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Establishment of CORONET, COVID-19 Risk in Oncology Evaluation Tool, to Identify Patients With Cancer at Low Versus High Risk of Severe Complications of COVID-19 Disease On Presentation to Hospital

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abstract

PURPOSE Patients with cancer are at increased risk of severe COVID-19 disease, but have heterogeneous presentations and outcomes. Decision-making tools for hospital admission, severity prediction, and increased monitoring for early intervention are critical. We sought to identify features of COVID-19 disease in patients with cancer predicting severe disease and build a decision support online tool, COVID-19 Risk in Oncology Evaluation Tool (CORONET).

METHODS Patients with active cancer (stage I-IV) and laboratory-confirmed COVID-19 disease presenting to hospitals worldwide were included. Discharge (within 24 hours), admission (≥ 24 hours inpatient), oxygen (O_2) requirement, and death were combined in a 0-3 point severity scale. Association of features with outcomes were investigated using Lasso regression and Random Forest combined with Shapley Additive Explanations. The CORONET model was then examined in the entire cohort to build an online CORONET decision support tool. Admission and severe disease thresholds were established through pragmatically defined cost functions. Finally, the CORONET model was validated on an external cohort.

RESULTS The model development data set comprised 920 patients, with median age 70 (range 5-99) years, 56% males, 44% females, and 81% solid versus 19% hematologic cancers. In derivation, Random Forest demonstrated superior performance over Lasso with lower mean squared error (0.801 *v* 0.807) and was selected for development. During validation (n = 282 patients), the performance of CORONET varied depending on the country cohort. CORONET cutoffs for admission and mortality of 1.0 and 2.3 were established. The CORONET decision support tool recommended admission for 95% of patients eventually requiring oxygen and 97% of those who died (94% and 98% in validation, respectively). The specificity for mortality prediction was 92% and 83% in derivation and validation, respectively. Shapley Additive Explanations revealed that National Early Warning Score 2, C-reactive protein, and albumin were the most important features contributing to COVID-19 severity prediction in patients with cancer at time of hospital presentation.

CONCLUSION CORONET, a decision support tool validated in health care systems worldwide, can aid admission decisions and predict COVID-19 severity in patients with cancer.

ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

To develop a clinically relevant model and decision support tool that could recommend admission and predict severity of COVID-19 disease in patients with cancer.

Knowledge Generated

We established the features at presentation to hospital associated with increased severity of COVID-19 disease in patients with cancer. The COVID-19 Risk in Oncology Evaluation Tool, a decision support tool, was then built with high sensitivity to recommend admission for those patients predicted to have severe COVID-19 disease and high specificity for prediction of mortality.

Relevance

We have designed a pragmatic model and decision support tool on the basis of easily available clinical and laboratory features, which can aid health care professionals in a decision to admit and in discussions with patients with cancer and their families regarding their likely prognosis after SARS-CoV-2 infection.

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INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has infected more than 30 million people to date, resulting in more than a million deaths worldwide.[1] A diverse spectrum of clinicopathologic syndromes have been reported, ranging from asymptomatic cases to multiorgan failure and death.[2] Although the standard medical care in those requiring hospitalization is evolving as our knowledge expands, at this time, it involves supportive therapies, with or without immune-modulating agents such as corticosteroids and/or anti–interleukin-6 agents as well as antiviral agents such as remdesivir or casirivimab plus imdevimab, depending on the severity of COVID-19 disease.[3-5] On the other hand, patients with milder or no symptoms have been safely managed as outpatients. Patients with cancer have significantly increased mortality and risk of severe complications from COVID-19 disease, including the need for invasive ventilation or death.[2,6-8] In three large case series and a meta-analysis of 18,650 patients, fatality rates of 10%-30% were observed in patients with cancer.[6,9-11] Older age, male sex, nosocomial infection, higher Eastern Cooperative Oncology Group performance status (PS), active cancer, hematologic cancer, and presence of other comorbidities such as pre-existing cardiovascular disease or cardiovascular risk factors were significantly associated with mortality from COVID-19 disease.[8-15]

Identifying oncology patients at risk of deterioration necessitating inpatient admission presents a unique challenge for health care professionals (HCPs) because of the heterogeneity of clinical manifestations of COVID-19 disease and difficulty in distinguishing these from the complications of cancer and its therapy. In addition, to reduce burden on the health system and risk of nosocomial/hospital staff infection, it is important to admit only those patients who are likely to require additional supportive measures.[16] A living review of risk prediction models has reported that current models are highly susceptible to bias and are poorly reported.[14] More recently, the ISARIC 4C model has been developed using data from 57,824 patients in the United Kingdom to develop a score on the basis of clinical/laboratory parameters.[15] Although patients with a history of cancer were included in model development, it was not specifically built to predict the risk of severe COVID-19 disease in this high-risk population, and it is unclear how well it performs in patients with active cancer.

We investigated clinical, hematologic, and biochemical features in patients with active cancer presenting to hospital with COVID-19 disease. Crucially, we wanted to create a pragmatic tool with parameters easily obtained through routine clinical history, examination, and laboratory assessment that can be readily applied in hospitals. We developed a model that aimed to predict the potential for safe discharge without serious sequelae versus severe disease requiring oxygen (O_2) or leading to death. Data were used from international cohorts of patients to increase the generalizability of the model. Using this model, we built an online tool, COVID-19 Risk in Oncology Evaluation Tool (CORONET), to guide HCPs and systems in decision making regarding the need for admission and to provide information regarding the likely severity of illness. This is the first step of an iterative process whereby the tool will have ongoing refinement as more data and knowledge regarding COVID-19 disease and its treatment in patients with cancer are obtained.

METHODS

Study Settings

Approval (reference 20/WA/0269) was granted from the UK Research Ethics Committee for the study. Information

regarding governance/regulatory approvals for each international cohort is available in the Data Supplement.

Study Population

Patients with active cancer defined as solid (stage I-IV) or hematologic cancer diagnosed in the past 6 months or undergoing treatment for cancer or recurrent or metastatic cancer or hematologic cancer not in complete remission for ≥ 6 months were included. Patients had to have a laboratory-confirmed SARS-CoV-2 infection (which, for the majority, was polymerase chain reaction–based). Asymptomatic patients who were screened and found to be positive as part of routine testing for surgical procedures were not included as data were not routinely captured. Patient data was collected worldwide from the United Kingdom, the United States, Spain, Denmark, and France and collectively from medical centers contributing to ESMO-CoCARE. More details regarding the study population are given in the Data Supplement.

Selection of Clinical, Hematologic, and Biochemical Features

Clinical, hematologic, and biochemical data were collected on the basis of a prespecified feature list including demographic/physiologic features, cancer-specific factors associated with poor cancer outcomes such as PS, literature review of features of COVID-19 severity, and our previous work examining patients with cancer and COVID-19 disease longitudinally.[7] Parameters were taken at presentation to hospital with symptoms of COVID-19 disease, which was later laboratory-confirmed, or if already an inpatient, taken as close to/at the time of positive COVID-19 result (see the Data Supplement for definitions of parameters).

Patient Outcomes

Admission (≥ 24 hours inpatient), O_2 requirement (including ventilator support), and death directly attributable to COVID-19 disease (not cancer) were used as measures of disease severity. Very few patients were admitted to the intensive care unit; therefore, it was not used as an outcome measure for analysis. We developed a tool to help determine the need to admit a patient to hospital on the basis of their likelihood of needing O_2 (as generally it is only given in hospital) and the severity of COVID-19 disease indicated by prediction for O_2 requirement and death. If patients were already on supplementary O_2 because of cancer (number unknown, but a small percentage), it was assumed that they had been assessed as requiring additional hospital care to be admitted by the treating clinicians. Modeling was therefore based on the combination of these key outcomes, arranged in a 0-3 point ordinal scale.

Study Design

Transparent reporting of multivariable prediction models for individual prognosis or diagnosis guidelines has been used to report findings.[17] The framework proposed by Riley et al[18] was adopted to estimate the sample size required to ensure sufficient model accuracy and generality. Assuming the proportion of each clinical outcome to be 25% (eg, death) and a minimum model R^2 of 0.2, we expected that a minimum sample size of 427 for training would be required. All statistical tests and modeling were performed using R (version 3.6.2) and Python (version 3.7).

Model Development

The model development workflow (Fig 1) consisted of three stages: (1) model derivation comprised multiple imputation of missing data, feature selection, hyperparameters tuning, and performance comparison between Lasso and Random Forest (RF) regression models; (2) creation of the CORONET model used for the online tool together with an explanation of feature contribution to the predicted score on the basis of Shapley Additive Explanations[19]; and (3) model validation using the external cohort. Further details regarding the model development are given in the Data Supplement.

RESULTS

Clinical Characteristics

Data collection for the model development cohort was conducted between March 2020 and March 2021 in 12 participating hospitals in the United Kingdom, two hospitals in Spain, four hospitals in the United States, and as part of the ESMO-CoCARE registry, hospitals throughout the world, excluding the United States, Canada, and Latin America (Data Supplement). This resulted in an international, heterogeneous group of local and tertiary centers, mainly in high-income countries. The entire data set for model derivation comprised 1,743 patients (1,530 with laboratory-confirmed SARS-CoV-2 infection); however, only 920 patients had ≤ 1 key feature missing identified in our previous work[7] and feasibility pilot assessment (one of National Early Warning Score-2 [NEWS2]), a standardized assessment of acute illness severity used within the National Health System in the United Kingdom (NEWS2[20]; C-reactive protein [CRP], albumin, age, and platelets), and were therefore used for the modeling. Clinical features of all patients are given in Table 1. For the entire cohort, the median age was 70 years, range 5-99 years, with 56% males, 44% females, and 81% having been diagnosed with a solid tumor, whereas 19% had hematologic cancer. At the time of data cutoff, the percentage of patients discharged within 24 hours (group 0) was 17%, admission to hospital (≥ 24 hours) without requiring O_2 (group 1) was 25%, required O_2 but did not die (group 2) was 29%, and admitted plus required O_2 plus death because of COVID-19 disease (group 3) was 29% with a minimum follow-up of 30 days.

The external validation cohort comprised a total of 394 patients. Notably, 52% of patients from France and 14% from Denmark had more than one key numerical variable missing (Data Supplement) and were removed from the validation data set (Data Supplement). In addition, certain

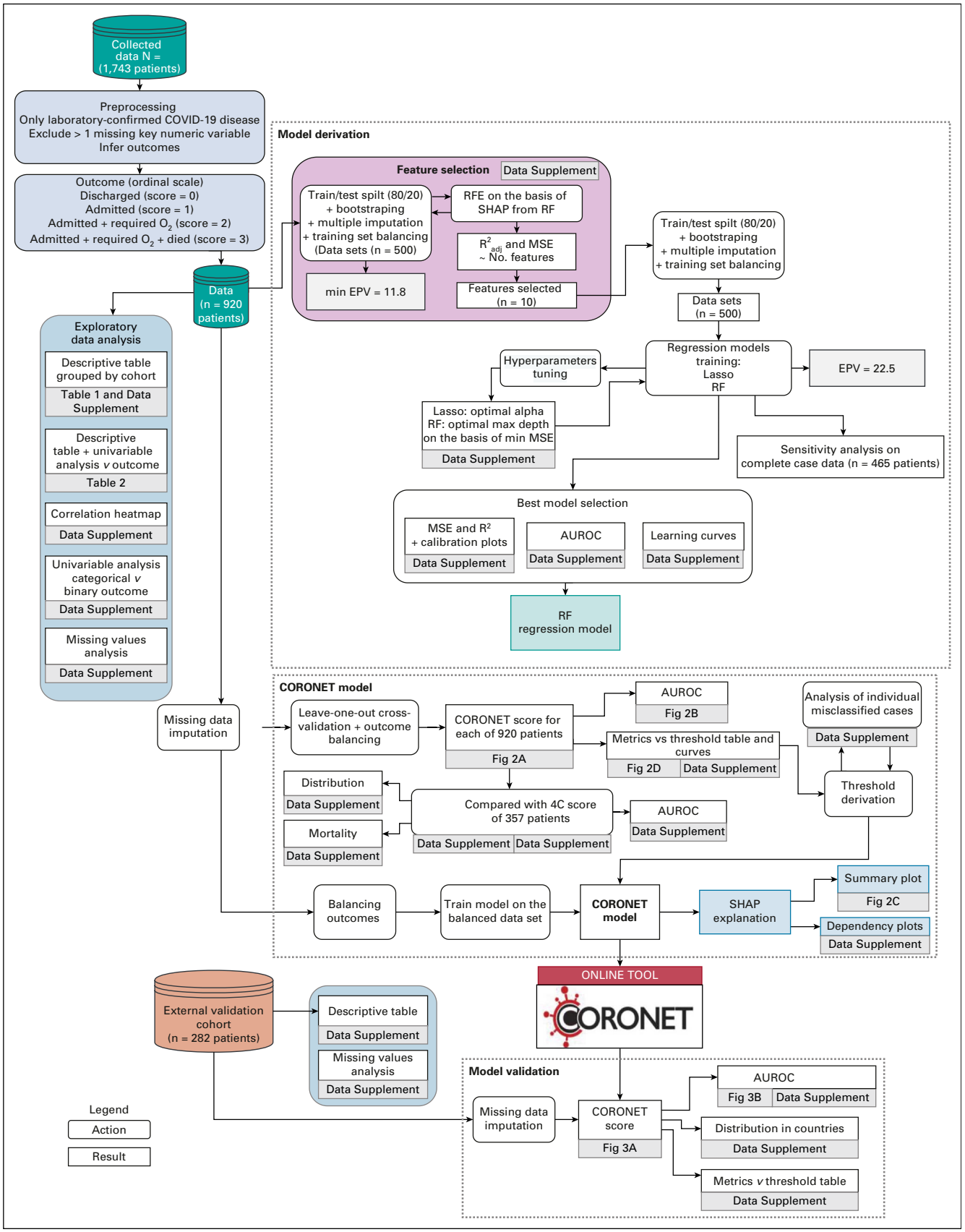

FIG 1. CORONET modeling diagram. AUROC, area under the receiver operating characteristic curve; CORONET, COVID-19 Risk in Oncology Evaluation Tool; EPV, event per variable; max, maximum; min, minimum; MSE, mean squared error; RF, Random Forest; RFE, Recursive Feature Elimination; SHAP, Shapley Additive Explanation.

TABLE 1. Characteristics of the Model Derivation Cohort

Variable	Overall	ESMO	Spain	United Kingdom	United States
No.	920	207	186	414	113
Age, years					
Median (range)	70 (5-99)	63 (5-86)	71 (34-95)	68 (19-93)	80.0 (53-99)
Biological sex, No. (%)					
Female	406 (44.1)	102 (49.3)	60 (32.3)	191 (46.1)	53 (46.9)
Male	514 (55.9)	105 (50.7)	126 (67.7)	223 (53.9)	60 (53.1)
Total No. of comorbidities					
Median [Q1, Q3]	2.0 [1.0, 3.0]	2.0 [1.0, 3.0]	2.0 [1.0, 4.0]	1.0 [0.0, 2.0]	3.0 [2.0, 4.0]
Missing	61	49	10	2	0
NEWS2					
Median [Q1, Q3]	3.0 [1.0, 5.0]	3.0 [2.0, 4.0]	2.0 [0.0, 6.0]	2.0 [1.0, 5.0]	4.0 [2.0, 6.0]
Missing	148	76	0	72	0
CRP					
Median [Q1, Q3]	58.0 [17.4, 127.6]	17.5 [5.0, 58.6]	62.0 [21.8, 136.7]	68.0 [24.0, 148.0]	71.9 [39.3, 129.1]
Missing	114	67	3	37	7
Albumin					
Median [Q1, Q3]	34.0 [28.0, 40.0]	39.0 [35.0, 43.0]	29.0 [24.0, 34.0]	35.0 [30.0, 40.0]	30.0 [26.0, 33.8]
Missing	50	8	17	14	11
Platelets					
Median [Q1, Q3]	205.0 [140.0, 280.0]	212.0 [137.0, 287.5]	207.0 [154.2, 278.8]	204.0 [122.0, 288.0]	200.0 [159.0, 241.0]
Missing	5	0	0	5	0
Lymphocytes					
Median [Q1, Q3]	0.8 [0.5, 1.3]	1.1 [0.8, 1.8]	0.8 [0.5, 1.2]	0.7 [0.4, 1.1]	0.9 [0.6, 1.4]
Missing	15	2	1	12	0
Neutrophils					
Median [Q1, Q3]	4.1 [2.5, 6.6]	3.6 [2.1, 5.8]	4.2 [2.7, 6.3]	4.1 [2.3, 7.1]	4.7 [3.7, 7.5]
Missing	12	2	0	10	0
Neutrophil:lymphocyte ratio					
Median [Q1, Q3]	4.6 [2.4, 9.2]	2.8 [1.5, 5.7]	4.6 [2.4, 8.7]	5.5 [3.0, 10.8]	5.2 [3.1, 10.4]
Missing	16	2	1	13	0
LDH					
Median [Q1, Q3]	271.5 [207.5, 407.8]	231.0 [186.0, 350.0]	235.0 [188.8, 400.2]	310.5 [241.0, 466.2]	298.0 [240.0, 416.5]
Missing	430	38	130	244	18
Urea					
Median [Q1, Q3]	5.5 [3.9, 8.0]	5.5 [4.1, 7.8]	4.0 [3.3, 4.6]	5.9 [4.4, 8.7]	4.7 [3.0, 6.5]
Missing	280	14	178	88	0
Respiratory rate					
Median [Q1, Q3]	18.0 [17.0, 21.0]	18.0 [16.2, 19.0]	15.0 [14.0, 21.0]	18.0 [17.0, 21.0]	20.0 [18.0, 24.0]
Missing	355	53	141	161	0
SATs					
Median [Q1, Q3]	96.0 [93.0, 98.0]	98.0 [96.0, 100.0]	93.5 [87.8, 96.0]	96.0 [94.0, 97.0]	95.0 [93.0, 96.0]
Missing	254	52	110	92	0

(Continued on following page)

TABLE 1. Characteristics of the Model Derivation Cohort (Continued)

Variable	Overall	ESMO	Spain	United Kingdom	United States
Cancer stage (solid tumor only) or type (solid *v* hematologic)					
Median [Q1, Q3]	3.0 [1.0, 4.0]	3.0 [0.0, 3.0]	4.0 [3.0, 4.0]	3.0 [1.0, 4.0]	1.0 [1.0, 2.0]
Missing	19	6	1	12	0
Stage I or II, No. (%)	196 (21.3)	18 (8.7)	34 (18.3)	56 (13.5)	88 (77.9)
Stage III, No. (%)	181 (19.7)	70 (33.8)	39 (21.0)	63 (15.2)	9 (8.0)
Stage IV, No. (%)	342 (37.2)	43 (20.8)	112 (60.2)	180 (43.5)	7 (6.2)
Hematologic cancer, No. (%)	171 (18.6)	59 (28.5)		103 (24.9)	9 (8.0)
Chemotherapy within 4 weeks of COVID-19 disease					
No. (%)	356 (38.7)	124 (59.9)	60 (32.3)	165 (39.9)	7 (6.2)
Immunotherapy within 4 weeks of COVID-19 disease					
No. (%)	54 (5.9)	16 (7.7)	14 (7.5)	23 (5.6)	1 (0.9)
Targeted therapy within 4 weeks of COVID-19 disease					
No. (%)	106 (11.5)	13 (6.3)	22 (11.8)	71 (17.1)	—
Radiotherapy within 4 weeks of COVID-19 disease					
No. (%)	47 (6.2)	17 (8.2)	11 (5.9)	17 (6.9)	2 (1.8)
Missing	167	0	0	167	0
Treatment intent					
Curative, No. (%)	198 (46.9)	—	58 (32.6)	35 (26.7)	105 (92.9)
Palliative, No. (%)	224 (53.1)	—	120 (67.4)	96 (73.3)	8 (7.1)
Missing	498	207	8	283	0
PS					
Median [Q1, Q3]	1.0 [1.0, 2.0]	1.0 [0.8, 2.0]	1.0 [1.0, 2.0]	1.0 [1.0, 2.0]	2.0 [2.0, 3.0]
Missing	191	15	34	142	0
Outcome, No. (%)					
Discharged	152 (16.5)	57 (27.5)	39 (21.0)	50 (12.1)	6 (5.3)
Admitted, no O_2 requirement/death	232 (25.2)	73 (35.3)	12 (6.5)	129 (31.2)	18 (15.9)
Admitted, required O_2, no death	265 (28.8)	38 (18.4)	80 (43.0)	100 (24.2)	47 (41.6)
Died because of COVID-19 disease	271 (29.5)	39 (18.8)	55 (29.6)	135 (32.6)	42 (37.2)

Abbreviations: CRP, C-reactive protein; ESMO, European Society for Medical Oncology Co-Care registry; LDH, lactate dehydrogenase; NEWS2, National Early Warning Score 2; PS, performance status; SATs, oxygen saturation.

assumptions were made regarding NEWS2 score because of missing components in these cohorts (Data Supplement). After removing patients with more than one key feature missing, the validation data set comprised 282 patients from France (n = 84) and Denmark (n = 92) before March 2021 and the United Kingdom (n = 86) and Spain (n = 20) from December 2020 to June 2021 (Data Supplement).

Association Between Variables and COVID-19 Outcomes

Correlations between features were generally weak (Data Supplement), with only 5.7% demonstrating correlation coefficients more than 0.4, although CRP correlated with NEWS2 score, lower albumin and higher lactate dehydrogenase (LDH) with lower oxygen saturations, platelets with neutrophils, and as expected, increasing age with the number of comorbidities and PS. Analysis of variance inflation factor revealed multicollinearity for age, albumin, cancer stage, and type (Data Supplement).

First, we sought an overview of univariable associations between features and COVID-19 outcomes (Table 2). To determine the feature importance for predicting the key outcomes previously described, we performed recursive feature elimination (RFE) on the basis of Shapley Additive Explanations values for RF modeling (Data Supplement).

TABLE 2. Numeric and Categorical Variables Associated With Outcomes

Variable	Overall	Discharged (score = 0)	Admitted (score = 1)	Admitted + Required O_2 (score = 2)	Admitted + Required O_2 + Died (score = 3)	Correlation[a]		Multivariable RFE SHAP
						r	*P*	
No. (%)	920	152 (16.5)	232 (25.2)	265 (28.8)	271 (29.5)			
Age, years, median [Q1, Q3]	70.0 [59.0, 78.0]	62.0 [54.8, 72.0]	66.0 [56.0, 74.0]	71.0 [62.0, 78.0]	73.0 [65.0, 81.5]	0.292	< .001	s
Biological sex, No. (%)								
Female	406 (44.1)	71 (46.7)	130 (56.0)	117 (44.2)	88 (32.5)	—	—	ns
Male	514 (55.9)	81 (53.3)	102 (44.0)	148 (55.8)	183 (67.5)	0.138	< .001	
Total No. Of comorbidities, median [Q1, Q3]	2.0 [1.0, 3.0]	1.0 [0.0, 2.0]	1.0 [0.0, 2.0]	2.0 [1.0, 3.0]	2.0 [1.0, 3.0]	0.209	< .001	s
NEWS2, median [Q1, Q3]	3.0 [1.0, 5.0]	1.0 [0.0, 3.0]	2.0 [1.0, 4.0]	3.0 [2.0, 6.0]	4.0 [2.0, 8.0]	0.396	< .001	s
CRP, median [Q1, Q3]	58.0 [17.4, 127.6]	15.5 [4.2, 49.3]	29.0 [10.9, 78.5]	67.9 [31.4, 117.3]	102.0 [44.5, 190.0]	0.409	< .001	s
Albumin, median [Q1, Q3]	34.0 [28.0, 40.0]	40.0 [35.0, 43.0]	38.0 [32.5, 41.0]	32.0 [27.0, 36.0]	30.0 [26.0, 37.2]	–0.371	< .001	s
Platelets, median [Q1, Q3]	205.0 [140.0, 280.0]	225.5 [165.0, 274.5]	218.0 [150.0, 297.0]	195.5 [143.0, 274.8]	185.5 [115.0, 273.8]	–0.131	< .001	s
Lymphocytes, median [Q1, Q3]	0.8 [0.5, 1.3]	1.1 [0.7, 1.6]	0.9 [0.5, 1.4]	0.8 [0.5, 1.2]	0.7 [0.4, 1.1]	–0.212	< .001	s
Neutrophils, median [Q1, Q3]	4.1 [2.5, 6.6]	3.5 [2.1, 4.8]	3.8 [2.1, 6.1]	4.1 [2.7, 6.5]	5.4 [3.2, 8.5]	0.215	< .001	s
Neutrophil:lymphocyte ratio, median [Q1, Q3]	4.6 [2.4, 9.2]	2.9 [1.8, 4.9]	4.0 [1.8, 8.1]	4.7 [2.8, 9.0]	7.0 [3.7, 14.4]	0.295	< .001	s
LDH, median [Q1, Q3]	271.5 [207.5, 407.8]	227.0 [184.5, 257.5]	253.0 [191.0, 351.2]	285.0 [214.0, 429.0]	360.5 [263.5, 524.8]	0.343	< .001	b
Urea, median [Q1, Q3]	5.5 [3.9, 8.0]	5.0 [3.8, 6.4]	5.0 [3.7, 6.8]	5.2 [3.9, 7.9]	7.0 [4.8, 9.9]	0.214	< .001	b
Respiratory rate, median [Q1, Q3]	18.0 [17.0, 21.0]	18.0 [16.0, 19.0]	18.0 [16.0, 19.0]	18.0 [17.0, 22.0]	20.0 [18.0, 24.0]	0.309	< .001	b
SATs, median [Q1, Q3]	96.0 [93.0, 98.0]	98.0 [96.0, 99.8]	97.0 [96.0, 99.0]	95.0 [92.0, 96.0]	94.0 [89.8, 97.0]	–0.475	< .001	b
Cancer stage, median [Q1, Q3]	3.0 [1.0, 4.0]	3.0 [2.0, 4.0]	3.0 [1.2, 4.0]	3.0 [1.0, 4.0]	3.0 [1.0, 4.0]	–0.013	NS	c
Cancer stage I or II, No. (%, no missing) of patients discharged, admitted, required O_2, and died	196 (21.8, 19)	25 (16.6, 1)	36 (15.9, 6)	78 (30.0, 5)	57 (21.6, 7)	0.072	NS	ns
Cancer stage III, No. (%) of patients discharged, admitted, required O_2, and died	181 (20.1)	47 (31.1)	58 (25.7)	53 (20.4)	23 (8.7)	–0.198	< .001	ns
Cancer stage IV, No. (%) of patients discharged, admitted, required O_2, and died	342 (38.0)	51 (33.8)	82 (36.3)	92 (35.4)	117 (44.3)	0.072	NS	ns
Hematologic cancer, No. (%) of patients discharged, admitted, required O_2, and died	171 (19.0)	26 (17.2)	47 (20.8)	32 (12.3)	66 (25.0)	0.046	NS	ns
Chemotherapy, No. (%) of patients discharged, admitted, required O_2, and death	356 (38.7)	70 (46.1)	116 (50.0)	78 (29.4)	92 (33.9)	–0.129	< .001	ns

(Continued on following page)

TABLE 2. Numeric and Categorical Variables Associated With Outcomes (Continued)

Variable	Overall	Discharged (score = 0)	Admitted (score = 1)	Admitted + Required O_2 (score = 2)	Admitted + Required O_2 + Died (score = 3)	Correlation[a]		Multivariable RFE SHAP
						r	*P*	
Immunotherapy, No. (%) of patients discharged, admitted, required O_2, and death	54 (5.9)	14 (9.2)	11 (4.7)	15 (5.7)	14 (5.2)	–0.041	NS	ns
Targeted therapy, No. (%) of patients discharged, admitted, required O_2, and death	106 (11.5)	22 (14.5)	25 (10.8)	29 (10.9)	30 (11.1)	–0.027	NS	ns
Radiotherapy, No. (%, no missing) of patients discharged, admitted, required O_2, and died	47 (6.2, 167)	7 (5.2, 18)	13 (6.7, 39)	18 (8.3, 47)	9 (4.3, 63)	–0.011	NS	ns
PS, mean [Q1, Q3]	1.0 [1.0, 2.0]	1.0 [1.0, 1.0]	1.0 [1.0, 2.0]	1.0 [1.0, 2.0]	2.0 [1.0, 3.0]	0.293	< .001	s

NOTE. $P \geq .05$.

Abbreviations: CRP, C-reactive protein; LDH, lactate dehydrogenase; NEWS2, National Early Warning Score 2; ns, not selected, no gain in performance; NS, not significant; PS, performance status; RFE SHAP, Recursive Feature Elimination on the basis of Shapley Additive Explanation; s, selected for modeling as it improved performance; SATs, oxygen saturation.

[a]Spearman correlation for numeric and point biserial correlation for categorical features.

[b]Excluded from RFE because of > 20% missing data.

[c]Excluded as hematologic cancer and cancer stage as separate features were included in the model.

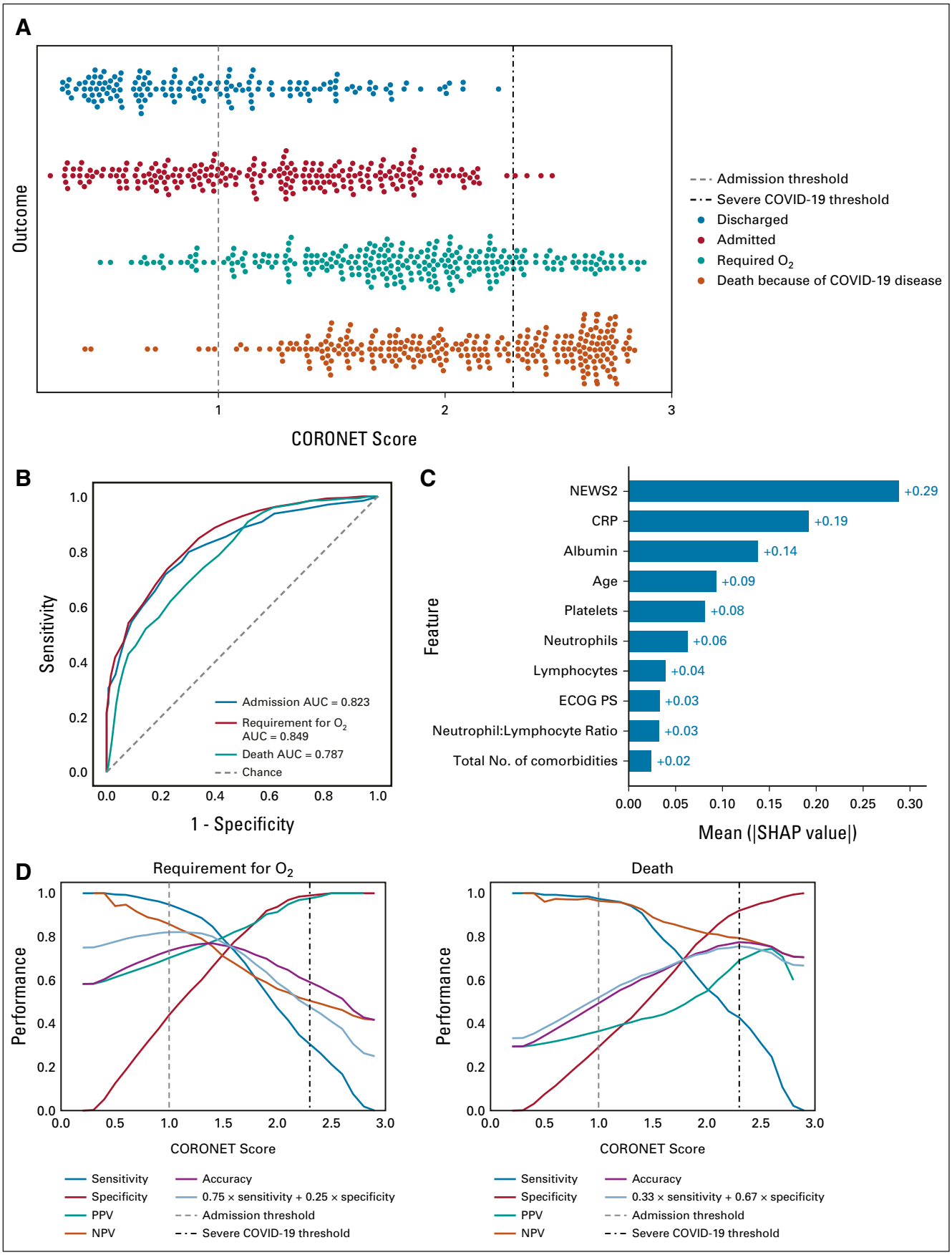

FIG 2. Final CORONET model characteristics: (A) predicted CORONET score for all 920 patients in the data set using leave-one-out cross-validation and Random Forest model; (B) receiver operating characteristic curves and AUC metrics for CORONET score used as (continued on following page)

FIG 2. (Continued). admission, requirement for O_2, and death determinants; (C) summary plot of feature contribution to CORONET prediction on the basis of SHAP explanation; and (D) metrics for requirement for O_2 and death depending on the CORONET score. The dotted line indicates admission threshold and severe disease threshold set at the maximum of the cost functions. AUC, area under the curve; CORONET, COVID-19 Risk in Oncology Evaluation Tool; CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group performance status; NEWS2, National Early Warning Score-2; NPV, negative predictive value; PPV, positive predictive value; SHAP, Shapley Additive Explanations.

This revealed 10 features: increasing age; PS; CRP; NEWS2; neutrophils; neutrophil:lymphocyte ratio; No. comorbidities; and decreasing lymphocytes, platelets, and albumin were predictive of COVID-19 outcomes in patients with cancer. Of note, certain features such as hematologic cancer and male sex, although significant for death (Data Supplement), did not add to the model performance as a whole and therefore were not selected. LDH, urea, oxygen saturations, and respiratory rate were not considered in RFE because of significant numbers of missing values (> 20%; Data Supplement). In the final feature set, only age and albumin achieve a high variance inflation factor (15.8 and 9.2, Data Supplement).

Model Derivation

To manage missing data and minimize bias, we performed bootstrapping followed by multiple imputation and oversampling, which resulted in 500 data sets and mean events per variable (EPV) of 22.5, before developing Lasso and RF models (Data Supplement). Tuning hyperparameters on the basis of mean squared error (MSE), we determined alpha (constant multiplying the L1 term) = .05 and maximum depth = 6 for Lasso and RF, respectively (Data Supplement). For both models, the learning curves flattened at ≈50% of the training set, suggesting that the current size of the data set provides sufficient model accuracy, with further increases in size of the data set only benefitting accountability and EPV (Data Supplement). The RF achieved lower MSE and higher R^2 and was more robust to multicollinearity compared with Lasso (Data Supplement). Therefore, this was selected to proceed to CORONET model development.

Threshold Derivation and Establishment of the Final CORONET Model

The area under the receiver operating characteristic curve (AUROC) was calculated for the CORONET model using the entire data set and Leave-one-out cross-validation (Fig 2A), resulting in a performance of 0.82 for admission, 0.85 for O_2 requirement, and 0.79 for death (Fig 2B and Data Supplement). The increasing importance of features used in the final CORONET model is shown in Figure 2C, in which the NEWS2 score followed by CRP and then albumin was considered as contributing the most to COVID-19 severity prediction. Dependency plots revealed clinically consistent relations between features and their contribution to the CORONET score (Data Supplement). In addition, nonlinearity in these relations supports the selection of RF over linear Lasso.

For CORONET, the threshold for admission was determined on the basis of pragmatic clinical reasoning that it is safer to preserve a lower threshold (to maintain high sensitivity) to admit patients who are more likely to require supplemental O_2 and have severe COVID-19 disease (sensitivity) at the cost of specificity. By contrast, in discussions with patients/families regarding the ability to predict prognosis and possibility of death, it would clinically be more useful for the tool to have better specificity and positive predictive value, even at the cost of sensitivity. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were therefore determined for each CORONET score (Data Supplement), and the threshold was established through finding maxima of cost functions for the importance ratio of sensitivity: specificity of 3:1 for admission and 1:2 for death (0.2-2.9 curves and formulas in Fig 2D). The cutoff for admission was determined to be 1.0, whereas that for mortality was 2.3. At these pragmatic thresholds, the model achieved a sensitivity of 43% and a specificity of 92% in predicting patient mortality. Critically, for prediction of the need for admission, it achieved a sensitivity of 85% and a specificity of 56%. The patients who required O_2 or who died, but were not predicted as requiring admission by CORONET (21 and seven patients respectively of 920), are shown in the Data Supplement. Manual inspection by clinical experts revealed no obvious clinical characteristic, which could have informed a severe outcome. In addition, we compared the CORONET score with ISARIC 4C score, achieving higher AUROCs for admission, O_2 requirement, and death (Data Supplement). Of note, 4C mortality scores in the CORONET-4C cancer-only cohort were lower than those in the original ISARIC 4C cohort [19], which was determined using predominantly noncancer populations (Data Supplement). In addition, patients with cancer were more likely to die at lower values of the 4C score (Data Supplement). For example, at a 4C score of ≤ 6, the mortality was 4.5% in the original ISARIC 4C validation cohort, whereas in the CORONET-4C cohort of patients with cancer only, it was 12% (Data Supplement).

External Validation

The performance of CORONET in the validation cohort is illustrated in the Data Supplement, with a significant geographical difference. Spain demonstrated the most accurate prediction overall (AUROC 0.85, 0.79, and 0.94 for admission, O_2 requirement, and death), whereas France had the lowest prediction (AUROC 0.69, 0.77, and 0.71 for admission, O_2 requirement, and death, Data

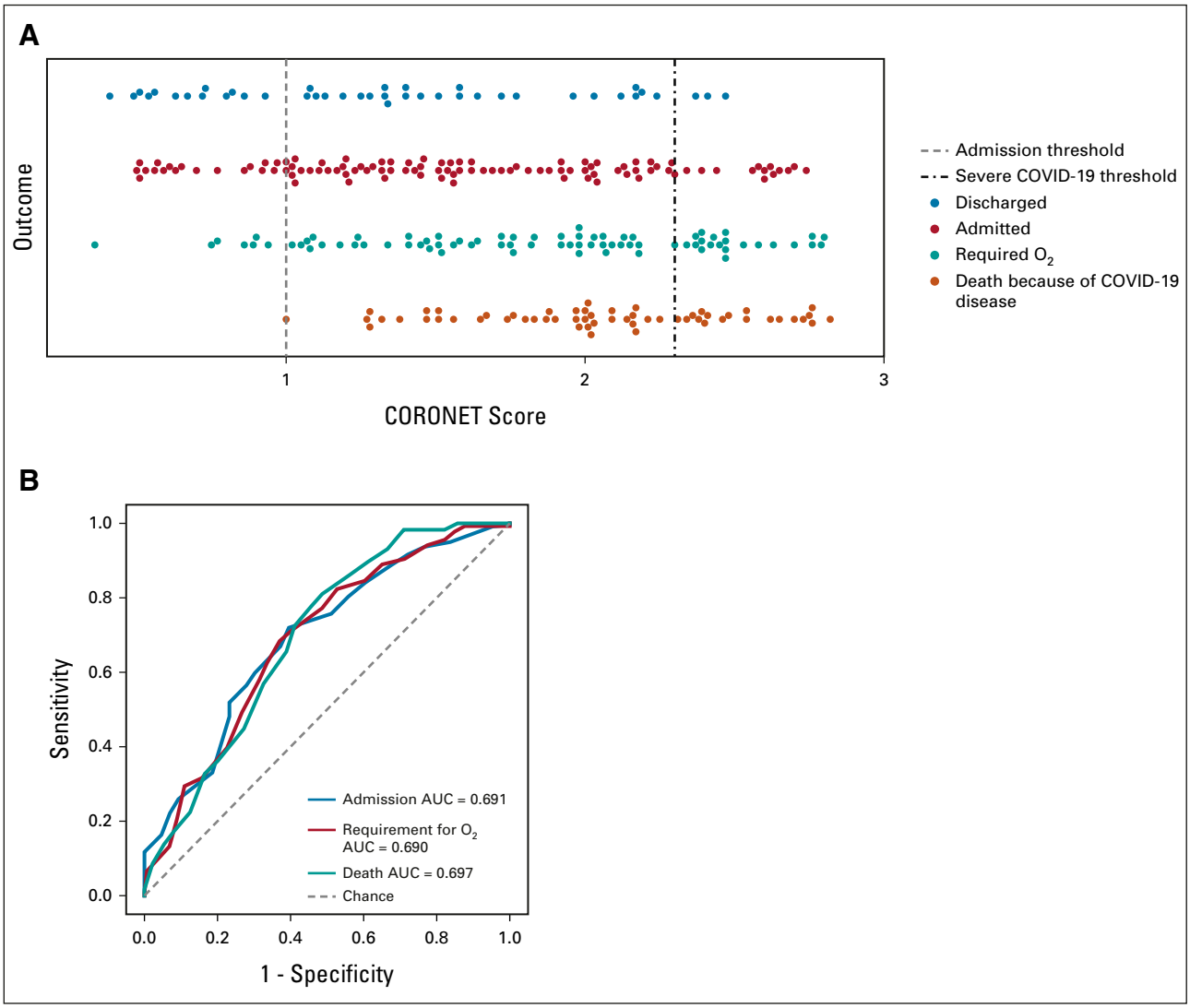

FIG 3. Validation of the CORONET model on the external cohort of 282 patients: (A) predicted scores stratified by outcome and (B) receiver operating characteristic curves and AUC metrics for CORONET score used as admission, requirement for O_2, and death determinants. AUC, area under the curve; CORONET, COVID-19 Risk in Oncology Evaluation Tool.

Supplement). On average, the AUROC in the entire validation cohort was 0.69, 0.69, and 0.70 for admission, O_2 requirement, and death, respectively (Fig 3B). On the basis of the defined thresholds, CORONET achieved a sensitivity of 88% and a specificity of 31% for predicting admission and a sensitivity of 33% and a specificity of 83% for predicting patient mortality (Data Supplement). Critically, it recommended admission for 94% of those patients eventually requiring oxygen and 98% of those who died.

DISCUSSION

Many studies have provided important data regarding risks of COVID-19–related outcomes in patients with cancer, which have helped to inform oncologists and patients in discussions regarding shielding, oncologic treatments, and management options in the event of contracting COVID-19 disease.[8,12,13,21] We focused on developing a cancer-specific model of risk and a decision support tool, which could aid the oncology and acute care communities in discussions and decisions at the point of admission assessment of patients with symptoms of COVID-19 disease. The CORONET model was developed on the basis of clinical and laboratory features that are routinely available, for it to be deployed easily in the clinical community. In this study, the RF model had the best performance with an AUROC of 0.82 for admission, 0.85 for O_2 requirement, and 0.79 for death in the data set used for model derivation. In the external validation cohort, the model achieved an average AUROC of 0.69, 0.69, and 0.70 for admission, O_2 requirement, and death respectively, considerably less than the performance from each individual country. This could be due to the heterogenous CORONET scores from

each country, where Denmark and France had significantly higher CORONET scores than the United Kingdom and Spain ($P < .001$, Kruskal-Wallis H-test, Data Supplement). Notably, there were significant missing data in cohorts from France and Denmark and consistent missing data of some NEWS2 components, which were managed through making specific assumptions and might have led to underestimation of the score (Data Supplement). Thus, data quality might have affected the CORONET performance in these cohorts.

Critically, in the entire cohort, CORONET recommended admission for 95% of patients who went on to require oxygen and 97% of the patients who died, and in external validation, it recommended admission for 94% of those eventually requiring O_2 and 98% who died. In establishing our cutoffs, we prioritized achieving high sensitivity for admission, which resulted in decreased specificity, but increased safety of the decision support tool. If we had based our decision to admit on thresholds defined by accuracy, the sensitivity of admission of patients requiring O_2 would drop from 0.95 to 0.85 and from 0.92 to 0.82 for the derivation and validation cohorts, respectively (Data Supplement). Thus, we felt that it would be unsafe to use those thresholds as they would unacceptably increase the likelihood of discharge of patients at risk of requiring O_2. Published models predicting for COVID-19 severity were mainly developed to model one individual clinical outcome (eg, death), a strategy that warrants good model performance but may result in data overfitting and does not reflect the whole clinical picture. We chose to model a combined COVID-19 outcome, comprising hospital admission, oxygen requirement, and death. This strategy might have reduced accuracy of classification for a specific outcome, but improved generality to reflect COVID-19 severity, important for overall decision-making regarding hospital admission. We were also less stringent regarding those patients who were admitted but survived and did not receive oxygen, as these patients could potentially be managed at home. In focusing on sensitivity regarding the decision to admit, specificity was decreased. In hospitals overwhelmed by the pandemic, this level of specificity may be an issue resulting in excess admissions. To address the challenge of a binary threshold being used for a complex decision, with the inevitable trade-off between ensuring safety versus number of admissions, we built the CORONET online tool to provide more detailed information (CORONET; COVID-19 risk in Oncology Evaluation Tool).[22] This provides the HCP with visuals as to where their patient sits within the entire cohort and the five most similar patients with outcome data (see the Data Supplement for an example of a borderline patient). Although the model provides a safety-oriented focus of only recommending discharge of patients who are highly unlikely to die/require oxygen, the HCP is provided with additional information to override the threshold and discharge the patient safely, taking into account their local pandemic context. Furthermore, it enables them to informatively prioritize patients if local health care systems are overwhelmed. In addition, the tool may highlight those more borderline patients who could be discharged but may benefit from careful home monitoring such as via a virtual ward or using home saturation devices. Patients might have been admitted because of oncologic problems rather than COVID-19 disease; therefore, it is important to stress that the decision support tool is specific to COVID-19 disease rather than cancer-related admission decisions.

Laboratory features such as CRP and clinical features such as age have been shown to be independent risk factors by a number of groups.[7,8,12,14,15] In other cohorts, male sex has been identified as an important independent negative prognostic factor; however, it did not add to the overall performance of our model.[9,12] Intriguingly, hematologic cancer and solid tumor stage in our multivariable modeling of COVID-19 severity at the point of presentation to hospital were outweighed by other numeric features, reducing their importance. Features such as CRP and low albumin were more important, suggesting that the COVID-19–induced inflammatory state is most critical in predicting severity even in patients with baseline inflammation because of cancer. We plan to improve the performance and complexity of the CORONET decision support tool through adding two further models with separate outcome measures of oxygen requirement and death to the combined current admission decision model (on the basis of admission, O_2 requirement, and death). We hypothesize that different features, for example, hematologic cancer and male sex, may be important for different outcomes, for example, death. In addition, NEWS2 is commonly used within the United Kingdom to identify patients who are at risk of severe illness.[20] Although NEWS2 has its own limitations and has been criticized, especially in applicability to primary care,[23] our validation of it as an important feature of severity in patients with cancer and COVID-19 disease suggests that it is helpful in the assessment of patients at least in the hospital setting.

We compared our model with the ISARIC 4C mortality risk score, created on the basis of data from more than 57,000 patients.[15] Although a smaller cohort, it is important to note that our analysis of patients with cancer using the 4C score showed that they were at higher risk of mortality with a lower 4C score compared with the original ISARIC population, which was mainly composed of patients without cancer. This observation highlights the importance of specifically assessing clinical decision models for patients with cancer. The 4C score had a comparable AUROC for mortality compared with CORONET; however, our model performed better in admitting patients requiring oxygen as a measure of COVID-19 severity, which was likely due to how our model was trained. In addition, all except two patients predicted by the 4C score to be at risk of mortality were

admitted using our CORONET model, which is an important validation of its safety.

There were several limitations in our model development. First, the cohort is relatively small; despite that, we obtained reasonable EPV, and according to the learning curves, we expect minimal improvement of the model accuracy with a larger data set size. Second, although we included data from 25 countries, the majority of these were higher-income countries, and therefore, the model should be interpreted with caution by users in middle-/low-income countries. Furthermore, through focusing on patients presenting to hospital, we selected a population biased toward more severe COVID-19 disease. In addition, although we excluded patients with more than one important numeric feature missing and managed remaining missing data through imputation (for $< 20\%$ missing), we still did not have sufficient data on features shown to be important in other cohorts such as ethnicity and LDH to incorporate into the analysis. We also observed an imbalance in missing data with more of the patients in the United States discharged without performing laboratory tests compared with those admitted, which might have affected the results of that cohort (Data Supplement). Further data from the United States will be required to assess the performance of the model in a larger population, accounting for regional variation in clinical practice. Lack of data regarding outcomes for patients discharged precludes assessment of how the tool could prevent discharge errors. Finally, there was less granularity regarding death being caused by COVID-19 disease versus other causes such as cancer in these data sets. This might have resulted in the heterogenous performance seen in different countries (Data Supplement).

Most HCPs have access to the internet, and hospital results are increasingly accessed online. Our companion online decision support tool enables our model to be easily used. However, we recognize that for those working in resource-poor settings, this may provide a barrier to use and can provide further assistance if required. The tool is planned to provide prognostic information regarding the outcome of the patient in addition to assessment of how features of the individual define the outcome reported by the tool. In this way, we aim to support greater recognition of features that are associated with more severe outcomes for patients with cancer and COVID-19 disease. We are currently testing how HCPs interact with the tool to determine its safety and usability.

Critically, we view the creation and ongoing development of the decision support tool as an iterative process. This first version is a foundation on which to improve as more data are obtained, particularly in patients infected with new variants, and more decision support features are created and validated in different hospitals. Using CORONET, HCPs can be supported in their management of cancer patients with COVID-19 disease. It aids discussions with patients and their families regarding likely prognosis, which is crucial to ensuring that they are fully informed. It will support decisions regarding safe early discharge of patients, reducing hospital stay with beneficial impacts to emergency services, cost savings, and reducing risk of infecting staff/other patients. Furthermore, it will provide information that can be used to identify those who might benefit from more intensive monitoring and to make early decisions regarding escalation to intensive care. In the future, it may be used to identify patients at risk of severe COVID-19 disease who might have greatest benefit from interventions. Individualized management of COVID-19 disease in patients with cancer is crucial to providing sustainable emergency oncology care during the COVID-19 pandemic and beyond.

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DATA SHARING STATEMENT

Code for the tool is available at GitHub (https://github.com/digital-ECMT/CORONET_tool). Raw data are available upon request to the corresponding author.

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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