A Prognostic Model for Death in COVID-19 Patients Presenting to the Emergency Room: The Added Value of Computed Tomography.

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Abstract

Objective: The added value of CT in prognostic models for coronavirus disease 2019 (COVID-19) patients is unclear. The aim of this study was to develop a prognostic model for death in COVID-19 patients using clinical and CT variables.

Methods: Consecutive patients who presented to the emergency room between February 27 and March 23, 2020 for suspected COVID-19, underwent chest CT, and had a positive swab within 10 days were included in this retrospective study. Age, sex, comorbidities, days from symptom onset, and laboratory data were retrieved from institutional information systems. CT disease extension was visually graded as < 20%, 20-39%, 40-59%, or ≥ 60%. The association between clinical and CT variables with death was estimated with univariable and multivariable Cox proportional hazards models; model performance was assessed using k-fold cross-validation for the area under the ROC curve (CvAUC).

Results: Of the 866 included patients (median age 59.8, women 39.2%), 93 (10.74%) died. Clinical variables significantly associated with death in multivariable model were age, male sex, HDL cholesterol, dementia, heart failure, vascular diseases, time from symptom onset, neutrophils, LDH, and oxygen saturation level (SO2). CT disease extension was also independently associated with death (HR=7.56, 95% CI=3.49; 16.38 for ≥ 60% extension). CvAUCs were 0.927 (bootstrap bias corrected-95%CI=0.899-0.947) for the clinical model and 0.936 (bootstrap bias corrected-95%CI=0.912-0.953) when adding CT extension.

Conclusions: A prognostic model based on clinical variables is highly accurate in predicting death in COVID-19 patients. Adding CT disease extension to the model scarcely improves its accuracy.

Summary

Take home message:

A clinical prognostic model is highly accurate in predicting death in COVID-19 patients presenting to the emergency room, with little extra value when adding CT disease extension to the model.

Key Points:

- Early identification of COVID-19 patients at higher risk of disease progression and death is crucial; the role of CT scan is unclear.
- A clinical model based on age, sex, comorbidities, days from symptom onset, and laboratory results, was highly accurate in predicting death in COVID-19 patients presenting to the emergency room.
- Disease extension assessed with CT was independently associated with death when added to the model but did not produce a valuable increase in accuracy.

Introduction

The clinical course of coronavirus disease 2019 (COVID-19) is variable; most patients experience a mild disease course, but a minority rapidly deteriorates to severe or critical illness [1]. The case fatality rate is over

10% in most European countries [2] but reaches 20% when 30-day follow-up is completed for all cases [3,4]. In hospitalized patients, 30-day survival is just over 70% [1,5,6].

Early identification of patients at higher risk of disease progression and death is crucial. Effective predictive models based on risk factors for death would help clinicians decide who needs hospitalization and what intensity of care each patient needs. Over the long term, this positive effect on clinical decision-making may improve patient management and outcome and may increase the appropriateness of resource utilization.

Different prognostic models to predict mortality, length of hospital stay, and critical illness have been proposed that use several clinical and laboratory variables, including age, male sex, comorbidities, C-reactive protein, lactic dehydrogenase, and lymphocyte count [1,7-10]. However, the studies proposing these models often lacked an adequate description of the study population, were generally conducted on hospitalized patients only, and frequently excluded from any analysis those patients who had neither recovered nor died within the time period considered for outcome assessment [7].

Chest imaging, especially by means of computed tomography (CT), has been used during the COVID-19 outbreak to rapidly identify patients with COVID-19 pneumonia while waiting for diagnostic reverse transcription-polymerase chain reaction (RT-PCR) confirmation and to assess disease extension at baseline [11,12]. Some studies have reported on the potential prognostic value of CT findings, especially disease extension assessed by means of visual estimation or software quantification [13-16].

The few studies that combined clinical, laboratory, and CT findings in predictive prognostic models [17-20] showed inconsistent results: some suggested a better performance of the model when adding CT [17], others showed that CT findings had insufficient prognostic power to be selected in multivariable models [19].

The aim of this study was to identify those clinical and CT variables that can be used to identify groups of COVID-19 patients with different probabilities of death. Using these factors, we aimed to develop a prognostic model for death in COVID-19 patients.

Methods

Setting

In the XXXXX province (XXXXX, 532,000 inhabitants, six hospitals), the first case of SARS-CoV-2 infection was diagnosed on February 27, 2020. Up to March 24, 2020, there were 1399 RT-PCR-confirmed COVID-19 cases and the daily number of new cases was still rising.

Study design and population

This observational study was approved by the Area Vasta Emilia Nord Ethics Committee on April 7, 2020 (protocol number 2020/0045199). Patients' informed consent to participate in the study was obtained whenever possible, given the retrospective nature of the study. We included all consecutive patients who presented to the provincial emergency rooms (ERs) between February 27 and March 23, 2020 for suspected

COVID-19, underwent chest CT at ER presentation, and were positive on RT-PCR for SARS-CoV-2 within 10 days from ER presentation.

During the COVID-19 outbreak, the diagnostic protocol for suspected COVID-19 patients presenting to the ER included nasopharyngeal/oropharyngeal swabs for RT-PCR, blood tests, chest X-rays, and CT in cases of suggestive X-rays or negative X-rays but with highly suggestive clinical features. A structured CT report was introduced on March 13, 2020. Baseline cross sectional data of patients presenting to the ER between March 13 and 23, 2020 were used for the assessment of CT diagnostic accuracy in another study [21] which also included patients with negative RT-PCR.

Data collection

Data including date of symptom onset, diagnosis, hospitalization, and death were retrieved from the COVID-19 Surveillance Registry, coordinated by the National Institute of Health and implemented in each Local Health Authority. Registry data were linked with the hospital radiology information system to search for CTs performed at or after the onset of COVID symptoms and with hospital discharge databases to collect information on comorbidities. Charlson index was calculated based on hospital admissions in the previous 10 years [22]. Diabetes was ascertained through linkage with the local Diabetes Registry [23]. The most recent lipid profile (measured in 2015-2018 and including total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol and triglycerides) and blood tests at ER presentation were retrieved from the laboratory information system.

Symptoms, body temperature, and respiratory frequency at ER presentation were manually collected from medical records only for the subset of patients presenting between February 27 and March 13, 2020. Fever was defined as a body temperature >37.5°C, or, when this value was not available, self-reported fever in preceding days. Dyspnea/polypnea was defined as a respiratory frequency >18 breaths per minute or reported dyspnea in preceding ten days.

Blood tests and RT-PCR

The levels of C-reactive protein (CRP), lactate dehydrogenase (LDH), white blood cell, lymphocyte, neutrophil, and platelet counts measured at ER presentation were collected. Oxygen saturation level (SO2) was also collected for patients who had an arterial blood gas analysis before being provided with oxygen support. The tests were carried out in the Hospital Clinical Laboratories with routine automated methods.

To diagnose SARS-CoV-2 infection, a commercial One-Step Reverse Transcription RT-PCR (GeneFinder ™ COVID -19 PLUS Real Real Amp Kit) was used and RT-PCR assay was performed on an Applied Biosystems 7500 Sequence Detection System.

CT acquisition technique

CT scans were performed using one of three scanners (128-slice Somatom Definition Edge, Siemens Healthineers; 64-slice Ingenuity, Philips Healthcare; 16-slice GE Brightspeed, GE Healthcare) without contrast media injection, with the patient in supine position, during end-inspiration. Scanning parameters were tube

voltage 120 KV, automatic tube current modulation, collimation width 0.625 or 1.25 mm, acquisition slice thickness 2.5 mm, and interval 1.25 mm. Images were reconstructed with a high-resolution algorithm at slice thickness 1.0/1.25 mm.

CT structured reporting and retrospective analysis

Between March 13 and March 23, 2020, each radiologist completed a routine CT report and a structured report that included the presence/absence of ground-glass opacities and consolidations, and the extension of pulmonary lesions using a visual scoring system (< 20%, 20-39%, 40-59%, ≥ 60%) [21].

CTs performed between February 27 and March 13, 2020 (before the introduction of the structured report) were retrospectively reviewed by a chest radiologist with 15 years' experience (LS) to collect the same parameters described above, including visual scoring. One hundred consecutive CTs were also reviewed by a radiologist with 3 years' experience (GB) to assess interrater agreement.

Statistical analyses

Continuous variables were reported as median and interquartile range, and categorical variables as proportions. Single imputation procedure using truncated regression adjusted for sex, age, and comorbidities was used to deal with the problem of any missing values (Supplementary Material).

Cox proportional hazards models were used to estimate Hazard ratios (HR) with 95% confidence intervals (95% CI) for death, first by univariable model adjusted for age, sex, and calendar time (weeks since the beginning of the outbreak). Statically significant clinical, laboratory, and imaging variables were then used to develop two prognostic multivariable models, with and without CT disease extension. Sensitivity analyses were performed by stratifying the models by time since symptom onset (<8 and ≥8 days) and SO2 levels (<95% and ≥95%) and by excluding patients aged over 85 years, with CT disease extension ≥ 60%, or who had died within 48 hours from admission. The performance of the models was assessed using receiver operating characteristic (ROC) curves for 30-day death rate. On the same original sample, we fitted a logit model and used K-fold cross-validation to obtain a bias-corrected estimate of predictive accuracy. This technique averages the AUCs corresponding to each fold and applies the bootstrap procedure to the cross-validated AUC. We used 10 folds, with the exception of sensitivity analyses for ≥8 days from symptom onset and SO2 level ≥95%, in which we applied 7 and 5 folds respectively, to ensure a minimum outcome frequency in each test set. We reported cross-validated mean AUC (cvAUC), and bootstrap bias-corrected (BBC) 95%CI, with and without CT extension.

We used the kappa-statistic measure of weighted interrater agreement for a double reading of CT disease extension.

We used Stata 13.0 SE (Stata Corporation, Texas, TX) software package.

Results

Study population

We included 866 consecutive subjects (median age 59.8, women 39.2%) (Fig.1). Median follow-up duration for death was 43 days. During follow-up, 93 (10.74%) patients died, while 363 (41.92%) were hospitalized.

Age, sex, lipid profile, and all the considered comorbidities with the exception of chronic kidney failure and obesity were significantly different in patients who died and those who were hospitalized compared to the overall cohort (Tab.1). The time interval between symptom onset and ER presentation was significantly lower both for patients who died and for patients who were hospitalized (P <0.001). Patients who died and those who were hospitalized had significantly higher neutrophils, CRP, and LDH and significantly lower lymphocytes, platelets, and SO2 at ER presentation. At CT scan, they had significantly higher CT disease extension of lung disease (P <0.001) and presented more frequently with consolidations (P =0.005 for deaths and P <0.001 for hospitalizations). For CT disease extension, the interrater concordance was excellent (weighted kappa 0.91) (Supplementary Tab.1).

Associations between clinical, laboratory, and CT variables with death and hospitalization

Increasing age and male sex were significantly associated with death (HR=1.11, 95% CI=1.1-1.1, and HR=2.6; 95% CI=1.55-4.36, respectively) and hospitalization (Tab.2). Probability of death and hospitalization progressively decreased as the epidemic went on: ER presentation in the first compared with the fourth week of the epidemic had an HR for death of 3.17 (95% CI=1.39-7.24).

After correcting for age, sex, and calendar time, the Charlson comorbidity index was associated with both death and hospitalization (HR=1.38, 95% CI=1.17-1.63, and HR=1.30, 95% CI=1.17-1.44). Comorbidities significantly associated with death were ischemic cardiopathy, dementia, heart failure, obesity, arrythmias, and vascular diseases, while diabetes, cancer, COPD, heart failure, arrhythmias, and dementia were associated with hospitalization. Among lipid profile data, low HDL, and high triglycerides increase were significantly associated with higher probability of death and of hospitalization.

Time from symptom onset was inversely associated with death (HR=0.88, 95% CI=0.83_0.94) and hospitalization). Dyspnea was significantly associated with both death (HR=1.96, 95% CI=1.15-3.32) and hospitalization. Among laboratory data, high neutrophil count, CRP and LDH level and low SO2 were significantly associated with both death and hospitalization.

Presence of consolidation at CT was significantly associated with death (HR=1.63, 95% CI=1.00-2.64) and hospitalization (HR=1.52, 95% CI=1.20-1.92). High CT visual extension was significantly associated with hospitalization for all CT classes and with death for ≥ 60% extension (HR=6.68, 95% CI=3.56-12.56).

Multivariable models for death

Variables which were associated with death in the univariable analysis and suitable for a prognostic model to be used in all clinical settings were selected for the multivariable analysis (Tab.3); we did not include the variable “calendar period” because its predictive value could not be generalized to other contexts. Demographic and clinical variables that remained significantly associated with death in the multivariable model were age, male sex, HDL cholesterol, dementia, heart failure, vascular diseases, time from symptom onset, neutrophil count, LDH, and SO2. When adding CT disease extension to the clinical model, 40-59% and

≥60% extensions were significantly associated with death (HR=2.41, 95% CI=1.18-4.93 and HR=7.56, 95% CI=3.49-16.38, respectively), while male sex, SO2, and LDH were not.

When evaluating the performance of the two multivariate models in the prediction of death, AUCs were 0.936 (95%CI=0.916-0.956) and 0.947 (95% CI=0.930-0.964) respectively for the clinical model and the model including CT extension. By applying cross-validation, the clinical model and the model including CT extension had cvAUCs of 0.927 (BBC 95%CI=0.899-0.947), and 0.936 (BBC 95%CI 0.912-0.953). (Fig.2).

Sensitivity analyses and stratifications

When stratifying patients according to time from symptom onset (< or ≥8 days) and to SO2 level (SO2 <95% or ≥95%), the cvAUC of the model with CT disease extension remained only slightly higher than the cvAUC of the clinical model (Fig.3, Tab.4). In each restricted population, when excluding patients with CT extension ≥60%, or excluding patients died within 48 hours, or excluding patients older than 85 years, the cvAUC of the model including CT was slightly higher, with the highest increase when excluding patients older than 85 years (cvAUC from 0.929 to 0.943) (Fig.4, Tab.4). Both models presented a higher cvAUC in patients with SO2>95% (cvAUC 0.952; BBC 95%CI=0.885-0.966 for the model including CT extension). Finally, when applying the multivariable models to the subcohort of patients with available data on symptoms, cough and gastrointestinal symptoms were significantly associated with death, both in the univariable (Supplementary Table 2) and in the multivariable models without CT disease extension (Supplementary Table 3). When adding CT disease extension, the associations remained similar (HR=0.56; 95% CI=0.32-0.99 for cough and HR=2.70; 95% CI=1.20-6.10 for gastrointestinal symptoms).

Discussion

A clinical multivariable model based on age, sex, comorbidities, days from symptom onset, and laboratory test results was highly accurate in predicting death in COVID-19 patients presenting to the ER (cvAUC=0.927). The extension of lung changes evaluated with CT (40-60% and ≥60%) was independently associated with death when added to the multivariable model. However, when compared to the clinical model, the model including CT disease extension presented only a slight increase in performance for the prediction of death (cvAUC =0.936). The slight added prognostic value was substantially similar when stratifying patients according to time from symptom onset and SO2 level, or when excluding patients with CT extension ≥60%, or excluding patients died within 48 hours, or excluding patients older than 85 years. Both models performed better in less severe patients in terms of oxygen saturation level (SO2≥95%).

Some clinical prognostic models have been proposed to predict severe/critical illness: only some had mortality as an outcome, and most were developed and tested on hospitalized patients only. The cvAUC achieved by our clinical model is similar or higher than those previously reported [1,7,10,19].

As in most previous studies [7,24], age and male sex were strong independent risk factors for death in COVID-19 patients, as was a shorter time between symptom onset and ER presentation. Most considered comorbidities were associated with death, but dementia, heart failure, and peripheral vascular diseases were included in our multivariable model. This result confirms the negative impact of cardiovascular

comorbidities on COVID-19 prognosis [24,25], while dementia is probably an indicator of frailty and poor nutritional status, which are typical of older patients, many of whom live in nursing homes. Since the role of metabolic derangement in COVID-19 patients has been underlined [25,26], we evaluated previous lipid profile. Both high triglycerides and low HDL cholesterol levels were associated with mortality, the latter being included in the predictive model. Among laboratory tests, variables included in the model were neutrophil count, LDH, and SO2, which reflect different disease pathways and manifestations, and confirming the results of previous studies [7,10,17].

The potential prognostic role of CT-based assessment of lung disease extension has been suggested [13-16,27], and a few studies have included it in combined prognostic models [17-20]. Colombi et al. found a slightly higher increase in AUC (from 0.83 to 0.86) when adding CT disease extension to a clinical model predictive of intensive care unit admission and/or death [17]. The main differences with our study are the outcome, the use of a logistic regression analysis rather than a Cox proportional hazards model, and a different CT assessment method, which focused on well-aerated lung. Finally, we used the cross-validation method to account for the lack of an external validation set. Interestingly, the clinical model proposed by Colombi et al., unlike ours, did not include SO2.

In our study, when adding CT disease extension to the clinical model, SO2 and LDH were no longer significantly associated with mortality. This seems to point out that CT disease extension and SO2 may describe the same phenomenon, with CT allowing a small gain in informational value, possibly because CT lung changes precede a clinically significant SO2 decrease. However, our results, particularly the high AUC of the clinical model and the limited improvement in its performance when adding CT disease extension, do not seem to support the routine use of CT for prognostic purposes in COVID-19 patients.

The major limitation of this study is the lack of a validation cohort to test the generalizability of the model. Nevertheless, in the statistical analyses we adopted the cross-validation, an internal validation approach for prediction models, used to generate a more realistic estimate of predictive performance when the number of observations is not very large [28]. Moreover, although we propose a prognostic model to be applied to COVID-19 patients presenting to the ER, the study population was somewhat selected: a small percentage of patients presenting to the ER did not undergo a CT. This selection may have introduced a bias if the decision to perform a CT had been influenced by factors, including comorbidities, which we used in the prognostic model. If this selection occurred, the consequence is an underestimation of the prognostic value of comorbidities associated with both the probability of being referred to CT and with death. However, since hospitalization is surely more influenced by these factors than the decision to perform a CT scan, this kind of bias affects more the studies conducted on hospitalized patients only. Finally, this study was conducted in an early phase of the epidemic, before that the prognostic role of other laboratory data, above all D-dimer [29], had emerged. These other tests were therefore not collected in this cohort.

In conclusion, a prognostic model based on sex, age, pre-existing clinical features, days from symptom onset, and laboratory test results at ER presentation is highly accurate in predicting mortality in COVID-19. CT-assessed disease extension is an independent predictive factor for mortality, but the increase in

performance of the prognostic model when including CT extension is limited. Further studies are needed to assess the generalizability of the prognostic model.

Abbreviations

COVID-19: coronavirus disease 2019

RT-PCR: reverse transcription-polymerase chain reaction

COPD: chronic obstructive pulmonary disease

LDL: low-density lipoprotein

HDL: high-density lipoprotein

CRP: C-reactive protein

LDH: lactate dehydrogenase

SO2: oxygen saturation level

HR: hazard ratio

cvAUC: cross-validated area under the ROC curve

Declarations

*the following are the members of the Working group: Massimo Costantini, Roberto Grilli, Massimiliano Marino, Giulio Formoso, Debora Formisano, Paolo Giorgi Rossi, Emanuela Bedeschi, Cinzia Perilli, Elisabetta La Rosa, Eufemia Bisaccia, Ivano Venturi, Massimo Vicentini, Cinzia Campari, Francesco Gioia, Serena Broccoli, Marta Ottone, Pierpaolo Pattacini, Giulia Besutti, Valentina Iotti, Lucia Spaggiari, Pamela Mancuso, Andrea Nitrosi, Marco Foracchia, Rossana Colla, Alessandro Zerbini, Marco Massari, Anna Maria Ferrari, Mirco Pinotti, Nicola Facciolongo, Ivana Lattuada, Laura Trabucco, Stefano De Pietri, Giorgio Francesco Danelli, Laura Albertazzi, Enrica Bellesia, Simone Canovi, Mattia Corradini, Tommaso Fasano, Elena Magnani, Annalisa Pilia, Alessandra Polese, Silvia Storchi Incerti, Piera Zaldini, Efrem Bonelli, Bonanno Orsola, Matteo Revelli, Carlo Salvarani, Carmine Pinto, Francesco Venturelli.

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Tables

Table 1. Patients’ pre-existing condition, and clinical, laboratory, and CT findings at admission

Variables		All Patients	Deaths		Hospitalizations	
			N (%)	P*	N (%)	P*
		866	**93 (10.74)**		**363 (41.92)**	
Age (years)		59.8 (50.2-72.5)	80.6 (72.0-85.9)	<0.001**	71.3 (60.4-80.0)	<0.001**
Female sex		339 (39.15)	18 (19.35)	<0.001	119 (32.78)	0.001
Total cholesterol (mg/dl)		200.6 (181-210)	181.7 (157-199.5)	<0.001**	195.0 (170-207.8)	<0.001**
Calendar time (Week 1)		36 (4.16)	8 (8.6)	<0.001	27 (7.44)	<0.001
(Week 2)		167 (19.28)	40 (43.01)		123 (33.88)	
(Week 3)		314 (36.26)	25 (26.88)		128 (35.26)	
(Week 4)		349 (40.30)	20 (21.51)		85 (23.42)	
HDL cholesterol (mg/dl)		52 (47-61)	48 (41-53)	<0.001**	51 (43-58)	<0.001**
LDL cholesterol (mg/dl)		125 (110-135)	109 (85-123)	<0.001**	117 (101-131)	<0.001**
Triglycerides (mg/dl)		110 (90-126)	121 (102-147)	0.001**	114 (92-137)	0.016**
Diabetes		94 (10.85)	18 (19.35)	0.005	71 (19.56)	<0.001
Charlson Comorbidity Index	0	715 (82.56)	45 (48.39)		249 (68.60)	
	1	51 (5.89)	13 (13.98)	<0.001	33 (9.09)	<0.001
	2	47 (5.43)	12 (12.90)		35 (9.64)	
	3	53 (6.12)	23 (24.73)		46 (12.67)	
COPD		22 (2.54)	8 (8.60)	<0.001	19 (5.23)	<0.001
Ischemic cardiopathy		53 (6.12)	22 (23.66)	<0.001	40 (11.02)	<0.001
Dementia		9 (1.04)	6 (6.45)	<0.001	9 (2.48)	<0.001
Chronic kidney failure		8 (0.92)	2 (2.15)	0.209	7 (1.93)	0.011
Cancer		96 (11.09)	20 (21.51)	0.001	59 (16.25)	<0.001
Hypertension		102 (11.78)	29 (31.18)	<0.001	77 (21.21)	<0.001
Obesity		15 (1.73)	4 (4.30)	0.067	9 (2.48)	0.152
Heart failure		27 (3.12)	15 (16.13)	<0.001	25 (6.89)	<0.001
Arrhythmias		48 (5.54)	19 (20.43)	<0.001	36 (9.92)	<0.001
Vascular diseases		11 (1.27)	6 (6.45)	<0.001	9 (2.48)	0.011

Days from symptom onset		7 (4-9)	5 (2-7)	<0.001**	6 (4-8)	<0.001**
White blood cells (10^9/L)		5.11 (4.02-6.56)	5.86 (4.31-7.96)	0.095**	5.36 (3.96-6.89)	0.042**
Lymphocytes (10^9/L)		1.04 (0.77-1.42)	0.82 (0.63-0.97)	<0.001**	0.9 (0.69-1.16)	<0.001**
Neutrophils (10^9/L)		3.66 (2.76-4.58)	4.62 (3.39-6.14)	0.001**	4.00 (2.75-5.30)	<0.001**
Platelets (10^9/L)		181 (146-223)	160.09 (128-201)	0.021**	172 (136-215)	0.040**
C-reactive protein (mg/dL)		3.31 (1.41-8.08)	8.54 (3.78-14.77)	<0.001**	6.26 (2.94-12.79)	<0.001**
LDH (U/L)		500.0 (414.0-575.7)	565.5 (487.0-751.0)	<0.001**	539.0 (474.0-666.0)	<0.001**
SO2 (%)		95.4 (93.8-96.7)	92.8 (89.9-94.8)	<0.001**	93.9 (91.8-95.7)	<0.001**
Ground-glass opacities		837 (96.65)	90 (96.77)	1.000	355 (97.8)	0.112
Consolidation		547 (63.16)	71 (76.34)	0.005	263 (72.45)	<0.001
CT extension	<20%	339 (39.15)	17 (18.28)		84 (23.14)	
	20-39%	340 (39.26)	23 (24.73)	<0.001	143 (39.39)	<0.001
	40-59%	120 (13.86)	24 (25.81)		83 (22.87)	
	≥60%	67 (7.74)	29 (31.18)		53 (14.60)	
Subcohort		**318**	**58 (18.24)**		**205 (64.47)**	
Body temperature >37.5°C		182 (57.23)	36 (62.07)	0.410	130 (63.41)	0.003
Cough		182 (57.23)	22 (37.93)	0.001	121 (59.02)	0.384
Dyspnea/Polypnea		122 (38.36)	33 (56.90)	0.001	94 (45.85)	0.000
Headache		8 (2.52)	0 (0)	0.359	4 (1.95)	0.461
Myalgia/arthralgia		22 (6.92)	2 (3.45)	0.390	11 (5.37)	0.142
Fatigue		27 (8.49)	5 (8.62)	1.000	22 (10.73)	0.060
Syncope		25 (7.86)	5 (8.62)	0.789	20 (9.76)	0.126
Gastrointestinal symptoms		33 (10.38)	8 (13.79)	0.346	26 (12.68)	0.069
Other symptoms		24 (7.55)	2 (3.45)	0.273	17 (8.29)	0.498

Table 1. Patients' pre-existing condition, along with clinical, laboratory, and CT findings at ER presentation in the whole cohort, and, only for the subcohort of patients who presented to the ER between February 27, 2020 and March 13, 2020, symptoms including body temperature at ER presentation. Continuous variables are presented as median (IQR), and categorical variables are presented as frequencies (%). * Pearson's chi-squared test or Fisher exact test and p-value for the hypothesis of independence in the two-way table. ** p-value nonparametric equality-of-medians test. HDL, high density lipoprotein; LDL, low density lipoprotein; COPD, chronic obstructive pulmonary disease; LDH, lactate dehydrogenase; SO2, oxygen saturation level.

Table 2. Associations of pre-existing conditions, and clinical, laboratory and CT findings at ER presentation with death and hospitalization, after adjustment for age, sex, and calendar time.

		Death		Hospitalization	
Variables		**Crude**		**Crude**	
		HR	**95% CI**	**HR**	**95% CI**
Age (years)		1.107	1.086-1.128	1.057	1.048-1.065
Gender	Female	1		1	
	Male	2.597	1.548-4.358	1.319889	1.060-1.644
Calendar time	Week 4	1		1	
	Week 3	1.245	0.690-2.245	1.869	1.420-2.460
	Week 2	2.846	1.658-4.885	3.841	2.900-5.08722
	Week 1	3.173	1.391-7.237	3.239	2.093-5.011
Total cholesterol (mg/dl)		0.996	0.990-1.002	0.996	0.992-0.999
HDL cholesterol (mg/dl)		0.973	0.953-0.993	0.987	0.977-0.997
LDL cholesterol (mg/dl)		0.992	0.984-1.000	0.996	0.992-1.000
Triglycerides (mg/dl)		1.005	1.002-1.008	1.003	1.001-1.005
Diabetes		0.883	0.509-1.530	1.680	1.269-2.223
Charlson Comorbidity Index		1.379	1.168-1.629	1.298	1.172-1.437
COPD		1.716	0.815-3.612	2.624	1.629-4.229
Ischemic cardiopathy		1.891	1.150-3.109	1.057	0.750-1.489
Dementia		6.502	2.702-15.645	3.964	2.010-7.818
Chronic kidney failure		1.277	0.311-5.234	1.490	0.696-3.187
Cancer		1.381	0.840-2.270	1.514	1.142-2.007
Hypertension		1.412	0.900-2.215	1.237	0.947-1.615
Obesity		3.931	1.415-10.924	1.383	0.712-2.689
Heart failure		3.006	1.715-5.270	1.856	1.220-2.823
Arrhythmias		2.347	1.393-3.956	1.475	1.033-2.108
Vascular diseases		3.701	1.570-8.724	1.397	0.717-2.722
Days from symptom onset		0.883	0.828-0.941	0.895	0.867-0.923
White blood cells (10^9/L)		1.019	0.979-1.060	1.009	0.976-1.044
Lymphocytes (10^9/L)		0.971	0.880-1.070	0.981	0.906-1.062
Neutrophils (10^9/L)		1.132	1.040-1.231	1.056	1.007-1.109

Platelets (10^9/L)		0.998	0.996-1.001	0.999	0.998-1.001
C-reactive protein (mg/dL)		1.061	1.031-1.092	1.049	1.033-1.065
LDH (U/L)		1.001	1.000-1.002	1.001	1.000-1.001
SO2 (%)		0.932	0.910-0.956	0.966	0.951-0.981
Ground-glass opacities		0.751	0.234-2.412	0.632	0.311-1.283
Consolidation		1.625	1.002-2.637	1.517	1.201-1.916
CT extension	<20%	1		1	
	20-39%	0.869	0.457-1.652	1.348	1.024-1.774
	40-59%	1.813	0.944-3.481	2.072	1.511-2.841
	≥60%	6.684	3.557-12.560	2.357	1.643-3.383
Body temperature >37.5°C		1.325	0.765-2.295	1.679	1.258-2.243
Cough		0.541	0.316-0.926	1.322	0.995-1.756
Dyspnea/Polypnea	-	1.957	1.153-3.321	1.519	1.149-2.009
Headache				0.686	0.253-1.856
Myalgia/arthralgia		0.796	0.189-3.362	0.887	0.481-1.635
Fatigue		1.140	0.448-2.900	1.084	0.694-1.695
Syncope		0.672	0.266-1.696	1.424	0.896-2.263
Gastrointestinal symptoms		1.802	0.812-4.000	1.092	0.715-1.669
Other symptoms		0.789	0.187-3.335	1.206	0.729-1.994

Table 2: Univariate associations of demographic and pre-existing conditions, as well as clinical, laboratory, and CT findings at ER presentation, with death and hospitalization, expressed as HR and respective 95% confidence intervals, adjusted for sex, age and calendar time. Missing value in the cohort are: 66 for White blood cells, 148 for Lymphocytes, 73 for Platelets and 76 for C-reactive protein. HR, hazard ratio; CI, confidence interval; HDL, high density lipoprotein; LDL, low density lipoprotein; COPD, chronic obstructive pulmonary disease; LDH, lactate dehydrogenase; SO2, oxygen saturation level.

Table 3. Multivariate models for death, with and without CT extension

		Multivariate model without CT		Multivariate model with CT	
Variables		**HR**	**95% CI**	**HR**	**95% CI**
Age (years)		1.083	1.062-1.103	1.092	1.070-1.114
Sex	Female	1		1	
	Male	1.736	1.009-2.989	1.622	0.934-2.819
HDL cholesterol (mg/dl)		0.974	0.955-0.994	0.971	0.952-0.991
Dementia		4.127	1.719-9.908	4.907	1.932-12.460
Heart failure		2.909	1.615-5.241	1.903	1.027-3.527
Vascular diseases		2.781	1.084-7.137	2.749	1.055-7.160
Days from symptom onset		0.894	0.839-0.953	0.868	0.813-0.927
Neutrophils (10^9/L)		1.159	1.067-1.260	1.098	1.009-1.196
LDH (U/L)		1.001	1.000-1.002	1.000	0.999-1.001
SO2 (%)		0.934	0.908-0.962	0.968	0.936-1.001
CT extension	<20%			1	
	20-39%			1.320	0.664-2.624
	40-59%			2.406	1.175-4.928
	≥60%			7.555	3.485-16.377

Table 3: Multivariate models (without and with CT extension) including factors associated in univariate analyses. HR, hazard ratio; CI, confidence interval; HDL, high density lipoprotein; LDH, lactate dehydrogenase; SO2, oxygen saturation level.

Table 4. Stratified models and sensitivity analyses for death, with and without CT extension

	Stratified by SO2 level		Stratified by symptom onset		Restricted populations		
	<95%	>=95%	<8 days before ER presentation	≥8 days before ER presentation	excluding patients over 85 y/o	excluding patients with >60% CT extension	excluding patients died within 48h
Number of observations (N)	358	508	564	302	818	799	859
Number of deaths (N)	73	20	76	17	67	64	86
HR of CT extension (95% CI)							
<20%	1	1			1	1	1
20-39%	1.40 (0.57-3.44)	1.30 (0.40-4.18)	1.12 (0.54-2.35)	1.86 (0.20-16.97)	1.72 (0.69-4.32)	1.28 (0.61-2.69)	1.48 (0.72-3.04)
40-59%	2.56 (1.00-6.50)	2.81 (0.67-11.73)	2.17 (0.99-4.75)	3.59 (0.36-35.27)	3.91 (1.52-10.08)	2.54 (1.16-5.57)	2.80 (1.32-5.94)
≥60%	8.11 (3.12-21.12)	10.11 (1.60-63.78)	5.75 (2.48-13.33)	9.44 (1.01-88.38)	9.96 (3.68-26.95)	-	8.95 (3.99-20.09)
cvAUC (BBC-95% CI)*							
Model with clinical variables only	0.889 (0.822-0.914)	0.949 (0.867-0.963)	0.918 (0.882-0.940)	0.921 (0.811-0.974)	0.929 (0.888-0.949)	0.907 (0.899-0.952)	0.924 (0.891-0.940)
Model with clinical variables + CT extension	0.907 (0.861-0.931)	0.952 (0.885-0.966)	0.920 (0.891-0.945)	0.929 (0.850-0.971)	0.943 (0.910-0.957)	0.915 (0.906-0.955)	0.936 (0.906-0.949)

Table 4: Characteristics of the sensitivity analyses, respectively stratified by SO2 and days before symptoms onset, and excluding patients older than 85 years, >60% CT extension, died within 48 hours. SO2, oxygen saturation level; HR, hazard ratio; cvAUC, cross-validated area under the curve; CI, confidence interval; BBC 95% CI, bootstrap corrected 95% confidence interval.

Figures

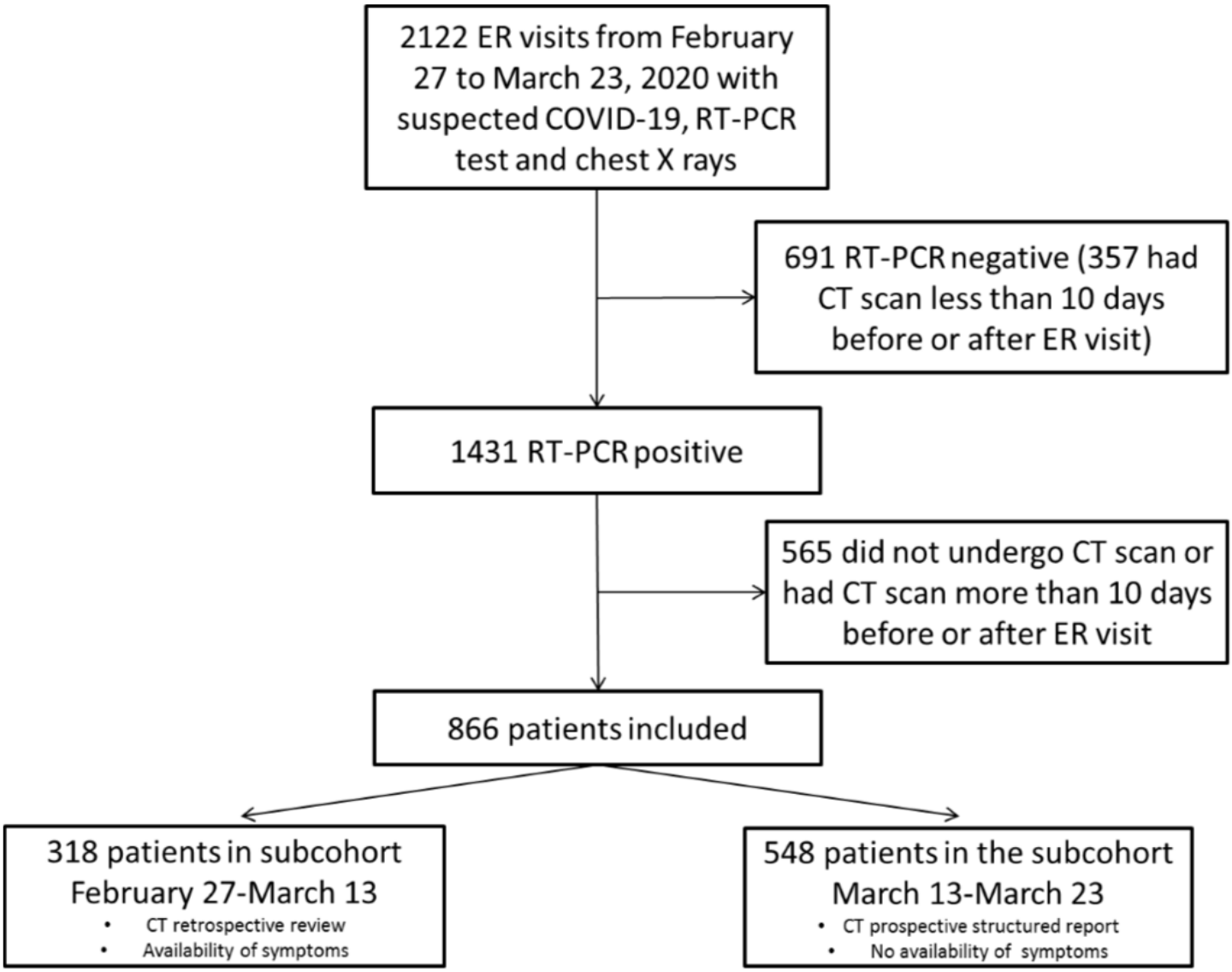
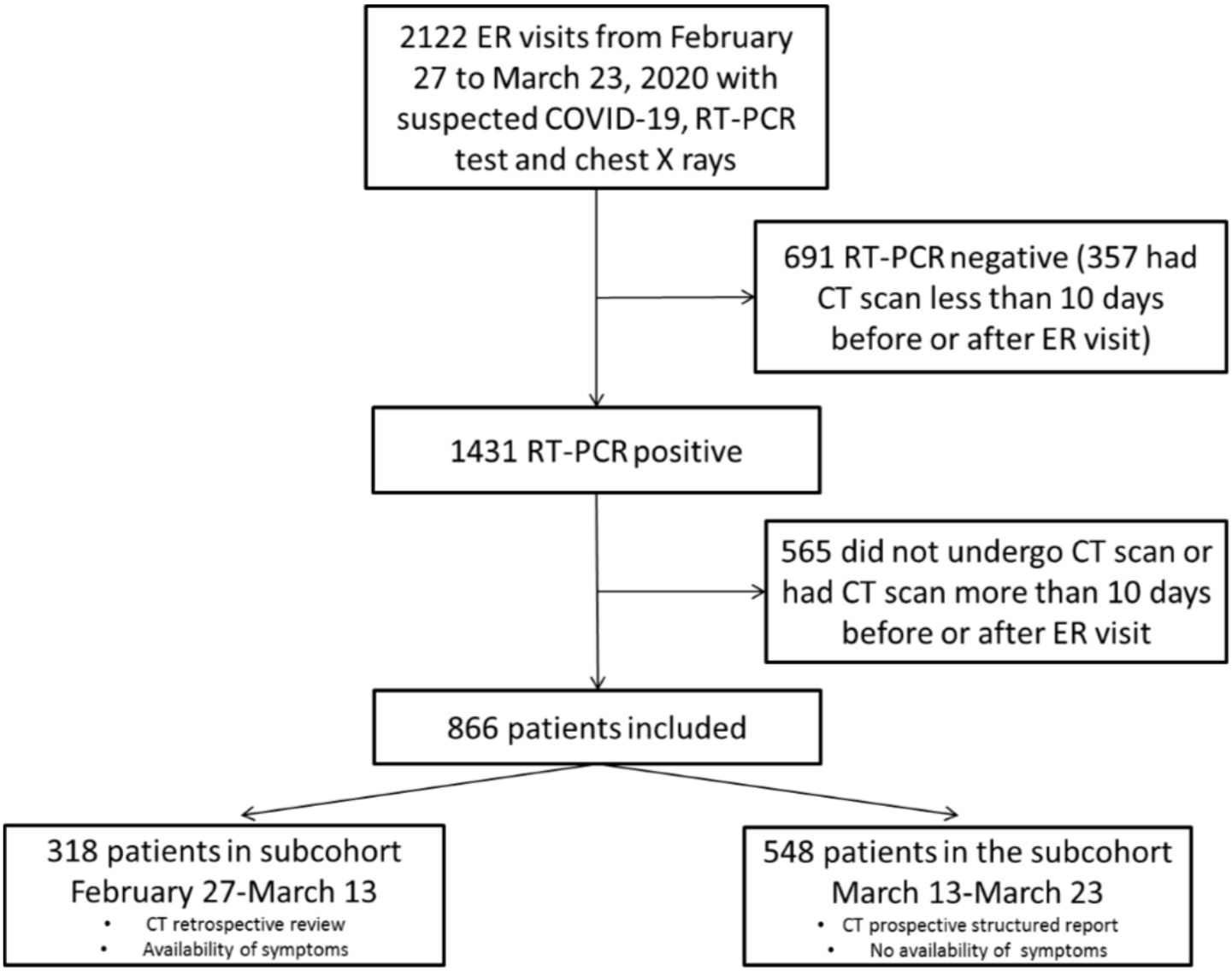


Figure 1

Flow diagram representing patient selection. ER, Emergency Room; RT-PCR, reverse transcription - polymerase chain reaction.



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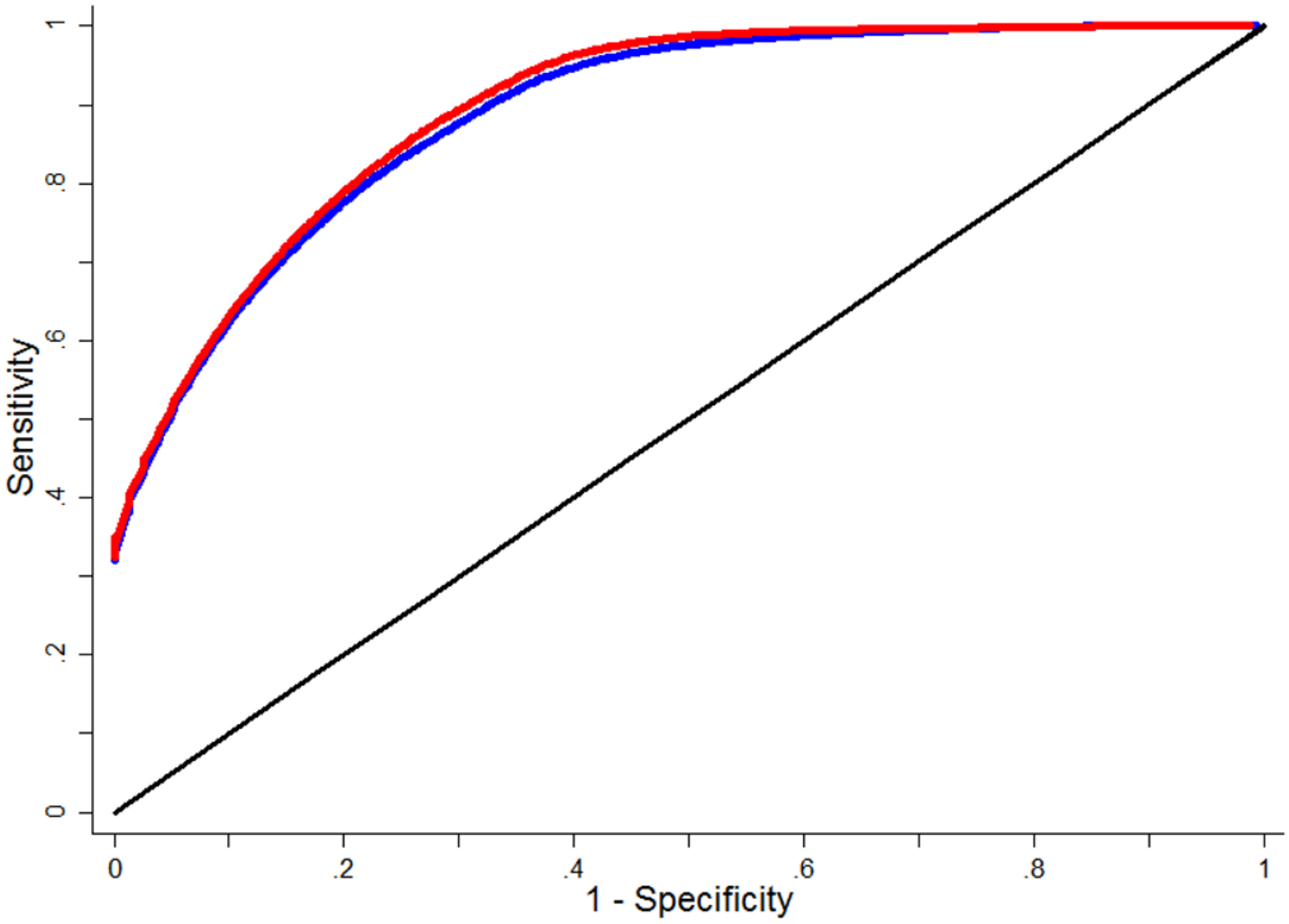
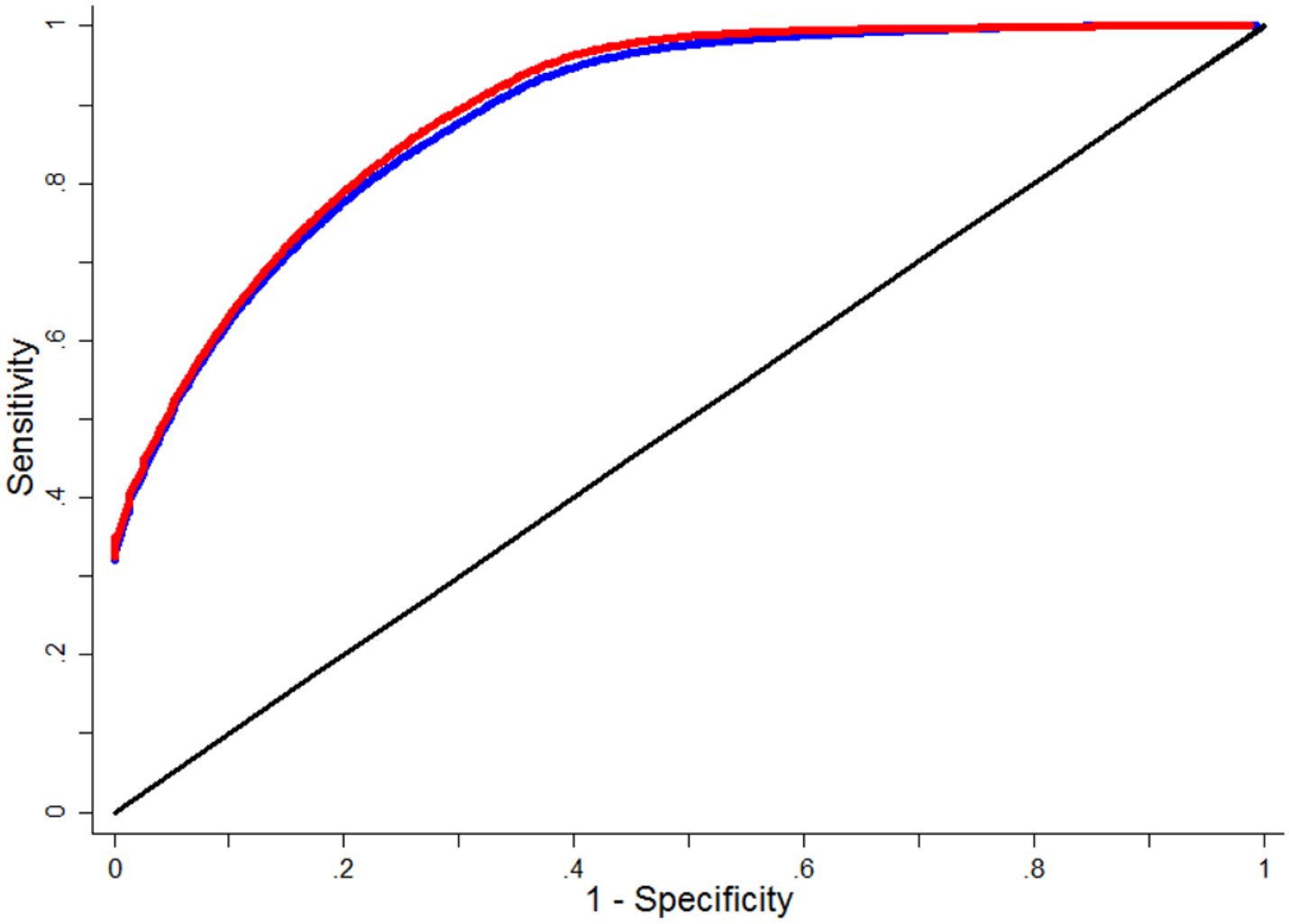


Figure 2

Cross validated ROC, receiver operating characteristic, curves of the prognostic multivariate models based on clinical data, without CT extension (blue line), and clinical data with CT extension (red line).



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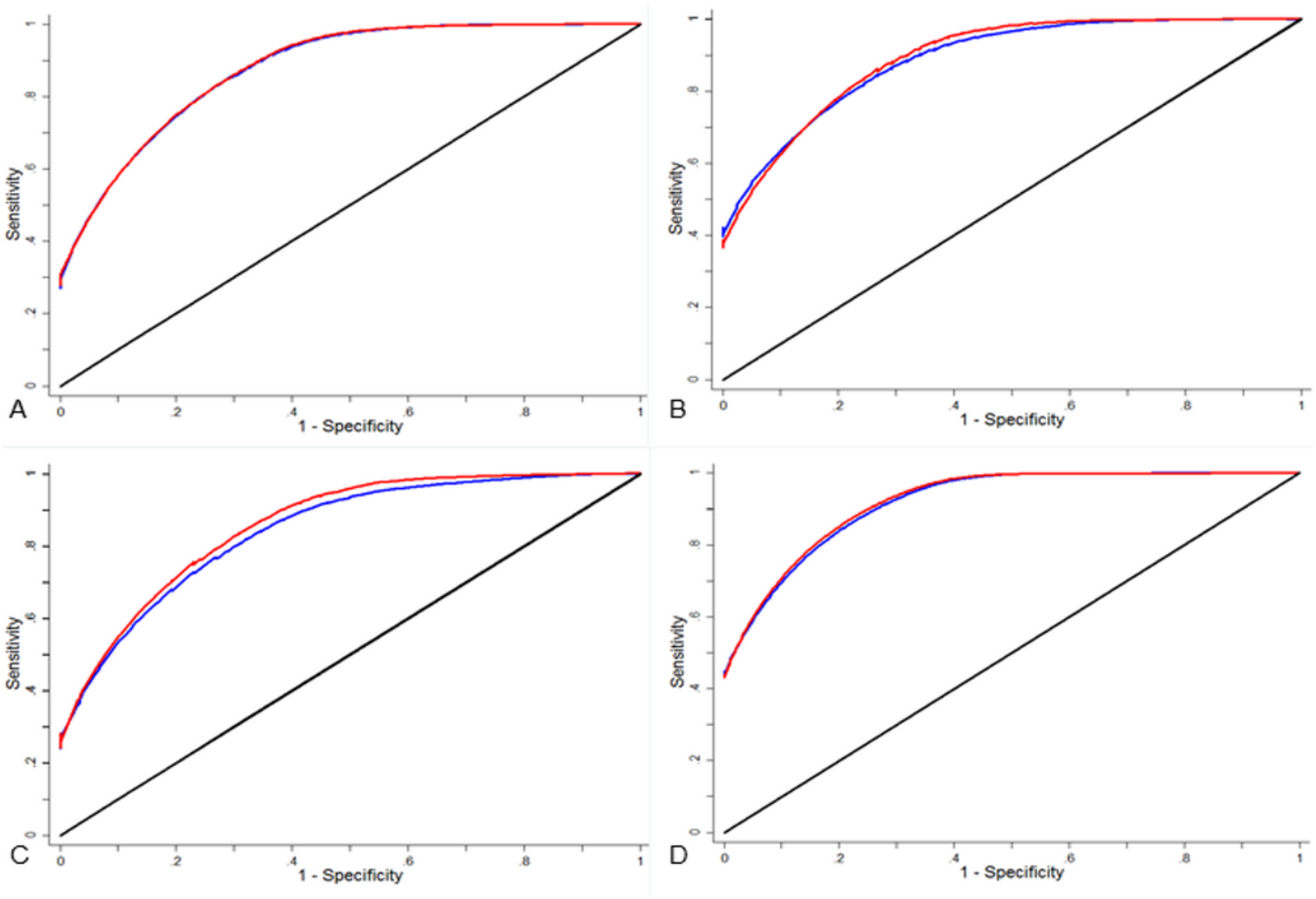
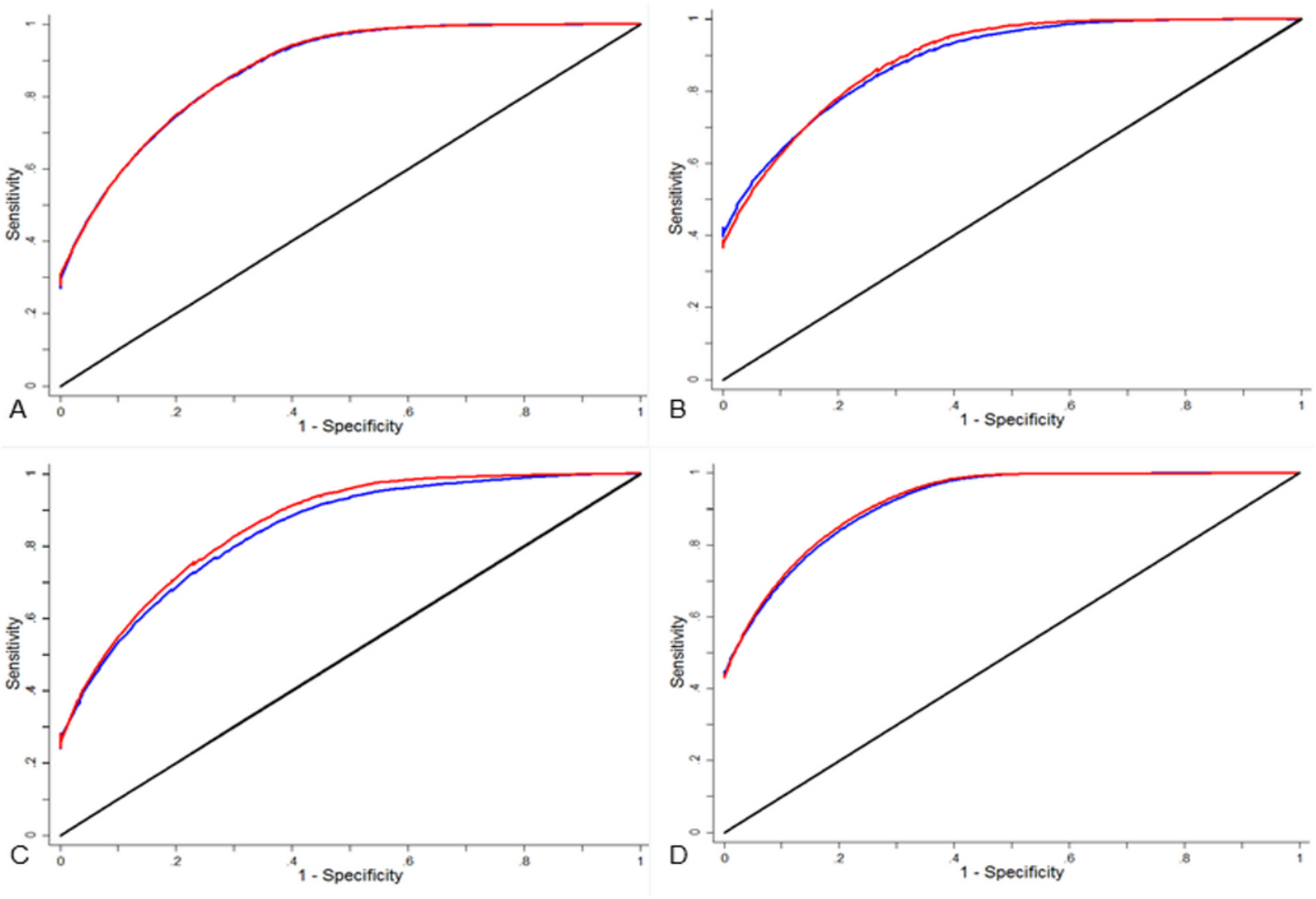


Figure 3

Cross validated ROC, receiver operating characteristic, curves of the multivariate models with (red line) and without (blue line) CT extension under different stratifications (<8 days from symptom onset, A; ≥8 days from symptom onset, B; SO2<95%, C; SO2≥95%, D).



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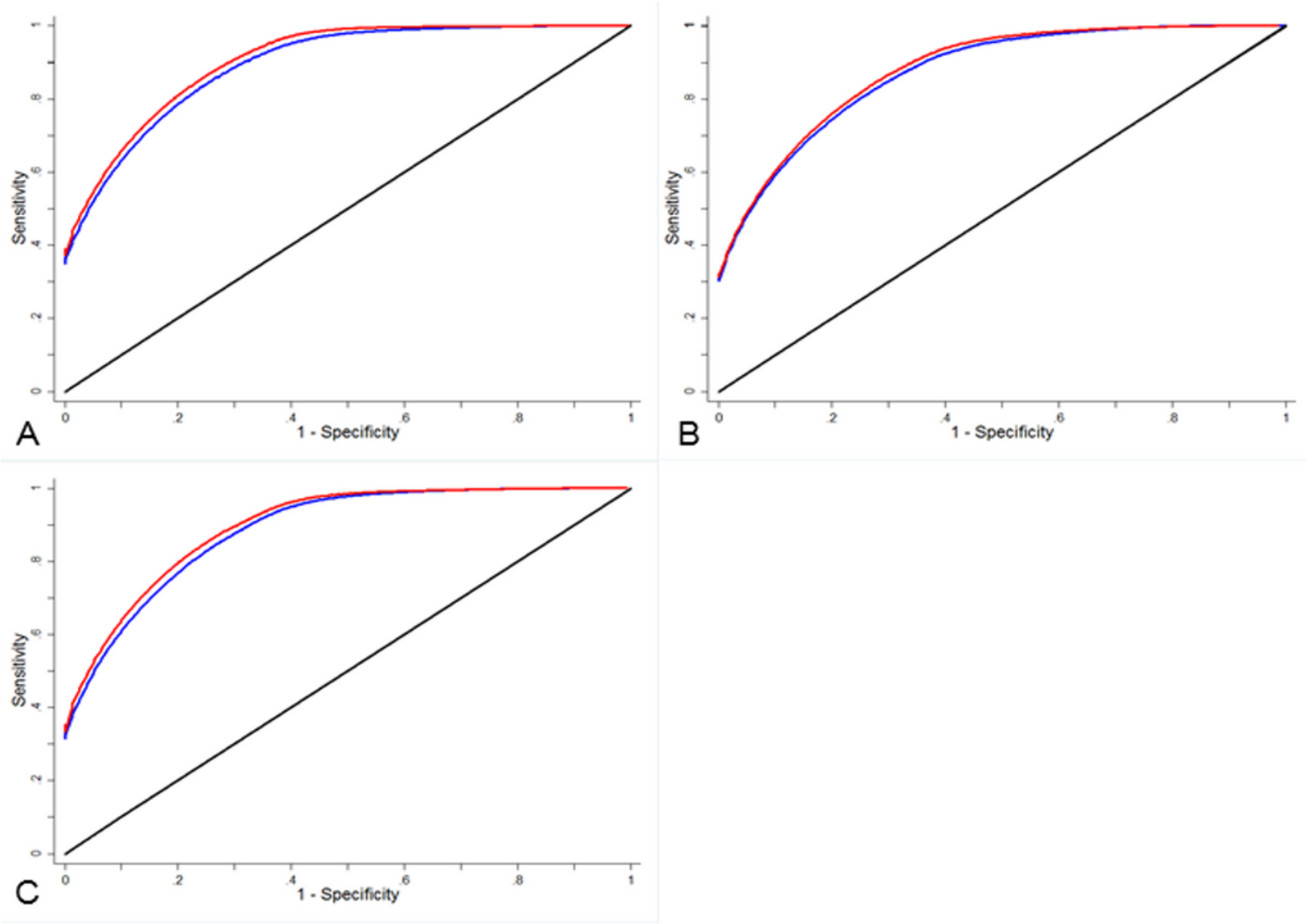
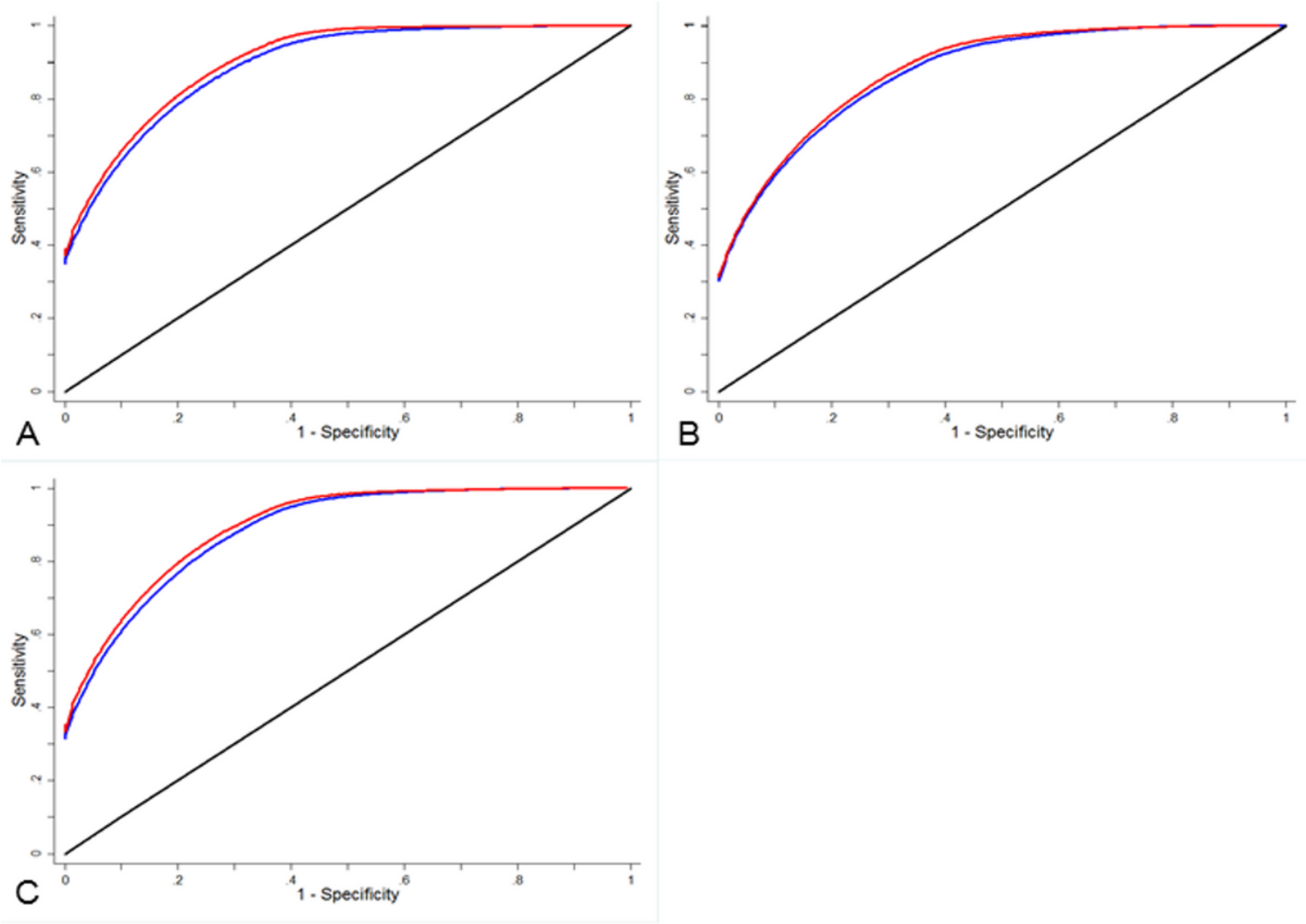


Figure 4

Cross validated ROC, receiver operating characteristic, curves of the multivariate models with (red line) and without (blue line) CT extension under different sensitivity analyses (excluding patients aged over 85 years, A; excluding patients with >60% CT extension, B; excluding deaths within 48 hours from ER presentation, C).



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Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMaterials.docx
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