 EWS) by colleagues from China (14): they retrospectively analyzed data from patients admitted for suspected COVID-19 (training dataset: 73 COVID+, 231 COVID-; validate dataset: 18 COVID+, 77 COVID-) and, as we did, they created an easy-to-get score for COVID-19 screening. The COVID-19 EWS included signs of pneumonia on CT, age older than 44 years, male gender, fever (in two different aspects: fever itself and fever more than 37.8°C), presence of respiratory symptoms, history of contact with confirmed COVID-19 cases, and neutrophil-to-lymphocyte ratio. Even if some risk factors were similar to our findings (sign of pneumonia on CT and neutrophil count), others were different. Among our construction sample, contact with a COVID-19 confirmed patient, male gender, presence of respiratory symptoms, and age older than 44 years were not significant risk factors in logistic regression analysis. We did not consider fever in the analysis because fever and/or respiratory symptoms were the criteria for our department's admission. Applying the COVID-19 EWS score on our internal validation cohort, we obtained an AUC of 0.772 (95% CI 0.668 - 0.877), a sensitivity of 84.6%, and a specificity of 67.6%. Thus, the performance measures of the COVID-19 EWS in our population were worse than the measures of Ri.S.I.Co. This fact could be explained in the different characteristics of the two populations. First of all, our patients were older, and fever and/or respiratory symptoms could be indicators of other pathologies (cardiac or respiratory diseases). Among the Italian population, a lower number of upper respiratory tract specimens were collected than in China, without mass screening programs. This fact could reflect the lower weight of contact with confirmed COVID-19 patients in predicting COVID-19 infection among our patients (many patients could have had contact with COVID-19 infected patients without knowing it). Furthermore, knowing the low sensitivity of the SARS-CoV-2 detection by RT-PCR in upper respiratory tract specimens, we did not use it to define infected patients. In the definition of COVID-19 infected patient, we included patients with negative SARS-CoV-2 swab but with strongly suspect radiological and clinical signs, after a review by a final diagnosis committee composed of internal medicine specialists and/or pneumologists.

The limitations of the present study were the relatively small sample size and its observational nature. Being a study performed to answer our on-the-field need to stratify patients, we were not able to take a longer period of time

Table 5. Performance Measures

	Ri.S.I.Co.			CT Ground Glass	SARS-CoV-2 Swab
	> 2	> 6	9		
Sensitivity	96.2%[a, b]	50.0%	23.1%	88.5%[b]	65.4%[a]
Specificity	32.8%	85.9%[c, d]	96.9%	75.0%[d]	100.0%[c]
PV+	36.8%	59.1%	75.0%	59.0%	100.0%
PV-	95.5%	80.9%	75.6%	94.1%	87.7%

Abbreviations: Ri.S.I.Co, risk score for infection with the new coronavirus
[a] $P < 0.001$
[b] $P < 0.001$
[c] $P = 0.332$
[d] $P < 0.001$

to collect a larger sample size to obtain an instrument that we needed immediately. Furthermore, the presented score was developed and validated only based on hospitalized patients, further studies would be necessary to understand if it is generalizable to non-hospitalized patients or to the populations of other countries with different mean ages, prevalence rates of comorbidities, and health policies.

The struggle against COVID-19 was, is and unfortunately will still be long. The validity of the diagnostic tests has yet to be fully confirmed; therefore, physicians should continue to consider potentially infected patients with fever and/or respiratory symptoms. We believe that tools such as the Ri.S.I.Co could offer valuable help in the management of suspected patients while waiting for diagnostic confirmation. It could allow separating admitted patients according to their risk and avoiding hospitals becoming the main COVID-19 carriers. Furthermore, it could guide clinicians in starting therapies early in severe-onset cases with a high probability of COVID-19, before molecular SARS-CoV-2 infection is confirmed.

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Footnotes

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Conflict of Interests: The authors declare that they have no competing interests.

Ethical Approval: Because of the national and local regulations in force which prohibit any meeting to reduce the spread of the COVID-19 infection, it was impossible to get the study approved by our Ethics Committee. However, the study is purely observational in nature, the data were collected in an absolutely anonymous manner, and the study was conducted in compliance with ethical principles originating from the Helsinki Declaration.

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